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TJ Tumori Journal

Abstract Book of the 26th National Congress of Italian Association of Medical Oncology (AIOM)

8-10 November 2024, Rome, Italy

Rome Marriott Park Hotel

Guest Editor

Francesco Perrone
President, Italian Association of Medical Oncology (AIOM)
Director of Clinical Trials Division, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples

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26th National Congress of Italian Association of Medical Oncology (AIOM)
8-10 November 2024 – Rome Marriott Park Hotel, Rome, Italy

Please note that Abstracts marked with an asterisk "*" are Oral Communications.

Francesco Perrone,
Director, Clinical Trial Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS Fondazione Pascale, Napoli

Dear Colleagues,

On behalf of the Scientific Board, it is a great pleasure for me to introduce the proceedings of the XXVI National Congress of Italian Association of Medical Oncology (AIOM).

It will be the first national congress of the second half century of AIOM. A new beginning, therefore, with the same hopes and determination that inspired the founders of AIOM, back in 1973. But it is a fortunate and facilitated beginning because, today, AIOM has strong shoulders thanks to the work of those who came before us.

The claim we chose for AIOM XXVI National Congress is "Eyes to the future" and has both a positive and a critical meaning, being consistent with nowadays trends of oncology that navigates between the positive dynamics of progress and the negative ones of sustainability on a global scale.

We look with confidence and optimism at the progress in diagnostics and therapy that are progressively changing the face of our discipline for the better. From the ability to probe the infinitely small to identify with ever greater precision the best therapies for those who fall ill, to the maturation of pharmacological research that seems capable of bringing together the therapeutic revolutions of the past decades (radiotherapy, chemotherapy, hormone therapy, molecularly targeted drugs and immunotherapy) producing new drugs that, we hope, will do more and more harm to cancer and less and less harm to patients.

But, as much as we appreciate all this, we don't ignore how and to what extent the efficiency of the diagnosis and treatment pathways for those who fall ill with cancer in every country is also linked to factors external to AIOM, national and international, on which we must keep our eyes critically open. Even when it seems that these are matters that go beyond our medical profession. We all know that progress loses much of its beauty if it does not reach the patients who need it. Indeed, it takes on the unpleasant appearance of wasted opportunities, of rights that are told but not guaranteed to everyone. We are convinced that the Italian National Health Service is among the best in the world, but we also believe with equal firmness that it needs maintenance and to be defended.

We will talk about these beauties and these necessary attentions together in Rome in 2024. With the young oncologists who now represent the majority of our members, with the nurses who share our work on a daily basis, with the patient associations who help us keep the bar of our mission straight and with all those who make an irreplaceable contribution to our research. The abstract published in this issue of "Tumori Journal" are frequently signed by young oncologists, and cover many topics of medical oncology, including prevention, screening, diagnosis, treatment, follow-up, simultaneous care, multidisciplinary approach.

Finally, I'd like to thank the Scientific Committee and all the reviewers for their invaluable work and I hope that the meeting will be the occasion of sharing knowledge and experiences, in order to enrich our skills.

Enjoy the meeting!

The Board of Directors for the years 2023-2025 includes

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Plenary Session

LBA01*

A-BRAVE TRIAL: A PHASE III RANDOMIZED TRIAL WITH AVELUMAB IN HIGH RISK EARLY TRIPLE NEGATIVE BREAST CANCER

Guarneri V.[1], Bisagni G.[2], Schmid P.[3], Fotia V.[4], Piacentini F.[5], De Laurentiis M.[6], Favaretto A.[7], Tamberi S.[8], Bianchi G.[9], Zamagni C.[10], Cinieri S.[11], Corsi D.[12], Del Mastro L.[13], Ferro A.[14], Gennari A.[15], Mion M.[16], Musolino A.[17], De Salvo G.L.[18], Conte P.[19], Dieci M.V.[1]

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Background: The A-BRAVE trial evaluated the efficacy of avelumab, an anti PD-L1 antibody, as adjuvant treatment for pts with early TNBC at high risk.

Methods: A-BRAVE is a phase III multicentric (70 centers in Italy and UK) study that randomized pts with high risk early TNBC to 1-year avelumab vs observation after completion of standard surgery and neoadjuvant/adjuvant chemotherapy. High risk was defined as: 1) ≥pN2/any pT, pN1/pT2, or pN0/pT3 after primary surgery (Stratum A), 2) invasive residual disease (breast and/or nodes) after neoadjuvant chemotherapy (Stratum B). Pts were randomized (1:1, balanced for strata A and B) to Avelumab 10 mg/kg I.V. q2w for 1 year or observation. Co-primary endpoints were disease free survival (DFS) in the ITT and in Stratum A. Overall survival (OS) in ITT was a secondary endpoint and distant disease-free survival (DDFS) was assessed as exploratory endpoint.

Results: From June 2016 to October 2020, 466 pts were randomized: 383 entered Stratum B (83%) and 83 entered Stratum A (17%). At a median follow of 52.1 months, the 3-year DFS in the ITT was 68.3% in the avelumab arm vs 63.2% in the control arm (HR 0.81, 95%CI 0.61-1.09, p=0.172). The 3-year DFS in Stratum B was 66.9% with avelumab vs 60.7% in the control arm (HR 0.80, 95%CI 0.58-1.10, p=0.170). The 3-year OS in ITT was 84.8% (95%CI 79.5-88.8) for avelumab group and 76.3% for the control group (HR 0.66; 95%CI 0.45-0.97, p=0.035). The 3-year DDFS was 75.4% with avelumab and 67.9% with observation (HR 0.70, 95%CI 0.50-0.96, p=0.0277). Subgroup analyses for DDFS and OS are shown in Table.

	OS			DDFS		
	HR (95% CI)	p	Interaction	HR (95% CI)	p	Interaction
Stratum A	0.50 (0.15-1.66)	0.256	0.578	0.93 (0.39-2.18)	0.862	0.519
Stratum B	0.69 (0.46-1.03)	0.070		0.67 (0.47-0.94)	0.021	
Age ≤50	0.88 (0.50-1.55)	0.653	0.226	0.85 (0.53-1.37)	0.510	0.283
Age >50	0.53 (0.31-0.90)	0.019		0.60 (0.39-0.93)	0.022	
ER 0%	0.70 (0.47-1.04)	0.075	0.302	0.73 (0.52-1.03)	0.069	0.573
ER 1-9%	0.22 (0.03-1.75)	0.150		0.49 (0.16-1.53)	0.222	
gBRCAmut	0.42 (0.08-2.16)	0.297	0.296	0.43 (0.11-1.68)	0.225	0.551
gBRCAwt/VUS	0.97 (0.56-1.69)	0.918		0.87 (0.56-1.37)	0.557	
gBRCA unknown	0.47 (0.27-0.83)	0.010		0.57 (0.35-0.94)	0.027	
Platinum yes	0.91 (0.44-1.88)	0.799	0.344	0.95 (0.53-1.73)	0.878	0.220
Platinum no	0.59 (0.37-0.93)	0.023		0.61 (0.42-0.91)	0.014	

Conclusions: Adjuvant avelumab for high-risk TNBC patients significantly reduces the risk of distant progression and death.

02*

FINDING EVIDENCE FOR DETECTION, PROGNOSIS AND PREDICTION OF RESPONSE IN PATIENTS WITH PROSTATE CANCER HARBORING DNA REPAIR PATHWAY ALTERATIONS. RESULTS FROM THE MULTICENTER ITALIAN PROGRESS STUDY

Incorvaia L.[1], Maruzzo M.[2], Basso U.[2], Bracarda S.[3], Mammone G.[3], Antonuzzo L.[4], Rizzo M.[5], Conteduca V.[6], Messina C.[7], Scagliarini S.[8], Maiorano B.[9], Santoni M.[10], Facchini G.[11], Lipari H.[12], Formisano L.[13], Malapelle U.[14], Santini D.[15], Caffo O.[16], Di Maio M.[17], Russo A.[1]

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Background: BRCA1/2 (likely) pathogenic variants (PVs) have been consistently associated with aggressive phenotypes and adverse clinical outcomes in metastatic prostate cancer (mPC) patients, providing practice changes in the care and preventive paths. The objective of this study was to investigate the prevalence and the clinical implications of homologous recombination repair (HHR) PVs in an Italian study population of mPC since genetic testing and PARPis were incorporated into daily clinical practice.

Patients and Methods: This was a real-world, observational study involving 15 Italian cancer centers. The study population included mPC undergoing BRCA/HRR germline (g), somatic (s), and liquid biopsy (lb) testing between January 2020 and April 2024. Mutation prevalence, type and time of testing, site of tumor testing, prognostic factors, treatment outcomes and adverse events to PARPis were assessed. Second primary tumor and family cancer history were also evaluated.

Results: A total of 962 mPC patients, aged 40 to 91 were included; 203 (21.1%) were carriers of germline (55/962, 5.7%) or somatic (148/803, 18.4%) PVs in HRR genes: 21 in BRCA1 (4 gBRCA1, 2%; 17 sBRCA1, 8.4%), 126 in BRCA2 (40 gBRCA2, 19.7%; 86 sBRCA2, 42.4%), and 56 in non-BRCA HRR genes (11 gHRR, 5.4%; 45 sHRR, 22.2%). CHEK2 was the HRR gene most frequently affected by germline PVs (27.2%), while the most frequent somatic PVs were in the ATM (35.%). Liquid biopsy identified PVs in 39 patients out of 238 tested (16.4%), including 12 (5%) not detected through s/g testing, considerably expanding the therapeutic window for PARPi use. When we compared BRCA1 and BRCA2 subgroups, median imaging-based PFS to PARPi was significantly longer for BRCA2 [7.0 months (95% CI 5.4-8.6) vs 11.0 months (95% CI 5.7-16.2), p=0.01]. PFS and OS of all genetic and prognostic subgroups were also assessed. Surprisingly, when we investigated the personal second cancer history, in the HRR wild-type patients the second tumors were predominantly colorectal, or other sites classically dominated by mismatch-repair deficiency. This observation may result in unexplored forms of hypermutable tumor phenotypes, potentially impacting cancer risk management and increasing therapeutic opportunities.

Conclusions: To our knowledge, this is the largest Italian real-world study providing novel insights into the prevalence, clinical behavior and outcomes of mPC in patients harboring germline, somatic or liquid biopsy genetic alterations in BRCA and non-BRCA HRR genes.

03*

PEMBROLIZUMAB PLUS CHEMOTHERAPY FOR HIGH-RISK LOCALLY ADVANCED CERVICAL CANCER: OVERALL SURVIVAL RESULTS FROM THE RANDOMIZED, DOUBLE-BLIND, PHASE 3 ENGOT-CX11/GOG-3047/KEYNOTE-A18 STUDY

Lorusso D.[1], Xiang Y.[2], Hasegawa K.[3], Scambia G.[4], Leiva M.[5], Ramos-Elias P.[6], Acevedo A.[7], Bednarik M.[8], Gomes A.[9], Contreras Mejía F.[10], Reiss A.[11], Zagouri F.[12], Lee J.[13], Saevets V.[14], Ayhan A.[15], Liu P.[16], Yamada K.[16], Puglisi M.[16], Pignata S.[17], Duska L.R.[18]

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Background: At the first interim analysis of the phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 study (NCT04221945), pembrolizumab (pembro) + concurrent chemoradiotherapy (CCRT) showed a statistically significant and clinically meaningful improvement in PFS vs placebo (pbo) + CCRT in patients (pts) with high-risk locally advanced cervical cancer (LACC). Based on this study, the US FDA has approved pembro + CCRT for pts with FIGO 2014 Stage III-IVA cervical cancer. We present the OS results from the second interim analysis.

Methods: Eligible pts with newly diagnosed, previously untreated, high-risk LACC (FIGO 2014 stage IB2-IIB with node-positive disease or stage III-IVA regardless of lymph node status) were randomized 1:1 to 5 cycles of pembro 200 mg or pbo Q3W + CCRT, then 15 cycles of pembro 400 mg or pbo Q6W. CCRT included 5 cycles (optional 6th dose) of cisplatin 40 mg/m^2 Q1W + EBRT then brachytherapy. Pts were stratified by planned EBRT type (intensity-modulated radiotherapy [IMRT] or volumetric-modulated arc therapy [VMAT] vs non-IMRT or non-VMAT), stage at screening (IB2-IIB vs III-IVA), and planned total radiotherapy dose (<70 Gy vs ≥70 Gy [EQ2D]). Primary endpoints are PFS per RECIST v1.1 by investigator and OS.

Results: 1060 pts were randomized to pembro + CCRT (n=529) or pbo + CCRT (n=531). At this analysis (January 8, 2024, data cutoff), median follow-up was 29.9 mo (range, 12.8-43.0). Pembro + CCRT showed a statistically significant improvement in OS compared with pbo + CCRT. The 36-mo OS rate was 82.6% with pembro + CCRT vs 74.8% with pbo + CCRT; median OS was NR in either group (HR=0.67 [95% CI, 0.50-0.90]; P=0.0040). The benefit of pembro + CCRT was generally consistent in all prespecified subgroups, including FIGO stages IB2-IIB (HR=0.89 [95% CI, 0.55-1.44]) and III-IVA (HR=0.57 [95% CI, 0.39-0.83]). Grade ≥3 TRAE incidence was 69.1% in the pembro + CCRT group and 61.3% in the pbo + CCRT group.

Conclusions: Pembro + CCRT showed a statistically significant and clinically meaningful improvement in OS vs pbo + CCRT in pts with high-risk LACC and had a manageable safety profile. These data provide further support for pembro + CCRT as a new standard of care for this population.

04*

LIQUID BIOPSY-BASED COMPREHENSIVE GENOMIC PROFILING CAPTURES TUMOR HETEROGENEITY AND IDENTIFIES CANCER VULNERABILITIES IN PATIENTS WITH RAS/BRAFV600E WILD TYPE METASTATIC COLORECTAL CANCER IN THE CAPRI 2-GOIM TRIAL

Ciardiello D.[1], Boscolo Bielo L.[2], Martinelli E.[3], Troiani T.[3], Napolitano S.[4], Latiano T.P.[5], Maiello E.[5], Pisconti S.[6], Tamburini E.[7], Avallone A.[8], Bordonaro R.[9], Lotesoriere C.[10], Lonardi S.[11], Borrelli B.[12], Garufi C.[13], Fazio N.[2], Zampino M.G.[2], Curigliano G.[2], Ciardiello F.[3], Martini G.[14]

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Background: Determination of KRAS/NRAS/BRAF *a*nd microsatellite instability is required for treatment choice for patients (pts) with metastatic colorectal cancer (mCRC). Emerging evidence support liquid biopsy (LB) as a non-invasive tool to capture tumor heterogeneity and provide dynamic assessment of mCRC mutational landscape.

Materials and Methods: The phase II CAPRI 2-GOIM trial investigates the efficacy and safety of biomarker-driven, cetuximab-based, sequence of three treatment lines in mCRC. Patients (pts) with RAS/BRAF^{V600E} wild type (WT) mCRC, as determined by local laboratory, were enrolled in the trial. Before first-line therapy, comprehensive genomic profiling by next generation sequencing (NGS) was performed with FoundationOne (F1) CDx and F1 Liquid (F1L) CDx (324 genes) on tumor tissue and plasma circulating tumor DNA (ctDNA), respectively. After progression to first-line therapy, subsequent lines of treatment are defined on ctDNA molecular profile.

Results: Of 240 screened pts, 201 entered the trial fulfilling all inclusion criteria. Only for 2 pts, no ctDNA was detected (2/201, 1%). 181/199 pts (90.9%) had RAS/BRAF^{V600E} WT disease. 17 pts presented gene alterations in RAS (14 KRAS or NRAS mutations and 3 KRAS amplifications), and 1 pt BRAF^{V600E} mutation, while 7 additional BRAF mutations or rearrangements were found. For 142 pts both F1 CDx and F1L CDx results were available. Among KRAS or NRAS mutated tumors, for 4 cases mutations were found only in tumor tissue and for 4 cases only in ctDNA (concordance 94.6%). LB comprehensive genomic profiling allowed the identifications of other potential mechanisms of resistance to EGFR blockade, including mutations of PI3KCA (31/199), MAP2K1 (17/199), NF1 (13/199), ERBB2 (13/199), PTEN (12/199), EGFR (8/199) and ERBB2 amplification (4/199). 154 actionable genomic alterations, which could be classified by the ESMO Scale of Clinical Actionability for Molecular Targets (ESCAT) as I-IIIA, were observed in 100/199 pts (50.2%). Of these, 2 were ESCAT IA, 4 IB, 19 IC and 129 IIIA.

Conclusions: Baseline plasma-based comprehensive genomic profiling is feasible with high concordance with tissue-based analysis. Liquid biopsy allows identification of misdiagnosed RAS/BRAF alterations and the ultra-selection of pts, which could benefit from anti-EGFR therapies. Finally, potentially actionable gene alterations were found in half of the pts.

A - Gastrointestinal Cancers

A01*

FIRST RESULTS FROM THE ITALIAN CHOLANGIOCARCINOMA DATASET (ANITA): EXTENDED MOLECULAR PROFILING (EMP), ACCESS TO TARGETED TREATMENT (TT) AND CLINICAL CHARACTERIZATION OF FGFR2-REARRANGED AND IDH1-MUTATED ADVANCED BILIARY TRACT CANCERS (BTC)

Salani F.[1], Rimini M.[2], Pressiani T.[3], Rizzato M.[4], Pircher C.[5], Salvatore L.[6], Antonuzzo L.[7], Silvestro L.[8], Diana A.[9], Leone F.[10], Vivaldi C.[1], Foti S.[11], Genovesi V.[12], Balsano R.[13], Soldà C.[4], Masi G.[1], Rimassa L.[13], Di Paolo G.[14], Casadei-Gardini A.[11], Fornaro L.[12]

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Background: Tumoral molecular profiling is recommended to tailor TT for BTC patients (pts). However, neither the EMP impact on prognosis, nor the availability of TT or the sensitivity of FGFR2 fusions/rearrangements or IDH1 mutations to first-line platinum-based chemotherapy (CT1) have been extensively reported.

Methods: ANITA is an observational study, enrolling 621 BTC pts treated at 10 tertiary Italian cancer centres (2017-2023), with primary aim to assess patients' disease management in different settings. Here we report: I) the results of the EMP analyses, EMP rate over time, its impact on access to TT and TT-influenced outcomes; II) the prognostic role of FGFR2 fusions/rearrangements and IDH1 R132 mutation. Progression-free (PFS) and overall (OS) survival were calculated since the first cycle of CT1 for advanced disease. In II), pts who received anti-FGFR2/anti-IDH1 TT were excluded.

Results: EMP was performed in 62% of the pts, and FoundationOne test was the most used (87.6%) method for assessment. Among pts with EMP available, 64.2% had intrahepatic cholangiocarcinoma and 69.8% received CT1 (36.1% cisplatinum-gemcitabine). With a progressive increase in EMP over years (2017-2023: +32%, $p<0.001$), 42% ESCAT I-IV mutations were identified and 15% of the pts received matched TT. After a median follow-up of 19 months, no differences were seen in OS and PFS according to EMP availability ($p>0.05$), whilst TT-receivers had a significantly longer OS (67.9 months, 95%CI 14.8-68.0) then untreated ones (19.1 months, 95%CI 16.6-23.0) and then those who did not undergo EMP (14.3 months, 95%CI 15.4-19.8) ($p=0.002$). Among ESCAT I-IV positive pts, 34 had FGFR2-fused/rearranged disease and 45 pts IDH1-mutated one. No predictive role for CT1 PFS was found for either FGFR2 or IDH1 (both $p>0.05$) alterations. When the prognostic role of FGFR2 and IDH1 alterations was assessed, FGFR2 fusions/rearrangements demonstrated a positive correlation with OS (HR 0.49, 95%CI 0.33-0.74, $p=0.005$) at univariate analysis, which was not confirmed at multivariate regression.

Conclusions: Despite a broader availability of EMP in advanced BTC in recent years, access to TT remains suboptimal even in referral Institutions. Our results demonstrate TT administration as a pivotal positive prognostic factor in a real-world setting, whilst FGFR2 or IDH1 alterations did not act as prognostic determinants per-se. Therefore, strategies aiming at improving the rate of patients receiving TT are warranted.

A02*

FOLFOXIRI/BEVACIZUMAB (BEV) VERSUS DOUBLETS/BEV AS INITIAL THERAPY OF UNRESECTABLE LIVER-ONLY (LL), RIGHT-SIDED AND/OR RAS OR BRAF MUTATED (MUT) METASTATIC COLORECTAL CANCER (MCRC): AN INDIVIDUAL PATIENT DATA-BASED POOLED ANALYSIS OF RANDOMIZED TRIALS

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Background: FOLFOXIRI/bev was associated with longer PFS and OS vs doublets/bev independently of the presence of LL disease and the secondary resection of metastatic lesions. In the CAIRO-5 trial pts with LL right-sided and/or RAS or BRAF mut mCRC experienced no OS difference, but higher ORR, R0 resection rate and longer PFS with the triplet/bev compared with doublets/bev. Here we aim at providing an estimation of the efficacy and activity of FOLFOXIRI/bev over doublets/bev in pts with unresectable LL, right-sided and/or RAS or BRAF mut mCRC.

Methods: We selected pts with LL, right-sided and/or RAS or BRAF mut mCRC, treated with upfront doublets/bev or FOLFOXIRI/bev in 4 phase II/III RCTs: TRIBE, TRIBE2, CHARTA and STEAM. Pts were deemed initially unresectable according to multidisciplinary evaluation and were not selected based on the potential conversion to resectability. We compared FOLFOXIRI/bev with doublets/bev in terms of PFS, OS, ORR, and R0 resection.

Results: Of 300 eligible pts, median age was 61 and most of them had an ECOG PS of 0 (83%) and synchronous metastases (91%). 130 (43%) and 170 (57%) pts received doublets/bev and FOLFOXIRI/bev, respectively. Baseline characteristics were homogeneous between groups. Pts receiving FOLFOXIRI/bev showed longer PFS (12.3 vs 10.3 months [mos] HR:0.75, p = 0.02) and a statistically not significant trend for better OS (29.1 vs 23.2 mos, HR:0.85, p = 0.25), than those treated with doublets/bev. FOLFOXIRI/bev was associated with higher ORR (64% vs 53%, OR:1.54, p = 0.08) but no differences in R0 resection rate (27% vs 24%, OR:1.15, p = 0.70). No significant interaction was found between treatment effect and the achievement of R0 resection in terms of both PFS (Pint=0.81) and OS (Pint=0.53).

Conclusions: As compared to doublets/bev, FOLFOXIRI/bev provides a meaningful advantage to pts with initially-unresectable, LL, right-sided and/or RAS or BRAF mut mCRC, in terms of activity and efficacy, thuscorroborating the choice of triplet as upfront therapy for these pts, regardless of the opportunity to achieve theR0 secondary resection of their liver metastatic lesions.

A03*

RAS/BRAF TESTING OF CIRCULATING TUMOR DNA (CTDNA) IN TISSUE RAS/BRAF WILD-TYPE METASTATIC COLORECTAL CARCINOMA (MCRC) PATIENTS (PTS) ENROLLED IN THE LIQUID BIOPSY MONOCLONAL ANTIBODIES (LIBIMAB) STUDY

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Background: The analysis of RAS/BRAF mutations is usually performed on tumor tissue samples to select mCRC pts for treatment with anti-EGFR monoclonal antibodies. RAS/BRAF mutations have been detected in ctDNA from up to 10% treatment-naive mCRC pts RAS/BRAF wild-type (RAS/BRAF^{wt}) on tissue, while approximately 30% of pts treated with anti-EGFR therapies shows RAS/BRAF mutations in ctDNA at progression.

The LIBImAb Study is a phase III, randomized, open-label, comparative, multi-center trial to assess the superiority in terms of efficacy of bevacizumab versus cetuximab in combination with FOLFIRI in mCRC pts, RAS/BRAF^{wt} on tumor tissue and RAS/BRAF mutant (RAS/BRAF^{mut}) at liquid biopsy. In particular, pts RAS/BRAF^{mut} on liquid biopsy at baseline are randomized to receive FOLFIRI/cetuximab or FOLFIRI/bevacizumab. Pts RAS/BRAF^{wt} on baseline plasma test are treated with FOLFIRI/cetuximab up to 8 cycles and, if not progressed, they are retested for RAS/BRAF mutations on ctDNA. Finally, RAS/BRAF^{mut} pts at re-screening are randomized to continue cetuximab or to switch to bevacizumab.

Methods: Blood samples from enrolled pts were collected and shipped to the centralized laboratory. ctDNA was isolated from plasma samples using the MagMAX Cell-Free Total Nucleic Acid Isolation Kit (ThermoFisher Scientific) and analyzed with the Idylla ctKRAS-ctNRAS/BRAF mutation assays (Biocartis). The LIBImAb study is supported by the Italian Drug Agency (AIFA).

Results: As of April 30 2024, plasma samples from 330 tissue RAS/BRAF^{wt} mCRC pts at baseline and 190 pts at re-screening were tested. The median turnaround time (TAT) from blood sampling to results was 48 hours (range

24-96). RAS/BRAF variants were detected in plasma baseline samples from 24/330 pts (7.2%). Fifteen mutations were found in KRAS (4.5%), 6 in NRAS (1.8%) and 3 in $BRAF^{V600}$ (0.9%). The overall concordance between tissue and ctDNA testing was 92.7%. RAS/BRAF alterations were also detected in 15/190 (7.9%) plasma samples obtained at re-screening, revealing the presence of 11 KRAS (5.8%), 3 NRAS (1.6%) and 1 $BRAF^{V600}$ (0.5%) variants.

Conclusions: These data indicate the feasibility of cfDNA-based prospective enrolment in an interventional trial using a test with a rapid TAT for screening of RAS/BRAF status in plasma. Our preliminary findings also suggest that ctDNA testing might better recapitulate the tumor heterogeneity of mCRC pts thus complementing tissue genomic profiling.

A04*

TRIFLURIDINE/TIPIRACIL PLUS CAPECITABINE AND BEVACIZUMAB AS UPFRONT TREATMENT FOR METASTATIC COLORECTAL CANCER: RESULTS OF THE PHASE 1 TRICOMB STUDY

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Background: Capecitabine (cap) plus bevacizumab (bev) is a standard option for previously untreated unresectable metastatic colorectal cancer (mCRC) patients (pts) deemed not fit for upfront chemotherapy doublets. A synergistic effect of the sequential administration of cap and trifluridine/tipiracil (FTD/TPI) has been shown both *in vitro* and *in vivo* models. Here, we present safety and preliminary activity results of the phase 1 TriComB study, an open-label, multicenter, phase 1/2 trial, evaluating FTD/TPI in combination with cap and bev in mCRC pts.

Methods: Patients with previously untreated mCRC, ineligible for oxaliplatin- and/or irinotecan- based regimens, were enrolled. A 3 + 3 dose escalation design was used to identify the recommended dose (RD) of FTD/TPI (days 15-19 and 22-26) in combination with cap (1000 mg/sqm/BID days 1-14) and bev (5 mg/kg day 1,15) in 28-days cycles. Adverse events (AEs) were reported according to CTCAE version 5.0 and tumor response was assessed by RECIST version 1.1.

Results: 11 pts (5 men, 6 women; median age: 77, range: 47-84 years) were enrolled. For the first three patients (FTD/TPI: 25mg/sqm BID) no dose limiting toxicities (DLTs) were observed. At 30 mg/sqm BID dose level, 3/5 DLTs were reported: 2 pts experienced a dose delay of >7 days from the scheduled timing and 1 patient was unable to receive ≥ 75% of study drugs' doses during the first cycle. FTD/TPI was de-escalated and 3 additional patients were treated at 25 mg/sqm BID. Since 1/6 pts experienced a DLT (grade 4 colonic perforation) that was identified as the RD. Grade 3/4 AEs are listed in the Table. As of January 2024, Overall Response Rate is 72.7% (8/11 pts) and 66.7% (4/6 pts) in the overall population and at the RD, respectively.

Conclusions: The sequential combination of cap and FTD/TPI with bev is feasible. The phase 2 of the study is ongoing to evaluate antitumor activity of this regimen in the same patients' population.

Clinical trial information: NCT04564898

Safety summary

Events, n (%)	Overall population (N= 11)	FTD/TPI 25 *mg/mq/bid* (N= 6)
All Grade ≥3 AEs	**8 (72.7)**	**4 (66.7)**
Neutropenia	4 (36.4)	0
Diarrhea	2 (18.2)	1 (16.7)
Thromboembolic event	1 (9.1)	1 (16.7)
Fatigue	1 (9.1)	0
AST/ALT increased	1 (9.1)	1 (16.7)
Hypokalemia	1 (9.1)	0
Colonic perforation	1 (9.1)	1 (16.7)

A05*

IMPACT OF CIRCULATING TUMOR DNA STATUS ON SURVIVAL OUTCOMES IN RESECTED STAGE IV COLORECTAL CANCER PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Approximately 30% of colorectal cancer (CRC) patients are diagnosed with metastatic disease (mCRC), necessitating systemic treatment. Clear guidelines for identifying mCRC patients who can be treated curatively are lacking. Circulating tumor DNA (ctDNA) detection has emerged as a novel tool for detecting minimal residual disease. This systematic review and meta-analysis (SR-MA) explores the role of ctDNA in predicting survival outcomes for mCRC patients undergoing curative surgery.

Materials and Methods: We conducted a SR-MA in accordance with the PRISMA guidelines, reviewing eligible articles published up to March 21, 2024. The analysis focused on the impact of ctDNA positive status on time-to-event outcomes, expressed as Hazard Ratios (HR) for Overall Survival (HR_{OS}) and Recurrence-Free Survival (HR_{RFS}).

Results: Seven studies were included in the meta-analysis (Table 1). A total of 461 patients were analyzed for RFS across 7 studies, and 291 patients for OS across 4 studies. A random-effects model was used due to significant heterogeneity detected in both RFS ($I^2 = 56.35\%$) and OS ($I^2 = 73.21\%$). The pooled effect size analysis indicated that post-operative ctDNA positive status was associated with worse outcomes. Specifically, the HR for RFS was 4.53 (95% CI 2.75-7.34, $p < 0.0001$) and the HR for OS was 5.57 (95% CI 1.74-17.87, $p = 0.0039$). Meta-regression showed significant associations between ctDNA positivity and metastatic localization with both HR_{RFS} (beta: 0.058 and 1.1718) and HR_{OS} (beta: 0.1113 and 1.976). Notably, publication bias suggested potential distortion in HRos results.

Conclusions: Our findings provide strong evidence that post-operative ctDNA status is an independent predictor of survival in patients with radically resected mCRC. Incorporating ctDNA testing into clinical practice could significantly enhance clinical decision-making for mCRC patients.

Table 1. Included Studies.

First Author	Year	Median follow-up (months)	Median RFS^{ctDNA+} (months)	HR_{RFS}	95% CI_{RFS}	P	Median OS^{ctDNA+} (months)	HR_{OS}	95% CI_{OS}	p
Loupakis et al.	2021	10,7	*Not Reported -NR*	5,800	3,50 – 9,70	0,001	*NR*	16,00	3,9 – 68	0,001
Lonardi et al.	2022	*NR*	*NR*	8,780	3,59 – 21,49	0,0001	*NR*	20,06	2,5 – 160, 25	0,0001
Tie et al.	2021	50,5	*NR*	3,130	1,00 – 9,82	0,05	*NR*	4,20	1,5 – 11,80	0,001
Jiang 2023	2023	9,67	5,930	3,596	1,49 - 8,744	0,001	*NR*	*NR*	*NR*	*NR*
Marmorino et al.	2022	77	12,7	1,840	1,01 – 3,35	.0460	78,8	1,65	0,78 – 3,47	0,183
Reinert et al.	2021	*NR*	*NR*	7,600	3,00 – 19,70	0,0001	*NR*	*NR*	*NR*	*NR*
Boysen et al.	2020	21	9,75	7,480	1,47 – 38,36	0,02	*NR*	NR	NR	NR

A06*

EVALUATION OF RISK OF DISEASE PROGRESSION IN FIRST-LINE THERAPY OF UNRESECTED METASTATIC COLORECTAL CANCER TO GUIDE INTERVALS OF RADIOLOGICAL ASSESSMENT- AN ANALYSIS OF ELEVEN RANDOMIZED TRIALS BY AIO AND GONO

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Background: We evaluated the distribution and risk of disease progression (PD) in first-line therapy of unresected metastatic colorectal cancer (mCRC) patients (pts) receiving chemotherapy + biologics. The aim of the analysis is to provide guidance for the timing of disease reassessments during first-line therapy.

Methods: Individual data of 2845 pts from TRIBE, MOMA, TRIBE2, VALENTINO, ATEZOTRIBE, TRIPLETE, FIRE-3, XELAVIRI, PANAMA, FIRE-4 and FIRE-4.5 were analyzed. The frequency and risk of PD events were calculated for individual time points during therapy. *RAS/BRAF* profiling, tumor sidedness and therapy were used to identify subgroups for risk assessment. Lastly, a nomogram to predict the risk of PD within the first 8 months (mo) of therapy was built.

Results: In the overall population, the maximum density of PD events was observed at 7.4 mo with a median PFS of 9.4 mo. Based on bimonthly restaging, the highest risk of PD was 23% at 14 mo in *RAS/BRAF* WT pts (n=1702), 25% at 10 mo in *RAS* MUT pts (n=964) and 35% at 8 mo *BRAF* MUT pts (n=179). Left-sided *RAS/BRAF* wt pts exposed to anti-EGFRs (n=997) had a plateau of the PD risk between 12-18 mo, with a maximum risk of 22% at 14 mo. Pts with *RAS* MUT or right-sided and *RAS WT* tumors treated with triplet (n=451) or doublets + bev (n=636) had an increase in the risk of PD at 8 mo (21% and 18%, respectively) and its maximum at 14 and 16 mo, (27% and 30% respectively). Among pts with *BRAF* MUT tumors the highest risk of PD with both the triplet (n=96) and doublets + bev (n=83) was at 8 mo (34% and 37%, respectively). ECOG-PS, primary tumor sidedness and its resection, peritoneal mts and *RAS/BRAF status* were associated with the risk of PD at 8 mo. A nomogram built on these features showed consistency across a training (C-index: 0.64) and a validation set (C-index: 0.61) of 1339 and 1506 pts of different trials, respectively.

Conclusion: The distribution of PD events does not follow a Gaussian pattern with the highest density prior to the median PFS suggesting that tumor assessments should focus on the interval between 6-10 mo. The nomogram might be helpful to identify subgroups of pts in which could be sound to diversify timings of tumor restaging.

A07*

ASSESSMENT OF PD-L1 ON MATCHED SURGICAL SPECIMEN AND BIOPSY IN RESECTABLE ESOPHAGOGASTRIC CANCER (EGC): THE APEROL STUDY

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Background: Programmed death-ligand 1 (PD-L1) expression determines eligibility for immunotherapy treatment (tx) in patients (pts) with advanced esophagogastric cancer (EGC). However, limited data exists on concordance rate between PD-L1 combined positive score (CPS) in diagnostic biopsies and matched surgical specimens and the effects of neoadjuvant (N-ADJ) tx on the expression of PD-L1 remain unclear. Our study aims to evaluate the reliability of PD-L1 expression on diagnostic biopsies compared with matched surgical specimens, in both pts resected upfront or after N-ADJ tx.

Material and Methods: This is a retrospective, monocentric, observational study including pts with resectable EGC (cTNM II-IVa) treated at Istituto Oncologico Veneto-IRCCS. Tissue microarray sections from diagnostic biopsies and resected specimens were evaluated by immunohistochemistry. PD-L1 CPS was defined as negative (< 1), low (1-4), intermediate (5-9) or high (≥10).

Results: From May 2014 to December 2023 a total of 179 pts having both biopsy and surgical specimen at our Institution (median age 62 year [range 32–89], male: 70%, ECOG PS 0: 58%, adenocarcinoma histology: 92 %, gastric and GEJ location: 86%), underwent surgery upfront (n=75, 42%) or were treated with chemotherapy (n=76, 42.4%) or concomitant chemoradiotherapy (n=28, 15.6%). In the whole population, the distribution of PD-L1 expression in biopsy and surgical specimens was similar: negative (n=13 vs. n=12), low (n=43 vs. n=47), intermediate (n=30 vs. n=32), and high (n=93 vs. n=88). However, matching biopsy and surgical samples the PD-L1 concordance rate was only 49.7%. In samples coming from patients treated with upfront surgery, the concordance rate between the two specimens was 56%, while in pts receiving N-ADJ tx was 45.2%. In pts undergoing N-ADJ tx, PD-L1 expression in surgical samples increased in 24 cases (23.1%), decreased in 33 cases (31.7%), and remained unchanged in 47 cases (45.2%). N-ADJ tx significantly altered PD-L1 expression (OR 1.82, p=0.05). PD-L1 expression was not significantly associated with overall survival.

Conclusions: In our study, PD-L1 expression exhibits temporal heterogeneity between primary biopsies and surgical

specimens in EGC, significantly increased in pts receiving N-ADJ tx. This heterogeneity should be taken into account when choosing treatment in a metastatic setting.

A08

ATEZOLIZUMAB PLUS BEVACIZUMAB VERSUS LENVATINIB FOR BCLC-B STAGE OF PATIENTS WITH HEPATOCELLULAR CARCINOMA: A LARGE REAL-LIFE WORLDWIDE POPULATION

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Background: The aim of the present study is to perform a real-world analysis on a large sample of patients with Barcelona Clinic Liver Cancer stage B (BCLC-B) hepatocellular carcinoma (HCC) treated with Atezolizumab plus Bevacizumab (A+B) vs Lenvatinib.

Methods: The study population included patients enrolled affected by intermediate (BCLC-B) HCC patients not suitable for locoregional therapies (LRTs) from eastern and western populations, who received A+B or Lenvatinib as first-line treatment. Univariate and multivariate analyses were used to evaluate predictor factors for overall survivor (OS) and Time to progression (TTP) while prognostic factors were analyzed by univariate and multivariate analysis using Cox regression model.

Results: 919 BCLC-B HCC patients were enrolled in the study: 561 (61%) received Lenvatinib and 358 (39%) received A+B. The median overall survivor (mOS) for patients receiving Lenvatinib was 21.3 months compared to 15.8 months for patients receiving A+B as first-line treatment (Lenvatinib Vs A+B): Hazard ratio (HRs) 0.84 p =0.22. The median time to progression (mTTP) for patients receiving Lenvatinib was 7.3 months compared to 8.7 months for patients receiving A+B as first-line treatment (Lenvatinib vs A+B): HR 1.15 p = 0.10. The multivariate analysis confirmed no different in terms of mOS and mTTP between the two treatments. Objective response rate (ORR) was 47.1% for patients receiving Lenvatinib and 27.1% for patients receiving A+B p < 0.000001. Patients receiving Lenvatinib experienced a significantly higher incidence of hand-foot skin reaction (HFSR), hypertension, diarrhea, fatigue, decrease appetite, hypothyroidism, and other toxicity compared to patients receiving A+B. Favorable prognostic factors for OS in Lenvatinib group were, platelets (PLT) >100.000 (HR 0.68 p= 0.02), HCC non-alcoholic steatohepatitis/non-alcoholic fatty liver disease (NASH/NAFLD) related (HR 0.53, p=0.03). No favorable prognostic factors were found for A+B group. Favorable prognostic factors for TTP in the A+B group were in TACE refractory patients (HR 0.76, p=0.02), PLT <100.000 (HR 0.62, p=0.0067), and Neutrophil-to-lymphocyte ratio (NLR) <3 (HR 0.78, p=0.04).

Conclusions: Although Lenvatinib had a greater response, the study showed no statistically significant differences between Lenvatinib and A+B in terms of efficacy, in these two cohorts of BCLC-B HCC patients.

A09

HOMOLOGOUS RECOMBINATION (HR) AND DNA DAMAGE REPAIR (DDR) SOMATIC ALTERATIONS IN METASTATIC COLORECTAL CANCER (MCRC): RESULTS FROM THE COMPREHENSIVE GENOMIC PROFILING (CGP) TRIAL FPG500

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Background: Treatment (tx) of MSS/MMRp mCRC relies mainly on oxaliplatin (oxa)- or irinotecan-based doublet chemotherapy regimens, with no biomarker reported so far, allowing the selection of one tx over the other. HR and DDR alterations have been associated with sensitivity to platinum agents in several neoplasms, however, evidence in this setting lacks.

Methods: Data from the mCRC cohort of the prospective monocentric study FPG500 (NCT06020625), which

performs a somatic CGP via TSO500HT (identifying SNVs, indels, CNVs in 523 genes and fusions and splicing variants in 55 genes), were mined through cBioportal, classifying tumors as HR-DDR altered (HR-DDRa) or proficient (HR-DDRp) on the basis of the presence of at least 1 oncogenic or likely oncogenic alteration (annotated according to OncoKB) involving genes of HR or DDR pathways. Pts' and tumors characteristics, tx administered and survival status were retrospectively collected. The objective of the study was to investigate the molecular phenotype of HR-DDRa and its predictive role.

Results: From Jan2022 to Apr2024 306 pts underwent to CGP, with a prevalence of HR-DDRa of 18.6%. Alterations involved mainly *ATM* (5%), *BRCA2* (4%), *NBN* (2%), *CHEK2* (2%), *MRE11* (1.6%), *BRIP1* (1.6%), *PALB2* (1.3%), *ATRX* (1.3%) and *BARD1* (1.3%); alterations of *ATR, RAD50, FANCA, FANCD2, BRCA1, FANCE, FANCL, BAP1, CHEK1* and *FANCC* were reported in ≤1%. HR-DDRa was significantly associated with MSI-H or TMB-H ($p<.0001$). Pts who received a first line tx and whose tx outcome and survival status were available constituted the survival cohort (n=191). At a mFU of 20 months, mPFS was 13.8 months, while mOS was not mature. No statistically significant difference was observed in terms of PFS according to HR-DDR status in the overall cohort and in pts treated with oxa-based tx. In pts with MSS HR-DDRa disease (n=22), oxa-based tx was associated with significantly longer mPFS (13.3 *vs* 3.2 months; $p<.001$). No other prognostic factor was associated with PFS at univariate analysis.

Conclusions: HR-DDRa is associated with MSI-H or TMB-H. Pts with MSS HR-DDRa tumors benefit from oxa-based first line treatment. Longer FU, allowing mature OS data, and wider cohorts are warranted.

A10

FIRST-IN-HUMAN STUDY OF ABBV-400, A NOVEL C-MET–TARGETING ANTIBODY-DRUG CONJUGATE, IN ADVANCED SOLID TUMORS: RESULTS IN COLORECTAL CANCER

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Background: c-Met is frequently overexpressed in several advanced solid tumors as colorectal cancer(CRC). ADC ABBV-400 comprises c-Met–targeting antibody telisotuzumab conjugated to a novel topoisomerase 1 inhibitor payload. Ph1 study of ABBV-400 was initiated for adults with advanced solid tumors and progression(NCT05029882); results from dose escalation(ESC) at doses 1.6–6.0mg/kg once every 3 weeks (Q3W) showed preliminary efficacy (Sharma et al. ASCO 2023.Abstract 3015). We present data from dose ESC and expansion(EXP) CRC cohorts.

Methods: In EXP, CRC patients(pts) were randomized to receive ABBV-400 at 1.6, 2.4, or 3.0mg/kg Q3W. Primary objectives: safety, tolerability, pharmacokinetics, preliminary efficacy and recommended ABBV-400 ph2 dose.

Results: As of Oct 2023, 122 pts(ESC:29; EXP:93) were included. Median age:56yr; 65(53%) males. Median prior treatments was 4. F/u was longer in ESC vs EXP(14.8 vs 3.8 mos). 78(64%) pts had a grade (G)=3 treatment-emergent adverse event(TEAE); 41% had a serious TEAE. Most frequent hematologic TEAEs were anemia(52%; G=3:30%), neutropenia(37%; G=3:25%), leukopenia(25%; G=3:12%) and thrombocytopenia(23%; G=3:12%); nonhematologic TEAEs were nausea(57%, G=3:3%), fatigue(43%; G=3:2%) and vomiting(39%, G=3:4%). G=3 diarrhea was<1%. Unadjudicated interstitial lung disease/pneumonitis rate was 7%(G=3:2%). 11(9%) pts discontinued due to treatment-related AEs. Table shows preliminary efficacy outcomes. Most tissues expressed c-Met. Increased ORR of>30% was observed at efficacious doses(=2.4mg/kg) in pts with higher c-Met expression. Activity was also seen at lower c-Met expression levels(10–15% ORR).

Conclusions: ABBV-400 at 2.4 and 3.0mg/kg Q3W has tolerable and manageable safety profile with promising antitumor activity. Long-term tolerability appears improved at 2.4 relative to 3.0mg/kg with higher relative dose intensity and generally lower TEAEs. The study is also evaluating ABBV-400 with bevacizumab in CRC pts.

Table. Preliminary efficacy outcomes.

	CRC dosing cohorts		
	1.6mg/kgQ3W (n=32)	**2.4mg/kgQ3W (n=40)**	**3.0mg/kgQ3W (n=41)**
Confirmed ORR,n(%)	0	6 (15%)	8 (20%)
CBR12,n(%)	11(34%)	23 (58%)	15 (37%)
Median duration of response,mos(95% CI)	-	4.1 (2.7,NE)	5.5 (2.8,NE)
Median progression-free survival,mos(95% CI)*	4.0 (2.6,NE)	5.3 (3.8,5.5)	4.5 (2.6,6.8)
Median overall survival, mos(95% CI)*	9.7 (4.3,NE)	8.7 (6.3,NE)	12.2 (5.9,NE)

*Immature data. CBR12,clinical benefit rate at 12 weeks; CI,confidence interval; NE,not estimable; ORR,objective response rate; mos,months.

A11

THE ROLE OF VARIANT ALLELE FREQUENCY (VAF) AT DISEASE PROGRESSION IN RASWT METASTATIC COLORECTAL CANCER (MCRC): FINDINGS FROM THE PLATFORM-B STUDY

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Background: Circulating tumor DNA (ctDNA) analysis is a minimally invasive and highly reproducible technique, emerging as the best method to assess real-time the tumor genomic landscape. The multicentric prospective PLATFORM-B study enrolled first-line (1L) mCRC patients (pts) undergoing longitudinal ctDNA analysis. Previously published data of this study demonstrated the role of variant allele frequency (VAF) variations (ΔVAF) during 1L therapy in predicting early response and progression. Here, we present findings on the role of VAF at disease progression (PD).

Methods: We analyzed baseline (BL) and PD plasma samples from all pts enrolled in the PLATFORM-B study. Cohort A consisted of 100 RAS^{WT} mCRC pts treated with chemotherapy (CT) + anti-EGFR therapy; cohort B (control) comprised 30 RAS^{MUT} mCRC pts treated with CT + anti-VEGF therapy. We applied a next-generation sequencing (NGS)-based method (Ion S5 system) covering 14 hotspot regions. VAF was calculated as the ratio of variant reads to total reads at each variant position. Trunk mutations were defined as somatic mutations with the highest VAF within a plasma sample, while relative VAF (rVAF) was assessed as the frequency of a single mutation relative to the trunk mutation in the sample. *RAS/BRAF/MEK/EGFR-ECD/MAP2K1* mutations were considered of resistance to anti-EGFR. Molecular results were correlated with clinical-pathological features and outcomes.

Results: We evaluated BL and PD samples from 126 pts: 97 in cohort A and 29 in cohort B. Considering all the analyzed genes in aggregate, ΔVAF between BL and PD showed a statistically significant increase (p =.00024). Among trunk mutations (*APC* and *TP53*), only *APC* showed a significant difference at the two time points (p =.0061). However, no statistically significant differences were found in mutations associated with anti-EGFR resistance genes in either study cohort. Specifically, ΔVAF_{KRAS} showed p =.095, ΔVAF_{BRAF} had $p = 1$, and ΔVAF_{PIK3CA} p =.59. Similarly, ΔrVAF demonstrated no significance in any of the analyzed genes. Uni- and multivariate analyses did not reveal significant correlations between ΔVAF, rVAF, clinical-pathological features, and survival outcomes.

Conclusions: We observed an increase of VAF_{APC} at PD, while mutations related to anti-EGFR resistance did not

exhibit significant differences between BL and PD. Further investigations are warranted to elucidate the clinical implications of these molecular changes and their impact on patient outcomes.

A12

BILIARY TRACT CANCERS (BTC): DESCRIPTIVE AND PROGNOSTIC ANALYSES FROM A LARGE REAL-WORLD DATASET. THE BITCOIN 2 STUDY

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Background: BTC have a poor prognosis with limited treatment options. This is coupled with a poor understanding of the biological background. Extensive genetic profiling allowed to distinguish different molecular entities. The incidence and the prognostic role of these molecular features have not been fully elucidated.

Material and Methods: This is a retrospective study conducted at Istituto Oncologico Veneto in Padua in which we expanded our previous dataset focusing on patients with diagnosis of advanced/metastatic intrahepatic cholangiocarcinoma. All consecutive patients with availability of tissue samples were considered eligible. Targeted alterations included: FGFR2/3 aberrations, IDH1/2 mutations, HER2 alterations, BRAF alterations, NTRK alterations and mismatch repair proteins deficiency (MMRd). These alterations were identified by means of immunohistochemistry, RT-PCR, next-generation sequencing, and fluorescence in situ hybridization.

Results: A total of 247 patients were enrolled. Twenty-three patients (9.3%) presented FGFR2 fusions/amplifications (F2F). IDH1/2 resulted mutated in 50 patients (20.2%). A total of 18 patients (7.3%) had a HER2 gene alteration, 9 patients (3.6%) had a BRAF gene alteration, 3 patients (1.2%) NTRK1 amplifications and 6 patients (2.4%) had a MMR deficit. Patients F2F had a lower risk of death compared to wild type patients (F2N) (HR 0.48, 95% CI 0.28 - 0.80, p = 0.005). F2F had a median overall survival (OS) of 24.5 months (95% CI 19.4 – NA) compared to 15.7 months (95% CI 13.4 – 18.6) of F2N patients. Fourteen patients received anti-FGFR2 drugs, censoring these patients from the survival analysis still maintains an advantage in OS for F2F patients (HR 0.23, 95%CI 0.10 – 0.52, p < 0.001). This advantage in OS was maintained also at multivariate analysis (p = 0.009).

Conclusions: Our data provide a strong proof - challenged with a robust and detailed multivariate model - that FGFR2 alterations can be prognostic for better survival. Our data should be considered in the design of new trials, for example as adjusting or stratification factors in prospective clinical studies.

A13

P16 IMMUNOHISTOCHEMICAL EXPRESSION PREDICTS BENEFIT FROM IRINOTECAN IN METASTATIC COLORECTAL CANCER: A TRANSLATIONAL ANALYSIS OF THE TRIBE AND TRIBE2 STUDIES

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Background: *CDKN2A* encodes the inhibitor of the cyclin-dependent kinase p16 and is frequently methylated in colorectal cancer (CRC), thus reducing p16 expression (exp) levels. In CRC preclinical models, *CDKN2A* demethylation induces topoisomerase I upregulation increasing the sensitivity to irinotecan. In metastatic colorectal cancer (mCRC) patients (pts), the role of p16 exp has been poorly investigated.

Methods: Tumor samples of pts from phase III TRIBE2 study comparing upfront FOLFOXIRI/bevacizumab (bev) versus (vs) FOLFOX/bev were assessed for p16 immunoistochemical exp. A validation analysis in pts treated with FOLFIRI/bev in the TRIBE study was conducted.

Results: 231 tumors of the TRIBE2 study were assessed for p16 exp. Overall, 152 (66%) and 79 (34%) were classified as $p16^+$ (IHC 2+ and 3+) and $p16^-$ (IHC 0 and 1+), respectively. In the $p16^+$ group, 69 (45%) and 83 (55%) pts received FOLFOXIRI/bev and FOLFOX/bev, respectively, while in the $p16^-$ cohort, FOLFOXIRI/bev was administered in 37 (47%) and FOLFOX/bev in 42 (53%) cases. Pts with $p16^-$ tumors had more frequently an ECOG PS of 1-2 (16% vs 6% p=0.0098) and a *BRAF* mut tumor (26% vs 7% p=0.0002). No PFS difference was observed between $p16^+$ and $p16^-$ pts, while a trend for a longer OS was shown for $p16^+$ pts (25.5 vs 21.3 months [m] HR 0.74 95% CI 0.53-1.02 p=0.068), though not confirmed at the multivariate analysis (p=0.61).

In the $p16^+$ cohort, pts treated with FOLFOXIRI/bev reported longer PFS (12.8 vs 9.4 m HR 0.55 95% CI 0.39-0.78 p=0.0008) and OS (30.0 vs 21.4 m HR 0.66 95% CI 0.46-0.95 p=0.026) than those receiving FOLFOX/bev. Conversely, no difference was observed among $p16^-$ pts in terms of both PFS (9.0 vs 9.4 m, HR 0.91 95% CI 0.57-1.46 p=0.69) and OS (21.3 vs 19.5 m, HR 0.95 95% CI 0.58-1.57 p=0.85), thus suggesting a differential treatment effect according to p16 exp ($p_{interaction}$ PFS =0.12; $p_{interaction}$ OS =0.19). Among pts treated with FOLFIRI/bev in the TRIBE study (*n*=58), pts with $p16^+$ tumors reported longer PFS and OS than those with $p16^-$ (HR PFS: 0.47 95% CI 0.22-0.99 p=0.041; HR OS 0.43 95% CI 0.21-0.91 p=0.024).

Conclusions: In mCRC, $p16^+$ expression seems associated with higher benefit from irinotecan. Prospective confirmation in independent randomized series is warranted.

A14

ISOLATED LUNG METASTASES IN PANCREATIC ADENOCARCINOMA PATIENTS IN A MULTICENTER ITALIAN COHORT: THE LU.M.A.CA STUDY

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Background: Isolated lung metastases (ILM) from Pancreatic Ductal Adenocarcinoma (PDAC) are generally associated with better prognosis and more indolent behavior compared to other metastatic sites. Limited data are available on prognostic factors and therapy outcomes in PDAC patients (pts) with ILM.

Methods: Clinical data of PDAC pts with lung as first unique site of metastases/recurrence were retrospectively collected from 19 Italian Institutes. Two years from ILM diagnosis was the minimum required follow-up for alive pts. The impact of clinical variables and therapeutic strategies on Overall Survival (OS), calculated from ILM diagnosis to death/last follow-up visit, was assessed by Kaplan–Meier test and multivariate (MV) Cox proportional-hazards model.

Results: 278 PDAC pts with ILM diagnosis (January 2001-March 2022) were included in the analysis (Table 1). Pts receiving only radical surgery (N=35) or stereotactic radiotherapy (N=6) as first treatment for ILM survived 85.1 (95% CI 36.9-131.4) and 35.3 (95% CI 16.5-55.1) months, respectively. Lower CA19.9 at ILM diagnosis, ECOG Performance Status (PS) 0, previous surgery on primary tumor and longer time to ILM onset were retained as positive prognostic factors at MV analysis, that showed no significant survival advantage for pts treated with standard polychemotherapy (nab-paclitaxel/gemcitabine-based, FOLFIRINOX) as opposed to monochemotherapy (gemcitabine, capecitabine). OS of 15 pts treated with no standard polychemotherapy was 12.0 (95% CI 6.8-36.4) months.

Conclusions: Our study showed that radical surgery of ILM from PDAC is associated with remarkable OS and should be considered for pts with limited disease. Moreover, monochemotherapy might be regarded as a valid treatment option, especially for pts with favorable prognostic features (low CA19.9, PS0, surgery on primary, ILM onset timing>2 years).

Table 1. Patients' characteristics and survival outcomes.

Variable	N	Median Overall Survival months	95% Confidence Interval	p
Age, y				***0.01***
≤68	140	29.3	24.0-42.3	
>68	138	19.6	16.5-23.0	
Gender				*0.92*
Male	108	23.1	18.7-26.7	
Female	170	24.2	19.7-27.4	
ECOG Performance Status				***<0.01***
0	142	30.6	24.6-44.1	
>0	110	16.5	14.0-19.4	
Surgery on Primary				***<0.01***
Yes	152	42.3	34.9-47.2	
No	125	15.6	13.0-18.3	
LM N°				***<0.01***
≤3	113	36.6	28.3-43.7	
>3	165	19.4	16.6-21.7	
LM timing				***<0.01***
M > 2 y	64	49.7	38.4-85.1	
M ≤ 2 y	95	23.5	17.0-30.2	
Synchronous	119	18.3	14.7-20.2	
Ca19.9				***<0.01***
≤35	73	40.4	24.7-47.0	
36-402 (median)	74	24.9	19.5-30.8	
>402	74	14.3	10.9-19.4	
LM first standard CT				
Mono-CT	42	17.3	12.2-25.0	0.56
Poly-CT	152	22.2	19.5-24.7	

y: years; LM: Lung Metastases; M: Metachronous; CT: chemotherapy.

A15

NEGATIVE HYPERSELECTION AND MECHANISMS OF ACQUIRED RESISTANCE TO FIRST-LINE CHEMOTHERAPY PLUS ANTI-EGFR IN PMMR RAS/BRAF WILD-TYPE (WT) METASTATIC COLORECTAL CANCER (MCRC) PATIENTS (PTS): A TRANSLATIONAL ANALYSIS OF THE TRIPLETE TRIAL

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Background: Anti-EGFRs plus doublets are the standard first-line treatment for pts with left-sided RAS/BRAF wt mCRC. According to PRESSING1/2 panels, anti-EGFR sensitivity seems restricted to negatively hyperselected RAS/BRAF wt cases. Analysing circulating tumor DNA in liquid instead of tissue biopsies is a promising strategy to optimize upfront therapy in RAS/BRAF wt mCRC pts and to identify mechanisms of

acquired resistance. TRIPLETE is a phase III trial where 435 pts with RAS/BRAF wt – per local assessment – mCRC were randomized to receive first-line FOLFOX/panitumumab (pan) or mFOLFOXIRI/pan.

Methods: Pts enrolled in the TRIPLETE trial with available tissue and plasma at baseline (BP), and plasma at the time of disease progression (PDP) were included. Tissue samples were profiled using FoundationOne CDx and Oncomine™Focus Assay, and plasma samples were analyzed by means of Oncomine™Pan-CancerCell-Free Assay. Pts with pMMR tumors were grouped as PRESSING-positive or negative based on the detection of PRESSING panel alterations.

Results: 134 (31%) pts were included. Tissue analysis revealed locally unknown RAS mutations in 6 (4%) cases. After excluding RAS mutated and dMMR/unknown cases (N=26), RAS was found to be mutated in 2 BP out of 102 pts (2%) with RAS/BRAF wt and pMMR tumors. PRESSING alterations were found in 15 (15%) tissue cases (HER2ampl: 9, HER2mut: 3, AKT1mut: 1, PIK3CAex20: 2). Matching results were achieved in 8 BP, and 2 additional alterations were found (AKT1mut and PTENmut). No differences between PRESSING positive and negative pts were reported in terms of ORR, PFS or OS, regardless of primary tumor location. In PDP, RAS mut were detected in 9 pts (9%), and BRAFV600E mut co-occurred in 2 cases. Pts with RAS mut ctDNA at PDP showed a significative shorter OS compared to RAS wt [HR 0.3 95% CI 0.13-0.9, p=.03]. MAP2K1 mut were found at PD in 2 cases, while no other PRESSING alteration was found.

Conclusions: In contrast to previous data, negative hyperselection both through tissue and plasma analysis failed to demonstrate a prognostic role among pMMR RAS/BRAF wt mCRC pts treated with first-line chemotherapy plus pan. The confounding effect of the associated chemotherapy is a potential explanation for this finding. Tissue and plasma analyses at baseline failed to provide fully concordant results. The occurrence of RAS mutations in ctDNA at the time of PD was significantly correlated with worse post- progression survival.

A16

A NETWORK META-ANALYSIS ON TRIPLET CHEMOTHERAPY COMBINED WITH ANTI-EGFR TREATMENT IN RAS WILD-TYPE COLORECTAL CANCER

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Background: The optimal first-line treatment for RAS wild-type (wt) metastatic colorectal cancer (mCRC) remains undetermined. Several studies have explored the efficacy of first-line regimens, including triplet chemotherapy (CT) combined with an anti-EGFR antibody (anti-EGFR Ab), in comparison to either doublet CT combined with an anti-EGFR Ab, triplet CT combined with an anti-VEGF treatment, or triplet CT alone. However, none of these trials yielded conclusive results.

Methods: A systematic review was conducted, including all phase II/III randomized clinical trials (RCTs) that compared a combination of triplet CT and anti-EGFR Ab with other first-line regimens for RAS-wt mCRC patients (pts). Both pairwise and network meta-analysis (NMA) were performed to establish direct and indirect comparisons of overall response rate (ORR) using a random effects model within the frequentist framework.

Results: A total of 1283 pts among 7 RCTs (TRIPLETE, VOLFI, TRICE, PANIRINOX, AIO-CELIM2, FOCULM, DEEPER) were included in the analysis. Overall, 4 arms were identified, encompassing all possible combinations of CT, anti-EGFR Ab, and anti-VEGF treatment: arm A (triplet + anti-EGFR), arm B (doublet + anti-EGFR), arm C (triplet alone), and arm D (triplet + anti-VEGF). All treatments associated with targeted therapy showed a benefit when compared to triplet alone; no difference was observed among groups A, B and D. Results of selected NMA comparisons are shown in Table 1. Additionally, we conducted a pairwise meta-analysis for ORR for groups A vs. B, A vs. C, and A vs. D, due to available comparisons; the results confirmed the NMA findings (pooled odds ratio (OR) of 4.23 (2.06 – 8.68) for groups A vs. C).

Conclusions: Through indirect comparisons, no significant ORR benefit was found for triplet CT associated with anti-EGFR treatment compared to doublet CT combined with anti-EGFR treatment or triplet CT combined with anti-VEGF treatment. All regimens incorporating targeted treatment demonstrated superior performance compared to

triplet CT alone. Our findings do not advocate for the routine use of triplet CT associated with anti-EGFR treatment in this patient population; more mature OS data from some of the trials included in our analysis are awaited.

Table 1. Direct and indirect comparison of Overall Response rate.

NMA Comparisons	OR (95% CI)	p-value
A vs B	0.97 (0.68-1.39)	0.869
A vs C	3.39 (1.71-6.70)	<0.001
A vs D	1.05 (0.67-1.66)	0.821
B vs C	3.49 (1.65-7.38)	0.001
B vs D	1.09 (0.62-1.91)	0.775
D vs C	3.21 (1.46-7.07)	0.003

A17

THE PRESENCE OF LIVER METASTASES DOES NOT PREDICT RESISTANCE TO IMMUNOTHERAPY IN PROFICIENT MMR METASTATIC COLORECTAL CANCER (MCRC): A SECONDARY ANALYSIS OF THE ATEZOTRIBE STUDY

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Background: Preliminary evidence suggests that liver metastases have an immune-suppressive tumor microenvironment and are associated with poor efficacy of immune checkpoint inhibitor (ICI)-containing therapies in different solid malignancies. However, limited data are available from randomized clinical trials investigating ICI-based treatments in mCRC. We performed a comprehensive evaluation of liver-metastatic (LM) disease among mCRC patients enrolled in the phase II randomized AtezoTRIBE trial, that showed a modest benefit from the addition of atezolizumab (atezo) to 1st line FOLFOXIRI/bevacizumab (bev) and identified Immunoscore IC as a predictor of ICI efficacy in the proficient mismatch repair (pMMR) population.

Material (patients) and Methods: We investigated the association of LM disease with tumor immune-related biomarkers – including MMR, TMB, Immunoscore IC, Immunoscore, Tumor-Infiltrating lymphocytes (TILs) assessed by optical microscope, PD-L1 expression by Tumor Proportion Score (TPS), and the immune 27-gene signature DetermaIO – and treatment outcome, in the cohort of patients with pMMR tumor enrolled in the AtezoTRIBE study.

Results: 151 (75%) out of 202 enrolled patients with pMMR tumor had LM disease. No differences in terms of immune-related features were observed between tumors with and without LM disease, with the exception of a lower prevalence of high TILs-tumors in the presence of LM disease (33% vs 52%, p = 0.03). Immunoscore IC was more frequently high in the absence of LM disease but without reaching statistical significance (45% vs 28%, p = 0.089). LM disease had a negative prognostic impact both in the FOLFOXIRI/bev (HR for PFS 1.81 [95% CI: 1.02-3.21]; HR for OS 2.00 [95% CI: 1.01-3.99]) and in the FOLFOXIRI/bev/atezo arm (HR for PFS 1.75 [95% CI: 1.18-2.61]; HR for OS 1.69 [95% CI: 1.04-2.75]), confirmed in the multivariable models. No interaction effect between the presence or not of LM disease and treatment arm was evident in terms of both PFS ($P_{interaction}$: 0.99) and OS ($P_{interaction}$: 0.80).

Conclusions: In our cohort of pMMR mCRC patients, the immune microenvironment of tumors with LM spread does not differ from that of tumors with no liver involvement. The presence or not of LM disease does not affect the efficacy of adding atezo to first-line FOLFOXIRI/bev, differently than Immunoscore IC.

A18

GLOBAL, RANDOMIZED, PHASE 3 STUDY OF TISLELIZUMAB PLUS CHEMOTHERAPY VERSUS PLACEBO PLUS CHEMOTHERAPY AS FIRST-LINE TREATMENT FOR ADVANCED/METASTATIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA (RATIONALE-306 UPDATE): MINIMUM 3-YEAR SURVIVAL FOLLOW-UP

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Background: RATIONALE-306 (NCT03783442) is the first global study to investigate anti-programmed cell death protein-1 (PD-1) therapy in combination with different chemotherapy (CT) options in the first-line (1L) treatment of advanced/metastatic esophageal squamous cell carcinoma (ESCC). At interim analysis (IA), tislelizumab (TIS; anti-PD-1 mAb) + CT demonstrated a statistically significant, clinically meaningful improvement in OS vs placebo (PBO) + CT, with a manageable safety profile. Here, we report updated efficacy and safety data with minimum 3 years' follow-up (FU) after unblinding at IA.

Materials (Patients) and Methods: Eligible adults with previously untreated unresectable locally advanced recurrent/metastatic ESCC were randomized (1:1; stratified by region, prior definitive therapy, and investigator [INV]-chosen CT) to receive TIS 200 mg (Arm A) or PBO (Arm B) IV every 3 weeks + CT (platinum + fluoropyrimidine or platinum + paclitaxel), until disease progression or intolerable toxicity. The primary endpoint was OS in the ITT population. Secondary endpoints included PFS, ORR, and DoR, all per INV, and safety.

Results: In total, 649 pts were randomized (Arm A, n=326; Arm B, n=323). At a minimum study FU of 36.0 months, improvements in OS, PFS, and DoR in Arm A vs B (**Table**) were maintained, similar to IA. The HR for OS with TIS + CT vs PBO + CT was 0.70 (95% CI, 0.59-0.83). Similar to IA, incidences of any-grade (96.6% vs 96.3%) or grade ≥3 (67.0% vs 64.5%) treatment-related adverse events (TRAEs) were comparable between Arms A and B, respectively. In Arm A versus B, TRAEs leading to death occurred in 1.9% and 1.2%, respectively.

Conclusions: After minimum 3 years' FU, 1L TIS + CT continued to demonstrate clinically meaningful improvements in OS and PFS and durable antitumor response benefit vs PBO + CT in pts with advanced/metastatic ESCC, with no new safety signals.

Table.

	Arm A: TIS + CT (n=326)	Arm B: PBO + CT (n=323)
Median OS, mo (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.0)
36-mo OS, % (95% CI)	22.1 (17.6, 27.0)	14.1 (10.4, 18.4)
36-mo PFS, % (95% CI)	15.0 (10.8, 19.9)	2.9 (1.1, 6.2)
36-mo DoR, % (95% CI)[a]	17.7 (12.3, 24.0)	5.0 (1.5, 11.8)

[a]Among responders (Arm A, n=207; Arm B, n=137)
mo, month(s)

A19

OFF-TARGETS EFFECTS FROM PEMIGATINIB MONOTHERAPY AND THEIR MANAGEMENT: IMPLICATIONS ON PROGNOSIS IN PATIENTS WITH CHOLANGIOCARCINOMA TREATED WITHIN REAL-WORLD ITALIAN PEMIREAL AND FRENCH PEMIBIL COHORT STUDIES

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Background: Pemigatinib is a kinase inhibitor against FGFR1-2-3 receptors used in metastatic/unresectable cholangiocarcinoma harboring FGFR2 variants. Evidence on treatment related side-effects and patients' prognosis and management is lacking. Aim of this study was to assess overall survival (OS) differences based on treatment related side effects and their management.

Patients and Methods: Patients eligible came from PEMIREAL-PEMIBIL trial that included patients treated wth Pemigatinib monotherapy for unresectable/metastatic cholangiocarcinoma in 2nd line setting or more. Nail changes, dry eye, retinal detachment, diarrhea, hand-foot-skin reaction (HFSR), fatigue, anemia, hyperphosphatemia or hypophosphatemia, myalgias, mucositis, and keratitis were recorded and their severity was ranked by NCI CTCAE ver 5.1. Side-effects severity and OS were correlated by log-rank test. OS was calculated by Kaplan-Meier method. Multivariate analysis was conducted by cox-regression. Level of statistical significance p was < 0.05.

Results: 72 patients were enrolled. HFSR (p=0.06), myalgias (p=0.44), anemia (p=0.22), skin rash (p=0.78), dry eye (p=0.17), retinal detachment (p=0.50), keratitis (p=0.60), mucositis (p=0.77), hyperphosphatemia (p=0.87) were not associated with OS. Nail changes (p=0.0284) were associated with better OS whereas hypophosphatemia (p=0.010) and fatigue (p=0.0078) were associated with worse OS. There was no difference in OS when treatment was stopped due to toxicity for one cycle (mOS:17.11 vs 18.39 months, HR:0.97, 95%CI:0.44-2.13, p=0.94). One-week delay of treatment was also not associated to reduced OS (mOS: 18.72 vs 10.55, HR:0.54, 95%CI:0.25-1.51, p=0.11). Dose reductions did not have an impact on OS (mOS: 17.11 vs 18.39 months, HR:0.67, 95%CI:0.30-1.53, p=0.35). Multivariate analysis confirmed G1 (p=0.02) or G2 (p=0.011) nail toxicity as prognostic factors associated with better OS whereas G3 hypophosphatemia (p=0.035) or either G2 (p=0.01) or G3 (p=0.002) fatigue were associated with worse OS.

Conclusions: Treatment with Pemigatinib proved to be safe in a real-life setting with manageable toxicities: fatigue and hypophosphatemia were associated with worse OS whereas nail changes were associated with better OS. Dose reductions and treatment holidays were not associated to significant differences in OS, albeit a trend suggesting better survival outcomes was observed for short-term (1 week) treatment holidays rather than dose reductions.

A20

PROGNOSTIC IMPACT AND CLINICAL MANAGEMENT OF PT4N0 COLON CANCER (CC): DATA FROM A LARGE REAL-WORLD DATASET

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Background: Among prognostic factors in stage II CC, pT4 appears to be crucial. However, the optimal management of stage II high-risk (pT4N0) CC pts, as well as the impact of DNA mismatch repair deficiency (dMMR), remains unclear. Here we present a large retrospective, multicenter, real-world analysis of pT4N0 CC pts.

Material and Methods: Retrospective data of pts treated at 9 Italian and 1 French institutions from April 2010 to November 2023 were collected. Clinical and pathological characteristics of pts with pT4N0 CC were analyzed. Pts were stratified according to MMR, type and duration of adjuvant chemotherapy (ACT). Primary endpoints were Relapse-Free Survival (RFS) and Overall Survival (OS).

Results: A total of 443 pts was included, and outcomes data were available for 339 pts. Median age was 73, 51% were males. In terms of primary tumor sidedness, 51% had left-sided/rectal tumors, 41% right-sided, 7% transverse CC. 24% onset with obstruction/perforation. MMR status was available for 256 pts and among these 23% were dMMR. 189 pts (56%) were treated with ACT: among these, 70% received oxaliplatin (oxa)-based CT. 6-months (6-mo) ACT was given to 68% of pts treated with

monotherapy and to 72% in those treated with oxa-based CT. After a median follow-up of 48.6 months, 3-y RFS and OS were 64% and 79.5%; 5-y RFS and OS were 52% and 66.5%, respectively. 3-y OS and RFS were significantly better in pts who received ACT, and the benefit correlated with the duration of the treatment. 3-y OS in pts with no ACT, 3-mo and 6-mo ACT was 60%, 83% and 98% (p<0.001), respectively. Similar results were observed in terms of RFS, with a 3-y RFS of 49%, 69% and 78% (p<0.001). Oxa-based ACT was associated with a significant improvement both in OS (HR 0.22; p<0.001) and RFS (HR 0.47; p=0.003) when compared to monotherapy. Overall, pts with dMMR did not differ to pMMR pts in terms of OS nor RFS.

Conclusions: In this large real-world dataset of stage II high-risk CC, pathological T4 confirmed to be a poor prognostic factor. Despite the known positive impact of dMMR in stage II CC, it did not appear to be impactful in pT4N0. ACT provides large benefit in this population with a significant reduction in risk of recurrence and death. The benefit was proportional to ACT duration, and 6-mo ACT correlates with significantly better survival outcomes. Lastly, oxa-based CT may be better than monotherapy.

A21

TRIFLURIDINE-TIPIRACIL (FTD/TPI) PLUS BEVACIZUMAB (BV) IN PATIENTS (PTS) WITH PRETREATED METASTATIC COLORECTAL CANCER (MCRC): A REAL-LIFE ITALIAN MULTICENTER EXPERIENCE

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Background: In the SUNLIGHT study, the addition of BV to FTD/TPI showed improved progression-free survival (PFS) and overall survival (OS) compared to FTD/TPI alone in pretreated mCRC pts, becoming a new third-line standard treatment (tx) for unselected mCRC pts. Here, we present an Italian real-world analysis of efficacy, activity and safety of this combination.

Material (patients) and Methods: Our multicenter retrospective study enrolled pretreated mCRC patients receiving FTD/TPI+BV at 15 Italian centers. Primary endpoints were PFS and OS; secondary endpoints were overall response rate (ORR) and safety.The Kaplan–Meier method was used to estimate efficacy outcome; log-rank test and Cox-regression model were used to compare the differences, considering a statistically significant p value < 0.05.

Results: A total of 226 pts were enrolled: median age was 66 years (34-89), 166 (73%) had left-sided primary tumor, and 147 (65%) had synchronous disease. 133 pts (59%) had received two prior lines of tx and 77 (32%) ≥3; all pts were previously exposed to BV.119 pts (53%) had ECOG PS 0 and 11 pts (5%) had ECOG PS 2; 32 pts (14%) had only one metastatic site and 194 pts (86%) had =2. All pts were analyzed for *RAS/BRAF* status: 132 pts (58%) had a *RAS* mutated tumor and 10 (4%) were *BRAF* mutated. ORR was 6.8%; mPFS to FTD/TPI+BV was 5.1 months (mos) (95% CI: 4-6.5); the estimated 6 and 9-mos OS rates were 74.6% (95% CI: 67.5-82.3) and 61.4% (95% CI: 52.7-71.5).Any grade adverse events (AEs) occurred in 81% of pts: the most frequent AEs were neutropenia (64%), asthenia (59%) and anemia (42%), the most frequent G3/4 AE was neutropenia (39%). No pts discontinued tx due to toxicity.At the univariate analysis, both number of metastatic sites (1 vs ≥2) [8.8 mos (95% CI: 5-Nr) vs 4.5 mos (95% CI: 3.8-6.5), p=0.03] and neutropenia (yes vs no) [6.7 mos (95% CI: 6-7.7) vs 3.7 mos (95% CI: 2.9-4.5), p<0.001] were associated to mPFS, while ECOG PS and RAS/BRAF status were not. At the multivariable analysis, both number of metastatic sites and neutropenia remained associated with mPFS. Post FTD/TPI+BV progression, 65% of pts received at least a further line of tx: the most used one was regorafenib (57%).

Conclusions: Our real-life data are consistent with those from the SUNLIGHT trial, confirming the safety profile and the efficacy of FTD/TPI+BV in pretreated mCRC pts. Neutropenia and disease burden emerged as possible predictive factors to this combination.

A22

THE MIRROR STUDY: MACROPHAGE POLARIZATION AND MONOCYTE-TO-LYMPHOCYTE RATIO IN STAGE III COLON CANCER

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Background: The immune microenvironment plays a key role in controlling cancer growth. Interestingly, polarized macrophages as M2, and a high monocyte-to-lymphocyte ratio (MLR) could indicate a tumor's recruitment of suppressive cells. Based on these premises, this study aimed to evaluate the prognostic role of MLR and immune-suppressive macrophages in stage III colon cancer (CC).

Material and Methods: A cohort of 1003 consecutive CC patients treated between 2008-2019 in 4 Italian and French Centers was retrospectively analyzed. The associations between MLR and survival outcomes (DFS, RFS and OS) were evaluated with Cox regression analyses. Test, training and bootstrap resampling method was applied and a nomogram scoring model was constructed.

Results: Overall, 16%, 67%, and 15% had IIIA, IIIB and IIIC CC, respectively. At a mFU of 53 months, mDFS was 13mo, while mRFS and mOS were not reached. Of note, thirty percent of pts relapsed and 21% died. In our study, an MLR>0.46 predicted shorter survival outcomes in both univariable and multivariable models (DFS: HR 1.70, p=0.03), (RFS: HR 1.81, P=0.019), and (OS: HR 1.80, p=0.014), including confounding variables. Moreover, data from the multivariable prognostic model for DFS was confirmed in both the test and training sets of the bootstrap resampling method. Finally, MLR, CEA, stage, and age were used in the final nomogram. High, intermediate, and low nomogram groups were identified with different impact on DFS (HR 2.27, p<0.001 intermediate vs. low; HR 3.88, p<0.001 high vs. low), RFS (HR 2.08, p<0.001 intermediate vs. low; HR 3.61, p<0.001 high vs. low), and OS (HR was 2.14, p=0.001 intermediate vs. low, HR 3.96, p<0.001 high vs. low). Notably, an early reduction in MLR within the first 4 month of therapy was associated with a better prognosis in multivariable analysis (HR for DFS HR 0.56, p=0.008; HR for RFS 0.56, p=0.012). Additionally, 103 cases were analyzed for macrophage infiltration. By multivariable analysis, CD163+/CD68+CT (HR 2.34, p=0.06) and stage (IIIC vs. IIIA, HR 3.44, p=0.032) were independently associated with shorter DFS.

Conclusions: In our study, stage III CC patients with high and intermediate score based on MLR, CEA, stage, and age, showed poor prognosis. Furthermore, early MLR reduction and CD163+/CD68+ were associated with survival outcomes. This study paves the way for prospective evaluation of both macrophage infiltration and MLR in stage III CC.

A23

ANTI-HER2 THERAPY IN METASTATIC COLORECTAL CANCER (MCRC): A META-ANALYSIS

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Background: HER2 amplification identifies a subgroup of colorectal cancer with poorer prognosis and resistance to anti-EGFR therapy. We conducted a systematic review and a meta-analysis of available data on anti-HER2 treatments (HER2Tx) in mCRC patients (pts).

Material and Methods: A systematic literature search was performed, encompassing all phase II/III clinical trials (CTs) investigating HER2Tx in HER2-overexpressed mCRC. CTs reporting HER2Tx in combination with chemotherapy or comparisons among different schedules were excluded. Primary endpoints were objective response rate (ORR) and disease control rate (DCR). Fixed and random-effect models were respectively applied according to heterogeneity assessed through I2 statistics. Progression free survival (PFS) and overall survival (OS) were compared descriptively and pooled using the weighted median of medians (WM) with approximated 95% CIs. Subgroup analyses by HER2Tx were carried out. Meta-analyses were performed using the "meta" and "metamedian" packages within R version 4.2.3 (R Core Team, 2023).

Results: The analysis included 10 CTs evaluating Trastuzumab-Pertuzumab (T+P, 5 CTs, 6 cohorts), Trastuzumab Deruxtecan (T-DXd, 2 CTs, 3 cohorts), Trastuzumab-Lapatinib (T+L, 1 CT), Pertuzumab-TDM1 (P+TDM1, 1 CT), and Trastuzumab-Tucatinib (T+Tu, 1 CT), for a total of 467 pts. The pooled ORR was 33.7% (29.6%-38.1%), and the pooled DCR was 68.5% (58.1%-77.4%). The WM OS was 13.4 months (10-24.1) and WM PFS was 5.5 months (4.1-6.9). The T-DX group showed

higher ORR and DCR (ORR: 38%, DCR: 85.1%) compared to the T+P group (ORR: 30%, DCR: 52.6%). T-Tu showed the highest DCR (73.2%), ORR (39%), PFS (8.2 m) and OS (24.1 m); as this combination was only assessed in one trial no further comparisons were allowed.

Conclusions: HER2Tx demonstrated efficacy in pretreated CRC pts, exhibiting good DCR and ORR alongside promising PFS and OS. T-DXd appears to outperform T+P; however, direct comparisons are lacking and further studies are needed.

Soubgroup	Pooled DCR (95% CI)	Pooled ORR (95% CI)	Weighted Median PFS (95%CI) months	Weighted Median OS (95% CI) months
T+L	59.3% (40.3%-75.8%)	29.6% (15.6%-49.0%) 5.3 (4.0-8.0)	5.3 (4.0-8.0)	11.5 (8.3-17.0)
T+P	52.6% (43.7%-61.4%)	30.0% (23.9%- 37.0%)	4.0 (3.1-4.4)	11.4 (8.2-15.0)
T+ Tu	73.2% (62.6%-81.6%)	39.0% (29.1%- 49.9%)	8.2 (4.2-7.0)	24.1 (20.3-36.7)
T-Dxd	85.1% (79.0%-89.6%)	37.9% (31.0%- 45.5%)	5.8 (5.5-6.9)	14.5 (13.4-15.5)
P+ TDM1	77.4% (59.6%-88.8%)	9.7% (3.2%- 26.1%)	4.1 (3.6-5.9)	NA

A24

MAINTENANCE THERAPY WITH REGORAFENIB (REGO) VERSUS PLACEBO AFTER FIRST-LINE (1L) PLATINUM AND FLUOROPYRIMIDINES-BASED CHEMOTHERAPY IN HER2 NEGATIVE ADVANCED GASTRIC (GC)/ GASTROESOPHAGEAL JUNCTION (GEJ) CANCER PATIENTS: RESULTS OF PHASE II RANDOMIZED A-MANTRA STUDY (GOIRC-05-2016)

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Background: To date, there is no established role for maintenance therapy following 1L chemotherapy for GC. The a-MANTRA study aimed to evaluate the efficacy and safety of REGO as maintenance after 1L therapy in advanced GC/GEJ tumors.

Materials and Methods: This is a randomized, double-blind, placebo-controlled, multicenter Phase II study in which HER2 neg GC/GEJ pts treated in 1L with platinum and fluoropyrimidines-based therapy and disease control were randomized (1:1) to maintenance placebo (ARM A) or REGO (ARM B) starting at 80 mg up to 160 mg (once daily on d1-21, q28 days). The primary endpoint was median PFS1. Two-sided 80% CIs were planned for HR=0.57, one-sided α=0.10 (90% power), corresponding to a 3-month increase in mPFS1. 118 subjects were needed to observe 88 events. The interim analysis (IA) was intended after 44 events.

Results: 67 pts were randomized in 18 Italian Cancer Centers of which 64 (33 in ARM A, 31 in ARM B) received treatment. Most of the pts were male (64.1%), Caucasian (96.8%), and ECOG PS 0 (81.2%); the median age was 66 (40-80) yrs. The main primary tumor side was proximal (64.1%) with intestinal subtype (54.7%), and peritoneum spread in 42.2%. IA revealed a 98% probability of achieving a significant result for mPFS1. The study was early halted due to the introduction of anti-PD1 in 1L. The responses to 1L were PR (50.0%), CR (7.8%), and SD (42.2%). At a median 31-month (mth) follow-up (IQR 19.1-33-8), 28 (84.8%) and 26 (83.8%) events were reported. The main reason for discontinuation was PD (66.7% and 35.5%). mPFS1 was 3.91 (80% CI, 2.27-5.98) and 5.19 mth (80% CI, 4.0-7.26) [HR= 0.736 (80%CI, 0.51-1.04; p=0.1318)]. mOS was 11.25 and 16.97 mth (95%CI, HR=0.596 [0.318-1.103], p=0.1003). The most common G3-4 AEs for each arm were fatigue (3.0 vs 6.4%), thrombocytopenia (3.0 vs 3.2%), and hand-foot syndrome (0 vs 12.9%).

Conclusions: Despite the favorable trend, since the sample was not sized for the statistical assumption, REGO as maintenance after 1L chemotherapy did not reach statistically significant effects in mPFS1. No safety concerns were raised. Novel study proposals succeeding REGO with immunotherapy are needed.

A25

PATIENTS WITH EARLY-ONSET METASTATIC COLORECTAL CANCER AS AN EMERGING DISTINCTIVE CLINICAL AND MOLECULAR PHENOMENON

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Background: Despite a reduction of both incidence and mortality from CRC in the elderly population, several studies published in the last decade have shown an increase in the incidence of early-onset CRC (EO-CRC), conventionally defined as cancer that occurs in adults between the ages of 18 and 49. Clinical and prognostic data on this setting are limited and conflicting. The aim of our study was to evaluate the clinical, prognostic, and molecular profiles of metastatic EO-CRC patients (age at diagnosis ≤ 50) in order to identify potentially relevant differences compared to a control group late-onset CRC (LO-CRC).

Methods: We retrospectively collected data from 1272 metastatic colorectal cancers from 5 different Italian Institutions: 693 (54.5%) EO-CRC and 579 (45.5%) LO-CRC as control group. All patients had one or more metastatic sites, molecular profiling available (including RAS, BRAF, and MSI status), and underwent at least one line of treatment for metastatic disease. The main objective of the study was to the evaluate clinical outcome for the global population of EO-CRC patients in different clinical and molecular subgroups according to RAS and BRAF status and in comparison to patients included in the control group.

Results: In the EO-CRC group median age was 42.8 (20.0-50.9) and 66.7 (51.0-86.2) in the control group. M/F ratios were 1:1 and 2:1, respectively. In the overall population, mOS was 34,7 in EO-CRC pts vs 43,0 months (mo) ($p < 0,0001$) in the control group. In the RAS/BRAF mutated subgroup mOS in EO-CRC pts was 30,3 vs 34,0 mo in the control group ($p = 0,0156$). In RAS/BRAF wild-type subgroup mOS in EO-CRC pts was 43,0 vs 50,0 mo ($p = 0,0290$). Finally, in the BRAF V600E mutated subgroup EO-CRC pts showed a 16 mo mOS vs 26 mo ($p = 0,04$). In the overall population, mPFS was 11,0 in EO-CRC pts vs 14,0 mo ($p < 0,0001$) in the control group. Furthermore, the overall response rate (ORR) was 63% in EO-CRC and 67% in LO-CRC.

Conclusions: Findings from a large population of EO-CRC patients indicate a general worse prognosis for patients with early-onset colorectal cancer compared to late-onset patients. Interestingly this seems to occur regardless of the molecular status. These observations might have a considerable impact on clinical practice and research. Subsequent investigations will be needed to further understand the specific clinical and molecular characteristics of this growing group of patients to better define the more appropriate treatment strategy.

A26

FOCUS ON HER2 POSITIVE METASTATIC COLORECTAL CANCER (HER2+ MCRC): A REAL WORLD RETROSPECTIVE ANALYSIS

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Background: HER2+ mCRCs, displaying HER2 overexpression or *ERBB2* amplification, represent a rare molecular subset, accounting for 2- 6%. While its prognostic value is debated, HER2 seems a negative predictor for antiEGFR agents. Recently, its role as a potential actionable target has emerged, with promising results in refractory mCRC. Despite that, nowadays HER2 testing is not routinely included in the diagnostic workup of mCRC.

Patients and Methods: This is an observational, retrospective, multicenter study, aiming to describe features and prognostic value of HER2+ mCRCs from real world pts. Pts with mCRC tested for HER2 status who received at least one line of therapy (tx) at 11 Italian Institutions within the Lazio Region between Mar2011 and Jan2024 were enrolled. HER2 status was assessed either for HER2

overexpression using IHC according to the HERACLES diagnostic criteria or for *ERBB2* amplification using NGS. Differences between groups were compared using the Chi Square test. Endpoint for prognostic assessment was OS. Endpoints for predictive assessment were PFS, RR and DCR. Statistical significance was set at *p*.05.

Results: 495 pts were included, of those 57 pts had a HER2+ mCRC (11.5%). HER2 positivity was more frequent among tumors with *RAS*wt compared to *RAS*mt (14.6 vs 8.5%; *p*.03), lung mts (*p*.04),synchronous metastatic disease (*p*.03), lymph node mts (*p*.02), brain mts (*p*.01) and liver mts (*p*.004). No correlation with primary tumor location (PTL) was observed (*p*.2). At a median FU of 19.2 months, OS did not significantly differ according to HER2 (*p*.1). 127 pts with *RAS*wt mCRC (109 HER2- and 18 HER2+) received an antiEGFR-based first line tx. PFS was significantly shorter (*p*.01) and RR was lower for HER2+ tumors (p.003), while no difference was observed for DCR (p.3). Of 57 HER2+ tumors, 12 received an antiHER2 tx (9 were *RAS*wt and 3 *RAS*mt), with *RAS* status not significantly impacting on antiHER2 activity.

Conclusions: We showed that HER2+ mCRCs are more frequently, though not exclusively, *RAS*wt, and display a specific metastatic tropism. No association with PTL was observed. HER2 does not impact on prognosis while confirms as negative predictor for antiEGFR tx. Target actionability seems to be retained irrespective of *RAS* status. The baseline molecular workup of mCRC must include HER2 assessment, irrespective of *RAS* mutational status and PTL.

A27

TISLELIZUMAB (TIS) PLUS CHEMOTHERAPY (CT) VS PLACEBO (PBO) PLUS CT AS FIRST-LINE (1L) TREATMENT OF ADVANCED GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA (GC/GEJC): FINAL ANALYSIS (FA) RESULTS OF THE RATIONALE-305 STUDY

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Background: TIS (anti-PD-1 antibody) + CT demonstrated significant overall survival (OS) benefit vs PBO + CT as 1L treatment in patients (pts) with advanced GC/GEJC at a pre-specified interim analysis of the PD-L1-positive (tumor area positivity score =5%) population in the global, phase 3 RATIONALE-305 study (NCT03777657). Here, we present primary analysis results in the ITT population at the pre-specified final analysis.

Material (Patients) and Methods: Adults with previously untreated, HER2-negative, locally advanced, unresectable, or metastatic GC/GEJC, regardless of PD-L1 expression status, were randomized (1:1) to receive TIS 200 mg or PBO IV once every 3 weeks plus investigator (INV)-choice of CT (5-FU + cisplatin or capecitabine + oxaliplatin). The primary endpoints were OS in PD-L1-positive and ITT populations. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR) by INV per RECIST v1.1, and safety.

Results: At data cutoff (February 28, 2023), 997 pts were randomized (n= 501, TIS+CT; n= 496, PBO+CT). Minimum study follow-up was 24.6 months (mo). OS was significantly improved in the TIS arm vs PBO arm in the ITT population (median OS: 15.0 mo vs 12.9 mo, respectively; HR= 0.80 [95% CI: 0.70, 0.92]; 1-sided *P*= 0.0011). Additional main efficacy results are presented in the **Table**. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 268 (53.8%) vs 246 (49.8%) pts; TRAEs led to treatment discontinuation in 16.1% vs 8.1% pts, and death in 1.2% vs 0.4% pts, in TIS vs PBO arms, respectively.

Conclusions: In the ITT population, TIS + CT showed statistically significant and clinically meaningful improvement in OS vs PBO + CT, and was well tolerated. These data support TIS + CT as a potential 1L treatment option for pts with advanced GC/GEJC.

Endpoint	TIS + CT (n=501)	PBO + CT (n=496)
OS		
Median, mo (95% CI)	15.0 (13.6-16.5)	12.9 (12.1-14.1)
HR (95% CI)	0.80 (0.70-0.92)	
1-sided *P*-value	0.0011	
PFS		
Median, mo (95% CI)	6.9 (5.7-7.2)	6.2 (5.6-6.9)
HR (95% CI)	0.78 (0.67, 0.90)	
ORR, % (95% CI)	47.3 (42.9-51.8)	40.5 (36.2-45.0)
Median DoR, mo (95% CI)	8.6 (7.9-11.1)	7.2 (6.0-8.5)

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A28

REAL-LIFE SECOND-LINE THERAPIES OUTCOME IN METASTATIC PANCREATIC CANCER (MPDAC) PATIENTS PREVIOUSLY TREATED WITH GEMCITABINE PLUS NAB-PACLITAXEL (GEM-NAB): AN ITALIAN MULTICENTER STUDY

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Background: More than half of mPDAC patients are eligible for second-line chemotherapy, but the optimal continuum of care is still debated. To date, nal-IRI+5-FU/LV stands as the most novel and robust option in the second-line setting.

The present study aimed to explore survival outcome of nal-IRI+5-FU/LV compared to other different second-line regimens in a real-world population of mPDAC patients previously treated with Gem-Nab.

Materials: This is a retrospective analysis including mPDAC patients consecutively treated between 2015 and 2018 at 39 Italian centers with second-line therapies after Gem-Nab failure. Survival analyses were performed using Kaplan-Meier method and log-rank test. Multivariate analysis was carried on by Cox regression.

Results: A total of 519 patients were enrolled, with 56% of males and a mean age of 66 years. In the overall population, second-line median PFS and OS were 3.8 (95%CI 3.7-4) and 6.8 months (95%CI 6.4-7.3), respectively. Nal-IRI+5-FU/LV was administered in 38.1% (n=198), FOLFIRI in 21.6% (n= 112), FOLFOX or XELOX in 18.5% (n=96), FOLFIRINOX in 13.5% (n=70), and capecitabine in 8.3% (n=43) of cases. In patients receiving nal-IRI+5-FU/LV, OS was 7.5 (95%CI 6.6-9.1) months compared to 6.6 (95%CI 6.2-7.1) in those who did not receive it ($p < 0.005$). Median OS according to the different regimens was 9.1 months (95%CI 6.7-11.5) in the FOLFIRINOX subgroup, 7.5 months (95%CI 6.6-9.1) in nal-IRI+5-FU/LV, 6.7 months (95%CI 6.3-7.8) in FOLFIRI, 6.2 months (95%CI 5.5-7.1) in oxaliplatin-based doublet and 5.7 months (95%CI 5.3-6.8) in subjects receiving capecitabine ($p< 0.0005$). At the multivariate analysis, a significant survival gain from second-line therapy correlated with partial response to the first-line, absence of liver metastases, improvement in performance status during the second-line, CA 19.9 <1000 U/ml, low neutrophil/lymphocyte ratio and nal-IRI dose reduction.

Conclusions: In the absence of randomized trials, these real-world data might strengthen the role of nal-IRI+5-FU/LV as the optimal second-line option after Gem-Nab, being FOLFIRINOX feasible in only a small subgroup of patients. Further analyses are ongoing to validate a propensity score with main prognosticators to tailor the continuum of care of mPDAC.

A29

INFLAMMATORY RESPONSE IN LIVER VS NON-LIVER METASTATIC MICROSATELLITE STABLE (MSS) COLORECTAL CANCER (MCRC). AN INDIVIDUAL PATIENT DATA ANALYSIS FROM THE OBSERVATIONAL STUDY BMI-QOL AND THE PHASE II AND III TRIALS MACBETH, MOMA, ATEZOTRIBE, TRIBE, TRIBE2, TRIPLETE

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Background: Liver metastases (mets) from MSS mCRC have been associated with worse clinical outcome with immunotherapy. We investigated whether this might be due to a significant difference in unfavourable systemic inflammatory indexes

Methods: Differences in 9 inflammatory markers were assessed in liver vs non-liver MSS mCRC patients (pts) treated with 1° line regimens. 128 pts from the BMI-QoL observational study (NCT03873064) were initially analysed. Findings from BMI-QoL were then validated in 2058 pts from phase II and III trials that were split in a discovery (70%) and a validation (30%) subset. The discovery subset was used to identify optimal variable cutoffs predictive of presence of liver mets which were then confirmed in the validation subset. The identified cutoffs were also assessed for prediction of progression free and overall survival (PFS and OS)

Results: In the BMI-QoL cohort neutrophils(NEU), platelets (PLT) and Systemic Inflammatory Index (SII= NEU*PLT/lymphocytes) were significantly different between liver and non-liver mets (p 0.003, 0.007 and 0.005, respectively). In the phase II/III trial cohort NEU, PLT, SII but also lymphocytes were found to be significantly different, with NEU being the most significant marker: median(m) NEU 5.0 vs $4.4*10^6/\mu L$ in liver vs non-liver mets, respectively, $p < 0.0001$. In the discovery subset the optimal NEU cutoff predictive of liver mets was $5.0*10^6/\mu L$ and this was confirmed in the validation subset. Prevalence of NEU $>5.0*10^6/\mu L$ (NEU^{high}) was 49% vs 37% in liver vs non-liver mets, respectively, $p<0.0001$. Moreover, NEU^{high} was associated with shorter mPFS in liver but not in non-liver mets pts: NEU^{high} vs NEU^{low} (i.e. $NEU \leq 5.0*10^6/\mu L$) 10.5 vs 12.1 months, HR 1.29, $p<0.0001$ and 11.7 vs 13.1, HR 1.09, p 0.489, respectively. Also in terms of mOS, NEU^{high} had the worst survival in liver mets pts: NEU^{high} vs NEU^{low} 23.7 vs 31.9 months,respectively, HR 1.55, $p<0.0001$. mOS of NEU^{high} vs NEU^{low} in non-liver mets pts was 28.3 vs 43.9 months, respectively, HR 1.60, p 0.002.

Conclusions: Liver mets from MSS CRC were associated with high NEU which may partly account for the reduced efficacy of immunotherapy observed in this subgroup. Given the particularly unfavourable outcome, there is an urgent need for effective treatments for these patients

A30

ADVANCED INTRAHEPATIC CHOLANGIOCARCINOMA (ICCA): INVESTIGATING CO-MOLECULAR ALTERATIONS

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Background: Recent advancements in genomic profiling have shed light on the molecular pathogenesis of cholangiocarcinomas (CCAs). The FGFR and IDH-1 pathways are the primary targets for therapy, with FGFR-2 and IDH-1 inhibitors, such as Pemigatinib and Ivosidenib respectively, already available on the market. This study prospectively examines the genetic profiles of a cohort of patients with intrahepatic CCAs (iCCAs) enrolled in the FIGHT-302 Study, aiming to identify synchronous co-mutations and rearrangements that could serve as potential additional molecular targets.

Material (patients) and Methods: Between July 1, 2020, and May 3, 2024, sixty-five consecutive patients (pts) with locally advanced or metastatic histologically confirmed intrahepatic cholangiocarcinoma (iCCA) were prospectively enrolled at our institutions. Tissue samples were collected through surgical resection or biopsy. Comprehensive

genomic profiling (CGP) was conducted using next-generation sequencing (NGS) to analyze 324 cancer-related genes (FoundationOne®CDx CTA).

Results: Three pts were excluded from the analysis: two due to inadequate sample size for gene analysis, one due to withdrawn informed consent. Among the 62 evaluable pts, the median age was 65 years (range: 38-82), with a male-to-female ratio of 39/23 (63%/37%). ECOG Performance Status was 0 for 38 pts (61%) and 1 for 19 pts (31%). The median Ca19.9 level was 64.2 U/L (range: 1.2 – 140000). FGFR2 fusions and rearrangements were observed in 13 (21%) and IDH1 mutations in 8 pts (13%). Other single gene mutations were: CDKN2A 24 (39%), CDKN2B 16 (26%), TP53 16 (26%), ARID1A 16 (26%), KRAS 14 (23%), MTAP 8 (13%), BAP1 6 (10%), BRAF 2 (3%), HER2 2 (3%), RET 1 (2%), NTRK 1 (2%), BRCA2 1 (2%). All patients had stable microsatellite status. Eleven pts (18%) presented the following mutations/rearrangements together with already known targets such as FGFR or IDH-1. Specifically, IDH1 alterations were associated with ARID1A (3 pts), FGFR2 (1 patient), TP53 (1 patient) and KRAS (2 pts), and FGFR2 alterations with ARID1A (2 pts), TP53 (1 patient), and NTRK1 (1 patient).

Conclusions: This prospective study validates the prevalence of mutations documented in the literature and underscores the significance of NGS in presenting supplementary therapeutic avenues. Moreover, we demonstrated the role of other potential targets co-expressed with FGFR2 or IDH1 which could represent a crucial opportunity for novel combinations or sequences therapies.

A31

LATE-ONSET PANCREATIC CANCER (LOPC) PATIENTS (PTS) TREATED AT AN ITALIAN CENTER: A REAL-WORD ANALYSIS FROM THE GEMELLI GENERATOR EXPERIENCE

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Background: Although major part of PC is diagnosticated in elderly, PC pts older than 70 years old are poorly represented in randomized clinical trials (RCT); therefore, limited efficacy and safety data are available. This study wants to evaluate the clinicopathological characteristics of advanced LOPC and the effectiveness of systemic treatment.

Methods: Real-world data were collected by the Gemelli GENERATOR facility within the Gemelli Science and Technology Park (G-STeP). Study population was identified from record of pts treated at our Institution from Jan-2018 to Jun-2023 matching three inclusion criteria: pts hospitalized with a diagnosis of PC (International Classification of Disease 9 (ICD-9) codes captured from structured data source), pts with a pathology report including PC evidence and pts with an hospital discharge letter including PC evidence (selected using clinically validated text mining techniques from unstructured data source). Clinicopathological variables of LOPC pts were extracted using SAS (SAS(R) Institute suite for ETL); statistical analyses were conducted using R software.

Results: A total of 915 pts treated at our Institution were included; of those, 210 (23%) had locally advanced or metastatic pancreatic cancer and were older than 70 years old (LOPC). Median age was 76.1 (75.6-79.9), 53% were female, the median BMI was 23.4 (95% CI 22.7-24). More than half of the population (54%) had at least 2 comorbidities at the time of diagnosis and only 9.3% of the pts had none; the most frequent were blood high blood pressure (55.4%) and diabetes (28.4%). Seventy-five pts (35.7%) had locally advanced PC and 135 pts (64.3%) had de novo metastatic disease. Median overall survival (mOS) was 9.9 months (95% CI 8.1-11.7) and 1st line's mPFS was 6.5 months (95% CI 5.7-7.3). Both ECOG PS (0-1 vs 2) and chemotherapy's regimen (FOLFIRINOX vs Gemcitabine-Nabpaclitaxel vs Gemcitabine) were associated with both mOS andmPFS at the univariate analysis, but only ECOG PS remained significant at the multivariate analysis (p<0.001).

Conclusions: Our experience showed that, despite their poor presence in RCT, advanced LOPC pts should be candidate to a first-line treatment in particular when in good general conditions.

A32

EARLY-ONSET PANCREATIC CANCER (EOPC) PATIENTS (PTS) TREATED AT AN ITALIAN THIRD LEVEL REFERRAL CENTER: A REAL-WORD ARTIFICIAL-INTELLIGENCE (AI) ANALYSIS FROM THE GEMELLI GENERATOR EXPERIENCE

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Background: Although PC is mainly diagnosed in pts older than 60 years, its incidence in younger pts is raising. Few data are available for EOPC (pts ≤ 50 years). We aim to evaluate clinicopathological characteristics and outcome of EOPC pts.

Methods: Real-world data were collected and analyzed by an AI tool of Gemelli GENERATOR facility within the Gemelli Science and Technology Park (G-STeP). Study population was identified from records of pts treated at our Institution from Jan-2018 to Jun-2023 matching 3 inclusion criteria: pts hospitalized with a diagnosis of PC (International Classification of Disease 9, ICD-9 codes), pts with at least one pathology report or one hospital discharge letter including PC evidence (selected using clinically validated text mining techniques from unstructured data source). Epidemiological, clinical and anatomopathological variables were extracted by SAS (SAS(R) Institute suite for ETL); statistical analyses were conducted by R software.

Results: A total of 915 pts were included; of those 83 (9%) were EOPC pts. Median age was 44 (25-50), 12/83 (14.5%) pts were ≤ 39 years, 55% were male, ECOG PS was 0-1 in 90%, median BMI was 21.3 (95% CI 20.3-22.4). 53% of pts had 0 comorbidities and 8.5% had two or more; the most frequent was diabetes (10%). Regarding tumor characteristics, 95% were adenocarcinomas, 58% were localized in pancreatic head, 22% of pts received surgery for resectable disease (RD), 33% had a locally advanced tumor (LA) and 45% had a de novo metastatic disease (MD). 72% of pts with RD received a (neo)adjuvant treatment (tx); 87% of pts with LA or MD received a first-line tx and 45% a second-line. Median OS was 35.7 months (95% CI 28-2-Not reached]) for RD pts, 18.1 (95% CI 15.8-28.3) for LA pts and 10.8 (95% CI 8.1-18.1) for MD pts. BMI, ECOG PS, number of comorbidities and sex were not associated with OS in any of these settings.

Conclusions: Our experience demonstrated the importance of an AI-based tool to evaluate EOPC pts treated at our Institution. Our data are in line with previous published results and confirmed the importance of this subgroup of pts. Molecular and DNA damage repair mutations are ongoing and will be presented at the congress.

A33

P53 PATHWAY GENES' MUTATIONS (MUTS) AS PROGNOSTIC FACTORS IN PATIENTS (PTS) WITH METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (MPDAC): A SINGLE CENTER STUDY

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Background: Muts in oncosuppressor genes have been associated with poor prognosis in different solid tumors. This study aims to evaluate the prognostic impact of p53 pathway muts in mPDAC pts.

Methods: mPDAC pts with available formalin-fixed, paraffin-embedded (FFPE) tumor tissue and treated at our Institution were enrolled. We investigated p53 pathway genes' muts by Next Generation Sequencing (NGS) using TSO500HT® assay (DNA [522 genes], RNA [55 genes]). Primary endpoint was overall survival (OS). The Kaplan–Meier method was used to estimate efficacy outcome; log-rank test, Peto-Peto test and Cox-regression model were used to compare the differences, considering a statistically significant p value < 0.05.

Results: A total of 149 mPDAC pts were enrolled; tp53 was mutated in 115/149 (77.2%) pts, CDKN2A in 28 (24.3%), CDKN2B in 8 (5.3%), ATM in 6 (4%), tp53BP1 and MDM2 in 2 pts each (1.3%) and ATR in 1 (0.7%). No muts were found in MDM4, CHEK1 and CHEK2 genes. Overall, 121 (81.2%) pts had at least one mut in a gene of p53 signaling pathway (p53sigmut) and 28 pts (19.8%) had wild-type tumor (p53sigwt). The most frequent tp53 alterations were single nucleotide variations (SNVs): R175 (10 pts-8.7%), R248 (9 pts-7.8%) and R273 (8 pts-7%); 27 tp53 muts (18.1%) occurred in exon 7, 26 (17.4%) in exon 5, 19 (12.8%) in exon 8 and 13 (8.7%) in exon 4. Median OS (mOS) was 19.6 months (mos) (CI 95%: 17.3-Not reached) in p53sigwt pts vs 15 mos (CI 95%: 12.8-18.2) in p53sigmut pts (p=0.04). The site of tp53 alteration was correlated with pts' survival: mOS was 34.9 mos (CI 95%: 31-Nr) in exon 4-mutated pts, 16.9 mos (CI 95%: 11.2-21.2) in exon 7-mut, 13.8 mos (CI 95%: 11.2-17.8) in exon 5-mut and 10.7 mos (CI 95%: 8.2-Nr) in exon 8-mut, p= 0.018. In terms of comutations, tp53 mutated pts had a higher frequency of *KRAS* muts compared to tp53 wt pts (94% vs 64.5%, p<0.001).

Conclusions: Our study suggests an important prognostic role of p53 signaling muts in mPDAC pts; wt pts resulted in a longer OS than mutated pts, although some muts, in particular tp53 exon4 mut, seem to be associated with longer survival. Further studies are needed to investigate these findings, including an in-depth analysis of structural proteomics.

A34

THE IMPACT OF TOTAL NEOADJUVANT THERAPY (TNT) IN LOCALLY ADVANCED RECTAL CANCER (LARC): A REAL WORLD ITALIAN MULTICENTRIC EXPERIENCE

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Background: TNT has recently changed treatment strategy of LARC thanks to increased clinical and pathological complete responses (cCR and pCR) and the possibility of avoiding major surgery by adopting a watch and wait (W-W) approach in case of cCR. The aim of this study is to evaluate in a real word retrospective analysis the applicability of TNT and its implications.

Material and Methods: In 6 centers we evaluated 185 LARC microsatellite stables patients (pts), M/F=107/78, with a median distance from anal verge 5-7 cm. 27 pts classified as cT3N0/c(any)TN+, underwent surgery followed by RT/CHT. The other 158 pts were treated with a neoadjuvant approach: 97 pts (62%) with standard RT/CHT (group A) and 61 pts (38%) with TNT (group B). Pts with bulky disease cT4N+ were 33% group B and 9% group A. Group B chemotherapy was FOLFOX/XELOX (55%) and FOLFOXIRI (45%).

Results: Surgery was performed in 124 pts, 84 pts (86%) group A and 40 pts (65%) group B (p=0.015), with 12% transanal resection in group B and 0% in group A. pCR in group A was 18% (radiological cCR 40% and near cCR/cRP 60%) vs 28% in group B (radiological cCR 45%, near cCR/cPR 36%, cSD 18%). In pts not achieving a pCR, radiological cCR was 10%. W-W was offered to 4 pts (4%) group A and 10 pts (16%) group B who had cCR/near cCR: 1 pt in group B recurred after 1y and wastreated with surgery. Overall, the 2y-DFS was 75,3% and the 5y-DFS 51,9%. In pts with upfront surgery 2y-DFS was 78,1% and 5y-DFS 71%, in pts treated with neoadjuvant therapy 2y-DFS was 73,9% and 5y-DFS 45,1%, probably because of more advanced disease. In neoadjuvant pts, 2y-DFS was 76,5% in group A vs 70,2% in group B and 5y-DFS was 52,7% vs 23,9%, respectively(p=0.043). In pts with bulky cT4N+, 5y-DFS was 24,7% in group B and 0% in group A, confirming long-term disease control in TNT. In the general population 2y-OS was 92,5% and 5y-OS 80%. For surgery upfront 2y-OS was 84,8% and 5y-OS 77,8%, in neoadjuvant pts 2y-OS 93,2% and 5y-OS 84,2% (numerically superior OS but p value not significant).

Conclusions: In our neoadjuvant population, TNT confirmed an increase in pCR but also in radiological major response. This encourages conservative transanal surgery or W-W when a multidisciplinary approach is strictly applied. This strategy needs to be further implemented.

A35

FINAL OVERALL SURVIVAL RESULTS FROM PHASE 3 SPOTLIGHT STUDY EVALUATING ZOLBETUXIMAB + MFOLFOX6 AS FIRST-LINE (1L) TREATMENT FOR PATIENTS (PTS) WITH CLAUDIN 18 ISOFORM 2 (CLDN18.2)+, HER2-, LOCALLY ADVANCED (LA) UNRESECTABLE OR METASTATIC GASTRIC OR GASTROESOPHAGEAL JUNCTION (MG/GEJ) ADENOCARCINOMA

Shitara K.[1], Van Cutsem E.[2], Lordick F.[3], Enzinger P.[4], Ilson D.[5], Shah M.A.[6], Xu R.[7], Lonardi S.[8], Yamaguchi K.[9], Hung Y.[10], Kukielka-Budny B.[11], Bhattacharya P.[12], Matsangou M.[12], Li R.[12], Moran D.[12], Ranganath R.[12], Pophale R.[12], Ajani J.A.[13]

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Background: The phase 3 SPOTLIGHT study showed statistically significantly improved PFS/OS with 1L zolbetuximab + modified folinic acid, 5-FU, and oxaliplatin regimen (mFOLFOX6) vs placebo (PBO) + mFOLFOX6 in pts with CLDN18.2+, HER2−, LA unresectable or mG/GEJ adenocarcinoma at prespecified interim and later updated analyses. We present prespecified final OS analysis.

Materials (patients) and Methods: Pts were randomly assigned 1:1 to zolbetuximab IV 800 mg/m^2 (cycle 1, day [D] 1) followed by 600 mg/m^2 (every 3 weeks) + mFOLFOX6 IV (D1, D15, D29) for four 42-day cycles or to PBO

+ mFOLFOX6; pts without PD continued with zolbetuximab/PBO, + folinic acid and 5-FU at investigator's discretion, until PD or discontinuation criteria were met. Endpoints included PFS (primary), OS (key secondary), ORR/safety (secondary), and PFS/OS in per-protocol set (PPS; pts adherent to protocol) and TTP by BOR (ad hoc).

Results: At data cutoff (Sept. 8, 2023), 565 pts were assigned to zolbetuximab (n=283) or PBO (n=282) arms. In zolbetuximab vs PBO arms, median follow-up was 18.04 vs 17.91 mo for PFS and 33.28 vs 31.38 mo for OS, respectively. Efficacy results are summarized in **Table**. Median PFS and OS were significantly longer in zolbetuximab vs PBO arms. Separation of PFS and OS curves occurred earlier in PPS (excluded majority of early withdrawals) vs ITT population. ORR was similar between treatment arms in ITT and pts with measurable lesions; TTP for patients with BOR of CR/PR was numerically longer in zolbetuximab vs PBO arms. Safety was maintained with no new findings.

Conclusions: Zolbetuximab + mFOLFOX6 continued to demonstrate statistically significant and clinically meaningful improvement in PFS and OS vs PBO + mFOLFOX6, with no new safety signals—supporting zolbetuximab + mFOLFOX6 as a new standard of care option for 1L treatment of pts with CLDN18.2+, HER2–, LA unresectable or mG/GEJ adenocarcinoma.

Table.

			Zolbetuximab + mFOLFOX6 vs PBO + mFOLFOX6
ITT, n=283 vs 282	PFS	Median, months; HR (95% CI); *P* value	11.04 vs 8.94; 0.734 (0.591–0.910); 0.0024
	OS	"	18.23 vs 15.57; 0.784 (0.644–0.954); 0.0075
PPS, n=213 vs 250	PFS	"	12.52 vs 10.28; 0.645 (0.506–0.823); 0.0002
	OS	"	21.49 vs 16.39; 0.687 (0.550–0.859); 0.0005
ITT, n=283 vs 282	ORR	% (95% CI)	48.1 (42.11–54.05) vs 47.5 (41.56–53.52)
Measurable lesions, n=211 vs 210	ORR	"	61.1 (54.20–67.75) vs 62.4 (55.45–68.95)
BOR: CR/PR, n=136 vs 134	TTP	Median, months; HR (95% CI); *P* value	15.28 vs 14.92; 0.760 (0.507–1.140); 0.0930

A36

BIOMARKER ANALYSIS OF PHASE II CAVE-2 GOIM STUDY OF THE COMBINATION OF AVELUMAB PLUS CETUXIMAB AS RECHALLENGE STRATEGY IN PRE-TREATED RAS/BRAF WILD TYPE METASTATIC COLORECTAL CANCER PATIENTS

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Background: CAVE-2 GOIM trial is the first randomized phase II study to assess the efficacy of avelumab plus cetuximab compared to cetuximab alone as rechallenge strategy in pre-treated *RAS*, *BRAF* WT mCRC patients.

Material and Methods: As of May 4, 221 patients have been screened and 120 patients have been treated. Before treatment, a blood sample is analyzed for circulating free tumor DNA (Foundation One Liquid CDx), to identify *RAS/BRAF* WT patients to be enrolled. The same procedure has performed at progression disease. Their correlations with clinical outcome were analyzed. In a subgroup of patients, peripheral blood mononuclear cell (PBMC) were collected at baseline, after 8 weeks and at progression disease. Cytotoxicity was evaluated through LDH-assay using co-culture of PBMC and SW48 mCRC cell line (1:1 ratio). Flow cytometry analysis was performed to assess NK cells subpopulation percentage (gating $CD3^{-}CD56dimCD107a^{+}$) in patient derived PBMC.

Results: Cetuximab plus avelumab treated patients were classified in responders (R) and non-responders (NR). A significant reduction of immune cells-mediated cytotoxicity ($p<0.0001$) was found after 8 weeks of treatment as compared to baseline from NR patients; whereas R patients did not show any significant variation in immune cells-mediated cytotoxicity towards SW48 mCRC cell lines as compared to baseline. Interestingly, flow cytometry analysis showed a lower percentage of NK cells in PBMCs derived from the NR cohort as compared to baseline (respectively, 2% vs 12.9%), while there was an increase of NK cells percentage in R patients (respectively, 26.0% vs 17.7%). In addition, qPCR showed a statistically significant increase in CCL5 fold change ($p<0.05$) after 8 weeks of treatment in the NR cohort. Moreover, CCL5 fold change after 8 weeks did not change compared to baseline in R patients. Ongoing experiments aim to assess *in vivo* CCL5 production on serum samples from mCRC patients to understand its role and cut-off as a putative predictive biomarker of treatment response.

Conclusions: These preliminary findings suggest that evaluation of *in vitro* cytotoxicity together with CD107a expression in mCRC patients derived PBMC could be a useful tool to identify early responders after only 8 weeks of treatment with cetuximab plus avelumab. In addition, we aim to further investigate the potential role of CCL5 secreted by peripheral immune cells and its cut-off as a predictive biomarker of mCRC progression in a larger cohort of patients.

A37

TISLELIZUMAB (TIS) PLUS CHEMOTHERAPY (CHEMO) VS PLACEBO (PBO) + CHEMO AS FIRST-LINE (1L) TREATMENT OF ADVANCED GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA (GC/GEJC): HEALTH-RELATED QUALITY OF LIFE (HRQOL) OUTCOMES IN RATIONALE-305

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Background: RATIONALE-305 (NCT03777657) showed-statistically significant and clinically meaningful improvements in overall survival (OS) with TIS+chemo (n=501) over PBO+chemo (n=496) as 1L treatment in patients (pts) with advanced GC/GEJC. We examined HRQoL in RATIONALE-305 at final analysis.

Materials (Patients) and Methods: Adults with previously untreated, unresectable, or metastatic GC/GEJC, were randomized (1:1) to TIS 200 mg or PBO IV once every 3 weeks plus investigator-choice of chemo. HRQoL was assessed using EORTC QLQ-C30 and the QLQ-STO22. A mixed model for repeated measures of PRO endpoints at Cycles 4 and 6 was performed. Time-to-deterioration was examined.

Results:TIS+chemo had improved outcomes (least-square mean change from baseline) vs PBO+chemo (Table) as indicated by the estimated mean treatment difference at Cycle 6 for QLQ-C30 GHS/QoL (2.52 [95% CI, 0.29-4.74]), physical functioning (2.46 [95% CI, 0.49-4.43]), fatigue (-3.01 [95% CI, -5.78 to -0.24]), and STO22 index score (-1.62 [95% CI, -3.12 to -0.12]), and maintaining upper gastrointestinal (GI) symptoms (-1.74 [95% CI, -3.55 to 0.06)] and pain (-1.88 [95% CI, -4.03 to 0.27]). Pts receiving TIS+chemo had lower risk of deterioration of GHS/QoL (HR, 0.77 [0.60-0.98]), physical functioning (HR, 0.72 [0.57-0.92]), STO22 index score (HR, 0.64 [0.45-0.92]), pain/discomfort (HR, 0.74 [0.58-0.96]), and upper GI symptoms (HR, 0.73 [0.56-0.95]).

Conclusions: The TIS+chemo group had better HRQoL outcomes vs the PBO+chemo group, particularly for GHS/QoL, physical functioning, fatigue, GC/GEJC symptoms, pain/discomfort, and upper GI symptoms. These results, along with prolonging of OS and other secondary efficacy endpoints, and tolerable safety, support the benefit of TIS+chemo as a potential 1L treatment option for GC/GEJC.

	Cycle 6 TIS+Chemo n=501 Mean (95% CI)	Cycle 6 PBO+Chemo n=496 Mean (95% CI)
QLQ-C30		
GHS/QoL	0.93 (–0.71, 2.57)	–1.58 (–3.24, 0.07)
Physical functioning	–2.76 (–4.22, –1.30)	–5.22 (–6.69, –3.75)
Fatigue	1.71 (–0.32, 3.75)	4.73 (2.68, 6.77)
QLQ-STO22		
Index score	–1.84 (–2.95, –0.74)	–0.22 (–1.34, 0.89)
Dysphagia	–2.79 (–3.93, –1.64)	–2.01 (–3.17, –0.86)
Pain/discomfort	–5.97 (–7.56, –4.38)	–4.09 (–5.69, –2.49)
Dietary restrictions	–0.25 (–1.79, 1.30)	1.08 (–0.48, 2.63)
Upper GI symptoms	–3.24 (–4.58, –1.90)	–1.49 (–2.84, –0.14)

A38

THE ROLE OF IMMUNE CHECKPOINT INHIBITORS IN THE FIRST LINE TREATMENT FOR ADVANCED BILIARY TRACT CANCER PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED TRIALS

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Background: Biliary tract cancer (BTC) includes a heterogeneous group of hepatobiliary tumors with different features and unfavorable prognosis. The association of gemcitabine plus cisplatin has been the standard first-line therapy for advanced BTC patients for several years. Immune checkpoint inhibitors have been examined in this setting with intriguing results in survival when associated with standard chemotherapy. Herein, we performed a systematic review and meta-analysis to further explore the impact of the addition of immunotherapy to gemcitabine – cisplatin as first-line treatment for advanced BTC patients.

Methods: According to PRISMA flow chart, literature research was performed and articles selected. From the individual studies, Hazard Ratio (HR) values and their 95% confidence intervals (95% CI) were extracted. Then, aggregate estimates of the logarithm of the HR and 95%CI were assessed by the inverse variance method. Heterogeneity among studies was assessed using the tau-squared estimator. The total Cochrane Q test (Q) was also assessed to indicate lack of homogeneity of the results of the included studies. Finally, the Higgins &Thompson's I-square inconsistency index was adopted and values were classified as low (25-50%), moderate (50- 75%) or high (75%). Additionally, we assessed the objective response rate (ORR) and the progression-free survival (PFS) in the selected studies.

Results: Data from two phase III clinical studies randomizing patients treated with gemcitabine and cisplatin with or without immune checkpoint inhibitors had been analyzed. A total of 1754 participants were included. Heterogeneity among the studies was found to be non-significant (P=0.78; tau 2 = 0 and I 2 = 0%). The model estimation results, and the Forest Plot suggested that the test for the overall effect was significant (Z=-3.51; P<0.01), so there was evidence favoring the experimental treatment.

Conclusions: The results of the current meta-analysis further confirmed the practice-changing role of immunotherapy in combination with standard chemotherapy (cisplatin plus gemcitabine) compared to standard treatment alone. Immunotherapy clinically improved OS and PFS rates in the BTC population, so far immune-checkpoint inhibitors plus cisplatin plus gemcitabine combination is the new standard in the first-line therapy in the advanced BTC setting. However, further studies will be required to identify those patients who may respond better to immune checkpoint inhibitors.

A39

PATTERN OF CARE, EFFICACY AND SAFETY OF ADJUVANT CHEMOTHERAPY IN ELDERLY PATIENTS (PTS) WITH RESECTED COLON CANCER (CC) IN THE REAL-WORLD PRACTICE: THE ELDERLY CC PROJECT

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Background: By 2030 70% of CCs will be diagnosed in older adults as result of aging of population. Nonetheless, elderly pts are underrepresented in clinical trials establishing the standard-of-care practice. More evidence is needed to inform the optimal postoperative management of elderly CC pts.

Methods: Medical records of resected high-risk stage II and stage III CC pts between 2013-2023 were retrospectively reviewed. Pts>70 years were defined as elderly. Differences between patients' characteristics with respect to age were tested using Pearson's chi-square test or Fisher's exact test as appropriate for categorical variables, whereas Student's t-test was used for numerical variables. The associations with categorical variables were analysed using logistic regression models and the results were reported as odds ratio. The Kaplan-Meier method and the Cox proportional hazard model were applied to assess the impact of variables on relapse-free survival (RFS).

Results: Overall, 250 pts were included, of whom 159 (63.4%) were >70 years. Adjuvant chemotherapy was less administered to elderly pts (37,1%). ECOG PS>0, age>80 years, stage II and higher Charlson Comorbidity Index (CCI) were linked to a lower chance of receiving adjuvant chemotherapy in the elderly. Among chemo-treated pts, the elderly were more likely to have higher ECOG PS ($p<0.001$) and CCI ($p<0.001$) and less likely to receive combination chemotherapy ($p<0.001$), while lymphatic ($p<0.001$) and vascular ($p=0.030$) invasion and complicated onset ($p=0.008$) occurred more frequently in youngers. Pathological stage was not different between the two age groups. No significant differences were recorded between elderly and younger CCs in terms of dose reduction, treatment delay, early treatment discontinuation and toxicities. The receipt of adjuvant chemotherapy resulted in a trend toward improved RFS compared to observation alone in elderly CCs (HR 0.55, 0.29-1.06, $p=0.07$), whereas no statistically significant survival difference was seen between younger and elderly chemo-treated pts ($p=0.3$).

Conclusions: Less than 50% of elderly CCs receive adjuvant chemotherapy in the clinical practice though properly selected pts can derive the same benefit as youngers without increased toxicities. The addition of postoperative treatment seemed to improve the outcome of elderly CCs. While age-specific trial data are warranted, our results add a real-world contribution to the existing evidence on this topic.

A40

TROP2 AND ITS OVEREXPRESSION IN METASTATIC COLORECTAL CANCER PATIENTS (MCRCP): BIOLOGICAL, CLINICAL AND THERAPEUTIC IMPLICATIONS

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Background: Trop-2 is a transmembrane intracellular calcium signal transducer glycoprotein encoded by the Tacstd-2 gene and it's related to tumor proliferation enhancement and poor prognosis. An antibody targeting Trop-2 was developed to treat metastatic triple-negative breast cancer but conflicting biological data are available regarding others neoplasms with supposed difference between metastatic sites and the primary tumors, reflecting a difference in the cancer molecular biology. Understanding Trop-2 expression in bone versus other sites mCRC to better understand site-specific differences with a glimpse on its prognostic and eventually therapeutic/predictive role.

Material and Methods: Between 2016 and 2023 a total of 56 consecutive upfront bone mCRCp was observed in comparison with a prospective control group of 56 pts nonbone mCRC. We evaluated the Trop-2 H-score distribution in the three cohorts: (1) primary tumor, (2) visceral metastases and (3) bone metastases. We analyzed also the relationship between clinicopathologic features and the common genomic signature, including RAS, B-RAF, MSI and Her-2/neu.

Results: There was no difference in Trop-2 H-score distribution between the first two cohorts (Mann–Whitney U test $p = 0.966$). Statistically different in Trop2 H-score was seen combining cumulative data of Cohort 1 and 2 versus Cohort 3 (Mann–Whitney U test $p<0.01$). Moderate-to-strong membranous expression of Trop-2 was present in about 25% of case in Cohorts 1 and 2 while the expression in Cohort 3 was always higher 80% of cases. There was significant difference in clinic-pathologic and genomic features between high vs low Trop-2 in all cohorts with an increased K-ras and B-raf mutational status 83% vs 17% ($p <0.01$). Trop2 H-score was an independent poor prognostic factor for overall survival in Cohort 3.

Conclusions: These data revealed the prognostic significance of Trop-2 expression and suggest for the first time that Trop-2 could be a strong prognostic biomarker for bone mCRC. Targeting Trop-2 might be a useful treatment approach for these patients but further evaluations and clinical trials on efficacy and predictive value of Trop-2 expression are needed.

A41

TRIFLURIDINE VS FOLFIRI IN THIRD-LINE METASTATIC GASTROESOPHAGEAL ADENOCARCINOMA (MGEA): THE TRIFOLIUM STUDY

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Background: Limited third-line options exist for mGEA. In this setting, trifluridine/tipiracil (FTD/TPI) is a standard treatment thanks to improved overall survival (OS) in a phase III study. FOLFIRI is another widely adopted regimen based on non-randomized, mainly single arm or retrospective studies. To our knowledge, no data comparing these two are available. We aim to evaluate their outcomes as third lines in a real-world cohort of patients (pts) treated at our Institution.

Methods: In this retrospective monocentric study pts with mGEA progressed after two lines of therapy containing fluoropyrimidines, platinum derivatives and taxanes and treated in third line with FOLFIRI or FTD/TPI at our Institution from January 2020 to March 2024 were included. Outcomes in terms of overall response rate (ORR), progression free survival (PFS), OS and toxicity were evaluated.

Results: Among a total of 350 pts treated for mGEA in the selected timeframe, 156 received third line treatment and 74 pts were deemed eligible according to inclusion criteria. Median age was 62 years, 72% had synchronous metastatic disease and 45% an ECOG PS≥1. Primary tumor site was GEJ in 38%. 72% received FOLFIRI and 28% FTD/TPI as third line therapy. ORR was 7% vs 0% (p=0.313) and mPFS 2.5 vs 2.3 months (mo) (p=0.122) in FOLFIRI and FTD/TPI treated pts, respectively. Grade 3-4 toxicity was reported in 18% vs 12% (p=0.160) of pts, respectively. In the overall population 39% received subsequent fourth line treatment: 22% vs 18% among FOLFIRI and FTD/TPI treated pts (p=0.017). Fourth line was FOLFIRI in 33% and FTD/TPI in 10% of pts. Median follow up was 21.9 mo in the whole population (44.2 mo in FOLFIRI and 12.6 in FTD/TPI population, p=0.015). In this selected cohort, mOS from diagnosis of metastatic disease was 21.4 mo and mOS from third line start was 5.9 mo. Third line mOS in FOLFIRI compared to FTD/TPI pts was 5.3 vs 9.5 mo (p=0.182). A positive effect of third line FTD/TPI treatment was noticed at multivariate analysis (HR 0.497, 95%CI 0.252 – 0.978, p=0.043).

Conclusions: Our data suggest that FTD/TPI, despite slightly lower response rates and similar mPFS, may have a positive impact on OS and lower toxicity compared to FOLFIRI, confirming its mainstay role as third line therapy.

A42

KRAS-MUTATED PATIENTS WITH LIVER-ONLY METASTATIC COLORECTAL CANCER TREATED WITH BEVACIZUMAB AND CHEMOTHERAPY. FUNCTIONAL ANALYSIS OF TP53 MUTATIONS AND OUTCOMES

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Background: TP53 missense mutations (MMs) may confer sensitivity to anti-angiogenics via cross-talk mechanisms between p53, vascular endothelial growth factor (VEGF) and VEGF receptors. Recently, we observed that in a population of patients affected by metastatic gastric adenocarcinoma, treated with Ramucirumab plus chemotherapy, those who had a p53 loss of function mutation showed an improvement in terms of survival[1]. In this context, here we present the results of a study conducted on a homogeneous subgroup of KRAS-mutated colorectal cancer (CRC) patients with liver-only metastases, treated with first-line 5-Fluorouracil/Irinotecan (FOLFIRI) chemotherapy plus Bevacizumab. The aim of the study was to assess whether TP53 MMs were associated with the patients' clinical outcomes.

Material (patients) and Methods: TP53 MMs were detected in primary tumors by next-generation sequencing of 62 patients. TP53 MMs were classified by mutant-specific residual transcriptional activity scores (TP53 RTAS) as transcriptionally inactive ($TP53_{Inactive}$ = TP53 RTAS < 1%) or transcriptionally active ($TP53_{Active}$ = TP53 RTAS ≥ 1%)[2,3]. TP53 RTAS results were used for categorizing patients to perform progression-free survival (PFS), response rate (RR) and overall survival (OS) analyses.

Results: The study population consisted of 62 KRAS-mutated colorectal cancer patients with liver-only metastases, who underwent first-line systemic therapy with FOLFIRI regimen combined with Bevacizumab. TP53 MMs were found in 39 patients (62%): 16 had $TP53_{Inactive}$ and 23 $TP53_{Active}$ MMs. The 16 patients with $TP53_{Inactive}$ MMs showed better PFS compared to those with wild-type TP53 or $TP53_{Active}$ (p=0.007). This effect was retained in the multivariate model (p=0.02) and a similar clinical impact was also observed in the OS analysis (p=0.04). Moreover, we observed a statistically significant difference in terms of overall RR (p=0.03) and rate of post-treatment resection of liver metastases between the 16 patients with $TP53_{Inactive}$ and those with wild-type TP53 or TP53 MMs (p=0.02).

Conclusions: Our study suggests that TP53 MMs could help in identifying those patients who may benefit the most from Bevacizumab-based systemic therapy.

A43

THE ELECTRA STUDY: TREATMENT STRATEGIES IN OLDER PATIENTS WITH METASTATIC COLORECTAL CANCER

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Background: The older population has been under-represented in clinical studies, mainly because of their frailty. Namely, treatment strategies in older patients with metastatic colorectal cancer (mCRC) is still undetermined. This study aimed to evaluate survival outcomes according to first-line treatments and factors associated with toxicity-related interruption.

Material and Methods: Data of 1678 older mCRC pts treated in 14 Italian Centers were retrospectively examined. Determinants of toxicity-related interruption were analyzed with logistic regression. Progression-free survival (PFS) was analyzed by log-rank test.

Results: Overall, 438 (38%) patients received a geriatric assessment at diagnosis of metastatic disease. During first-line,18% were hospitalized with a median length of stay of 12 days. Of note, older age was not significantly associated with lower survival outcomes (mPFS <75y 23.9 mo; 75-80y 21.3 mo; >80y 21.34 mo; P=0.61) neither with toxicity-related interruption. High risk patients assessed with the modified G8 score (OR 1.48, 95% C.I. 1.07-2.05, P=.017), mono-CT (OR 2.58, 95% C.I. 1.61-4.14, P<.0001) and doublet-CT (OR 2.37, 95% C.I. 1.49-3.76, P<.0001) without biologic were associated with higher probabilities of toxicity-related interruption compared to CT plus biologic. Chemotherapy without biological therapy did not significantly improved PFS (mono-CT HR 2.38, 95% C.I. 1.49-3.82; P<.0001; doublet-CT HR 2.18, 95% C.I. 1.40-3.41, P=0.001). Moreover, monoCT predicted lower probability of receiving II line treatment (OR 0.58, 95% C.I. 0.39-0.87, P=.009).

Conclusions: This large series of older mCRC patients showed that age is not the main variable to consider in prescribing first-line chemotherapy. While an appropriate patient' categorization to estimates fitness of each patient and chemotherapy toxicity risk could help clinician in deciding which is the most effective and safe treatment. Interestingly, monoCT and doubletCT use was associated with a higher probability of chemotherapy-related toxicity, with no benefit on PFS compared to chemotherapy plus biologic.

A44

SAFETY AND EFFICACY OF FIRST-LINE IMMUNE CHECKPOINT INHIBITORS IN ELDERLY COLORECTAL CANCER PATIENTS: AN ITALIAN REAL-WORLD MULTICENTER EXPERIENCE

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Background: Immunotherapy (IO) demonstrated remarkable efficacy with limited adverse events (AEs) in dMMR/MSI metastatic colorectal cancer (mCRC) patients (pts). The real benefit among elderly pts, who often present with dMMR/MSI, is uncertain due to their underrepresentation in clinical trials.

Methods: We retrospectively evaluated safety and efficacy of IO as first-line treatment of stage IV/unresectable stage III dMMR/MSI CRC pts aged ≥70 years (yrs), treated across 6 italian centers.

Results: N. 67 pts, 37 (55%) were female, 50 (75%) had right-sided and 38 (61%) BRAF V600E mutated CRC. Median age was 76 yrs (range 70-93, IQR 73-82), with 23 (34%) pts aged <75, 18 (27%) 75-79, 26 (39%) ≥80. Only 20 (30%) pts had a baseline geriatric evaluation, with G8

score ≤14 in 17 (85%), while 53/67 (79%) had ECOG PS 0-1.Primary tumor was resected in 47 (70%) pts. On 64 stage IV pts, 37 (58%) had synchronous metastases, with liver only in 11 (17%), >1 site in 20 (31%) and peritoneal involvement in 25 (39%).All pts received pembrolizumab, except 1 nivolumab/ipilimumab.47 (70%) pts reported ≥1 AE, with G1-2 in 55% and no G4-5. The most common were fatigue (45%), skin toxicities (19%), hypothyroidism (22%), arthralgia (18%). IO was temporarily or definitively withheld for AEs in 9 (13%) and 5 (7%) pts.On 60 pts with evaluable response, 28 (47%) had an ORR (CR: 6 [10%]; PR: 22 [37%]), 49 (82%) a DCR, with 11 (18%) primary PD. Having an AE was not predictive of response (p=0.97).At a median follow up of 13.5 months, mPFS was 28.4 months (23.5-NE) and mOS 34.1 (NE-NE). At multivariable model for pts characteristics, liver-only (p=0.05) and age ≥80 yrs (p=0.04) were related to better OS; among AEs, gastrointestinal were worse for PFS (p=0.03) and OS (p=0.04), hepatotoxicity for OS (p<0.05), while rheumatological were related to better OS (p=0.05).

Conclusions: First-line IO demonstrated safety and efficacy in elderly mCRC pts, even in >80 yrs old. These findings support the use of IO in elderly CRC pts, warranting further investigation.

A45

PATTERN OF EXPRESSION, TRANSCRIPTIONAL STATES AND CLINICAL IMPLICATIONS OF TUMOUR-INFILTRATING LYMPHOCYTES (TILS) IN CURATIVELY-TREATED CHOLANGIOCARCINOMA (CCA) PATIENTS (PTS): THE TILBIL STUDY

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Background: Deciphering the role of the adaptive immune system is key to fully realize the potential of immuno-oncology in CCA. TILs are major components of the immune microenvironment with a prognostic value across cancer types yet understudied in CCA.

Methods: Tissue blocks from 70 CCA pts undergoing radical surgery between 2013-2023 at the University Hospital of Modena were retrieved. IHC for CD4, CD8 and Foxp3 was performed for the intratumoural (i) and stromal (s) compartment. TILs were recorded as continuous variables and dichotomized to the median. Both bulk RNAseq and spatial trascriptomics were applied through TempO-seq and GeoMx. Correlation analyses and survival models were performed using IBM SPSS Statistics version 25.0.

Results: Overall, 55% and 42% pts had iCD4+high and sCD4+high CCAs, 54% and 27% of them had iCD8+high and sCD8+high CCAs, and 28% and 34% of them had iFoxp3^{+}high and sFoxp3^{+}high CCAs. iCD4+ high CCAs were associated with pN0 status and a significantly longer RFS than CD4+ low cases (p=0.02). Contrariwise, pts with increased iCD8+ T cell density had significantly shorter RFS than iCD8+ T cells low tumours (p=0.05). iCD4+ T cells together with ECOG PS, nodal status, and adjuvant chemotherapy were independent predictors of outcome. Among iCD4+ high cases, adjuvant chemotherapy significantly prolonged survival compared to observation alone (p=0.01), while no difference was seen within the iCD4+ low subgroup (p=0.06). Compared to CCAs with lower TILs infiltration, iCD4+ high and iCD8+high subsets exhibited 342 and 393 differentially expressed genes, enriched in metabolic, beta-catenin and KRAS pathways and interferon alfa, DNA repair and VEGF networks, respectively.

Conclusions: We showed that more than 50% of CCAs displayed high intratumour infiltration of CD4+ and CD8+ TILs, which defined transcriptionally distinct entities with different clinical implications. Interestingly, higher iCD4+ density predicted a favourable prognosis and a benefit from adjuvant chemotherapy in our cohort. These preliminary findings prompt future studies diving into the biomarker potential of TILs in CCA.

A46

TISLELIZUMAB + CHEMOTHERAPY (CT) VS PLACEBO + CT AS FIRST-LINE TREATMENT FOR LOCALLY ADVANCED UNRESECTABLE OR METASTATIC GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA: RATIONALE-305 EUROPEAN/NORTH AMERICAN PATIENT SUBGROUP

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Background: Tislelizumab (TIS), an anti-programmed cell death protein-1 monoclonal antibody, plus CT, demonstrated significant overall survival (OS) benefit vs placebo (PBO) + CT as first-line therapy in patients (pts) with advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC) in the randomized, double-blind, global, phase 3 RATIONALE-305 study (NCT03777657). Here we present results from the European/North American (Eu/NA) pts subgroup analysis.

Material (Patients) and Methods: Adults with previously untreated, HER2-negative, locally advanced unresectable, or metastatic GC/GEJC, regardless of programmed death-ligand 1 (PD-L1) expression status were enrolled. Eligible pts were randomized (1:1) to receive TIS 200 mg or PBO intravenously once every 3 weeks plus CT (5fluorouracil + cisplatin or capecitabine + oxaliplatin). The primary endpoint was OS in the PD-L1+ (tumor area positivity score ≥5%) and intent-to-treat (ITT) analysis sets. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), and safety.

Results: Of 997 pts enrolled, 249 (25.0%) were from Eu/NA (TIS+CT, n= 125; PBO+CT, n= 124). After a minimum follow-up of 26.6 months (mo), TIS+CT resulted in OS improvements vs PBO+CT in the PD-L1+ (hazard ratio [HR]= 0.75, [95% CI, 0.52-1.07]; 24 mo rate 27.6% vs 12.5%) and ITT analysis sets (HR= 0.71, [95% CI, 0.54-0.94]; 24 mo rate 27.6% vs 13.6%). TIS+CT resulted in favorable PFS vs PBO+CT (HR= 0.84, 95% CI, 0.63-1.11), numerically higher ORR (36.0% vs 31.5%), and longer DoR (median 7.5 mo [95% CI, 4.4-12.0] vs 5.0 mo [95% CI, 3.9-6.7]). Sixty (48.8%) pts in the TIS+CT arm and 61 (49.2%) pts in the PBO+CT arm experienced grade =3 treatment-related adverse events (TRAEs). Sixteen (13.0%) and seven (5.6%) pts discontinued treatment due to TRAEs in the TIS+CT and PBO+CT arms, respectively. Deaths due to TRAEs occurred in two (1.6%) pts in the TIS+CT arm and one (0.8%) pt in the PBO+CT arm.

Conclusions: TIS+CT showed OS benefit vs PBO+CT and a manageable safety profile in pts in the Eu/NA subgroup with previously untreated, HER2-negative, locally advanced unresectable, or metastatic GC/GEJC. These findings are consistent with the published results in the overall study population.

A47

PROGNOSTIC IMPACT OF BASELINE EXOSOME-DELIVERED IMMUNOMODULATORY MOLECULES IN ADVANCED CHOLANGIOCARCINOMA PATIENTS: CAN IMMUNE CHECKPOINTS ACT AS A SENTINEL FOR PREDICTING SURVIVAL?

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Background: Cholangiocarcinoma (CCA) is a group of rare and aggressive malignancies arising from the biliary tree. Due to its high heterogeneity, the clinical manifestations are atypical and diagnosis is often late, resulting in poor prognosis with a 5-year overall survival rate of only about 10%. Although immune checkpoints inhibitors (ICIs) have recently changed the treatment landscape of advanced CCA, the improvement in survival remains only a few weeks, suggesting the need to identify new prognostic biomarkers. In this context, the aim of our study was to investigate if baseline plasma exosomes-delivered immunomodulatory proteins may predict prognosis of patients with advanced CCA.

Patients and Methods: Exosomes were isolated from plasma of advanced CCA patients using exoEasy Maxi kit and characterized by transmission electronic microscopy, nanosight and western blot. Through specific ELISA tests we measured the exosomal concentrations of PD-L1, PD-1, butyrophilin sub-family 3A/CD277 receptor (BTN3A1), pan-BTN3As, butyrophilin sub-family 2 member A1 (BTN2A1), and B- and T-lymphocyte attenuator (BTLA) in 40 patients affected by advanced CCA, before starting first-line treatment with durvalumab and standard cytotoxic therapy. The Kaplan–Meier method was used to generate the survival curves, while univariate analysis was performed using Cox proportional hazard regression models.

Results: For each analyzed exosome-delivered biomarker, advanced CCA patients were discriminated based on long (≥6 months) versus short progression-free survival (PFS<6 months). The concentration cut-offs, obtained by receiver operating characteristic (ROC) analysis, allowed to observe that a lower median PFS was associated with higher baseline levels of PD-L1 (>0.32 ng/mL), PD-1 (>2.28 ng/mL), BTN3A1 (>4.45 ng/mL), pan-BTN3As (>10.06 ng/mL), BTN2A1 (>4.69 ng/mL) and BTLA (>2.18 ng/mL).

Conclusions: Our results suggested that high-risk advanced CCA patients could be identified through determination of the plasma exosome-delivered PD-L1, PD-1, BTN3A1, pan-BTN3As, BTN2A1 and BTLA levels.

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A48

PATHOMICS OUTPERFORMS POOR-PROGNOSTIC FACTORS IN PREDICTING RESISTANCE TO CHEMOTHERAPY IN METASTATIC COLORECTAL CANCER

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Background: The identification of reliable predictive biomarkers for first-line chemotherapy (CT) response in metastatic colorectal cancer (mCRC) patients remain elusive. The current multimodal multidisciplinary therapeutic approach could hamper new biomarker discovery potentially key for driving upfront clinical decision.

Methods: Clinicopathological characteristics (CPC) were collected from a retrospective cohort of 206 real-world mCRC patients at seven major cancer centers across Italy and Spain. Patients with complete or partial responses lasting more than 10 months (Sensitive, S; N=105) or primary progression (Resistant, R; N=101) to first line CT were included. Patients who underwent locoregional procedures at best response were not eligible for this study. Whole-slide Imaging (WSI) data were available for 126 patients (59 S/67 R). CPC correlation with treatment response was analyzed by using Fisher's exact test, and a 12-month landmark survival analysis was conducted. WSI from resected primary tumors were processed into 224x224 pixel (0.5μm/pixel) patches classified as tumoral or non-tumoral by an already trained deep-learning algorithm. A k-means clustering algorithm was exploited to obtained homogenous clusters using either first order and Gray-Level Co-Occurrence Matrix (GLCM) texture features (k=9) or GLCM features alone (k=12). Then, for each patient, the percentage of tiles belonging to each tiles' cluster was computed to represent new features (called "bag of words") with which different machine learning classifiers were trained.

Results: The median follow-up was 4.6 years (95%CI 3.5-5.8). Mucinous histology only was associated with the R cohort (p=0.007) at multivariate analysis for CT resistance. Survival multivariate analysis identified particularly signet ring cell histology (p=0.011; HR 15.1; 95% CI 2.9-79.4) and resistance to first line CT (p=0.0002; HR 3.0, 95% CI 1.7-5.4) as predictors of poorer survival. Conversely, using pathomics, the best result was obtained using a polynomial Support Vector Machine (SVM) classifier and only GLCM features, obtaining a negative predictive value (NPV), i.e., precision in identifying R pts, of 90% (95%CI 79-95) in the construction set (N=94; 47 R/47 S), and 82% (95%CI 63-93) in the validation set (N=32; 20 R/12 S).

Conclusions: CPC did not predict outlier CT responses in mCRC patients, contrasting with pathomics achieving an 82% NPV. Further validation also beyond response outliers is ongoing.

A49

ROLE OF SOMATIC MUTATIONS IN HOMOLOGOUS RECOMBINATION (HR) AND DNA DAMAGE REPAIR (DDR) GENES IN METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (MPDAC)

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Background: First-line therapy's (tx) choice between the two most efficacious approved regimens (FOLFIRINOX and Gemcitabine plus Nab-Paclitaxel - GemNab) in mPDAC is usually based on patients' (pts) baseline characteristics. Germline mutations in HR and DDR genes are the only known predictive factors of response to platinum-based therapy or PARP inhibitors in this setting.

Patiens and Methods: This is a retrospective study aiming to assess the predictive role of somatic alterations in HR-DDR genes in mPDAC pts treated with first-line tx. Pts with mPDAC who underwent Comprehensive Genomic Profiling with TSO500 within the framework of the prospective monocentric FPG500 study (NCT06020625) at our institution in 2022-2023 and received first-line tx with either platinum-based or platinum-free regimens were included. Somatic HR-DDR alterations were correlated with PFS and OS at univariate and multivariate analyses. Statical significance was set at p=.05.

Results: 109 pts were included in the analysis. 37 pts received a platinum-based (81% FOLFIRINOX) and 72 a platinum-free first-line tx (94% GemNab). Seventeen tumors (16%) displayed HR-DDR somatic alterations. At a mFU of 21 months (m), mPFS was 7.9 m and mOS was 14.3 m. HR-DDR alterations did not significantly correlate with survival in pts treated with platinum-based tx. On the contrary, in pts treated with platinum-free tx, HR-DDR alterations correlated with significantly worse mPFS (4.1 Vs 7.3 m, p.0001) at univariate analysis, retaining statistical significance at multivariate analysis alongside with presence of lung metastases. In the subgroup of HR-DDR altered pts, platinum-based tx was associated with significantly longer mPFS (10.8 Vs 4.1 m; p.001) at univariate analysis; statistical significance was not retained at multivariate analysis. In the subgroup of HR-DDR wild type pts, no significant difference was observed in terms of survival between platinum-based and platinum-free regimens.

Conclusions: HR-DDR somatic alterations emerged as possible predictor of lower benefit from platinum-free regimens. Thus, platinum-based regimens should be preferred in this setting. Validation in wider cohorts and correlation with HR-DDR germline mutations are warranted.

A50

PROGNOSTIC IMPACT OF CONCOMITANT GENOMIC ALTERATIONS IN PATIENTS AFFECTED BY FGFR2-POSITIVE LOCALLY ADVANCED UNRESECTABLE OR METASTATIC CHOLANGIOCARCINOMA TREATED WITH PEMIGATINIB AS SECOND OR FURTHER LINE OF SYSTEMIC TREATMENT: MOLECULAR ANALYSIS OF THE REAL-WORLD ITALIAN PEMIREAL AND FRENCH PEMIBIL COHORT STUDIES

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Background: Pemigatinib is approved for patients with pretreated, locally advanced or metastatic cholangiocarcinoma (CCA) harboring FGFR2 fusions or rearrangements. Genomic profiling conducted on patients enrolled in the pivotal FIGHT-202 study have suggested that co-occurrent genomic alterations (GA) in the genes related to cell-cycle regulation and tumor suppression might be related with worse survival outcomes. We assessed the prognostic impact of concomitant GA in patients affected by FGFR2-positive CCA, treated with pemigatinib in a real-world setting.

Patients and Methods: Patients eligible were those who received pemigatinib for locally advanced unresectable or metastatic FGFR2-positive CCA as 2nd or further line of treatment and included in the observational Italian PEMIREAL and French PEMIBIL cohort studies. For the purpose of this analysis, only patients who performed extensive DNA or RNA-based NGS sequencing were included. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan-Meier method. The prognostic impact of the identified variants was assessed by log-rank test comparing PFS and OS between mutant and wild-type patients. For all analyses statistical significance was set at $p < 0.05$.

Results: 8 out of 72 patients were excluded from the present analysis (NGS analysis not performed or data not available). Among 64/72 (88.9%) patients who were tested for FGFR2 fusion or rearrangements by using DNA-based or RNA-based NGS platforms (predominantly FoundationOne® CDx and Archer® Fusion Plex NGS platforms), 30 patients harbored at least one concomitant GA. The most frequent concomitant GA were found in *BAP1* (7/64, 10.9%), *CDKN2A* (7/64, 10.9%), *TP53* (6/64, 9.4%), *CDKN2B*(4/64, 6.3%), *PTEN* (3/64, 4.7%), *IDH1* (3/64, 4.7%) genes.

A statistically significant worse PFS was observed for *CDKN2A* mutant compared to *CDKN2A* wild-type tumours (mPFS 4.79 vs 8.69 months, respectively, HR:10.50, 95%CI:2.66-41.37, p=0.0008), and for *BAP1* mutant compared to *BAP1* wild-type tumours (mPFS 5.97 vs 8.69 months, respectively, HR:4.98, 95%CI:1.33-18.60, p= 0.0167). No differences in OS were found.

Conclusions: Our results seem to confirm the negative prognostic role in terms of PFS of GA in *BAP1* and *CDKN2A* genes in patients affected by locally advanced or metastatic FGFR2-positive CCA treated with pemigatinib in a real-world setting.

A51

PREVALENCE OF MICROSATELLITE INSTABILITY IN LOCALLY ADVANCED RECTAL CANCER: RESULTS FROM THE STAR-01 STUDY

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Background: There are significant differences amongst series when it comes to the incidence of microsatellite instability (MSI) in locally advanced rectal cancer (LARC). It is essential to identify the prevalence of MSI in LARC. We assessed MSI in a cohort of LARC from the STAR-01 study.

Materials and Methods: Samples from 271 LARC patients who had been previously enrolled in the phase III STAR-01 study were retrieved for the present analysis (152 pre-therapy biopsies and 119 surgical samples). Immunohistochemical analysis (IHC) was done to evaluate MLH1, MSH2, MSH6 and PMS2 expression. If all four proteins were detected by IHC, the tumors were classified as MMR proficient (pMMR) and MMR deficient (dMMR) if, at least, one of the four proteins was not detected by IHC. To ascertain MSI in a tumor DNA, the microsatellite phenotype was examined using an eight mononucleotide panel, which included BAT-25, BAT-26, NR-21, NR-22, NR-24, NR-27, CAT25 and MONO-27. If at least two of the eight markers displayed instability, a tumor was classified as MSI. There were no germline analyses carried out.

Results: Out of the 267 cases (98.5%) evaluable for analysis, 35 cases were tested using MSI analysis alone, and 206 cases were evaluated using IHC alone; 26 cases were tested using both IHC and MSI analysis because at least one of the four MMR proteins was indeterminate. Six cases (2 cases with MSI alone and 4 cases with both IHC and MSI analysis) out of 267 patients (2.2%) were dMMR. Of the 4 patients with dMMR LARC on IHC, 1 had loss of PMS2 expression alone and 1 had loss of MLH1 and PMS2. One of the two remaining patients had loss of MSH6, while the other had a loss of MSH2. Out of the six patients with dMMR LARC, five (83%) were 50 years of age or older, including two (33%) who were over 70. No known Lynch syndrome was described.

Conclusions: Compared to previous reports we detected a lower percentage of MSI LARC. The importance of universal screening is confirmed by the relatively older median age of patients with MSI rectal adenocarcinoma upon presentation.

A52

THE ITALIAN RARE BILIARY TRACT CANCER INITIATIVE (IRABICA)°: AN INTERIM ANALYSIS ON 107 PATIENTS OF A MULTICENTER OBSERVATIONAL STUDY OF GRUPPO ONCOLOGICO DELL'ITALIA MERIDIONALE (GOIM) IN COLLABORATION WITH GRUPPO ITALIANO COLANGIOCARCINOMA (GICO)

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Background: Rare histotypes account for 10% of biliary tract cancer. Due to their rarity, there is a little knowledge about the biological behaviour, molecular characterization and sensitivity to therapies. An Italian task force on these rare tumors has been created whose initiative has been a multicentric study[1]

Methods: Until today, clinical data of the first 107 patients were collected. A descriptive database analysis was performed by stratifying according to the histotype.

Results: Overall, 61% male (mean age 68) and 49% (mean age 65) were enrolled. The following rare histotypes were analysed: signet ring cell carcinoma (SRCC-27%), adenosquamous carcinoma (ASC-21%), hepatocholangiocarcinoma (18%), iCCA with ductal plate malformation pattern (ICCA-DPMp -18%), clear cell carcinoma (CCC-7%), cholangiolocellular carcinoma (CoCC-6%), squamous cell carcinoma (SC-1%), sarcomatous cholangiocarcinoma (1%). More than 60% showed intrahepatic localization (35% right, 30% left) and 13% originated from the gallbladder (stage I 1%, stage II 27 %, stage III 37 %, stage IV 18 %). Seventy-seven percent underwent surgery and 41% received adjuvant therapy. First and second lines therapies were administrated in 37% e 30% of cases, respectively. Data concerning the schedule was available from 50%. The most used was GemCis alone (43%) or with durvalumab (15%). The main features, stratified by histotype, are shown in table 1.

Conclusions: Seventy-two percent of diagnoses occurred in advanced stages. The mean age at diagnosis was similar among all histotypes with the exception for CoCC (59 years). Hepato-cholangiocarcinoma and ICCA-DPMp was more frequent in males and almost exclusively had intrahepatic localization. The most frequent histotype of the gallbladder was ASC. In more than 50% of cases, the histological diagnosis was subsequent to surgery. The accrual is ongoing.

Table 1. Main features stratified by histotype.

Histotype (*n* pts)		Sex(%)		Site(%)			Stage(%)							
	Age	M	F	iCCA	eCCA	GBC	I	II	III	IV	Surgery(%)	Adjuvant(%)	I Line(%)	II Line(%)
SRCC(*29*)	68	55	45	41	24	10		24	41	21	79	28	17	20
ASC(*23*)	69	48	52	22	26	42		22	35	35	70	25	35	37
Hepato-cholangiocarcinoma (*19*)	69	79	21	95			5	32	11	16	47	55	58	27
iCCA-DPMp(*19*)	66	74	26	94	5			26	53	5	100	58	32	50
CCC(*8*)	66	50	50	100				12	50	12	87	43	50	50
CoCC(*7*)	59	71	29	100				57	43		100	43	57	25

A53

EARLY-ONSET COLORECTAL CANCER (EOCRC), AN EMERGING DILEMMA: A 30-YEAR RETROSPECTIVE ANALYSIS FROM A SINGLE INSTITUTION

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Background: Despite a recent overall decrease in colorectal cancer (CRC) incidence and mortality, there has been a significant rise in CRC diagnoses in young adults (<50 years old - yo).

Methods: In this retrospective observational study, we analyzed both population- and hospital-based data of 147 patients (pts) younger than 50 yo with a newly-diagnosed CRC treated at the Modena Cancer Center. We compared three time periods: 1995-2004 (A); 2005-2014 (B); 2015-2023 (C).

Results: Overall, 30 pts, 56 pts and 60 pts were diagnosed during period A, B and C, respectively. The mean age was 44 yo during A and C and 43 yo during B. They were predominantly males across all the study periods (p=0.774). Among the risk factors considered, family history of malignancy and smoking habit increased over time, although the finding was not statistically significant. The most frequent primary tumour site was the left colon across the three decades (p=0.872). An increase in T4 (34% vs 27%) (p 0.033) and a decrease in T3 (51% vs 73%) (p 0.033) was seen in C compared with A. Moreover, during period C there was an increase in N0 (29% vs 9%) and a decrease in N2 (29% vs 64%) (p 0.004) compared with A. Stage IV was the most common stage at presentation: 73% during A, 81% during B and 58% during C (p=0.138). Resectable pts increased over time (27% during A vs 44% during C, p=0.020), whereas metastatic pts decreased (73% vs 56%, p 0.020). Although first- and second-line progression free survival (PFS) curves are comparable between the three-time frames (HR=1.263, p=0.345), overall survival (OS) showed a statistically significant improvement from period A to C, in both resected (HR=0.53, p=0.027) and metastatic pts (HR=0.34, p<0.001).

Conclusions: In this study, we reported a rise in EOCRC cases diagnosed from 1995 to 2023 at our institution, confirming the emerging literature. No differences in the distribution of risk factors emerged across the study periods. Interestingly, our data showed less advanced stages at diagnosis and improved OS for EOCRC pts over recent years, probably because earlier detection, increased awareness and better anticancer treatments.

A54

TRANSCRIPTOMIC-GUIDED DECITABINE (DEC) REPURPOSING FOR THE TREATMENT OF KRAS-DEPENDENT ADVANCED PANCREATIC DUCTAL ADENOCARCINOMA (PDAC): PRELIMINARY RESULTS FROM THE ITALIAN ORIENTATE STUDY

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Background: PDAC is the most lethal of solid tumors, with KRAS mutations found in 90% of cases. Transcriptomic analysis effectively identifies KRAS-dependent tumors (dKRAS). DEC has shown promising antitumor and antimetastatic activity in preclinical studies against dKRAS PDAC. We present the preliminary results of the ORIENTATE trial, which tested DEC in chemorefractory PDAC patients (pts) with transcriptomically identified dKRAS tumors.

Methods: The ORIENTATE trial is a phase II, open-label, multicenter, single-arm study designed to evaluate the efficacy and safety of DEC in pts with advanced, refractory (1 or 2 previous lines for metastatic disease) PDAC and dKRAS. Molecular assessment of dKRAS status was conducted by RNAseq analysis of a fresh tumor biopsy, using validated transcriptomic KRAS-dependency scores. The primary endpoint was the best overall response (BOR) according to RECIST 1.1 criteria. Simon's two-stage design was employed, with 9 pts required to evaluate progression to the second step.

Results: A total of 33 pts consented between May 2022 and August 2023 (median age 61 years, range 43-77; males were 22 (64%), females were 11 (36%); pts received 1 or 2 previous lines of treatments. Fourteen biopsies (42%) were not evaluable for transcriptomic analysis due to highly

necrotic samples or <30% tumor cellularity. Among 19 pts evaluable for RNAseq, 10 (52%) exhibited dKRAS, according to at least one out of two dependency scores. Seven dKRAS pts underwent DEC treatment. Grade 3-4 febrile neutropenia was reported in 3/4 pts treated at the starting DEC dose level (DL 0) of 10 mg/m2/d (d1-5 and d8-12 of each 28-day cycle), despite prophylactic G-CSF support, starting 48 hrs after the last DEC infusion. Sepsis occurred in 1 of 2 pts treated at DL -1 (7.5 mg/m2/d, same schedule). One pt received DEC at DL -2 (10 mg/m2/d, d1-5 of each 28-day cycle). All patients discontinued treatment after the first cycle of therapy due to radiological evidence of progressive disease.

Conclusions: The ORIENTATE study shows that evaluating transcriptomic profiles for KRAS dependency in advanced PDAC pts is feasible but challenging. In dKRAS tumors DEC, at the dose and schedule selected from previous phase I studies, caused severe toxicity and serious adverse events in all pts. Given the >50 clinical trials investigating DEC repurposing in solid tumors, our results provide useful insights into assessing a different schedule with an improved safety profile for chemorefractory solid tumors.

A55

QUALITY OF LIFE IN RECTAL CANCER TREATMENT: A SYSTEMATIC REVIEW OF RANDOMIZED CLINICAL TRIALS PUBLISHED IN THE LAST 10 YEARS

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Background: Rectal cancer (RC) management requires a multidisciplinary approach that integrates surgery, pre/post chemo-(CT) and/or radiotherapy (RT), and patient care strategies, all of which can have impact on quality of life (QoL). This systematic review aims to synthetize the best evidence-based studies published in the last ten years on QoL in RC patients (pts).

Methods: A systematic review of the literature over the past 10 years regarding QoL in RC pts were performed using PUBMED, EMBASE, MEDLINE and SCOPUS. Only randomized controlled trials (RCTs) that measured QoL through validated instruments were included.

Results: Among 600 studies screened, 41 met the inclusion criteria: 16 focused on surgical interventions (including 3,507 pts), 15 on CT/RT (including 5,114 pts), and 10 on patient's care strategies (including 619 pts). When comparing abdominoperineal resection (APR) and sphincter saving procedures, QoL is worsened only in the area of body image and sexual function in the APR group. Conversely, when comparing rectum sparing approaches (RSA) with rectal resection, overall QoL is better in the RSA groups. Trials investigating the type of colorectal anastomosis, the type of techniques (robotic/laparoscopic/open surgery) and the time of stoma closure failed in demonstrating differences in QoL. When investigating different planning of therapy, only the administration of RT is related to worse QoL. When considering patient's care studies, continuity of care packages improved QoL in ostomy pts, while transanal irrigation was associated with improved QoL after ostomy closure. Due to clinical heterogeneity, it was not possible to perform a meta-analysis of the trials.

Conclusions: RSAs are related to better QoL than rectal resection. No differences were related to surgical techniques. In the preoperative setting, the increase of RT worsened QoL while in the postoperative one, continuity of care improves QoL in pts with ostomy or post-ostomy closure.

A56

COLORECTAL CANCER UNDER 50 YEARS OLD: RETROSPECTIVE ANALYSIS FROM THE ONCOLOGY UNIT OF CARPI HOSPITAL, AUSL MODENA

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Background: There is evidence of an increasing frequency of early-onset colorectal cancer (CRC) in young individuals in several Countries, although heterogeneity has been reported in Italy. We aimed to evaluate our cohort of CRC young patients together with characteristics, symptomatology, and tumour features.

Methods: We conducted a retrospective chart review of all patients < 50 years of age at time of CRC diagnosis between January 2014 and December 2023 at the Oncology Unit of Carpi General Hospital, Italy. We collected patient demographics, clinical symptoms, and tumour characteristics.

Results: Among 829 newly diagnosed CRC patients, 56 (6.75%) were under 50 years. The median age at diagnosis was 47 years (range 21-49), with a slight male predominance (53.5%). Of these young CRC patients, 30% were overweight, 23% had a history of smoking, 20% had a family history of CRC, while 11% had previous malignancies.

At presentation, 76% were symptomatic, with the most common symptoms being rectal bleeding and/or severe anaemia (27%), changes in stool habits (21.4%), sub-occlusion (14%), and weight loss (9%). Most cancers were left-sided (68%) and advanced at diagnosis (27% stage III, 38% stage IV). Genetic mutations in BRAF, NRAS, and KRAS genes were present in 30% of young CRC patients. Notably, 72% of young CRC patients are still alive, while 28% (primarily aged 45-49 and highly symptomatic at diagnosis) died from left side CRC, most of them (62,5%) had genetic variants and any additional risk factor. Finally, the proportion of CRC patients <50 years increased from 4.9% (colon) and 3.4% (rectal) in 2014-2019 period to 9.4% and 10.6% in 2020-2023, respectively.

Conclusions: Our retrospective analysis confirmed significant increasing trend in young CRC diagnoses, particularly after the COVID-19 restrictions period. Our data revealed that a significant proportion of patients aged 45-49 years were diagnosed with advanced-stage CRC, confirming the increased frequency in the last years. While tumour biology plays a crucial role in determining the stage at diagnosis, also influencing survival outcome, clinicians should remain vigilant for CRC alarm symptoms in young patients, such as bleeding and severe anaemia, regardless of CRC family history or past malignancies. A more thorough assessment of patients' lifestyle habits, including inflammatory diet, physical activity, and binge drinking, could help to identify risk factors for early-onset CRC.

A57

COMPARISON AMONG DIFFERENT PROGNOSTIC INDEXES IN HCC PATIENTS TREATED WITH ATEZOLIZUMAB+BEVACIZUMAB: PRELIMINARY RESULTS FROM A MULTICENTER OBSERVATIONAL STUDY

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Background: Atezolizumab+Bevacizumab is one of the most active treatments for BCLC stage B and C hepatocellular carcinoma (HCC). Several scores have been used to estimate patients' prognosis. Bevacizumab clearance estimation in different tumor types was reported in a previous pharmacokinetics study. Aim of this analysis was to calculate time-to-bevacizumab clearance (TTBC) in HCC patients, to assess its role as prognostic factor and to compare its value as prognostic factor with respect to other well-known prognostic scores.

Patients and Methods: Patients with HCC treated with 1st line atezolizumab+bevacizumab were enrolled. Bevacizumab clearance and distribution volume were calculated as previously described by Kelong Han, using serum albumin, alkaline phosphatase, patient's sex and weight. TTBC was calculated by the ratio of bevacizumab distribution volume per bevacizumab clearance. Other scores used for prognosis stratification and comparison were MELD, MELD-NA, ALBI, EZ-ALBI and neutrophil-to-lymphocyte ratio (NLR). Finally, C-reactive protein (CRP) and alphafetoprotein were also used as stratification factors. Cut-off values were established by median value for normally distributed parameters or by ROC curve analysis in all other instances. Overall survival (OS) was estimated by Kaplan-Meier method and differences were compared by log-rank test. Multivariate analysis was conducted by Cox-regression. Level of statistical significance was set at $p < 0.05$.

Results: Thirty-eight patients were enrolled from 2 Italian Oncology Departments. Median TTBC was 97.75 hours (range 65.76-128.04 hours). TTBC was normally distributed. Median OS in the whole population was 14.56 months. Higher TTBC was associated with better OS (mOS not-reached vs 5.8 months, respectively, p=0.00091). ALBI score (p=0.0055), EZ-ALBI score (p=0.01), high PCR value (p=0.035) were associated with OS whilst NLR (p=0.071), alphafetoprotein (p=0.17), MELD (p=0.51) and MELD-NA (p=0.15) were not associated with OS. Multivariate analysis suggested that TTBC was the only factor maintaining an independent prognostic role (p=0.0077).

Conclusions: Our preliminary results suggest that a prognostic score based on serum albumin, alkaline phosphatase levels, patient's weight and sex, derived from a population pharmacokinetic study focused on bevacizumab clearance, might have a higher likelihood of being able to estimate prognosis of this group of patients compared to other well-known prognostic estimators.

A58

SINGLE CENTER ANALYSIS OF DNA DAMAGE REPAIR (DDR) GERMLINE MUTATIONS IN PATIENTS WITH ADVANCED PANCREATIC DUCTAL ADENOCARCINOMA (APDAC)

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Background: DDR pathway has been introduced as a new target of treatment in solid cancers, through the exploitation of synthetic lethality. The aim of the present study is to evaluate the incidence of germline mutations (GM) in DDR genes in aPDAC pts and to establish their prognostic and predictive role and their family implications.

Methods: Pts received a 26-genes Next Generation Sequencing by Sophia Genetics' multigenic panel; when the panel could not be performed only BRCA 1/2 genes were analyzed by PCR. According to test results, patients were divided into three groups: pts with pathogenic variants (PVs), pts with variants of uncertain significance (VUS) and pts with no alterations. Primary endpoints were progression-free survival (PFS) and overall survival (OS). The Kaplan–Meier method was used to estimate efficacy outcome; log-rank test and Cox-regression model were used to compare the differences, considering a statistically significant p value < 0.05.

Results: From September 2019 to August 2023, 214 pts were enrolled; 154 (72%) pts received the entire panel and 64 (28%) pts were evaluated only for BRCA 1/2. BRCA 1/2 PVs were found in 13 pts (6%), VUS were found in 19 pts (8.9%) and 182 pts (85.1%) were BRCA wt. Among 154 pts tested with the entire panel, 20 (13%) pts had a PV of one of the other 24 genes, 39 (25.3%) had a VUS and 95 (61.7%) had no GMs; the genes with PVs were: 9 (5.8%) ATM, 7 (4.5%) MUTYH, 1 (0.6%) BARD1, 1 (0.6%) PALB2, 1 (0.6%) XRCC2, 1 (0.6%) NBN. A statistically significant association emerged between cancer family history and DDR genes' alterations: 77% in PVs pts, 82% in VUS pts and 59% in pts with no GMs; p 0.005. First-line therapy mPFS was 7.8 months (CI 95% 6.7-8.8) and mOS was 14.6 (CI 95% 12.7-17). A statistically significant difference in mOS was observed between the 3 groups: PVs pts 19.5 ms (CI 95% 14.5-not reached), VUS pts 13.4 ms (CI 95% 10-19.9), pts with no GMs 14.6 ms (CI 95% 12.5-17.5), p=0.017. Platinum-based treatment was not associated neither with PFS nor OS in any of the three groups.

Conclusions: Our datas show a high incidence rate of DDR genes' GM and confirm the importance of genetic testing (where available with a multigenic test) in all PDAC pts, due to the therapeutic implications and cancer risk prevention in patients' relatives. The prognostic role of DDR GMs and the impact of VUS remain unclear.

A59

ESTABLISHMENT OF PATIENT-DERIVED TUMOR ORGANOIDS TO IN VITRO STUDY DIFFERENT SEQUENTIAL TREATMENT IN HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) is one of the most deadly cancers worldwide and its incidence is steadily increasing. Recently, immune checkpoint inhibitors (ICIs) have revolutionized the treatment of HCC and the combination of atezolizumab and bevacizumab has been shown to improve overall survival. Patient-derived tumor organoids (PDTOs) represent an unmatched model to elucidate tumor resistance to therapy, due to their high capacity to resemble tumor characteristics. We set up a model of HCC PDTO to test the efficacy of sequential treatment with clinical-approved ICIs.

Methods: We used viable tumor biopsies from patients with HCC for PDTOs in vitro culture generation. The derived models were subjected to a 6-day single treatment with lenvatinib (10 uM), cabozantinib (10 uM) or sorafenib (2uM) alone or combined with anti-PD-L1 atezolizumab (10 ug/ml). In addition, we performed sequential treatment of Atezolizumab in combination with anti-VEGF Bevacizumab (2 ug/ml) for 3 days followed by tyrosine kinase inhibitor (TKI) Lenvatinib for additional 3 days (sequence scheme: B+A – L) or following the opposite scheme (L — B+A). We then measured the effect on cell viability by MTS assay and western blot (WB) analysis.

Results: The most significant reduction in cell viability (%) was obtained with sorafenib alone (54%) as compared to cabozantinib (79%) and lenvatinib (72%) treatment alone. The addition of atezolizumab strongly affected cell viability when combined with cabozantinib, being the most synergistic overall. Both the sequence treatment of B+A–L and L—B+A were the most effective in terms of reduction of cell proliferation, with B+A—L giving the lowest percentage of cell viability (32%). Moreover, the sequence treatment of B+A — L showed the highest effect on reduction of cell proliferation pathways (EGFR, MAPK and AKT) and EMT markers (slug, snail and vimentin) and increased pro-apoptotic pathway.

Conclusions: Using PDTO as a model, we have evaluated the sequential treatment with B+A—L as a potential applicable treatment strategy for HCC patients.

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PROGNOSTIC NUTRITIONAL INDEX (PNI) IS CORRELATED WITH VITAMIN D (VITD) AND PREDICTS OVERALL SURVIVAL (OS) IN METASTATIC COLORECTAL CANCER (MCRC)

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Background: Low circulating level of vitamin D (vitD) is associated with worse prognosis in patients with mCRC. Previous studies have demonstrated that systemic inflammation reduces vitD. It remains unclear whether vitD prognostic effect is secondary to adverse cancer-related inflammation or is nutrition-based inflammation-independent.

Patients and Methods: Consecutive mCRC patients with available vitD at baseline from January 2014 to January 2024 were included in the analysis. VitD association with overall survival (OS) was analyzed using Kaplan-Meier curves, using a cut-off of 10 ng/mL obtained from previous analyses. Wilcoxon-Mann-Whitney and Chi-square test were used to evaluate significant differences in serum inflammatory or nutritional parameters (namely: neutrophil-to-lymphocyte ratio, Platelets-to-lymphocyte ratio, C-reactive protein, Prognostic Nutritional Index (PNI), Sistemic Inflammatory Index, and modified Glasgow Prognostic score), between patients with low (<10ng/ml) vs high (>10 ng/ml) vitD. The independent prognostic effect of significant variables was assessed by means of multivariate Cox regression analysis.

Results: One-hundred eighty-nine patients were included. VitD was <10 ng/ml in 37.6% of patients and it was confirmed to be a significant prognostic factor [median OS 30.8 vs 43.7 months for low vs high vitD, respectively, Hazard Ratio(HR) 1.69, 95%Confidence Interval (CI) 1.15 to 2.49, p 0.007]. Among the analyzed variables, only the nutritional variable PNI was associated with vitD deficiency (median PNI value 34 vs 37 in vitD low and high, respectively, p 0.014). Moreover, vitD lost its prognostic value (p 0.06) when entered into a multivariate Cox model with PNI. PNI demonstrated a significant and independent prognostic value (PNI > vs <40 HR 0.40, 95%CI 0.24 to 0.67, p 0.0005).

Conclusions: In our analysis, PNI is a strong prognostic factor for OS in mCRC and significantly associated with VitD. Further studies are needed to assess if the disappointing results of vitD supplementation trials are due to inadequate nutritional support of patients enrolled in these trials.

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ADJUVANT CHEMOTHERAPY AND SURVIVAL OUTCOMES IN RESECTED BILIARY TRACT CANCER: RESULTS FROM A RETROSPECTIVE MULTICENTRE ITALIAN EXPERIENCE

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Background: Biliary tract cancers (BTC) are classified as gallbladder tumours (GBC) and intrahepatic (iCCA) or perihilar and distal extrahepatic cholangiocarcinomas (eCCA). Surgery remains the only curative treatment option but less than 35% of BTC present with resectable disease. Capecitabine (CAP) is the standard for adjuvant (adj) chemotherapy (CT). We collected a retrospective multicentre Italian series of resected BTC and analysed the impact of adj CT on survival.

Methods: Main variables were ECOG performance status (PS), pre-surgical (SUR) Ca 19.9 value, type of SUR, site, histology, invasion (T), nodal status (N), vascular invasion (V) resection margins (R), grade (G). Median follow-up (FU) was estimated with reverse Kaplan-Meier (KM) approach; median RFS (RFS) and median overall survival (OS) were estimated by KM method.

Results: We included 151 all-stages BTC resected from 2005 to 2023, adj CT was given to 74 BTC. With median FU of 84.6 months (mo), overall RFS and OS were 21.9

and 30.1 mo. Lower ECOG PS was associated with longer RFS and OS (p<0.001). A pre-SUR Ca19.9 ≤ 29 was associated with longer RFS (p=0.0153) and OS (p=0.0097) in iCCA. Lower T was associated with longer RFS (p=0.0026) in iCCA and OS in iCCA (p=0.0152) and GBC (p=0.0026). N0 status correlated with longer RFS (p<0.0001) and OS (p=0.0002) only in iCCA. R0 status was associated with longer RFS in eCCA (p=0.0398) and GBC (p=0.0007), showing longer OS only in GBC only (p<0.0001). V0 status was associated with longer RFS (p=0.0087) and OS (p=0.0006) only in iCCA. Multivariate Cox regression analysis for RFS and OS was stratified for iCCA, eCCA and GBC: ECOG-PS retained significant correlation with RFS and OS in all subgroups. R0 status was correlated with longer RFS both in eCCA (p=0.0066) and GBC (p=0.032). N status was associated with longer OS in eCCA (p=0.0499) and iCCA (p=0.0419). V and T status were associated with longer OS only in iCCA (p=0.0143 and p=0.0437, respectively). Adj CT did not impact on survival except for GBC, with longer RFS (p=0.035).

Conclusions: In our series, adj CT didn't impact on OS, prolonging RFS only in GBC. ECOG-PS=0 was the strongest predictor of improved RFS and OS across all subgroups.

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EXPLORING THE ROLE OF METRONOMIC MAINTENANCE CYCLOPHOSPHAMIDE IN METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA PATIENTS

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Background: Although multidrug regimens have improved the outcomes in metastatic pancreatic ductal adenocarcinoma (PDAC) patients, their use until progression is not supported by scientific evidence of a risk-benefit advantage. Maintenance therapy aims to postpone future combination chemotherapies and to prevent treatment- and disease-related quality of life deterioration. Low-dose metronomic cyclophosphamide (mCTX) may extend disease control in PDAC patients by exerting immunomodulatory and anti-angiogenic effects.

Methods: Metastatic BRCA1-2 wild-type PDAC patients who did not show disease progression after at least six months of chemotherapy were administered 50 mg/day of maintenance mCTX. The primary endpoint was 6-month Progression Free Survival (PFS-6). PFS and overall survival (OS) were calculated from mCTX start.

Results: 77 patients were included in the analysis. After a median follow-up of 23.0 months (95% CI: 19.0-29.0), 67 patients had disease progression and 38 (49.4%) died. Median PFS was 3.2 months (range 0.6–31.0), with PFS rates of 23.3% and 11.7% at 6 and 12 months, respectively. Median OS was 19.8 months (95% CI: 13.3-27.4). OS rates were 91.4% and 66.0% at 6 and 12 months, respectively. Two patients reported Grade-3 adverse events and no Grade-4 toxicity was observed.

Conclusions: Maintenance mCTX is a promising and well-tolerated strategy to extend PFS and OS in BRCA1–2 wild-type metastatic PDAC patients who are progression-free after initial chemotherapy. Prospective validation of these findings is warranted.

Table 1. Patients' characteristics [N (%)].

	Patients 77
Age	
Median (range)	64 (34–80)
Gender	
Male	49 (63.6)
Karnofsky Performance Status	
≥90	54 (70.1)
70-80	22 (28.6)
NA[a]	1 (1.3)
Number of metastatic sites	
1	57 (74.0)
2	16 (20.8)
>2	4 (5.2)
Site of metastasis	
Liver	51 (66.2)
Lung	16 (20.8)
Peritoneum	20 (26.0)
Other[b]	13 (16.9)
Previous surgery	
Yes	21 (27.3)
No	56 (73.7)
Number of chemotherapy lines	
Median (range)	1 (1–2)
1	53 (68.8)
2	3 (3.9)
Neoadjuvant + 1	19 (24.7)

(Continued)

Table 1. (Continued)

	Patients 77
Adjuvant + I	2 (2.6)
CA19.9	
Median (range)	23 (2–7671)
≤35	53 (68.8)
>35	24 (31.2)

[a]: Not available; [b]: lymph node, ovary, muscle, brain.

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S100A FAMILY PROTEINS AS POTENTIAL BLOOD BIOMARKERS IN PDAC DIAGNOSIS

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Background: The most of PDAC patients do not exhibit symptoms until advanced stages, therefore, the identification of biomarkers for early diagnosis may really improve patients' survival. Here, by using publicly available dataset and real life cohorts of patients and healthy subjects we investigated potential biomarkers for aiding the diagnosis of individuals with PDAC.

Methods: An in silico approach was used to re-analyze single-cell gene expression data from peripheral blood mononuclear cells (PBMCs) of 16 PDAC patients and 4 healthy controls in the Gene Expression Omnibus (GEO) dataset. Differential expression analysis of genes (DEG) was conducted to perform gene set enrichment analysis (GSEA) in individual cell clusters of PBMCs from PDAC and healthy samples. Flow cytometry analysis of PBMCs from 19 PDAC patients and 10 healthy controls was used to validate protein expression of most significantly DEGs. The immune cells population predictive of diagnosis was analyzed by univariate ROC analysis with AUC greater than 0.8 and 95% CI.

Results: Single cell GSEA analysis demonstrated that S100A6, S100A8, and S100A12 were significantly upregulated in PBMCs of PDAC patients compared to healthy subjects and mainly in monocytes and DC population. Validation analysis performed in real-world cohorts of PDAC patients and healthy subjects highlighted a significant enrichment of the S100A6+ monocyte population and S100A6+ and S100A8+ dendritic cell populations in PBMCs of PDAC patients. Notably, we also found the percentage increase of activated S100A6+, S100A8+ and S100A12+ monocytes and S100A12+ plasmacytoid DCs. Preliminary univariate ROC analysis highlighted that CD11c+CD303A+S100A6+ and CD11c+CD303+S100A8+ plasmacytoid DCs, and CD14+CD86+S100A8+ activated monocytes predicted the diagnosis of PDAC with AUC greater than 0.8 and $p<0.05$.

Conclusions: Recently, S100 family proteins have emerged as potential biomarkers that can predict the onset, development, or prognosis of pancreatic cancer. Collectively, our results highlighted a role for S100A8 and S100A6, expressed in DCs and monocytes, as potential biomarkers to discriminate PDAC patients from healthy subjects. Further investigations are needed to identify the diagnostic potential of evaluating the expression of S100 proteins in PBMCs.

A64

HIGHER RISK OF GALLBLADDER CANCER COMPARED INTRA AND EXTRAHEPATIC CHOLANGIOCARCINOMA IN PATIENTS WITH PREVIOUS BREAST CANCER HISTORY

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Background: This study was based on clinical observation of possible correlation between biliary tract cancer (BTC) and breast cancer. To validate the hypothesis of a differential association of breast cancer with gallbladder cancer (GC) patients and other BTCs, both a training and a validation cohort were analyzed.

Material and Methods: Data from 1687 patients were collected and analyzed, 12% (n=204) in the training and 88% (n=1483) in the validation cohort. Patients were selected according to BTC diagnosis and secondarily to positive history of breast carcinoma. Data were extracted by applying odd radio and fisher tests to characterize each population.

Results: In the training cohort, 6.9% of the entire population (n=14/204) had a previous history of breast cancer, 9 out of 35 patients (25.7%) with GC and 5 out of 169 (2.9%) with non-GC (OR 11.35, 95% CI 3.33- 26.54, $p<0.001$). In the validation cohort, 2.9% of the entire population

(n=43/1483) had a previous history of breast cancer, 13 out of 252 patients (5.2%) with GC and 30 out of 1231 (2.4%) with non-GC (OR 2.12, 95% CI 1.12- 4.24, p=0.0219). GC patients with positive breast cancer history had higher expression of ARIDI1A (33% vs 19%, p=0.385) and MDM2 gene mutation (44% vs 14.3%, p=0.061) compared to negative history.

Conclusions: A higher association between GC and breast cancer, as compared to non-GC was observed. Future analyses are needed to better understand the correlation between hormonal levels and development of both neoplasms.

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ROLE OF NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) AND EOSINOPHIL COUNT (EOC) IN MISMATCH REPAIR DEFICIENT (MMRD) METASTATIC COLORECTAL CANCER (MCRC) TREATED WITH IMMUNOCHECKPOINT INHIBITORS (ICIS)

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Background: Recently ICIs have become a standard of care in dMMR mCRC treatment. Despite being superior to chemotherapy, around 15-30% of pts experience primary resistance. Nonetheless, no predictive factor has been identified so far in this setting. ICIs have been previously approved for melanoma treatment and some baseline pts' features, such as NLR, derived NLR (dNLR), and relative and absolute EoC have been reported as predictive biomarkers.

Material and Methods: This is a monocentric, retrospective study, aiming to assess the predictive role of NLR, dNLR, and relative and absolute EoC, in dMMR mCRC treated with ICIs. Pts with dMMR mCRC who received ICIs (antiPD1 monotherapy with pembrolizumab or nivolumab, or antiPD1+antiCTLA4 combo with nivolumab+ipilimumab) in first or subsequent lines at our institution from 2020 to 2023, and whose baseline full blood count was available, were included. Baseline NLR (ANC/ALC) and dNLR (ANC/(WBC−ANC)) were calculated and, along with relative and absolute EoC and other baseline characteristics, correlated with PFS and OS in univariate and multivariate analyses. Median values were used as cutoff. Statical significance was set at p=0.05.

Results: 35 pts were included in the analysis. 13 were females; median age was 65 yrs. 20 pts received pembrolizumab, 5 nivolumab and 10 nivolumab+ipilimumab. 25 pts received ICIs in first line. At a mFU of 24.3 months, mPFS was 30.6 months and mOS was not reached (NR). Median relative EoC was 2; 19 pts displayed a high basal value. mPFS was NR vs 19.1 months for pts with high vs low basal relative EoC. At univariate analysis, only basal relative EoC was significantly associated with PFS (p=.016). At univariate analysis, lung metastases (p=.002), age (p=.033), basal relative EoC (p=.004) and absolute EoC (p=.028) were associated with OS. At multivariate analysis none of them retained statistical significance. No significant association with tumor response was observed.

Conclusions: Basal relative EoC could represent a simple, inexpensive and readily available biomarker that could be used to help predict efficacy of ICIs in pts with dMMR mCRC. The predictive role of NLR and dNLR was not demonstrated.

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PROGNOSTIC VALUE OF NUTRITIONAL RISK SCREENING-2002 (NRS) IN METASTATIC GASTRIC CANCER (MGC) PATIENTS: A SINGLE-CENTER, RETROSPECTIVE ANALYSIS

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Background: mGC represents the third leading cause of cancer-related deaths and it is frequently associated with nutritional disorders. Malnutrition is a common multifactorial condition among cancer patients. It's estimated that 50% - 80% of them are malnourished and that lead to death in up to 20% - 40% of patients. Several studies underline the importance of a specific nutritional management for these patients from diagnosis to end-stage. Therefore the identification of novel prognostic factors represents a new field of research. NRS is a very simple tool that allows to quickly identify a risk of malnutrition; higher NRS, defined as ≥ 3, depicts malnutrition.

Materials (patients) and Methods: From February 2023 to March 2024 a total of 35 patients with mGC were treated at our Insitution. The goal of this study was to explore the correlation between NRS and Overall Survival (OS) as an independent prognostic factor in gastric cancer patients.

Main clinical-pathological variables were reported as follows: NRS High and Low, ECOG PS 0 and ≥1. Statistical analysis was performed using R, version copiatuo, packages survival, survminer, gtsummary.

Results: Among the 35 patients, a total of 22 (62.9%) males and 13 (37.1%) females were enrolled; NRS High and Low status was reported in 17 (48.6%) and 18 (51.4%) patients, respectively. More than half of patients (n=20, 57%) were in good clinical condition, defined as ECOG PS status equal to 0. In the univariate analysis, NRS status significantly predicts poorer OS (High vs Low HR 4.48, 1.05-19.2, p=0.043). Median OS numerically differs in two groups, reporting 16 (95%CI 10 - Not reached – NR) and 8 (7.5-NR, respectively. 1-year Survival Rate was 69% (95% CI 44-100) in the NRS low group, compared to 48% (95%CI 25-93) in NRS High group. Multivariate Cox analysis was performed adjusting for sex, age at diagnosis, ECOG PS; the analysis reported that NRS status and ECOG PS significantly predict poorer survival outcomes (HR 10.5, 95%CI 1.26-88.155, p=0029 and HR 4.89, 95%CI 1.004-23.85, p=0.049, presctively). Likelihood ratio test indicated statistical significance.

Conclusions: Our retrospective analysis strongly supports the role of NRS as independent prognostic factor for OS in mGC. Further prospectives trials are needed to confirm these results.

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COMPARING COMBINATION VS. MONOCHEMOTHERAPY IN LATE-ELDERLY PATIENTS WITH ADVANCED PANCREATIC CANCER: INSIGHTS FROM A SINGLE-CENTER STUDY

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Background: The incidence of pancreatic ductal adenocarcinoma (PDAC) increases with age, and is frequently diagnosed at a inoperable stage, which restricts treatment options. There is limited evidence concerning patients over 75 years old, and clinical practice often lacks clear guidance regarding the choice of first-line therapy. This retrospective study evaluates the efficacy and safety of first line polychemotherapy versus monochemotherapy in this setting.

Patients and Methods: This retrospective single-center cohort study analyzed the records of 150 patients aged 75 or older with confirmed PDAC treated with first-line chemotherapy at Piacenza General Hospital, Italy. The primary objective was to assess overall survival (OS) in elderly patients receiving first-line monochemotherapy versus combination therapy. Secondary objectives included progression-free survival (PFS) and safety. Univariate and multivariate analyses were conducted to evaluate the impact of treatment type on survival outcomes, adjusting for potential confounders such as performance status, comorbidities, and demographic characteristics.

Results: 72 patients received monotherapy while 78 underwent polychemotherapy. The majority of patients (93.3%) were administered reduced doses; within this group, 67.9% had their doses reduced by more than 80%. Most patients (80%) presented with comorbidities, predominantly hypertension and diabetes. The median survival was significantly higher in the polychemotherapy group (8.2 months, 95% CI 6.3-10.4) compared to the monotherapy (4.7 months, 95% CI 3.6-6.2), with a p-value of 0.0022. The median PFS was 5.7 months (95% CI 4.5-6.2) for the polychemotherapy and 2.8 months (95% CI 2.4-3.6) for the monotherapy, showing a statistically significant difference (p= 0.004). In the multivariate analysis, a performance status >1, high CA19.9 levels, and monotherapy were significantly associated with worse OS. Patients treated with polychemotherapy had a 37% lower likelihood of death within the year compared to those treated with monotherapy (HR 0.58 [0.38-0.87], p=0.009).

Conclusions: Polychemotherapy demonstrates a significant survival advantage over monotherapy in the late-elderly population, albeit with considerations for dose adjustments due to comorbidities and polypharmacy. Our findings support the use of polychemotherapy in late-elderly patients when feasible, balancing effectiveness and tolerability to enhance outcomes in this age group.

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PROGNOSTIC AND PREDICTIVE VALUE OF SEX IN PATIENTS RECEIVING REGORAFENIB AND/OR TRIFLURIDINE/TIPIRACIL FOR REFRACTORY METASTATIC COLORECTAL CANCER: REAL-WORLD DATA FROM THE MULTICENTER RETROSPECTIVE "RETRITA" STUDY

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Background: Sex has been linked to a variety of characteristics of colon cancer therapy and outcomes. In several areas of medicine, the relevance of sex as critical determinant of health and disease is becoming more widely acknowledged. But in the recent past, the field of cancer research has mostly been sex-blind. The aim of this real-world substudy was to evaluate sex as prognostic and predictive marker in patients (pts) receiving treatment with regorafenib (R) and/or trifluridine/tipiracil (T) for refractory metastatic colorectal cancer (mCRC). The endpoints were median overall survival (mOS), median progression-free survival (mPFS) and disease control rate (DCR).

Materials and Methods: Clinical data of pts treated with R and T between 2012 and 2023, were retrospectively collected at 17 Italian cancer centers.

Results: 1156 pts who received sequential T and R (T/R, N=261; R/T, N=155) or T (N=427) or R (N=313) alone, were retrospectively enrolled. The majority of pts were male (58.4% vs. 41.6%). In pts who were treated with sequential R and T or vice versa, we observed a significantly longer mOS in men who received R/T (17.4 months) (N=86) than in women in the R/T group (16.2 months) (N=43) and than in males (N=123) and females pts (N=80) in the T/R cohort (12.9 and 12.3 months, respectively) (95%CI= 0.51-0.96; HR=0.70; p=0.0031). In the same context, we found a significant mPFS benefit in male pts who received the R/T sequence (11.5 months) (N=90) compared to females in the R/T group (10.3 months) (N=55) and men (N=142) and women (N=100) in the T/R group (8.7 and 7.8 months, respectively) (95%CI=0.40-0.72; HR=0.53; p=<0.0001). In addition, we observed that sex had no significant impact on survival outcomes in pts treated with R or T alone (mOS 4.7-6 months; N=647; p=0.8023) (mPFS 3-3.2 months; N=706; p=0.9658). In terms of DCR, we reported that pts who received the R/T treatment sequence experienced the greatest advantage (56.4% in women vs. 49.5% of the men; p=0.25).

Conclusions: Based on our real-world subanalysis, it seems that in refractory mCRC pts, men who receive the R/T therapeutic sequence have a more extended survival time, whereas women would have better cancer growth control if they also receive R/T. Treatment options, however, also need to consider other patient's characteristics, including age, ECOG Performance Status, and metastatic sites. However, to confirm our findings, a further prospective studies would be required.

A69

FUNCTIONAL ASSESSMENT OF HOMOLOGOUS RECOMBINATION (HR) CAPACITY INTEGRATES GERMLINE MUTATIONAL STATUS IN PREDICTING RESPONSE TO PLATINUM-BASED TREATMENT IN PANCREATIC CANCER (PC) PATIENTS

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Background: Germline BRCA1/2 pathogenic mutations (and possibly germline/somatic mutations in BRCA1/2 or other HR-related genes) sensitize PC to platinum-based chemotherapy (P-CHT) and/or PARP inhibitors (PARPi). However, response to either treatment is highly variable in PC patients; moreover, to what extent different mutations in HR-related genes result in functional HR deficiency (HRD) in PC remains to be established.

Material and Methods: We explored functional HRD assessment using immunofluorescence-based detection of RAD51 nuclear foci (Cruz et al. Ann Oncol 2018; 29:1203–1210) in tissues from PC patients with known germline mutations in HR-related genes and sought for correlations between the two functional tests and response to P-CHT and/or PARPi treatment, when available.

Results: Tissues from 14 PC patients (8 females, 6 males; median age 56 yrs, range 39-70), carrying known germline

pathogenic mutations in HR-related genes (BRCA1: 3 pts; BRCA2: 6 pts; PALB2: 4 pts; RAD50: 1 pt) have been analyzed so far. The mean percentage of RAD51 foci, as measured in 5 different tumor tissue areas in each individual sample, varied from 9.8% to 79.1% (median 55 ± 22%). Eight pts were evaluable for response to P-CHT: 4 pts were classified as "responders" (1 with liver CR to I-line treatment, 2 with objective PR to neaodjuvant treatment, 1 with no recurrence after adjuvant treatment) and 4 as "non-responders" (3 with liver PD within 6 mos from the start of I-line treatment; 1 with advanced - M1 - disease at surgery and no CA19.9 decrease during neoadjuvant treatment). Median ± SD percentages of RAD51 foci were 31 ± 16% in "responders" versus 63 ± 22% in "non-responders"; these differences were statistically significant (p=0.03) by one-tailed Student's t-test and of borderline statistical significance (p=0.06) by one-way Anova test. Response to PARPi was available for only 2 of the PC patients tested; interestingly, RAD51 foci were detected in only 9.8% of the cells in the tissue from a patient with a >40-mos, ongoing response to olaparib and 71.5% of the cells in the tissue from a patient not responding to PARPi.

Conclusions: Although preliminary, these suggest that integrating functional HRD assessment may refine the predictive ability of the presence of pathogenic mutations in HR-related genes. Analysis of the correlation between RAD51 nuclear foci and putative HRD signature(s) is ongoing.

A70

MULTI-OMICS DRUG REPORPOSING APPROACH IN CMS4 COLON CANCER MOLECULAR SUBTYPE

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Background: Colon cancer (CC) is one of the most common malignancies worldwide. With the progress of sequencing technologies and bioinformatic approaches, many molecular classifications for CC were proposed. Guinney et al. proposed a transcriptomic-based molecular subtyping of CC in 4 Consensus Molecular Subtypes (CMS). Among these, the mesenchymal CMS4 subtype is associated to the poorest prognosis and therapy resistance, and shows high expression of genes related to EMT, matrix remodelling, TGFb signaling and inflammatory-related system, and a peculiar enrichment in stromal cells. In this research, we present the preliminary results of multi-omic drug repurposing approach for CMS4.

Methods: Using TCGA biolinks R package, we retrieved STAR Counts transcriptome profiling data, for COAD and READ. CMS classifier was used to determine the CMS of the samples. We separated the coding genes from the long noncoding RNAs (lncRNAs) using annotation databases generated from Ensembl. We estimated the fraction of cell populations throughout the CIBERSORTx. Features selection approach was performed both for coding genes and lncRNAs. To identify CMS and potential biomarkers, we adopted mixOmics N-integration method. Our independent validation cohort consisted of 100 patients, upon local Ethical Committee approval. Features contributing to CMS4 subtype have been extracted and used to construct drug-gene interaction network.

Results: To set-up the classification model, the DIABLO approach was used, reaching a mean AUCROC of 0.9022. Contributing features related CMS4 subtypes included 9 coding genes, 6 lncRNAs and, regarding CibersortX deconvolution, Macrophage M0 and M2. The drug-gene interaction network included 6 subnetworks centered to ALOX5, KCNMA1, AQP9, TGFB3, THBS4 and DPYSL3. The role of TGFb pathway was confirmed, as exprected by the classification. Interestingly, we found interactions with Non-Steroid Anti-Inflammatory Drugs (NSAIDs), such as Mesalazine. Moreover, THBSA gene, involved in cell-to-cell, cell-to-matrix and stromal response, could also be targeted.

Conclusions: The results of our drug repositioning approach were biologically validated, as evidenced by notable enrichment of CMS4 subtype for TGFb pathway and stromal cells. The chance to modulate the macrophagic activity in the tumor microenvironment through NSAIDs could be evaluated. Experimental validation on patient-derived organoids derived by samples from the validation cohort is ongoing.

A71

EVALUATING THE EFFECT OF LENVATINIB-RESISTANCE IN HEPATOCELLULAR CARCINOMA CELLS

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Background: Hepatocellular carcinoma (HCC) accounts for ~80% of primary liver carcinomas. HCC is the only major cancer for which there has been no improvement in mortality rates over the past 10 years. Sorafenib, a multikinase inhibitor that targets cell growth and angiogenesis, was approved in 2007 for the treatment of advanced unresectable HCC. Since then, other multikinase inhibitors have been approved. Lenvatinib has been shown to be non-inferior to sorafenib as a first-line treatment. Advances in the immunotherapy of HCC have also brought new hope

to patients, but the efficacy of these therapies remains limited. A significant proportion of patients with advanced HCC do not receive long-term benefit from systemic therapy due to primary and acquired drug resistance. In this work we aimed to identify molecular pathways involved in acquired resistance to lenvatinib in HCC cell lines.

Methods: Two HCC cell lines were selected, namely Huh-7 and SNU449. The study includes HCC cell lines in well- (Huh7) and poorly (SNU449) differentiated stages. We established Lenvatinib-resistant (LR) HCC cell lines by increasing doses of Lenvatinib (from 1 to 40 μM) and we explored drug resistance mechanisms by Western Blot (WB) analysis in 2D cultured liver cancer cells.

Results: WB analysis of the parental Huh-7 and SNU449 cell lines and the LR counterpart showed a reduction in phosphorylated EGFR in the Huh-7/LR cell lines as compared to the parental Huh-7 cell line. In contrast, there were no changes in p-EGFR in SNU449/LR in comparison to SNU449 and Huh-7. Interestingly, SNU449/LR showed the highest levels of p-AKT compared to parental SNU449 and Huh-7. Both Huh-7/LR and SNU449/LR cell lines showed an increased EMT phenotype, i.e. a decrease in E-cadherin together with an increase in vimentin and snail. These results suggest that the resistance of HCC cell lines may be due to the occurrence of EMT, regardless of the differentiation stage of the primary tumour.

Conclusions: Our work may help to identify new pathways of resistance to find new combination strategies to treat lenvatinib-resistant HCC.

A72

PHASE 2 TRIAL OF ZOLBETUXIMAB IN COMBINATION WITH MFOLFOX6 AND NIVOLUMAB IN PATIENTS WITH METASTATIC OR ADVANCED UNRESECTABLE CLAUDIN 18.2-POSITIVE, HER2-NEGATIVE GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA

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Background: Zolbetuximab, a chimeric immunoglobulin G1 monoclonal antibody, binds to claudin 18.2 (CLDN18.2) and mediates tumor cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In the pivotal phase 3 SPOTLIGHT study, first-line zolbetuximab in combination with modified FOLFOX6 (mFOLFOX6; leucovorin [folinic acid], fluorouracil [5-FU], and oxaliplatin) significantly prolonged progression-free survival (PFS) and overall survival (OS) in patients with CLDN18.2-positive, HER2-negative gastric and gastroesophageal junction (G/GEJ) adenocarcinoma. The phase 2 ILUSTRO trial is investigating the efficacy and safety of zolbetuximab, alone and in multiple combinations, in patients with CLDN18.2-positive, HER2-negative G/GEJ adenocarcinoma.

Patients and Methods: The ILUSTRO trial includes Cohorts 4A (safety cohort; enrollment complete; N=12) and 4B (expansion cohort; enrolling; approximately N=65) to assess safety and efficacy of the combination of zolbetuximab, mFOLFOX6, and nivolumab in advanced/metastatic G/GEJ adenocarcinoma in the first-line setting. Patients must have HER2-negative, CLDN18.2-positive tumors (high or intermediate expression by central immunohistochemistry). Cohort 4A assessed dose-limiting toxicities (DLTs) at 2 loading dose levels. The DLT period was defined as Days 1–14 from the first dose. A total of 12 patients were evaluated in Cohort 4A; patients received a loading dose of 800 mg/m^2 zolbetuximab (n=6) or 600 mg/m^2 zolbetuximab (n=6) with nivolumab 240 mg and mFOLFOX6 on Cycle 1 Day 1, followed by 400 mg/m^2 zolbetuximab with nivolumab 240 mg and mFOLFOX6 every 2 weeks (Days 15 and 29 of each 42-day cycle). Patients could receive up to 12 mFOLFOX6 treatments (4 cycles) and thereafter continue to receive 5-FU and folinic acid alongside zolbetuximab and nivolumab. The loading dose of 800 mg/m^2 was deemed tolerable and was selected to be administered in Cohort 4B, which is actively enrolling patients. Zolbetuximab, nivolumab, and mFOLFOX6 will be administered to patients in Cohort 4B following the same dosing schedule as was used in Cohort 4A. Efficacy endpoints include PFS, objective response rate, duration of response, and OS. Safety and tolerability, pharmacokinetics, immunogenicity, and health-related quality of life will also be evaluated. Currently, 10+ sites are recruiting in 6 countries (France, Italy, Japan, Korea, Taiwan, United States); more US sites are planned (NCT03505320).

A73

TRIFLURIDINE/TIPIRACIL PLUS BEVACIZUMAB FOR THIRD-LINE TREATMENT OF REFRACTORY METASTATIC COLORECTAL CANCER (MCRC): THE ITALIAN RESULTS OF THE PHASE 3 RANDOMIZED SUNLIGHT STUDY.

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Background: In the global phase 3 SUNLIGHT study, Trifluridine/tipiracil (FTD/TPI) plus bevacizumab (Bev) demonstrated a statistically significant and clinically meaningful efficacy improvement compared to FTD/TPI monotherapy in pre-treated patients (pts) with mCRC. Here we report the results of the Italian pts subset.

Material (patients) and Methods: The global phase 3 SUNLIGHT study enrolled pts aged ≥18 years with histologically confirmed mCRC, ECOG PS 0/1, and treated with 1-2 prior chemotherapy regimens in an advanced setting, including fluoropyrimidines, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (if medically considered) and/or anti-EGFR monoclonal antibody for RAS wild-type tumors. Pts were randomized (1:1) to receive FTD/TPI (35 mg/m^2 twice daily on days 1–5 and 8–12 of each 28-day cycle) alone or combined with Bev (5 mg/kg on days 1 and 15). The primary endpoint was overall survival (OS).

Results: Between Dec 2020 and Feb 2022, in Italy **39** pts were randomized to receive FTD/TPI + Bev (n = **20**) or FTD/TPI (n = **19**). Baseline characteristics were balanced between arms, except for primary tumor localization right /left (20% FTD/TPI + Bev *vs* 42.1% FTD/TPI), time from diagnosis of 1st metastasis to randomization <18 months/≥18months (25% FTD/TPI + Bev vs 42.1% FTD/TPI) and RAS mutant status (90 % FTD/TPI + Bev *vs* 73.7% FTD/TPI). FTD/TPI + Bev significantly extended OS over FTD/TPI, median OS was **14.5** months vs **6** months, respectively (HR, 0.33; 95% CI, 0.15 - 0.77; P=0.01). OS rates at 12 months were 57% in the FTD/TPI + Bev arm and 18% in the FTD/TPI arm.

Median progression-free survival was **9.6** months in the FTD/TPI + Bev arm and **1.9** months in the FTD/TPI arm (HR, 0.16; 95% CI, 0.07 - 0.38; P <0.001).

Grade ≥3 adverse events (AEs) were not significantly increased in the FTD/TPI + Bev arm vs the FDT/TPI arm (80% vs 63.2%). No new safety signals were noted.

Conclusions: In the SUNLIGHT study Italian sub-population, FTD/TPI + Bev provided a statistically significant and a clinically meaningful **8.5 months** improvement in OS, extending mOS up to **14.5 months**, with a **67**% reduction in the death in pts with refractory mCRC and with a predictable and acceptable safety profile.

Funding

Clinical trial information: NCT04737187

A74

PREDICTIVE AND PROGNOSTIC CHARACTERIZATION OF VIRAL HEPATITIS IN INTRAHEPATIC CHOLANGIOCARCINOMA PATIENTS

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Background: Advanced intrahepatic cholangiocarcinoma (ICC) is the second primary liver malignancy. Despite a biologically established causative role of viral hepatitis (VH), i.e. HBV and HCV infections, most epidemiological studies come from Eastern countries, characterized by higher incidence of both ICC and VH. Only few large Western cohorts exploring the association between viral VH and ICC development are available. The prognostic significance of VH in ICC is debated, and no data are available regarding a predictive role for standard first-line CT (CT1), consisting of gemcitabine +/- platinoids. VH-positivity definition is often clinically incomplete and inconsistent among studies.

Patients and mehods: Five different VH conditions, three for hepatitis B, and two for hepatitis C, were derived from laboratory and anamnestic data, and investigated in a multicentric retrospective cohort of ICC cases.

Results: Among 472 ICC patients, 139 (29.4%) to 194 (41.1%), depending on the specific VH condition considered, could be categorized according to the presence of the mentioned VH conditions. HBV and HCV prevalence were 9.3-25.3%, and 10.8-18.1%, respectively. No VH

condition showed an impact on survival, although a non-significant worse outcome was observed in some HBV-related conditions. The two HCV-related conditions were associated to lower pre-CT1 biomarkers of inflammation, markedly higher disease control (87.5% in positive patients vs 41.5% in negative patients [p 0.014], and 84.6% vs 30.0% [p 0.001], respectively), and numerically longer time-to-progression (TTP) with CT1 (*p* ns). Interestingly, no benefit on TTP was demonstrated for the addition of platinoids to gemcitabine in VH-positive patients (HR 0.77, $CI_{95\%}$ 0.41-1.45).

Conclusions: High prevalence of VH was observed in a Western cohort of patients with ICC, suggesting a role for past, resolved, HBV infection. No clear prognostic role emerged for VH, while no significant benefit of the standard doublet over gemcitabine monotherapy in VH-related ICC was demonstrated, at least in HBV-related cases.

A75

PLATELET TO LYMPHOCYTE RATIO AND PLATELET COUNT AS PROGNOSTIC FACTORS IN METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH ANTI-ANGIOGENIC AGENTS: A SINGLE CENTER EXPERIENCE

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Background: Anti-angiogenic agents represent a milestone of metastatic colorectal cancer (mCRC) pts) treatment. However, to date, no prognostic biomarkers have been validated yet. Recently, hematological parameters became of particular interest in solid tumors, including mcRC. Here, we present the results of our research in order to identify potential prognostic factors among clinical and laboratory parameters in mCRC pts receiving anti-angiogenics.

Methods: We retrospectively collected clinical and laboratory data of mCRC pts treated with anti-angiogenic drugs at the Medical Oncology Unit of Cagliari University Hospital (2018-04/2024) in order to identify a potential prognostic tool. Statistical analysis was performed with MedCalc (survival distribution: Kaplan-Meier; survival comparison: log-rank test; cut-off: ROC curves).

Results: Globally, 42 mCRC pts were included in our study. 25 were male, 17 female; 17 had a RAS wild-type tumor, 30 had a left-sided primary). 14 pts received anti-angiogenic agents in the the first-line, 15 in the second-line (4 bevacizumab and 11 aflibercept) and 13 in the first and further lines. Median OS was 31.4 months (95% CI: 18.3 -39.5).

When assessing the correlation between clinical and laboratory parameters and prognosis of the study polulation, a statistically significant improvement in overall survival (OS) was found in patients with platelet to lymphocyte ratio (PLR) equal or lower than 179.23 (31.4 months [95% CI: 20.3-47.1] versus 10.5 months [95%: CI 6.8 - 39.5], p=0.0315, HR= 0.27) and platelet count equal or lower than 360/µl (31.4 months [95% CI: 20.3-41.8] versus 10.3 months [95%: CI 6.8-10.5], p<0.0001, HR=0.0002).

Then, according to these findings, we separated pts in two prognostic groups: good prognostic group (no unfavorable variables) and poor prognostic group (≥1 unfavorable variables). We observed a trend for longer OS in patients belonging to the good prognostic group (31.4 months [95% CI: 20.3-41.8] versus 10.5 months [95% CI: 6.8 - 39.5], p=0.0521, HR=0.3166).

Conclusions: Our study showed a promising prognostic role of baseline platelet count and PLR in mCRC patients receiving with anti-angiogenic drugs in a limited population at our center. Further prospective studies with larger sample size are needed to confirm our findings.

A76

OVERALL AND PROGRESSION-FREE SURVIVAL OF PATIENTS WITH METASTATIC COLORECTAL CANCER (MCRC): A REAL-WORLD PROSPECTIVE, LONGITUDINAL COHORT STUDY ON THE CONTINUUM OF CARE (PROMETCO) – THE ITALIAN EXPERIENCE

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Background: PROMETCO is the first international, prospective, real-world study to investigate the continuum of care in patients (pts) with mCRC after two disease progressions since diagnosis.

Material (patients) and Methods: Adult mCRC pts who were willing to receive subsequent treatment were included. Endpoint data presented include Overall Survival (OS), progression-free survival (PFS), pts characteristics and treatment patterns. The following data refer to 82 patients enrolled in Italy.

Mean age (range), yrs. 68 (46-85)
Male sex, % 57,3
ECOG PS, % 0-1 63.0-34.6
<3 metastatic sites, % 93.9
Synchronous metastases, % 57.3
Metastasis site %
Liver 69.5
Lung 36.6
Other 26.8
Peritoneal carcinomatosis 15.9
Disease sidedness, % Right-Left 39 - 40.2

Results: These results represent 89% of the Italian population enrolled in the study. 57.3% of pts were RAS mutant; 35.3 % RAS/BRAF wild type; 3.7% BRAF mutant. 42.7% of pts had unknown microsatellite instability (MSI) status; 2.4% were MSI high; 3.7% were MSI low; 51.2% were microsatellite stable. Median time from mCRC diagnosis to PROMETCO inclusion was 25.8 mos. During the course of their disease, most pts had received fluoropyrimidine (100%), oxaliplatin (93.9%), irinotecan (98.8%), an anti-VEGF (78%) or an anti-EGFR antibody (39%), FTD/TPI (91.5%) or regorafenib (32.9%). 61% and 18.3% of pts had colorectal or liver surgery, respectively. For 79 pts who completed the study, mOS from mCRC diagnosis was 37.1 mos.; mOS from start of third-line treatment was 7.4 mos. Median PFS was 11.7 mos. in first-; 4.2 mos. in second-; 2.7 mos. in third- and 2.6 mos. in fourth line.

Conclusions: These data provide interesting insights on mCRC pts characteristics, survival, and treatment patterns in the Italian real-world, which are consistent with ESMO and AIOM guidelines.

Clinical trial identification: NCT03935763.

A77

ADVANCED GASTRIC CANCER: ATTRITION RATE ACROSS REGIMENS AND ASSOCIATED FACTORS

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Background: Advanced gastric cancer (GC) patients (pts) have a poor prognosis and despite the availability of novel agents, rapid clinical evolution often prevents further treatments. However, real-world data on attrition rate (AR) are scarce and clinician choice is often made on a case-by-case basis. Here we describe a single institution experience.

Methods: We retrospectively identified a cohort of consecutive GC pts treated at National Cancer Institute of Aviano between 2017 and 2023 with 1st line (1L) chemotherapy (CT), who experienced disease progression. AR for 2nd (2L) and 3rd line were calculated. Association between clinico-pathological features, treatment regimens, and AR were evaluated with logistic regression, while their independent role in predicting AR was evaluated with the Cox regression model.

Results: Overall, 122 pts were included, 73.8% male. Median age at diagnosis was 67 [58;74] years. Gastroesophageal junction cancers represented 25.8% of cases, 36.9% had signet ring cell/poorly cohesive pattern. MMR status was known for 63.1% and defective in 5.7% of pts. PDL-1 CPS was known in 20.7% and = 5 in 7.4% of cases; 15.8% had HER2 positive disease. Pts had mostly de novo metastatic disease (64.0%), while 26.1% received neoadjuvant CT and 35.2% underwent surgery. Data for 1L are shown in table 1, with an AR of 35.2%. Most pts (79.7%) received Paclitaxel-Ramucirumab as 2L, with a median Progression Free Survival (mPFS2) of 2 months and 1-year Overall Survival (OS) rate of 28.8%. AR after 2L was 65.9%. Performance status at 1L start and end were both significantly associated with 1L AR (OR 0.47 [0.25-0.87] p=0.016 and OR 0.16 [0.06-0.38] p<0.005, respectively), as were albumin levels (OR 1.10 [1.02-1.18]

p=0.013 and OR 1.12 [1.05-1.19] p=0.001). Clinical progression (OR 0.057 [0.02-0.15] p<0.005), anemization (OR 0.15 [0.04-0.59] p=0.007), Prognostic Nutritional Index (OR 1.07 [1.02-1.13] p=0.005) and Neutrophil/lymphocyte ratio (OR 0.85 [0.76-0.94] p=0.002) at 1L stop were all significantly associated with 1L AR.

Conclusions: AR is still an open issue in advanced GC. Clinical deterioration, together with worsening of biochemical markers (i.e. albumin, bone marrow function) seem to predict patients capability to receive further treatments even with the availability of newer agents. Further evaluations on larger numbers are needed.

Table 1.

	1L	1L AR	mPFS1 (months)	mOS1 (months)
Doublet CTGloba	42.6%	30.8%	5	10
Triplet CT	36.1%	31.8%	4	13
Trastuzumab+CT	13.9%	41.2%	6	13
Immuno-CT	6.6%	100%	2	4
Global	99.2%*	35.2%	4	12

*1 pt received different CT.

A78

DURVALUMAB PLUS CISPLATIN AND GEMCITABINE AS FIRST LINE THERAPY FOR ADVANCED BILIARY TRACT CARCINOMA (ABTC): A MONOCENTRIC RETROSPECTIVE EXPERIENCE

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Background: The addition of durvalumab to cisplatin-gemcitabine standard chemotherapy resulted in improved efficacy in patients with aBTC in TOPAZ1 trial. We present a real-world analysis of effectiveness and safety in patients with aBTC treated with first line chemo-immunotherapy (CHT) at our Institution.

Methods: This monocentric retrospective study included patients with aBTC treated with CHT as first-line therapy from June 2022 to March 2023. The primary endpoints were progression-free survival (PFS) and overall survival (OS); the secondary endpoints were response rates and safety. The Kaplan–Meier method was used to estimate efficacy outcome; log-rank test and Cox-regression model were used to compare the differences, considering a statistically significant pvalue <0.05. Patients were stratified according to neutrophils/lymphocytes ratio (NLR cutoff value 3) and increased AST/ALT. Next generation sequencing (NGS) was performed by TSO500HT® assay.

Results: A total of 25 patients were enrolled; mean age was 63 years, ECOG PS was 0-1, 18/25 patients had advanced disease at the time of diagnosis while 7/25 pts had disease recurrency after tumor surgery. Overall response rate was 36%; 7 pts had a stable disease as best response, with a disease control rate of 68%. At the data cutoff, median duration of follow-up was 8.3 months (CI 95%: 4.8-11.8); median PFS was 7.7 months (95% CI: 5.1-10.2) while median OS was not reached. At the univariable analysis mPFS was associated with both NLR (NLR<3: 10 [CI 95%: 6.3-13.6] vs NLR>3: 3.5 [1.8-5.3] m; p 0.003) and increased AST/ALT (10 [CI 95%: 8.4-11.6] vs 3.5 [CI 95%: 1.2- 7.6] ms; p 0.002). For 15/25 pts NGS was available; most frequent mutations were p53 (5/15 pts) and KRAS (5/15 pts) but neither of them was associated to mPFS. NGS analysis also provided TMB values: 4/13 pts had high TMB and 9/13 had low TMB; TMB did not result associated to mPFS. Any grade adverse events (AEs) occurred in 20/25 pts; grade 3/4 AEs occurred in 11/25 pts. The most common G3/4 AEs were neutropenia, anemia and fatigue.

Conclusions: The data presented in this study are consistent with the results of TOPAZ1 trial. However about a third of patients do not respond to CHT or have a short response duration. In our experience both NLR and basal elevated AST/ALT seem to be associated with an improved mPFS and a better outcome but further studies are needed. Safety profile was as expected and no patient had to interrupt treatment due to toxicity.

A79

THE POTENTIAL ROLE OF CELL-FREE DNA (CFDNA) DETECTION IN ADVANCED GASTRIC CANCER (GC): EARLY DATA FROM A PROSPECTIVE REGISTRY DATA-BASE.

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Background: GC is the 3rd tumor for mortality. More accurate prognostic and predictive factors could improve management and prognosis. Literature shows a few but promising data with liquid biopsy (LB). On May 2018 the Italian Research Group for GC (GIRCG) started a multicentric prospective observational trial for stage IV GC based on registry data-base (Mura et al. Abstract C58, Tumori Journal, Vol 109 n. 2S Oct 2023). According to every sigle centre availability, LB was allowed in order to identified circulating biomarker. As previosuly reported (Pancrazzi A et al. Glob Med Genet 2023;10:172–187), in our Intitution is ongoing a project to investigate the efficacy of next-generation sequencing (NGS) and clinical interpretation of the cfDNA levels in some solid tumor, included GC. We tested patient (pts) enrolled in GC Registry with LB.

Material and Methods: LB is executed at time 0 (T0), and 2 types of NGS panels are performed, comprising 17 genes in panel 1, which is already used in the routine tissue setting, and 52 genes in panel 2. From the 7th month after enrollment, 10 sequential LBs were performed up to the 17th month (T1 to T10). The variant allele frequency (%) and cfDNA levels (ng/mL) are measured in every plasmatic sample. All pts were staged with TC. Systemic treatment was according to AIOM guidelines.

Results.From April 2022 to April 2024 n. 12 pts underwent to LB. Female 4, male 8, median age 65 yrs, median follow-up 9 months. Due to early disease progression (PD) 5 pts were not evaluable. Two pts are waiting for data. Five pts were fully evaluable (4 female, 1 male): all HER2 neg, 1 pt CPS+ and MSI+, 1 pt CPS+ and have high changes from T0 cfDNA values during therapy: A- 1 pt T0 cfDNA 73 to 233 pg/µl at PD after 1st line, then swinging during 2nd line from 172 to 256 pg/µl (T6) with stable disease (SD). B- 1 pt T0 cfDNA 1080 pg/µl decreased in all the next evaluations until 160 pg/µl (T5) with TC showing a very good partial response (PR) during 1st line, which is still ongoing. C- 1 pt T0 cfDNA 152 pg/µl increased at T1 to 386 during 1st line, while clinical disease was PR. Next evalutations shows a continuous decrease in cfDNA until 64 pg/µl (T6). D- 1 pt T0 cfDNA 437 to 1060 pg/µl (T4) during 1st line, with PD. E- 1 pt T0 cfDNA 50 to 153 pg/µl (T3), during 1st line, with PD.

Conclusions: Early observations show that cfDNA changes, may relate to response to treatment. Enrollment of pts and data analysis will continue.

A80

PREDICTIVE FACTORS IN THE SECOND-LINE TREATMENT OF ADVANCED GASTRIC CANCER (ADG): CAN IMMUNOTHERAPY CHANGE THE FUTURE SCENARIO?

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Background: Recently, molecular biomarkers including programmed cell death ligand 1 (PDL1), microsatellite instability (MSI) and human epidermal growth factor receptor 2 (HER2) have modified the first-line treatment paradigm of AGC. The REGARD and RAINBOW trials have demonstrated an improvement in survival in the second-line setting before the advent of first-line chemo-immunotherapy. However, predictive factors are lacking in this clinical scenario.

Material and Methods: We retrospective collected medical data from patients (pts) receiving second-line therapy with ramucirumab alone or combined with paclitaxel for AGC between 2015 and 2023 at the Modena Cancer Center. Treatment effects and potential prognostic factors were evaluated by univariate and multivariate Cox proportional hazards model and by logistic regression analysis. Progression free survival (PFS) curves were estimated using the Kaplan-Meier method.

Results: Overall, 75 pts with AGC were treated with ramucirumab alone (3.75%) or in combination with paclitaxel (96.25%) as second-line therapy. The median age was 62 years. In the first-line setting, 64 pts received platinum-fluoropyrimidines doublet, while in 8 pts and 3 pts trastuzumab and nivolumab, respectively, were added to backbone chemotherapy. The median PFS to first line therapy was 6.6 months. At the univariate analysis: lower ECOG, lower systemic inflammatory index, higher prognostic nutritional index, lower pan-immune inflammation value and absolute neutrophile count (ANC) were linked to a better second-line PFS. Notably, the ANC remained the only independent prognostic factor at the multivariate analysis.

With regards to response prediction, ECOG 0 and lymphocyte/monocyte ratio were associated with the achievement of a clinical benefit. ($p < 0.001$ and $p=0.0028$)

Conclusions: Against a backdrop of a total lack of predictive factors, we identified ECOG PS and peripheral blood inflammation indices as promising predictors of treatment benefit in pts receiving ramucirumab-based regimens. Although in need of a further validation, these are readily-available and inexpensive parameters that can aid in treatment decision by selecting pts more likely to respond to second-line. Whether the advent of upfront immunotherapy may impact the efficacy of second-line therapies remains an open question to be answered in the future.

A81

NEW PREDICTIVE BIOMARKERS IN ADVANCED HEPATOCELLULAR CARCINOMA (AHCC) PATIENTS TREATED WITH ATEZOLIZUMAB PLUS BEVACIZUMAB (AB)

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Background: Currently AB is recommended as first line therapy for aHCC. However, a significant number of patients exhibit primary resistance; therefore, there is a need to develop and verify predictive biomarkers that can identify patients most likely to benefit from AB.

This study aims to evaluate the predictive impact of various hematological ratios, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), hemoglobin-to-red cell distribution width ratio (HRR), systemic inflammation response index (SIRI), and systemic immune-inflammation index (SII), in patients with aHCC undergoing AB treatment.

Methods: A retrospective analysis was conducted on clinical and baseline laboratory data of aHCC patients treated with AB at our Institute from December 2022 to December 2023. Patients were stratified into low and high score groups based on optimal cut-off values derived from the survival cut-point algorithm using the survival R package, to determine better progression-free survival (PFS). Statistical analysis included the log-rank test, and both univariate and multivariate Cox regression analyses.

Results: Overall 22 aHCC patients were enrolled, of whom 15 (68.2%) were male, with a median age of 72.6 ± 7.2 years. Liver disease etiology included viral (68.2%), alcohol (9.1%), NASH (18.2%) and multifactorial (4.5%). BCLC stages were B (31.8%) and C (68.2%). Seven patients (68,2%) had ECOG PS 1; the remaining PS 0. At the time of analysis, 18 (81.8%) patients were alive. Optimal cut-off values for better PFS were established: 0.53 for MLR, 6.08 for NLR, 312.5 for PLR, 503.82 for SII, 4.24 for SIRI, and 0.66 for HRR. High NLR (HR: 0.18; 95% CI: 0.03 - 1.06; p=0.02), high PLR (HR: 4.46; 95% CI: 0.89 - 22.31; p=0.04), and low HRR (HR: 0.14; 95% CI: 0.02 - 0.84; p=0.01) correlated with better PFS. Trends were observed for MLR (p=0.07), SII (p=0.07), and SIRI (p=0.05). Univariate analysis indicated a significant correlation between baseline HRR and PFS (HR=0.14; p=0.03). Multivariate analysis, adjusting for age, sex, ECOG score, and viral infection presence, identified high PLR (HR=2.69, adj-p=0.03) and low HRR (HR=0.106, adj-p=0.01) as independent predictors of better PFS.

Conclusions: This study is the first to identify baseline HRR as a potential biomarker for predicting PFS in aHCC patients treated with AB. These findings suggest the need for further research with larger cohorts to validate these results.

A82

FOLFOX VERSUS FOLFIRI AS SECOND-LINE (2L) TREATMENT IN PATIENTS (PTS) WITH ADVANCED PANCREATIC CANCER (APC): A RETROSPECTIVE, SINGLE-CENTER STUDY

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Background: Gemcitabine plus nab-paclitaxel and modified FOLFIRINOX are extensively used as first-line (1L) treatment in pts with aPC. However, it is still not clear which is the best 2L treatment after disease progression. Our aim was to compare survival outcomes in pts receiving FOLFOX or FOLFIRI after progression to 1L.

Methods: We selected consecutive pts with aPC, who received at least one cycle of 2L FOLFOX or FOLFIRI between 2015 and 2023. Progression-free survival (PFS) and overall survival (OS) were calculated form start of 2L and date of diagnosis, respectively, until progression, death or last follow-up, using the Kaplan-Meier method.

Results: Overall population included 83 pts. 55 pts (66%) were treated with 2L FOLFOX. Median age at diagnosis was 64 years (range, 42-78), and 15 pts (27%) underwent previous surgery with curative intent. 52 pts (95%) received 1L gemcitabine plus nab-paclitaxel, whereas 3 pts (5%) received FOLFIRI. 14 pts (25%) reported partial response (PR) as best response; 14 pts (25%) had stable disease (SD). 28 pts (34%) received 2L FOLFIRI. Median age at diagnosis was 66 years (range, 52-75) and 13 pts (46%) underwent surgery. The majority of pts (21, 75%) received 1L gemcitabine plus nab-paclitaxel; 4 pts (14%) received first-line FOLFOX, whereas 2 (7%) and 1 pts (4%) received PAXG and GEMOX, respectively. 2 pts (7%) reported a PR and 7 pts (25%) had SD. Median PFS was 8 months (95% CI, 6-12) with FOLFOX, and 5 months (95% CI, 3-10) with FOLFIRI (p = 0.255). Median OS was 24 months (95% CI, 21-31) with FOLFOX vs 26 months (95% CI, 24-45) with FOLFIRI (p = 0.864). 12-month survival rate was 79.8% (95% CI, 69.8-91.2) and 78.6% (95% CI, 64.8-95.3) with FOLFOX and FOLFIRI, respectively.

Conclusions: There was no statistically significant difference in survival (both PFS and OS) between 2L FOLFOX and FOLFIRI, although better response and disease control was achieved with oxaliplatin-based treatment. Therefore, fluoropyrimidine-based 2L treatment should be further investigated in larger prospective trials.

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MFOLFIRINOX VERSUS GEMCITABINE AND NAB-PACLITAXEL (GN) AS INDUCTION THERAPY (IT) FOR PATIENTS (PTS) WITH BORDERLINE RESECTABLE PANCREATIC ADENOCARCINOMA (BRPDAC): A RETROSPECTIVE, SINGLE-CENTER TRIAL

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Background: Current evidence supports the use of IT over upfront surgery for brPDAC. However, the most appropriate regimen is yet to be determined and both mFOLFIRINOX and GN are used in clinical practice as equally effective options. We aimed to compare their efficacy in a real-life cohort.

Methods: We selected consecutive pts from a prospectively maintained dataset who received IT for brPDAC with mFOLFIRINOX or GN between 2014 and 2024 at a single tertiary center. Overall survival (OS) was calculated from diagnosis, progression-free survival (PFS) from start of IT until disease progression (PD) resulting in inoperability, recurrence after surgery or death. The Kaplan-Meier method was used in both cases.

Results: 48 pts were included. 26 pts (54%) received mFOLFIRINOX. 15 pts (58%) in the mFOLFIRINOX group and 12 (55%) in the GN one were male (p=0.82). Median age at diagnosis was 60.5 years (IQR, 56-64) vs 70 years (IQR, 66-74; p=0.0007) in the mFOLFIRINOX and GN cohorts, respectively. Median CA 19-9 at diagnosis was 264 IU/mL (IQR 50-642) in the mFOLFIRINOX group vs 133 IU/mL (IQR 0.8-324; p=0.11) in the GN one. 13 (50%) and 15 pts (68%; p=0.20) underwent preoperative biliary stenting in the mFOLFIRINOX and GN arms, respectively. Median duration of treatment was 3 months (IQR, 2-5) with mFOLFIRINOX and 4 months (IQR, 3-6) with GN. The resection rate (RR) was 54% (14 pts) with mFOLFIRINOX and 41% with GN (9 pts; p=0.37) with an R0 rate of 71% and 44% (p=0.38), respectively. 3 pts (11%) in the mFOLFIRINOX group and 7 pts (32%; p=0.15) in the GN one underwent definitive radiotherapy, while 9 (35%) and 6 pts (27%; p=0.29) achieved PD as best response. At a median follow-up of 41 months, median OS was 31 months (95% CI, 15-46) vs 23 months (95% CI, 15-35) with mFOLFIRINOX and GN, respectively (HR 0.87; 95% CI, 0.40-1.87; p=0.72). Median PFS was 11 months (95% CI, 5-18) with mFOLFIRINOX vs 11 months (95% CI, 7-22) with GN (HR 1.14; 95% CI, 0.56-2.29; p=0.70).

Conclusions: With the limitations of a small sample size and single-center accrual, mFOLFIRINOX and GN had similar outcomes as IT in brPDAC. However, there was a positive trend in favor of mFOLFIRINOX in terms of RR and R0 rate as well as OS, the latter possibly due to the younger median age at diagnosis in this group. Prospective trials are ongoing to identify the best IT strategy.

A84

THE ROLE OF IMMUNE-INFLAMMATORY INDEXES IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (AHCC) TREATED WITH IMMUNOTHERAPY-BASED REGIMENS: A SINGLE-INSTITUTION EXPERIENCE

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Background: The efficacy of first-line atezolizumab-bevacizumab (AB) combination in patients (pts) with aHCC was established in both the phase III IMbrave150 trial and real-world analyses. Moreover, nivolumab (N) monotherapy provided sustained activity in selected patients with previously-treated aHCC. However, only a limited proportion of pts experience a durable benefit from immunotherapy-based treatments and no reliable predictive biomarkers are available to inform decision-making.

Matherial and Methods: Medical records of aHCC pts treated with immunotherapy-based regimens both in first and subsequentlines from September 2020 to September 2023 at the University hospital of Modena were reviewed and clinicopathological and biochemical parameters of potential clinical interest were retrieved. Their association with radiological response according to RECIST 1.1 criteria was evaluated using the logistic regression analysis.

Results: In total, 24 aHCC pts were included in the analysis, of whom 11 pts were treated with first-line AB and 13 pts with N in second and later lines. The median age was 64 years, 83,3% of pts were males and 70,8% of them had a ECOG PS of 0.The 96% of cases arose in a background of cirrhosis, which was of viral aetiology in 83% of pts. Macrovascular invasion was present in 50% of cases. Among pts treated with AB, partial response was obtained in 36.4% of cases, with 72,8% them deriving clinical benefit (partial response + stable disease). Among pts treated with N, we observed no objective responses, while disease stability was achieved in one third of cases. Neutrophil-lymphocyte ratio (p=0,0053), lymphocyte-monocyte ratio (p=0,0098), prognostic nutritional index (p=0,05), CRAFITY score (p=0,0226) and AFP decline (p=0,0067) were associated the likelihood of attaining a radiological response to systemic treatment.

Conclusions: In this experience, in addition to confirme the clinical activity of immunotherapy-based options in aHCC, we identified favorable inflammatory indexes predicting the benefit to AB combination and N monotherapy. Although these data are preliminary and thus in need of validation, they provide an initial base of evidence for the exploitation of blood-based biochemical parameters as potential biomarkers in aHCC.

A85

CLINICAL UTILITY OF SYSTEMIC INFLAMMATORY MARKERS AS BIOMARKERS OF BENEFIT FROM CHEMO-IMMUNOTHERAPY IN PATIENTS WITH ADVANCED CHOLANGIOCARCINOMA: A REAL-WORLD, RETROSPECTIVE ANALYSIS

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Background: Durvalumab combined with cisplatin and gemcitabine (DCG) is the new standard first-line therapy for patients (pts) with advanced cholangiocarcinoma (CCA). However, prognosis remains poor and biomarkers of benefit to identify a responsive population are lacking. Routinely assessed markers of systemic inflammation could reflect different activation status of the tumor microenvironment, which ultimately affects treatment response. We aimed to assess the association of c-reactive protein (CRP) and neutrophil-to-lymphocyte ratio (NLR) with response to chemo-immunotherapy in pts with CCA.

Material (patients) and Methods: We retrospectively analyzed pts with advanced CCA starting DCG from April 2022 to October 2023 at a single tertiary center. Patients were divided into disease control (DC+) and non-disease control (DC-) groups based on their best overall response (BOR) according to RECIST v1.1. DC+ included pts with complete response (CR), partial response (PR), or stable disease (SD), DC- pts with disease progression. CRP and NLR were measured from peripheral whole-blood samples at baseline and at BOR and analyzed using Mann-Whitney test (continuous variables) and Fisher's exact test (categorical variables according to their median value). Overall survival (OS) curves were estimated with the Kaplan-Meier method and compared with the log-rank test. Two-sided p-values <0.05 were considered statistically significant.

Results: Of the 33 pts with CCA included, 31 (94%) had metastatic disease at diagnosis, and 22 (67%) had intrahepatic CCA. DC rate was 76% (2 CRs, 7 PRs, 16 SDs) and objective response rate (ORR) 27%. Median OS was

significantly longer in DC+ vs DC-patients (13.4 vs 3.6 months, p<0.0001). Patients with DC+ had significantly lower CRP at baseline (1.08 vs 9.12; p=0.0003) and at BOR (0.77 vs 4.29; p=0.0029) and lower NLR at baseline (3.00 vs 6.80; p=0.0019) and at BOR (3.30 vs 8.50; p=0.0157). When stratified as NLR-high or low according to the median value at BOR (3.45; IQR 2.425-5.175), NLR-low was significantly associated with higher ORR (OR 0.05, p=0.04).

Conclusions: Lower CRP and NLR at baseline and BOR are associated with better disease control and NLR < 3.45 with tumor response in our real-world cohort of CCA patients treated with DCG. While our study is ongoing on a larger cohort, prospective validation of their role as predictors of response to chemo-immunotherapy in CCA is warranted.

A86

CLINICAL OUTCOMES IN ELDERLY GASTRIC CANCER PATIENTS TREATED WITH PERIOPERATIVE CHEMOTHERAPY

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Background: Managing gastric and gastroesophageal junction (G/GEJ) adenocarcinoma (ADC) in patients (pts) over 70 years old remains challenging due to the complexity in balancing treatment intensity / toxicity (tox) and the limited representation in clinical trials of older pts. Multidimensional geriatric assessment (MGA) can help to address these issues.

Methods: This is a retrospective, observational, monocentric study of pts with locally advanced G/GEJ ADC over 70 years old, who received neoadjuvant chemotherapy (NACT), at Veneto Institute of Oncology. Groups' differences were tested with X^2 or Fisher's test. Odds ratio (OR) was calculated with a logistic regression model. Survival analysis was performed with the Kaplan-Meier method.

Results: Between 2018 and 2023 45 older pts were treated with NACT, 28 (62.2%) with FLOT and 17 (37.8%) with FOLFOX, respectively. The median age of pts was 74 years (interquartile range 72 - 77), 35 (77.8%) were males, 42 (93.3%) pts had ECOG PS 0-1 and 3 (6.7%) had PS 2. Globally, MGA was performed in 29 (64.4%) pts: 21 (72.4%) were fit, 6 (20.7%) vulnerable and 2 (6.9%) frail. The majority presented a cTNM stage III (84.2%) but videolaparoscopy was performed only in 14 pts (31.1%); one case was HER2 3+ and 5 were MSI. Pts assessed with MGA were more likely to have NACT dosing reduced compared to pts who did not undergo MGA; OR was 7.61 (95% confidence interval 1.81 - 38.1, **p=0.008**). NACT dosing was reduced for 29 pts (70.7%) with a low rate of G3-4 tox: 4 pts had G3-4 hematological tox in the FLOT group and 1 in FOLFOX group (p=0.611), gastrointestinal G3–4 were found in 2 pts, both in the FLOT group, and none had G3-4 neurotoxicity. No statistical differences in tox were found between the 2 regimen groups. Prophylactic G-CSF was given in 11 (26.2%) pts. Four (9.1%) pts stopped NACT, 3 in FLOT and 1 in FOLFOX group (p=1), due to tox but all were assessed for surgery; 4 did not undergo surgery for progressive disease. Regarding MGA evaluation, all pts treated with FLOT were fit (16, 55.2%) fit except one (3.4%) while none of the 7/29 pts (24.1%) treated with FOLFOX were fit (**p = 0.007**). Median follow-up was 19.4 months. Survival data are immature, the median overall survival was not reached in the FLOT group and 23.1 months in the FOLFOX group.

Conclusions: Selecting the appropriate NACT scheme based on age, clinical status and reducing NACT dosing, guided by MGA, can prevent interruption due to toxicity and does not rule out surgery.

A87

MONOCENTRIC EXPERIENCE OF PREOPERATIVE SHORT-COURSE RADIOTHERAPY (SCRT) FOLLOWED BY NEOADJUVANT CHEMOTHERAPY (CHT) AND ROBOTIC SURGERY (RSURG) IN LOCALLY ADVANCED RECTAL CANCER (LARC): UPDATE WITH AN EXTENDED FOLLOW-UP

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Background: The results of RAPIDO and PRODIGE-23 trials changed the standard of care (SOC) in in the management of LARC. The best scheme of treatment is still object of debate. At the end of 2020, during pandemic period, we used the RAPIDO scheme of treatment (SCRT followed by CHT before surgery (SURG)) to reduce patients (pts) staying at the Radiotherapy Unit. As previosuly reported (Bloise F et al, Tumori Journal 2023 109:2_ suppl, 120-121) in our experience RAPIDO schedule was feasible and well tolerated. Most pts undergone RSUG without unexpected adverse events (AEs). High pathological complete response (pCR) and high downstaging were observed.

Material (patients) and Methods: An interdisciplinary document for the clinical management of patients (Pts) with histology confirmed diagnosis of rectal adenocarcinoma with cT4 or cN+ stage were redacted. Pts were discussed to the Multidisciplinary Oncological Group and staged with thorax-abdomen TC and MRI of the pelvis. Planned treatment: SCRT 5 x 5 Gy; CHT started 11-18 day after the end of SCRT (FOLFOX4 for 9 cycles or CAPOX for 6 cycles); SURG, according to the total mesorectal excision principles, 2-4 weeks from the end of CHT and restaging. If possible RSURG was performed. After the completion of treatment pts undergone regular follow up.

Results: From April 2021 to March 2023 16 pts started the program. Last SURG was performed in June 2023. Male n. 7, female n. 9. Median age 67 (range 39– 77) yrs. Clinical stage: T4 n.2; T3 n. 14; N+ n. 15. Distance from the anal verge < 5 cm n. 6. CHT was: CAPOX n. 14; FOLFOX4 n.2. One pts didn't complete the CHT due to haematological G3 AE. RSURG was done in 13 pts and open in 3. The planned RSURG was converted in open in 2 pts. Five pts (31%) obtained a pCR. Pathological T stage was: ypT0 n.5, ypT1 n. 1, ypT2 n. 5, ypT3 n. 5. Pathological N stage was: ypN0 15/16. Downstaging occurred in 15/16 (94%) pts. With a median follow-up of 17.5 (range 10-28) months no disease relapse or deaths occurred. No long term AEs CHT or SCRT related were reported.

Conclusions: In our experience a longer follow up confirmed the feasibility, the activity and safety of the RAPIDO schedule. Since is not defined the best SOC in LARC treatment, this strategy may be considered. A multidisciplinary discussion is mandatory to evaluate the best strategy for each pts.

A88

ACTIVITY AND SAFETY OF GEMCITABINE + DURVALUMAB COMBINATION IN CISPLATIN-INELIGIBLE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BILIARY TRACT CANCER

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Background: The combination of Cisplatin+Gemcitabine +Durvalumab was compared with doublet-chemotherapy as first-line in patients with unresectable locally-advanced/metastatic biliary tract cancer (La/mBTC) in a randomized, phase III trial, resulting in a significant improvement in Overall Survival(OS). However, evidence supporting the role of Gemcitabine+Durvalumab combination therapy in Cisplatin-ineligible patients is limited. The aim of our work was to provide early evidence on activity and safety of this combination in a real-world series of La/mBTC Cisplatin-ineligible patients.

Material and Methods: We conducted a retrospective, observational study of patients with La/mBTC, ineligible for cisplatin chemotherapy, defined by: ECOG Performance Status≥2 and/or creatinine-clearance<60 ml/min and/or CTCAE-Grade≥2 hearing loss and/or CTCAE-Grade≥2 neuropathy and/or NYHA>2. Patients were treated with first line therapy combination of Gemcitabine1000mg/mq day1,8+Durvalumab1500mg day1 every 3weeks for up to 8cycles, followed by Durvalumab 1500mg day1 every 4weeks until disease progression/unacceptable toxicities. Clinicopathological characteristics, disease control rate(DCR), PFS and safety-data were retrospectively collected and analysed.

Results: We recorded 8 patients treated from January2023 until May2024. Median age was 76years-old (range64–86), 62%were female. All patients were affected by La/mBTC: 62.5%intrahepatic cholangiocarcinoma, 12,5%perihilar cholangiocarcinoma, 25%gallbladder carcinoma. Four patients were metastatic at diagnosis, 1 patient with unresectable LaBTC, 3 patients with localised cholangiocarcinoma initially resected and then relapsed. Metastatic sites: nodes(87.5%), liver(50%), peritoneum(25%), lung(12,5%), soft tissue(12.5%). The reasons for cisplatin exclusion were: ECOG PS2(50%); NYHA>2(25%); Chronic-Kidney-Disease(CDK) IIIb-stage(12.5%); bilateral severe hearing loss(12.5%). DCR was 62.5%(all patients with

Stable Disease as best response; no partial or complete response were reported). Median PFS was 12,4months (95%confidence interval[CI] 0-27.8months). Adverse events of any grade were reported in 87,5%of patients, the most common: anaemia(37.5%), asthenia(37,5%) and immune-related diarrhoea(12,5%). The only grade3 toxicity was anaemia(12,5%). No treatment-related deaths occurred.

Conclusions: Our series provides early evidence on activity and safety of Gemcitabine+Durvalumab combination treatment in a La/mBTC patients' real-world series.

A89

NIVOLUMAB AND CHEMOTHERAPY AS FIRST-LINE THERAPY IN METASTATIC HER-2 NEGATIVE GASTRIC CANCER: REAL-WORLD DATA FROM A SINGLE INSTITUTION EXPERIENCE

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Background: The phase 3 Checkmate 649 trial has assessed the role of Nivolumab in combination with chemotherapy as the new standard of care in the first-line treatment for patients with metastatic HER-2 negative, PD-L1 CPS ≥5 gastroesophageal adenocarcinoma (GEA). This retrospective analysis aimed to evaluate the efficacy and safety of this regimen in a real-life cohort of patients treated at a single institution.

Patients and Methods: Patients who received first-line treatment with Nivolumab and chemotherapy (platin and fluoropyrimidines-based doublet) at the Medical Oncology Unit, Ospedale del Mare, Naples (Italy) for metastatic HER-2 negative, PD-L1 CPS ≥5 GEA were included in the analysis.

Results: 12 patients received Folfox plus Nivolumab as first-line treatment from November 2022 to April 2024. The main tumour and patient characteristics were: M/F: 75/25%, ECOG Performance Status 0/1: 25/75%, microsatellite stable: 100%, median PD-L1 CPS: 15 (range: 5-90). Median progression-free and overall (from the start of the first-line) survivals were 8 months (95% confidence interval: 4.3-11.6 months) and 15 months, respectively. The overall response and disease control rates were 33% and 50%, respectively. The safety profile was good and showed manageable adverse events (AEs); asthenia was the most frequent (50%, grade 1). Haematological AEs were reported in 4 patients (neutropenia grade 2 and 3: 1 and 1 patient, respectively; anaemia grade 2: 1 patient; thrombocytopenia grade 2: 1 patient). No immune AEs were reported in this cohort. No patient discontinued treatment due to toxicities.

Conclusions: Folfox plus Nivolumab's efficacy in a real-life setting aligned with the literature data. The treatment was well tolerated as first-line therapy for patients with metastatic HER-2 negative and PD—L1 CPS ≥5 GEA.

A90

CORELATION OF K-RAS MUTATION IN COLORECTAL CANCER AND THROMBOSIS/ THROMBOEMBOLISM: OUR EXPERIENCE

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Background: Patients with cancer are at high risk for subsequent venous and arterial thrombosis. The identification and integration of tumor molecular genomics into clinical assessment and risk stratification would be a major advance in the management of patients with cancer. K-ras mutation is a relatively common activator mutation, with approximately 42–52% of colorectal cancer (CRC) patients harboring a form of KRAS mutation. There are conflicting data regarding the role of k-ras mutation on the risk of venous thromboembolism (VTE) in CRC patients. To analyzed the incidence of VTE in a cohort of patients with CRC based on K-ras status.

Material and Methods: We performer a retrospective review of patients of with unresectable locally advanced and metastatic CRC and known K-ras status attended in the Medical Oncology Department of Termoli (CB). The k-ras stastus and comorbidities were collected and VTE (at scan TC or doppler) was reported. We correlated presence with Kras mutation and VTE.

Results: Thirty patients (17M/13F) were identified and included in the analysis. Overall, median age of 69 years; most had metastatic disease (80%) and cardiovascular risk factors (hypertension in 25%). On 22 patients with k-ras mutation 9 patients had VTE; on 8 patients k-ras wild type only one reported VTE. The most frequently reported event was thrombosis on central venous catheter (thrombosis of the subclavian vein); 3 patients had pulmonary embolism.

Conclusions: VTE are common in patients with CRC and represent a significant contributor to morbidity and mortality. We reported an incresead risk of VTE in CRC patients with k-ras mutation. Further studies are necessary.

B - Thoracic Cancers

B01*

ADVANCED ALK-POSITIVE NON–SMALL CELL LUNG CANCER (NSCLC) PATIENTS: REAL-WORLD TREATMENT PATTERNS AND OUTCOMES FROM THE ITALIAN BIOMARKER ATLAS DATABASE

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Background: Treatment of advanced *ALK*+ NSCLC is rapidly improving with the approval of several ALK tyrosine-kinase inhibitors (TKIs) of growing efficacy. Here we report treatment patterns and outcomes from the Italian real-world registry ATLAS.

Methods: Clinical-pathological features, treatment effectiveness and safety were retrospectively collected from the ATLAS registry.

Results: Data of 463 *ALK*+ advanced NSCLC patients receiving 1st line therapy from July 2019 to March 2024 across 37 Italian centers were analyzed. Median age was 61 years old, most patients were females (264, 57%), with adenocarcinoma subtype (447, 96.5%). 121 (26.1%) had baseline brain metastases. Overall, 431 (93%) patients were treated with 1st line ALK TKI, mostly with Alectinib (82.5%). Factors driving 1st line treatment choice were reported in 142 cases and were mainly related to drug access as first (31%) or subsequent lines (40.1%) according to regulatory indications, and to safety profile (21.8%). Among the 382 patients receiving 1st line alectinib, overall survival (OS) rate was 88.7% and 73.3% at 24 and 60 months (mo), respectively. Median progression-free survival (mPFS) was 43.1 mo (95%CI: 29.5-57.0). 11 patients out of 306 (3.6%) had brain as a new site of progression. Among the 77 patients with baseline brain metastases intracranial PFS rate was 73.1% and 59.1% at 24 and 36 mo, respectively, with an intracranial response rate of 64.7%. Grade≥3 adverse events were reported in 41(10.7%) patients and included hepatic toxicity (13, 3.4%) and asthenia (5, 1.3%). At disease progression tissue rebiopsy and/or liquid biopsy were performed in 28 (23.5%) and 20 (16.8%) cases, respectively, with ALK G1202R as the most frequent mechanism of resistance identified (11%). Out of 80 patients receiving 2nd line therapy after alectinib failure, 67 (83.8%) received lorlatinib achieving mPFS of 7.5 (95% CI: 6.2-8.8) and mOS of 26.4 mo (95% CI: 19.1-33.7).

Conclusions: These real-world data confirm the effectiveness and safety of alectinib, used as preferred upfront ALK-TKI. The recent 1st line lorlatinib approval might change this scenario. Tissue or liquid biopsy at the time of disease progression are underperformed in clinical practice, highlighting the need of a raising awareness on the importance of resistance mechanisms identification.

B02*

NSCLC PATIENTS WITH POOR PERFORMANCE STATUS RECEIVING FIRST-LINE TREATMENT IN THE IMMUNOTHERAPY ERA: AN OBSERVATIONAL, PROSPECTIVE STUDY ON CLINICIANS' ATTITUDES AND SURVIVAL OUTCOMES (PICASO STUDY, GOIRC-04-2020)

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Background: Up to 30% of patients with advanced NSCLC have an ECOG performance status (PS) 2 at diagnosis. This group of patients is often excluded from clinical trials, including those with immunotherapy. Interrogating clinicians' attitudes towards the available treatments and collecting the corresponding outcomes can provide useful evidence for the clinical practice.

Patients and Methods: We led a prospective, observational study in 20 Italian centers focused on patients with advanced NSCLC and ECOG PS 2. Patients with EGFR mutations, ALK fusions or receiving first-line targeted therapies were excluded. We recorded physicians' attitudes in addressing first-line treatments and clinical outcomes. The primary endpoint was progression-free rate at 6 months (6-mos PFR).

Results: From March 2022 to October 2023, 199 consecutive patients were included in the study. Among the 196 patients with complete information at data lock (April 30th, 2024), median age was 73 years (range 43-91), with 60% males. PS 2 was attributed to tumor burden in 175 pts (89%). 42 patients (21%) were candidate to best supportive care (BSC), 48 (24%) to mono-chemo, 14 (7%) to doublet-chemo, 40 (20%, all PD-L1 >= 50%) to anti-PD-1/PD-L1 monotherapy (IO-mono), 52 (27%) to chemo-immunotherapy combinations (chemo-IO). 80% of patients with PD-L1 >= 50% received IO-mono, and 41% of patients with PD-L1 < 50% received chemo-IO. At a median follow-up of 8.9 months, 6-mos PFR was 15.9%, with a median PFS of 1.6 months (95%CI 1.3-1.9). For 154 patients receiving active treatment, 6-mos PFS was 18.2%, with median PFS 1.9 months (95%CI 1.6-2.2). 6-mos PFR was 7.3% for BSC, 8.3% for mono-chemo, 0% for doublet-chemo, 29.6% for IO-mono, 22.9% for chemo-IO. Overall survival rate at 6 months (6-months OSR) was 28.9%, with median OS 2.8 months (95% CI 2.1-3.6). For patients receiving active treatment, 6-months OSR was 32.8% and median OS 3.5 months (95%CI 2.5-4.5). 6-mos OSR was 14.2% for BSC, 25.7% for mono-chemo, 30.1% for doublet-chemo, 41.8% for IO-mono, 33% for chemo-IO. Median OS was 4.3 months (95% CI 1.7-6.9) for IO-mono and 3.7 months (95% CI 2.8-4.6) for chemo-IO. Safety data will be presented at the meeting.

Conclusions: Less than half of patients with NSCLC and ECOG PS 2 were candidates to the regimens recommended for fit patients (i.e. IO-mono or chemo-IO according to PD-L1 expression). Even with immunotherapy, most of these patients have a poor outcome, questioning the role of active treatments.

B03*

ALECTINIB AS NEOADJUVANT TREATMENT IN POTENTIALLY RESECTABLE STAGE III ALK-POSITIVE NSCLC: INTERIM ANALYSIS OF ALNEO PHASE II TRIAL (GOIRC-01-2020-ML42316)

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Background: The role of neoadjuvant alectinib in stage III ALK-positive Non-Small Cell Lung Cancer (NSCLC) is still unclear. We designed a phase II, open-label, single-arm, multicenter study aimed at investigating the activity and safety of alectinib in potentially resectable locally advanced stage III ALK-positive NSCLC patients (ALNEO trial, EUDRACT number 2020-003432-25).

Methods: Treatment-naïve patients with potentially resectable stage III ALK-positive NSCLC, ECOG PS≤1 were registered to receive neoadjuvant alectinib for 2 cycles (8 weeks) followed by surgery and adjuvant

alectinib for 24 cycles (96 weeks). The primary endpoint was major pathological response (MPR). Secondary endpoints included pathological complete response (pCR), objective response (OR), event-free survival (EFS), disease-free survival (DFS), overall survival (OS), adverse events (AEs). According to the Simon's two stage design (P0=20%, P1=40%), an interim analysis was conducted to test if at least 5 major pathological responses (MPR) were documented among the first 18 enrolled patients.

Results: To date, the results are available in 25 patients registered in 20 Italian Oncology Centers from May 2021. Median age was 56 years (Interquartile Range [IQR], 49–67 years), 17 (68%) patients were female and 14 (56%) were never smokers. Clinical stage according to the 8th AJCC TNM was IIIA in 14 (56%) and IIIB in 11 (44%) patients. All the patients completed the neoadjuvant phase and 21 (84%) underwent surgery, which consisted of lobectomy in 17 (81%), pneumonectomy in 2 (9.5%) and other surgery in 2 (9.5%) patients. Among patients who completed surgery, R0 was achieved in 18 (86%) patients. Overall, an OR was observed in 17 of 25 (68%) patients. In the interim analysis population, MPR was achieved in 7 (39%) patients and pCR in 3 (17%) patients. Presently, adjuvant treatment was started in 17 (68%) patients with a median interval from surgery of 5.1 weeks (IQR, 2.7–6.0 weeks). After a median follow-up of 10.8 months (IQR, 5.6–22.5 months), median EFS, DFS and OS were not reached. None of the patients experienced treatment-related Grade≥3 AEs during neoadjuvant phase.

Conclusions: Results of the first stage interim analysis allowed to continue the accrual in order to reach the total of 33 planned patients. Neoadjuvant alectinib appeared to be safe in potentially resectable locally advanced stage III ALK-positive NSCLC patients. The study is partially supported by Roche S.p.A.

B04

PROGNOSTIC SIGNIFICANCE OF CIRCULATING TUMOR CELLS NUMBER AND PHENOTYPE IN A COHORT OF EARLY STAGE NON-SMALL-CELL LUNG CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY

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Background: Platinum-based neoadjuvant chemotherapy (pb-NACT) is the mainstay of treatment for early stage non-small-cell lung cancer (esNSCLC), although with limited overall survival (OS) benefits. Preclinical evidence from NSCLC models showed that cell damage caused by cisplatin activates the SDF-1/CXCR4 axis, leading to the recruitment of metastasis initiating cells (MICs), a pro-metastatic cell subset co-expressing the stemness marker CD133 and CXCR4 (SDF-1 receptor). Through the longitudinal monitoring of circulating tumor cells (CTCs) in esNSCLC patients (pts) treated with pb-NACT, we aim to evaluate the potential prognostic significance of CTCs number and phenotype.

Patients and Methods: From February 2019 to May 2024, 73 esNSCLC pts deemed surgical candidates after pb-NACT (stage II-IIIB) were enrolled in the study. Blood samples were collected at baseline (T1), after pb-NACT (T2) and after surgery (T3) for CTCs enumeration and characterization for CXCR4 and CD133 markers (total CTCs, CXCR4+CTCs and MICs), using a validated marker-independent strategy combining Parsortix® and DEPArray™ technologies. The association between CTCs and response to pb-NACT [(Disease Control Rate (DCR), Overall Response Rate (ORR)] was evaluated through logistic regression models, while the association with survival endpoints [event free survival (EFS), disease free survival (DFS), OS] was assessed through Cox-regression models.

Results: Of 73 enrolled pts, 47 had CTCs available for analysis. Within this population, DCR was 72.3% and ORR was 36.2%. Surgery was performed in 23 out of 47 (48.9%) pts. With a median follow-up of 36.4 months, a higher number of all CTC subsets at T1, particularly CXCR4+CTCs, was associated with inferior DCR (OR 0.01, p=0.03) and ORR (OR 0.12, p=0.02), as well as shorter EFS (HR 4.5, p<0.01) and OS (HR 5.1, p<0.01). All CTC subsets negatively correlated with EFS (HR 1.9, p<0.01) and OS (HR 2.0, p=0.01) at T2. Among the 21 pts who underwent surgery and had available CTC data at T3, an increased number of CTCs, especially CXCR4+CTCs and MICs, appeared to be correlated with inferior DFS.

Conclusions: CTCs may represent a novel biomarker for monitoring chemotherapy efficacy in NSCLC. An increased number of CTCs baseline and after pb-NACT, as well as after surgery represent a negative prognostic factor for survival. A higher number of CXCR4+CTCs at baseline correlated with inferior response outcomes after pb-NACT, prompting consideration for treatment intensification in pts with higher baseline levels of this CTC subtype.

B05

BRAF-MUTANT METASTATIC NON–SMALL-CELL LUNG CANCER: REAL WORLD DATA FROM THE ITALIAN BIOMARKER ATLAS DATABASE

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Background: *BRAF*mutations identifies a subgroup of oncogene addicted non-small cell lung cancer (NSCLC) patients (pts). Dabrafenib/trametinib (D/T) combination is associated with high response rates and durable anti-tumor activity in *BRAF*-V600-mutants, albeit the optimal sequence with immunotherapy-based therapies, the prognostic role of patients and disease-related factors and the efficacy in pts with brain metastases (BMs) still remain debatable. Here we report outcomes among advanced *BRAF*-mutant NSCLC pts from the Italian ATLAS registry(https://biomarkersatlas.com).

Methods: Retrospective data were collected and analyzed using ATLAS, a web-based platform created to collect clinical and molecular data on NSCLC pts among Italian centers. *BRAF*-mutated NSCLC pts diagnosed from 2019 to 2023 in 18 Italian centers were enrolled.

Results: A total of 244 *BRAF*-mutated NSCLC pts were enrolled, including 70% of V600E mutations, 27.5% non-V600E mutations (G466A, G469A, G464A; D549G, K601E, and others) and 2.5% non-otherwise specified *BRAF*mutations. D/T was used as 1stline therapy in 79.5% of BRAF-V600E-mutated pts and as 2stline in 5% of non-V600E BRAF mutated pts. Median progression-free survival (mPFS) of first line D/T was 19.8 months (mos) (95% CI: 10.3-29.3), with a 2-year (2-yr) overall survival (OS) rate of 64.9%. PFS2 in these pts was 6.6 mos (95% CI: 0-14.3). Non-targeted 1stline treatment was associated with 12 mos mPFS (95% CI: 4.3-19.7) and 77.1% 2-yr OS rate. Among 66 pts treated with 2ndline therapy, mPFS was not reached with D/T (1-yr PFS rate: 69.3%) as compared with 10.5 mos with other treatments. 2-yr OS rates were 100% with D/T and 45.9% with other treatments, respectively. Among pts with BMs (11.8%), 1stline D/T was associated with a 9.2 mos mPFS (95% CI: 0.8-17.6) and 2-yr OS rate of 49.5%. The activity of D/T differs among selected subgroups, including sex (mPFS was 13.6 mos and 25.3 mos and 2-yr OS rate were 54.9% and 72.3% in males and females, respectively) and smoking status (mPFS was 18.4 mos, 25.6 mos and 24 mos in never, former and current smokers, respectively).

Conclusions: This large retrospective study confirms the efficacy of D/T in *BRAF*V600E mutants in a real-world setting, with a sustained activity in treatment-naïve pts, including those with BMs. Activity of immunotherapy w/o chemotherapy in *BRAF*-mutants either as first line or after D/T among PD-L1 level and molecular subgroup is under evaluation.

B06

LONG-TERM SAFETY AND EFFICACY OF IMMUNE-CHECK POINT INHIBITORS TREATMENT BEYOND 24 MONTHS IN REAL-WORLD ADVANCED NSCLC PATIENTS: INSIGHTS FROM THE I-STOP STUDY

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Background: Data on the optimal duration of immune-check point inhibitors (ICI) treatment for advanced NSCLC (aNSCLC) are limited, particularly in real-world (RW) settings. The right duration of ICI treatments is not clearly established so far and may differ in clinical practice, as no predictive biomarkers exist to guide the decision to stop treatment or continue until disease progression or the onset of unacceptable toxicity.

Methods: I-STOP is an ongoing observational, multicenter, retro-prospective study focusing on aNSCLC patients (pts) treated with single-agent ICI for a minimum of 24 months across 17 centers in Italy. Cohort 1 (C1)

consists of pts who, based on clinical decisions, continued treatment beyond 24 months, while Cohort 2 (C2) comprises pts who halted treatment at the 24-month mark. One loco-regional procedure was allowed for oligo-progressive disease (PD). The objective of the study is to evaluate the safety and efficacy in both cohorts.

Results: As of May 2024, 137 pts were enrolled. Most received ICI as a second or subsequent line (59.8%); 36 (26%) received radiotherapy for oligo-PD during the first 24 months, and 45 (32.8%) had ECOG PS =2. 106 (77.4%) pts continued ICI after 24 months (C1), 31 (22.6%) discontinued (C2). No statistically significant difference in progression-free survival (PFS) was found between the two cohorts (p=0.3; mPFS not reached in both cohorts) nor between the rates of disease progression (PD). After 24 months, 12 pts (11.9%) in C1 and 2 (6.4%) in C2 underwent radiotherapy for oligoprogression. No statistically significant difference was found in Overall survival (OS) between C1 and C2 (p=0.07, mOS not reached in both cohorts). Among the baseline characteristics considered (smoking status, performance status, presence of liver or brain metastasis, PD-L1 expression, presence of KRAS mutation, neutrophil/lymphocyte ratio), none correlated with improved outcomes in either cohort. In C2, 3 pts (10.3%) had ICI rechallenge after PD, achieving complete remission (CR) in 2 cases and stable disease (SD) in 1 case, with a median duration of response of 28.4 months. No grade 3-4 events were reported after the 24-month treatment, and no patient discontinued treatment due to irAEs in C1 after 24 months.

Conclusions: In this RW population, ICI demonstrated effectiveness beyond 24 months irrespective of discontinuation. No unexpected serious AEs rate emerged. Enrollment is still ongoing to better assess differences between the two cohorts.

B07

TIME TO ACCESS TO TREATMENT AND OUTCOMES OF LUNG CANCER (LC) PATIENTS (PTS) WITHIN AN ITALIAN COMPREHENSIVE CANCER CENTER

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Background: Timely management of Pts with suspected LC is a critical requirement of cancer hospitals, but few data are available regarding the outcome of LC Pts based on time span from symptom onset to diagnosis (time-to-biopsy; TTB) and treatment start (time-to-treatment; TTT). Our analysis aims at assessing effects of earlier diagnosis and identifying subgroups of Pts that may benefit more in terms of overall survival (OS).

Matherial and Methods: We retrospectively assessed symptomatic LC Pts submitted to clinical oncologists of an Italian Comprehensive Cancer Center excluding incidental findings of LC and Pts who had already received treatments before oncological evaluation. Differences in terms of TTB and TTT across sub-groups were assessed through Mann-Whitney. Secondly, we compared OS of stage IV LC Pts divided into TTB quartiles.

Results: 392 consecutive Pts were included, with the following characteristics: Median age: 71 years; males/females: 232/160; ever smoker vs. never smoker: 324 vs. 53 (+15 unknown); ECOG PS: 0: 142; 1: 165; 2: 62; 3: 13; 4: 1; unknown: 9; Stages: Non-metastatic (II-III): 93; metastatic: 293; unknown: 6. Median time from first symptom to diagnostic report was 56 days, while median TTT was globally 108 days and 94 days for stage IV Pts (n=194). No significant differences in OS were observed across TTB quartiles for stage IV Pts (P=0.7807).

Conclusions: Longer time to biopsy was associated with worsening of the first occurring symptom, shedding light on the relevance of an early recognition of possible cancer-related symptoms to prevent their worsening before diagnostic procedures. Also, non-metastatic LC is associated with a longer TTB and TTT, possibly due to a more complex differential diagnosis and reduced perception of urgency. For stage IV Pts, TTB did not impact OS. Data collection is ongoing and Pts with incidental findings of LC and Pts treated with upfront radical approaches will be included in subsequent analyses.

Characteristic	TTB (days)	P	TTT (days)	P
Age ≥70 vs <70 years	65 vs 49	0.2381	105 vs 103	0.5749
Male vs Female	63 vs 51	0.4861	108 vs 90	**0.0427**
Ever smoker vs never smoker	53 vs 83	0.0647	104 vs 136	0.0748
Worsening of first symptom (yes vs no)	84 vs 48	**<0.0001**	138 vs 96	**0.0003**
ECOG PS 0-1 vs 2+	61 vs 47	0.1336	105 vs 83	0.2285
Metastatic vs non-metastatic disease	48 vs 81	**0.0013**	96 vs 134	**0.0002**

B08

PHASE 1B STUDY OF TELISOTUZUMAB VEDOTIN (TELISO-V) AND OSIMERTINIB IN PATIENTS (PTS) WITH ADVANCED EGFR-MUTATED (MUT), C-MET OVEREXPRESSING (OE) NON-SMALL CELL LUNG CANCER (NSCLC): FINAL EFFICACY AND SAFETY UPDATES

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Background: Clinical evidence supports c-Met as target in pts with advanced EGFR-mut NSCLC after progression on osimertinib(O; 3rd-generation EGFR-TKI). We report final results of Teliso-V(T; 1st-in-class c-Met–targeting ADC)+O combination arm of phase 1b study(NCT02099058) in pts with advanced/metastatic EGFR-mut, c-Met OE NSCLC with progression on prior O.

Methods: Pts(=18 yr) with advanced/metastatic EGFR-mut, c-Met OE(centrally assessed by IHC[Clinical Trial Assay]: 3+ in=25% tumor cells) NSCLC with progression on O received T(IV Q2W 1.6 or 1.9mg/kg)+O(oral 80mg QD). Pts in expansion phases had=2 prior lines(L) of therapy, including O.

Results: As of March 23, 2023, 41 pts were enrolled. Data for 38 pts with sufficient follow-up are shown(T [1.6mg/kg, n=20; 1.9mg/kg, n=18]+O); median age was 60yr; 40/42/18% of pts received 1/2/>2 prior L for metastatic NSCLC, including platinum-based therapy in 47%. Median number of T cycles(28 d/cycle) was 6(range, 1–30). No DLTs were observed in safety evaluation cohorts. AEs possibly related to T occurred in 37(97%; any grade[G]) pts; most common(=20%) were peripheral sensory neuropathy(50%), peripheral edema(21%) and nausea(21%). Of these, G=3 were reported in 12(32%) pts; most common(=5%) were anemia(11%) and peripheral motor and sensory neuropathy(5% each). AEs leading to T discontinuation/interruption/reduction occurred in 24/58/37% of pts. No deaths related to T or O were reported. Table shows overall T+O efficacy.

Conclusions: T+O showed tolerable safety and encouraging efficacy in pts with EGFR-mut, c-Met OE NSCLC with progression on O, regardless of MET amplification status or number of prior L, with ORR of 53/50% and DCR of 71/76% as per investigators/ICR. T+O may be a potential option for these pts and warrants further clinical investigation.

Table shows overall T+O efficacy**.**

Table.

		N=38	
		Per investigator	**Per ICR**
ORR,*n/n(%)†		20/38(53) [36,69]	19/38(50) [33,67]
Dose,mg/kg	1.6	11/20(55) [32,77]	10/20(50) [27,73]
	1.9	9/18(50) [26,74]	9/18(50) [26,74]
*MET*amp‡	Yes	3/6(50) [12,88]	4/6(67) [22,96]
	No	10/21(48) [26,70]	6/21(29) [11,52]
No. of lines of prior therapy	1	7/15(47) [21,73]	8/15(53) [27,79]
	2	9/16(56) [30,80]	8/16(50) [25,75]
	>2	4/7(57) [18,90]	3/7(43) [10,82]
DCR,*n/n(%)†		27/38(71) [54,85]	29/38(76) [60,89]
Median DOR, mo†		8.0 [5.6,NR]§	NR [5.6,NR]¶
Median PFS, mo†		6.8 [5.3,9.2]#	7.4 [5.4,NR]**
PFS(%) at 4, 6, 8, 12 mo		75, 51, 35, 25	78, 63, 48, 48

*RECIST v1.1. All PR;†95% CI;‡FISH data missing for 11 pts; No. events/No. pts censored:§9/11;¶3/16;#24/14;**17/21.

B09

PATHOLOGICAL RESPONSE TO NEOADJUVANT TISLELIZUMAB (TIS) PLUS PLATINUM-DOUBLET (PTDB) CHEMOTHERAPY (CT) IN RESECTABLE STAGE II-IIIA NSCLC PATIENTS (PTS) IN THE PHASE 3 (PH3) RATIONALE-315 TRIAL

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Background: Neoadjuvant (NA) CT with anti-PD-(L)1 mAb has shown promising major pathological response (MPR) and pathological complete response (pCR] rates in pts with resectable NSCLC. The Ph3 RATIONALE-315 study (NCT04379635) investigated the efficacy and safety of NA TIS (anti-PD-1 mAb) or placebo (PBO) + CT, then adjuvant TIS or PBO, in pts with resectable stage II-IIIA NSCLC.

Material (Patients) and Methods: This study enrolled pts with treatment (tx)-naïve, resectable, confirmed squamous (sq) or non-sq (nsq) stage II-IIIA NSCLC who were eligible for PtDb CT, with no known *EGFR* mutation (nsq) or *ALK* gene translocation (sq & nsq). Pts were randomized (1:1) to 3-4 cycles of TIS 200 mg IV Q3W or PBO, + PtDb CT, followed by surgery + 8 cycles of adjuvant TIS 400 mg IV Q6W or PBO. Primary endpoints: MPR rate + EFS per RECIST v1.1 by blinded independent review committee (IRC). Key secondary endpoint: pCR rate.

Results: As of 20 Feb 2023 (median follow-up: 16.8 mo), 453 pts (TIS + CT, n=226; CT, n=227) were randomized (ITT population). Of 452 (99.8%; n=226 both arms) pts treated in the NA phase, 421 (92.9%) completed NA tx (TIS + CT, n=211 [93.4%]; CT, n=210 [92.5%]); 90 (19.9%) did not undergo surgery (TIS + CT, n=36 [15.9%]; CT, n=54 [23.8%]). Efficacy and safety data from the NA phase are summarized in the table; MPR and pCR rates were significantly improved with TIS + CT vs CT (P<0.0001). TIS + CT did not impact the feasibility of surgery.

Conclusions: TIS + CT showed clinically meaningful and statistically significant improvements in MPR and pCR rates vs PBO + CT as NA tx, and was manageable in pts with resectable stage II-IIIA NSCLC. These data support TIS + CT as a novel tx option for these pts.

Table.

Efficacy	**TIS + CT**	**CT**
	ITT Analysis Set	
	n=226	**n=227**
MPR, % (95% CI)[a]	56.2 (49.5-62.8)	15.0 (10.6-20.3)
Difference, % (95% CI); *P* value[b]	41.1 (33.2-49.1); *P*<0.0001	
OR (95% CI)	7.5 (4.8-11.8)	
pCR, % (95% CI)	40.7 (34.2-47.4)	5.7 (3.1-9.6)
Difference, % (95% CI); *P* value[b]	35.0 (27.9-42.1); *P*<0.0001	
OR (95% CI)	11.5 (6.2-21.5)	
Safety[c]	**Safety Analysis Set**	
TEAEs	**n=226**	**n=226**
	n (%)	
Pts with ≥1 TEAE	224 (99.1)	225 (99.6)
Grade ≥3	157 (69.5)	148 (65.5)
Serious	25 (11.1)	24 (10.6)

[a]Assessed by IRC.
[b]1-sided.
[c]Randomized pts who received ≥1 dose of any study drug; OR, odds ratio; TEAE, treatment-emergent adverse event.

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B10

PROSPECTIVE EVALUATION OF SYSTEMIC NUTRITIONAL STATUS AND BODY COMPOSITION IN PATIENTS WITH ADVANCED NSCLC TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background: Patients' (pts) nutritional status appears to impact on the immune cells' ability to fight tumor cells. We aim to investigate how body composition (BC) and nutritional status relate to prognosis in pts receiving immune checkpoint inhibitors (ICIs) for advanced non-small cell lung cancer (NSCLC).

Methods: From June 2021, we enrolled in a prospective monocentric trial pts with advanced NSCLC treated with ICIs +/- chemotherapy. Pts' nutritional status at baseline was evaluated using CONUT score, SARC-F questionnaire and median daily fiber intake. Comprehensive BC evaluation was assessed by body mass index (BMI) and bioelectrical impedance analysis (BIA). Data were correlated to progression-free/overall survival (PFS/OS). The predictive accuracy of the baseline parameters for 6-months PFS was assessed using receiver operator characteristic (ROC) analysis and the area under the curve (AUC).

Results: Among 69 pts enrolled, median age was 72 years-old (range 45-88), 81% (N=56) were male, 94% (N=65) had an history of smoking, 74% (N=51) had adenocarcinoma histology, 85.5% (N=59) were treated with ICIs in first line, 63.8% (N=44) as monotherapy, 92.8% (N=64) had an Eastern Cooperative Oncology Group Performance Status of 0-1, 43.5% (N=30) had PD-L1= 50%. At a median follow up of 19.8 months (95%CI 13.7-27.9), compared to those with high CONUT score (>4) and poor nutritional status, pts with low CONUT score (≤4) had longer PFS (HR 0.4, 95%CI 0.22-0.7, p<0.001) and longer OS (HR 0.38, 95%CI 0.2-0.72, p=0.002). Compared to pts with bad daily fiber intake (<20 gr), pts with appropriate fiber intake had longer PFS (HR 0.52, 95%CI 0.29-0.95, p=0.03), and numerically longer OS (HR 0.52, 95%CI 0.26-1.05 p=0.07). Pts with low risk of sarcopenia (SARC-F questionnaire score <4) had longer OS (HR 0.34, 95%CI 0.16-0.73, p=0.004), compared to those with a higher risk. Non-sarcopenic pts with high skeletal muscle index (SMI: skeletal muscle/height^2) (=8.9 for males, =6.4 for females) assessed by BIA had longer PFS (HR 0.4, 95%CI 0.2-0.78, p=0.006), and longer OS (0.32, 95%CI 0.15-0.68, p=0.002) compared to sarcopenic pts defined by low SMI. The AUC value for 6-months PFS, considering: CONUT score, daily fiber intake, SMI and SARC-F, together with PD-L1, was 0.77 (sensitivity=0.73, specificity=0.77).

Conclusions: A good nutritional status and skeletal muscle mass at baseline show up to be a valuable predictor of improved clinical outcomes in advanced NSCLC pts receiving ICIs.

B11

SMARCA4 DEFICIENCY IDENTIFIES ONCOGENE-ADDICTED NSCLC WITH POOR OUTCOMES

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Background: MARCA4 (also known as BRG1) mutations account for 5-7% of molecular alterations in non-small cell lung cancer (NSCLC), especially in lung adenocarcinoma. BRG1 immunohistochemistry (IHC) loss has been associated with smoking history and worse outcomes, although solid data are still lacking especially in oncogene addicted patients (pts). Here, we show preliminary data on the prevalence and clinical features of BRG1 deficient(d) NSCLC.

Material and Methods: This is a retrospective single-center analysis of consecutive pts with stage III/IV NSCLC treated with first-line systemic therapies between 2018 and 2021. The lack of adequate histological material for IHC analysis and the unavailability of follow-up data at 12 months were the main exclusion criteria. IHC analysis was performed with an antibody against BRG1 (EPNCIR111A clone, Abcam). The primary objectives were to compare first-line treatment efficacy by progression-free survival (PFS) and overall survival (OS) in pts with/without BRG1 deficiency. Secondary objectives were BRG1 association with other clinically meaningful molecular alterations and clinical outcomes in specific molecular-defined subgroups. All survival outcomes were estimated with the Kaplan-Meier method.

Results: In total, 134 pts were considered, mostly adenocarcinoma (71.6% *n*=96). Among these, 56.7% (*n*=76) were men and 51.4% (*n*=69) had a smoking history. EGFR and KRAS resulted the most frequent driver mutations, respectively 32.0% (*n*=43) and 11.9% (*n*=16), followed by ALK and ROS-1 rearrangements, both 3.7% (*n*=5). Chemotherapy with/without immunotherapy (IO) was the most used first-line regimen for wild-type pts, 45.5% (*n*=61), followed by IO alone, 14.9% (*n*=20) according to PD-L1 expression. Front-line tyrosine kinase inhibitors (TKIs) were used in the 39.5% (*n*=53) oncogene-addicted pts. In total, 13.4% (*n*=18) resulted as BRG1d. Sex and smoking habits did not correlate to BRG1. In the overall population, BRG1 did not show a significant correlation with PFS or OS. Nonetheless, in oncogene-addicted NSCLC pts treated with TKI (mostly EGFR mutant), BRG1d pts showed a significantly worse PFS with a mPFS of 12.2 vs 23.6 months (*p*=0.015).

Conclusions: Our results show that BRG1d oncogene-addicted pts may be characterized by worse response to first-line TKIs. Additional studies are required to validate this observation, given the limited sample size our cohort.

B12

MULTI-OMIC PROFILING FOCUSED ON AKKERMANSIA MUCINIPHILA IN ADVANCED NON-SMALL CELL LUNG CANCER DURING IMMUNOTHERAPY-BASED TREATMENT

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Background: Biomarkers of response to immune checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) are critically needed. Previous studies have demonstrated that the relative abundance of fecal Akkermansia muciniphila (Akk) is associated with clinical benefit, defined by response rate and survival.

Material and Methods: Patients (pts) with advanced NSCLC amenable to upfront ICI, +/- chemotherapy (CT), were prospectively enrolled between June 2021 and March 2024 at Gustave Roussy (NCT04567446). Stool (n=182) and blood (n=202) samples were collected at two different time points: before starting ICI (T0) and after 2 cycles of ICI (T1). Metagenomics (MGS) analyses were used to determine the prevalence and relative abundance of Akk in stool samples. Anti-Akk IgG and IgA antibodies were assessed by flow cytometry and ELISA/VIDAS assays were performed on fresh blood to characterize memory T_H17 (IL17) and T_H1 (IFNg; after 22h stimulation by pasteurised Akk) responses. Objective Response Rate (ORR) and Progression-Free Survival (PFS) were assessed.

Results: Among 104 pts with advanced NSCLC, 72% were treated with ICI+CT and 28% with ICI alone. The median follow-up and PFS were 14.6 months (mo) and 9.15 mo, respectively. MGS analyses on 59 pts showed that Akk+ pts (36%) tended to have longer PFS than Akk- pts (64%). After categorizing pts by relative abundance - Akk^{hi} (>4.799), Akk^{lo} (=4.799), or Akk^{0} (absence of Akk)-, we found both Akk^{hi} and Akk^{0} pts demonstrated a significantly higher proportion of progressive disease (PD) compared with Akk^{lo} (p=0.001). Furthermore, Akk^{hi} pts had a significantly shorter PFS (p=0.020). Among pts with longitudinal MGS data in the ICI+CT subgroup, 59% showed no change in Akk group, while 41% presented a shift from Akk^{0} to Akk^{lo} between T0 and T1. Moreover, high levels of IgG anti-Akk tended to be correlated with higher rates of PD (p= 0.2779) and shorter OS (p=0.065). Interestingly, pts who lacked T_H1 and T_H17 memory T cell responses against Akk also had significantly better PFS (p=0.02 / p=0.033, respectively).

Conclusions: These findings suggest that immune responses targeting a clinically relevant and immunogenic commensal (such as Akk) can be deleterious, prompting the use of Akk products to increase response rates, especially in Akk-negative patients.

B13

FIRST-LINE IMMUNOTHERAPY-BASED REGIMENS IN PATIENTS WITH ADVANCED KRAS NON-G12C MUTANT NSCLC: PRELIMINARY INSIGHTS FROM THE ATLAS STUDY

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Background: Kirsten Rat Sarcoma Viral Oncogene Homologue (KRAS) mutated non-small cell lung cancer (NSCLC) have heterogeneous responses to immunotherapy-based regimens, particularly the G12C and G12D isoforms, but rarer subsets of mutations were less explored.

Methods: Retrospective data were collected and analyzed using ATLAS, a web-based platform created to collect and share data among Italian centers on patients with NSCLC. KRAS-mutated NSCLC patients diagnosed from 2019 to 2023 in 18 Italian centers were enrolled.

Results: We enrolled 134 patients who received first-line immunotherapy-based regimens for advanced or metastatic

non-G12C mutant NSCLC. 59.0% (n=79) were male, 92.3% (n=120) were ever smokers. G12D was the isoform with more never-smokers (14.3%). Most of the patients had an adenocarcinoma diagnosis (93.2%, n=124). PD-L1 was =50% in 34.1% (n=44), 1-49% in 29.5% (n=38), <1% in 36.4% (n=47), and unknown in 5 cases. Single-agent immunotherapy was chosen for 36.6% (n=49) of patients and for 84.1% (n=37) of cases who had a PD-L1 >50%. Chemo-immunotherapy regimens were chosen for 63.4% (n=85) of patients and for 87.1% (n=74) who had a PD-L1 <1% or 1-49%. Patients with a KRAS G12 mutation were 60.4% (n=83) and patients with a KRAS non-G12 mutation were 39.6% (n=51). The shortest median progression-free survival (mPFS) among the whole cohort was for G12D patients (4.8 months). Without considering patients with G12D mutation (n=21), patients with G12 mutations (group 1) had a higher proportion of progressions as best responses (34.0%) compared to those who had KRAS non-G12 mutations (group 2, 19.6%). The median PFS was 10.7 months in group 2 and 7.1 months in group 1, with a hazard ratio (HR) of 0.67 (95% CI 0.42-1.07, p=0.09). The median OS was 25.4 months for group 2 and 16.5 months for group 1, HR 0.87 (95% CI 0.49-1.54, p=0.63).

Conclusions: In our cohort, KRAS non-G12 mutant NSCLC patients showed a non-statistically significant trend for better outcomes with immunotherapy-based treatments compared to rarer G12 mutation subsets. Further study is needed better to understand immune-checkpoint inhibitors' efficacy for these patients.

B14

ARTIFICIAL INTELLIGENCE-BASED EARLY PREDICTION OF RADIATION PNEUMONITIS IN STAGE III NSCLC PATIENTS

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Background: Treatment approaches for NSCLC patients differ depending on stage, histology, genetic alterations, and patient's condition. Stage III NSCLC patients are non-surgical candidates and currently treated with chemoradiotherapy eventually followed by immunotherapy. For these patients, the occurrence of treatment-related diseases such as radiation pneumonitis could be observed. Thus, an early identification of which patients are more prone to develop radiation pneumonitis via artificial intelligence (AI)-based models could be crucial to define personalized treatment approaches and improve patients' prognosis.

Methods: We designed an AI approach to identify Stage III NSCLC patients at high risk of developing radiation pneumonitis. For this purpose, we analyzed pre-treatment CT images belonging to 54 Stage III NSCLC patients afferent to Istituto Tumori "Giovanni Paolo II" of Bari (Italy), in which radiation pneumonitis was observed for 24 patients. For each patient we identified the CT slide presenting the largest tumor area. Then, starting from this CT slide, we selected other four CT slides, the two immediately preceding and the two immediately following the one with largest tumor area. Subsequently, for all the selected CT slides, we defined a bounding box around the extremal points of the tumour in the four planar x-y dimensions. Finally, we exploited these images to train the last few layers of a pre-trained Convolutional Neural Network, that is ResNet50, adopting a 5-fold cross-validation scheme after identifying each time a validation set containing the 15% of the starting dataset.

Results: On the test and validation set, our model achieved respectively an AUC value of 90.60% [85.08-93.99] and 62.06% [61.25-67.38], a Sensitivity value of 94.12% [73.03-99.96] and 66.67% [60.02-75.69], a Specificity value of 76.31% [69.43-91.17] and 75.20% [59.52-75.20], and an Accuracy value of 81.81% (73.23-93.63] and 65.50% [62.50-67.88].

Conclusions: The proposed Artificial Intelligence-based model represents a promising procedure for early identifying Stage III NSCLC patients at high risk of developing radiation pneumonitis, with the purpose of defining personalized treatment approaches and improving patients' prognosis.

B15

IMPACT OF OSIMERTINIB DOSE REDUCTION ON EFFICACY IN EGFR-MUTATED NSCLC FROM A REAL-WORLD EXPERIENCE

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Background: Osimertinib 80 mg once a day (OD) is the first-line standard of care treatment for non-small cell lung cancer (NSCLC) harbouring epidermal growth factor receptor (EGFR) mutations. For patients developing intolerable

side effects, dose reduction to 40 mg OD is permitted, however data regarding the impact of a reduced dose of osimertinib on efficacy are limited.

Material and Methods: We conducted a monocentric retrospective observational analysis on a cohort of patients with advanced EGFR-mutated NSCLC treated with first-line osimertinib between May 2015 and April 2024 at San Luigi Gonzaga University Hospital. Patients were grouped according to whether they received a standard dose of osimertinib (80 mg OD) or experienced a dose reduction (40 mg OD) and were evaluated for progression-free survival (PFS) and overall survival (OS). Modified PFS was calculated to reduce immortal-time bias, considering only patients with early dose reduction (within the first 6 months) and excluding those who progressed within the first 6 months of treatment.

Results: A total of 99 consecutive patients (66 female, 33 male) were included in this analysis. With a median follow up of 42.4 months (95% IC: 34.4-50.4), 53 patients progressed to osimertinib. Of those, 13 patients developed an encephalic progression. 14 patients experienced a dose reduction due to adverse events (AEs), 7 within the first 6 months. Median time to dose reduction was 4,8 months (range: 3 weeks-27 months). Median age was 70 years in standard dose group and 77 in dose reduction group (p=0.014). The most common reasons for dose reduction were gastrointestinal toxicity (n=5) and pneumonitis (n=4, of which 3 patients with grade 3 toxicity), followed by fatigue (n=2), cardiotoxicity (n=1), skin rash (n=1), and paronychia (n=1). Median PFS (mPFS) was 28.1 months in the standard dose group and 25.3 months in the dose reduction group (p=0.566). Also, no difference was observed in mPFS after adjusting for immortal-time bias (modified mPFS 28.6 vs 25.8 months, p = 0.354) and in median OS (44.1 vs 29.1 months, p = 0.245). Among 13 patients with encephalic progression, only 2 reduced the dose of osimertinib.

Conclusions: Our results confirm osimertinib as an easy-manageable first-line treatment. Dose reduction due to AEs occurs more frequently in older patients but does not seem to affect efficacy. Results are consistent even for patients with an early dose reduction within the first 6 months.

B16

IMMUNE-RELATED ADVERSE EVENTS IN PATIENTS TREATED WITH IMMUNOTHERAPY FOR LOCALLY ADVANCED OR METASTATIC NSCLC IN REAL- WORLD SETTINGS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Immune checkpoint inhibitors (ICIs) are drugs that have changed the treatment scenario for non-small cell lung cancer (NSCLC). Immune- related adverse events (irAEs) could become life-threatening events, when not timely managed. We performed a systematic review and a meta-analysis over the real-world (RW) impact of irAEs through the years.

Methods: The systematic review focused on irAEs occurred in locally advanced or metastatic NSCLC patients, treated with ICIs in a RW setting. We queried Embase and Medline from 1996 to 2022. We then conducted a meta-analysis of RW observational studies on the prevalence of irAEs in NSCLC patients receiving ICIs, dividing the results in two cohorts (2015-2018 and 2019-2021). We described the prevalence of patients with irAEs of any grade and with irAEs of grade 3 or higher (G≥3). We considered irAEs all combined and by type. IrAEs of interest were those involving skin, liver, endocrine system or gastro-intestinal system.

Results: After the screening process, 21 RW studies were included in the quantitative and qualitative synthesis. Poor performance status and disease burden were associated with an unfavorable prognosis. IrAEs occurrence was associated with clinical benefit, but not always with a longer overall survival (OS). The prevalence of G≥3 irAEs was slightly lower in the 2015-2018 subgroup, while the prevalence of irAEs of any grade was similar for both study periods. We examined the trends of different types of G≥3 irAEs: we observed a higher ES for gastrointestinal (ES 0.22, 95% CI 0.13-0.31), hepatic (ES 0.31, 95% CI 0.20-0.41) and lung irAEs (ES 0.35, 95% CI 0.26-0.43), while a lower ES was reported for skin (ES 0.06, 95% CI 0.03-0.08) or endocrine irAEs (ES 0.09, 95% CI 0.05-0.12). Notably, endocrine irAEs were only reported in 10 out of 21 studies, while cutaneous toxicities were mostly reported in two studies lead within the first time-period. Pulmonary, gastrointestinal, and hepatic toxicities showed a more heterogeneous distribution of ES over time.

Conclusions: The frequency of irAEs remained stable across the two periods examined. This finding suggests that RW data might not be able to identify a potential learning curve in detection and management of irAEs. This need could be addressed through the prospective and

complementary collection of RW data and pharmacovigilance registries and by improving the quality of RW evidence, using stringent workflows from standardized published guidelines.

B17

STARDUST PHASE II TRIAL EVALUATING THE EFFICACY OF DURVALUMAB (MEDI4736) AS SECOND-LINE THERAPY IN NSCLC PATIENTS RECEIVING CONCOMITANT STEROIDS

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Background: PD-(L)1 inhibitors prolonged survival in metastatic NSCLC progressed to platinum-based chemotherapy. Along with clinical benefit, IT can cause immune-related adverse events (irAEs) requiring corticosteroids. However, due to their immunosuppressive role, steroids could potentially reduce the IT efficacy. STARDUST, a prospective, multicenter, phase II clinical trial, investigates whether concomitant steroids reduce the risks of irAEs without affecting efficacy of Durvalumab in 2nd line.

Patients and Methods: Patients with pretreated advanced or metastatic NSCLC, EGFR/ALK wild type, candidate for second-line IT, were treated with combination of Durvalumab 1500 mg every 4 weeks concomitantly with 10 mg/day of prednisone (or equivalent) and nutritional support (Ginseng and Isoquercetin). Primary endpoints were efficacy, assessed by Objective Response Rate (ORR), and incidence of irAEs.

Results: From March 2020 to April 2024, among 46 patients screened, 37 were enrolled onto the study. The majority were male, past or current smokers (89%), with median age 68 years (range 37-86), 92% had non-squamous and 8% had squamous histology. Twenty-seven patients (82%) had PD-L1 <50%. The most frequent site of metastasis were lymph nodes (29.7%) and bones (29.7%). 10% patients early progressed after neo/adjuvant or chemoradiotherapy. At data cut off April 2024, at median follow up of 25 months (IQR 11-32), ORR was 10.8% (4 patients with partial response) with DoR of 6 months, while 9 patients (24%) had stable disease lasting ≥ 6 months. Median PFS was 2.3 months (95% CI:1.6-3.0) with a 1yearPFS of 24.0%. Median OS was 6.2 months (95% CI:3.1-9.2) with a 1yearOS of 35.7%. Study treatment was well tolerated, with ≥ G3 irAEs in 2%. Most patients experienced mild TrAEs (G1 55%, G2 24%) with the most common being fatigue (13%) and pruritus (6%). Three patients discontinued treatment for adverse events (for ircolitis, dyspnea and arthritis).

Conclusions: The combination of Durvalumab and steroids reduced irAEs. However, it's not possible to exclude a detrimental effect of concomitant steroids on IT efficacy. The trial suffered from negative patient selection due to approval of IT in 1st line treatment. That led to the enrollment of patients with poor prognosis, in particular patients progressing to neo/adjuvant or chemoradiotherapy within six months. This trial was closed prematurely due to current IT 1st line indication.

B18

RADIOTHERAPY FOR LUNG CANCERS IN PATIENTS WITH INTERSTITIAL LUNG DISEASE: AN AIRO (ITALIAN ASSOCIATION OF RADIOTHERAPY AND CLINICAL ONCOLOGY) DELPHI CONSENSUS.

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Background: Interstitial lung diseases (ILD) are a heterogeneous group of disorders affecting the lung parenchyma. Patients with ILD have a greater risk of developing lung cancer and generally have a worse prognosis. Furthermore, ILD makes the patient more prone to developing toxicities related to radiotherapy (RT) and combined treatment resulting from exacerbation of the ILD itself. To date, there are no clear recommendations or guidelines regarding the management of patients with

lung cancer and ILD candidates for RT combined or not with systemic therapy. This work aims to create a consensus regarding ILD assessment, patient selection, risk/benefit index, and clinical management of patients with lung cancer and ILD who are eligible for thoracic RT.

Methods: The consensus process was first performed using the Estimate-Talk-Estimate method. The items of interest were independently identified by a board of experts of 4 radiation oncologists, two pneumologists, one radiologist, and one medical oncologist. Board members then individually drafted one or more statements for every item. An extended panel of 24 experts (12 radiation oncologists, six pneumologists, three radiologists, and three medical oncologists) expressed their degree of consensus according to the UCLA appropriateness method using a 9-point numerical rating scale (1 = entirely disagree to 9= entirely agree). A median score =7 represented the consensus threshold for each statement.

Results: Sixteen statements from 10 items were formulated concerning radiological and clinical definition, risk stratification, risk of toxicity, predictive and preventive factors, SBRT and RT for early and locally advanced stages and combinations with systemic treatment, follow-up and role of multidisciplnary team. All statements reaching a consensus agreement.

Conclusions: The present work describes the results of a multidisciplinary consensus process regarding the role of thoracic RT for patients with lung cancer and ILD. The resulting agreements may constitute a valuable tool for all clinicians and facilitate decision-aking in this challenging context.

B19

OBSERVATIONAL STUDY OF SECOND LINE NINTEDANIB FOR NON-SMALL CELL LUNG CANCER IN THE IMMUNO-ONCOLOGY ERA (OVIDIO)

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Background: Nintedanib (Vargatef®) is an orally available, multi-target small-molecule with anti-angiogenic activity against the vascular endothelial growth factor receptors (VEGFR) 1-3, the platelet-derived growth factor receptor (PDGFR a/ß) and the fibroblast growth factor receptors (FGFR). This agent is approved in combination with docetaxel for locally advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (nsNSCLC) therapy, after first line platinum-based chemotherapy. Approval comes from results of the randomized phase III LUME-Lung1 trial, carried out in the pre-immunotherapy era.

Methods: Recurrent nsNSCLC patients (pts) from 8 Italian oncological centres were prospectively enrolled in the OVIDIO observational study after failure of first-line treatment, mainly performed with chemo-immunotherapy. Per standard of care, they received docetaxel (weekly or q3wks, according to investigator choice) plus continuous oral nintedanib, with the possibility of maintenance at the end of combination therapy. Aim of the study was to explore, in a real life setting, efficacy and safety of these agents in the immuno-oncology era.

Results: Between November 2020 - September 2023, 37 nsNSCLC pts were enrolled (30 males, 7 females; median age: 66 yrs). 26 were former/active smokers at enrollment. All of them were EGFR WT, 1 ALK and 2 ROS1 translocated, 2 BRAF mutated (not V600E). During first line 28 pts (75.6%) received carboplatin-pemetrexed-pembrolizumab, 2 a chemo-doublet, 4 mono immunotherapy, the others a scheme with gemcitabine. After a 19.6 months follow-up, mPFS was 4.14 months (95% CI, 0.77 – 7.52) based on 17 pts data; mOS was 8.29 months (95% CI, 1.61 – 14.97) on 34 pts data. Treatment was well tolerated and toxicities mainly attributable to docetaxel (better accepted in the weekly schedule). Drug related G2 AEs were asthenia and GI disorders; G3-G4 AEs were rare (haematological toxicity).

Conclusions: In the era of immunotherapy this real life prospective study evaluating second line docetaxel-nintedanib for nsNSCLC resulted effective and safe. With the limitation of the small sample size, the results are globally in agreement with literature data and this combination may be considered as a doable second line therapeutic option.

B20

TP53 TRUNCATING AND MISSENSE MUTATIONS ARE LINKED TO DIFFERENTIAL RESPONSE TO CHECKPOINT BLOCKADE IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Several evidences indicate a link between TP53 mutations and response to ICI in patients with NSCLC with conflicting results. While TP53 missense mutations have been associated with anti-tumor immune response, mechanistic studies suggest an immune-suppressive role for TP53 loss.

Methods: Patients with advanced, non-oncogene addicted NSCLC, treated with ICI-based regimens from Sep 2017 to Nov 2023 at 6 European institutions with available TP53 profiling were included. Patients were categorized as TP53 truncating (nonsense/frameshift), TP53 missense, TP53 others (splice sites, deletion), TP53 wild type. TP53 missense mutations were additionally screened through the GenomeNexus.org web tool. Clinical outcomes were overall survival (OS), real-world progression free survival (rwPFS). Data cut-off was March 2024.

Results: The final population consisted of 219 patients, mostly tested with F1DX1 (89%), of whom 81 (37.0%), 79 (36.1%), 43 (19.6%) and 16 (7.3%) were TP53 wt, TP53 missense, TP53 truncating and TP53 others. None of the baseline clinic-pathologic features was associated with the TP53 status, except for the increased PD-L1 expression, TMB and higher KRAS mutation rate reported for the TP53 missense group. The median FUP was 35.1 months. TP53 missense mutation was associated with a longer OS compared to TP53 truncating group (HR 0.62, 95%CI: 0.39-0.99) and longer PFS (HR 0.69, 95%CI: 0.49-0.97) compared to the TP53 wt group. In the multivariable analysis (including TMB, PD-L1, KRAS and STK11 and all available clinic-pathologic factors) confirmed that both TP53 wt (HR 0.58, 95%CI: 0.34-0.99) and TP53 missense (HR 0.49, 95%CI: 0.29-0.83) groups had a significantly decreased risk of death compared to TP53 truncating group, and that only the TP53 missense group had a significantly decreased risk of disease progression compared to both TP53 wt (HR 0.64, 95%CI: 0.42-0.95) and TP53 truncating (HR 0.56, 95CI%: 0.34-0.91) groups.

Conclusions: Our results highlight the heterogeneity linked to the TP53 mutational status, with tumors harbouring TP53 missense mutations possibly more immune-responsive than TP53 truncating/TP53 wt.

B21

ASSESSING THE BENEFIT-TO-RISK RATIO OF IMMUNOTHERAPY-BASED TREATMENTS FOR ELDERLY PATIENTS (80 YEARS-OLD OR OLDER) WITH ADVANCED NSCLC

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Background: Immune checkpoint-inhibitors (ICIs) are the standard of care for patients with advanced non-oncogene-addicted non-small cell lung cancer (NSCLC). However, there is a significant lack of data about their efficacy and safety in patients aged 80 or older, who are underrepresented in clinical trials.

Material and Methods: Our single-center, observational study involving patients with advanced NSCLC treated with first-line ICIs, either as single agents or combined with chemotherapy (CT-ICI), aimed to assess the efficacy and safety of these treatments in elderly patients (≥ 80 year-old). Primary endpoints were high-grade toxicity (≥G3) and hospitalization rates. Median overall survival (mOS) and median progression-free survival (mPFS) were secondary endpoints.

Results: Among 267 patients, 36 had ≥ 80 years-old. Most of them were male (61.1%), with ECOG PS 0-1 (72.2%). 15 elderly patients received CT-ICI (41.7%) and 21 ICI alone (58.3%). No significant age-related differences in clinical (ECOG PS, sex, BMI, smoke history) and pathological (histology, PD-L1) features were observed. Patients ≥ 80 years-old had more frequently a high Charlson Comorbidity index score (CCI > 9) than those younger (38.9% vs 20.8%, p=0.031). ≥ G3 toxicity rates were similar across age subpopulations (≥80 vs. <80) and not influenced by treatment received. Hospitalization rates were higher in elderly patients treated with CT-ICI compared to those under 80 (46.7% vs 18.9% p=0.021), but not in those treated with ICI alone (19% vs 14.1%, p=0.518). Intrahospital mortality was comparable across ages regardless of treatment. Elderly patients had a mOS of 15.3 months (95% CI, 10.65-31.5) versus 11.6 months (95% CI, 8.62-16.9) of younger patients (p=0.73), while mPFS was 8.2 and 5.9 months, respectively (p=0.4). In patients ≥ 80 years- old receiving chemo-immunotherapy, 100% had chemotherapy dose reduction, compared to 81% of younger patients. Median first-reduction dose was ~ 40% for elderly patients and ~ 21% for those under 80, with elderly patients generally mantaining reduced doses in subsequent cycles.

Conclusions: Our study supports the safety and efficacy of ICI for ≥ 80 year-old patients, although their combination with CT may increase hospitalization rate while not affecting hospital deaths. Higher baseline chemotherapy first-dose reduction in elderly patients might not impact survival outcomes, although further studies are warranted.

B22

LIQUID BIOPSY IN NEXT GENERATION SEQUENCING (NGS) FOR TUMOR MOLECULAR PROFILING IN ADVANCED NSCLC IN UMBRIA POPULATION: A REAL-WORLD EXPERIENCE

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Background: Liquid biopsy has emerged as a highly promising and non-invasive diagnostic tool for tumor molecular profiling examining circulating tumor DNA (ctDNA) and RNA (ctRNA). The aim of this retrospective real-world study was to assess liquid biopsy impact on enhancing treatment therapy for NSCLC patients at new diagnosis when no tumor tissue is available.

Material (patients) and Methods: Between January 2019 and May 2024 a total of 157 liquid biopsy (LB) samples from advanced lung adenocarcinoma patients were collected at Medical Oncology Umbria Regional Cancer Network and analysed at Medical Oncology Laboratory of S.Maria della Misericordia Hospital of Perugia. Next generation sequencing (NGS) was performed using Oncomine Pan-Cancer Cell-Free Assay (panel that targets 272 amplicons within 52 known cancer genes) starting from 5 to 50 ng of cell-free total nucleic acid (cfTNA) on Ion Torrent S5 System.

Results: A total of 116 molecular alterations was identified in 13 genes. The most frequently mutated genes were KRAS (22.9%), TP53 (18.5%) and EGFR (14.6%). The most frequent molecular alteration was single nucleotide variant (SNV) (87%) followed by indels (12%), gene fusion (0.9%) and copy number variation (CNV) (0.9%). The majority of point mutations and indels were found in EGFR (19.8%) while gene fusion involved RET(0.9%). Among co-occuring alterations TP53 mutation was the most common (56%). Clinical evidence of actionability was found in 44 out of 157 pts (28%) according to ESCAT (ESMO Scale for Clinical Actionability of molecular Targets) Tier I-II (EGFR,14.6%,; KRAS-G12C, 9.5%; BRAF-V600E, 1.3%; MET Exon14 skipping, 0.6%; ERBB2, 1.3% and RET Fusion 0.6%;) For 41 out of 157 pts (26%) tumor tissue biopsy was available and concordance with LB was 92%, in 2 out of 3 pts with no concordance a EGFR Tier I molecular alteration was identified in LB. 29 out of 116 pts (25%) with only LB available were eligible for target therapies.

Conclusions: Blood-based LB performed by NGS is a non-invasive viable alternative tool for molecular genotyping and identifiy tumor-derived somatic alterations to increase the number of pts elegible to target therapy and guide personalized medicine.

B23

STUDY OF AGNOSTIC BIOMARKERS AND MET-AMPLIFIED ALK-POSITIVE CO-ALTERED GENES IN LUNG CANCER (NSCLC): ONE CENTRE'S EXPERIENCE IN SOUTHERN ITALY LAST YEAR

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Background: In the management of non-small cell lung cancer (NSCLC), molecular testing has become an important component. Identification of EGFR, BRAF and MET mutations and analysis of ALK, ROS1, RET and NTRK translocations are already part of the NSCLC diagnostic standard, and inhibitors of these kinases are in routine clinical use. There are emerging biomarkers, such as the presence of MET protein overexpression and MET gene amplification. Targeted agents are being developed for these biomarkers. Besides genetic testing, NSCLCs are commonly tested for PD-L1 protein expression to guide immune checkpoint inhibitor use. Our aim was to evaluate intratumoural MET heterogeneity and its potential impact on biomarker-based patient selection, as well as potential surrogate biomarkers of MET activation.

Methods: In order to describe the global molecular landscape of the co-altered genes, we studied 74 patients who had undergone surgery for NSCLC at the IRCCS "G. Pascale" (Na, Italy) during the last year. ALK, ROS1 and MET alterations were quantified by fluorescence in situ hybridisation (FISH); PD-L1 alterations were quantified by ihc. MET copy number status was assessed using the Zyto Light SPEC MET/CEN 7 dual-color probe in samples and three different scoring systems (UCCC, Cappuzzo, PathVysion) were examined.

Results: ALK, ROS1 and MET were positive at 9.5%, 2.3% and 29.1% respectively, and PD-L1 was positive at 75.7%. Regarding *MET* FISH analysis, when evaluated as a categorical variable (*MET* disomic, *MET* gain, *MET* positive). NSCLCs altered by MET and ALK were more likely to show a papillary growth pattern (18/74 cases). FISH identified 8 tissue samples with ALK + MET + mutation, 3 with polysomy and 5 with true amplification. Of the Met amplification cases, 22 were PD-L1 positive and significantly correlated with high TPS (>50%) (p-value 0.024). Evaluating the smoking status of MET positive patients, 20 are non-smokers, while among the ALk+ MET+ co-mutated, 6/8 were smokers.

Conclusions: In summary, our preliminary study shows that MET status is highly heterogeneous within NSCLC and is significantly correlated with other PD-L1 expression. ALK + MET+ co-detection was found in 6 smokers, whereas MET+ status is more common in non-smokers (20). To better understand any resistance factors with patient status, the study will continue to expand the case series and investigate the relationship of genetic markers with clinical outcomes.

B24

HEME-OXYGENASE-1 (HO-1): A POTENTIAL BIOMARKER FOR ICIS IN PATIENTS WITH ADVANCED LUNG CANCER

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Background: Immune checkpoint inhibitors (ICIs) have significantly improved the outcome of patients with lung cancer. However, heterogeneity in clinical benefit and absence of a reliable biomarker still represent an unmet need. We evaluated the role of monocytes and heme-ossigenase-1 (HO-1) expression on their surface in resistance to ICIs in patients affected by advanced lung cancer.

Methods: "ImmunoEGA" is a prospective, observational study in patients with advanced tumors, treated with ICIs at the 'Maggiore della Carità' Hospital in Novara, IT. Overall, 122 patients affected by lung cancer have been recruited from 2018 to 2023. In the present study we used cytofluorimetry to analyse monocytes subpopulations and HO-1 expression on their surface, on blood samples collected at baseline, before start of treatment and at the time of disease progression (34 patients). The primary endpoint was treatment outcome in terms of progression free (PFS) and/or overall survival (OS).

Results: At baseline, the frequency of classical monocytes was higher as compared to non-classical and intermediate subgroups, independently from type and duration of response (mean percentage: 48,4% vs 7,8 vs 23,9%; p<0.0001). A significant correlation between higher frequency of classical monocyte at baseline and PFS was observed (14.0 vs 6.5 mos, p= 0,0171), as well as a relative increase in the frequency of classical monocytes at the time of disease progression (PD) (p=0,0554). No differences were detectable in HO-1 expression across monocytes subtypes at baseline. Patients with lower HO-1 expression on classical and intermediate monocytes had an improved PFS (15,5 vs 6,5 mos p=0,0057), as well as an improved OS (18 vs 11.5 m, p=0.0378).

Conclusions: In patients with advanced lung cancer treated with ICIs a higher frequency of classical monocytes is predictive of an improved outcome. Lower HO-1 expression on intermediate and classical monocytes correlates with an improved outcome. Conversely, the expression of HO-1 in classical and intermediate monocytes increases at PD, suggesting its implication in promoting cancer progression. These data suggest that the level of HO-1 expression might be used as a potential biomarker of ICIs benefit. Additional data will be presented.

B25

THE ROLE OF RADIOTHERAPY IN OLIGOPROGRESSION OF ADVANCED NON-SMALL CELL LUNG CANCER IN THE IMMUNOTHERAPY ERA: A REAL-WORLD ANALYSIS

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Background: In the era of immunotherapy (IT), patients (pts) with advanced Non-Small lung cancer (aNSCLC) are increasingly experiencing oligoprogression (OPD), defined as the progression of a limited number of metastases during systemic treatment. The role of adding radiotherapy (Rt) in this context remains unclear, both in terms of benefits and toxicity.

Methods: All pts with aNSCLC treated with IT alone or in combination with chemotherapy were retrospectively evaluated. Pts who received at least two cycles of treatment between January 2020 and January 2024 were included. Outcomes of OPD pts continuing systemic treatment with or without the addition of RT were assessed. Progression-free survival (PFS), time to treatment failure (TTF), and overall survival (OS) were assessed using the Kaplan-Meier method, with statistical significance set at $p<0.05$. Data cut-off date was March 31, 2024. Data on safety was also collected.

Results: A total of 113 patients (pts) were analyzed, with a median age of 68 years (range 64-70). Most pts (93; 82%) had an ECOG PS of 0-1. The most common histological subtype was adenocarcinoma (81%). 65% of pts (73) received chemotherapy-immunotherapy (CHT-IT), while 35% (40) received IT alone. In the overall population, the mPFS was 5.3 months, mTTF was 8.5 months, and mOS was 11.9 months. Disease progression (PD) occurred in 95 pts (84%), with 47 pts (49%) experiencing OPD and continuing systemic treatment beyond PD. Among OPD pts, 22 received directed RT on oligoprogressive sites, among them 6 (27%) receiving palliative treatment and 16 (73%) receiving high-dose RT (HdRT >30 Gy). The main sites of HdRT were the primary tumor (9 pts) and brain (6 pts), while the main site of palliative RT was bone (3 pts). The mTTF was 13.4 months in OPD pts receiving RT (OPD-RT) compared to 8.7 months in those continuing with systemic treatment alone (OPD-Sy) (p=0.099). The mOS was 35.9 months in the OPD-RT group versus 11.9 months in the OPD-Sy group (p=0.030). In the OPD-RT group, 8pts (33%) manifested toxicity, however, none were higher than grade 2.

Conclusions: Our findings suggest that the addition of RT to systemic treatment for OPD may offer potential benefits in terms of prolonged TTF and OS, with manageable toxicity profiles. However, further prospective studies are needed to validate these observations and elucidate the optimal integration of RT in the management of OPD in aNSCLC patients undergoing IT or CH-IT.

B26

SEXUAL DIMORPHISM-BASED DIFFERENCES IN EFFICACY AND ADVERSE EVENTS IN PATIENTS WITH ADVANCED STAGE NON-SMALL CELL LUNG CANCER: COULD AN OLD CLINICAL PARAMETER DEFINE A NEW PRECISION ONCOLOGY?

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Background: Immunotherapy (IT) has revolutionized the treatment of advanced Non-small Cell Lung Cancer (ad-NSCLC), yet not all patients (pts) experience the same benefit. Many biomarkers are under investigation, but fundamental clinical parameters are sometimes neglected. One such parameter is sex, a well-known variable that influences both innate and adaptive immune responses. Despite its importance, less than 10% of publications on IT consider sex in their methodological planning. This oversight has led to a lack of understanding regarding the true benefits of IT for female pts, both in terms of efficacy and potential differential toxicities between the sexes.

Methods: We retrospectively analyzed pts with ad-NSCLC treated with IT alone or in combination with chemotherapy, between July 2020 and December 2023 at Modena University Hospital.

Results: A total of 113 pts were analyzed: 73 male and 40 female. The median (m) age was 66.5 years (95% CI: 64 to 68). The median progression-free survival (mPFS) for the entire population was 6.48 months (mo) (95% CI: 5.29 to 10.03), and the median overall survival (mOS) was 11.52 months (95% CI: 7.45 to 14.00). No significant differences in outcomes were observed between male and female pts. Immune-related adverse events (irAEs) of any cause and grade were reported in 43 patients (38%). The mOS of patients who developed irAEs was significantly higher compared to those who did not: 14.00 mo (95% CI: 10.52 to 26.06) vs. 6.81 mo(95% CI: 4.71 to 13.06), p=0.007. Regarding irAEs and sex, a higher percentage of female pts experienced irAEs compared to males (50% of females vs. 32% of males). The mOS for females with irAEs was significantly higher than for females without them: 34.10 months (95% CI: 7.45 to not reached) vs. 4.94 months (95% CI: 3.71 to 19.26), p=0.004. However, the mOS difference between males with irAEs and those without was smaller and not significant: 11.52 months (95% CI: 7.81 to 18.16) vs. 7.42 months (95% CI: 4.71 to 13.06), p=0.11.

Conclusions: Our study found that female pts with ad-NSCLC treated with IT had a higher propensity to develop irAEs. The development of irAEs correlated with OS in the entire population, but this correlation was more pronounced in females. These results suggest that sex-related hormonal and chromosomal differences may affect immune response and immunotherapy efficacy. These findings highlight the importance of considering sex as a critical factor in immunotherapy research.

B27

EFFICACY AND EFFECTIVENESS OF FIRST-LINE IMMUNOTHERAPY FOR ADVANCED NSCLC: SURVIVAL OUTCOMES AND PROGNOSTIC FACTORS

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Background: Immune checkpoint inhibitors (ICIs) significantly improved outcomes for advanced Non-Small Cell Lung Cancer (NSCLC). However, evidence regarding the safety and efficacy-effectiveness gap of ICI in unselected patients (pts) is limited.

Methods: We retrospectively analyzed a cohort of 501 consecutive pts with stage IIIC-IV NSCLC treated at Pisa University Hospital from 2017 to 2024. Pts received pembrolizumab as monotherapy or in combination with chemotherapy, based on PD-L1 status. We assessed survival outcomes and safety in unselected versus trial-eligible pts.

Results: Of the 501 pts, 355 were male, with a median age of 69 years (range 37-87). Most of tumors (76.8%) were non-squamous; 445 pts had metastatic and 55 stage IIIC disease. 284 were classified as "trial-eligible" and 217 as "trial-ineligible" based on main inclusion criteria of randomized trials. With a median follow-up of 33.3 months (mo), the median overall survival (OS) was 19.2 mo (95% CI: 15.3-24.0). In pts with high PD-L1 expression, median OS was 21.4 mo (15.0-27.5), with 31.3 (24.01-47.1) in trial-eligible and 11.5 mo (9.01-17.4) in trial-ineligible pts (HR 0.52, 0.38-0.71, p<0.001). Among analyzed factors, NOS histology (HR 1.75, 1.10-2.81, p=0.019), ≥4 sites of metastasis (HR 4.22, 1.85-9.66, p=0.001), trial eligibility (HR 0.59, 0.42-0.81, p=0.001), and ICI-related adverse events (HR 0.530.37-0.75, p<0.001) were significant independent prognostic factors for OS in both univariate and multivariate analyses. Among all the inclusion criteria, ECOG PS (HR multivariable 4.71, 1.89-11.75, p=0.001) and systemic glucocorticoids (HR 1.94, 1.28-2.94, p=0.002) had the strongest association with OS in multivariate analysis. Compared to registration trials, our median OS for high PD-L1 expression was 81%, rising to 119% for trial-eligible pts. Adherence to inclusion criteria was linked to higher objective response rates (ORR; p<0.001; OR 2.53, 1.53-4.20). Trial eligibility (p<0.001), brain metastases (p=0.003), and ICI-related adverse events (p<0.001) were independent predictors of ORR at multivariate logistic regression.

Conclusions: Real-world data align with trial outcomes, especially in selected pts, but highlight a significant proportion of trial-ineligible pts. Poor ECOG PS and steroid therapy were primary factors in the worse OS of trial-ineligible pts, rather than other exclusion criteria.

B28

ROLE OF ANTIBIOTICS IN PATIENTS WITH ADVANCED NON SMALL CELL LUNG CANCER TREATED WITH IMMUNE CHECKPOINT INHIBITORS: A META-ANALYSIS

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Background: In the last decade, immune checkpoint inhibitors (ICIs) targeting the programmed cell death-1 (PD-1)/ programmed cell death ligand-1 (PD-L1) and the cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) pathways alone or in combinations with chemotherapy, has revolutionized the treatment of non small cell lung cancer (NSCLC) patients improving outcomes with a favourable toxicity profile. NSCLC patients have a higher risk of contracting infections due to the oncological disease and co-morbidities. Several analyses in metastatic patients with different types of tumor showed that the use of broad-spectrum antibiotics reduce the bacterial diversity and the function of intestinal flora with a detrimental effect on patient response to ICIs and progression free survival (PFS).

Materials and Methods: A systematic search has been performed to identify studies including patients with advanced NSCLC treated with a ICIs based schedule. As inclusion criteria, studies must have presented results of outcomes as overall survival (OS), PFS, objective response rates (ORR) based on the use of antibiotics (ATB).

Results: In the overall patient population, ATB exposed patients (n = 6598) experienced worse OS (HR 1.54; 95% CI 1.37-1.74) and worse PFS (HR 1.29; 95% CI 1.17-1.43) compared to the ATB-unexposed counterparts (n=23176 for OS; n=23284 for PFS). On the contrary, ATB-exposed patients (n=3055) seem to experience better ORR (HR 0.71; 96% CI 0.51-1.00) compared to the ATB-unexposed counterparts (n=9045).

Conclusions: Our meta-analysis reveals that the use of antibiotics is associated with a worse OS and PFS in

patients with advanced NSCLC patients treated with ICIs, as single agents or in combination with chemotherapy. In contrast, the higher ORR observed in patients treated with antibiotics could be related to the more frequent employment of these drugs and the higher rate of infections in patients treated with chemo-immunotherapy.

B29

WEEKLY ALTERNATING DOXORUBICIN, CYCLOPHOSPHAMIDE, VINCRISTINE, CARBOPLATIN, AND ETOPOSIDE (ACOCEV) FOR SMALL-CELL LUNG CANCER IN FRAGILE PATIENTS: A RETROSPECTIVE OBSERVATIONAL STUDY

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Background: Small cell lung cancer (SCLC) is an aggressive type of carcinoma, featuring high chemo- and radiation-sensitivity but bad prognosis. Today standard of care is platinum-based doublet plus immunotherapy, however this treatment can be burdened with severe toxicity, and may not be feasible for many patients because of comorbidity, performance status or old age. Second line treatment with in-vein topotecan is, too, burdened by heavy toxicity and only a few patients are able to undergo this treatment. To this date, many alternatives, less toxic options have been evaluated; however, none has entered clinical practice, leaving us with an unmet need on how to treat these patients.

Materials and Methods: In this retrospective study, we report our experience with ACOCEV, a weekly chemotherapy regimen alternating cyclophosphamide + doxorubicin (Day 1), vincristine (Day 8 and 22) and carboplatin + etoposide (Day 15) for 4 cycles of 28 days each, as I or II-line treatment in fragile patients with SCLC referred to 2 different institutions in Veneto (Italy). We evaluated the following endpoints: OS, PFS, ORR and safety.

Results: A total of 73 patients were evaluated (49 treated in I line, 24 in II line). Objective response rate was 59.7%, while median progression-free survival (mPFS) and overall survival (mOS) were 4.40 and 6.18 months. In I and II line, ORR was, respectively of 72.1% and 20.8%. mPFS and mOS were 5.26 and 7.1 months in first line and 2.62 and 4.08 months in second line. Adverse events occurred in 76.8% of patients, while G3-4 toxicity occurred in 23.2% of cases, both being slightly more frequent in patients receiving ACOCEV as II line. Most common severe adverse event was neutropenia, with an overall incidence of 13%.

Conclusions: Based on our results, ACOCEV seems a feasible first-line option for patients affected by SCLC and unfit for standard treatment. Although results were inferior when utilized in second line, our schedule may also be utilized in this setting in patients unfit for standard irinotecan, having shown slightly inferior efficacy but significantly less haematological adverse events compared to literature data. However, our result come from retrospective data, and need to be validated in a prospective setting.

B30

IMPACT OF GENOMIC ALTERATIONS MEASURED IN CIRCULATING TUMOR DNA (CTDNA) ON CLINICAL RESPONSE TO TELISOTUZUMAB VEDOTIN TREATMENT IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: ADC telisotuzumab vedotin(Teliso-V) is composed of c-Met–targeting antibody telisotuzumab (ABT-700) linked to the microtubule inhibitor monomethyl auristatin E. In LUMINOSITY study(NCT03539536) efficacy of Teliso-V was seen in patients(pts) with EGFR-wt NSQ NSCLC and c-Met OE(=25% tumor cells at 3+ intensity by IHC); overall response rate(ORR):36.5%. Data are limited on whether specific driver oncogene states affect responses. We investigated genomic alterations(alts) in relation to Teliso-V response.

Methods: Pts received 1.9mg/kg Teliso-V monotherapy q2wk. At different timepoints ctDNA was isolated from plasma. The PGDx elio plasma complete assay was used to identify genomic alts in ctDNA samples. This assay included 521 genes for single nucleotide variants and insertion-deletion mutations(muts), 38 for amplifications(amp), 21 for translocations.

Results: 52 pts were included; ctDNA from 48 pts was analyzed. The ORR among pts with ctDNA results was 37.5%(18 pts with partial response) vs 36.5% for the ITT population. Genomic alts are listed in Table. 3 out of 4 pts with METamp at baseline responded, accounting for 17% of total responses. The METamp frequency in this MET IHC preselected cohort was 8%, like the prevalence observed in tissue analysis by FISH. 1 nonresponder harbored a METex14del mutation at baseline(bl) and a responder had low-frequency mutation(mut) at final visit. Muts in KRAS were the most common genomic alteration and were detected in 13(27%) pts at bl. 3 pts with a KRASmut were responders; 2 out of 3 had a KRAS G12C mut(seen in 3 pts total). Response rates were higher in pts with METamp(75%; 95% CI: 0.30, 0.95) vs pts without METamp(34%; 0.22, 0.49) and higher in pts without KRASmuts(43%; 0.28, 0.59) vs pts with KRASmuts(23%; 0.08, 0.50); however, confidence intervals were wide and larger sample sizes are needed.

Conclusions: METamp occurred more frequently in responders; but Teliso-V activity wasn't restricted to these pts: most responders weren't METamplified. Specific genomic alts beyond MET may influence clinical response. The current analysis demonstrated numeric differences between pts with identified drivers who did or didn't respond to Teliso-V. Additional research is needed in larger cohorts and/or with tissue-based NGS analyses.

Table. Genomic alts at bl.

n(%)	Responders n=18	Nonresponders n=30
Amplification		
MET	3 (17)	1 (3)
Translocations		
RET	2 (11)	0
ALK	0	1 (3)
FGFR1	0	1 (3)
ROS1	0	1 (3)
Mutations		
KRAS	3 (17)	10 (33)
*MET*ex14del	0	1 (3)
BRAF	0	1 (3)

B31

EXPLORING RADIOMIC SIGNATURES FOR PROGNOSTICATION IN METASTATIC NON-SMALL-CELL LUNG CANCER (MNSCLC) PATIENTS (PTS) TREATED WITH FIRST-LINE IMMUNOTHERAPY (IO) BASED REGIMENS

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Background: Although radiomics has been widely used as prognostic factor for mNSCLC, it suffers from high data dimensionality when a limited sample size is available. Univariate analysis is the common strategy to investigate the correlation of radiomic features with clinical outcomes, limiting the possibility of discovering confounding factors. Conversely, unsupervised techniques do not directly exploit outcomes, allowing for the identification of hidden data patterns.

Methods: We retrospectively analysed pre-treatment contrast-enhanced CT scans of 76 pts who received first-line IO (PDL1 over 50%) or chemo-IO (PDL1 0-49%) for mNSCLC from 2020 to 2022. Each primary lung tumor was contoured using a semi-automatic approach by an expert radiologist. Clinical outcomes were collected as follows: RECIST best response focusing on early progression (EP), defined as progression or death as best response to (CT-)IO, and progression-free survival (PFS). 100 radiomic features were computed from each volume of interest (VOI) and 20 features were kept after removing correlated ones (Spearman < 0.8) and verifying the absence of volume dependence. After features normalization, univariate analysis was performed with Mann-Whitney U test, while clustering was performed using K-means with elbow method.

Results: At univariate analysis, pts not experiencing EP (67%) had significantly higher values of 2 radiomic features derived from Grey Level Size Zone Matrix compared to EP patients (33%) (SizeZoneNonUniformityNormalized and SmallAreaEmphasis). At unsupervised analysis, the optimal number of clusters was 3 (22, 27 and 27 pts each), defined exclusively by radiomic features. Cluster A comprised pts with the worst prognosis, despite being balanced according to treatment (55% vs 45% CT-IO vs IO), with an EP rate of 40% versus 30% of Clusters B and C. PFS rates under 3 and 12 months were 27% and 68% for Cluster A versus 22-25% and 59-66% for Clusters B and C.

Conclusions: Radiomic features quantifying grey level heterogeneity emerged as preliminarily associated with short-term response to treatment in mNSCLC pts, with lower values predicting lack of response to standard IO-treatments. Unsupervised clustering, on the other hand, introduced a more complex features analysis. Even in presence of a limited dataset, unsupervised methods showed that similar imaging patterns characterize pts with similar outcomes without any a priori clinical overseeing and independently from treatment choice.

B32

DOSE DEPENDENT DETRIMENTAL EFFECT OF BASELINE PANTOPRAZOLE ON CLINICAL OUTCOMES FROM FIRST-LINE CHEMO-ICI REGIMENS IN PATIENTS WITH ADVANCED STAGE NSCLC

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Background: Several evidence indicates that proton pump inhibitors (PPIs) taken before immune checkpoint inhibitor (ICI) treatment may worsen outcomes in patients (pts) with solid tumors due to their gut microbiome disruptive effects. In NSCLC, the impact of PPIs in ICI-chemotherapy combos is debated, with no data on their potential dose-dependent effect.

Patients and Methods: Pts with advanced stage NSCLC treated with 1st line chemotherapy plus pembrolizumab at the Fondazione Policlinico Campus Bio-Medico from Dec 2019 to Sep 2023 were included. Acknowledging the absence of mechanistic link between PPIs dosage and their detrimental effects we chose to limit the present analysis to pts receiving pantoprazole (PP) (the most prescribed PPI in our cohort), using non-PPIs pts as the control group. Data cut-off was March 2024.

Results: The main endpoints were overall survival (OS) and real-world progression-free survival (rw-PFS). Out of 134 pts, 101 (75.4%) were on PPIs at baseline. After the exclusion of 22 pts, the final population consisted of 112 pts with 16 (14.3%) and 63 (56.2%) of pts on 20 mg and 40 mg PP respectively. Treatment with PP was associated with the presence of CNS metastases (p=0.03) and with non-squamous histology (p=0.02). In addition, we reported a linear trend between increasing PP dose and concomitant corticosteroids treatment (12.2%, 31.2%, 54.0%, p<0.01). At the median follow-up was 26.9 months, PP 40 mg was associated with worse OS (HR 2.39, 95%CI: 1.34-4.29) and shorter rw PFS (HR 2.01, 95%CI: 1.22-3.29) compared to no-PPIs. Importantly, we found no significant difference between PP 20 mg and no PPIs. The multivariable analysis confirmed PP 40 mg as independent determinant of disease progression (HR 2.06, 95%CI: 1.16-3.63) and death (HR 1.94, 95%CI: 1.03-3.64). Interaction tests between PP and corticosteroids/PS ECOG, confirmed PP 40 mg exposure's independent prognostic role.

Conclusions: Our results indicate a dose-dependent negative impact of baseline PP on NSCLC patients treated with ICI regimens. While these findings require validation in larger groups, they could inform clinical practice for potential adjustments in pts initiating chemo-ICI therapy.

B33

MOVING THROUGH THROMBOSIS EVENTS(TES) LANDSCAPE IN PATIENTS WITH NON-SMALL CELL LUNG CANCER(NSCLC) TREATED WITH TARGET THERAPIES: SHOULD WE CONSIDER A PERSONALIZED TE PROPHYLAXIS?

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Background: Tyrosine kinase inhibitors(TKIs) have changed the treatment scenario of NSCLC harboring actionable genomic alterations. Many patients experienced TEs(i.e. venous thrombosis, VTE, or pulmonary embolism, PE) which seriously impair their prognosis. However evidence for TEs prophylaxis is still lacking.

Methods: Clinical, molecular and treatment information were retrospectively collected at the San Luigi Gonzaga University Hospital. Details about TEs(PE/VTE) and treatment with Low-Molecular-Weight Heparin(LMWH) or direct oral anticoagulants(DOACs) were collected at the time of TKIs start(baseline) and 6 months later, to assess their prognostic implications.

Results: 94 consecutive patients(pts) with metastatic NSCLC, treated with TKIs, were included(see Table 1). Median follow-up was 25.9 months. 24 pts(25.5%) received LMWH at baseline; of these, 18 had a TEs(*n*=10 PE, *n*=6 VTE and *n*=2 VTE+PE). After 6 months, 19 pts(20.2%) were still receiving LMWH, 13 of them for TEs(*n*=10 PE, *n*=2 VTE and *n*=1 VTE+PE). 4 pts(4.3%) received DOACs(*n*=1 Apixaban, *n*=1 Edoxaban, *n*=1 Dabigatran, *n*=1 Rivaroxaban) at baseline and after 6 months, none of them for TEs.

Pts treated with LMWH at baseline had numerically shorter median progression free survival(mPFS) and overall survival(OS) compared to LMWH naïve[11.1 vs 23.6 months, *p*=0.065; 20.4 vs 31.4 months, *p*=0.060, respectively]. However, VTE/EP did not correlate with mPFS and mOS, neither at baseline(*p*=0.152 and *p*=0.154, respectively) nor at 6 months(*p*=0.175 and *p*=0.203). Lastly, EP alone at baseline was not associated with mPFS and mOS(*p*=0.173 and *p*=0.415). None of pts who were TEs free, treated with DOACs or LMWH at baseline, experienced thrombosis at 6 months.

Conclusions: TEs may represent a poor prognostic factors for NSCLC pts treated with TKIs, although that was a preliminary analysis. The role of TEs prophylaxis should be better defined and identifying predictive factors is warranted.

Table 1.

	N° of patients(%)
Sex	
Female	57 (60.6)
Male	37 (39.4)
Median Age	65.3 year
ECOG PS	
0	49 (52.1)
1	38 (40.4)
³2	7 (7.5)
Smoke History	
Current	15 (16)
Former	32 (34)
Never	47 (50)
Thoracic Sites	
Lymph Node	79 (84)
Lung	59 (62.8)
Mutational Profile	
EGFR mutations	60 (63.8)
ALK rearrangement	14 (14.8)
ROS-1 rearrangement	8 (8.5)
BRAF mutations	4 (4.3)
MET exon skipping 14	4 (4.3)
RET fusions	4 (4.3)
Thrombosis (VTE/EP) at baseline	
EGFR mutations	11 (61.2)
ALK rearrangement	2 (11.1)
ROS-1 rearrangement	2 (11.1)
Other (MET, RET and BRAF)	3 (16.6)

B34

BLOOD BASED INDEXES AS PREDICTORS OF CLINICAL RESPONSE AND OVERALL SURVIVAL IN ADVANCED NON–SMALL CELL LUNG CANCER PATIENTS TREATED WITH FIRST LINE CHEMOIMMUNOTHERAPY

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Background: Combination therapy with immune checkpoint inhibitors (ICIs) and chemotherapy is the first-line treatment for advanced non-small cell lung cancer (NSCLC) with PD-L1 tumor proportion score lower than 50% in immunohistochemistry. Limited data are available regarding the role of systemic inflammation indexes in patients with NSCLC treated with chemo-immunotherapy.

Methods: Consecutive patients with advanced NSCLC treated with chemotherapy + Pembrolizumab or chemomotherapy + Nivolumab/Ipilimumab from January 2019 to December 2023 were retrospectively enrolled. Clinical data were retrieved from clinical records and transferred in a specific digital database. Routine laboratory tests performed before treatment were considered. The neutrophil to lymphocyte (NLR), monocyte to lymphocyte (MLR), platelet to lymphocyte (PLR), Systemic Inflammation Response Index (SIRI), Systemic Inflammation Index (SII), and the Aggregate Inflammation Systemic Index (AISI) were investigated. Clinical outcomes used for biomarker evaluation were overall response rate (ORR), progression free survival (PFS) and overall survival (OS). Statistics performed with MedCalc.

Results: A total of 62 patients were included in the study. 47 patients (75.8%) were responders and 15 (24.2%) were non-responders. Responders demonstrated significantly reduced mortality rates (22% vs. 80%) and prolonged overall survival (median 14.5 months vs. 7.5 months) compared to non-responders. Non- responders exhibited elevated levels of NLR and NMR. In univariate logistic regression analysis NLR (p=0.012) and NMR (p=0.03) were significantly associated with ORR. In addition, NLR (p=0.005) and NMR (p=0.015) were significantly associated with OS. These relations were also confirmed by multivariate logistic regression. With respect to survival, the optimal cut-off values identified by ROC analysis were: NLR, 4.0; NMR, 11.8. The values of the area under the curve (AUC) were 0.749 for NLR and 0.707 for NMR. The Kaplan–Meier survival curves, after classifying the patients on the basis of Youden cut-offs obtained by ROC curves, showed significantly lower survival with higher values of both the NLR ($p = 0.0001$) and NMR ($p < 0.0001$).

Conclusions: Increased NLR and NMR values were associated with lower ORR and shorter OS in NSCLC patients treated with first-line chemo-immunotherapy. NLR showed a better performance than NMR in predicting OS, with an AUC of 0.749, and might potentially have a clinically applicable predictive and prognostic value.

B35

SURVIVAL OUTCOMES OF PD-L1 HIGH KRAS-MUTATED ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH FIRST-LINE IMMUNE CHECKPOINT INHIBITORS: A SINGLE-CENTER RETROSPECTIVE STUDY

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Background: Mutations in the Kirsten rat sarcoma viral oncogene homolog (KRAS) gene are found in approximately 20%-30% of patients with non-squamous non-small cell lung cancer (NSCLC). To date, it is unclear whether KRAS mutational status can predict the efficacy of immune checkpoint inhibitors (ICI), and most studies in this field have included heterogeneous populations of patients treated with ICI regardless of treatment line or programmed death-ligand 1 (PD-L1). The primary objective of this study was to evaluate the impact of KRAS mutations on the efficacy of single-agent immunotherapy as first-line treatment in patients with advanced NSCLC.

Patients and Methods: We included patients with locally advanced, unresectable, or metastatic NSCLC with PD-L1 ≥50% who were treated with single-agent programmed death-1 (PD-1)/PD-L1 inhibitors at the Division of Medical Oncology of Livorno Hospital (Department of Oncology Azienda Usl Toscana Nord Ovest, Italy). The KRAS mutation status was detected using Next-Generation Sequencing (NGS). PD-L1 status was determined using the immunohistochemistry SP263 assay. The primary outcomes were median progression-free survival (mPFS) and median overall survival (mOS).

Results: We identified forty-seven patients (33 non-squamous, 14 squamous), but we included only non-squamous patients in KRAS mutation analyses. Thirteen patients (39%) were KRAS-MT (mutant), and the most common mutation subtypes were G12C (54%), G12F (15%), and G12D (15%). There was a non-significant trend towards better mOS in KRAS-MT patients compared to KRAS-WT (wild-type) (43 vs 32 months, p = 0.857). We found no significant differences in PFS (16 vs 15 months, p = 0.674). Patients with squamous histology had a mPFS and mOS of 13 and 15 months, respectively.

Conclusions: KRAS mutation status did not significantly influence ICI efficacy, although a non-significant trend towards better survival was observed in KRAS-MT patients treated with first-line ICI. These findings contribute to the ongoing research in this field.

B36

CONCORDANCE AMONG THREE PROGRAMMED DEATH-LIGAND 1 (PD-L1) SCORING METHODS AND THEIR ASSOCIATION WITH CLINICAL OUTCOMES OF TISLELIZUMAB (TIS) MONOTHERAPY IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA (ESCC)

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Background: We retrospectively investigated concordance between three programmed death-ligand 1 (PD-L1) scoring methods and clinical outcomes in RATIONALE-302 (NCT03430843), a phase 3 study of the anti-PD-1 antibody TIS vs. investigator-chosen chemotherapy (ICC) as second-line treatment for advanced unresectable/metastatic ESCC.

Materials (Patients) and Methods: Enrolled patients with evaluable PD-L1 expression by tumor area positivity (TAP) score (visual estimation of positive tumor cells [TCs] and tumor-associated immune cells [ICs]; VENTANA PD-L1 [SP263]) were categorized at 10% cutoff. Stained slides were rescored post hoc using both combined positive score (CPS; positive TCs and ICs) at cutoff 10 and TC (positive TCs only) score at 1% cutoff. Concordance at these thresholds and overall survival (OS) for PD-L1 subgroups were assessed.

Results: Of 512 pts enrolled, 364 had evaluable TAP scores (TIS, n=180; ICC, n=184), of whom 355 had evaluable post-hoc CPS and TC scores (TIS, n=175; ICC, n=180). TAP score and CPS showed high concordance

(overall percentage agreement ([OPA]; 90% [95% CI, 86-93]) and Cohen's Kappa (0.79 [95% CI, 0.72-0.85]), while TAP and TC scores had lower concordance (OPA 78% [95% CI, 73-82]; Cohen's Kappa 0.56 [95% CI, 0.47-0.64]). OS benefit with TIS vs. ICC in PD-L1 subgroups defined by TAP, CPS, and TC score cutoffs were generally similar (Table).

Conclusions: OS subgroup analysis showed comparable treatment effect by TAP score at 10% cutoff, CPS at cutoff 10, and TC score at 1% cutoff. TAP score and CPS at these cutoffs exhibited substantial concordance. Results indicate that the quicker, visually estimated TAP score and CPS may be interchangeable for clinical measurement of PD-L1 expression in patients with ESCC.

Table. OS Benefit in PD-L1 Subgroups by Scoring Method.

	Median OS, months (95% CI) [event/total]		Hazard ratio (95% CI)
	Tislelizumab	ICC	
TAP ≥10%	10.0 (8.5-15.1) [54/80]	5.1 (3.8-8.2) [53/62]	0.52 (0.35-0.76)
TAP <10%	7.5 (5.5-8.9) [83/100]	5.8 (4.8-6.9) [106/122]	0.86 (0.64-1.14)
CPS ≥10	10.0 (8.5-13.2) [56/80]	5.1 (3.7-8.2) [59/65]	0.54 (0.37-0.78)
CPS <10	7.5 (5.3-8.7) [80/95]	5.8 (4.9-7.4) [100/115]	0.83 (0.62-1.12)
TC ≥1%	9.9 (7.5-11.4) [69/94]	5.1 (3.8-6.1) [69/77]	0.56 (0.40-0.79)
TC <1%	7.7 (5.2-9.8) [67/81]	6.9 (4.9-8.6) [90/103]	0.83 (0.60-1.14)

B37

CURRENT APPROACHES TO THE DIAGNOSIS AND TREATMENT OF BONE METASTASES (BOM) IN PATIENTS (PTS) WITH NON-SMALL CELL LUNG CANCER (NSCLC): AN ITALIAN SURVEY

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Background: This study investigates the current approaches to BoM diagnosis and treatment in pts with NSCLC.

Methods: A web-mail questionnaire was administered to Italian oncologists/radiotherapists. After a literature revision, the self-reported survey was designed and revised by dedicated experts. The questionnaire included 40 items and was composed of five sections: i) general and work characteristics, ii) diagnosis, iii) bone-targeted agents (BTA), iv) radiotherapy (RT), v) supportive care. Descriptive statistics was applied.

Results: Overall, the survey was completed by 108 clinicians (mean age 41.6y, 52% female, 82% oncologists). Among the diagnostic questions, 18F-FDG PET is the preferred method for skeletal assessment for both pts with (56.5%) and without (63.0%) BoM at the TC scan; RM (65.7%) and 18F-FDG (60.2%) are the most frequently chosen techniques when a bone oligoprogression is suspected. The main factors for deciding to start BTA were the occurrence of skeletal-related events (SRE) (56.5%) and life expectancy (56.5%); in about 50% of participants, the expected response to systemic treatment influences this choice. Renal toxicity (64.8%) is the main factor clinicians consider in choosing the BTA, and denosumab is the most adopted (64.8%). The RT timing is mainly driven by the presence of symptoms in pts with bone oligometastatic disease. Over half of the participants do not stop the systemic treatment during stereotactic RT (65.7%) and consider re-irradiation on progressive BoM at least 6 months after the prior RT (60.2%). Body weight and physical activity were assessed by 65.0% and 40.0% of participants, respectively. Oral nutritional supplements or a specific diet were recommended by 32.0% and 43.0% of clinicians, 38% of them also advised their pts to increase exercise levels, while 55.6% are worried that exercise may increase the SRE risk. Pts with NSCLC and BoM always/often ask about diet (62.0%), oral nutritional supplements (63%), physical activity (55%), and safety of daily routine activities (67%).

Conclusions: In the current era of lung cancer, the detection and management of BoM are fundamental to guarantee patients' prognosis. Strict adherence to BTA recommendations, as well as the appropriate integration of supportive care still represents areas of improvement.

B38

CLINICAL, PROGNOSTIC AND THERAPEUTIC FEATURES IN V600 AND NON-V600 BRAF MUTATED NON-SMALL CELL LUNG CANCER: A REAL-WORLD STUDY

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Background: BRAF mutations occur in approximately 2-4% of NSCLC patients. As first-line treatment for BRAF V600-mutated NSCLC, BRAF/MEK inhibitors are recommended. However, patients with BRAF non-V600 mutations are treated with immunotherapy (IO) or chemo-immunotherapy (CT-IO) based on PD-L1 expression. The objective of this study is to assess potential prognostic differences between V600 and non-V600 populations, with a focus on non-V600 mutated patients treated with IO or CT-IO regimen.

Methods: Demographic, molecular and clinical data of NSCLC BRAF-mutated patients were retrospectively collected from medical records and FFPE tissue samples at Careggi University-Hospital between 2019 and 2024.

Results: 31 patients with BRAF-mutated NSCLC are included in this study, 15 (48.4%) with V600 and 16 (51.6%) with non-V600 mutations. 29% of patients had localized disease, with a median DFS of 8.5 months (CI 95%: 1.8 - NA) for V600 patients and 10.5 months (CI 95%: 4.4 - NA) for non-V600. The most common sites of recurrence were lymph nodes, bone and lung (33.3%, 22.2% and 11.1%, respectively). The median overall survival (mOS) and progression-free survival (mPFS) for the 22 patients with metastatic disease were 9.8 months (95% CI: 4.6 - NA) and 8.7 months (95% CI: 4.8 - NA), respectively. Although longer median survival outcomes were observed in V600 compared to non-V600 patients, no significant differences were found between the two groups for either mOS (21.7 vs 7.9 months; p=0.93) or mPFS (8.7 vs 5.6 months; p=0.91). In the BRAF non-V600 population, mOS was 7.9 months (CI 95%: 6.3 - NA) for the combination regimen and was not-reached for patients treated with IO alone (p=0.43). The mPFS was comparable (7.5 vs 5.6 months for CT-IO and IO respectively, p=0.82).

Conclusions: No significant differences were observed in clinical outcomes.between BRAF V600 and non-V600 mutated populations, thereby confirming the negative prognostic role of the mutation. For patients with BRAF-mut non-V600 either a CT-IO or an IO-based regimen may be considered, however prospective, randomized trials are needed.

	BRAF V600 (n = 15) n (%)	BRAF Non-V600 (n = 16) n (%)
Advanced disease indication		
First line	11 (73.3%)	7 (43.8%)
BSC	2 (13.3%)	2 (12.5%)
Targeted therapy (n = 11)		
DCR	8 (72.7%)	0 (0%)
PD	2 (18.2%)	0 (0%)
ND	1 (9.1%)	0 (0%)
CHT-IO/IO (n = 7)		
DCR	0 (0%)	4 (57.1%)
PD	0 (0%)	1 (14.3%)
ND	0 (0%)	2 (28.6%)

B39

MULTI-OMICS ANALYSIS IN LIQUID BIOPSY OF SMALL CELL LUNG CANCER PATIENTS HIGHLIGHTS THE PURINE METABOLIC PATHWAY AS A POTENTIAL BIOMARKER

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Background: Small cell lung cancer (SCLC) has limited therapeutic options and is characterized by a lack of reliable biomarkers to stratify patients. Combining omics data can offer a comprehensive view of the complex biology of SCLC. We report preliminary results of an integrated metabolomics and transcriptomics analysis in patients with SCLC.

Methods: We compared metabolomic profiles of 24 SCLC patient serum samples at diagnosis with those of a control group matched for sex and age. To validate the identified disrupted metabolic pathways, we performed transcriptomic

analysis using data from the Gene Expression Omnibus (GEO) database.

Results: A notable difference emerged in serum metabolite expression between patients and controls (log2 Fold-change>1.4, p<0.01). SCLC patients exhibited elevated levels of acetone and reduced glutamine. Nitrogen bases like inosine and hypoxanthine, involved in the purine salvage pathway, were significantly upregulated. Interestingly, preliminary survival analysis revealed better outcomes for patients with high serum inosine and hypoxanthine expression (p=0.05, p=0.34, respectively). The transcriptomic analysis of gene expression profiles in 18 pairs of SCLC tumor tissue and matched adjacent healthy tissue corroborated our findings, demonstrating an upregulation in SCLC tissue of both de novo biosynthesis and purine salvage pathways (p<0.001, p=0.003, respectively). Moreover, the key gene within the purine salvage pathway, HPRT1, exhibited significantly higher expression in tumor tissue compared to healthy tissue (p<0.005).

Conclusions: We propose an integrated approach combining metabolomic and transcriptomic analysis in liquid biopsy as a promising strategy for the evaluation of novel biomarkers. Omics data integration highlighted the purine metabolic pathway as a potential prognostic indicator in SCLC. We are currently exploring prospective metabolomic analysis during treatment.

B40

COMBINATION OF OLAPARIB AND TEMOZOLOMIDE IN PATIENTS WITH PREVIOUSLY TREATED SMALL-CELL LUNG CANCER: A MONOCENTRIC REAL-WORLD CASE SERIES

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Background: Small cell lung cancer (SCLC) is an aggressive malignancy characterized by high mortality. Despite its initial sensitivity to first-line chemo-immunotherapy, most patients (pts) experience early relapse, and response rates in second-line settings are significantly lower. In a phase II trial, the combination of temozolomide and PARP inhibitors (Olaparib) has demonstrated clinical efficacy in relapsed SCLC, attributed to the synergistic effect of these agents.

Materials and Methods: We conducted a retrospective analysis of a cohort of patients with advanced small cell lung cancer (SCLC), treated with Olaparib and Temozolomide (OT) under off-label use authorization as a subsequent-line treatment, from January 2019 to October 2023 at the Department of Oncology, Modena University Hospital.

Results: a total of 15 pts were analysed: 6 (40%) were male and 9 female (60%), with a median age of 67 years (95% CI 56.3 to 72.2). 6 (40%) pts were treated with OT as a second-line, 7 (46.6%) as a third-line and 2 (13.3%) as a fourth-line. 11(73%) pts experienced clinical benefits in terms of symptom improvement; in particular, 5 pts (33.3%) experienced an improvement in respiratory symptoms. Treatment was discontinued after a median number of 3.6 cycles, due to progression of disease (PD) or death. The treatment was generally well tolerated, the most frequent adverse effects being fatigue (7;46.6%) and hematologic toxicities (9;60%); no patients discontinued the treatment due to toxicity. The disease control rate (DCR), including partial response (PR) or stable disease (SD), was 40% (6 pts). Median progression-free survival (mPFS) was 3.3 months (mo) (95% CI 2.7-4.8) and median overall survival (mOS) was 3.8 mo (95% CI 3.3-5.5).

Conclusions: In this real-world study, the survival outcomes, as measured by PFS and OS, were lower than those reported in the pivotal clinical trial. This discrepancy may be attributed to the small cohort size and the heterogeneous number of prior therapy lines. However, the DCR was 40%, a significant result for pretreated advanced SCLC. Additionally, treatment with OT demonstrated good tolerability and provided clinical benefits for most patients. Prospective observational studies with longer follow-up periods and larger sample sizes are necessary to confirm whether OT can be considered a viable therapeutic option for pretreated advanced SCLC.

B41

REAL-WORLD STUDY OF FIRST-LINE NIVOLUMAB PLUS IPILIMUMAB COMBINED WITH TWO CYCLES OF CHEMOTHERAPY IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER (“FINN-ITALY”)

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Background: The immune checkpoint inhibitors nivolumab (nivo) and ipilimumab (ipi) have distinct but complementary mechanisms of action. The randomized, open-label, phase III CheckMate 9LA trial (NCT03215706) demonstrated a significant improvement in overall survival (OS),

progression-free survival (PFS) and overall response rate for patients treated with nivo+ipi combined with two cycles of chemotherapy (chemo) compared to chemo alone. Based on these results, the European Medicines Agency gave approval and Agenzia Italiana del Farmaco (AIFA) agreed reimbursement for nivo in combination with ipi and 2 cycles of platinum-based chemo for the 1L treatment of metastatic NSCLC in adults whose tumours have no sensitising EGFR mutation or ALK translocation and PD-L1 expression <50%. As experience with this combination therapy is largely based on data from randomized clinical trials, the FINN study was designed to collect real-life data during the early post-market authorization approval period. The study aims to describe patient characteristics, outcomes, safety profile, and treatment patterns in routine clinical practice.

Material (patients) and Methods: FINN is a national, prospective, observational, multicentre study. Overall, 400 patients diagnosed with metastatic or recurrent NSCLC, who start systemic therapy with nivo+ipi+2 cycles of chemotherapy in accordance with the AIFA market authorization will be enrolled. The study will collect data from ~50 oncology centres. Patients will be followed for 5 years from Day 0 (treatment initiation) until death, withdrawal of consent, loss of follow-up, or end of the study. During the follow-up period, assessments will be performed according to routine clinical practice. Data entry in the electronic case report form will occur on Day 0, Week 6, Month 3, 6, 9, 12, 18, 24, 36, 48, and 60. The primary objective is OS; secondary objectives include PFS, treatment duration, patient characteristics, safety profiles and patient-reported outcomes (assessed by EQ-5D and NSCLC-Symptom Assessment Questionnaire).

Results and Conclusions: The FINN study will provide long-term outcome data for patients with NSCLC treated with nivo+ipi+chemo in routine clinical practice. To date, 60 patients have been enrolled in 30/50 active sites. The baseline characteristics of the first enrolled patients will be provided in the congress presentation.

B42

EGFR MUTATION SUBTYPES IN ADVANCED NSCLC: IMPACT ON METASTATIC PATTERNS AND PROGNOSTIC IMPLICATIONS

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Background: In advanced non-small-cell lung cancer (NSCLC), clinical and prognostic patterns seem to vary depending on the type of epidermal growth factor receptor (EGFR) gene mutation. However, identifying predictive or prognostic factors among patients with exon 19 deletion (ex19del) and exon 21 L858R mutation (L858Rmut) remains challenging.

Methods: This retrospective study examined a cohort of 68 patients with advanced NSCLC harboring EGFR mutations, diagnosed between 2017 and 2023 at a single center (Careggi University Hospital). All patients received Osimertinib as first-line therapy. Clinicopathological features and prognostic outcomes were compared based on EGFR mutational status.

Results: Ex19del was detected in 36 patients (52.9%), L858Rmut in 31 patients (45.6%), and an uncommon EGFR mutation in 1 patient (1.5%). The median age at diagnosis was 69 years (range: 30–87). Of the 68 patients, 20 (29.4%) were male and 48 (70.6%) females. ECOG performance status was 0 in 35 patients, 1 in 25 patients, 2 in 7 patients, and 3 in 1 patient. At diagnosis, 4 patients were current smokers (5.9%), 44 former smokers (64.7%), and 20 never smokers (29.4%). Bone metastases were observed in 44.1% of patients, brain metastases in 29.4%, liver metastases in 22.1%, and other sites in 67.6%. The response rates were: Partial Response in 76.1% (n=51), Complete Response in 3% (n=2), Stable Disease in 14.9% (n=10); four patients were not evaluable. Median overall survival (OS) was 37.1 months, and median progression-free survival (PFS) was 17.8 months. Twenty patients received second-line treatment, with 12 having ex19del and 8 having L858Rmut. Both mutations were more common in never-smokers and females. A notable association was found between the ex19del and occurrence of liver metastases in comparison to the L858Rmut (p=0.068). Additionally, the prevalence of brain metastases was higher in patients with ex19del (33.3% vs. 25.8%). Despite the higher incidence of brain and liver metastases, patients with the ex19del exhibited superior PFS with first-line treatment (21.2 vs. 14.1 months), second-line treatment (12.6 vs. 6.8 months), and time-to-second progression (15.2 vs. 10.2 months).

Conclusions: Our results are consistent with those reported in the literature. The specific EGFR mutation subtypes influence the pattern of metastasis. Although ex19del is more frequently associated with liver and brain metastases, patients exhibit a more favorable prognosis than those with L858Rmut.

B43

EXPLORING THE COMPLEX RELATIONSHIP BETWEEN SYSTEMIC SCLEROSIS AND ADVANCED LUNG CANCER: A SINGLE-CENTER EXPERIENCE

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Background: Systemic sclerosis (SSc) is an autoimmune disease characterized by an excessive production of collagen, associated with a high risk of developing lung cancer. In this analysis, data from patients (pts) with advanced lung cancer and concomitant SSc treated at the Oncology Section of the University and Hospital Trust of Verona (Italy) were collected and analyzed.

Methods: Pts were retrospectively identified from the SSc database of the University of Verona (data cut-off on 30 April 2024). Pts affected by both lung cancer and SSc were included as *SSc group*, while a series of pts affected by lung cancer and without SSc with similar baseline characteristics were considered as *control group*. Descriptive statistics were used to analyze the socio-demographics data of patients and their disease characteristics, whereas progression-free survival (PFS) and overall survival (OS) were explored using the Kaplan-Meier method and log-rank test.

Results: Overall, 5/253 pts collected in the SSc database of the University of Verona were included as *SSc group*; 80% were men and 60% were never smokers. The median age at the rheumatological diagnosis was 34.8 years, while the median age at the oncological diagnosis was 47.2 years. All the pts presented positivity for anti-Scl-70 antibodies and suffered from interstitial lung disease.

Three pts had squamous cell carcinoma, one adenocarcinoma, and one small-cell carcinoma. No pts had Programmed Death-Ligand 1 (PD-L1) overexpression (4 PD-L1 1-49% and 1 PD-L1 <1%) and no druggable alterations were found at molecular profiling. 4 pts received 1st-line chemotherapy without immunotherapy, obtaining one partial response (PR), one stable disease (SD) and two progressive disease (PD) as best response.

The exploratory comparison between the two groups highlighted that pts in the *SSc group* had a younger age (47.2 y vs 60.8 y, *p=0.014*) and a worse PFS (5 m vs 34 m, *p=0.013*) and OS (9 m vs NR, *p=0.018*) compared to pts included in the *control group*.

Conclusions: Despite the small sample size, our series provides interesting insights regarding pts with lung cancer and SSc. Translational analyses on these pts are currently ongoing. Considering the young age, the poor prognosis, and the limited treatment options, we will expand the sample size to explore the complex relationship between lung cancer and SSc.

B44

LUNAR-2: PIVOTAL, RANDOMIZED, OPEN-LABEL STUDY OF TUMOR TREATING FIELDS (TTFIELDS, 150 KHZ) CONCOMITANT WITH PEMBROLIZUMAB AND PLATINUM BASED CHEMOTHERAPY FOR THE TREATMENT OF METASTATIC NON-SMALL CELL LUNG CANCER

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Background: Tumor Treating Fields (TTFields) are electric fields that disrupt processes critical for cancer cell viability. TTFields are delivered by a noninvasive portable device that has the European CE Mark and FDA approval for glioblastoma and mesothelioma. Preclinical non-small cell lung cancer (NSCLC) studies demonstrated that TTFields enhance the antitumor immune response, through disruption of mitosis and subsequent induction of immunogenic cell death. The pivotal, phase III LUNAR study (NCT02973789) in metastatic NSCLC progressing on/after platinum-based therapy demonstrated that TTFields with an immune checkpoint inhibitor (ICI) or docetaxel provided a statistically significant and clinically meaningful 3.3-month improvement in median overall survival (OS) vs an ICI or docetaxel alone, with no added systemic toxicities and no clinically significant difference on quality of life between groups.

Methods: LUNAR-2 (NCT06216301) is a pivotal, global, randomized study investigating the efficacy and safety of TTFields concomitant with pembrolizumab (P) and platinum-based chemotherapy (C) in patients (pts) with metastatic NSCLC, with a planned global enrollment of 734 pts at approximately 130 sites, including 9 sites in Italy. Pts

with NSCLC, radiologically evaluable disease in the thorax, ECOG PS of 0–1, and no prior treatment for metastatic disease are eligible. Pts will be stratified by histology, PD-L1 Tumor Proportion Score (TPS) and prior treatment with immunotherapy. Randomization is 1:1 to TTFields/P+C or P+C alone. Standard doses of P+C will be administered to both arms on day 1 of a 21-day cycle for 4 cycles of induction followed by up to 31 cycles of maintenance with TTFields/P or P alone. TTFields generated by the NovoTTF-200T System will be delivered to the thorax ≥ 18 h/day until local disease progression per iRECIST. The primary endpoints are OS and progression-free survival (PFS) per RECIST v1.1 as assessed by a blinded independent central review (BICR). Secondary endpoints include OS and PFS according to histology or PD-L1 TPS, objective response rate, duration of response, and disease control rate, all per RECIST v1.1 as assessed by BICR and by investigator, comparing TTFields/P+C vs. P+C alone. Other secondary endpoints include PFS rates at 6, 12, 24 and 36 months per RECIST v1.1 as assessed by BICR, 1-, 2-, and 3-year survival rates and safety. The trial is currently recruiting.

B45

LUNAR-4: PILOT, SINGLE ARM, OPEN-LABEL, MULTINATIONAL STUDY OF TUMOR TREATING FIELDS (TTFIELDS, 150 KHZ) CONCOMITANT WITH PEMBROLIZUMAB FOR THE TREATMENT OF METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) PREVIOUSLY TREATED WITH A PD-1/PD-L1 INHIBITOR AND PLATINUM-BASED CHEMOTHERAPY

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Background: Tumor Treating Fields (TTFields) are alternating electric fields that disrupt crucial processes essential for cancer cell survival. Administered via non-invasive portable device with both European CE Mark and FDA approval for glioblastoma and mesothelioma, TTFields have shown promise in enhancing anti-tumor response in NSCLC through the disruption of mitosis and subsequent induction of immunogenic cell death in preclinical studies. Recent pivotal, phase III LUNAR/EF-24 trial (NCT02973789) on metastatic NSCLC progressing after platinum-based chemotherapy demonstrated that the combination of TTFields with an immune checkpoint inhibitor (ICI) led to a statistically and clinically meaningful 7.7-month improvement in median OS compared to treatment with ICI alone. This served as the foundation for our current investigation, aimed at elucidating the efficacy and safety of combining TTFields + Pembrolizumab in stage IV NSCLC subjects previously treated and progressed on or after platinum-based chemotherapy and PD-1/PD-L1 inhibitors.

Patients and Methods: LUNAR-4 is a pilot, single arm, open-label, multinational study designed to evaluate the safety and efficacy of TTFields, generated by the NovoTTF-200T device, together with Pembrolizumab in patients (pts) with metastatic NSCLC, with a planned enrollment of 69 pts at 32 sites. Pts with metastatic NSCLC, ECOG 0-1, positive tumor PD-L1 expression (TPS ≥1%), who progressed on or after platinum-based chemotherapy and received prior PD-1/PD-L1 inhibitor are eligible. The primary endpoint is OS in pts treated with TTFields + Pembrolizumab compared to the OS of pts treated with docetaxel alone in the EF-24 study. Secondary endpoints include PFS per RECIST v1.1, OS and PFS according to PD-L1 TPS or histology, and safety profile. Enrolled pts will receive continuous TTFields treatment (≥ 18 h/day), together with Pembrolizumab at the approved dose, delivered intravenously q3w (200mg) or q6w (400mg). Device Support Specialists will provide technical and lifestyle integration training for pts and caregivers throughout TTFields therapy.

C – Head and Neck Tumors

C01*

LONGITUDINAL ASSESSMENT OF PLASMA EBV-DNA IN NON-ENDEMIC EBV-RELATED NASOPHARYNGEAL CANCERS (NPC): LEA STUDY

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Background: Plasma EBV-DNA is a well-known biomarker for EBV-related nasopharyngeal cancer (NPC) patients (pts) in endemic areas; data about its use in non-endemics is limited. Our study (n.150/23) aims to **L**ongitudinally assess the plasma **E**BV-**D**N**A** (LEA) during all curative journey of non-endemic EBV-related NPC.

Methods: From 2012 to 2023 all EBV-related NPC pts, curatively treated at INT Milan, were retrospectively reviewed. Plasma EBV-DNA was evaluated at: pre-treatment (T1); early (T2a) and/or late (T2b) post-treatment (within 6 and 14 weeks after treatment end, respectively); follow-up (FUP) (T3). Only pts with at least 1 EBV-DNA assessment available at T1, T2a or T2b, and T3, were selected. The post-induction chemotherapy (ICT) EBV-DNA (T4) was also considered if available. EBV-DNA results (log IU/ml) were classified as negative vs. positive. Descriptive statistics and predictive values were calculated to assess the ability of plasma EBV-DNA to forecast recurrence at T1, T2a/T2b, T3, T4.

Results: At a median FUP of 60 months (IQR: 9-134), 169 EBV-related NPC pts were retrieved. Median age was 50 years (IQR: 22-75). Most were male (72%) and staged as III-IV (84%) [AJCC, VIII Ed.]. Out of evaluable 167 pts (2 oligometastatic pts were excluded), 42 (25%) recurred. Median viral load of T1 EBV-DNA was 2.57 log IU/ml (0-5.11) while it was undetectable in 6 pts (3.5%). All recurrences occurred in T1 detectable EBV-DNA pts without any predictive cut-off value. For T2a/T2b EBV-DNA, accuracy, sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were 75.9%, 23.8%, 93.5%, 78.3%, 55.5%, respectively. The true negative and true positive rate at T2a and T2b were equivalent (81% and 19% respectively at both T2a and T2b). NPV and PPV of T4 sample (N=74) were 92% and 49%, respectively. In FUP, one isolated positive plasma EBV-DNA did not significantly differ recurrent (15%) vs. not recurrent (9%) pts. Moreover, pts with all negative FUP EBV-DNA values had 90% of chance of not recurring. NPC recurrence was anticipated by at least a positive EBV-DNA in 65% of pts with an average time of 64 days (st. dev. 86 days).

Conclusions: Undetectable pre- and post-curative treatment EBV-DNA are both positive prognostic factors. The dynamics of post-ICT EBV-DNA is highly informative (NPV 92%; PPV 49%). In FUP, 65% of NPC recurrences were anticipated by positive EBV-DNA. In the curative NPC journey, plasma EBV DNA assessment is highly recommended.

C02*

PROGNOSTIC GENE EXPRESSION SIGNATURES FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Background: Despite optimal multimodal therapies, only a few therapeutic advances have been witnessed in locoregionally advanced head and neck squamous cell carcinoma (LA-HNSCC) in the last decades. There is an urgent need to develop prognostic biomarkers to identify patients (pts) who could benefit from more intensive treatments. We aimed to explore publicly available gene expression prognostic signatures (GEPS) in a cohort of HNSCC pts.

Methods: We analyzed the Italian cohort of non-metastatic LA-HNSCC pts treated with curative treatments included in the BD2Decide study (primary diagnosis from 2008 to 2017) [PMID 33107152]. GE of primary tumor specimens was obtained by Affymetrix ClariomD chips and processed using the Transcriptome Analysis Console Software (ThermoFisher). We assessed 3 validated GEPS: i) a 3-cluster model (3Cl) in HPV+ [PMID 34738049]; ii) a 172-gene GEPS (172GS) in HPV- [PMID 24827125]; iii) radiosensitivity index (RSI) in both cohorts [PMID 19735873]. We analyzed GEPS distribution; disease-free (DFS) and overall survival (OS) were estimated with Kaplan-Meier method. Hazard ratio (HR) was estimated with Cox proportional hazard model.

Results: The characteristics of the 339 pts (90 HPV+, 249 HPV-) are reported in Table 1.

Table1. Patient characteristics.

Characteristics	HPV+ (90)	HPV- (249)
Median age (IQR) [years]	60 (14)	62 (15)
Male	69 (77%)	155 (62%)
Primary site		
Oral cavity	-	166 (67%)
Oropharynx	90 (100%)	32 (13%)
Hypopharynx	-	21 (8%)
Larynx	-	30 (12%)
Stage (AJCC/UICC 8th edition)	I. 33 (37%) II. 23 (25%) III. 34 (38%)	III. 58 (23%) IVa/b. 191 (77%)
Median follow-up	40.26 months [m] (95% CI: 35.59-48.58)	47.89 m (95% CI: 41.81-63.39)
2-year DFS	88.8%	62.2%
2-year OS	96.6%	74.1%

3Cl risk distribution in HPV+ pts was: low 37 (41%), intermediate 43 (48%), high 10 (11%). Median 172GS was 0.057 (IQR 0.4034) in HPV- pts. Median RSI was significantly lower in HPV+ than in HPV- pts (0.1605 vs. 0.3226, p<0.0001).

Stage and RSI were not significantly associated with OS, while HPV-specific GEPS were (Table 2).

Table 2. HPV-specific GEPS.

	HR (95% CI) for OS	p value
3Cl for HPV+ (low/intermediate vs. high risk)	0.217 (0.054-0.87)	0.031
172GS for HPV- (continuous variable)	2.192 (1.163-4.132)	0.015

Conclusions. HPV-specific GEPS have an independent prognostic role in forecasting OS of HNSCC pts. Intensifying treatments in pts with high-risk disease may improve oncologic outcomes. Confirmatory biomarker-driven clinical trials including these GEPS are warranted.

C03

NEUTROPHIL/LYMPHOCYTE RATIO (NLR): A POTENTIAL BIOMARKER IN PATIENTS WITH HEAD AND NECK SQUAMOUS CELL CARCINOMA TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background: Prognostic factors for assessing the response to immunotherapy in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) have not yet been clearly defined. Several studies have shown that there is a correlation between increased circulatory inflammatory factors, high neutrophil/lymphocyte ratio (NLR) and a negative prognosis. The aim of this research is to investigate the predictive and prognostic role of the NLR relationship in R/M HNSCC patients, treated with

immunotherapy, assessing the correlation between the NLR and the Overall Survival (OS) and the Progression Free Survival (PFS).

Material and Methods: This multicentric study coordinated by the Oncology Unit of University of Campania "Luigi Vanvitelli" retrospectively collected data from 142 patients diagnosed with R/M HNSCC from 13 Italian oncological centers. Two groups were made using the median NLR value of 4.2. Primary endpoint was the stratified OS; secondary endpoint the PFS and the Objective Response Rate (ORR), stratified on the values of the NLR. A univariate and multivariate survival analysis was performed to confirm the independent prognostic value of the NLR.

Results: 135 patients were included in the study, stratified on the NLR in two groups. 85 patients (63%) received first-line immunotherapy (alone or in association with platinum-based chemotherapy) and 50 (37%) in second line single agent. Median NLR was 4.2, with 71 patients (52.6%) with NLR>4 and 64 patients (47.4%) in the group with NLR<=4. Mean OS of patients with NLR>4 was significantly shorter than that of patients with NLR<=4 (23.1 vs 37.4 months, HR of 0.45, p= 0.002). Univariate analysis showed statistically significant correlation between OS and NLR value, p=0.002, and between OS and ECOG, p=0.022. Median PFS stratified by NLR value, was statistically significant: 6.5 vs 20 months in patients with NLR>4 and NLR<=4, respectively (HR 0.57, p= 0.013). ORR in the general population was 32.6%. NLR-stratified ORR confirmed the unfavorable prognostic role of high NLR: ORR was 20% if NLR<=4, and 12.5% if NLR>4. Furthermore, Progression Disease (PD) in the <=4 group was 21.9%, in the >4 group was 46.5%.

Conclusions: Our study shows that a basal NLR value lower than the cut off of 4 is independently associated with better OS, PFS and ORR in patients with R/M HNSCC treated with immunotherapy, in first or second line.

C04

PEMBROLIZUMAB AND OLAPARIB IN RECURRENT/METASTATIC, PLATINUM RESISTANT NASOPHARYNGEAL CANCER: THE POINT STUDY

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Background: Treatment of platinum-pretreated recurrent/metastatic (RM) Nasopharyngeal Carcinoma (NPC) with pembrolizumab didn't improve overall survival (OS) vs investigator-choice chemotherapy; its objective response rate (ORR) was 21.4% vs 23.3%. We aimed at assessing the combination of anti PD-1 and PARP inhibitor in this disease setting.

Methods: This is a multicentre, open-label, single-arm phase II study enrolling platinum-resistant RM NPC patients (pts). Eligible pts received pembrolizumab 200 mg every 3-weeks and olaparib 300 mg twice a day every day. Treatment continued until objective disease progression, any prohibitive toxicity or up to 2 years. Primary endpoint was investigators assessed ORR by the 3rd radiological examination (week 27). Secondary endpoints: safety, Progression-Free Survival (PFS), OS, quality of life and translational analysis.

Results: A total of 34 pts (2 screening failure) from 9 Italian centres were enrolled between April 2022 and November 2023. Overall, 25 were males (74%), with a median age of 55 (range 33-75). At baseline, 41% of pts had locoregional disease only, 53% were metastatic and 6% had both; 81% had ECOG PS 0. Circulating EBV DNA tested positive in 74% of pts. The median follow-up on trial was 5.2 months (range 1.9 – 20.6+ months). The median number of administered cycles was 8.7 (range 2-30); 8 patients were still on treatment at data cut-off.

The ORR was 13%, with one complete response reported (3%); disease control rate was 38%. Median PFS was 4 months (range 1.7 – 20.6+ months); median OS was not reached.

Overall, 84% patients experienced at least one adverse event (AE), while 22% experienced a ≥G3 AE, the most common ones being anaemia (9%) and lymphopenia (6%).

Conclusions: Pembrolizumab plus olaparib failed in enhancing ORR of platinum-refractory RM NPC pts compared to historical data. The combination strategy was well tolerated, with no new safety signals. Further studies aiming at improving the activity and efficacy of immunotherapy in RM NPC are needed.

C05

DIFFERENT PATTERNS OF TREATMENT FAILURE BETWEEN P16+ AND P16- PATIENTS AFFECTED BY OROPHARYNGEAL CARCINOMA (OPC) UNDERGOING (CHEMO) RADIATION

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Background: The available data regarding different patterns of recurrence (DPR) between p16+ and p16- OPC patients (pts) are conflicting, and the present study aims at clarifying it.

Methods: We retrospectively collected data on anyT, anyN, M0 OPCs treated with definitive IMRT (66-72 Gy) ± systemic therapy in 14 South-European Centres from 2007 to 2019 evaluating DPR (incidence of distant (DR) and/or locoregional recurrence (LR)) between p16+ and p16- pts and among p16+ subgroups.

Results: We analyzed 674 pts with a median follow-up time of 6 (5.7-6.3) years (CI 95%). The DPR between p16+ and p16- pts are reported in Table 1. In the p16+ group the incidence of exclusive DR or DR +/- LR was greater than the p16- cohort (38.5% vs 28.4% and 51.3% vs 35.8%), while p16- OPCs experienced more exclusive LR or LR +/- DR (64.2% vs 48.7% and 71.6% vs 61.5%). Subgroup analyses of p16+ OPCs by smoking history (>10 pack-years (PY), <10 PY, never smokers (NS)) showed that the statistical difference in the DPR between p16+ and p16- holds true only when >10 PY p16+ pts were included in the analysis. Actually, the proportions of exclusive DR (and DR +/- LR) is greater in the >10 PY p16+ group (43.5% and 31.3%) when compared with <10 PY (36.4% and 45.5%) and NS (28.6% and 38.1%) p16+ pts.

Conclusions: p16- and p16+ OPCs showed DPR after (chemo)radiation, with a higher risk of LR and DR for p16- and p16+ respectively, with potential implications on both the pattern of observation after treatment and the salvageability of clinical failures. Surprisingly, the different behavior of p16+ OPCs is mostly observed in heavy smokers, while oligo/no smokers have a pattern of recurrence more similar to p16- OPCs. Table 1. DPR in OPCs

	p16 –	p16 + total	p16+ NS	p16+ <10 PY	p16+ (NS + <10 PY)	p16+ >10 PY
n° pts	249	425	146	65	211	214
Recurrence	109	78	21	11	32	46
Exclusive DR	31/109 - 28.4%	30/78 - 38.5%	6/21 - 28.6%	4/11 - 36.4%	10/32 – 31.3%	20/46 - 43.5%
DR +/- LR	39/109 - 35.8%	40/78 - 51.3%	8/21 - 38.1%	5/11 - 45.5%	13/32 – 40.6%	27/46 - 58.7%
Exclusive LR	70/109 - 64.2%	38/78 - 48.7%	13/21 - 61.9%	6/11 - 54.5%	19/32 - 59.4%	19/46 - 41.3%
LR +/- DR	78/109 - 71.6%	48/78 - 61.5%	15/21 - 71.4%	7/11 - 63.6%	22/32 – 68.7%	26/46 -56.5%

C06

EXPLAINABLE PREDICTION MODEL FOR THE HUMAN PAPILLOMAVIRUS STATUS IN PATIENTS WITH OROPHARYNGEAL SQUAMOUS CELL CARCINOMA USING CNN ON CT IMAGES: A MULTICENTRIC STUDY

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Background: Several studies have emphasized how human papillomavirus (HPV) -positive (HPV+) and -negative (HPV–) oropharyngeal squamous cell carcinoma (OPSCC) has distinct molecular profiles, tumor characteristics, and disease outcomes. Different radiomic-based prediction models have been proposed in the state-of-the-art, also using innovative techniques like convolutional networks. Although some of these models showed promising results in terms of model performances, there is a lack of works explaining the role of radiomic features in achieving a specific outcome.

Methods: In this paper, we propose the preliminary results related to an explainable HPV status prediction model by analysing the Gross Tumor Volume (GTV) extracted from pre-treatment CT images. We used images of 499 patients

(356 HPV+ and 143 HPV-) from OPC-Radiomics public dataset to train an end-to-end Inception-V3 convolutional neural network (CNN). In addition, we collected a multicenter dataset consisting of the same kind of images related to 92 patients, which was used as independent test set (43 HPV+, 49 HPV-). Finally, we applied Gradient-weighted Class Activation Mapping (Grad-CAM) interpretability technique.

Results: On the independent test, the proposed model reached an AUC value of 73.50%. The performed XAI algorithm, i.e. GRADcam, showed how the most informative areas in the decision-making process of the classifier, are localed either into the intratumoral. With reference to correctly classified HPV+ patients, the most informative areas are those more internal to the tumor, whereas for correctly classified HPV- patients, the areas most involved seem to be concentrated on the edges.

Conclusions: Finally, the classification model provided an additional information with respect to the accuracy of the classification, given by the visualization of the areas of greatest interest for predictive purposes for each case examined. Such a support tool could help to increase confidence in using the AI model, less understood as a black-box.

C07

PREDICTIVE MULTI-OMIC SIGNATURE IN LOCALLY ADVANCED LARYNGEAL/ HYPOPHARYNGEAL (LH) SQUAMOUS CELL CARCINOMA (SCC) TREATED WITH INDUCTION CHEMOTHERAPY (IC)

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Background: Only limited evidence exists about predictive factor(s) in locally advanced (LA) LHSCC. We aim at assessing a multi-omics signature of response to IC and laryngeal-esophageal dysfunction (LED).

Methods: A retrospective, multicentric, case series of stage III-IV LHSCC patients (pts) treated with IC followed by locoregional treatments were collected. Clinical data (comorbidities, smoking, primary site, T and N categories, performance status), baseline histological samples and radiological imaging were retrieved and correlated with response to IC and LED. Transcriptomic data were derived through RNA-sequencing of biopsy samples. Genes were filtered based on gene-level false-discovery rate comparing response to IC or LED. Radiomic features were entered using 24 principal components.

Several classification algorithms were fit and compared using different metrics (e.g. Classification error-CE), using a repeated 5-fold cross-validation. Three different settings were compared: only clinical data, clinical + genomic and clinical + genomic + radiomic.

Results: We retrieved 282 pts treated in Italy, Spain and Germany until 2022. Data for clinical, genomic and radiomic analysis were available for 282, 197 and 80 cases, respectively. Median follow-up was 89.4 months ($IC_{95\%}$ 77.7-108.8).

88% of pts were male, 64% current smokers and 68% had larynx primary subsite; 25% were T4, while 54% had a N category >1. After IC, 78% of pts achieved a partial/complete response.

Upon RNA-sequencing based transcriptomic analysis, we generated a multi-omic model based on clinical + genomic information, fitted using Support Vector Machine, that achieved a cross-validated AUC > 85% with CE < 30%. A similar approach applied to LED achieved an AUC > 90% with CE < 20%. Adding radiomic features failed to improve the model further.

Conclusions: Using an integrated clinical and omics data, we were able to define the performances of classification algorithms in assessing response according to either IC or LED in LA LHSCC. These algorithms will be applied within a prospective, pilot phase II trial of tailored IC treatment.

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C08

SAFETY OF NEOADJUVANT PARP INHIBITOR AND IMMUNOTHERAPY IN LOCALLY ADVANCED HPV-NEGATIVE HEAD AND NECK SQUAMOUS CELL CARCINOMA (PRIME H&N STUDY)

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Background: Local relapse and/or distant failure after primary treatment are an unresolved clinical issue in locally advanced (LA) head and neck squamous cell carcinoma (HNSCC). The PRIME trial evaluates combination of dostarlimab (D) and niraparib (N) as neoadjuvant and adjuvant treatment for LA HPV-negative HNSCC. Here we present the safety profile of the neoadjuvant part of the trial.

Methods: This is a phase II, single arm, multicenter trial. Patients (pts) with HPV-negative, stage III-IV HNSCC, amenable for surgical treatment received: N 200 mg/day (day -49 to day -21) and D 500 mg iv (day -49 and day -28). On day -21, clinical and radiological evaluations were performed and in case of no response, pts were addressed to curative surgery +/- adjuvant (chemo)radiotherapy ((C)RT); otherwise, pts continued treatment until day -7 and then were addressed to curative surgery +/- adjuvant (C)RT. The primary endpoint was the major pathological response. Secondary endpoints were activity and safety.

Results: From 3/2021 to 12/2023**,** we enrolled 39 pts; 93 treatment-related (TR) adverse events (AEs) of any grade were reported (79.6% G1-2 and 20.4% G3-4). Overall, 74.4% of the pts experienced TRAEs (67% of G1-2 and 33% of G3-4) during neoadjuvant phase. Overall, TRAEs were 20.4% gastrointestinal (1.1% G3-4), 20.4% AST/ALT increase (4.3% G3-4), 11.8% hematological (7.5% G3-4), 10.8% systemic (1.1% G3-4), 10.8% cutaneous (all G1-2), 4.3% endocrinological (all G1-2), 2.2% ocular (1.1% G3-4) and 15% others (1.1% G3-4). Delay in surgery was observed in 1 pts (10 days) due to elevation of CK and troponin T, that were not linked to any cardiac event. In terms of surgical toxicities, 4 pts experienced G3 AEs that were not considered related to treatment: postoperative orocutaneous fistula; flap death; necrosis of the flap skin; postoperative haemorrhage with loss of the flap.

Conclusions: The PRIME trial demonstrated acceptable safety and tolerability of study treatment. Translational data and primary endpoint analysis are still ongoing to define study treatment efficacy.

C09

THYROID HORMONES RATIO HAS A PROGNOSTIC ROLE IN PATIENTS WITH RECURRENT/METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background: The ratio of free triiodothyronine (fT3)/free thyroxine (fT4) has a prognostic role in several tumor types. However, its role in patients with head and neck squamous cell carcinoma (HNSCC) is currently unclear. The aim of this retrospective study was to investigate the relationship between baseline fT3/fT4 ratio and outcome in patients with recurrent and/or metastatic HNSCC (RM-HNSCC) treated with immune checkpoint inhibitors (ICIs).

Methods: We retrospectively reviewed the clinical records of 106 consecutive patients with RM-HNSCC treated with ICIs (monotherapy or in combination with platinum/5fluorouracil) between January 2018 and June 2023 at the Istituto Oncologico Veneto of Padua. Eligible patients should have available baseline measurement of fT3 and fT4. Patients were stratified into three groups according to fT3/fT4 ratio based on tertile distribution. Overall survival (OS) and progression-free survival (PFS) were evaluated using the Kaplan-Meier method. Univariate and multivariate Cox proportional hazards models were used to identify prognostic factors for OS and PFS.

Results: A total of 82 patients were eligible for the analysis. 55 patients (67 %) with platinum-refractory disease received single-agent nivolumab. All 27 patients (33 %) with platinum-sensitive disease were PD-L1 positive

(CPS≥1) and received pembrolizumab-based treatment. Median follow-up was 9 months.

Median OS of patients with low, intermediate and high fT3/fT4 ratio was 6.1, 10.1 and 14.9 months, respectively (p=0.001). Median PFS was 2.1, 2.5 and 8.0 months in the low, intermediate and high fT3/fT4 subgroups, respectively (p<0.001).

At the multivariate analysis, the fT3/fT4 ratio was an independent predictor of OS (Table 1).

Conclusions: Present data support the independent prognostic role of baseline fT3/fT4 ratio in patients with RM-HNSCC treated with ICIs. Low fT3-fT4 ratio is an independent predictor of poor outcome.

	Univariate Analysis for OS			Multivariate Analysis for OS		
	HR	**(95% CI)**	**p value**	**HR**	**(95% CI)**	**p value**
Age (> 70 vs <70)	0.81	(0.46 - 1.58)	0.609	-	-	-
Gender (female vs male)	2.69	(1.36 - 5.32)	**0.005**	1.33	(0.93 - 1.90)	0.112
ECOG 0 vs > 1	0.29	(0.13 - 0.65)	**0.002**	0.69	(0.29- 1.66)	0.405
p16+ vs p16-	0.66	(0.33 - 1.30)	0.232	-	-	-
Platinum sensitive yes vs no	0.50	(0.27 - 0.91)	**0.024**	0.75	(0.55- 1.03)	0.072
Metastatic only vs LR+/-M1	0.32	(0.20 - 0.58)	**<0.001**	0.45	(0.25 - 0.81)	**0.008**
fT3/fT4 ratio:						
high vs intermediate	0.67	(0.37 - 1.22)	0.193	-	-	-
high vs low	0.31	(0.16 - 0.58)	**<0.001**	0.42	(0.21- 0.87)	**0.011**

C10

TRANSDERMAL GRANISETRON IN PREVENTING NAUSEA/VOMITING INDUCED BY CISPLATIN AND RADIOTHERAPY IN HEAD AND NECK CANCER PATIENTS: A PHASE 2, MULTICENTER, PROSPECTIVE TRIAL

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Background: Head and neck cancer (HNC) patients (pts) treated with concurrent chemo-radiotherapy (CRT) suffer from nausea and vomiting, induced by the synergistic effect of both modalities (CINV/RINV). Such symptoms affect pts health, quality of life (QoL) and compliance to cancer therapy, therefore potentially affecting treatment outcomes.

Patients and Methods: We conducted a phase II, open-label, single-arm, prospective, multicentre trial, aimed to assess the activity and safety of transdermal granisetron (TG) in preventing CINV/RINV and evaluate the impact on QoL in HNC pts candidates to IMRT with concomitant 3-weekly cisplatin (> 70 mg/m2 q3w). Enrolled pts received standard anti-emetic treatment (5HT3 antagonist at week 1; dexamethasone and NK1 antagonist at week 1, 4, and 7) and weekly TG from week 4. Adverse events (AEs) were collected according to CTCAE v5.0. From week 4 of treatment, pts were asked to fill in daily the Nausea and Vomiting Diary (NVD), reporting nausea intensity on a VAS scale (from 0 mm to 100 mm): NV control was considered complete if VAS < 25 mm, with no vomiting and no rescue treatment (historical data = 5% of NV complete control). MDASI HN questionnaire was administered weekly for the whole CRT treatment duration (7 weeks). The academic study was promoted by GONO and supported by Kyowa Kirin.

Results: Among 68 pts enrolled, 11 did not apply TG and 13 filled in less than 7 days of NVD; 44 pts filled in ≥ 1 NVD week (intention-to-treat population, ITT), and 30 had ≥ 4 NVD weeks (compliant population). 4 AEs (2 constipation, 1 dry mouth, 1 dysgeusia) were deemed potentially related to TG, none of grade ≥ 3. Complete NV control was reached in 25% and 26% in ITT and compliant population, respectively; rescue treatment was used in 56.8% and 51.6% cases by ITT and compliant population,

respectively. According to MDASI HN questionnaire, cancer-related symptoms, HNC specific symptoms, and QoL interference significatively increased from week 4, and peaked by weeks 6 to 8.

Conclusions: TG is safe and seems to be more active in preventing CINV/RINV in HNC pts undergoing IMRT with concomitant cisplatin in respect to historical data. Its transdermal use may improve pt compliance. Results obtained from patient-reported outcome questionnaires provide a prospective library of pts symptoms during CRT.

C11

HEAD AND NECK SARCOMAS: A SINGLE CENTER RETROSPECTIVE ANALYSIS

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Background: Head and neck sarcomas are rare and aggressive tumor representing about 1% of all sarcomas and 5% of all head and neck cancers. This types of sarcomas are extremely heterogeneous and have different clinical features. With this study, we want to analyze clinical and histological features that impact on prognosis.

Methods: This is an observational, retrospective, monocentric study aiming to describe features, management and prognosis of patients with head and neck sarcomas treated at our Institution between Apr2002 and Dec2023 were included.PFS and OS were estimated with the Kaplan-Meier method.Univariate analysis was performed using margin status,size (<4cmvs>4cm),grade (G1/G2vsG3)

Results: 21 patients were included. T he median age at diagnosis was 50,9 years (range 8-79).Most of the tumors were stage IV (10/21;47.6%) due to size, in fact (47.6%) had a T4 while only one patient had distant metastasis.66% had tumor sizes = 4 cm.Histologically, the tumors were extremely heterogeneous the most frequent was osteosarcoma (19%).Most of the tumors were G3 (66%). In addition, the majority of patients, 58.8% underwent radical surgery with R0. The median follow-up was 40,3m.A statistically significant difference in mPFS of 18.8 m [CI95%;11,9 to 25,6] and 10.9 m [CI95%; 5,9 to 15,9] was observed in the group with G1-2 tumors vs G3 tumors,respectively (p=0,018).In addition, the mPFS in the group of patients with =4 cm was 24,6 m [CI95%; 7,86 to 107], and in patients with =4 cm was 4,8m [CI95%; 2,7 to 23] (p=0.017). In patients with R0 mPFS was 24,6m [CI95%; 7,86 to 107] and in patients with R 1-2 the mPFS was 4,8 m [CI95%; 2,7 to 23] (p=0.017). In mOS there was no statistical significant differences in group of G1-2 and in G3, with mOS of 54 m [CI95%; 21,2 to 197,3] and 19,1m [CI95%; 9,5 to 34,7], respectively (p=0,38). In the group of patients with =4 cm was 54,3m [CI95%; 44 to 197,3], and 22,2m in patients with =4 cm was [CI95%; 4,3 to 34,7],(p=0,24).

Conclusions: Despite the retrospective nature of the study, we have demostreted some characteristics such as surgical resection margin, grade and size are associated with a statistically significant difference in PFS. In contrast, OS was not statistically significant, however, it is associated with a clear trend of benefit in patient with "good characteristics." It is highly notable that in this population we found that some features of the disease have an impact on prognosis. In our opinion, it should be considered in the treatment planning.

C12

THE ROLE OF NEUTROPHIL-LYMPHOCYTE RATIO AS A POTENTIAL BIOMARKER IN PATIENTS TREATED WITH IMMUNOTHERAPY WITH METASTATIC/ RECURRENT HEAD AND NECK SQUAMOUS CELL CARCINOMA: A SINGLE-INSTITUTIONAL RETROSPECTIVE STUDY

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Background: Neutrophil-lymphocyte ratio (NLR) is indicative of tumor inflammation, and is associated with poor prognosis in many malignancies. Here, we present a retrospective real-world study evaluating the NLR as a predictive biomarker in patients with recurrent/metastatic squamous cell carcinoma of the head/neck (R/M HNSCC) treated with immunotherapy

Methods: This is an observational restropective monocentric study including patients with R/M HNSCC pretreated with immunotherapy (pembrolizumab/pembrolizumab +chemotherapy in first-line or nivolumab in second-line) in our institution between 08/2019 and 10/2024. The Kaplan–Meier method was used to estimate efficacy outcome; log-rank test was used to compare the differences, considering a statistically significant p value < 0.05. Patients were stratified according to NLR at the baseline and at the end of the treatment (NLR2) and finally according to the difference between NLR2 and NLR (delta)

Results: 25 patients were included in the study. With a median follow-up of 27,6 months, no statistically significant difference was observed in mOS in NLR-low (NLR<3,5) and NLR-high (NLR>3,5) group, respectively (14.7 m and 14.5 m, log rank: p<0.95), whereas the NLR2 was associated with a statistically significant difference in mOS and mPFS: mOS was not reached in NLR2-low group (5/7 patients were still alive) and mOS was 14.7 m in NLR2-high group ([CI 95%;7.6 to 18.1] p= 0.038); mPFS in the NLR2-low group was 15,2 m [CI 95%; 7,5 to 36,8] and the NLR2-high group was 6,9 m [CI 95%; 5,6 to 8,9] p<0,0021).

Moreover, in patients who had a delta <1.5 the mOS was 15,1 m [CI 95%; 13.9 to 28.1] while in patients with a delta >1.5 was 11.7 m [CI 95%; 7.6 to 14.1] (log rank test: p<0.0053).The mPFS was not associated to a statistical significance differences in both groups (delta< 1,5 mPFS 9,4 m [CI 95%; 6,324 to 21,113] and delta >1,5 mPFS was 6,9 m [CI 95%; 5,287 to 9,229])

Conclusions: Despite the limited number of patients and the retrospective nature of the study, we have shown that patients with NLR2 <3.5 and with a delta <1.5 are associated with a good prognosis. This results highlights the importance of the change in the value of neutrophils and lymphocytes over time.

The optimal cut-off remains an unmet need, and further studies are needed to determine it, especially the delta on a larger population. In conclusion, the NLR value could be an excellent reproducible, dynamic and low-cost marker of response to immunotherapy.

C13

XEVINAPANT, CISPLATIN AND RADIOTHERAPY IN INTERMEDIATE RISK HPV POSITIVE OROPHARYNGEAL CANCER: A RANDOMIZED, PHASE 2 TRIAL - THE "GRETA" TRIAL

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Background: Intermediate risk, HPV-positive locally advanced oropharyngeal cancers (LA OPC) are defined as patients (pts) with a smoking history > 10 pack/years and/or a high nodal stage (N2b-N3). Despite a more favorable prognosis in respect to the HPV-negative counterpart, both locoregional and distant relapse are more frequent than the low-risk HPV-positive. Xevinapant, a first-in-class inhibitor of apoptosis protein (IAP) inhibitor has shown promising results in LA HPV-negative HNSCC with an acceptable toxicity profile. This study aims at evaluating the combination of standard chemoradiotherapy (CRT) with xevinapant in intermediate risk HPV-positive LA OPC.

Material and Methods/Trial design: This is a phase II, randomized 2:1, multicenter trial of xevinapant vs placebo combined with standard cisplatin-containing CRT in pts with intermediate risk, HPV-positive LA OPC. Pts will be enrolled in Italian and Greek Centers and will receive concurrent treatment of weekly cisplatin (40 mg/m2) with intensity-modulated RT (70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fr, 5 days a week), with three cycles (3 weeks per cycle) of xevinapant (200 mg/day, days 1–14) or placebo, followed by an adjuvant phase consisting of three cycles of xevinapant (200 mg/day, days 1–14, 3 weeks per cycle) or placebo monotherapy. The primary objective is to demonstrate superior efficacy of xevinapant vs placebo in terms of 3-year event-free survival; secondary objectives are efficacy (in terms of locoregional and distant recurrence free survival), activity (in terms of objective response rate and overall survival), safety, and quality of life. As exploratory analysis we will evaluate prognostic/predictive biomarkers such as HPV-DNA load, the immune UWO3 score, and gene-expression of IFN-α and IFN-γ, usually suppressed in smokers. With a sample size of 140 patients randomized in a 2:1 ratio, a total of 33 EFS events provides 80% power at a 1-sided alpha of 0.1 to detect an HR of 0.45 (assuming 3-yr EFS of 78% in the patients treated with xevinapant, cisplatin and radiation compared with 58% in the standard of care group).

Conclusions: By adding xevinapant to standard CRT we aim at improving prognosis of intermediate risk HPV-positive LA OPC by boosting the sensitivity of concurrent CRT.

Funding

This is a trial in progress - The trial is supported by MERCK.

C14

LOW DOSES CISPLATIN + PEMBROLIZUMAB AS FIRST LINE IN FRAGILE PATIENTS WITH RECURRENT OR METASTATIC HNSCC

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Background: head and neck cancer is a neoplasm that also affects patients over 70 years of age with comorbidities that can often limit the use of the first line consisting of Cisplatin, FluoroUracil and Pembrolizumab. In case of PDL-1 CPS higher than 20, the possibility of using the immunotherapy in monotherapy is considered, considering the risk/benefit balance of the combination, but in the intermediate zone between 1 and 20 this indication is not supported by evidence in the literature. The definition of fit or unfit to cisplatin is well known, linked to ECOG, neuropathy, hearing loss and creatinine clearance. However, comorbidities over the age of 70 can involve numerous systems, even outside those considered in this definition, often leading to under-treatment or non-treatment of the fragile patient. In our study we wanted to evaluate the use of a 2-drug scheme for the treatment of this type of patient.

Patients and Methods: patients with recurrent or metastatic head and neck heteroplasia with CPS PDL-1<20, age over 70 years, ECOG 0-1, without absolute contraindications to the use of Cisplatin or Pembrolizumab were included in the study. These patients followed a regimen consisting of Cisplatin 50-70 mg/m2 + Pembrolizumab 200 mg threeweekly. After 6 combination cycles, they continued with maintenance immunotherapy alone until progression or unacceptable toxicity.

Results: from January 2022 to January 2024, 12 patients who met the inclusion criteria were included in the study, 7 men and 5 women, with an average age of 77.8 years (72-84). These patients, in addition to the neoplasm, presented cardiological comorbidity in 10 cases, hypertension in 8 cases, dyslipidemia in 6 cases, diabetes mellitus in 5 cases, 3 patients presented previous cerebral ischemic episodes without significant sequelae. All patients had CPS PDL-1 between 2 and 20. Eight patients are still on maintenance treatment, 4 have relapsed and continued with a second line with weekly paclitaxel. The average response duration at the time of data processing is 13 months. During treatment, comorbidities were monitored in a multidisciplinary setting. No G3-4 toxicities were detected. All patients are still alive.

Conclusions: The combined treatment was well tolerated and appears to be a real possibility for frail patients who could not tolerate the triplet combination, but who have intermediate or too low CPS PDL-1 values ??to expect a prolonged response with immunotherapy alone.

C15

BILATERAL HEAD AND NECK PARAGANGLIOMAS: REPORT OF A RARE CASE AND LITERATURE REVIEW

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Background: Bilateral head and neck paragangliomas are rare vascular tumors that develop from paraganglia. We performed a literature review on this unusual pathological finding, depicting epidemiology and diagnosis.

Material and Methods: We present a case of a 49-year-old woman experiencing tinnitus, unilateral deafness, dizziness worsening with movement, burning headache, weight loss, insomnia, dysphagia, swelling of the left posterior mandibular angle, and pain increased on palpation. Diagnostic imaging revealed an enhancing expanding lesion located in both jugular foramina. A diagnosis of a right tympano-jugular paraganglioma with extra and intracranial extension and a contralateral jugular-carotid paraganglioma was made.

Discussion: We presented a rare case of cervical bilateral paraganglioma occurring in a young woman, with the two paragangliomas expressing different growth patterns and different behavior. Familial paragangliomas represent approximately 40% of all paragangliomas, and are more commonly multicentric and common in females; in particular, female sex predilection is most common in the jugular and tympanic subtypes. Bilateral carotid body tumors represent approximately 3%of all paragangliomas. Patients who exhibit clinical symptoms that are suggestive of a paraganglioma, as well as those who come from families where paragangliomas are hereditary, may be candidates for MRI and CT imaging. In this scenario, in addition to the detection and staging of the lesions, it is also necessary to evaluate whether multicentric tumors are present.

Conclusions: Use of the most sensitive available imaging techniques is crucial to correctly detect and stage head-and-neck paragangliomas. Imaging plays a major role in the diagnosis, as well as in management design and follow-up, which is influenced by lesion location, neurovascular involvement, and malignancy potential.

D - Genitourinary and Gynaecological Tumors

D01*

OVERALL SURVIVAL (OS) RESULTS IN PHASE II TRIAL OF CABOZANTINIB (CABO) PLUS DURVALUMAB (DURVA) IN PATIENTS WITH UROTHELIAL CARCINOMA (UC) OR NON-UC VARIANT HISTOLOGIES (VH) AFTER PLATINUM CHEMOTHERAPY (ARCADIA)

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Background: Combining multitargeted receptor tyrosine kinase inhibitor (TKI) with checkpoint inhibitors has shown synergistic effect in pts with in various solid tumors due to the immunomodulatory propriety of VEGFR inhibitors. We aim to investigate the safety and efficacy of the combination of cabozantinib plus durvalumab in advanced UC and VHs (NCT03824691). Herein we present the overall survival results of the interim analysis

Methods: Patients affected by UC or non-urothelial carcinoma (VHs) recurred/progressed after at least one line of platinum-based chemotherapy for metastatic disease have been treated with CABO 40 mg daily, orally, and DURVA 1500 mg IV, q28 days, until disease progression (PD, by RECIST 1.1) or onset of unacceptable toxicity. Response was evaluated by RECIST criteria v.1.1 every 8 wks. The primary endpoint of the study was OS. Secondary endpoints included safety (CTCAE v.4.03), objective response-rate (ORR), duration of response (DoR), progression-free survival (PFS).

Results: As of February 10, 2024 data cut, 61 pts were enrolled and were evaluable for response; median follow-up was 26 months (interquartile 16.38-35.82), median age was 64 yrs and 21 pts (24%) had pure/predominant VHs: 10 (47.6%) squamous differentiation/sarcomatoid tumor, 4 (19%) adenocarcinoma, 5 (24%) small-cell neuroendocrine tumor, 1 (4.7%) clear-cell tumor, and 1 nested VH (4.7%). 12/61 (20% liver mets.12 pts (20%) had ≥ 2 prior lines of therapies. Median OS and PFS were 12.9 months (95% CI, 7.1-25.5) and 6 months (95% CI, 3.9-9.4), respectively. Confirmed ORR was 42.6% (range 30-55.9),18% CR in 11 pts. For VHs subgroup, median OS and PFS were 17.6 months (95% CI, 5.3-NR), and 5.3 (95% CI, 2.8-NR), respectively and ORR was 31%. At analysis, 9 pts remained on treatment. 2/61(3%) pts received EV as subsequent therapy. 38/61 pts had treatment-related adverse events of any grade and 25 (41%) had grade 3/4.

Conclusions: CABO in combination with DURVA suggests promising prolonged survival and acceptable tolerability in pts with advanced UC, especially those with VHs. Further randomized controlled studies will be required in a larger patient population.

D02*

LEVERAGING REAL-WORLD DATA FROM A DE-IDENTIFIED CLINICO-GENOMIC DATABASE TO FULFILL THE TREATMENT GAP IN HIGH-GRADE SEROUS OVARIAN CANCER (HGSOC) PATIENTS

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Background: HGSOC poses substantial therapeutic challenges due to its genomic heterogeneity. This study exploits the extensive dataset from the Flatiron Health-Foundation Medicine Clinico-Genomic Database (FH-FMI CGDB) to enrich our understanding of HGSOC's genomic intricacies and to assess the utility of comprehensive genomic profiling (CGP) in clinical settings.

Patients and Methods: We conducted a retrospective observational analysis on adult patients with HGSOC profiled with FMI genomic tests, retrieved from FH-FMI CGDB and originating from ~280 US cancer clinics(from Jan 2011 to Sep 2023), applying basic descriptive statistics with SAS Studio v9.4 and R software v4.1.2 to explore the dataset.

Results: The study included 856 HGSOC patients (pts), median age 69 ys (range 30-93). 439 pts were selected, presenting both FMI test performed on specimen collected at the time of surgery and initiation of 1st line therapy within ±8 months from surgery: 78.36% were in stage III-IV and 64.46% had ECOG 0-1, categorized into no surgery (NS, n=74), interval surgery (IS, n=157), and upfront surgery (US, n=208) groups, each comparable by clinical features. Overall, *BRCA* mutation were found - at similar frequency in the 3 groups - in 32/341 pts (9.3%), 24 referred as germline, mainly *BRCA1* (20/32=62.5%), based on ad-hoc complementary test from different providers where available. Loss-of-heterozygosity (LOH), a proxy for Homologous Recombination Deficiency provided by FMI CGP, was found in 142/439 (33%) pts, different across treatment groups (12.8% NS; 9% IS; 8.8% US). We focused on those patients for whom neither BRCA complementary test gave positive result, nor LOH was detected by CPG. In these 206 pts, the analysis exhibited further potentially targetable genomic pathogenic alterations, highlighting *CCNE1* amplification in 41 (20%) pts; amplification or mutations of *FGFR1/2/3/4*, *HER2*, *CDK12* in 16 (7,7%), 12 (5,8%) and 9 (4.3%) pts, respectively; mutations of *PIK3CA*, *ARID1A*, *BRAF* in 8 (4%), 4 (1,9%) and 3 (1,4%) pts, respectively Interestingly, CPG revealed *BRCA1/2* mutations in 9 pts additional to complementary tests.

Conclusions: CGP significantly enhances the identification of molecular targets in HGSOC, supporting its importance in the clinical practice to provide pts with more therapeutic options.

D03*

POLE MUTATIONAL STATUS AS PROGNOSTIC MARKER IN ENDOMETRIAL CANCER: A MITO POLE-END REAL-LIFE STUDY

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Background: Approximately 3-5% of endometrial tumors harbor pathogenic mutations in the POLE gene. Currently, adjuvant treatment is not deemed necessary for these tumors when diagnosed at an early stage, though uncertainty remains regarding later stages. Our multicenter observational study aims to assess the clinical outcome of patients with mutated POLE endometrial neoplasia, specifically focusing on Recurrence-Free-Survival and to correlate these data with other prognostic factors and treatment modalities.

Materials and Methods: We enrolled patients from MITO group centers between January 2020 and May 2024. All patients were diagnosed with a POLE mutated endometrial cancer, identified using Next-Generation Sequencing (NGS). Data on demographic characteristics, risk factors, histotype, grading, lymphovascular invasion (LVI), FIGO stage, molecular mutations status, treatments, and follow-up were collected. We are presenting an interim analysis as the study is ongoing.

Results: Of the 82 patients enrolled in the study so far, the median age at diagnosis was 59 years (range 54-66). Among the cases, 76(92.7%) were of endometrioid histotype while 4(4.9%) were serous, 1(1.2%) clear cell, and 1(1.2%) undifferentiated; 57.3% had a grade 3 tumors. Regarding stage distribution, 84.1% of patients were diagnosed with stage I disease, 8.5% with stage II, 4.9% with stage III, and 2.4% with stage IV. The most frequently mutated exons in POLE were exon 9(47.6%) and exon

13(40.2%), with the predominant mutations being p.Pro286Arg (41.5%) and p.Val411Leu (34.1%), respectively. Additionally, 22(26.8%) patients exhibited mutations in the TP53 gene, 30(36.6%) in the PIK3CA e 21(25.6%) cases showed MMRd. 47 patients (57.3%) underwent surgery only; 18(22%) underwent surgery and adjuvant radiotherapy; 7(8.5%) underwent surgery, radiotherapy, and chemotherapy; and 1(1.2%) underwent surgery and chemotherapy. To date, one patient has died and one has relapsed; both were stage IV.

Conclusions: Our preliminary results show that, although 63.4% of cases harbored negative prognostic factors such as p53 positivity and high-grade tumors, only 7.3% were in an advanced stage. RFS was optimal, except for one death in a patient with stage IV disease and brain metastases at diagnosis, confirming that POLE mutation is a driver mutation. We found a frequent association between POLE and/or PI3K mutations and Mismatch Repair (MMR) deficiency, which is under investigation in a larger cohort.

D04*

PIK3CA MUTATIONS IN ENDOMETRIAL CANCER: A PRE-PLANNED BIOMARKER ANALYSIS FROM THE PHASE II MITO END-3 STUDY OF CARBOPLATIN AND PACLITAXEL WITH OR WITHOUT AVELUMAB IN ADVANCED OR RECURRENT ENDOMETRIAL CANCER

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Background: Immunotherapy with chemotherapy significantly improves progression-free survival in advanced endometrial cancer (EC) especially in microsatellite-instability high (MSI-H) cases. New predictive biomarkers to select patients (pts) that could benefit from immunotherapy are highly needed, especially for microsatellite-stable (MSS) tumors, which comprises approximately 70% of all EC pts. More effective therapies are needed also for MSI-H pts progressing after immunotherapy. The PI3K pathway is frequently altered in gynecological tumors representing a potential treatment target in EC.

Patients and Methods: In a pre-planned molecular anlysis of the MITO END-3, we retrospectively analyzed the genomic abnormalities of 107 pts with samples eligible for Next Generation Sequencing analysis (FoundationOne CDx) focusing on PIK3CA mutational status.

Results: In our analysis the 4 most frequently mutated genes were *TP53, PIK3CA, ARID1A, PTEN. PIK3CA* mutations were detected in 51.4% (55/107 pts) of tissue samples. A total of 68 different *PIK3CA* mutations were observe, of which 64 were considered pathogenic with the co-expression of 2 different pathogenic mutations in 2 patients and 4 variants of uncertain significance. The most frequent *PIK3CA* mutations were found in the kinase domain H1047R (11/68), H1047Y (3/68), and in the helical domain such as E545K (4/68) and E542K (3/68). Notable, 24 different *PIK3CA* mutations out of 68 reported in MITO END-3 are considered as predictive of response to PI3K inhibition by the current literature in breast cancer based on SOLAR-1 and BYLieve studies (C420R, E542K, E545A, E545D, E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y). According to the new molecular classification, *PIK3CA* mutations were observed in all the TCGA categories. Indeed, there were 13 pts with *PIK3CA* mutations in *TP53* wild-type group, 21 pts in *TP53* mutated, and one case with *POLE* mutation. Interestingly, *PIK3CA* mutation were reported in 20 pts of the MSI-H group.

Conclusions: The frequent alterations of the PI3K pathway in gynecological cancers could emerge as new treatment target. Our data confirm the high frequency of *PIK3CA* mutations establishing EC as an ideal candidate for testing of PI3K inhibitors regardless of the TCGA classification. Moreover, these data confirm that other targetable mutations are present also in MSS EC group thus suggesting that new target agents should be explored.

D05*

LEVERAGING THE BLACK BOX: EVALUATION OF MACHINE LEARNING (ML) ALGORITHMS FOR THE ANALYSIS OF COPY NUMBER VARIANTS (CNVS) IN ADVANCED EPITHELIAL OVARIAN CANCER (EOC) PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY (NACT)

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Background: In patients with advanced EOC undergoing NACT plus interval debulking surgery (IDS) the chemotherapy response score (CRS) is a prognostic surrogate. We analysed ML models feature importance for potential biomarkers of CRS.

Materials and Methods: A comprehensive genomic profiling evaluating CNVs in 514 genes was performed in chemotherapy-naïve EOC patients addressed to NACT plus IDS. Exploratory analyses were conducted using uniform manifold approximation & projection (UMAP) and hierarchical clustering with Ward distance. A custom ML pipeline was developed: after windsoring of copy number neutral segments a zero-variance filter was applied. SelectKBest and recursive feature elimination (RFE) were considered as feature selection algorithms followed by XGboost as classifier. Hyperparameters tuning was conducted using 5-folds cross validation to avoid overfitting and the Tree-structured Parzen Estimator for sampling, using the area under the receiver operating characteristic (AUROC) curve as objective function. Potential biomarkers of response were evaluated using SHAP values, measuring the contribution of each predictor.

Results: Overall, 96 patients were included in the analysis, 67 CRS1-2 and 29 CRS3. DNMT3B amplifications were more common in CRS1-2 patients (OR 7.90, $p<0.01$). While UMAP analysis revealed no clear separability of patients according to CRS status, hierarchical cluster identified a subgroup of CRS1-2 patients with recurrent amplifications, mainly in KDM5A, FGF23, FGF6, DNMT3B and AURKA. In the supervised analysis, CNVs were discretized and ordinally encoded as loss/deletion, copy number neutral and gain/amplifications. Using RFE, 14 genes were selected with a mean AUROC on the 5 folds of 0.65. The genes with the higher discriminative capability (corresponding to a greater mean absolute SHAP value) were FRS2, RAD52, ETV5, DNMT3B and NOTCH1. In detail, amplifications of FRS2, ETV5, DNMT3B and PDK1 were associated with negative SHAP values and CRS1-2, while RAD52 and NOTCH1 amplifications, as well as PLK2 loss were associated with positive SHAP values and CRS3.

Conclusions: CRS1-2 and CRS3 patients may exhibit a different CNV landscape, reflecting the differences in response to NACT. The combination of feature selection methods with local explanations of ML models predictions has the potential to guide biomarker discovery for the identification of subgroups of patient with different response to platinum-based chemotherapy.

D06

IMPACT OF EXPOSURE ON OUTCOMES WITH ENFORTUMAB VEDOTIN IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL CANCER

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Background: Enfortumab vedotin (EV) is approved as monotherapy or plus pembrolizumab (EV+P) for patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC). EV and EV+P improved overall survival (OS) with generally manageable safety profiles in pts with la/mUC. Dose modifications are recommended to manage EV-related AEs. Here we evaluated associations between EV plasma exposure and safety and efficacy outcomes.

Methods: Pts in EV-101 (EV 0.75, 1.0, and 1.25 mg/kg on days 1, 8, 15 of 28-day cycles [3Q4W]), EV-201 (EV 1.25 mg/kg 3Q4W), and EV-301 (EV 1.25 mg/kg 3Q4W) were characterized for dose- and exposure-response for efficacy and exposure-response for safety outcomes. Time-averaged exposure up to an event of interest, Cavg, was computed using a population pharmacokinetics (PK) model. PK included multiple samples in cycles 1–2 and pre-dose samples in subsequent cycles.

Results: Dose modifications were common, including reductions to 1.0 mg/kg (EV-201 42.1%; EV-301 35.1%) and 0.75 mg/kg (EV-201 13.6%; EV-301 11.1%). EV improved median progression free survival (PFS) and OS vs chemotherapy across exposure quartiles in EV-301 (Table). Greater initial EV exposure was associated with higher objective response rates (0.75 mg/kg 21.4% [n=14]; 1.0 mg/kg 18.5% [n=27]; 1.25 mg/kg 40–51.1% across studies [n=613]). Lower EV exposure was associated with fewer EV-related Grade (Gr)≥3 rash/skin reactions, Gr=2 peripheral neuropathy, and Gr=3 hyperglycemia (all P<0.0001).

Conclusions: EV improved survival vs chemotherapy in pts with la/mUC across exposures. Starting doses of 1.25 mg/kg 3Q4W maximized likelihood of response. Dose modifications effectively manage EV-related AEs and should be used as clinically indicated.

EV-301 ADC Cavg	ADC Cavg				
	Q1‡ (n=74)	Q2 (n=74)	Q3 (n=74)	Q4 (n=74)	Chemotherapy§ (n=307)
Median EV ADI (mg/kg/4 week)† (range)	2.37 (1.15, 3.77)	2.96 (1.57, 3.82)	3.26 (2.36, 3.86)	3.59 (2.50, 3.93)	
Received EV dose reduction (%)	54.0	39.2	28.4	20.3	
To 1.0 mg/kg	52.7	39.2	28.4	20.3	
To 0.75 mg/kg	21.6	14.9	6.8	1.4	
Median time to EV dose reduction, months (range)	2.02 (0.79, 9.27)	2.96 (0.95, 12)	3.06 (0.72, 6.64)	2.79 (0.89, 9.04)	
Median PFS, months (95% CI)	4.44 (3.75, 6.77)	7.16 (5.39, 8.21)	5.62 (5.09, 7.26)	5.65 (5.32, 7.23)	3.71 (3.52, 3.94)
Median OS, months (95% CI)	11.0 (7.89, 15.2)	15.1 (10.8, NE)	15.2 (9.63, NE)	12.6 (9.79, NE)	8.97 (8.05, 10.74)

†Intended ADI was 3.75 mg/kg/4 weeks. ‡Lowest exposure group. §Planned treatment arm. ADI, absolute dose intensity, NE, not evaluable

D07

LIVMONIPLIMAB WITH OR WITHOUT BUDIGALIMAB IN PATIENTS WITH ADVANCED SOLID TUMORS: RESULTS FROM THE COMBINATION THERAPY IN THE UROTHELIAL CARCINOMA DOSE EXPANSION COHORT

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Background: Checkpoint inhibitors(CPIs) are approved for advanced(adv) urothelial carcinoma(UC). Many patients(pts) present with/develop resistance. Release of active transforming growth factor beta-1(TGF-β1) from glycoprotein-A repetitions predominant(GARP):TGF-β1 complex on regulatory CD4+ T cells suppresses antitumor response. Inhibiting active TGF-β1 release from GARP:TGF-β1 complex could address CPI resistance in UC. Livmoniplimab(livmo), antibody targeting GARP:TGF-β1 complex, is being investigated as monotherapy and in combination with budigalimab(budi), anti–PD-1 antibody, in ph1 study(NCT03821935). We present expanded results from livmo+budi dose expansion(EXP) UC pts.

Methods: This is dose escalation(ESC) and EXP study. UC EXP cohort enrolled pts(≥18 yr) with UC of bladder and urinary tract progressed on platinum-based therapy and CPI in metastatic setting. Max tolerated dose was NR in ESC part. Pts in EXP cohorts received max administered dose of 1500mg livmo(IV, Q2W) and 500 mg budi(IV, Q4W) until PD/intolerable toxicity. Primary efficacy endpoint: ORR per RECIST v1.1. Additional efficacy outcomes: DOR and PFS. Safety and PK were assessed.

Results: As of 30 Mar 2023, 200 pts were enrolled, 57 in ESC and 143 in livmo + budi EXP, including 48 pts in UC EXP cohort. In UC cohort, median age was 66 yr(49–85), 77% of pts male, 40%/60% had ECOG PS 0/1 and median prior lines of therapy was 3(1–9). Livmo PK wasn't impacted by budi coadministration and no on-treatment

anti-drug-antibodies were detected. All pts had TEAEs; most common: pruritus(44%) and decreased appetite(21%). Grade 3/4 TEAEs occurred in 23 pts(48%); most common: anemia and malignant neoplasm progression(10% each); 11 pts(23%) died. No death related to livmo or budi. 29 pts(60%)/26 pts (54%) had TRAEs for livmo/budi; most common: pruritus(livmo:33%; budi:31%) and rash(17% for both). Among 45 response evaluable pts, best response rate was 24%(n=11; 95% CI:12.9, 39.5); confirmed ORR was 18%. Median restricted mean DOR: 7.9 mo(95% CI: 6.0, not reached); median/75th percentile PFS: 1.8 mo(95% CI: 1.6, 4.2)/8.0 mo (95% CI: 2.7, 14.9).

Conclusions: Livmo+budi had manageable safety and promising efficacy in pts with adv UC progressed on platinum-based therapy and CPI. UC cohort ORR(pts postprogression with platinum+CPI therapy) are comparable with CPI-naive pts ORR with pembrolizumab(KN-045) and nivolumab(CM-275) monotherapy. A subpopulation of pts in UC cohort had durable response to livmo+budi.

D08

MISMATCH REPAIR (MMR) AND HOMOLOGOUS RECOMBINATION (HR) DEFICIENCY: REAL-LIFE APPLICATIONS OF BIOMARKERS FOR COMPLEMENTARY APPROACHES IN EPITHELIAL OVARIAN CANCER

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Background: BRCA1/2 mutational status and homologous recombination deficiency (HRD) are key biomarkers for guiding the use of PARP inhibitors (PARPis) in the epithelial ovarian cancer (EOC) patients. Methods for identifying and interpreting DNA damage need clinical refinement. Recent research also highlights the role of mismatch repair (MMR) genes in the pathogenesis of a subgroup of EOC.

Material and **Methods:** This real-life study evaluated the HRD status in newly-diagnosed EOC patients employing HRR multigene panels including HRR and MMR genes, along with HRD genomic instability assessments. Initial evaluations determined tumor (t) and/or germline (g) BRCA pathogenic variants (PVs). In cases of BRCA wild-type (WT) tumors, HRD status was also assessed using the myChoiceCDx (Myriad) and SOPHiA DDM™ assays. A 20-gene NGS panel was performed for patients with a notable personal/family cancer history.

Results: Between January 2017 and April 2024, 620 unselected EOC patients, aged 27 to 82, were examined for BRCA status. Of these, 124 (20%) had gPVs in BRCA1/2 genes, and 27 (4.4%) had tPVs. Among the 82 BRCA WT patients who underwent multigene panel testing, 15 gPVs were found in non-BRCA genes, including 5 MUTYH (35.7%), 2 ATM (14.3%), 2 MLH1 (14.3%), 2 PMS2 (14.3%), 2 RAD51C (14.3%), 1 RAD51D (7.14%), and 1 CHEK2 (7.14%). Out of 135 samples analyzed for HRD genomic instability, 51 (37.8%) were identified as HRD positive, and 69 (51.1%) as HRD negative. Notably, the HRD-negative group showed a higher prevalence of endometrioid histology (12.6% vs. 3%, p=0.02), a higher proportion of EOC patients with a personal history of endometrial cancer (5.2% vs. 0.7%, p=0.01), and fewer cases of EOC or breast cancer in family histories (p=0.04), suggesting a complex biological backdrop in HRD negative tumors, that could involve unrecognized non-HRR genes.

Conclusions: HRD genomic instability tests and multigene panel assessments serve as synergistic tools in EOC clinical settings, proving essential for identifying patients likely to benefit from PARPi therapy. These tools also enhance the detection of HRR and MMR gene variants, aiding in preventive care. Further investigations into the genetic profiles of HRD-negative tumors are crucial for advancing cancer risk management and developing novel therapeutic avenues.

D09

LIVMONIPLIMAB AND BUDIGALIMAB COMBINATION THERAPY IN TREATING PATIENTS WITH METASTATIC OVARIAN GRANULOSA CELL TUMORS: RESULTS FROM DOSE ESCALATION IN A FIRST-IN-HUMAN STUDY

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Background: Ovarian granulosa cell tumors(OGC) are rare, accounting for 5–7% of all ovarian cancers, fatal when metastatic. There are no approved targeted therapies for metastatic OGC. Several agents with different targets, such as pembrolizumab, nirogacestat, orteronel and STM 434, are being evaluated but to date without clinical benefit. Most OGC carry a C134W mutation in the *FOXL2*

gene, which manifests its protumor effects via the transforming growth factor(TGF)-β signaling pathway. Livmoniplimab(livmo), monoclonal antibody(mAb), specifically binds to the TGF-β1–glycoprotein-A repetitions predominant protein complex, blocking release of active TGF-β1. Livmo has been assessed with or without budigalimab(budi), antiPD-1 mAb, in dose escalation(ESC) part of first-in-human study in patients(pts) with advanced solid tumors including OGC. We report results of 4 pts with OGC enrolled into the combination ESC part of this ph1 study(NCT03821935).

Methods: Pts≥18 years with ECOG PS 0–1 were enrolled in ESC, including pts with metastatic OGC refractory to/not eligible for standard therapies. Max tolerated dose was NR and pts received max administered dose of 1500mg livmo (Q2W IV)+ 500mg budi(Q4W IV). Safety and ORR per RECIST v1.1 were assessed.

Results: As of 28 Sep 2023, 57 pts were enrolled in ESC, including 4 with metastatic OGC aged 50–63yr with 3–7 prior lines of systemic therapy. In total, 98%(n=56) pts in ESC experienced TEAEs, most common: fatigue(42%), nausea(37%) and anemia(37%). 1 pt with OGC was enrolled with metastatic target lesions in lung, liver and peritoneum at screening. She had received 7 prior lines of therapy including doxorubicin, bevacizumab, anastrozole, tamoxifen and carboplatin+paclitaxel. Upon treatment with livmo+budi, she had a deep partial response(-92% from baseline) and complete response in target liver lesion. The pt responded for ~2.5 years before death due to an event unrelated to study drugs. 2 other pts with metastatic OGC had partial response(ORR=75%) and none of the 4 pts experienced PD(DCR=100%).

Conclusions: Livmo+budi had promising antitumor efficacy and tolerablesafety profile in pts with metastatic OGC. All enrolled pts showed tumor shrinkage and 1 pt had durable and near-complete response. Since single-agent pembrolizumab exhibited an ORR of 0%(How et al. Invest New Drugs, 2021;39:829-835). We conclude OGC is a proof-of-mechanism indication for livmo and targeting TGF-ß may represent an effective strategy for OCG pts.

D10

ROLE OF PLASMA EXOSOME-DELIVERED IMMUNOMODULATORY MOLECULES IN INTERPLAY BETWEEN IMMUNE SYSTEM AND HEREDITARY OVARIAN CANCER: OPPORTUNITY OR CHALLENGE?

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Background: Ovarian cancer (OC) is a prevalent gynaecological malignancy characterized by high mortality and low overall survival rates. About 15% of OC women harbours a germline *BRCA1/2* pathogenic variant (PV) which predispose them to hereditary cancer forms. Specific tumour-derived extracellular vesicles, called exosomes, are considered as potential key players in cross-talk between immune system and tumour microenvironment in several solid tumours. In fact, exosomes play a crucial role in intercellular communication, by transporting biologically active molecules such as proteins, lipids, enzymes, mRNA, and miRNAs. Since scientific evidence highlighted a correlation between *BRCA1/2*mutational status, immunogenicity and survival in OC, our study aims to understand whether the exosomes can be used in clinical practice as a source/vehicle of biomarkers able to predict survival in OC women.

Patients and Methods: Exosomes were isolated from plasma collected from one hundred metastatic OC patients before surgery and therapy, consecutively enrolled from March 2021 to February 2024 at the University Hospital Policlinico "P. Giaccone" of Palermo (Italy), in order to measure concentrations of some immunomodulatory molecules, such as PD-1, PD-L1, BTN3As, BTN3A1, BTN2A1 and BTLA. The exosomes have been isolated from plasma using exoEasy Maxi kit (Qiagen). All patients were genetically tested for germline *BRCA1/2* PVs by next-generation sequencing analysis.

Results: The mutational screening showed that less than a third of patients were carriers of an inherited *BRCA* alteration (61.3% in *BRCA1* and 38.7% in *BRCA2*), with a median progression-free survival (PFS) longer than women without mutation. Germline *BRCA1/2* PV carriers, with absence of basal peritoneal carcinomatosis, normal body mass index (18.5≥BMI<25) and exosomal concentrations of butyrophilin sub-family 3 member A1 ≤4.75 ng/mL showed a longer PFS (≥30 months) and better prognosis compared to *BRCA-wild-type* OC women.

Conclusions: This emerging research data suggests that exosomes could serve as carriers of prognostic biomarkers with immunomodulatory functions, and as potential targets for future therapeutic strategies aimed at eliciting antitumor immune responses in inherited OC.

D11

This abstract was withdrawn at the request of the Authors.

D12

OLAPARIB FIRST-LINE (1L) MAINTENANCE THERAPY IN BRCA1/BRCA2-MUTATED (BRCAM) ADVANCED OVARIAN CANCER (AOC) PATIENTS (PTS): EFFECTIVENESS AND SAFETY AT 3-YEAR FOLLOW-UP IN ITALIAN PTS IN THE OVAL-1 STUDY

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Following statistical significance and clinically meaningful benefit of olaparib vs placebo in the SOLO-1 trial, AstraZeneca launched a global early access program (EAP) to provide olaparib tablets to eligible AOC pts. OVAL-1 (NCT04532645) is a pan-European non-interventional, retrospective study of BRCAm AOC pts who received olaparib maintenance after response to 1L Platinum-based chemotherapy during EAP and reimbursement periods. Here we present 3-year effectiveness and safety data from cohort of 124 pts treated in Italy. Pts diagnosed with BRCAm AOC (FIGO stage III-IV) were included from 19 sites after receiving their 1st olaparib dose between March 2019 and June 2020. 3-year investigator assessed progression free survival was 68.5% (CI 60.40;76.70) while overall survival was 87.90 %(CI 82.20;93.60); 39 pts (31.5%)

received a first subsequent treatment; overall response rate was 98.4%. Adverse events (AEs) were only collected if AEs resulted in dose reduction, treatment interruption or discontinuation and are reported in Table 1. No AEs of special interest occurred. After a median follow-up of 40.5 months, 117 (94.4%) pts discontinued olaparib while 7 (5.7%) remained on treatment. Main reason for discontinuation was the completion of 24 months treatment. This descriptive analysis provides insights into the real-world management in the setting of eligible AOC pts with complete or partial response to last PBC. Olaparib effectiveness and safety profile in this Italian cohort are consistent with SOLO-1 trial results. Table 1: Per protocol

Per protocol AE profile N (%)	Total (N=124)
Number of events	152
Patients with any AE n (%)	99 (80.0)
Median time to first occurrence (days)	114
Median duration of AEs (days)	15.5
AEs any grade	
Nausea	9 (7.3)
Vomiting	3 (2.4)
Anemia	36 (29.0)
Neutropenia	9 (7.3)
Thrombocytopenia	5 (4.0)
Fatigue	5 (4.0)

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D13

IMPACT OF POLYMERASE EPSILON EXONUCLEASE DOMAIN MUTATION ON PROGNOSIS IN ENDOMETRIAL CANCER (EC): OUR EXPERIENCE IN AZIENDA USL TOSCANA NORD-OVEST (ATNO)

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Background: Although the recent progress in therapeutic approach, EC mortality is increasing. The Cancer Genome Atlas (TCGA) has identified four classes of risk based on specific signatures of EC: polymerase epsilon exonuclease domain mutated (POLE EDM), mismatch repair deficient (MMRd), p53 wild-type/copy-number-low (p53 wt), and p53-mutated/copy-number-high (p53 abn). POLE mutations occur in about 8-10% of EC and leads to an excellent prognosis.

Material and Methods: The aim of our analysis was to investigate incidence, characteristics and behavior of POLE mutated EC referred to Pathological Anatomy Unit of ATNO from 2022 to 2024. We performed the molecular profiling by immunohistochemical evaluation of p53 and MMR proteins (MLH1, PMS2, MSH2, MSH6) by Ventana Benchmark Ultra - Roche Ventana platform whereas POLE hot spot mutation was investigated by gene sequencing (panel 17 genes) with kit "Myriapod NGS Cancer Panel DNA", CE-IVD, company Diatech Pharmacogenetics S.r.l.

Results: 87 EC comprehensive of molecular profiling, were identified. A pathogenic mutation of POLE was found in 11 patients (12,6%) affected by stage I or II EC; of these, 6 were pure endometrioid carcinomas and 5 mixed endometrioid carcinomas with a component of clear cell carcinoma (CCC) or serous carcinoma (SC). For the good prognosis due to mutations in the exonuclease domain of POLE, none of these 11 patients received adjuvant treatments despite aggressive histology, myometrial infiltration over 50% in 7 out of 11 patients and the presence of diffuse vascular invasion (LVI) in 54% of cases. Up today, in none of patients relapse of the disease occurred. With regard to the specific POLE mutations, in addition to the most frequent ones (P286R, V411L, S297F, A456P, and S459F), we identified in one EC the mutation c.829G>A; p.E277K in exon 9, not previously described for EC (only rare cases in colon cancer described in the literature).

Conclusions: In the present analyses, the incidence of POLE mutations was slightly higher than expected in the literature. The status of POLE predicts the prognosis in I-II stage of EC and when pathogenetic mutations are present in the exonuclease domain, despite the presence of aggressive pathological feature (high grading, severe myometrial invasion, diffuse LVI), adjuvant treatments are not proposed. In our series, a POLE mutation (c.829G>A; p.E277K) not previously described in EC, was identified.

D14

COMPARISON OF THE HEMATOLOGICAL TOXICITY PROFILE BETWEEN NIRAPARIB-BASED AND OLAPARIB-BASED TREATMENTS IN PATIENTS WITH OVARIAN CANCER: A PHARMACOVIGILANCE ANALYSIS

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Background: PARPs-inhibitors have improved the outcome of patients suffering from ovarian cancer; however, they are associated with many adverse events (AEs). Herein we attempted to compare haematological toxicities between niraparib and olaparib.

Methods: We analyzed Individual Case Study Reports (ICSRs) reported from 01/01/2017 to 30/04/2024 in the EudraVigilance databases. Descriptive analyses were performed, stratifying the data by age, seriousness of adverse drug reactions (ADRs), and Preferred Terms (PT). Relative Risks (RRs), with their 95% confidence interval (CI), were used as a measure of disproportionality.

Results: We selected 3897 ICSRs (1882 associated with niraparib 48.3%). The largest age group observed was 18-64 years (36.2% of total selected schedules). Out of the 1504 serious adverse events (SAEs) reported, 62.4% were associated with niraparib, and among these, 1.9% resulted in patient death, compared to 1.3% with olaparib. The most frequently reported Preferred Terms (PT) were anaemia (66.1%), thrombocytopenia (37.6%), and neutropenia (13.1%). Patients treated with olaparib were significantly more likely to report the following adverse events, than those treated with nirabarib: anaemia (RR 0.68; CI 0.65-0.71; p<0,001) and myelodysplastic syndrome (RR 0.027; CI 0.13-0.53; p<0,001). In contrast, patients who received niraparib more frequently reported neutropenia (RR 1.53; CI 1.38-1.82; p<0,001), pancytopenia (RR 1.84; CI 1.33-2.54; p<0,001), myelosuppression (RR 2.73; CI 2.14-3.47; p<0,001), thrombocytopenia (RR 7.33; CI 6.42-8.40; p<0,001), leukopenia (RR 3.17; CI 2.33-4.33; p<0,001). Other significant AEs reported in patients treated with niraparib include cytopenia, platelet count abnormalities, and white blood cell count disorders.

Conclusions: The analysis performed showed a difference in the reported hematologic toxicities among niraparib-treated patients compared with olaparib-treated patients for ADR such as anemia, myelodysplastic syndrome, pancytopenia, thrombocytopenia, and myelosopression. Such information could be supporting the choice between PARPs-inhibitors in clinical practice.

D15

BASELINE CHARACTERISTICS AS CRITERIA FOR CHOOSING FIRST-LINE THERAPY IN METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS (PTS): THE MEET-URO 33 STUDY

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Background: In the context of mRCC there is currently a lack of established comparative analyses and standardized

criteria to guide first-line treatment choice. The ongoing Meet-URO 33 study will recruit up to 80 Italian centers to address many clinical unmet needs.

Methods: The Meet-URO 33 study is a multicenter prospective/retrospective registry of a real-world mRCC population treated with first-line therapy from January 2021. As of April 2024, 421 pts from 25 Italian centers were evaluated. We examined how various clinical and tumor characteristics (age, ECOG PS, comorbidity type/number, steroid use, primary tumor surgery, histology, sarcomatoid features, metastasis type/number, IMDC and Meet-URO scores) influenced treatment choice among IO-IO, IO-TKI, and TKI.

Results: Overall, 263 pts (62.5%) received IO-TKI, 81 (19.2%) received IO-IO, and 77 (18.3%) were treated with TKI. Univariate analysis revealed significant correlations ($p<0.05$) between therapeutic choice and factors including IMDC and Meet-URO scores, age, presence of bone or pancreatic metastases, high-dose steroid use, and various comorbidities such as renal, cardiac, hematological, metabolic, and gastroenteric, especially when =2 comorbidities were present. At the multivariate analyses, in the comparison of IO-IO versus IO-TKI, higher IMDC scores and metabolic comorbidities were associated with IO-IO ($p<0.001$ and $p=0.005$ respectively), while the presence of bone metastases correlated with IO-TKI ($p=0.024$); in the IO-IO vs TKI comparison, a higher IMDC score was associated with IO-IO ($p<0.001$), whereas older age leaned toward TKI ($p=0.09$); in the IO-TKI vs TKI comparison, a higher number of metastases correlated with IO-TKI ($p=0.037$) while a higher age, gastroenteric/renal comorbidities and =2 comorbidities with TKI ($p<0.001$, $p=0.024$, $p=0.024$ and $p=0.046$).

Conclusions: The preliminary data from the ongoing Meet-URO 33 study presents a real-world snapshot of the current first-line treatment landscape in mRCC patients. While certain prognostic factors like ECOG PS, sarcomatoid features, and lung/liver metastases may not seem pivotal in therapeutic decision-making, others such as IMDC score, bone metastases, number of metastases, age, and comorbidities were confirmed to direct therapeutic choices. These findings prompt deeper investigation with a larger sample size.

D16

EVALUATION OF NEW CLINICAL AND TISSUE-BASED FACTORS TO REFINE PREDICTION OF PROGNOSIS IN METASTATIC RCC

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Background: Despite advances in overall management and systemic treatment, advanced/metastatic renal cell carcinoma (mRCC) remains incurable in most cases, although across a wide prognostic variability. Clinical/laboratory risk scores represent the mainstay of prognosis assessment and, based on prognostic risk groups, the choice of first-line treatment. However, in clinical practice, the outcome of a sizeable proportion of pts does not reflect what is expected based on risk group assignment.

Material and Methods: We analyzed a total of 193 pts diagnosed with mRCC who underwent I-line treatment with VEGFR TKIs in 4 Italian Hospitals between 2013 and 2021. Additional clinical/laboratory parameters, complementing the IMDC score were explored uni- and multivariate analysis. In parallel, seventeen "outliers" (pts whose actual prognosis was significantly worse or better than expected according to IMDC) were analyzed for chromosome 9p loss by FISH, PBRM1/BAP1 mutations, PD-L1 expression, and characterization of the immune infiltrate by IHC.

Results: Sites of metastases, histology (clear vs. non-clear cell, sarcomatoid features), and neutrophil-to-lymphocyte ratio were analyzed together with individual IMDC factors. Among IMDC factors, anemia, hypercalcemia, and neutrophilia confirmed their significance at multivariate analysis; among additional factors, non-clear cell histology, bone, lung, and pancreatic metastases entered the multivariate model. The resulting 7-factor model discriminated pts with good (0-1 factors), intermediate (2-3 factors), and poor (>4 factors) prognosis with 77.4% concordance with IMDC; however, the new proposed model had better accuracy than the "classical" IMDC

model (AUC as assessed by ROC curve comparison: 0.69 vs 0.65). Analysis of the "outliers" suggests that presence of PBRM1/BAP1 mutations was significantly associated with better-than-expected survival (p=0.008), especially if associated with positive CD56 staining in the absence of CD8+ infiltrating lymphocytes (p=0.0003).

Conclusions: These analyses confirm that introducing selected metastatic sites and histology may allow for more precise mRCC pts stratification. Relatively limited genomic profiling and characterization of the tumor microenvironment may provide further insights into cancer behavior and prognostic assessment. Prospective studies are required to validate such novel potential biomarkers.

D17

SAFETY OF PEMBROLIZUMAB IN ENDOMETRIAL CANCER (EC): A PHARMACOVIGILANCE REAL WORLD ANALYSIS BASED ON EUDRAVIGILANCE SYSTEM

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Background: In high-income countries, EC stands out as the leading gynecological cancer, and its incidence is rapidly increasing. Pembrolizumab as monotherapy or in combination is indicated for the treatment of advanced or recurrent EC. Herein, we attempted to assess the safety of pembrolizumab in EC treating.

Methods: For the current analysis, Individual Case Study Reports (ICSRs) reported in the EudraVigilance from 2022 to 30.04.24 were collected. A descriptive analysis was performed, and data were stratified by age, adverse drug event (ADR) seriousness, System Organ Classes (SOCs) and Preferred Term (PT).

Results: Of the 3455 reports analyzed, the 33% involved 18-64 years patients and the 40% 65-85. The 66,9% of reported ADRs were serious and mortality was reported in 17,6% of cases. The most recurrent SOCs were general disorders and administration site conditions, which accounted for 34% (with 'feeling unwell' at 9.7%). To follow in order, gastrointestinal disorders for 27.5% (particularly diarrhea at 8.6%) and endocrine disorders for 26.4% (with hypothyroidism for 16.2%). Skin and subcutaneous tissue disorders were reported in 22,7% with 6,9% of hand and foot syndrome cases; vascular disorders in 20,7% with 17,9% of hypertension; Neoplasms benign, malignant and unspecified (incl cysts and polyps) interested 18,8% of patients and 16% of these had progression of malignant cancer. Respiratory, thoracic and mediastinal disorders were referred in 16,6% with 6,2% pneumonia. Immune system disorders in 8,7% with 3,6% cases of immune-mediated hypothyroidism. The most common PT emerged from EudraVigilance database were in order: hypertension (17,9%), hypothyrodism (16,2%), malignant neoplasm progression (16%) and thrombocitopenia (9,8%).

Conclusions: From the analysis performed, the toxicity profile of pembrolizuab in the real word is overlapping with that described in the Common Technical Document (CTD). Deviating from this are AEs such as hypertension and thrombocytopenia, which in the CTD are reported as uncommon adverse reactions while they appear to be among the most reported PTs.Further studies are needed to better define the correlation between pembrolizumab use and the incidence of hypertension and thrombocytopenia.

D18

MRI-INFORMED BIOPSY TO IMPROVE RISK ALLOCATION OF MEN AT INCLUSION OF ACTIVE SURVEILLANCE: RESULTS FROM SPRINT STUDY

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Background: Sampling error with omission of high-grade cancer may be a concern in active surveillance (AS) programs for low-risk prostate cancer (PCa). This can be compensated for by mpMRI and MRI-informed derived biopsy. To evaluate the systematic use of initial mpMRI in low-risk PCa patients (pts) who are candidates for AS, we initiated a specific protocol (SPRINT) aimed at evaluating the possible decrease in upgrading (upG) at the first AS biopsy.

Materials and Methods: The single-institution SPRINT protocol prospectively enrolled low risk PCa pts in AS after undergoing baseline mpMRI (within 7 months from diagnosis), irrespective of number of positive cores and PSA density. Systematic biopsies were provided and integrated with target MRI-informed biopsies in case of

mpMRI lesions PI-RADS 3-5 (PI-RADS v 2.1 classification). A first AS systematic +/- target biopsy was scheduled at 12 months (mos) (max 18 mos) from AS enrollment. The primary endpoint was the rate of upG at the first AS biopsy (within 18 mos). The hypothesis of the study provided a reduction of upG compared to the historical cohort which included men with GG1 PCa, < 4 positive cores, PSA density < 0.2, no baseline MRI (two sided, z-test for proportions) [1].

Results: From Dec 2016 to Feb 2022, 241 pts signed SPRINT informed consent. 109 pts underwent a biopsy to complete the MRI-driven selection process and 27 out of 109 (25%) were reclassified to higher grade thus not included in AS. Among those with confirmed GG1, 93 underwent the examinations within the planned time frame (per-protocol subset). Further 65 patients completed initial selection workout (MRI and MRI-informed biopsy if indicated) within 24 mos due to an unplanned delay in administration. The remaining 56 pts did not complete the required examination and were excluded from this analysis. At the first AS biopsy, 21 out of 93 (22%) per protocol pts and 15 out of 65 (23%) pts showed upG. Compare to the historical cohort, per protocol subset of pts with on-time biopsy had a significant increase in upG (22% vs 15%; p 0.048).

Conclusions: In this population of pts with GG 1 prostate cancer undergoing MRI and MRI informed biopsy, grade reclassification at first AS biopsy remains relevant. Wider entry criteria may partly explain these findings. Longer follow-up may clear long-term impact of early MRI.

D19

PROSTATE CANCER (PC) AND HOMOLOGOUS RECOMBINATION REPAIR GENES MUTATIONS (HRRM): A RETROSPECTIVE, MONOCENTRIC, OBSERVATIONAL STUDY AIMED AT RECORDING HISTOPATHOLOGICAL AND CLINICAL DATA AND THEIR ASSOCIATIONS WITH ONCOLOGICAL OUTCOMES

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Background: This study aimed to evaluate histopathological and baseline clinical characteristics in PC patients with HRRm, their prevalence, and clinical outcomes.

Material (patients) and Methods: From 2019 to 2023, we screened 400 patients with metastatic PC for HRR alterations. HRRm were identified using archival primary or metastatic tumor samples and/or circulating tumor DNA (ctDNA). We retrospectively analysed clinical and tumor characteristics in 45 patients with HRRm, recording histopathological and clinical data and their association with Progression-Free Survival (PFS) in metastatic hormone-sensitive PC (mHSPC) setting as oncological outcome

Results: Out of the 400 screened patients, 45 (11%) had at least one mutation, with BRCA2 being the most commonly altered gene (46.7%), followed by BRCA1 (11.1%) and ATM (11.1%). Other rare HRRm were found in 5 patients (11.1%). Median age was 70 years. HRRm were associated with poorly differentiated PC: about 72% of patients had Gleason score = 8 and, among these, 22.7% had a Gleason score of 10. 58% of patients had metastatic disease at diagnosis, with 40% having High Volume disease. The most common sites of metastasis were bones and lymph nodes, with only 13% having visceral metastasis. In patients with non-metastatic disease at diagnosis, advanced stage (T3-T4) and nodal involvement were frequent, 53% and 35% respectively. 43 patients received medical treatment for mHSPC with androgen deprivation therapy (ADT) alone (37.8%), ADT plus androgen receptor targeting agents (42.2%), or ADT plus chemotherapy (15.5%). 29 patients had disease progression with a median PFS of 16.8 months, regardless the therapy.

Conclusions: PC with HRRm had more frequently Gleason ≥ 8, T3/T4 stage, nodal involvement, and metastases at diagnosis, confirming the need to early search for mutations in patients with advanced disease and these characteristics. mHSPC patients had significantly lower PFS compared to the literature, with a median PFS of 16.8 months, suggesting HRRm disease could have worse prognosis. These data support the need for tailoring a specific clinical management of these patients.

Table 1. BRCA1, BRCA2, ATM, VUS and rare mutations in tissue, liquid and germline biopsy.

	Somatic biopsy	Liquid biopsy	Germline
BRCA1	5 (11.1%)	1 (2.2%)	0
BRCA2	21 (46.7%)	6 (13.3%)	8 (17.8%)
ATM	5 (11.1%)	1 (2.2%)	2 (4.4%)
VUS	2 (4.4%)	1 (2.2%)	0
RARE MUT	5 (11.1%)	8 (17.8%)	1 (2.2%)

D20

RISK OF EARLY PROGRESSION IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA (RCC) UNDERGOING FIRST-LINE TREATMENT WITH IMMUNOTHERAPY COMBINATIONS: THE TIAR RETROSPECTIVE MULTICENTER STUDY

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Background: Currently, combination of an immune checkpoint inhibitor with VEGFR-tyrosine-kinase inhibitor (ICI-TKI) or combination of nivolumab and ipilimumab (ICI-ICI) represent the standard first-line treatment for patients with advanced RCC. Considering the lack of predictive factors and of direct comparisons among the approved combinations, post-approval real-world studies (RWS) can add important evidence. RWS allow describing outcomes in less selected, more heterogeneous pts, with potentially higher risk of early treatment failure.

Methods: The retrospective, multicenter, real-world TIAR study enrolled patients with metastatic RCC treated with 1 of 4 available first-line combinations. Primary endpoint was the rate of early progression (EP), defined as instrumental progression or clinical deterioration within the first 4 months. According to study protocol, 120 patients would have allowed sufficient precision in estimating the EP rate.

Results: Out of 194 patients from 14 Italian and 1 Swiss center, 184 were eligible for the primary analysis. Median age was 67 (41% older than 70). 155 patients (84%) had clear cell histology. ECOG performance status (PS) was 0 / 1 / 2 in 59% / 35% / 6%. Out of 169 patients with information available, IMDC category was good in 22.5% and intermediate/poor in 77.5%. EP was observed in 26 patients (14.1%, 95%CI 9.4–20.0). In detail, 19 patients (10.3%, 95% 6.3–15.7) had EP at the instrumental restaging, and 7 patients (3.8%, 95%CI 1.5–7.7) had early clinical deterioration. EP was seen in 10.6% of patients treated with ICI-TKI and in 30.3% of patients treated with ICI-ICI (p=0.003). EP was seen in 9.3% / 21.5% / 18.2% of patients with ECOG PS 0 / 1 / 2, respectively (p for trend=0.05). Median PFS was 15.3 months (95%CI 9.9-20.7) in the whole population, 15.4 months in the ICI-TKI group and 9.6 months in the ICI-ICI group (p=0.34). In 131 patients with intermediate/poor prognosis, EP was seen in 13.3% of patients treated with ICI-TKI and in 34.6% of patients treated with ICI-ICI (p=0.01); median PFS was 12.0 months (14.7 months in the ICI-TKI group vs 7.1 months in the ICI-ICI group, p=0.58).

Conclusions: Despite the efficacy of new combinations in clinical practice is globally consistent with the evidence of clinical trials, some patients experience EP. The risk of EP is higher with ICI-ICI combination and in symptomatic patients.

D21

PREDICTIVE FACTORS OF TREATMENT-RELATED ADVERSE EVENTS (TRAES) IN PATIENTS WITH METASTATIC RENAL CELL CARCIOMA (MRCC) TREATED WITH PEMBROLIZUMAB PLUS AXITINIB: DATA FROM PROPAXI STUDY

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Background: The aim of this analysis was to delineate potential predictors of TRAEs among patients with mRCC received treatment with Pembrolizumab plus Axitinib (PAXI) combination in real-world clinical settings.

Methods: The ProPaxi study is a prospective study involving patients diagnosed with mRCC who underwent PAXI therapy as first-line treatment across seven Italian centres from April 2021 to September 2023. Safety data concerning clinically significant TRAEs, defined as adverse events requiring corticosteroids, hormone replacement therapy, treatment delay, discontinuation, or dose reduction, were systematically collected. Our analysis aim to discern factors associated with the incidence of TRAEs.

Results: Among the patients included in the study, 70% (119/170) experienced TRAEs. The most common TRAEs were diarrhea (25.2%), hepatitis (18.5%), cardio-toxicity (11.8%), and dermatologic toxicity (10.9%). The multivariate logistic analysis revealed that a body mass index of =25 (odds ratio [OR] 2.33, 95%CI 1.12-4.87, p=0.024) and presence of at least one comorbidity in personal history (OR 2.59, 95%CI 1.21-5.56, p=0.015) were predictive factors significantly associated with the occurrence of clinically relevant TRAEs. A favourable Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 is associated with a reduced likelihood of TRAEs occurrence (OR 0.22, 95%CI 0.11-0.47, p=0.000). Furthermore, our analysis revealed that the absence of comorbidity is significantly lower associated with high grade of severity (=3) TRAEs occurrence (OR 0.11, 95%CI 0.09-0.42, p<0.001). Additionally, an ECOG PS of =1 emerged as a predictive factor for higher severity grades of TRAEs (OR 2.54, 95%CI 1.25-5.14, p=0.009). Specifically, the type of TRAE was found not to be a significant predictors of poor prognosis. Management of TRAEs through a drug delay appeared to be associated with better survival outcome (HR 0.49, 95%CI 0.27-0.9, p=0.021), whereas requiring drug discontinuation is associted with worst survival outcome (HR 2.4, 95%CI 1.2-4.7, p=0.10)

Conclusions: Body mass index, comorbidity and ECOG PS are potential predictive biomarkers of TRAEs, while comorbidity and ECOG PS are potential predictors of serious TRAEs. The predictive effect of TRAEs occurrence on survival benefit may depend on the type of TRAEs management.

D22

PROGNOSTIC VALUE OF SYSTEMIC INFLAMMATION INDEX (SII) AND BODY MASS INDEX (BMI) IN THE THERAPEUTIC LANDSCAPE OF PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (MRCC)

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Background: Recent case series have reported that nutritional and inflammatory indexes may be predictors of survival outcomes in mRCC patients. In this single-centre real-world case series, we evaluate the prognostic role of SII and BMI in mRCC patients.

Methods: We evaluated the clinical and pathological characteristics of 174 mRCC patients who received first-line (1L) systemic therapy between 2020 and 2024. SII was calculated using the following formula: neutrophils/mm3 x platelets/mm3: lymphocites/mm3. Both SII and BMI were assessed at baseline and at the end of 1L treatment.

Results: The population had a median age at diagnosis of 56 years (range 28-84), 66,6% male. The median number of therapy lines was 2 (range 1-8). Regarding 1L therapy, 40.3% of patients (pts) received immune checkpoint inhibitors (ICI) + vascular endothelial growth factor receptor – tyrosine kinase inhibitors (VEGFR-TKI), 17.2% ICI+ICI, 42.5% VEGFR-TKI monotherapy. Pts with a baseline SII higher than the population median (≥654) had a worse median overall survival (mOS; HR 1.72, CI 95% 1.46-1.98, p 0.034) than patients with a lower SII (<654). The prognostic value of SII in the overall mRCC population was also confirmed in a multivariate analysis. Baseline BMI ≥25 kg/m2 and BMI reduction ≥0.8 kg/m2 at the end of 1L treatment were not predictive of OS. In the subpopulation of pts receiving 1L immune-based combinations (ICI+ICI or ICI+VEGFR-TKI), BMI ≥25 kg/m2 was predictive of better 1L median progression-free survival (mPFS; HR 0.52, CI95% 0.22-0.82, p 0.029) and OS (HR 0.48, CI95% 0.07-0.89, p 0.067), whereas BMI reduction ≥0.8 kg/m2 showed no prognostic significance. In the subpopulation of pts receiving 1L VEGFR-TKI monotherapy, BMI above 25 kg/m2 had no prognostic value, but BMI reduction ≥0.8 kg/m2 was predictive of worse OS (HR 2.63, CI95% 2.25-3.01, p 0.009) and PFS (HR 1.6, CI95% 1.33-1.87, p 0.09).

Conclusions: In our analysis, a low baseline SII was a positive prognostic factor for the overall mRCC population.

Pts receiving 1L ICI-based combinations with a high baseline BMI had a significant prognostic advantage, probably due to the pro-inflammatory environment promoted by excess body fat. Pts receiving 1L VEGFR-TKI monotherapy who experienced BMI reduction during treatment had poor survival outcomes, which could be explained by the known VEGFR-TKI-induced sarcopenia. Therefore, early nutritional assessment and support should be considered in the management of mRCC pts receiving VEGFR-TKI.

D23

THE IMPACT OF CARBOPLATINUM CUMULATIVE DOSE ON FIRST LINE PARP INHIBITORS PROGRESSION-FREE SURVIVAL IN PATIENTS WITH HIGH GRADE SEROUS OVARIAN CARCINOMA

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Background: Carboplatinum (CBDCA)-based chemotherapy followed by maintenance treatment with poly (ADP-ribose) polymerase inhibitors (PARPi) represents a standard approach for patients (pts) with platinum-sensitive high-grade serous ovarian carcinoma (HGSOC). Since CBDCA and PARPi act by interfering with the homologous recombination DNA repair pathway, their profile of sensitivity and resistance partially overlap. Resistance to platinum CT strongly predicts resistance to PARPi and pts who progress to PARPi do not benefit from subsequent platinum-based CT regimens. In this context, we aimed to investigate the impact of CBDCA cumulative dose on the efficacy of first line PARPi maintenance treatment.

Methods: A retrospective analysis was conducted among 48 consecutive pts with HGSOC who received a platinum-based regimen and subsequent first line PARPi between November 2019 and March 2024 at the University of Naples Federico II. Patients' demographics, clinical-pathological features, and CBDCA cumulative dose were retrieved from electronic medical records. Multivariate logistic regression for continuous explanatory variables was performed to evaluate the association between CBDCA cumulative dose and PARPi progression-free survival (PFS). Survival curves were estimated using the Kaplan-Meyer method and the log-rank test.

Results: Overall, 19 pts harbored a BRCA1m, 9 harbored a BRCA2m, and 20 had BRCA1/2 wild type. Survival analysis for continuous explanatory variables set the CBDCA cut point at 3587 mg, and patients were divided into CBDCA high (>3587 mg) and low (<3587 mg) groups. CBDCA high was independently associated with a higher risk of disease progression, recurrence, or death from PARP inhibition (HR 5.22, 95% CI: 1.19-22.9, p = 0.029) in a multivariate model including residual disease and BRCA status. At a median follow-up of 21 months, the CBDCA high group experienced the worst outcome in terms of PFS compared with the CBDCA low group (log-rank p = < 0.001).

Conclusions: CBDCA cumulative dose may affect the efficacy of first line PARPi treatment. Future studies are needed to confirm our data and to further elucidate the interplay between CDBCA and PARPi resistance.

D24

THERAPEUTIC DECISIONS AND OUTCOME OF PATIENTS WITH STAGE I TESTICULAR GERM CELL TUMOR: SINGLE-CENTRE EXPERIENCE

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Background: Testicular cancer (TC) is the most common solid neoplasm affecting men aged 15 to 40, with stage I being the predominant form. Despite excellent prognosis, optimal post-surgical management remains controversial, comprising adjuvant chemotherapy or active surveillance (AS).

Methods: This study aimed to compare relapse-free survival (RFS) in patients (pts) with stage I TC undergoing adjuvant therapy (AT) versus AS. Additionally, traditional histopathological prognostic factors for relapse were assessed, and seminoma cases were reclassified according to the new EAU risk group classification. Overall Survival (OS) was also investigated. Clinical histories of pts with stage-I TC treated at our institution were retrospectively collected. Pts with inadequate follow-up, insufficient information, or histologies other than seminoma and non-seminoma were excluded.

Results: Out of 144 cases treated between 2016 and 2023, 131 (80 seminomas, 50 non-seminomas, 1 unspecified) met the elegibility criteria. AT (almost exclusively based on chemotherapy) was administered to 53.8% of seminoma

and 58.0% of non-seminoma pts. With a median follow-up of 39.4 months, 5-yr RFS was 98.2% for pts treated with AT and 85.2% for those undergoing AS (p=0.014). Particularly, 5-yr RFS was 97.1% vs 89.7% in seminoma (p=0.27) and 100% vs 76.4% in non-seminoma pts (p=0.015). The proportion of seminoma pts undergoing AT was 16.7% among those with T<4 cm and no rete testis invasion, 55.6% among those with 1 risk factor, and 82.1% among pts with 2 risk factors. AT was received by 4.8% and 96.6% of non-seminoma pts without and with lymphovascular invasion, respectively. The EAU risk group classification classified 22.5%, 50.0% and 18.8% of seminoma cases into the very-low, low, and high risk categories (8.8% not evaluable), respectively. As expected, AT receipt significantly increased with risk: very-low 16.7%, low 62.5%, high 86.7% (p<0.001). 5-yr OS was 96.9% (98.4% in seminoma and 94.5% in non-seminoma).

Conclusions: This study contributes to the ongoing debate on optimal post-surgical management in patients with stage I TC. Both AS and AT are associated with favourable prognosis, underscoring the importance of individualized treatment decisions. Histopathological factors and the EAU risk classification provide valuable prognostic information, aiding in treatment stratification. Further research is needed to refine treatment algorithms and optimize outcomes for stage I TC patients.

D25

A MULTICENTER RETROSPECTIVE REAL-WORLD STUDY WITH PEMBROLIZUMAB IN PLATINUM-REFRACTORY METASTATIC UROTHELIAL CARCINOMA (MUC)

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Background: Immune checkpoint inhibitors (ICI) have significantly improved the prognosis of a subgroup of patients (pts) with mUC. However, most of these pts do not respond to immunotherapy. Particularly, pts with a progressive disease (PD) as best response to chemotherapy typically have a poor outcome. This study aims to identify predictors of ICI treatment response in pts with platinum-refractory mUC treated with pembrolizumab.

Methods: Pts affected by mUC treated with pembrolizumab at six Italian Oncology Units from Dec 2019 to April 2024 were included. In particular, pts with PD as best response to first line platinum-based doublet or pts who experienced disease progression within one year from the end of a (neo)adjuvant treatment for localized disease, were included. Univariate and multivariate Cox regression analyses were performed to evaluate clinical characteristics and laboratory data at the beginning of immunotherapy as possible predictors for progression-free survival (PFS) and overall survival (OS).

Results: Sixty-one pts were evaluable for this analysis. Pts characteristics are shown in Table 1. The objective response rate was 21.3%, with a median PFS of 2 months and a median OS of 8 months.

On multivariate analysis, factors predicting shorter PFS could not be identified. Conversely, basal hemoglobin <10 g/dL (HR = 3.13, p = 0.045), elevated basal LDH (HR = 4.89, p < 0.001), metastatic disease at diagnosis (HR = 5.44, p = 0.001) and bone metastasis (HR 4.01, p = 0.009) were significantly associated with poor OS.

Conclusions: In this retrospective study, low hemoglobin, elevated LDH, bone lesions, and, synchronous metastatic disease was identified as independent risk factors for OS in pts with platinum-refractory mUC treated with pembrolizumab. In these pts, an intensification of radiological restaging should be evaluated in order to anticipate subsequent treatment lines.

Table 1.

Median Age (range)	70 (25-85)
Male sex – no. (%)	43 (70.5)
ECOG PS 0-1 – no. (%)	51 (83.6)
Previous (neo)adjuvant treatment -no. (%)	19 (31.1)
Metastatic at diagnosis -no. (%)	20 (32.8)
Sites of mts -no. (%)	
Lymphnode only	11 (18)
Liver	10 (16.4)
Bone	26 (42.6)
Basal hemoglobin <10 g/dL -no. (%)	17 (27.9)
Basal elevated LDH -no. (%)	11 (18)

D26

CORRELATION BETWEEN BODY COMPOSITION(BC) AND OUTCOMES IN MRCC PATIENTS (PTS) IN FIRST LINE THERAPY (1L TP)

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Background: Finding the most effective tailored 1L tp in mRCC is a challenge and biomarkers for choice are limited. Sarcopenia, loss of muscle mass and strength, may impact on clinical outcomes in mRCC pts. We evaluate correlation between BC-related markers and prognosis in mRCC pts treated with 1L tp.

Patients and Methods: We conducted a multicentric retrospective analysis of 76 mRCC pts with intermediate (int) and high risk according to the international mRCC Database Consortium (IMDC) score who underwent 1L tp with tyrosine kinase inhibitor (TKI)(25pts)(A), immunotherapy (IT)(28)(B), TKI+IT (23)(C) between 2019 and 2023. General characteristics, BC and inflammatory parameters were recorded at baseline (BL) and at 1st revaluation (1R). BC parameters were calculated from CT scan quantifying: total, visceral and subcutaneous fat (TF, VF and SF), skeletal muscle area (SMA), skeletal muscle density (SMD), skeletal muscle index (SMI) and adjusted SMI (aSMI) at 3L vertebral level. We used Kaplan-Meier method to estimate survival and Spearman's test to correlate variables.

Results: We had 17% female, 71% mRCC at diagnosis, 81,6% clear cell. At diagnosis, median (m) BMI was 24,4, m age 64 years (range 25-81). Sarcopenic pts defined with Fearon et al 2011 were 56,57 % at BL. Among the non-sarcopenic pts, 30,3% became sarcopenic at the 1R, of them 90% were int IMDC, 100% had disease progression. Among parameters, BMI correlates ($p<0,05$) with NLR, SII (Systemic immune inflammation index), SMI, aSMI, TF, VF, SF; age with VF and aSMI; SII with SF and SMI; TF, VF and SF with SMI. At BL, predictors of better OS were better ECOG (p=0,006), int IMDC (p=0,043), tp with B or C vs A (p=0,002), low NLR ($p<0,0001$) and low SII (p=0,017). Higher muscle mass (SMI codified with Fearon or Martin and aSMI codified with m) showed better OS (p=0,015, p=0,011 and p=0,022, respectively). Among subgroups, in B high aSMI showed better OS (p=0,018). At 1R, low NLR, high SMD, SMI, aSMI and loss of SF, SMD and SMI predicted better OS (p= 0,004, p=0,006, p=0,002, p=0,006, p=0,009, p=0,02). In C, we had significant impact of aSMI (p=0,037), SMI with m (p=0,013) and TF (p=0,043).

Conclusions: Sarcopenia seems to be a prognostic factor in mRCC in 1L tp despite our limited series. Jointly with scores already used in clinical practice, it can contribute to a better selection of treatments.

D27

SUBGROUP ANALYSES FROM THE MALVA (MEET-URO 25) STUDY: REAL-WORLD DATA OF AVELUMAB MAINTENANCE (AM) TREATMENT FOR ADVANCED UROTHELIAL CARCINOMA (AUC)

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Background: Avelumab maintenance (AM) in patients (pts) with advanced urothelial cancer (aUC) responsive to first-line platinum-based chemotherapy (1L-CT) is a first-choice treatment option. We present subgroup analyses from the MALVA study, an ongoing, multicenter, observational, ambispective study.

Methods: aUC pts receiving AM after a response to 1L-CT in 15 Italian centres from 2021 to 2024 were included. Demographic, tumor and treatment information were collected. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meyer method.

Results: At the cut-off date (24 April 2024), 158 pts were evaluable, with a median follow-up of 21 months (mts). Median age was 72 yrs, 41% of patients (65) had Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥1, 27.8% (44) had lymph node only, 27.2% (43) bone and 37.2% (59) visceral metastases. For 1L-CT, 58% received carboplatin/gemcitabine, 42% cisplatin/gemcitabine, overall, 28.6% (45) achieved partial or complete response (PR/CR) and 39.4% (62) stable disease (SD). Median PFS (mPFS) was 4.9 mts (95%CI: 3.73-6.63; 1-year PFS rate: 25.3%) and median OS (mOS) from AM start was 16.7 mts (95%CI: 11.9-not reached; 1-year OS rate: 41.1%). Disease Control Rate with AM was 68%. Pts with ECOG PS = 0 had better mOS than those with ECOG PS ≥1 (HR: 0.49, p: 0.0022). Lymph node only metastases were associated with better mPFS (HR: 0.69, p: 0.058) and mOS (HR: 0.34, p: 0. 0018) than other metastatic sites; on the other hand, pts with bone metastases had worse mPFS (HR: 1.45, p: 0.046) and mOS (HR: 2.87, p < 0.0001) than those without bone metastases. Pts achieving PR/CR at 1L-CT had better mPFS (HR: 0.76, p: 0.055) than those with SD. No significant differences in survival outcomes were observed between age groups, presence/absence of liver and visceral metastases, different regimens and duration of 1L-CT. The toxicity profile of AM was consistent with previous reports. AM was discontinued due to toxicity in 5.8% pts.

Conclusions: Our real-world analyses confirmed Avelumab maintenance's effectiveness and corroborated the prognostic value of clinical features in tailoring therapeutic strategy.

D28

RETROSPECTIVE OBSERVATIONAL STUDY ON PATIENTS WITH METASTATIC RENAL CELL CARCINOMA TREATED IN FIRST LINE WITH PEMBROLIZUMAB + AXITINIB: A REAL WORLD PROJECT OF THE CAMPANIA ONCOLOGY NETWORK

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Background: Regional Oncology Networks play a crucial role in promoting the use of Real-World Data (RWD), which has the potential to generate Real-World Evidence (RWE) important for healthcare decision-making. In 2016, the Campania region established the Campania Oncology Network (ROC) to ensure equal access and quality standards of oncology care for all patients. The ROC involves both private and public oncology centers, where Multidisciplinary Oncology Groups (GOM) have been created. A ROC digital platform records patients discussed in the GOM, contributing to the generation of RWD. Within the ROC, we conducted a non-profit retrospective observational study to collect and analyze data of patients, discussed by the GOMs, affected by metastatic renal carcinoma candidates for first-line treatment with Pembrolizumab + Axitinib.

Material (patients) and Methods: The primary objective was to evaluate progression-free survival (PFS) and overall survival (OS) in clinical practice. Secondary aims included prognostic clinical factors and safety.

Results: Data were collected for 117 patients who started treatment with Pembrolizumab + Axitinib from 2021 to November 2023 in eight ROC centers. 47% of patients had an intermediate IMDC (International Metastatic RCC Database Consortium) risk group and about 48% had an ECOG (Eastern Cooperative Oncology Group) of 1. The median age at diagnosis was 59 years. The most common reason for treatment discontinuation was progression of disease (PD), with 58 (49%) patients experiencing PD. The median PFS was 18.7 months (range 11.4-26.7), while the median OS was not reached. An ECOG ≥2 was a significant risk factor for both PFS and OS. The most common drug-related adverse events were diarrhea G2 (23.9%), asthenia G2 (18.0%), hypothyroidism G2 (12.8%), hypertension G2 (9.4%), and mucositis G1 (7.7%). An indirect comparison between the use of Pembrolizumab + Axitinib in the real world setting of the ROC and KEYNOTE 426 trial showed non-substantial differences.

Conclusions: Our study confirms the replicability of the Pembrolizumab + Axitinib combination in real-world clinical settings. Currently, there is no evidence proving the superiority of any frontline treatments for metastatic renal cell carcinoma (Pembrolizumab + Axitinib Vs Ipilimumab + Nivolumab Vs Nivolumab + Cabozantinib Vs Pembrolizumab + Lenvatinib). Using real-world data to compare these treatments could assist clinicians in making more personalized therapeutic decisions.

D29

TP53 MUTATION AS PREDICTIVE FACTOR FOR PLATINUM RESPONSE IN BRCA-MUTATED OVARIAN CANCER: A PROSPECTIVE CASE-SERIES ANALYSIS

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Background: Platinum sensitivity (PS) is a prerequisite for 1st-line PARP inhibitors (PARPi) in locally advanced/relapsed high grade serous ovarian cancer (HGS-OC). BRCA mutations are predictive of PS and of PARPi response. Notably, platinum and PARPi cytotoxic action is mainly related to p53-mediated apoptosis induction. Therefore, the integrity of p53 machinery is crucial for platinum-related activity whereas TP53 mutation is fairly frequent in HGS-OC and in BRCA-mutated (MT).

Material (patients) and Methods: We prospectively analyzed 208 patients (pts) with primary ovarian cancer undergoing surgery at the Department of Gynecologic Oncology, ARNAS G. Brotzu, Cagliari, Italy, between 2019 and 2023. Somatic NGS analysis was performed to detect BRCA and HRD mutations. TP53 mutations were classified according to hotspot, structural (missense/nonsense) and functional classification as gain of function (GOF) or loss of function (LOF), based on the IARC TP53 database. Comparative testing with Fisher's exact test was used to examine TP53 mutation distribution and associations with clinicopathologic factors and PS. BRCA mutation status was further used to stratify the analysis.

Results: Globally, we included 127 adult HGS-OC pts (84.2% stage III-IV). TP53 mutation was found in 83.4% and somatic BRCA mutations in 28.3%. Overall, BRCA-MT HGS-OC had higher TP53 mutation frequency than BRCA wild type (WT) (88.8% vs 81.3%, p=0.1510). According to the structural classification, 76.5% had a missense TP53 mutation. LOF TP53 mutations were found in 59.4% while GOF in 31.2%, without significant disparity in the distribution of specific TP53 mutations within each classification between BRCA-MT cases and WT. As for BRCA-MT pts, TP53 WT were all PS. In TP53-MT, GOF mutations were related to PS in 7 pts and platinum resistance (PR) in 3 pts; LOF with PS in 7 pts and PR in 12 pts, with significant different distribution of PS (p=0.0291). As for BRCA WT pts, TP53 WT were all PS. Among TP53-MT, GOF mutations were associated with PS in 14 pts and PR in 10 pts; viceversa, LOF mutations with PS in 19 pts and PR in 25 pts (p=0.2357). Notably, 5 cases LOF TP53-MT with null IHC p53 expression were platinum refractory.

Conclusions: Even if preliminary, our data show that HGS-OC with TP53 null mutations are the poorest prognostic subgroup, especially in terms of PS. Further studies are needed to confirm our findings and the role of TP53 mutation as a biomarker of inherent or acquired platinum resistance.

D30

NUTRITIONAL STATUS AND SYSTEMIC INFLAMMATION AS PROGNOSTIC FACTORS IN PATIENTS WITH ADVANCED UROTHELIAL CARCINOMA (AUC) RECEIVING AVELUMAB IN FIRST-LINE MAINTENANCE THERAPY ENROLLED IN THE MALVA STUDY (MEET-URO 25)

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Background: The prognostic role of body mass index (BMI), prognostic nutritional index (PNI) and systemic inflammation index (SII) in aUC has recently been documented. We evaluate BMI, PNI and SII as potential prognostic factors in aUC patients (pts) receiving avelumab maintenance (AM) in the MALVA study, a real-world, multicenter, observational, ongoing study.

Methods: We included aUC pts receiving AM after first-line chemotherapy in 15 Italian centres from 2021 to 2024. Treatment and patient information was collected from clinical reports. We used a restricted cubic spline to investigate the relationship between BMI and survival and identified a cut-off of 23.5 Kg/m2. As reported in the literature, the cut-off used for PNI was 40. In line with other similar studies, we chose the median as the cut-off for SII: it was 569 at baseline and 495 at the third AM administration. Kaplan-Meyer methods were used to calculate progression-free survival (PFS) and overall survival (OS). RStudio was used to run a machine learning algorithm (random forest) to predict patient survival based on key clinical and laboratory variables.

Results: 113 pts were analysed with a median follow-up of 21 months. High baseline BMI (≥ 23.5 kg/m2) was predictive of better median PSF (mPFS) (HR: 0.61, p: 0.0065) and median OS (mOS) (HR: 0.57, p: 0.019) from the start of AM. PNI ≥40 prior to AM was predictive of worse mPFS (HR: 1.59, p: 0.011) and mOS (HR: 1.51, p: 0.088). Pts with higher SII (≥ 569) prior to AM had better mPFS (HR: 0.71; p: 0.09) than those with lower SII (<569). Conversely, pts with high SII (≥495) after 3 Avelumab administrations had worse mOS (HR: 2.03; p: 0.0057) than those with low SII (<495). However, pts with a reduction in SII between baseline and the third AM dose had significantly better mPFS (HR: 0.67, p: 0.067) and mOS (HR: 0.41, p: 0.0014). Multivariate analysis confirmed the prognostic role of baseline BMI and SII. The breakdown of the machine learning prognostic model we elaborated showed that BMI and PNI at baseline and SII decrease were all classified as positive-importance variables for the model.

Conclusions: This is the first analysis to evaluate the prognostic role of nutritional and inflammatory indexes in a homogeneous population of aUC pts receiving AM. A high baseline BMI, a low baseline PNI and a decrease in SII during AM are all factors that positively influence survival outcomes.

D31

HEREDITARY GYNECOLOGICAL CANCER SYNDROMES: A MONO-INSTITUTIONAL EXPERIENCE OF THE NATIONAL CANCER INSTITUTE OF NAPLES (INT)- FONDAZIONE G. PASCALE

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Background: Hereditary ovarian cancer syndromes and hereditary endometrial cancer related to Lynch syndrome account for about 20% of high-grade non-mucinous epithelial ovarian cancer and for about 3-5% of endometrial cancer cases. The objective of the multidisciplinary oncology team for hereditary cancer syndromes is to identify these cases and consequently the healthy family members carrying the pathogenic mutation. In this retrospective analysis, we report the hereditary gynecological syndromes cases of National Cancer Institute "Pascale Foundation", Naples.

Materials From 2021 to 2023, data were collected from all patients and healthy subjects with suspected hereditary syndromes who underwent counseling at the hereditary-familial cancer clinic. The subjects who met the criteria, had access to the germline test by showing a referral prescribed by the general practitioner. The access to germline test has been allowed in Campania region by the Decree 100 (2019).

Results: 142 patients with ovarian cancer have made germline testing, with 21% showing a pathogenic mutation. The genes involved were BRCA1 (66%), BRCA2 (27%), both BRCA1 and BRCA2 genes (3%), PALB2 (3%) and only one patient had a pathogenic mutation in the gene RAD51D.

We found a percentage of pathogenic mutations on 37% of the 108 healthy subjects referred to the clinic; the gene involved were BRCA1 (52%), BRCA2 (41%), PALB2 (6%) and only one subject presented a pathogenic mutation in both BRCA1 and 2 genes.

47 patients with endometrial cancer and mismatch repair deficient (dMMR) on the universal test were sent for oncogenetic consultancy for suspected Lynch syndrome. Out of these, 7 patients were excluded from the germline analysis because showed loss of MLH1 expression on IHC but MLH1 hypermethylation. 39 patients were tested for suspected Lynch syndrome and in only 4 patients the diagnosis has been confirmed (3 patients reported a pathogenic mutation of the MSH6 gene and one of EPCAM gene), therefore reporting a percentage of hereditary endometrial cancer of 1.4%.

Conclusions: Hereditary cancer syndromes are a prime target for early detection and prevention. One of the main objectives of our Institute is the identification of families carrying genetic mutations that predispose to the development of tumors. In our case study, we confirm the known percentage in the literature of hereditary ovarian tumors while the percentage of hereditary endometrial cancer was, at the moment, lower.

D32

IDENTIFICATION OF INFLAMMATORY BIOMARKERS AS PREDICTORS OF RESPONSE IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA RECEIVING THE IO-TKI COMBINATION PEMBROLIZUMAB-AXITINIB IN FIRST LINE SETTING: A MONOCENTRIC EXPERIENCE

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Background: Blood-peripheral inflammatory ratios have demonstrated a role in predicting response and prognosis in pts with renal cell carcinoma.They are:NLR (neutrophil-to-lymphocyte ratio),PLR (platelet-to-lymphocyte ratio),LMR (lymphocyte-to-monocyte ratio) and SII (systemic inflammation index).The aim of our retrospective analysis is to identify if and which biomarkers could be predictors of response during treatment with Pembrolizumab and Axitinib (P+A).

Patients and Methods: 37 patients with mRCC were included.Pts had completed at least 5 cycles of P+A as 1st treatment line and they had performed at least 1 imaging assessment of tumor response between 5th and 6th cycle of therapy.Values of LMR, NLR, PLR and SII were calculated at baseline and from the 2nd to the 5th Pembrolizumab infusion.The variations between the value at each treatment cycle compared to the baseline were calculated.

Results: The significant baseline inflammatory biomarker respect to first CT response at 5 cycles of treatment was SII (cut-off 1096.7, accuracy 76%, AUC 75%, sensitivity 65%, specificity 85%).Baseline SII demonstrated significative correlation with IMDC group.Other significant inflammatory biomarkers were: NLR at the 5th cycle;SII on the 3rd, 4th, 5th cycle;PLR at the 4th and 5th cycle.Value of SII at 5th cycle demonstrated the best accuracy (95%), specificity (95%), PPV (94%), NPV (95%), sensitivity (94%);cut-off value between PD and no-PD groups of 894.48.PLR resulted significant predictor of response at 4th and 5th cycle, with better performance at 5th cycle (cut-off 153.4;accuracy 89%, AUC 88%).Values of NLR resulted significant in predicting response only at 5th cycle with inferior performance (accuracy 84%; cut-off of 3.9). LMR did not result significative at any timepoints.The variations of SII and NLR between 5th cycle and baseline showed a better performance than the variation between 4th cycle and baseline.PLR showed a significant variation between 5th cycle and baseline in pts with PD compared to responders/SD.

Conclusions: SII is a significant inflammatory biomarker in predicting response to P+A treatment at different timepoints. While its baseline value showed an accuracy of 76% in predicting radiological response, its monitoring during the first 5 cycles of treatment demonstrated better performances,both as variation between 1st and 5th cycle and as absolute value at the 5th cycle.Early variations of NLR and PLR were significantly associated with radiological response.

D33

ENHANCING EFFICIENCY THROUGH PATIENT EXPERIENCES: A STUDY OF THE CORO GYNECOLOGY ONCOLOGY OUTPATIENT CLINIC AT IRCCS GIOVANNI PAOLO II CANCER INSTITUTE

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Background: The Giovanni Paolo II Cancer Institute in Bari, serves as the primary oncology reference center for the Puglia region, housing the Oncology Orientation Center (COrO). The clinic is run by a researcher nurse who manages the reception of patients, explains service organization, gathers clinical and laboratory data also for research purposes, collects patient histories, and acts as a responsible case manager. Subsequently, by gynecologist, patients undergo medical history completion and gynecological evaluations by a physician, followed by report delivery, instructions, and prescriptions.The nurse and physician collaborate in reviewing reports, with the nurse acting as a case manager, scheduling diagnostic tests or consultations. The Multidisciplinary Team collaborates to define treatment pathways.

Objective: The study aims to assess the efficiency of the COrO Gynecology Oncology outpatient clinic, incorporating user-perceived experiences for continuous improvement. This includes: -Structured interviews to explore patient emotions, perceptions of the clinic, research activities, and case management. -Quarterly assessment of wait times for first visits, tests, consultations, and intervention timelines.

Materials and methods: The study utilizes a prospective, observational, mixed-method, sequential exploratory design. Inclusion criteria encompass women accessing the clinic, while exclusion criteria involve major psychiatric disorders, neurocognitive deficits, and inability to provide informed consent. Data collection involves a custom database for quantitative measures and structured interviews

for qualitative insights. Ethical considerations align with the Helsinki Declaration, providing participants with informed consent and data confidentiality. Results will be aggregated to ensure participant anonymity.

Expected Results: A nticipated outcomes from quarterly data analysis include: -Timely patient management within 72 hours in at least 95% of cases. -Adherence to national guidelines for test and consultation scheduling. -Completion of tests within 15 days in 90% of cases. -Compliance with Class A intervention timelines in 90% of cases.

Conclusions: The study's findings will guide improvements in service efficiency and effectiveness.

D34

INTERLEUKIN-8 AS A POTENTIAL PROGNOSTIC BIOMARKER IN RENAL CELL CARCINOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Treatment strategies for advanced-stage disease are based on risk stratification models, but new prognostic/predictive biology-based biomarkers are needed.

Interleukin-8 (IL-8) is a key chemokine involved in inflammation and primary immune response. It is produced by several cell types, including immune cells and cancer cells. Elevated IL-8 levels have been associated with a poorer outcome in several tumors, and high IL-8 expression in RCC has been associated with higher tumor burden and therapy resistance (both immunotherapy and TKIs). However, IL-8 prognostic role in RCC has not been formally demonstrated.

Material and Methods: The literature review and meta-analysis were conducted following the PRISMA guidelines. A systematic literature search in the PubMed, Embase and Scopus databases included all publications from 01/January/2008 to 31/October/2021, investigating the potential prognostic role of IL-8 in RCC, using among others the MESH terms for "IL-8" and "Renal cell carcinoma". Overall survival (OS) and Progression-free survival (PFS) were analyzed as clinical outcomes. A meta-analysis comparing the results of the studies was performed. The HR was calculated for time-dependent variables and the small study effect was addressed by Egger's test and funnel plot.

Results: Out of 1818 studies identified through a systematic literature search, only 9 met the pre-defined inclusion and exclusion criteria for the meta-analysis. All 9 were retrospective or prospective cohort studies, and their quality was evaluated using the Newcastle Ottawa scale (NOS), resulting in 8 final studies with good or excellent scores. Out of these 8 studies, all were evaluated for the OS endpoint (total 2501 patients), and 6 were assessed for the PFS endpoint (total 2228 patients).

High levels of serum and on-tissue IL-8 were associated with statistically lower OS (HR 1.94, 95%CI 1.53-2.35). These findings were also corroborated for the PFS endpoint where elevated levels of IL-8 were associated with a worse outcome (HR 1.28, 95%CI 1.06-1.49).

Conclusions: As initially hypothesized, the prognostic role of both circulating and tissue IL-8 levels in predicting outcomes for both OS and PFS has been confirmed in RCC. Further confirmatory analysis should be conducted to perspectively confirm the IL-8 prognostic role and its potential predictive role in relation to the treatment strategy adopted.

D35

REAL-WORLD DATA ON THE EFFICACY AND SAFETY OF IMMUNE-CHECKPOINT INHIBITORS IN ELDERLY PATIENTS WITH ADVANCED UROTHELIAL CANCER

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Background: Immune-checkpoint inhibitors (ICIs) are effective against urothelial cancer (UC). Recently the association of immunotherapy with ADCs has brought about a breakthrough in the treatment of metastatic UC. However, this combination is not yet available in many countries and immunotherapy alone is still used in many patients. Furthermore, whether the efficacy and safety of ICI treatment in elderly patients are similar to those in

younger patients is unclear. This study was designed to address this question.

Methods: We enrolled patients who received ICI monotherapy between March 2017 and March 2024; those ≥70 years of age comprised the elderly group. We compared the efficacy and safety of ICI monotherapy in elderly patients with those in younger patients and explored prognostic factors in elderly patients.

Results: We enrolled 40 patients; 22 (55%) were assigned to the elderly group. The median age of the elderly and younger groups was 78 (range, 70-88) and 64 (range, 42-69) years. The median progression-free survival (4.9 months vs. 5.8 months) and median overall survival (7 months vs. 8.8 months) were similar between the elderly and younger groups. Overall, nine pts (22,5%) of the elderly group had immune related AEs and the most common irAE was cutaneous such as maculopapular rash/pruritus (17,5%). Only one patient experienced colitis with grade 2 diarrhoea. No severe irAEs (grade > 3) were observed and no elderly patients discontinued the treatment or died for immune related adverse events. Interestingly, survival was higher in pts who experimented irAEs.

Conclusions: ICI is effective in elderly patients with advanced urothelial cancer. Our study demonstrated a good tolerability profile of ICI also in the elderly, that seem to be similar to those reported in younger pts. Prospective studies including geriatric pts are needed.

D36

CLINICAL PARAMETERS FOR FIRST-LINE IMMUNO-COMBINATIONS CHOICE IN METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS (PTS): THE MEET-URO 33 STUDY

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Background: Despite several first-line immuno-combinations in mRCC, there are no formal comparisons or biomarkers to guide the treatment choice. In this context, the ongoing Meet-URO 33 study will recruit pts in up to 80 Italian centers to answer many clinical unmet needs.

Methods: The Meet-URO 33 study is a multicenter prospective/retrospective registry of a real-world mRCC population receiving first-line therapy from January 2021. As of April 2024, 421 pts from 25 Italian centers were included. We investigated which clinical parameters (age, ECOG PS, type/number of comorbidities, steroid use, surgery of primary tumor, histology, sarcomatoid features, type/number of metastases, IMDC and Meet- URO scores) influenced investigators' choice.

Results: Overall, 344 (81.7%) pts received an immuno-combo: 160 (46.5%) Pembro + Axi (P+A), 81 (23.6%) Nivo + Ipi (N+I), 63 (18.3%) Nivo + Cabo (N+C), 40 (11.6%) Pembro + Lenva (P+L). At univariate analysis, the IMDC and Met-URO scores, histology, bone and pancreatic metastases, and metabolic comorbidities significantly associated with an immuno-combo choice. Specifically, N+I population had a higher percentage of IMDC intermediate-risk pts while P+L poor-risk pts (p=0.002). According to the Meet-URO score, the worst prognostic group (group 5) was predominantly treated with P+A and N+C (p=0.043). Metabolic comorbidities correlated with a more frequent choice of N+I and less of P+L (p=0.019). P+L option was significantly preferred in clear-cell histology, while N+C with the higher percentage of papillary histology (p=0.047). Bone metastases correlated with N+C and less with N+I and P+L (p=0.021), while pancreatic metastases were associated with P+L and less with N+I and N+C (p=0.006).

Conclusions: Despite the bias linked to the different prescription indications over time, the associations observed from this real-world scenario confirmed the consideration of well-known prognostic factors in the therapeutic choice; however these findings should be also interpreted as a general reflection of the oncologists experience. Associations of clinical parameters will be assessed within a larger sample size.

D37

THERAPEUTIC DRUG MONITORING AND PHARMACOGENETICS TO PERSONALIZE DRUG DOSING IN METASTATIC RENAL CELL CARCINOMA PATIENTS TREATED WITH SUNITINIB

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Background: The tyrosine kinase inhibitor sunitinib (SUN) is used for the treatment of metastatic renal cell carcinoma (mRCC). It is orally administered at fixed dose and shows significant interpatient differences in drug exposure (exp). Since exp-response and exp-toxicity relationships were established, the incorporation of therapeutic drug monitoring (TDM) and pharmacogenetics (PGx) assessment holds promise for improving treatment outcomes. We investigated the feasibility and clinical utility of pharmacological counselling using TDM and PGx for SUN treatment in mRCC patients.

Methods: Blood samples were collected from participants in the CRO-2022-14 trial at CRO Aviano. Samples were obtained at minimum steady-state plasma concentration (Cmin), and plasma exp was assessed by quantifying SUN and N-desethyl-SUN plasma concentrations using a validated LC-MS/MS method. Target Cmin ranges for efficacy and safety were 37.5-75 ng/mL for continuous dosing and 50-87.5 ng/mL for intermittent dosing. Polymorphisms in SUN-related cytochromes and transporters were analyzed. Oncologists received counseling based on the interpreted data.

Results: Eight pts undergoing SUN therapy were enrolled, with a median duration of SUN treatment of 34 months at baseline. SUN dosing was adjusted based on observed clinical toxicity, resulting in dose reductions in 6/8 pts. Six pts achieved a mean Cmin ranging from 53 to 68 ng/mL, within the desired exp for effective and safe therapy. One pt exhibited a mean Cmin of 84 ng/mL despite a dose reduction to 25 mg/day and experienced recurrent G2 toxicity, indicating a possible need for a lower but still efficacious dosing. Another pt had his dose reduced from 50 to 25 mg/day due to G3 toxicity, resulting in a Cmin of 39 ng/mL. No further serious toxicities were observed, so a higher dose (37.5 mg/day) could have been considered, with exposure remaining within the target range. PGx analyses were conducted, although the limited sample size prevented definitive conclusions.

Conclusions: Adjusting doses based on toxicity resulted in SUN exposure consistent with the therapeutic range over an average treatment duration of 34 months. Implementing TDM from the beginning could have optimized SUN dosing to achieve the Cmin target range during the initial treatment phases. This might have improved tolerability and compliance, prevented potential treatment delays or suspensions, and maintained plasma concentrations within the effective threshold.

D38

UPPER TRACT UROTHELIAL CARCINOMAS (UTUC): SINGLE-CENTER EXPERIENCE OF A RARE TUMOR

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Background: UTUC account for 5–10% of urothelial carcinomas with an estimated annual incidence of almost 2 cases per 100,000 inhabitants in Western countries. New therapy (tp) are emerging. Finding prognostic indicators and molecular targets will become necessary to treat UTUC.

Material and Methods: We retrospectively analized data from patients (pts) with diagnosis of UTUC from 2018 to 2023. We collected clinical and molecular features, histotypes, occurrence, sites of metastasis and lines of tp to investigate clinical and pathological correlations. Kaplan-Meier method was used to estimate Overall Survival (OS).

Results: A total of 59 pts were included. Median (m) age at diagnosis was 71 years. Only 12% were females, 80% presented pure transitional cell features, rarer histotypes included 2 poorly differentiated carcinomas, 1 signet ring cell variant, 1 nested type and 1 neuroendocrine one.

Moreover, 14 pts (23%) had synchronous metastases at diagnosis; 7 (12%) developed metachronous ones: 19 started a first-line, 9 received a second-line, only 2 were given a third-line tp. Two pts had synchronous tumors of pelvis and ureter. PDL1 expression was evaluated in 12 pts, a positivity rate of ≥1% was observed in 50% of them. Out of the 11 cases analyzed for MMR, one tested positive for microsatellite instability. Next generation sequencing was performed in 9 pts founding 1 amplification of EGFR, 1 BRAF and KRAS variants in a pt with

lung metastasis at the onset and 2 FGFR3 alterations without metastatic disease.

mOS was 65 months (mo) (95% CI 28.3-101.7).

Pure urothelial carcinoma was associated with better OS compared to mixed histologies (mOS 66 vs 21 mo), though it didn't prove statistically significant. We found a statistically significant association between T and OS: early stages (T1 and T2) showed better prognosis with mOS 66 mo (95% CI 66.0-66.0) and 65 mo (95% CI 6.0-65.0) for T1 and T2, respectively, vs 56 mo for T3 (95% CI 40.6-73.1) and 3 mo for T4 (95% CI 26.0-66.0) (p=0.0006).

Moreover, pts with synchronous tumors of pelvis and ureter achieved poor OS compared with pts with exclusively localization of pelvis or ureter (mOS of 32 vs 65 and 66 mo, respectively).

Conclusions: Despite small population, our findings seem to confirm a poorer prognosis for non-pure transitional cell UTUCs and higher T stages of disease. Further studies with greater cohorts of pts will be needed to investigate molecular characterization and its possible clinical impact.

D39

MONOCENTRIC REAL WORLD ANALYSIS OF BRCA IN MCRPC: SO MANY SHADOWS, STILL!

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Background: Prostate cancer represents one of the tumors with the highest incidence in men. The developments of recent years have led to a significant increase in the weapons at our disposal and made the study on the search for pathogenic mutations affecting the BRCA1/2 genes indispensable given the possibility of specific target therapies. However, the widespread use of these techniques has also made it possible to identify further alterations whose meaning remains obscure or uncertain.

Patients and Methods: from November 2021 to February 2024, all patients referred to our center with a diagnosis of mCRPC for whom we had the possibility of analyzing the histology from biopsy or prostatectomy. Exons and exon-intron junction tracts were analyzed with automatic extractor, using a kit certified for massively parallel sequencing. In case of a doubtful response or anamnestic finding of synchronous or metachronous tumors or relevant oncological family history, the patients were also subjected to peripheral blood sampling and search for mutations with NGS technique.

Results: 70 patients diagnosed with mCRPC were enrolled, average age 71 years (56-89). Among these, two pathogenic mutations were found in the BRCA2 gene and none in BRCA1. In addition to these results, 2 mutations of uncertain significance in BRCA1 and 6 in BRCA2 were identified. All these mutations had VAF with values ??around 50%, except for one BRCA1 mutation which had 5.6%. In 5 cases a copy number alteration was found in BRCA2 and in 3 cases in BRCA1. In 5 of these 8 cases, the search for germline mutations was started on peripheral blood with NGS analysis of the exome, identifying only in one case the mutation of uncertain significance of probable clonal origin in PTEN with VAF 0.73%. Among the total patients, 12 had synchronous or metachronous tumors or relevant family history of tumors. Furthermore, two patients were identified as carriers of a mutation in the FANC gene and one in KYNU gene.

Conclusions: Somatic research for BRCA1 and 2 mutations is opening up new scenarios not only aimed at the use of new drugs in mutated patients, but also identifying alterations whose prognostic or predictive significance we are currently unable to grasp. response to the therapies available to us. The possibility of using PARP inhibitors associated with ARTA could probably provide some answers in this sense which are currently lacking.

D40

SOMATIC BRCA MUTATIONS AND CLINICAL OUTCOME OF COMBINATION TREATMENTS IN METASTATIC HORMONE SENSITIVE PROSTATE CANCER (MHSPC): A RETROSPECTIVE, MULTICENTER STUDY

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Background: Addition of novel androgen receptor targeting agents (ARTAs) and/or docetaxel to androgen deprivation therapy (ADT) has significantly improved clinical outcome in patients (pts) with mHSPC. The presence of

somatic BRCA1 and BRCA2 mutations is associated with worse prognosis in pts with metastatic castration resistant prostate cancer (mCRPC). Currently, the role of BRCA alterations in mHSPC remains unclear. This study aims to assess the prognostic impact of somatic BRCA mutations in pts who received combination therapies for mHSPC.

Methods: Pts with mHSPC treated with combination treatments (ADT+ARTA, ADT+Docetaxel or ADT+ ARTA+Docetaxel) and available somatic mutational status of BRCA1 and BRCA2 (determined with next-generation sequencing) were retrospectively selected between January 2020 and March 2024. Time to CRPC (ttCRPC) and overall survival (OS) according BRCA status were calculated with Kaplan Meier method; best confirmed prostate-specific antigen (PSA) decline over 50% from baseline (PSA50) or to 0.2 ng/mL (PSA02) were also evaluated.

Results: Out of 51 selected pts, 8 (15.7%) had a pathogenic somatic BRCA1 or BRCA2 mutation. Baseline characteristics are reported in table 1. ttCRPC was significantly longer in pts without BRCA mutation compared to those carrying one (median ttCRPC 29.73 vs 10.53 months, log rank p=0.048); OS was similar between two groups of pts (median OS not reached vs 46.7 months, log rank p=0.808). No difference was observed between BRCA wild type and mutated pts according PSA response (PSA50: 97.7 vs 87.5%, Fisher p=0.2918; PSA02 51.2 vs 50%, Fisher p=1).

Conclusions: Presence of somatic BRCA mutations could have a key role in mHSPC, identifying pts with shorter ttCRPC. Ongoing prospective trials will clarify the impact of the addition of novel drugs (particularly, PARP inhibitors) to standard combination treatment in these pts.

Table 1.

	BRCA mutated (N=8)	BRCA wild type (N=43)
Age at diagnosis of mHSPC, median (range)	67 (51-81)	68 (37-83)
Gleason score≥8	7 (87.5%)	33 (76.7%)
PSA at mHSPC diagnosis, median (range) [ng/mL]	75 (9-2665)	64,3 (2,1-5000)
De novo mHSPC	8 (100%)	33 (76.7%)
High volume disease	5 (62.5%)	35 (81.4%)
Combination treatment		
ADT+Docetaxel	2 (25%)	15 (34.9%)
ADT+ARTA	5 (62.5%)	16 (37.2%)
ADT+ARTA+Docetaxel	1 (12.5%)	12 (27.9%)

E – Breast Cancers

E01*

CLINICAL AND PROGNOSTIC IMPACT OF IMMUNOHISTOCHEMISTRY (IHC) EXPRESSION IN HER2-POSITIVE (HER2-POS) METASTATIC BREAST CANCER (MBC): EXPLORING DIFFERENCES BETWEEN IHC 2+ AND IHC 3+ POPULATIONS

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Background: The complexity of IHC expression in HER2-pos mBC has gained notable interest in order to optimize therapeutic strategies in HER2-low tumors. Aim of our study was to compare clinical variables, metastatic patterns, and prognosis between IHC 2+ and IHC 3+ populations (pop), since limited data is available.

Material and Methods: Data of patients (pts) with HER2-pos mBC, determined by HER2 IHC staining of 3+ or 2+

with amplification at the in situ hybridization assay, were extracted from the GIM14 study database. Logistic regression was used to assess associations among variables. Prognostic factors for overall survival (OS) and time to treatment failure (TTF) were evaluated through Cox regression model.

Results: A total of 762 HER2-pos mBC pts were included in the analysis. Among them, 297 (39%) had IHC score of 2+ and 465 (61%) had a IHC score of 3+. IHC 3+ compared to IHC 2+ was significantly associated with skin metastasis (mts) (OR 1.76, P=0.043) and less likely to be associated with liver (LI) (OR 0.71, P=0.031), lung (OR 0.70, P =0.036), and lymph node (LN) (OR 0.63, P=0.002) mts. In multivariable (multi) analysis, LN mts retained statistical significance (OR 0.62, P=0.004). Factors associated with worse OS at multi were central nervous system (CNS) (HR 1.73, P=0.028) and LI mts (HR 1.47, P=0.017) in IHC 3+. The only negative prognostic factor for OS in IHC 2+ pts was LI mts (HR 1.67, P=0.005). In the overall HER2-pos pop, neoadjuvant (neo) chemotherapy (CT) (HR 1.47, P=0.034), CNS (HR 1.78, P=0.003) and LI mts (HR 1.50, P=0.036) were associated with worse OS at multi analysis, while neo CT (HR 1.49, P=0.009), pleural (HR 1.74, P=0.048) and CNS mts (HR 1.53, P=0.003) were associated with a shorter TTF.

Conclusions: Our study revealed that the metastatic site exhibits prognostic significance in HER2-pos mBC, as CNS mts are associated with worse OS in IHC 3+ pts, while LI mts are associated with worse OS in both IHC 2+ and 3+ pop. The IHC score itself (2+ or 3+) does not have independent prognostic value, but it is associated with a differential distribution of metastatic sites. Further investigation is needed to better understand the influence of HER2 IHC staining on treatment outcomes and its potential impact on clinical practice.

E02*

EFFICACY OF FIRST-LINE PALBOCICLIB, RIBOCICLIB OR ABEMACICLIB IN PATIENTS WITH HR+/HER2- ABC: REAL-WORLD COMPARISON FROM THE MULTICENTER, ITALIAN STUDY PALMARES-2

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Background: The cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) palbociclib (P), ribociclib (R) and abemaciclib (A) in combination with Endocrine Therapy (ET) represent the standard first-line treatment for patients (pts) with Hormone Receptor-positive, Human Epidermal growth factor Receptor 2-negative, advanced Breast Cancer (HR+/HER2- aBC). However, no large real-world studies have compared the efficacy of the three CDK4/6i so far.

Methods: The multicenter, Italian PALMARES-2 study is collecting real-world data from HR+/HER2- aBC pts treated with first-line P, R or A plus ET in 18 Italian cancer centers. Here, we compared real-world Progression-Free Survival (rwPFS), as defined as the time interval between ET plus CDK4/6i initiation and disease progression, in pts treated with P, R or A. Multivariate Cox regression models were used to adjust the association between individual CDK4/6i and rwPFS for clinically relevant variables.

Results: We included 1982 pts who initiated first-line ET+CDK4/6i between January 2016 and September 2023. Of them, 1333 (67.3%) pts had endocrine-sensitive disease, while 649 (32.7%) pts had endocrine-resistant tumors. 789 (39.8%), 736 (37.1%) and 457 (23.1%) pts received P, R and A, respectively. Median rwPFS in the entire cohort was 31.3 months (95% CI 29.7-33.4). In pts with endocrine-sensitive disease, A was associated with independently better rwPFS when compared to P (aHR 0.76, 95% CI 0.62-0.93, p=0.007 for A; aHR 0.75, 0.56-0.99, p=0.044 for R). In the endocrine-resistant population, both A and R were associated with better rwPFS than P (aHR 0.76, 95% CI 0.66-0.89, p<0.001 for A; aHR 0.90, 0.64-1.27, p=0.565 for R). R and A were not associated with significantly different rwPFS (p=0.729 in endocrine resistant, p=0.353 in endocrine sensitive population). Differential benefit from individual CDK4/6i was observed in clinically relevant subgroups: A and R were more effective than P in patients who were premenopausal, had luminal B-like or de novo metastatic disease, while A was more effective than R or P in patients with high metastatic burden.

Conclusions: In HR+/HER2- aBC pts, the three CDK4/6i are associated with different efficacy depending on the specific clinical setting. Our results may help clinicians in personalizing the use of P, R or A in this clinical setting.

E03*

DOSE-DENSE ADJUVANT CHEMOTHERAPY IN HER2-LOW EARLY BREAST CANCER PATIENTS: AN EXPLORATORY ANALYSIS OF THE GIM2 TRIAL

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Background: Dose-dense (DD) adjuvant chemotherapy represents the standard treatment for patients with node-positive early-stage HER2-negative breast cancer (BC), but its role in HER2-low disease is unknown. In this exploratory analysis of the GIM2 trial, we investigated efficacy of DD chemotherapy among patients affected by HER2-negative BC according to HER2 immunohistochemistry (IHC) score (low vs. zero).

Methods: Patients with node-positive early BC were randomized to receive either DD or standard schedule anthracycline- and taxane-based chemotherapy. HER2 status was assessed locally. BC with HER2 score 0 were classified as HER2-zero, while those with a HER2 score 1+ or 2+ without FISH amplification were defined as HER2-low. Some BC were classified as HER2-negative with unknown IHC score. Survival outcomes were compared between patients with HER2-zero vs HER2-low BC.

Results: Among 2003 patients enrolled in the GIM2 trial, 1243 subjects were eligible for this analysis. Median age was 52 years (IQR 44-59) and hormone receptor status was positive in 87.9% of BC. 475 BC were classified as HER2-zero (38.2%), 446 (35.9%) as HER2-low and 322 (25.9%) as HER2-negative with unknown IHC score. No significant differences were found in terms of baseline characteristics between the three subgroups. At a median follow-up of 14.9 years (IQR 8.4-16.2), no significant interaction was observed between treatment effect and HER2 status in invasive disease free-survival (iDFS) (p for interaction=0.46) nor in overall survival (OS) (p for interaction=0.43). Comparing patients with HER2-zero BC with those with HER2-low BC, no significant differences in iDFS were observed (15yr iDFS: 61% vs. 54%, respectively, p=0.25), nor OS differences (15yr OS: 75% vs. 72%, respectively, p=0.19). When investigating DD schedule efficacy among patients with HER2-zero BC, hazard ratio (HR) for iDFS was 0.64 (95% confidence interval [CI] 0.46-0.87) and HR for OS was 0.57 (95%CI 0.38-0.88). Within patients with HER2-low BC, HR was 0.83 (95%CI 0.62-1.11) for iDFS and 0.83 (95%CI 0.57-1.22) for OS. These results were consistent with the efficacy results of DD chemotherapy in the overall population of this analysis (HR for iDFS 0.73 [95%CI 0.61-0.89]; HR for OS 0.69 [95%CI 0.54-0.88]).

Conclusions: In this exploratory analysis of the GIM2 trial, HER2 status (i.e. HER2-zero vs HER2low) did not show prognostic value and in patients with high-risk early BC, the benefit of DD chemotherapy was observed irrespective of HER2 status.

E04*

VALIDATION OF PREDICT TOOL VERSION 2.2 IN EARLY-STAGE BREAST CANCER (BC) PATIENTS ENROLLED IN ADJUVANT TRIALS BY THE GRUPPO ITALIANO MAMMELLA (GIM) AND MAMMELLA INTERGRUPPO (MIG)

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Background: PREDICT, an online prognostic tool developed from population registries, estimates the potential benefit of different treatments (i.e., surgery alone, chemotherapy, trastuzumab, endocrine therapy, and/or bisphosphonates) for early-stage BC patients (pts). We aim to investigate its prognostic performance among pts enrolled in randomized trials (RCTs) using individual patient data from the GIM and MIG adjuvant studies.

Methods: We evaluated the performance of PREDICT on a population enrolled in five RCTs (i.e., MIG1, MIG5, GIM2, GIM3, GIM6) between 1992 and 2012 with complete baseline information. Women diagnosed with primary unilateral invasive breast cancer from 1992 to 2012 and who had a minimum of five years of follow-up were included in the study. Enrollment was open to patients of any age. We used Uno's concordance index (C-index) to

assess the model's discriminative power over all the time range, and Poisson regressions to assess the 5- and 10-year predictions calibration.

Results: A total of 6205 pts were included. The median age at BC diagnosis was 57 (IQR 48-65), with 5364 (86.5%) pts having estrogen receptor-positive, 2226 (35.9%) pts having node negative and 2088 (33.7%) pts having grade 3 tumors. Median tumor size was 18 mm (interquartile range (IQR) 13-25 mm). After a median follow-up of 9.3 years (IQR, 5.9–14.8), 1083 deaths were observed. PREDICT assigned higher risk to subjects who had earlier events 62% of the times (C-index 0.62 95%CI 58–65). Overall, the 5- and 10-year OS was underestimated by 5.1% (95%CI 3.9–6.4; observed 5-year OS was 92.2% vs. predicted 87.1%) and by 2.1% (95%CI 0.3–4.0; observed 10-year OS was 74.4% vs. predicted 72.3%), respectively; with 60% and 93% of the expected events respectively observed (calibration intercepts -0.50 and -0.08). The OS underestimation was consistent across subgroups, with worse predictive performance for pts with estrogen receptor-negative, large tumor size, or HER2-positive disease.

Conclusions: Our analysis showed that PREDICT underestimates 5- and 10-year OS in early breast cancer patietns. Oncologists need to be aware of this limitation when they use this tool to provide prognostic information to pts with early-stage BC treated with modern chemotherapy and endocrine regimens.

E05*

IMPACT OF HORMONE RECEPTOR STATUS AND TUMOR SUBTYPES ON CLINICAL BEHAVIOR AND OUTCOMES OF BREAST CANCER IN YOUNG BRCA CARRIERS

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Background: Hormone receptor expression is a known positive prognostic and predictive factor in breast cancer (BC). However, limited evidence exists on the impact of hormone receptor status on clinical behavior and outcomes in young patients harboring BRCA pathogenic variant (PV).

Patients and Methods: This is an international, multicenter, hospital-based, retrospective cohort study including young patients (≤40 years) diagnosed with invasive BC between January 2000 and December 2020, harboring germline PVs in BRCA genes. Our analysis investigates the impact of hormone receptor status on clinical behavior and outcomes of BC. The type and pattern of recurrence and survival outcomes (disease-free survival [DFS], BC specific survival [BCSS] and overall survival [OS]) were first investigated according to hormone receptors expression (positive vs. negative), and then according to BC subtype (luminal A-like vs. luminal B-like vs. triple-negative vs. HER2-positive BC).

Results: From 78 centers worldwide, 4,709 BRCA carriers were included in this analysis, of whom 2,143 (45.5%) had hormone receptor-positive and 2,566 (54.5%) hormone receptor-negative BC. Patients with hormone receptor-positive BC were more likely to harbor BRCA2 PVs while less frequently had grade 3 tumors and nodal involvement. Median follow-up was 7.88 (IQR 4.47-12.61) years. The rate of distant recurrences was higher in patients with hormone receptor-positive BC (13.1% vs. 9.6%, p<.001), while the rate of second primary BC was lower (9.1% vs. 14.7%, p<.001) when compared to patients with hormone receptor-negative disease. The 8-years DFS was 65.8% in patients with hormone receptor-positive and 63.4% in those with hormone receptor-negative BC. No differences in terms of OS nor BCSS were observed. Among the 4,363 patients eligible for subtypes analysis, 612 had luminal A-like, 1,038 luminal B-like, 2,373 triple-negative and 340 HER2-positive BC. Patients with Luminal A-like BC had the worst prognosis in DFS compared to all the other subgroups (8-years DFS: 60.8% in luminal A-like vs. 63.5% in triple-negative vs. 65.5% in HER2-positive and 69.7% in luminal B-like subtype).

Conclusions: In young BRCA PVs carriers with early BC, differences in pattern of recurrence and second primary BC among hormone receptor-positive vs. negative disease warrants consideration in counseling patients on treatment, follow-up strategies and indication for risk-reducing surgery.

E06*

CLINICAL BEHAVIOR OF BREAST CANCER IN YOUNG BRCA CARRIERS AND PROGNOSTIC IMPACT OF THE TIMING OF GENETIC TESTING: RESULTS FROM AN INTERNATIONAL COHORT STUDY

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Background: Germline BRCA testing is recommended for patients (pts) diagnosed with breast cancer (BC) at age 40 or younger. Limited evidence exists on BC behavior in young *BRCA1* and *BRCA2* carriers and the impact of genetic testing timing on tumor characteristics and patient outcomes.

Methods: This international, multicenter, hospital-based, retrospective cohort study included pts with germline pathogenic variants (PVs) in *BRCA1* or *BRCA2* with stage I-III invasive BC at age 40 or younger between January 2000 and December 2020 (NCT03673306). Baseline pts, tumor, and treatment characteristics, as well as survival outcomes (disease-free survival [DFS] and overall survival [OS]) were compared between *BRCA1* and *BRCA2* carriers. A further comparison was made between patients who underwent genetic testing before (any time up to 2 months prior to BC diagnosis) or at (between 2 months prior and up to 6 months after diagnosis) BC diagnosis.

Results: From 78 centers worldwide, 4,752 pts were included, of whom 3069 harbored *BRCA1* and 1683 *BRCA2* PVs. Compared to *BRCA2, BRCA1* carrier were younger, had more grade 3 tumors, less nodal involvement, lobular histology, hormone receptor and HER2 positivity, received chemotherapy more frequently, and endocrine therapy less frequently. Median follow-up was 7.8 years (range 4.4-12.6 years). Second primary BCs (13.7% vs. 9.3%) and non-breast new primary malignancies (4.5% vs. 3.0%) were significantly more frequent among *BRCA1* carriers, while distant recurrences were less frequent (9.7% vs. 13.6%). *BRCA1* carriers had worse DFS and OS in the first 5 years due to a peak in DFS events in the first 2 years while *BRCA2* carriers had a constant risk of recurrence over time and worse OS after year 9. Pts tested for *BRCA* before BC diagnosis (n=411) had significantly smaller tumors (T1: 61.3% vs 32.4%) and less nodal involvement (N0: 65.9% vs 50.8%) compared to those tested at BC diagnosis. 8-year DFS and OS in patients tested before and at BC diagnosis were 73% vs 70% (HR 1.25; 95% CI 0.99-1.58) and 91% vs 87% (HR 1.65; 95% CI 1.08-2.52), respectively.

Conclusions: This global study provides evidence on the different clinical behavior of BC in young *BRCA1* and *BRCA2*carriers. Identifying *BRCA* PVs in healthy individuals led to earlier BC diagnosis and improved OS. These findings highlight the importance of identifying women at risk for carrying BRCA1 or BRCA2 PVs, offering genetic counseling and testing to inform prevention, early detection, treatment, and follow-up strategies.

E07*

BREASTFEEDING AFTER BREAST CANCER IN YOUNG BRCA CARRIERS: RESULTS FROM AN INTERNATIONAL COHORT STUDY

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Background: Pregnancy after breast cancer (BC) diagnosis and treatment is safe for patients (pts) carrying germline *BRCA* pathogenic or likely pathogenic variant. No data so far are available on feasibility and safety of breastfeeding in *BRCA* carriers.

Methods: This was an international, multicenter, hospital-based, retrospective cohort study including *BRCA* carriers diagnosed with stage I-III invasive BC at age 40 years or younger between January 2000 and December 2020 (NCT03673306). Pts that delivered a child after BC, were divided into two groups: women who breastfed after delivery and those who did not. Locoregional and contralateral BC recurrences, disease-free survival (DFS) and overall survival (OS) were compared among the two groups.

Results: Among 4732 pts included in the study from 78 centers worldwide, 659 had a pregnancy after BC diagnosis, of whom 474 delivered a child. After delivery, 110 (23.2%) pts breastfed (median duration 5 months), 68 (14.4%) did not breastfeed, 225 (47.5%) underwent bilateral risk-reducing mastectomy before delivery (thus were unable to breastfeed) and 71 (15.0%) had unknown breastfeeding status. Compared to pts in the no breastfeeding group (n=68), those in the breastfeeding group (n=110) were more frequently nulliparous at the time of BC diagnosis (61.8% vs 45.6%, p=0.026) and did not report prior smoking habit (71.8% vs 57.4%, p=0.019).

After a median follow up of 7.0 (IQR 3.6-10.5) years after delivery, no difference in cumulative incidence of locoregional and/or contralateral BC events between the breastfeeding (n=110) and no breastfeeding (n=68) groups was observed (adjusted sHR=1.08, 95%CI 0.57-2.06, p=0.82). Similarly, no impact of breastfeeding on DFS (adjusted HR=0.83, 95%CI 0.49-1.41, p=0.49) nor OS (9 OS events in patients that breastfed and 3 in those that did not breastfeed) was observed.

Conclusions: Our study provides the first evidence on the safety of breastfeeding after BC in young *BRCA* carriers. Our data suggest that breastfeeding is feasible and safe with no difference in locoregional recurrence or second primary BC events, emphasizing the possibility of achieving a balance between maternal and infant needs without compromising oncological safety.

E08*

SAFETY OF ASSISTED REPRODUCTIVE TECHNIQUES IN YOUNG BRCA CARRIERS WITH A PREGNANCY AFTER BREAST CANCER: RESULTS FROM AN INTERNATIONAL COHORT STUDY

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Background: Very limited evidence is available on the safety of assisted reproductive techniques (ART) in breast cancer (BC) patients harboring *BRCA1/2* pathogenic variants (PVs). Hence, concerns remain among physicians counseling young *BRCA* carriers with BC on the safety of ART use.

Methods: This is an international, multicenter, hospital-based, retrospective cohort study including women harboring known *BRCA*1/2 PVs and diagnosed at ≤40 years with stage

I-III BC between January 2000 and December 2020 (NCT03673306).

This analysis explored safety of ART to achieve a pregnancy. Maternal and fetal outcomes were compared between patients achieving a pregnancy spontaneously (spontaneous pregnancy group) vs. using ART (ART group).

Results: Out of 4732 patients included across 78 centers worldwide, 543 with a pregnancy after BC entered the present analysis. Among them, 436 conceived naturally and 107 using ART. In the ART group, 45 (42.1%) underwent oocyte/embryo cryopreservation at BC diagnosis, 33 (30.8%) ovarian stimulation following use of anticancer therapies, 21 (19.6%) embryo transfer following oocyte donation and for 8 ART type was missing.

As compared to the spontaneous pregnancy group, patients in the ART group were significantly older at the time of conception (37.1 vs. 34.3 years), had more often hormone receptor-positive BC (43.4% vs. 30.8%) and a longer median time from BC diagnosis to conception (4.2 vs. 3.3 years). No statistically significant differences in pregnancy complications were observed between cohorts (p=0.382). However, patients who conceived with ART had more miscarriages (11.3% vs. 8.8%) and less induced abortion (0.9% vs. 8.3%) than those who conceived spontaneously.

At a median follow up of 9.1 years (IQR 6.4-13.4), no detrimental effect of ART on disease-free survival (DFS) was observed with 13 and 118 DFS events in the ART and spontaneous pregnancy groups, respectively (log-rank p=0.147; HR 0.64, 95% CI 0.36-1.14; adjusted HR 0.72, 95% CI 0.38-1.33).

Conclusions: This global study showed that ART to have a pregnancy appears to be safe in BC survivors harboring *BRCA*1/2 PVs, with no apparent worsening of maternal prognosis or fetal outcomes.

E09

APPLICATION OF GENERALIZED PAIRWISE COMPARISON IN THE GIM2 TRIAL EVALUATING EFFICACY OF DOSE DENSE ADJUVANT CHEMOTHERAPY IN EARLY-STAGE BREAST CANCER

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Background: GIM2 trial is a randomized phase 3 trial comparing 6 cycles of adjuvant chemotherapy administered with a dose-dense (DD) vs standard-interval (SI) schedule. At a median follow up of 15 years, both disease-free survival (DFS) and overall survival (OS) were improved in the DD arm compared to the SI arm (HR(DFS)=0.77, 95%CI 0.67–0.89; HR(OS) =0.72, 95%CI 0.60–0.86). Overall, higher toxicity (G3-4) was observed in the SI arm. However, toxicity was lower in the SI arm if exclusion of peg-filgrastim potentially related adverse events was made (peg-filgrastim was administered in the DD arm only). Generalize pairwise comparison (GPC) is an innovative statistical technique that estimates the risk-benefit of a new treatment by prioritizing several different outcomes. We applied two GPC models with different toxicity priorities to assess the net benefit of DD adjuvant chemotherapy in early stage breast cancer.

Methods: The first priority outcome was OS in both models, differences in OS that exceeded 5 years were considered clinically meaningful. The second priority outcome was toxicity: the first model included any G3-4 toxicities, the second model excluded neutropenia, bone pain and fever (possibly related to peg-filgrastim). The overall treatment effect was quantified using the proportion in favour of DD chemotherapy, which can be interpreted as the net proportion of patients who have a better outcome with DD as compared with SI chemotherapy. Different thresholds were also considered.

Results: Among the 1972 patients included in the per protocol population, the first toxicity model confirmed an overall treatment effect in favour of DD chemotherapy that was statistically significant (overall proportion in favour of DD chemotherapy=20.7%, 95%CI 15.5%-25.8%; p<0.001). With the second model results indicated no significant benefit (overall proportion in favour of DD chemotherapy=1.0%, 95%CI -4.1%-6.2%; p=0.694). The net benefit was in favour of the DD arm in the first model considering thresholds up to 15 years, while in the second model the 95%CI of the net benefit estimate contained the value of 0 (meaning no effect) considering any threshold up to 15 years.

Conclusions: GPC assesses the benefit–risk balance of new treatments using a single statistical test for any number of prioritised outcomes. Our results highlight the importance of selecting specific toxicity events, as outcomes can be significantly affected by varying priorities regarding toxicity.

E10

IMPACT OF YOUNG AGE AT DIAGNOSIS ON SURVIVAL OUTCOMES IN PATIENTS WITH EARLY BREAST CANCER ACCORDING TO TUMOR SUBTYPE: POOLED ANALYSIS OF 5 RANDOMIZED CLINICAL TRIALS FROM THE MAMMELLA INTERGRUPPO (MIG) AND GRUPPO ITALIANO MAMMELLA (GIM)

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Background: The incidence of breast cancer (BC) among young women is on the rise. Young age itself has been known historically as a poor prognostic factor for BC. More limited evidence exists on the impact of age at diagnosis on survival outcomes according to tumor subtype.

Patients and Methods: We included individual patient (pt)-level data from pt with newly diagnosed stage I to III BC from in 5 randomized clinical trials run by Mammella InterGruppo (MIG) and Gruppo Italiano Mammella (GIM) study groups. According to age at BC diagnosis, pts were divided into the following age groups: <=40, 41-50, 51-60, 61-70, >70 years (yr). Multivariable Cox proportional hazards models were used to assess the relationship between age and breast cancer–free interval (BCFI) and breast cancer specific survival (BCSS).

Results: 8,338 pts with stage I to III BC were included: 778 (9%) aged <=40 years, 1,629 (20%) 41-50yr, 2,595 (31%) 51-60yr, 2,435 (29%) 61-70yr, and 901 (11%) >70yr. Young pts were more likely to have tumors with ductal histology, larger than 2 cm, with nodal involvement, G3 and triple negative (TN) or HER2-positive subtypes. With a median follow-up of 9.0 years (IQR 5.5-14.4), 2,161 BCFI and 927 BCSS events were observed. Pts <=40yr at diagnosis had a greater risk of reporting BC event (adjHR for BCFI 1.27, 95% CI 0.93-1.74) vs 51-60yr (reference group), while pts 41-50yr had a lower risk (adjHR 0.74, 95%CI 0.55-0.99). Pts aged <=40yr presented some evidence of lower risk of BCSS events (adjHR 0.80, 95%CI 0.50-1.26) compared to pts aged 51-60yr, while pts aged 41-50yr had the lowest risk (adjHR 0.50, 95%CI 0.32-0.78). There was evidence of interaction between age and tumor subtype, nodal status both for BCFI and BCSS. A significant increase in risk of BC events was observed among pts <=40yr with hormone-receptor positive/HER2 negative tumors (HR 1.70 for BCFI) and among <=40yr with node-negative tumors (HR for BCFI 2.43).

Conclusions: The prognostic role of young age at diagnosis may vary according to tumor subtypes and nodal status, showing poorer outcomes for young pts with hormone-receptor positive/HER2 negative and node-negative tumors.

E11

EXPLORING THE INTERPLAY BETWEEN CIRCULATING TUMOR CELLS (CTCS) AND BRAIN METASTASES (BMS) IN METASTATIC BREAST CANCER (MBC): A RETROSPECTIVE POOLED ANALYSIS

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Background: The validated cutoff of 5 CTCs/7.5 mL allows for prognostic stratification in mBC, between indolent ($StIV_{ind}$; < 5) and aggressive ($StIV_{agg}$; ≥ 5) disease. BMs

occurrence is usually a late event, which negatively affects survival. Our study aims to investigate possible relationships between CTCs and BMs in mBC patients (pts).

Methods: We carried out a retrospective analysis by pooling the EPAC and MDACC datasets comprising mBC pts, characterized for CTCs at baseline (BL), before initiating a new treatment line. CTCs were dichotomized according to the 5 CTCs/7.5 mL threshold. Logistic regression tested the association with relevant prognostic factors, including the presence (BM_{yes}) or absence (BM_{no}) of BMs at BL, and survival was analyzed using Cox regression.

Results: 2387 pts with available BMs data at BL were stratified in: 1175 (49.2%) $StIV_{ind}/BM_{no}$, 129 (5.4%) $StIV_{ind}/BM_{yes}$, 981 (41.1%) $StIV_{agg}/BM_{no}$ and 102 (4.3%) $StIV_{agg}/BM_{yes}$. Luminal-like (Lum), HER2-positive ($HER2^+$) and triple negative (TNBC) subtypes were 60.9%, 24.0% and 15.1%, respectively; 50.2% of pts received first-line therapy. After stepwise logistic regression, no significant associations were observed in the overall population (OP) and in the TNBC cohort. Instead, $StIV_{agg}$ led to an increased risk of BMs in the Lum (OR 1.88, p = 0.016) and, interestingly, a decreased risk of BMs in the $HER2^+$ subgroups (OR 0.44, p = 0.001). Across all subtypes, pts with $StIV_{agg}/BM_{yes}$ disease had worse survival (PFS and OS) compared with $StIV_{ind}/BM_{no}$; only numerical differences were described in pts with either $StIV_{agg}$ or BM_{yes}.

HR (95% CI) p-value	**$StIV_{ind}/BM_{yes}$**	**$StIV_{agg}/BM_{no}$**	**$StIV_{agg}/BM_{yes}$**
OP			
PFS	1.63 (1.33-1.99) **< 0.001**	1.79 (1.61-1.98) **< 0.001**	2.59 (2.05-3.28) **< 0.001**
OS	2.51 (1.99-3.17) **< 0.001**	2.59 (2.27-2.94) **< 0.001**	4.63 (3.60-5.94) **< 0.001**
Lum			
PFS	1.94 (1.24-3.04) **0.004**	1.71 (1.50-1.94) **< 0.001**	2.30 (1.66-3.19) **< 0.001**
OS	2.93 (1.79-4.81) **< 0.001**	2.44 (2.06-2.89) **< 0.001**	3.78 (2.65-5.37) **< 0.001**
$HER2^+$			
PFS	2.08 (1.57-2.74) **< 0.001**	1.91 (1.51-2.42) **< 0.001**	3.00 (1.87-4.79) **< 0.001**
OS	3.06 (2.19-4.28) **< 0.001**	2.64 (1.98-3.52) **< 0.001**	6.00 (3.70-9.73) **< 0.001**
TNBC			
PFS	1.75 (0.92-3.34) 0.088	1.93 (1.50-2.49) **< 0.001**	2.71 (1.58-4.65) **< 0.001**
OS	2.33 (1.21-4.50) **0.012**	3.02 (2.25-4.06) **< 0.001**	4.93 (2.76-8.79) **< 0.001**

Conclusions: Our results point towards subtype-specific relationships between CTCs count and BMs. Furthermore, survival is significantly worsened when BMs and $StIV_{agg}$ coexist. Future studies will clear upon these relationships, as well as monitor their dynamics.

E12

PROGNOSTIC OUTCOME OF METASTATIC LOBULAR BREAST CANCER (MLBC): ANALYSIS ACCORDING TO HISTOLOGY FROM THE MULTICENTER GIM14/BIOMETA STUDY

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Background: In clinical practice, mLBC is treated like ductal carcinoma (DC), despite clinico-pathological differences. Moreover, evidence regarding mLBC prognosis is limited. This analysis aims to investigate treatment and survival outcome of patients (pts) with mLBC, comparing them with mDBC.

Methods: A retrospective analysis of metastatic luminal/HER2-negative pts, enrolled in the GIM14/BIOMETA study from 2000 to 2022, was conducted. Clinico-pathological/survival data of pts affected by mLBC were compared with mDBC. Outcomes were progression-free survival (PFS) and overall survival (OS). Kaplan-Meier curves were compared with the Log-Rank test. Hazard Ratios (HR) estimation by the multivariate proportional Cox regression model and propensity score matching analysis was performed.

Results: Data from 1673 pts were retrieved: 336/1337 with lobular/ductal histology. mLBC/mDBC: median age 63.6/60.6 years (p<0.001); Ki67<20% 55.3%/32.2% (p<0.001); liver metastases at diagnosis 14.6%/21.8% (p=0.003); lung metastases 8.9/21.6% (p<0.001); peritoneum metastases 8%/1.2% (p<0.001). The mLBC 1st line therapy was: chemotherapy (CT) 44.6%, endocrine therapy (ET) 30.4% and ET plus CDK4/6i 25.0%; no differences between histologies. The type of 1st line therapy changed over time. At a median follow up of 34.2 months, in the lobular cohort median PFS/OS was 20.1/51.3 months. No significant difference was observed between histologies, as confirmed by the propensity score analysis (PFS/OS in mLBC vs mDBC: HR 1.077 95%CI 0.894-1.298; p=0.44/HR 1.199, 95%CI 0.959-1.499; p=0.11). The Table shows multivariate analysis in mLBC for PFS and OS.

Characteristics	Subcategories	PFS HR (95% CI) [p] (N=238)	OS HR (95% CI) [p] (N=250)
Age		1.007 (0.989-1.025) [0.43]	1.029 (1.007-1.052) [0.010]
DFI		0.994 (0.990-0.998) [0.005]	0.990 (0.985-0.994) [<0.001]
IV stage at diagnosis	Yes	0.459 (0.209-1.010) [0.05]	0.814 (0.393-1.688) [0.58]
1st line therapy	ET	0.548 (0.366-0.819) [0.01]	0.589 (0.384-0.904) [0.015]
	ET + CDK4/6i	0.380 (0.239-0.605) [0.003] Ref	0.637 (0.342-1.187) [0.16] Ref
	CT		

In mLBC, median PFS and OS according to 1st line therapy (CT/ET/ET plus CDK4/6i) was 14.1/19.1/28.1 (p=0.0013) and 43.2/53.2/43.2 months (p=0.12). The 1st line therapy was an independent factor also in the ductal cohort (median PFS/OS: 14.1/18.1/29.2 (p<0.0001)/45.3/51.3/NR months (p<0.0001).

Conclusions: The study suggests no major prognostic differences between mLBC and mDBC pts undergoing standard therapy. The type of 1st line therapy significantly impacts the PFS in both cohorts.

E13

COULD HER2 MAINTENANCE TREATMENT BE DISCONTINUED IN HER2+ METASTATIC BREAST CANCER (MBC) PATIENTS (PTS) WHO ACHIEVED A PROLONGED DISEASE CONTROL? A RETROSPECTIVE MONOCENTRIC EXPERIENCE

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Background: The combination of trastuzumab (T), pertuzumab (P) and chemotherapy (CT) is the first-line standard therapy for HER2+ mBC pts. Although the dual HER2 blockade is given as a maintenance therapy until disease progression, some retrospective works suggest that its interruption could be considered in selected pts with a prolonged disease control.

Patients and Methods: In this retrospective, observational, monocentric study we reviewed a consecutive series of HER2+ mBC pts treated with the association of T, P and CT as first-line therapy from the 1st of January 2014 to the 31st of December 2022 at the Udine Academic Hospital, Italy. Clinicopathological features and survival outcomes of the entire population and of pts who discontinued the maintenance therapy in absence of disease progression were recorded.

Results: 75 pts with mBC treated with a combination of T, P and CT were included. Median follow up time was 5.6 years (yrs). 49.3% of pts were still alive at the end of the follow up. Median age at diagnosis of mBC was 58 yrs (range 28-85) and 47.3% of pts presented with a de novo mBC. 81% of pts had an HER2 immunohistochemistry (IHC) score 3+. Median duration of first-line therapy was 23.5 months, while median overall survival (mOS) and median progression free survival (mPFS) were 4.3 and 1.47 yrs, respectively. 11 pts (14%) discontinued HER2

maintenance therapy without progressive disease: 8 by virtue of a prolonged disease control, 1 for cardiac toxicity and 2 for adverse events not related to the oncological treatment. Within this small cohort, HER2 IHC score was 3+ in 91% of pts and ER>10% was found in 63% of cases. Most of pts had a de novo metastatic disease (72.7%) with a limited metastatic involvement (one metastatic site in 63.5% of cases). Only 1 patient had brain metastases, while liver secondary lesions were present in 63.4% of cases. Median treatment duration was 53.7 months. With a median follow up of 8.2 yrs, a progressive disease was observed in only 1 patient, so that mPFS and mOS were not reached.

Conclusions: Suspension of dual HER2 blockade maintenance therapy could be considered in a very selected cohort of HER2+ mBC pts with favorable prognostic features (limited metastatic burden and long-lasting disease control with first line therapy). This would probably reduce cardiac toxicity and would limit drug-related costs and hospital admissions. Further research is needed with inclusion of a larger cohort of pts.

E14

ONE-YEAR CHANGE OF E2/SHBG AND IGF-I/IGFBP-3 AS PREDICTORS OF EFFICACY OF LOW-DOSE TAMOXIFEN IN NON-INVASIVE BREAST CANCER IN A PHASE-III TRIAL

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Background: Low-dose tamoxifen (babytam, 5mg/day for 3 years) is recommended by NCCN for the treatment of DCIS. Here we investigated the effect of the 1-year changes in E2/SHBG and IGF-I/IGFBP-3 as surrogate biomarkers of babytam efficacy.

Material (patients) and Methods: In a randomized phase-III trial of babytam or placebo, 406 out of 500 participants consented to blood sampling at baseline, 1 and 3 years. Serum E2, SHBG, IGF-I, IGFBP-3, and their ratios were measured by CLIA. Biomarker changes at 1-year on the continuous scale of E2/SHBG and IGF-I/IGFBP-3 were analysed by Subpopulation Treatment Effect Pattern Plot (STEPP - Bonetti et al, Biostatistics, 465, 2004) to explore and display the cumulative incidence rates and hazard ratios of primary endpoint (invasive breast cancer or DCIS) after 10 years.

Results: Compared to placebo, IGF-I/IGFBP-3 decreased by 22% (15-29%), whereas E2/SHBG decreased by 9% (-84-66%) in postmenopausal women (n=247) after 1 year of babytam. The STEPP technique, including cumulative incidences and hazard ratios, is summarized in table 1. We generated 6 subpopulations for IGF-I/IGFBP-3 and 8 for E2/SHBG according to the sliding window approach. The cumulative incidence was lower in the babytam arm starting from the median subpopulation value of -0.08 upward of E2/SHBG, whereas no trend was noted for IGF-I/IGFBP-3.

Conclusions: Our findings suggest that babytam efficacy is greater when the E2/SHBG ratio increases, whereas no association was noted for IGF-I/IGFBP-3.

Table 1. Cumulative incidence estimates generated by STEPP stratified by treatment arm on 1 year change of E2/SHBG and IGF-I/IGFBP-3 ratio at 10 years of follow-up.

10y follow-up	BabyTam	Placebo		
	Cumulative Incidence (%)	Cumulative Incidence (%)	Cumulative Incidence difference	HR
IGF-I/IGFBP-3†				
Subpop 1 (-0.06)	6.4	12.8	-6.4	0.36
Subpop 2 (-0.04)	10.7	24.6	-13.9	0.36
Subpop 3 (-0.02)	22.7	28.4	-5.7	0.81
Subpop 4 (-0.01)	20.4	23.1	-2.7	0.90
Subpop 5 (0.01)	12.6	17.1	-4.5	0.72
Subpop 6 (0.03)	4.8	15.7	-10.9	0.44
Overall	12.2	19.6	-7.4	0.58

(Continued)

Table 1. (Continued)

10y follow-up	BabyTam	Placebo		
	Cumulative Incidence (%)	Cumulative Incidence (%)	Cumulative Incidence difference	HR
E2/SHBG††				
Subpop 1 (-0.42)	13.2	12.5	0.7	0.96
Subpop 2 (-0.25)	13.6	13.8	-0.2	0.79
Subpop 3 (-0.17)	16.5	13.5	3.0	1.05
Subpop 4 (-0.08)	9.3	16.0	-6.7	0.45
Subpop 5 (-0.04)	7.7	16.0	-8.3	0.37
Subpop 6 (0.01)	3.7	17.4	-13.7	0.32
Subpop 7 (0.09)	0	21.3	-21.3	0.25
Subpop 8 (0.21)	0	21.3	-21.3	0.26
Overall	10.1	18.1	-8.0	0.49

†: all women, (nmol/L)/(nmol/L); ††: postmenopausal women, (pmol/L)/(nmol/L)

E15

OVER HALF OF BREAST CANCER BIOPSIES LABELED AS HER2-0 ARE QUESTIONED IN THE FINAL SURGICAL SPECIMEN

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Background: The reliability of core needle biopsy (CNB) in assigning HER2-positive status has been extensively documented, while there's limited data on HER2-low negative cases. This study aimed to compare CNB with surgical samples and to identify factors contributing to the discrepancies found.

Methods: Consecutive early-stage breast cancer patients who underwent surgery between 2011 and 2021 and had paired CNB and surgical samples were retrospectively reviewed. Concordance in HER2 IHC evaluation between CNB and surgical samples was analyzed using the Cohen kappa statistics (Kc) and corresponding 95% Confidence Interval (95%CI). The determinants of discordance in HER2-negative cases, including HER2-0 or HER2 low on immunohistochemistry (IHC) 1+ or 2+ in absence of ERBB2 gene amplification, was assessed by logistic regression models in terms of odds ratio (OR) and 95%CI, with OR of 1 denoting no association under the null hypothesis, and 95%CIs excluding 1 indicating significant associations.

Results: A total of 776 patients with paired CNB and surgical samples were identified, of whom 78 (10%) initially diagnosed with HER2-positive breast cancer and 698 with HER2-negative, specifically 567 (73%) HER2-low and 131 (17%) HER2-0. The concordance between CNB and surgical samples for HER2-positive cases was 96.3% (Kc 0.76, 95% CI 0.69-0.84), which is in line with literature and showed consistency across the years of observation. By contrast the concordance was as low as 75.7% (Kc 0.26, 95% CI 0.17-0.34) in HER2-negative cases. Specifically, 72 (55%) initially classified HER2-0 became HER2-low in surgical samples; and 95 (17%) initially diagnosed HER2-low were finally scored as HER2-0. There was no difference in patient characteristics, primary tumor hormone receptor status, grade and proliferation whether CNB/surgical samples were concordant or discordant. Instead, tumor size larger than 2 cm (OR: 1.70, 95%CI:1.18;2.44) emerged as significant factor influencing discordance in HER2-negative cases.

Conclusions: These findings highlight a potential CNB misdiagnosing of HER2-low cases as HER2-0, especially in large tumors. This is important, as CNB may be the only source of HER2 status information in patients with recurrent breast cancer or undergoing primary systemic therapy with novel HER2-low targeting drugs. In both scenarios, it's crucial to carefully assess and reassess CNB results while awaiting further research developments.

E16

EVALUATING THE CLINICAL RELEVANCE OF MONARCHE AND NATALEE STUDIES BY THE APPLICATION OF THE ELIGIBILITY CRITERIA TO A REAL-WORLD (RW) EARLY BREAST CANCER (EBC) POPULATION

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Background: The randomized clinical trial (RCT) NATALEE broadened the use of adjuvant Cyclin Dependent Kinase 4/6 inhibitor (CDK4/6i) beyond what was established by the MonarchE trial in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2 negative (Her2-) eBC at high and intermediate risk of recurrence. Here, we evaluate the potential clinical relevance and differences in patient characteristics eligible for adjuvant ribociclib or abemaciclib when applying the inclusion criteria of the NATALEE and MonarchE RCTs in a real-world (RW) setting, including the use of Recurrence Score (RS) for patient selection.

Material and Methods: Between January 2021 and December 2022, a retrospective cohort of 762 consecutive HR+/HER2- eBC patients who underwent surgical treatment at Humanitas Research Hospital in Milan (Italy) was examined. The RW patients were assessed for eligibility criteria as established in the MonarchE and NATALEE RCTs. Descriptive statistics and chi-square (χ^2) tests were employed to evaluate any potential disparities in characteristics between the RW vs RCTs population.

Results: Out of 762 patients in the study population, 167 (21.8%) and 318 (41.7%) met the eligibility criteria for the MonarchE and NATALEE trials, respectively. Compared to both MonarchE and NATALEE trials, the RW patients were older (median age 53 *vs* 51 and 54 *vs* 52, respectively) and with less advanced tumor stage. Namely, the eBC staging of RW *vs* MonarchE included stage IIa: 31.1% *vs* 11.5%; stage IIb: 33.5% *vs* 14% and stage III: 35% *vs* 74.1% ($p < 0.001$); likewise, the RW *vs* NATALEE presented with stage IIa: 49% *vs* 19%; stage IIb: 31% *vs* 21% and stage III: 20% vs 60%, ($p < 0.001$). Furthermore, a lower proportion of RW patients received adjuvant chemotherapy compared to those in the NATALEE trial (35.5% *vs* 48%). Notably, none of the RW patients in stage IIA-N0 were deemed eligible for adjuvant ribociclib based solely on high genomic risk ($RS \geq 26$).

Conclusions: This retrospective analysis of a consecutive cohort of RW patients with HR+/HER2- eBC demonstrates that their clinical characteristics significantly differ from those in the NATALEE and MonarchE RCTs, with a higher proportion of patients presenting with earlier-stage tumors. Additionally, the number of patients eligible for adjuvant CDK4/6i is twice as large when using the NATALEE inclusion criteria *vs* MonarchE, with the use of RS not resulting in a greater patient eligibility.

E17

SUBOPTIMAL OVARIAN SUPPRESSION DURING ADJUVANT ENDOCRINE THERAPY FOR PREMENOPAUSAL WOMEN WITH BREAST CANCER: AN EXPLORATORY ANALYSIS OF THE PREFER AND GIM 23 STUDIES

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Background: Adjuvant endocrine therapy (ET) with exemestane combined with LHRH analog (LHRHa) is the standard of care for premenopausal women. However, LHRHa may not always achieve complete ovarian suppression in these patients.

Methods: The PREFER-Fertility (NCT02895165) and GIM 23-POSTER (NCT05730647) are prospective, observational studies that enrolled premenopausal women eligible to receive (neo)adjuvant chemotherapy and/or ET. We conducted an exploratory analysis of patients achieving suboptimal suppression of ovarian function, defined as estradiol levels greater than 25.1 ng/L or resumption of menstruation at least 3 months after the start of exemestane plus LHRHa.

Results: As of February 2024, a total of 1616 patients were enrolled (766 in the PREFER and 850 in the GIM 23), of whom 528 were included in our center. Among them, 26 patients (4.9%) did not achieve optimal ovarian suppression. The median age of these patients was 39.5 (IQR 35.5.-46.25). The median body mass index (BMI) was 21.8 kg/m^2(84.6% BMI<25). Tain histopathological characteristics are summarised in the Table. 65.4% of these patients received chemotherapy, mainly anthracycline plus taxane (93.8%), and 3 patients received adjuvant abemaciclib. The median time from the last chemotherapy was 7 months, with 17 patients already on LHRHa during chemotherapy. Monthly leuprorelin was given in 65% of the cases, while the others received monthly triptorelin. The median time to suboptimal ovarian suppression was 7 months (range: 3-47). At a median follow-up of 5 years (range: 1-8), 3 patients (11.5%) had a relapse of disease.

Conclusions: in our cohort, almost 5% of premenopausal patients did not achieve ovarian suppression with LHRHa. Oncologists should be aware that serial monitoring of estradiol levels should be performed to address this eventually.

Table.

Characteristics	N of patients (%)
TNM – Stage	
IA	14 (53.9)
IB	3 (11.5)
IIA	5 (19.2)
IIB	2 (7.7)
IIIA	2 (7.7)
Grading	
1	1 (3.8)
2	18 (69.3)
3	5 (19.2)
NA	2 (7.7)
Histology	
Ductal	21 (80.8)
Lobular	1 (3.8)
Other	4 (15.4)
Ki67	
<20	12 (46.2)
≥20	14 (53.8)
HER2 status	
0	12 (46.1)
1+	5 (19.2)
2+	2 (7.7)
2+ FISH amplified or 3+	7 (27)

E18

IMPACT OF AUTOIMMUNE DISEASES (AD) ON PROGRESSION-FREE SURVIVAL (PFS) IN HORMONE RECEPTOR POSITIVE (HR+)/ HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 NEGATIVE (HER2-) BREAST CANCER (BC) PATIENTS UNDERGOING CDK4/6 INHIBITOR (CDK4/6I) COMBINED WITH ENDOCRINE THERAPY

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Background: CDK4/6i enhance antitumor immunity but may trigger autoimmune reactions by disrupting immune tolerance and activating autoreactive T and B cells. This study aims to elucidate the prevalence and nature of AD in early and metastatic HR+/HER2- BC patients, identify potential predictive biomarkers and assess the impact of these conditions on disease progression.

Methods: In this monocentric, retrospective cohort study, we included consecutive HR+/HER2- BC patients treated with CDK4/6i in early and advanced settings at Humanitas Research Hospital from Aprile 2017 to April 2024. Baseline patient characteristics, tumor clinicopathological features, treatment data, occurrence of AD and blood tests at various time points were extracted from electronic medical records. Descriptive statistics were used to determine the prevalence of AD, while Kaplan-Meier analysis assessed PFS differences between patients with and without AD, as well as those with stable or worsened/new-onset AD.

Results: We identified 352 patients (98.9% women and 1.1% men), with a median age of 54 years (range 45-63). Most had metastatic disease (87.2%) and received palbociclib (51.8%), ribociclib (27.4%) or abemaciclib (20.8%), while 12.8% had an early disease and received abemaciclib. AD were present in 49 patients (13.9%), with 42 having pre-existing conditions and 7 developing new-onset AD. Among those with pre-existing AD, 38 had stable conditions and 4 experienced worsening during treatment. The most common AD was Hashimoto's thyroiditis (53.1%), followed by vitiligo (16.3%) and rheumatoid arthritis (8.2%). Regarding patients with metastatic disease, the median PFS was significantly longer in patients with AD compared to those without (27.9 vs. 20.1 months, p=0.0013). The course of AD seemed to influence PFS, with patients with worsened or new-onset AD showing a better PFS (p=0.0015). No significant predictive biomarkers were found in baseline characteristics, tumor features, or blood biomarkers between patients with and without AD.

Conclusions: Our findings suggest that treatment with CDK4/6i is feasible in patients with pre-existing AD. The onset or worsening of AD during treatment for metastatic BC is associated with improved PFS, indicating a potential immune activation against tumors induced by CDK4/6i. Future studies should focus on understanding the underlying mechanisms driving these observations and identifying predictive biomarkers.

E19

REAL-WORLD OUTCOMES OF EARLY-STAGE HER-2-POSITIVE BREAST CANCER PATIENTS TREATED WITH APT

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Background: The combination of 12 cycles of weekly paclitaxel and trastuzumab (APT) represents the standard treatment for most stage I HER2+ breast cancer (BC) patients based on results of the single arm phase II APT trial. Confirmation of long-term outcomes of this regimen in independent cohorts with similar clinical characteristics is of interest.

Methods: This monocentric retrospective study included patients diagnosed with early HER2+ BC (pT≤ 3 cm; pN0/N1mic) at our institution, which started APT regimen from 01/2014 to 10/2023. Patients with bilateral BC diagnosis, concomitant diagnosis of HER2- BC, previous diagnosis of BC or previously treated with chemotherapy due to other oncological diagnosis were excluded. Patient characteristics and follow-up were retrospectively collected from medical records. Recurrence free survival (RFS), distant relapse free survival (DRFS), and invasive breast cancer free survival (IBCFS) from BC diagnosis were calculated by STEEP definition (Tolaney et al.,2021).

Results: This study included 276 patients. Median age at BC diagnosis was 56 years (range 26-83). Most patients presented hormone receptor (HR) positive (75%, N=207), grade 3 tumors (65.6 %, N= 181), and were post-menopausal (65.6%, N=181). Most patients presented pT≤ 2 cm tumors (92.4%, N=255) and had no nodal involvement (93.1%, N=257), with only 19 patients (6.9 %) presenting N1mic. Therefore, anatomical stage distribution was IA 86.2% (N=238), IB 6.2% (N=17), IIA 7.6% (N=21). At a median follow-up of 3.9 years (IQR 3.5-4.2 years), the 3-year RFS was 97.1% (95% CI, 94.7-99.4), the 3-year DRFS was 97.5% (95% CI, 95.3- 99.6), the 3-year IBCFS rate was 97.1% (95% CI, 94.7-99.5). No significant difference in RFS outcomes was observed according to HR status (positive vs. negative), grade, HER2 status (IHC 3+ vs 2+/amplified), and menopausal state. A statically significant difference in RFS was observed according to anatomical stage (log-rank p < 0.001), with a 3-year RFS rate of 98.8% (95% CI, 97.1- 100) for stage IA tumors, 84.8% (95% CI, 65.2- 100) for IB tumors and 88.2 % (95% CI, 73- 100) for IIA tumors.

Conclusions: This real-world study confirms that the use of APT regimen is associated with good survival outcomes in stage IA HER2+ BC patients. Although limited by small sample size, our results warrant caution when applying this regimen to stage IB/ IIA (pT≤3 cm) tumors.

E20

IMPACT OF RECURRENCE SCORE (RS) ON TREATMENT CHOICES IN PREMENOPAUSAL PATIENTS (PTS) WITH EARLY BREAST CANCER (EBC)

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Background: Oncotype DX informs adjuvant treatment decisions for pts with hormone receptor-positive/HER2-negative (HR+/HER2-) eBC. However, its relevance and interpretation in premenopausal women, especially those with pN1 disease, is debated. Here, we report the impact of Oncotype DX results (RS) on the adjuvant treatment decision-making process for premenopausal pts with HR+/HER2- eBC treated at San Raffaele Hospital.

Material and Methods: We identified all pts with HR+/HER2- eBC who underwent Oncotype DX according to multidisciplinary discussion between January 2017 and April 2024. The group of interest comprised premenopausal pts under 50 years old. Clinicopathological features, including age, tumor size, nodal status, grading, Ki-67, ER and PgR status, were retrieved. Pts were categorized by nodal status (pN0 vs pN1) and RS categories as proposed for premenopausal women in TAILORx trial: RS<16 (no chemotherapy (CT) benefit), RS 16-25 (uncertain/likely CT benefit), and RS>25 (CT benefit). Post-test administered treatment, either endocrine therapy (ET) or chemo-endocrine therapy (CT/ET), was recorded.

Results: Among 321 pts tested with Oncotype DX, 96 (30%) were premenopausal, including 57% and 43% pN0 and pN1, respectively. Median age was 42 years (range 27-49); pT1, pT2 and pT3 tumors were 67%, 30% and 3%, respectively. Grade 2/3 tumors were 93%, median Ki-67 was 22% (range 5%-60%). All tumors had an ER expression ≥70%, while 4% had a PgR<10%. RS<16 was found in 38% of the pN0 group and 51% of the pN1 group. Among these, all pts received ET, except for two pN1 pts (9%) treated with CT/ET. RS 16-25 was found in 47% and 41% of the pN0 and pN1 group, respectively. In this subgroup, 31% of the pN0 group and 47% of the pN1 group received CT (p=0.3). In the RS 16-25 pN0 group, the only factor associated with CT administration was RS (all pts with RS 16-20 received ET; only 33% of pts with RS 21-25 received ET alone). In the RS 16-25 pN1 group, CT/ET indication was not strongly associated with any factor. RS>25 was observed in 28%, 15% and 7% in postmenopausal, premenopausal pN0 and pN1 patients, respectively (p=0.015).

Conclusions: In our real-world series, Oncotype DX contributed to identify a substantial proportion of premenopausal pts who could be spared by adjuvant CT regardless of nodal status. The low proportion of RS>25 in premenopausal pN1 pts indicates a selection bias toward testing less biologically aggressive tumors.

E21

EVALUATING THE INCIDENCE OF EMESIS INDUCED BY ANTIBODY-DRUG CONJUGATES (ADCS) IN METASTATIC BREAST CANCER (MBC): A COMPARISON OF MULTIPLE TREATMENTS BEYOND THE FIRST LINE THROUGH META-ANALYSIS

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Background: ADCs therapy in MBC is associated with various adverse events, with nausea and vomiting being particularly significant. This meta-analysis (MA) aimed to evaluate the incidence of ADC-induced emesis in patients with MBC undergoing treatments beyond the first line (1L).

Material and Methods: We performed a systemic search of literature of phase II-III randomized controlled trials (RCTs) published before April 2024. MA of logit-transformed values of single proportions were performed using random-effects generalized linear mixed models to determine the pooled proportion of nausea and vomiting. Heterogeneity across studies was evaluated with the I^2 statistic. Subgroup analyses based on molecular subtype and treatment type were conducted.

Results: A total of 38 studies were selected, comprising 12 involving HER2-positive (HER2+) and 26 including HER2-negative (HER2-) patients with MBC treated beyond the first line (1L). Investigations into ADC-based regimens, considering Trastuzumab-emtansine (T-DM1), Trastuzumab-deruxtecan (T-DXd), Trastuzumab-duocarmazine (T-Duo), Sacituzumab govitecan (SG) and Datopotamab-deruxtecan (Dato-DXd), were conducted across 11 trials. The 38 trials reported the incidence of nausea and vomiting within the study population, revealing an overall rate of nausea at 26.2% [95% CI: 20.9-32.4] and of vomiting at 15.1% [95% CI: 12.5-18.0]. Nausea was significantly less frequent in HER2- MBC patients [15.1%, 95% CI: 10.2-21.9] and had a higher rate in those treated with PARP inhibitors (PARPi) [54.8%, 95% CI: 51.0-58.6], ADCs [50.8%, 95% CI: 37.9-63.5], and tyrosine kinase inhibitors (TKIs, lapatinib/neratinib + capecitabine) [46.6%, 95% CI: 42.6-50.6] compared to those receiving endocrine therapy (ET) and chemotherapy (CT). Vomiting was most recurrent in HER2+ and gBRCA1/2-mutated HER2- MBC patients [22.7%, 95% CI: 18.3-27.7 and 25.6%, 95% CI: 20.8-31.2, respectively] and in those treated with TKIs [33.3%, 95% CI: 26.8-40.5%], PARPi [29.9%, 26.1-34.0] and ADCs [23.5%, 95% CI: 17.3-31.1].

Conclusions: Among the treatment options available, ADCs, TKIs and PARPi show a significantly higher incidence of nausea and vomiting, compared to ET, targeted therapy, and even CT, in patients with MBC treated beyond the first line.

E22

WEAK IMMUNE-PROFICIENCY IN TRIPLE-NEGATIVE BREAST CANCER WITH HER2-LOW: INSIGHTS FROM GENE EXPRESSION ANALYSIS

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Background: There is limited data on the impact of HER2-low on the immune microenvironment, possibly due to the current dichotomous classification of breast cancer into HER2-positive and HER2-negative. In this study, we investigated immune variance in newly diagnosed tumors categorizing HER2 by discrete immunohistochemistry categories and continuous gene expression values.

Materials and Methods: Clinico-pathological and gene-expression data of newly diagnosed early-stage breast cancer patients were obtained from our own experimental serie (n=304) for discovery purposes, and from publicly available TCGA (n=783) and SCAN-B (n=403) datasets for validation. HER2 was defined as 0 or low according to the immunohistochemistry categories 0 or 1+/2+ without gene amplification, as well as using our previously published 20 gene-expression-based classifier. Associations between tumor-infiltrating immune cells (TIICs) defined by CIBERSORTx deconvolution were examined using the Spearman correlation coefficient (r) and reported with the corresponding 95% confidence interval (CI). Uni- and bivariate analyses were conducted to identify determinants of specific TIICs. Multiple testing corrections were performed using the Bonferroni method.

Results: HER2-low tumors are significantly depleted of M1-macrophages and CD8+ T cells, as indicated by a

negative and moderate to strong (r values ranging between -0.3 and -0.6) correlation in both experimental and confirmatory settings. This observation holds true in both hormone receptor-positive and negative tumors, without any significant interaction. According to the literature, univariate analysis showed that most of the TIICs tested were significantly enriched in triple-negative breast cancer, except for resting mast cells and resting dendritic cells. Remarkably, bivariate analysis using continuous genomic expression values of HER2-low leveled the observed differences, with only resting mast cells showing association with hormone receptor-positive status.

Conclusions: HER2-low tumors have a less active immune microenvironment characterized by an inverse macrophage polarization and a depletion of immune effectors regardless hormone receptor status. Our findings support further research especially in triple-negative breast cancer as low HER2 expression diminishes their distinct immunological profile potentially influencing response to therapy.

E23

INHIBITION OF SYSTEMIC AND INTRATUMOR GLUCOSE METABOLISM IS ASSOCIATED WITH RESPONSE TO FASTING-MIMICKING DIET PLUS CHEMOTHERAPY IN PATIENTS WITH EARLY-STAGE TNBC

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Background: The BREAKFAST study is a phase II randomized trial that investigated if severe calorie restriction, in the form of 5-day fasting-mimicking diet (FMD), plus/minus metformin, in able to increase pathological complete response (pCR) rates in patients (pts) with localized triple-negative breast cancer (TNBC) treated with neoadjuvant chemotherapy (NACT). Among prespecified, exploratory objectives we analyzed the treatment-induced modulation of systemic and intratumor metabolism, as well its association with pCR probability.

Patients and Methods: 30 pts with stage I-III TNBC were randomized to receive anthracycline plus taxane based CT (triweekly AC followed by weekly paclitaxel) in combination with triweekly 5-day FMD cycles (arm A), or CT + FMD + daily metformin (1700 mg) (arm B). Tumor samples were collected from core biopsies performed at baseline and after one treatment cycle to study precocious changes of intratumor metabolic transcriptomic profiles through bulk and single cell (sc) RNA sequencing. Metabolomics in blood samples collected before and after FMD cycles, and body composition parameters estimated through CT scans performed at baseline and before surgery were used to study changes in systemic metabolism.

Results: The experimental treatment resulted in a precocious reduction of blood glucose, insulin and LDH concentration. Of note, LDH reduction predicted pCR, also after adjusting for T and N stage, Ki-67 and treatment arm (p=0.04). At the completion of neoadjuvant treatment, we observed a reduction of total, subcutaneous and visceral adipose tissue, which was more pronounced in patients with higher baseline BMI. Transcriptomic analysis of tumor samples showed a precocious downmodulation of glycolysis and TCA cycle metabolism, which was only observed in patients undergoing pCR and with higher baseline total and visceral adiposity. scRNAseq analysis revealed that these changes specifically occurred in highly glycolytic cells of the tumor microenvironment, i.e., cancer cells, myeloid cells and pericytes.

Conclusions: The precocious downmodulation of systemic and intratumor glucose metabolism is associated with the rate of pCR in TNBC treated with NACT plus FMD. Glucose metabolism inhibition represents a potentially novel metabolic biomarker predictive of response to FMD-based combinations.

Funding

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E24

PREVALENCE OF TREATMENT-RELATED ADVERSE EVENTS (TRAES) WITH ANTIBODY-DRUG CONJUGATES IN METASTATIC BREAST CANCER PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS BASED ON STUDIES' DESIGN

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Background: The development of antibody-drug conjugates (ADCs) has revolutionised the cancer treatment landscape for metastatic breast cancer (BC), thus improving survival outcomes. Compared to chemotherapy, ADCs

showed a better overall safety profile; nevertheless, treatment-related adverse events (TRAE) have been widely reported in clinical trials worldwide. Quantifying the incidence of TRAEs is fundamental to overcome symptom burden outcomes. In this context, we performed a proportional meta-analysis to estimate the pooled prevalence of the TRAEs related to currently FDA-approved ADCs in metastatic BC patients.

Materials and Methods: We interrogated the PubMed, Embase, Scopus, CINAHL, and Cochrane databases for papers published from 2013 to 2023. Metaprop command estimates 95% confidence intervals employing the exact binomial and score test-based confidence intervals with the Freeman-Tukey double arcsine transformation of proportions for the single-outcome assessment. The pooled effect size of each TRAE was then quantitatively aggregated to evaluate the proportion of the most common TRAEs. PROSPERO registration number: CRD42023462629.

Results: A total of 21 clinical studies, of which 8 randomised controlled trials (RCTs) and 13 cohort studies, including a total of 3001 and 1945 subjects respectively, were analysed in this review. The meta-analysis of RCTs showed a significant pooled prevalence of the most common side effects of 33% for Trastuzumab deruxtecan (T-DXd) and 12% for Trastuzumab emtansine (TDM-1); whereas cohort studies revealed a significant pooled prevalence of the most common side effects of 26%, 18%, and 29% for the treatment with T-DXd, TDM-1, and sacituzumab govitecan (SG), respectively. Specifically, gastrointestinal, general, and blood system disorders were highly prevalent during T-DXd, TDM-1, and SG therapy, respectively. Overall, nausea registered the highest prevalence during T-DXd therapy: 77% (95% CI: 72%-81%), $p<0.05$.

Conclusions: To the best of our knowledge, this meta-analysis is the first to provide a single summary estimation of specific ADC-related TRAEs in clinical trials by comparing effects across different study designs (RCTs and cohort studies). Overall, gastrointestinal symptoms were highly prevalent in all types of therapy, although each ADC showed specific toxicities. The present review may lead to the foundational groundwork for the development of personalised risk-stratified cancer-care treatments.

E25

EXPLORING THE INCIDENCE OF INTERSTITIAL LUNG DISEASE (ILD) IN METASTATIC BREAST CANCER (MBC): A COMPREHENSIVE META AND NETWORK ANALYSIS OF ANTIBODY-DRUG CONJUGATES (ADCS) COMPARED TO AVAILABLE TREATMENT OPTIONS BEYOND FIRST LINE (1L)

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Background: ADCs have revolutionized the treatment of MBC, independently from the molecular subtype, with ILD emerging as a significant adverse event. Aim of this meta-analysis (MA) was to evaluate the incidence of ADC-induced ILD compared to other available treatment options beyond 1L in patients (pts) with MBC.

Methods: A generalized linear mixed model was used for a random effects meta-analysis of logit transformed single proportions to calculate a pooled proportion of ILD. Subgroup analyses were conducted based on molecular subtype and treatment type. We also conducted a network MA (NMA) ranking treatments according to the surface under the cumulative ranking curve (SUCRA).

Results: Thirty-eight studies were identified, of which12 in HER2-positive (HER2+) and 26 in HER2-negative (HER2-) MBC beyond 1L. ILD incidence was reported in 11 trials including BOLERO-3, DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, TULIP, BOLERO-2, SOLAR-1, TROPION-Breast01, TROPiCS-02 and EMBRACE. The overall ILD rate was 0.96% (95% CI: 0.38-2.4). Among the 6,121 analyzed pts, 214 ILD events were reported. A higher ILD incidence was present in HER2+ MBC (3.42%, 95% CI: 1.33-8.47) compared to HER2- MBC (*p-value* 0.003). Furthermore, a greater ILD rate was observed in pts treated with ADCs such as Trastuzumab-emtansine (T-DM1), Trastuzumab-deruxtecan (T-DXd), Trastuzumab-duocarmazine (T-Duo), Sacituzumab govitecan (SG), and Datopotamab-deruxtecan (Dato-DXd) compared to endocrine therapy (ET), chemotherapy (CT) and target therapy [including TKIs like lapatinib/neratinib/tucatinib and PARP inhibitors (PARPi)] (5.55% incidence in ADCs group vs 0.39% in non-ADC group, 95% CI: 2.45-12.09; *p-value* <0.0001). NMA showed that the worst-ranked ADC was T-DXd (SUCRA 0.2%), while the best-ranked treatment was CT (SUCRA 85%).

Conclusions: A higher incidence of ILD was noted in pts treated with ADcs compared to those receiving ET, TKIs, PARPi, and CT, including regimens containing everolimus. These data may inform treatment and monitoring decision making, especially for pts with respiratory risk factors.

E26

THE ROLE OF ONLINE HOME-BASED PHYSICAL ACTIVITY ON HEALTH-RELATED QUALITY OF LIFE, OXIDATIVE-STRESS PATHWAYS AND PROMOTER-SPECIFIC DNA METHYLATION IN POST-SURGERY BREAST CANCER PATIENTS

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Background: Most anticancer treatments used against breast cancer (BC) leverage the oxidative-stress pathways by producing Reactive Oxygen Species (ROS) to kill cancer cells, which carries alongside effects and toxicities commonly resulting in a decrease of health-related quality of life (QoL). Physical activity (PA) has arisen as an integrative cancer therapy able to provide patients with enhanced fitness and positive health effects, even in redox homeostasis. In this work, we investigated the impact of an online supervised PA on physical fitness and mental well-being by measuring functional parameters, body mass index, body composition, health-related QoL, and fatigue on BC patients undergoing oncological treatments. Moreover, we investigated the effect of PA on promoter-specific DNA methylation, and corresponding gene expression/activity, in 3 antioxidants (SOD1, SOD2, and CAT) and 3 BC-related genes (BRCA1, L3MBTL1 and RASSF1A) in a subsample of these patients.

Methods: Forty BC patients were enrolled after surgery and randomly divided into two groups: exercise group (EX) performed 4 months of training, twice a week, while control group (UC) underwent the usual care.

Results: In the EX group we found improved functional parameters (6 min walking test ≈+3.95%, $p<0.05$; scratch right ≈-20.36%, and left ≈-11.96%, $p<0.01$) and body composition (free fat mass ≈+5.06%, $p<0.01$; fat mass ≈-12.45%, $p<0.01$) as well as the QoL (physical function ≈+3.38%, $p<0.05$) and fatigue (cognitive fatigue ≈-35%, $p<0.05$) scores. Moreover, EX group maintained levels of SOD activity in blood plasma, with a significant increase of SOD2 mRNA expression at the cellular level (≈+77 %). This change was inversely correlated with DNA methylation in SOD2 promoter (≈-20%). Similarly, we found a significant effect of PA only on L3MBTL1 promoter methylation (≈-25%), which was inversely correlated with its mRNA (≈+43%). Finally, PA increased TET1 mRNA levels (≈+15%) and decreased expression of DNMT3B mRNA (≈-28%).

Conclusions: These results suggest that a specific PA program, while improving functional and anthropometric parameters, seems to impact on DNA methylation that affects several signaling pathways/biological activities involved in the cellular oxidative stress response, chromatin organization/regulation, antioxidant activity and DNA/protein binding. These changes may positively impact clinical outcomes and improve the response to adjuvant cancer treatments in BC.

E27

SERIAL CTDNA TO TRACK FRAGMENTOMIC AND EPIGENETIC ALTERATIONS IN FIRST-LINE CYCLIN-DEPENDENT KINASE INHIBITORS (CDK4/6I) TREATMENT FOR HORMONE RECEPTOR (HR) POSITIVE, HER2 NEGATIVE METASTATIC BREAST CANCER (MBC)

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Background: CDK4/6i plus endocrine therapy (ET) represent the standard first-line treatment for luminal MBC, but no randomized comparisons are available between palbociclib (PAL), ribociclib (RIB) and abemaciclib (ABE). Aim of this analysis was to explore the differential clinical impact of CDK4/6i by leveraging new ctDNA biomarkers in a prospective clinical study.

Methods: A total of 114 patients (pts) with luminal-like MBC were prospectively recruited in the MAGNETIC.1 study (CRO-2018-56) from January 2018 to January 2023. At baseline (BL) and every 3 months (mos), ctDNA samples were collected concurrently with radiological restaging and analyzed through methylation-specific (MS) droplet digital PCR (ddPCR), ddPCR fragmentomics, and

next generation sequencing. Matched pairs of variations were tested through the Wilcoxon signed rank test, and survival was analyzed by the log-rank test.

Results: Of the 114 pts enrolled, 59 received PAL, 48 RIB, and 16 ABE. Among pts receiving PAL, 7 had an *ESR1* mutation at BL. Additionally,12 pts had *PIK3CA* mutations, and 2 pts had *AKT1* mutations. In the RIB group, 5 and 2 pts, respectively, had a *PIK3CA*- and *AKT*-mutated MBC, while no *ESR1* mutations were detected. When comparing matched pairs of variations at BL, first radiological restaging (T1), and 6 mos after CDK4/6i start (T2), only PAL showed significantly higher levels of promoter A and B methylation (promA and promB) at T1 (P = 0.0005 and P = 0.0056, respectively for promA and promB). A significant decrease in promA and promB levels was detected at T2 for PAL (P=0.0005 and P<0.0001, respectively, for promA and promB), but not for RIB. Both PAL and RIB demonstrated a significant decrease in ctDNA short fragments at T1 (P=0.0263 for PAL and P=0.0001 for RIB), However, only PAL showed a significant rebound at T2, with an increase in 80% of samples (P=0.0014). At a median follow-up of 34.8 mos, no significant differences between PAL and RIB in terms of PFS (P=0.2573) and OS (P=0.3783) were detected. PFS rates at 12 and 24 mos were 69% and 48% for PAL, and 76% and 64% for RIB. OS rates at 12 and 24 mos were 94% and 84% for PAL, compared to 97% and 82% of RIB, respectively.

Conclusions: This analysis showed that pre-treatment and dynamic assessment of epigenetic changes in luminal MBC are a promising informative biomarker of ET resistance in the CDK4/6i era. Further biomarker-driven clinical trials leveraging this concept are needed to refine the sequencing algorithms for CDK4/6i.

E28

CYCLIN-DEPENDENT KINASE 4 AND 6 INHIBITORS AS FIRST-LINE TREATMENT IN LUMINAL METASTATIC BREAST CANCER: CORRELATION BETWEEN HER2 LOW AND HORMONE RECEPTORS EXPRESSION AND THERAPEUTIC EFFICACY - THE CYCLHER STUDY

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Background: Identifying biomarkers for resistance to Cyclin-Dependent Kinase 4 and 6 Inhibitors (CDK4/6i) in hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR+/HER2) metastatic breast cancer (MBC) remains a critical need. Although HR+ status guides first-line treatment, 65% of HR+ cases are classified as HER2 low (1+ or 2+ with SISH negative). Hence, we aimed to investigate the role of estrogen receptor (ER), progesterone receptor (PgR) levels and HER2 low status in CDK4/6i treatment outcomes.

Material and Methods: We retrospectively analyzed a multicentric Italian cohort of 597 HR+/HER2- MBC patients (pts) treated with CDK4/6i plus endocrine treatment (ET) (aromatase inhibitor or fulvestrant) as first-line therapy (NCT:06243432). Cut-off Finder v1.0 was used to identify optimal values for ER and PgR impacting progression-free survival (PFS) curves in terms of log-rank test. Uni- and multivariable Cox regression analyses assessed associations with clinical characteristics.

Results: The main histology was ductal carcinoma (70.6%); 28.1% of pts had de-novo metastatic disease, and 55.4% had visceral involvement. With a median follow-up of 41 months (mo) (IQR: 30-53), the median PFS (mPFS) was 28.1 mo (95% CI: 24.3-31.8). Optimal cut-offs were 71% for ER (*p=0.013*) and 60% for PgR (*p<0.001*). mPFS was 20.6 *vs*. 29.5 mo (*p=0.003*) and 22.1 *vs*. 41.0 mo (*p<0.001*) for low and high ER and PgR subgroups (i.e., under or over the cut-off), respectively. Five-year-overall survival (OS) rate was 26.2% *vs.* 54.9% (*p=0.042*) and 45.3*% vs.* 59.2% (*p=0.002*) for low and high ER and PgR subgroups, respectively. HER2 low pts had worse outcomes compared to HER2-0 ones (mPFS: 25.9 *vs.* 32.1

mo, *p=0.036*; 5-year-OS: 48.3% vs. 56.7%, *p=0.047*). ER ≥ 71% (HR=0.74; 95% CI: 0.55-1.00, *p=0.049*), PgR ≥ 60% (HR=0.62; 95% CI: 0.50-0.77, *p<0.001*), and HER2 low status (HR=1.32; 95% CI: 1.06-1.65, *p=0.01*) were independent prognostic factors in multivariable analysis for PFS. Additionally, ER (*p=0.02*) and PgR (*p=0.001*) expression significantly affected the disease control rate, with only PgR influencing the duration of response (*p=0.002*). Neither ER, PgR, nor HER2 low status affected second-line outcomes, regardless of ET or chemotherapy-based strategies.

Conclusions: ER and PgR expression significantly impacted first line CDK4/6 treatment outcomes. The prognostic significance of HER2 low status needs further investigation. Additional analyses are planned to characterize early disease progression.

E29

INVESTIGATING THE IMPACT OF FIRST-LINE STRATEGIES ON ORGANOTROPISM EVOLUTION OF LUMINAL-LIKE METASTATIC BREAST CANCER

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Background: Organotropism is a well-established yet poorly understood phenomenon in metastatic breast cancer (mBC). This study aims to describe trends in metastatic sites and how they might be influenced after progression (PD) to a first-line (1L) treatment.

Materials and Methods: This study retrospectively analyzed a multicentric cohort of consecutive Luminal-like mBC patients (pts) treated with 1L systemic therapy between 2008 and 2020. McNemar and Fisher's exact tests were used to explore pairwise differences and associations between newly identified metastatic sites and the proposed 1L treatments.

Results: Overall, 796 mBC pts were included in the analysis: 352 received endocrine therapy (ET), 223 chemotherapy (CT), and 219 ET plus a cyclin-dependent-kinases 4/6 inhibitor (CDK4/6i). The most common metastatic site at baseline was bone (70.1%), followed by lymph nodes (38.8%), lungs (28.6%) and liver (21.44%), while soft tissues and central nervous system (CNS) were less frequently involved (7.9% and 2.4%, respectively). A statistically significant impact of ET plus CDK4/6i was observed in the increase of liver metastases (mets) (P = 0.0196, OR = 0.125, 95% CI 0.002–0.932), followed by lung mets (P = 0.0345, OR = 0.14, 95% CI 0.003–1.09). No significant pairwise changes were highlighted for bone, CNS, and pleura. 1L CT significantly impacted the increase in liver (P = 0.014, OR = 0, 95% CI 0–0.849), lung (P = 0.0067, OR = 0.1, 95% CI 0.002–0.703), and lymph node involvement (P < 0.0001, OR = 0.05, 95% CI 0.001–0.296). No significant pairwise changes were observed for CNS and bone mets. Finally, 1L ET was associated with a statistically significant increase in liver (P < 0.0001, OR = 0, 95% CI 0–0.115), lung (P < 0.0001, OR = 0, 95% CI 0–0.105), lymph nodes (P < 0.0001, OR = 0.073, 95% CI 0.023–0.180), and bone mets (P = 0.010, OR = 0.29, 95% CI 0.085–0.83), with no significant pairwise changes highlighted for CNS lesions.

Conclusions: Different 1L treatment strategies may have distinct impacts on the evolution of metastatic spreading in Luminal-like mBC. Based on these exploratory results, future research projects could further explore the influence of 1L treatments, especially ET plus CDK4/6i, on organotropism.

E30

BRIDGING THE GAP BETWEEN REAL-WORLD STUDIES (RWSS) AND RANDOMIZED CONTROLLED TRIALS (RCTS) OF 1ST-LINE PALBOCICLIB+AROMATASE INHIBITORS (P+AI) IN HORMONE RECEPTOR-POSITIVE (HR+)/HER2-NEGATIVE(-) METASTATIC BREAST CANCER (MBC)

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Background: RCTs remain the gold standard to assess the efficacy of a treatment seeking regulatory approval. However, RWSs provide insights into patients (pts)' outcomes in routine clinical practice. We assessed the real-world (RW) efficacy of 1st-line P+AI and compared it to RCTs' results.

Methods: A systematic review was performed to identify RWSs published from 2019 to 2023 including pts with HR+/HER2- mBC treated with 1st-line P+AI, with available median progression-free survival (mPFS) and/or overall survival (mOS). A meta-analysis was performed to estimate the pooled mPFS/OS using the median of the medians (MM) and weighted median of medians (WM). The RW estimates were deemed comparable to PALOMA1/2 RCTs' mPFS/OS, if MMPFS/OS or WMPFS/OS were in RCTs' mPFS/OS 95% confidence intervals (CI). Similar criteria applied to pooled hazard ratios (HR) of PFS/OS for P+AI vs. AI in visceral/non-visceral subgroups.

Results: Among 8 included RWSs (n=4624 pts) a MMPFS of 22.5 months (95%CI: 19.5-31.8) and WMPFS of 20.0 (95%CI: 19.3-31.8) were observed with 1st-line P+AI. The MMPFS was comparable to those of PALOMA1 (20.2, 95%CI: 13.8-27.5) and PALOMA2 (27.6 months, 95%CI: 22.4-30.3). The WMPFS was inferior to that of PALOMA2. A RW MMOS of 51.2 months (95%CI: 49.1-53.3) and WMOS of 49.1 (95%CI: 49.1-53.3) were observed, outperforming the PALOMA1 mOS of 37.5 months (95%CI: 37.5-47.8) and being comparable to PALOMA2 mOS of 53.8 (95%CI: 49.8-59.2). P+AI vs. AI in RW in visceral disease had superior PFS (HR: 0.56, 95%CI: 0.46-0.68) and OS (HR: 0.61, 95%CI: 0.49-0.77), similarly to the PALOMA2 PFS (HR: 0.62, 95%CI: 0.47-0.81) and better than PALOMA1 (HR: 1.13, 95%CI: 0.68-1.88) and PALOMA2 (HR: 0.86, 95%CI: 0.65-1.13) OS. In RW non-visceral disease, P+AI vs. AI had lower PFS benefit (HR: 0.76, 95%CI: 0.65-0.88) than PALOMA2 (HR: 0.50, 95%CI: 0.37-0.67). RW OS (HR: 0.82, 95%CI: 0.69-0.99) was similar than that of PALOMA2 (HR: 0.98, 95%CI: 0.74-1.31).

Conclusions: Our findings add to the understanding of the generalisability of RCTs results to RW and confirm the benefit of palbociclib+AI vs. AI alone.

E31

HER2+ EARLY-STAGE BREAST CANCER TREATED WITH EXTENDED ADJUVANT NERATINIB IN THE CONTEXT OF THE EUROPEAN EARLY ACCESS PROGRAM: NEAR STUDY FINAL RESULTS

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Background: Neratinib is approved based on the phase III ExteNET study in Europe to treat adult patients with HR+/HER2+ early breast cancer (eBC) completing adjuvant trastuzumab-based therapy <1 year ago (EU label). A 2017 Early Access Program (EAP) granted neratinib access to patients awaiting product availability. The eBC treatment landscape has evolved since ExteNET, and there is a need to assess neratinib safety and effectiveness in the recent treatment landscape.

Material and Methods: NEAR is a retrospective, observational study in Belgium, Croatia, France, Italy, and Spain in adults with HER2+ eBC receiving ≥1 dose of neratinib in the context of the EAP between Aug 1, 2017, and Dec 31, 2020. Here we present data on neratinib treatment patterns, safety, and 2-year effectiveness.

Results: As of Jan 31, 2023, 108 patients were included in the full analysis set (FAS), of which 92 were HR+ and 74 met the EU label criteria; median follow up was 28 months. Key patient characteristics are summarised in the Table. Initial neratinib dose was 240 mg in 87% of both the FAS and the EU label group; the rest received <240 mg. The most common adverse event (AE) was diarrhoea (all grades/grades 3–4: 58%/8% in the FAS; 53%/8% in the EU label group), followed by other gastrointestinal AEs. Prophylactic antidiarrhoeal treatment was given in 44% of the FAS and in 47% of the EU label group. At 2 years, in the HR+ and EU label groups,

invasive/distant disease-free survival were 93%/94% and 95%/96%, respectively; overall survival was 98% and 97%. No central nervous system metastases were observed.

Conclusions: This study provides additional data supporting the use and management of extended adjuvant neratinib in clinical practice.

Clinical trial identification NCT05599334

Table. Key patient characteristics, pre-treatments received and neratinib therapy patterns.

	FAS (n=108)	EU label group (n=74)
Median age [min-max], years	48 [30-72]	49 [30-72]
Pre-menopausal, %	37	41
Stage I	17	15
%Stage II+III%	74	74
Missing %	9	11
High recurrence risk profile‡, %	81	81
Prior neoadjuvant therapy, %	58	65
Prior anti-HER2 adjuvant therapy, %	91	91
Of which on trastuzumab, %	88	90
Median months [min-max] from adjuvant therapy to neratinib initiation	4.6 [0.3-24]	3.2 [0.3-12]
Median [min-max] months on neratinib	12.3 [0.03-16]	12.1 [0.3-16]

‡Stage II/III or N+ or no pathologic complete response

E32

THE IMPACT OF CHEMOTHERAPY RELATIVE DOSE INTENSITY ON EVENT-FREE SURVIVAL IN PATIENTS WITH HORMONE RECEPTOR POSITIVE BREAST CANCER TREATED WITH NEOADJUVANT CHEMOTHERAPY

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Background: Neoadjuvant treatment represents a highly effective therapeutic approach for both triple negative and HER2 positive locally advanced breast cancer (LABC). Remarkedly, pathologic complete response (pCR) rate is high, and is associated with improved event-free survival (EFS) and overall survival (OS). Conversely, the role of neoadjuvant chemotherapy (NACT) in hormone receptor positive (HR+) breast cancer is controversial. Indeed, the rate of pathological complete response (pCR) in HR+ BC is poor and predictive biomarkers for treatment efficacy are lacking.

Methods: A retrospective analysis was conducted among 147 patients with HR+ LABC who received NACT between June 2015 and October 2022 at the University of Naples Federico II. Patients' demographics, clinical-pathological features, and type of CT schedules were retrieved from electronic medical records. RDI was calculated as the ratio of delivered to the standard planned chemotherapy dose intensity. RDI was defined as low if < 85% or high if ≥85%, respectively. EFS curves according to RDI were estimated using Kaplan-Meyer method and log-rank test. Cox regression was used to evaluate the association between RDI and EFS in a multivariate model with tumor stage and treatment regimens.

Results: Median age at diagnosis was 49 years (range 26-71). Eighty-four (57%), and 63 (43%) pts were diagnosed with stage II and stage III HR+ BC, respectively. Seventy-three (49%) and 74 (51%) pts received no-dose dense and dose dense anthracycline plus cyclophosphamide based regimens, respectively. Overall, 129 (88%) received a RDI HIGH CT, whereas 18 (12%) pts received a RDI LOW CT. At univariate analysis ($p < 0.805$) RDI HIGH was not significantly associated with pCR. In addition, pCR was not significantly associated with EFS ($p= 0.256$) After a median follow up of 52 months, 6 out 18 (33%) in the RDI LOW group and 13 out 129 (10%) in the RDI HIGH group had disease progression, recurrence, or died from any cause (log rank $p=0.02$). In a multivariate survival model including RDI, tumor stage, and CT regimen dose type, RDI LOW was independently associated with a higher risk of disease progression, recurrence or death (HR 3.39, 95% CI: 1.19-8.78, $p = 0.021$).

Conclusions: Our data suggest that RDI LOW is associated with an inferior survival outcome in HR+ LABC. Larger prospective studies are needed to confirm the association of RDI with clinical outcomes in HR+ BC patients undergoing NACT.

E33

INSIGHTS ON THE PROGNOSTIC IMPACT OF LIQUID BIOPSY (LB) BIOMARKERS ON SECOND-LINE (2L) TREATMENT (TX) OUTCOMES IN METASTATIC BREAST CANCER (MBC) PATIENTS (PTS): THE MAGNETIC.1 STUDY EXPERIENCE

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Background: Despite the increasing availability of new therapies for luminal-like (HRpos) mBC, the current lack of reliable biomarkers for endocrine therapy (ET) makes defining the 2L Tx algorithm extremely challenging. Aim of the study was to assess the impact of LB biomarkers at the diagnosis of metastatic relapse before first line (1L) ET on 2L progression-free survival (PFS2) and overall survival (OS2).

Methods: In the prospective multicenter MAGNETIC.1 trial (NCT05814224,) patients (pts) with HRpos mBC treated with 1L ET were longitudinally characterized through LB. Cox regression analysis was used to assess the prognostic impact of LB and clinical features, while survival estimates were generated using the Kaplan-Meyer method.

Results: Out of the 148 enrolled pts, 88 pts (59%) experienced disease progression (PD). 2L Tx options were chemotherapy (CT) (53%), CDK4/6i beyond PD (20%), ET alone (15%), ET + everolimus (8%), and ET + alpelisib (1%). The main baseline (BL) metastatic (mts) sites were bone (73%) and lymph nodes (55%), while new mts sites at PD included liver (44%), bone (19%), and lung (8%). LB biomarkers strongly associated with PFS2 were BL methylation of the ESR1 promoter A (PromA) and promoter B (PromB) dichotomized at 75th percentile (high versus low) (respectively P=0.05 and P=0.022), PromA at 6 months (T5) (P=0.013), and BL Actin short (As) fragments (P=0.007). The latter was confirmed after correction for 2L Tx type (CT versus ET) and 1L progression free survival (PFS1) (P=0.007). PromA dynamics was also prognostic, regardless of BL Prom A (P=0.013). Clinical features did not impact on PFS2. BL As, AKT1 and ERBB2 mutational status, as well as liver mts and 2L Tx type were prognostic for OS2. At multivariable analysis corrected for PFS1 significance was confirmed for BL As (P=<0.001), BL AKT1 (P=0.001) and BL ERBB2 (P=0.003).

Conclusions: LB biomarkers at relapse exhibit prognostic significance for both 1L and 2L Tx, regardless of clinical variables. Characterization through plasma As fragments may offer insights into both PFS2 and OS2, potentially guiding Tx choice after 1L.

E34

IMPACT OF PROGESTERONE RECEPTOR (PR) STATUS ON ENDOCRINE THERAPY (ET) SENSITIVITY IN ESTROGEN RECEPTOR POSITIVE, HER2 NEGATIVE METASTATIC BREAST CANCER (MBC): INSIGHTS FROM EPIGENETIC AND CTDNA FRAGMENTOMICS

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Background: In estrogen receptor (ER) positive (pos), HER2 negative (neg) MBC, absence of PR expression is associated with a poorer response to ET. This study aimed to evaluate the prognostic impact of PR status and its association with the methylation levels of ESR1 promoters A (promA) and B (promB) at various time points in ERpos HER2neg MBC undergoing first-line ET.

Methods: Patients (pts) treated with first-line ET were enrolled in the prospective multicenter MAGNETIC.1 trial (CRO-2018-56). ctDNA samples were collected at baseline (T0) and every 3 months (T3 and T6) and analyzed using droplet digital PCR (ddPCR) and next-generation sequencing (NGS). Clinico-pathological differences across the PR expression spectrum were assessed using Fisher's exact test. Matched pairs variations across time points of liquid biopsy features were evaluated using the Wilcoxon signed-rank test.

Results: Among the 111 enrolled pts, 28 had PRneg MBC. Prognostic impact of PR status was evident for progression-free survival (PFS) (median 38 mts for PRpos vs 14 mts for PRneg, P = 0.0048) and overall survival (OS) (median not reached for PRpos vs 33 mts for PRneg, P = 0.001). A significant increase in promB methylation was noted at T3 vs T0 and at T6 vs T3 only in the PRpos group (P = 0.0158 and P < 0.001, respectively). When comparing T6 to T0, no significant differences were found. At T3, significant reductions in levels were observed for both PRpos and PRneg groups in $ACTB_{short}$ (P < 0.001 and P = 0.03 for PRpos and PRneg, respectively), $ACTB_{medium}$ (P = 0.0049 and P = 0.035 for PRpos and PRneg, respectively), and $ACTB_{long}$ (P < 0.001 for both PRpos and PRneg) compared to T0. Significant changes in $ACTB_{short}$ levels were seen in both groups (P < 0.001 for PRpos and P = 0.012 for PRneg) for T6 vs T3, while a notable reduction in $ACTB_{medium}$ levels was observed at T6 vs T0 only in the PRpos group (P < 0.001).

Conclusions: Compared to PRpos status, PRneg was confirmed as an unfavorable prognostic factor for both PFS and OS, possibly due to different ET sensitivities. Epigenetic ctDNA profiling revealed differential dynamics of *ESR1* promB between PRpos and PRneg MBC, indicating a potential distinct role of *ESR1* in the onset of ET resistance across the two subgroups.

E35

PROGNOSTIC IMPACT OF NUTRITIONAL STATUS AND IMMUNE-INFLAMMATORY SYSTEM IN ADVANCED HR+ HER2- BREAST CANCER TREATED WITH CDK4/6 INHIBITORS

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Background: Worldwide, the standard first-line therapy in hormone receptor positive (HR+) HER2 negative (HER2-) metastatic breast cancer (mBC) is represented by CDK4/6 inhibitors (CDK4/6i) associated to endocrine therapy (ET), according to prognostic progress. Aim of our retrospective study was to identify new prognostic factors in this setting.

Patients and Methods: All patients (pts) affected by HR+/HER2- mBC referred to our Institutions from February 2017 to August 2023 and treated with CDK4/6i + ET as first-line setting were included.

Results: 220 pts were included. Median PFS (mPFS) was 35.2 months (m) (0.4-71.8) and median OS (mOS) was 4.3 years (y) (0.13-5.97). According to nutritional status, Body Mass Index (BMI) was not correlated to mPFS (p=0.71), while Prognostic Nutrition Index (PNI) resulted prognostic for mPFS (47.3m if >44.85 vs 12.5m if ≤44.85, p<0.0001). Similarly, mOS was not related to BMI (p=0.52), while it was correlated to PNI (not reached (NR) if high vs 2.65y if low, p=0.0006). About immune-inflammatory system, baseline Systemic Inflammation Index (SII) resulted prognostic for mPFS (47.3m if ≤710.87 vs 24.1m if >710.87, p=0.0135), but not for mOS (p=0.053). Conversely, neither better response SII (p=0.12) nor progression SII (p=0.28) were prognostic for mPFS and mOS (p=0.23 and p=0.72, respectively). Moreover, mPFS was related to Neutrophil to Lymphocyte Ratio (NLR) at baseline (47.3m if ≤2.9 vs 24.1m if >2.9, p=0.0019) and at better response (40.5m if low vs 18.6m if high, p=0.0023). Similarly, NLR was prognostic for mOS, both at baseline (5.4y if low vs 3.4y if high, p=0.0173) and at better response (5.2y if low vs 3.9y if high, p=0.0179). NLR at progression was not correlated to mPFS (p=0.74), while it was prognostic for mOS (3.1y if low vs 2.0y if high, p=0.0441). Finally, mPFS was related to baseline Platelet-to-Lymphocyte Ratio (PLR) (47.3m if ≤166.38 vs 21.5m if >166.38, p=0.0034) and progression PLR (15.8m if >166.38 vs 9.5m if ≤166.38, p=0.0019); the latter association was confirmed at multivariate analysis (p=0.0166). PLR at better response was not related to mPFS (p=0.47) and mOS (p=0.43) and mOS was not correlated neither to baseline PLR (p=0.10) nor to progression PLR (p=0.17).

Conclusions: Our study pointed out new prognostic factors in HR+ HER2- mBC treated with CDK4/6i + ET, regarding nutritional status and immune-inflammatory system, such as PNI, SII, PLR and NLR. Our findings could be useful and easily applicable in clinical practice.

E36

EARLY TRIPLE NEGATIVE BREAST CANCER WITH HOMOLOGOUS RECOMBINATION REPAIR DEFICIENCY MAY SPARE NEOADJUVANT IMMUNOTHERAPY

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Background: Currently, there are no predictive biomarkers available for neoadjuvant immunotherapy (IT) in early-stage triple negative breast cancer (TNBC). The RAD51 test can identify homologous recombination repair (HRR)-deficient (HRD) tumors sensitive to platinum salts (CBBD), potentially offering predictive value in this patient subset and guiding neoadjuvant treatments to minimize toxicities.

Material and Methods: We assessed functional HRD by observing RAD51 nuclear foci through immunofluorescence and evaluated tumor-infiltrating lymphocytes (TILs) content by hematoxylin and eosin stain and immunohistochemistry on diagnostic tumor biopsies from 22 histologically confirmed TNBC patients. Patients were treated with CBBD-based neoadjuvant therapy with or without IT at the University Hospital of Parma. Functional HRD was defined as a RAD51 score =10% (RAD51-low). Tumors with TILs extent =30% were classified as high-TIL.

Results: Among 22 patients, 11 (50%) harbored HRR germinal mutations: 8 g*BRCA1* (36%), 2 g*BRCA2* (9%), and 1 g*ATM* (4.5%) mutations. 13 out of 22 tumors (59%) were HRD by RAD51: 10/13 (77%) had HRR mutations and 3/13 (23%) were HRR-wt. HRD status, pathological complete response (pCR) rates, and TILs extent by neoadjuvant treatment type are summarized in **Table 1**. pCR rates in HRD tumors were similar regardless of IT use (60% vs 66.7%, respectively); however, pCR rates increased from 25% to 40% in HR-proficient (HRP) tumors when pembrolizumab was administered. 2-years DFS was 100% in HRD patients treated with and without IT; notably, it increased from 66% to 80% in HRP tumors receiving neoadjuvant IT.

Conclusions: The RAD51 test is able to identify HRR-altered tumors, beyond g*BRCA1/2* mutations, and to select a cohort of early TNBC patients with high sensitivity to CBBD who may spare IT, avoiding useless toxicities. Biomarker analyses on a larger cohort of patients are ongoing. Results will be available for the congress.

Table 1.

	pCR	no pCR	High-TIL	Low-TIL
HRD	61.5	38.5	7.7	92.3
HRP	33.3	66.7	0.0	100.0
HRD/CBBD	60.0	40.0	14.3	85.7
HRP/CBBD	25.0	75.0	0.0	100.0
HRD/IT	66.7	33.3	0.0	100.0
HRP/IT	40.0	60.0	0.0	100.0

E37

USE OF ONCOTYPEDX IN WOMEN WITH ER+/HER2- BREAST CANCER AFTER SURGERY: THE EXPERIENCE OF ANCONA BREAST UNIT

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Background: OncotypeDx (ODX) is a multigene assay used to establish the probability of recurrence of breast cancer (BC) and its response to chemotherapy (CTx), predicting which patients (pts) may avoid it. It is indicated in women operated for ER+/HER2- early-stage invasive BC with or without involved lymph nodes. The test defines a Recurrence Score (RS) as a number from 0 to 100: in post-menopausal pts, a RS between 26-100 indicates an increased risk of recurrence and adding CTx to hormone therapy (HT) helps in reducing it; conversely, a RS below suggests a low risk of relapse with HT alone and CTx can be avoided. In premenopausal pts CTx is helpful with lower RS (at least 16). Our study aims to evaluate ODX use within our Breast Unit (BU).

Patients and Methods: We evaluated all HR+/HER2- BC pts referred to our BU from January 2017 to February 2024 and submitted to ODX. Chi-squared model was used for univariate analysis.

Results: Among 109 pts evaluated, 77 (70.6%) were in menopause; 14 pts (12.8%), 67 (61.5%) and 28 (25.7%) had respectively low, intermediate and high RS; 13 pts (11.9%) received CDK-4/6 inhibitors, of whom 7 (6.4%) were treated with CTx in addition to HT. 3 pts (3.3%) had low RS but G3 BC with high Ki-67, while 15 (13.8%) had high RS with G1-2 and/or low Ki-67 BC. Before ODX, CTx was indicated in 49 pts (44.9%), but after ODX it was used only in 30 cases (27.5%). Currently, only 2 pts (1.8%) experienced BC recurrence and 95 (87.2%) are still in adjuvant treatment. At a univariate analysis, Progesterone Receptor expression was related to RS (p=0.0164); conversely, no significant correlation was found between RS and phenotype (p=0.2721), histology (p=0.4743), Ki-67 (p=0.7506), grading (p=0.0592) and nodal involvement (p=0.0538). As expected, there was a strong correlation between RS and the subsequent change of the proposed therapy (p=0.0011). The same was found between the initial treatment choice and its post-ODX change (p<0.0001). After ODX, among pts at high risk of recurrence, CTx was administered in 37.5% of cases less than initially proposed; similarly, among pts at low risk of recurrence, CTx was necessary in 8% of cases more than initially thought. Post-ODX change of therapy choice was independent of factors other than ODX, in particular nodal involvement.

Conclusions: According to literature, and TailorX trial data, our study confirms the importance of ODX as a tool able to guide therapeutic choices and ensure patients the most appropriate adjuvant treatment.

E38

SAFETY AND EFFICACY OF SACITUZUMAB GOVITECAN (SG) IN PRETREATED METASTATIC TRIPLE NEGATIVE BREAST CANCER (MTNBC) PATIENTS: AN ITALIAN, MULTICENTRIC, REAL-LIFE STUDY (SARELIFE)

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Background: mTNBC is an incurable disease, so treatment primarily aims to prolong patients (pts) survival and improve quality of life. SG is an anti-TROP2 that increased overall survival (OS) in pretreated pts. However, real-world data remain limited and fragmented.

Patients and Methods: SARELIFE is an observational, retrospective and prospective study, aimed to evaluate the safety of SG in a real-world population. The secondary objectives included: treatment adherence, safety of concomitant radiation therapy (RT) and drug-drug interactions (DDI). Treatment-related adverse events (AEs) were categorized and graded according to NCI-CTCAE v5.0. Data were analysed for safety, activity and survival outcomes, and the results were reported using descriptive statistics.

Results: Between 8/2023 and 5/2024, 103 pts were enrolled from 26 Italian centres. Median age: 55.6y (range:30-86); PS(ECOG)0-1: 91.3%; gBRCAmut carriers:11.3%; de novo metastatic disease:21.3%. Visceral metastases (mts) were present in 65% of pts; 11.7% had brain mts. Median number of prior treatment lines: 2(range:0-8); 31% of pts had received >2 prior lines of treatment; 26% had been treated with immunotherapy, 7.7% with PARP inhibitors.

For the safety analysis, 100 pts were considered: 69% experienced at least one AE of any grade. The most frequent were: neutropenia(55.1%,G3/G4:27.5%), nausea (45%),fatigue(42%,G3:5.8%),diarrhoea(33.3%,G3:3.3%), anaemia(30.4%,G3:5.5%) and febrile neutropenia(5.8%, G4:3.3%). 1 case of G3 pneumonitis was recorded. Dose reductions were needed for 38 pts. 3 pts discontinued SG due to toxicities. UGT1A1 status was evaluated in 18 pts: 4 were(*28/*28), 6 were(*1/*28), 1 patient in the(*28/*28) group had G3 anaemia. Interestingly, 15 pts received RT during SG treatment, including 7 concurrent treatments, without any additional AEs. Data analyses on DDI are still ongoing.

Best response was evaluable in 69 pts: 26.1%PR, 0%CR, 40.6%SD, 33.3%PD. With a median follow-up of 9.4 months, the mPFS was 5.6 months (95%CI:4.4-6.7), while

the mOS was 12.8 months(95%CI:9.9-15), consistent with data reported in the ASCENT study.

Conclusions: SARELIFE is the largest Italian study on the use of SG in unselected real-world mTNBC pts. No new safety signals were reported. Survival outcomes are similar to those reported in the registration trial. Although based on a small group, concomitant RT appears to be safe. These are preliminary results, with longer follow-up more robust data will be provided.

E39

DEVELOPMENT AND VALIDATION OF RSC4ALL: A MACHINE LEARNING (ML) NOMOGRAM TO PREDICT RSCLIN™ RESULTS AND GUIDE ADJUVANT TREATMENT OF NODE-NEGATIVE (N0) HORMONE RECEPTOR POSITIVE (HR+)/HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR NEGATIVE (HER2-) EARLY BREAST CANCER (EBC)

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Background: RSClin™ is a proprietary algorithm that combines clinicopathological (CP) factors (age, tumor size and grade) with genomic risk to refine the prognosis of distant recurrence (DR) and chemotherapy (CT) benefit in patients with N0 HR+/HER2- eBC. Since RSClin™ is only available in the USA, we aimed to develop an automated ML-based nomogram, RSC4All, to predict RSClin™ outcomes and provide free access to this predictive tool via a web-based link. Additionally, we generated synthetic data (SD) using Generative Adversarial Networks (GANs) to augment the initial dataset and enhance the tool's predictive accuracy.

Methods: We retrospective collect CP and genomic data from 290 patients with N0 HR+/HER2- eBC who underwent OncotypeDX from 2020 to 2022 at Italian and Belgian hospitals, with available RS and RSClin™ outputs of DR risk and CT benefit. Patients were randomly split into 2 groups, 70% allocated to the training set and 30% to the validation set. The ML-nomogram was developed using classification and regression models, including linear and logistic regression, to predict the categories (high vs mid/low for DR and yes vs no for CT) as well as the precise value for DR and CT benefit. Additionally, 177 synthetic patient records were generated through GANs and included in the training set to enhance the tool's predictive capability.

Results: Compared to RSClin™ outcomes, the classification model for DR, trained on the original dataset, achieved a ROC AUC of 0.97, while for CT benefit achieved a score of 0.99. The regression analyses for DR and CT benefit yielded significant R2 scores of 0.84 and 0.72, respectively. The inclusion of SD improved the dataset's diversity and representativeness, closely mirroring the real cohort's characteristics. Incorporating SD improved both classification and regression metrics, notably increasing the regression accuracy for predicting precise DR and CT benefit values. A web application was developed to provide easy and free access to the developed ML models (https://rsc4all.streamlit.app).

Conclusions: RSC4All accurately reproduces RSClin™ results to support treatment decisions for patients with N0 HR+/HER2- eBC. The incorporation of SD further enhanced the predictive accuracy of the ML tool, supporting the value of AI-driven data augmentation in oncology.

E40

PROGNOSIS ROLE OF BODY COMPOSITION PARAMETERS IN PATIENTS WITH EARLY BREAST CANCER RECEIVING ADJUVANT ENDOCRINE-THERAPY

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Background: Weight gain and obesity after breast cancer (BC) diagnosis have been found to increase the risk of recurrence and mortality. Body composition could be significantly affected by the hormonal imbalance caused by endocrine treatment, regardless of weight gain and BMI. However, there are few data available in the literature on this topic. The study's purpose was to investigate the significance of body composition measures for prognosis in early BC patients receiving AIs.

Methods: This is a retrospective, single-centre, observational i study. Fat body mass (FBM), lean body mass (LBM) as well as other DXA measures of adiposity were assessed by dual-energy X-ray absorptiometry scans (DXA). The relationship between body composition parameters and baseline clinical and pathological prognostic parameters (age, pT, pN, grading, Ki67, % of estrogen and progesterone receptor) and long-term outcomes (PFS and OS) was analyzed.

Results: The study included 723 consecutive patients treated at the Medical Oncology and Breast Unit of the ASST-Spedali Civili Hospital in Brescia between September 2014 and June 2022. Median age was 61 years. Most patients had pT1 and pN0 tumors. The median value of Ki67/ER/PgR was 24/96/60. Aromatase inhibitors (AIs) and ovarian suppression (OS) were administered to 80% and 16% of patients respectively, 44% of patients had received adjuvant chemotherapy. Recurrence of the disease was experienced by 2% of patients. Our analysis showed that patients who had fat body parameters above the median value were more likely to have lower levels of Ki67% and G1-G2 tumors.

Conclusions: Our study did not confirm the role of body composition in favoring the aggressiveness of breast cancer disease. The low rate of events meant that establishing the prognostic role of body composition parameters was not possible.

E41

PROGNOSTIC FACTORS RELATED TO CDK 4/6 INHIBITORS AS FIRST LINE TREATMENT IN METASTATIC HR+ HER2- BREAST CANCER: CONFIRMATIONS AND NOVELTIES

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Background: CDK4/6 inhibitors (CDK4/6i) with endocrine therapy (ET) constitute the standard first-line therapy in hormone receptor positive (HR+) HER2 negative (HER2-) metastatic breast cancer (mBC). The aim of our research is to understand its prognostic factors.

Patients and Methods: In our retrospective study, we analysed all patients (pts) affected by HR+/HER2- mBC referred to our Institutions from February 2017 to August 2023 and treated with CDK4/6i + ET as first-line setting.

Results: 220 pts were included. Median age was 62 years (y) (range 29-87). Median PFS (mPFS) was 35.2 months (m) (0.4-71.8). At univariate analysis, mPFS was correlated to adjuvant ET (44.5m if not received vs 26.0m if received, p=0.0048), visceral disease (22.4m if present vs 41.9m if absent, p=0.0012), endocrine sensibility (40.5m if yes vs 15.5m if not, p<0.0001) and ECOG performance status (ECOG PS) (41.4m if ECOG 0 vs 17.4m if ECOG 1 vs 24.6m if ECOG 2, p=0.0007). Median OS (mOS) was 4.3y (0.13-5.97) and similarly it was correlated to adjuvant ET (5.5y if not received vs 3.7y if received, p=0.0313), visceral disease (not reached (NR) if absent vs 3.85y if present, p=0.0063), endocrine sensibility (5.2y if yes vs 2.5y if not, p=0.0016) and ECOG PS (5.2y if ECOG 0 vs 2.6y if ECOG 1 vs 2.5y if ECOG 2, p=0.0023). According to side effects, neutropenia occurred in 95.5%, causing 38.2% of dose reduction and 4.1% of discontinuation. At univariate analysis, mPFS was positively correlated to neutropenia (35.3m if yes vs 9.8m if not, p=0.0103) and dose reduction (not reached (NR) if yes vs 26.2m if not, p=0.0002), while treatment interruption resulted in worse prognosis (2.4m if yes vs 35.3m if not, p=0.0024). Only neutropenia was confirmed at multivariate analysis (p=0.0279). Finally, in relation to disease response, 10.0% of pts obtained complete response (CR), 46.8% partial response (PR), 32.7% disease stability (DS) and 10.5% disease progression (DP). Disease response resulted as a prognostic factor for mPFS (NR if CR vs 37.1m if PR vs 35.2m if DS vs 4.3m if DP, p<0.0001) and for mOS (NR if CR vs 4.3y if PR vs 5.3y if DS vs 1.3y if DP) at univariate (p<0.0001) and multivariate (p=0.0445) analysis.

Conclusions: Efficacy of CDK4/6i in HR+ HER2- mBC was confirmed in our study, underlying known prognostic factors (adjuvant ET, endocrine sensibility, visceral disease, ECOG PS and disease response) and new ones, such as neutropenia and dose reduction, of whom little data are present in literature.

E42

PATIENTS', CAREGIVERS', AND HEALTHCARE PROFESSIONALS' EXPERIENCES AND INSIGHTS ON EARLY BREAST CANCER IN ITALY: A SOCIAL MEDIA LISTENING STUDY

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Background: Published evidence on the patient experiences and perspectives of early breast cancer (eBC) in Italy is limited. This social media listening (SML) study was conducted to understand the patient journey, treatment perceptions, quality of life (QoL) and unmet needs.

Methods: Social media data were extracted between December 2021 and November 2023 using "breast cancer" related keywords via Sprinklr, an online SML tool. English and Italian language posts were extracted from Italy. eBC

relevant conversations were, screened, mapped, and analysed to understand different concerns.

Results: Out of 1580 posts screened, 530 were relevant to patients with eBC. Patients contributed to 60% of posts (n=318/530), with 95% (n=493/518) willing to share information, whereas only 27% (n=141/518) sought information. Patients shared information about their symptoms, diagnostic and treatment journey, QoL, and sought information about diagnosis dilemmas, treatment options, and second opinion from health care professionals (HCPs). Caregivers contributed to 21% (n=111/530) of posts, with 53% (n=57/107) being children discussing their mother's diagnosis and treatment challenges. HCPs contributed to 16% (n=85/530) of posts, sharing updates on eBC, including clinical trials and drug approvals. Unidentified persons contributed to 3% (n=16/530) of posts. Patients complained about multiple tests, repeated visits for the same tests, and ineffective communication with HCPs. Lack of understanding, misinterpretation, and lack of timely communication of test results were some of the key barriers for patient-HCP communication. Patients were relieved by surgery but had concerns about the long duration and side effects of chemotherapy and endocrine therapy, leading them to seek information for more effective treatment strategies. eBC significantly impacted patients' QoL, affecting emotional well-being (91%, n=80/88), physical functioning (36%, n=32/88), functional well-being (11%, n=10/88) and social well-being (8%, n=7/88). Patients' key unmet needs were limited treatment knowledge, lack of trusted online peer groups for support, diagnosis and treatment related communication issues with HCPs, and lack of awareness and limited access to specialty breast care units in their cities.

Conclusions: There is a large scope for improving the patient journey especially through better treatment strategies, enhanced patient-HCP communications and better patients' coping mechanisms.

E43

CLINICIANS' PREFERENCES ON ADJUVANT CDK4/6 INHIBITORS IN HIGH-RISK HR+/HER2- BREAST CANCER

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Background: Abemaciclib and Ribociclib with endocrine therapy recently demonstrated a significant improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) in adjuvant treatment of HR+/HER2- early breast cancer. Although the inclusion criteria of Monarch E and Natalee trials differ, some patients could be eligible for both of them. The aim of this analysis was to investigate clinicians' preferences between abemaciclib and ribociclib when both are indicated and which factors mostly influence their decision.

Material and Methods: This retrospective single-institution analysis evaluated clinical and pathological characteristics of patients diagnosed with HR+/HER2- breast cancer and candidate to a CDK4/6i in the adjuvant setting. Ten representative clinical cases were used to create a questionnaire that was administrated to 9 breast oncologists.

Results: 450 patients underwent breast surgery for HR+/HER2- breast cancer at the Modena Hospital in 2021. 44 (9.8%) patients would have been eligible for adjuvant abemaciclib, whereas 100 patients (22.2%) would have been eligible for ribociclib. No statistically significant differences were found in the distribution of age range, body mass index, menopausal status and histology between patients eligible for abemaclib or ribociclib. In 9 out of 10 (88%) cases there was not a full agreement among oncologists on the selection of adjuvant CDK4/6i. When abemaciclib was preferred, the most common reason was the longer follow up or the strength of data of the Monarch E trial. On the other hand, when ribociclib was preferred, the most common reasons were the good safety profile and the inclusion of more intermediate-risk patients and men in the Natalee trial. Gastro-intestinal and cardiac comorbidities were taken in consideration in the decision making process. On the other hand, pharmacological interactions, treatment duration and schedule of administration were less considered. In the case of a BRCA2 patient with CPS&EG score 2, 3 out of 9 (33.3%) oncologists chose to ask for olaparib with personalized indication.

Conclusions: Several patients are eligible both for ribociclib and abemaciclib in the adjuvant setting. Today, there is no consensus on the most appropriate CDK4/6i for each patient, and criteria for decision making mostly includes data from clinical trials and toxicity profile. Maturation of data and real world evidence will probably reduce this variability.

E44

PROGNOSTIC ROLE OF HER2 CHANGE IN EARLY BREAST CANCER RECEIVING NEOADJUVANT TREATMENT: A MONOCENTRIC EXPERIENCE

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Background: Human epidermal growth factor receptor 2 (HER2) expression significantly influence disease prognosis and therapeutic response in patients (pts) with breast cancer (BC). Neoadjuvant treatment (chemotherapy +/- anti HER2 therapy, NAT) can determine a change of HER2 status between diagnostic biopsy and surgical tumor samples, even though data regarding its prognostic significance are still limited. This retrospective analysis aims to investigate the rate of conversion of HER2 expression following NAT in BC, its correlation with biological features and prognostic role.

Patients and Methods: This retrospective study included all pts with early-stage breast cancer (stage I-III), regardless of HER2 status, treated with NAT from May 2016 to March 2023, at the Oncology Department of AOU Marche (Italy).

Results: 85 patients were included. Median age was 48 years (range 30-69). At the initial biopsy 40 pts (47,1%) were HER2-negative, 24 pts (28.2%) were HER2-positive and the remaining 21 pts were HER2-low (24.7%). A significant proportion of pts (35.3%) achieved complete pathological response (pCR), while a smaller group of pts (14.1%) did not have any pathological response following NAT. Among the subset of pts having residual disease (RD), the 44.7% (38/85) exhibited HER2 status expression stability following NAT, the 12.9% (11/85) showed reduced HER2 expression and only 1.1% (1/85) had increased HER2 expression. Patients initially diagnosed as HER2-positive or HER2-low showed a higher probability of HER2 expression variation after NAT in comparison to those with HER2-negative tumors (p=0,0004). At the statistical analysis HER2 variation resulted significantly associated with Ki-67 expression (p<0.0001), stage of disease (p=0,0128), estrogen receptor (ER) and progesteron receptor (PgR) expression in the surgical tumor sample (p<0.0001). Median follow-up of these pts was 37,5 months; median DFS was not reached (2.1-101 months). Among the subset of pts having RD, DFS did not differ between stable or at least once HER2 variation after NAT (p=0.12).

Conclusions: Despite the limited sample of patients and the retrospective nature of the analysis, this study confirmed the potential role of NAT in changing HER2 status and the association between this change and specific biological parameters of the disease, as well as the increased tendency of certain subtypes to exhibit this change. However, longer follow up and larger analyses are needed to clarify its prognostic value.

E45

EV DERIVED MIR-21 AS A PROMISING BIOMARKER FOR EARLY DIAGNOSIS AND TUMOR ACTIVITY IN DISCRETE BC SUBTYPES: THE EXOBREAST PROJECT

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Background: Emerging evidence highlights the key role of microRNA (miR)-21 in cell-to-cell communication and tumorigenesis. Limited knowledge exists on the expression and clinical meaning of miR-21 in extracellular vesicles (EVs) of breast cancer (BC) patients. Thus, the aim of this study has been to assess EV-derived miR-21 expression in different BC subsets.

Patients and Methods: One hundred women were enrolled: 30 with early BC, 30 with metastatic BC on treatment progression, 30 cancer survivors on follow up and 10 healthy controls matched for age and BMI. EVs, isolated from serum samples, were characterized by nanoparticle tracking analyzer (NTA), scanning electron microscopy (SEM) and atomic force microscopy (AFM) to detect their concentration, size and structure. The miR-21 in EVs was evaluated by Real Time PCR. The expression of miR-21 was compared between groups by calculating the ΔΔCt statistic and the fold change, considering miR-16 as the housekeeping gene. The ΔΔCt was calculated using a linear mixed model approach with gene group interaction as the parameter of interest, adjusting for age, BMI and menopausal status, and considering random intercept and random slope terms to account for individual variability.

Results: No differences in EVs size and concentration among the four groups were detected. Considering the early BC group, the clinical stage at diagnosis and tumor subtype did not influence miR-21 expression. Higher expression of miR-21 has been found in metastatic versus healthy controls (p= 0.029 95% CI -1.549 to -0.079), mainly in HER2+ and hormone receptor positive patients (p 0.0005 and 0.036, respectively). In particular, in HER2+ miR-21 was significantly higher in patients with active BC (early and metastatic) (p 0.002 95% CI -1,707 to -0,376) compared to control group.

Conclusions: While further investigations shall be requested, our data on serum EV suggest that miR-21 may become a promising biomarker for early diagnosis and tumor activity, mainly in HER2+ BC.

E46

ANALYZING CDK4/6 INHIBITOR THERAPY IN ELDERLY PATIENTS WITH METASTATIC HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE BREAST CANCER: REAL-LIFE INSIGHTS FROM AN OBSERVATIONAL RETROSPECTIVE MULTICENTER STUDY

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Background: Breast cancer in elderly patients is increasingly recognized as a significant health concern due to demographic shifts and extended life expectancy. However, despite predominantly manifesting as hormone receptor-positive (HR+) breast cancer in the metastatic setting, elderly breast cancer patients often encounter fewer conventional treatment options, resulting in a unique and challenging treatment landscape. To date, no study has explored the patterns of CDK4/6 inhibitor therapy in Italian elderly metastatic breast cancer patients. To address these gaps, we conducted an observational retrospective multicenter analysis focusing on CDK4/6 inhibitor therapy among elderly women (≥70 years) with HR+/HER2- metastatic breast cancer.

Patients and Methods: We retrospectively analyzed data from elderly patients (age 70 and above) with breast cancer who received CDK4/6 inhibitor therapy. Patient demographics, tumor characteristics, treatment details, and clinical outcomes were extracted from medical records. The G8 geriatric score was assessed. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of CDK4/6 inhibitor initiation to disease progression, death, or last follow-up. Treatment response rates were determined based on RECIST criteria. Toxicity profiles and reasons for treatment discontinuation were also assessed.

Results: A total of 73 elderly patients were included in the analysis. The median age at diagnosis was 75 years and the median age at CDK4/6 inhibitor initiation was 76 years. The median PFS and OS were 19 months and 27 months, respectively. The overall response rate was 70%, with 8 % achieving complete response (CR) and 62% partial response (PR). The most common toxicities observed were neutropenia (48%) and asthenia (23%). Treatment discontinuation occurred in 41% of patients, primarily due to disease progression (43%) or toxicity (57%).

Conclusions: CDK4/6 therapy demonstrated promising efficacy and manageable toxicity in elderly patients with breast cancer. The observed PFS, OS, and response rates compare favorably with existing literature. However, careful monitoring for toxicities and individualized treatment decisions are warranted to optimize outcomes in this population.

E47

IMPACT OF CHEMOTHERAPY USE AND STROMAL TUMOR-INFILTRATING LYMPHOCYTES (STILS) IN STAGE I TRIPLE NEGATIVE BREAST CANCER

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Background: The optimal systemic treatment for stage I TNBC remains unclear, given the lack of well-designed randomized trials. sTILs have emerged as a prognostic biomarker in early TNBC. We aimed to study the impact of (neo)adjuvant CT use and sTILs in the prognosis of pts with stage I TNBC.

Methods: Pts with stage I TNBC (ER<10% and HER2-0/low) treated at Vall d'Hebron Hospital between 2006 and 2021 were reviewed. sTILs were evaluated at the surgery specimen and/or at the diagnostic biopsy, as per the international immuno-oncology working group guidelines. The effect of (neo)adjuvant CT and sTILs on invasive disease-free survival (iDFS), distant disease-free survival (DDFS), and overall survival (OS) was evaluated. Statistical significance ($p<0.05$) was determined using the log-rank test.

Results: 108 patients were identified (median age 56, 35% pre-menopausal). The majority of patients had tumors =10mm (75%), grade 3 (61%), and received CT (79%). Patients not receiving CT had a median age of 75, 17% were pT1a tumors and 30% had favorable histotypes. sTILs could be assessed in 79/108 (73%); 34% had sTILs >50%, which associated with higher grade and Ki67. With a median follow-up of 7.2 years (IC: 3.0 – 21.8), 19/108 (18%) had a progression event, 9 (8%) distant metastases. 5y iDFS, DDFS, and OS rates are presented in the Table. (Neo)adjuvant CT was not associated with better iDFS (p=.53), DDFS (p=.66) or OS (p=.89). In multivariate analyses for the survival endpoints, no interaction was

observed between sTILs (both as categorical and continuous variables) and CT use.

Conclusions: In this retrospective cohort, a high proportion of patients with stage I TNBC received CT, which was not associated with better outcomes, irrespectively of the abundance of sTILs. The role of (neo)adjuvant CT in stage I TNBC should be studied in prospective trials to identify patients that can be spared systemic treatment.

5-year rates	N	iDFS (%)	DDFS (%)	OS (%)
Overall population	108	83.6	91.2	98.9
sTILs >50% sTILs <50%	27 52	88.7 85.6*	100 93.8†	100 97.6‡
CT, overall CT and sTILs>50% CT and sTILs<50%	85 23 36	83.1 87 89	91.3 100 97	100 100 100
No CT, overall No CT and sTILs>50% No CT and sTILs<50%	23 416	86.1 100 80	90.9 100 87	95.2 100 93

*p=.63; †p=.34; ‡p=.68.

E48

BTRAPP (BEHIND THE TRIAL APPLICATION): AN INNOVATIVE DIGITAL TOOL FOR ADVANCING BREAST CANCER CLINICAL RESEARCH BY FACILITATING INFORMATION SHARING ON ONGOING TRIALS AND PROMPT COMMUNICATION AMONG ONCOLOGISTS FOR PATIENT REFERRAL

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Background: Promoting clinical cancer research and patient participation in clinical trials are cornerstones of best clinical practice. However, obstacles to implementation exist, such as the difficulty in identifying active studies for individual patients and contacting principal investigators (PIs) for timely patient referrals. To address these issues, we developed the digital tool BTRAPP (Behind the TRial APPlication) to support sharing information on ongoing clinical trials and to facilitate prompt communication between oncologists, enhancing the referral process for eligible patients within a regional context.

Methods: The BTRAPP application features two access pathways: the first allows users to search for clinical trials suitable for individual breast cancer (BC) patients based on simplified selection criteria, and the second allows users to propose clinical trials and provide referrals for eligible BC patients, with full privacy safeguarding and data-protection. BTRAPP is an interrogable platform with metrics for usability and efficiency, linked to the AIOM clinical trials website.

Results: Between September 2023 and April 2024, the BTRAPP digital tool was developed and preliminarily tested (alpha test) in a limited number of 3 Breast Units (BUs) in Lombardy to enhance its functionality and user-friendliness. The beta-test was then conducted in 14 regional BUs, resulting in 21 active BC clinical trials being registered on the platform, including 17 phase II-III and 4 phase I trials. The digital tool is available for various devices (i.e., laptop, tablet, smartphone) and garnered over 100 views in the first month of usage, generating 12 direct contact requests for the patient referral process. This indicates active and rapid uptake from the Breast Units (BUs) in Lombardy.

Conclusions: BTRAPP stands as Italy's pioneering, scalable, open-source digital solution dedicated to advancing breast cancer (BC) clinical research. It empowers Breast Unit (BU) networks, bolstering awareness of ongoing clinical trials and broadening avenues for patient engagement in clinical research endeavors, wherever feasible.For more information, visit and register at BTRAPP (www.btrapp.it)

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E49

SAFETY AND EFFICACY PROFILE OF NEW ANTIBODIES DRUG-CONJUGATED IN METASTATIC BREAST CANCER ACCORDING TO SARCOPENIA

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Background: Sarcopenia is defined as a condition characterized by low skeletal muscle mass. Several studies have shown that sarcopenia in breast cancer (BC) patients (pts) could influence toxicities and efficacy of chemotherapy agents. Few data are available about the effect of sarcopenia on the efficacy of antibodies drug-conjugated (ADCs) used in metastatic setting. Our goal is to evaluate a potential correlation between sarcopenia and ADCs' efficacy and toxicities in a retrospective cohort of metastatic (M) BC pts treated with Sacituzumab-govitecan (Sg) or Trastuzumab-deruxtecan (TDXd).

Material and Methods: We reviewed the electronic medical records of 47 MBC pts treated with an ADC from March 2020 to November 2023 at Modena Cancer Center. The Skeletal Muscle Index (SMI) was obtained from the ratio between the total lumbar muscles area (including psoas muscles, paraspinal muscles and wall muscles) and the square of the height (cm2/m2). SMI was calculated at the third lumbar vertebra from the baseline CT scans imaging for all pts. SMI less than 41 cm2/m2 was diagnostic for sarcopenia. Objective Response Rate (ORR) evaluated at CT scans after 4-6 months of ADC-based therapy was used to assess ADCs efficacy. Safety was defined according to CTCAE v5.0. Fisher's test was applied to investigate the association between ADCs' toxicity/efficacy and sarcopenia. All tests were carried out at the 5% significance level.

Results: Among 47 MBC pts, 31 (66%) were treated with TDXd, 16 (34%) with Sg. 18 (38%) have HER2+ve disease, 11 (23%) were classified as HER2-low, and 13 (28%) as triple-negative. At baseline, 13 pts (28%) were classified as sarcopenic according to SMI value. At first CT scan of restaging, 35 (74%) pts showed an objective response. Grade >/=2 toxicities were observed in 36 (77%) pts. No statistically significant correlation between sarcopenic and non-sarcopenic patients have been seen in terms of both ORR (84% vs 71% respectively, p= 0.46) and grade >/=2 toxicities (69% vs 79% in sarcopenic and non-sarcopenic group respectively, p= 0.47).

Conclusions: To the best of our knowledge, this is the first analysis investigating the correlation of sarcopenia and ADCs attivity and safety profile in a cohort of MBC pts. Sarcopenia does not seem to influence ADCs efficacy as well as toxicity. Due to the retrospective nature of the study and the small simple size further investigations are need.

E50

ADVANCING FRONTIERS: DEVELOPMENT OF AN AI AGENT FOR BREAST CANCER CARE

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Background: The promise of integrating artificial intelligence (AI) in medicine is substantial, offering potential applications across various domains such as personalized care, precision medicine, automated clinical data analysis, and enhancing clinical decision-making and patient communication. Large language models (LLM), particularly, excel in processing extensive datasets including clinical information, lab results, medical histories, and genetic data. In this study, we developed an AI agent specifically designed to assist in making therapeutic decisions for breast cancer (BC) patients. Our system includes a reasoning engine based on GPT-4o, a vector-based semantic search engine (QDrant), a web search engine focused on PUBMED (filtered for clinical studies), the ReAct prompt paradigm, and integrates the most recent AIOM and NCCN guidelines.

Patients and Methods: We aim to evaluate the clinical relevance and applicability of AI-generated recommendations for BC board decision-making. A retrospective real-world analysis was conducted to assess the initial applicability of AI responses and their subsequent alignment with physician choices regarding CDK4/6 inhibitors in first-line treatment. We randomly selected 23 patients diagnosed with metastatic (MBC) between 2019 and 2020, all with HER2 negative. The data provided to the model includes variables such as comorbidities, biomolecular characteristics, ER and PR status, stage at diagnosis, previous treatment for BC, metastasis occurrence date, and sites. In our cohort, 35% were diagnosed with luminal A, while 65% were Luminal B HER2 Negative subtype. Of these, 43% presented with MBC at diagnosis. The average age was 66.8 years, 44% of patients were over 65 years old at metastasis diagnosis. Comorbidities were prevalent, with 74% reporting one or more conditions. Specifically, 48% had cardiac issues, 23% had liver problems, and 17% had diabetes.

Results: All model responses consistently adhered to AIOM guidelines. In CDK4/6 inhibitor selection, there was notable alignment between the LLM recommendations and physician choices for half of the patient profiles (58.8%), with a correlation coefficient (V de Cramer) of 0.624. The average response time per query was 2 minutes.

Conclusions: Personalizing therapies with AI algorithms marks a significant advancement in contemporary oncology. The information furnished by the AI agent demonstrates accuracy and concordance with prevailing guidelines. Further investigation is warranted to assess the consistency of results.

E51

UPDATE ON BREAST CANCER RISK IN LYNCH SYNDROME FEMALE PATIENTS: A SINGLE INSTITUTION RETROSPECTIVE ANALYSIS

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Background: Lynch syndrome (LS) is a germ pathogenic mutations involving DNA Mismatch Repair (MMR) genes is linked with the development of MMR-deficient (MMRd) cancers and is associated with an increased risk of several malignancies including gastrointestinal, genitourinary, gynecologic, skin, and brain cancers. Whether patients with LS have higher risk of developing breast cancer (BC) or not is controversial and is a relevant clinical question.

Methods: From the Santa Maria alle Scotte Hospital registry, we retrospectively identified female patients with LS diagnosed showed by the detection of a germ heterozygous pathogenic or likely-pathogenic variant in MLH1, MSH2, MSH6 or PMS2 on molecular genetic testing within April 2016 to April 2023. We compared our sample size to SEER of 2017 NCI database.

Results: Overall, 50 female patients with LS were identified. Of those, 13 (26%) had primary BC (95% CI 1.463% to 26.7189% Chi-squared 5.95 p<0.0001). Among the BC LS patients, 91% (12) have a hormone receptor positive tumor and BC is the only diagnosis of cancer to date. 7 patients (45%) with BC LS have germinal MSH2 mutation, 45% of 13 patient has MSH6 alteration and has a more aggressive breast cancer. Median age at diagnosis is 54.5 years, median follow up is 7 years : All patients are still alive and under treatment,

Conclusions: In our single institution analysis, 26 % of female patients with LS developed BC. According to our data seems that LS enhances BC risk. This is important either for screening than for therapy for example immunotherapy. Further investigation with prospective clinical studies with larger samples is warranted to validate our data.

E52

HEMATHOLOGICAL SAFETY OF NEO/ ADJUVANT CHEMOTHERAPY WITH EPIRUBICIN, CYCLOPHOSPHAMIDE AND PACLITAXEL DOSE DENSE (ECP DD) AND DAILY CSF (DCSF) SUPPORT IN EARLY BREAST CANCER (EBC). REAL WORLD RESULTS IN MODENA CANCER CENTER

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Background: ECP DD is an option in the neo/adjuvant setting. In order to maintain the biweekly schedule, support with G-CSF is mandatory. In GIM2 trial, Pegfilgrastim, administered after 24 hours from chemotherapy (CT), was used as the preferred treatment. Few data are existing in the real world setting regarding the dCSF support of the ECP DD regimen.

Patients and Methods: Clinical data of the patients (pts) who received the ECP DD as adjuvant or neoadjuvant therapy in the period 2020-2023, were collected. EBC pts received dCSF or, if granted by the Pharmacy Unit, with Peghilated form (Peg).

Results: 95 pts were included in the study. The characteristics were as follow: median age 56 ys (37-79); Pre/postmenopausal 41/58%; T> 2 cm 73%; nodal status positive 74%, G2/3 were 61%/38%, ki 67 >20%: 61%.; 90% was her 2 negative; 60% was ER+. Mastectomy performed in 66%, axillary dissection in 65%. ECP DD was administered as neoadjuvant in 57% and adjuvant in 43% %; 94,8% received dCSF and 5,2% Peg. Median days of dCSF administration were 5.4 (range 4-8 days). Fifty-five % pts received 5 dCSF and 40% 6 dCSF. Hematological toxicities were as follow: Grade 1-2 and Grade 3-4 neutropenia in 24% and 7% of EC; 2% in P; Grade 1 Anemia 1% in EC; thrombocytopenia Grade 1-2 in 33% of EC and P. Two pts developed febrile neutropenia fully recovered. Adjuvant or neoadjuvant treatment has been temporary suspended in 13% of cycles for EC and 3% for P. The median time of interruptions was 8 days on EC and 7day in P. In 16% CT doses were reduced in EC, 8% in P. Permanent interruptions were observed in 7% in EC (6 pts all in the first cycles) and 1% (1 pts) in P in the third cycle. The relative dose intensity (RDI) was 86% for EC and P. In twelve pts the adjuvant or neoadjuvant regimen has been modified

to other regimen due to toxicities. Although not comparable, comparing the incidence of neutropenia with GIM2, a significant increase in G1-G2 toxicity (p 0.3; OR 1.88) was found, no statistically significant differences in G3-G4 toxicity (p 0.9; OR 0.36) was observed.

Conclusions: The ECP DD regimen represents an option for EBC pts candidates to adjuvant or neoadjuvant treatment, dCSF support (+3,+10) or Peg (+24 hours) is recommended. Although recommended for 8 consecutive days, we observed a median days of dCSF support ranging from 4 to 8 days without worsening of hematological toxicities.

E53

FACILITATORS AND BARRIERS TO SWITCHING FROM INTRAVENOUS (IV) TO SUBCUTANEOUS (SC) DELIVERY OF TRASTUZUMAB/PERTUZUMAB (PT): PERSPECTIVES FROM PATIENTS (PTS) WITH BREAST CANCER (BC) AND HEALTHCARE PROFESSIONALS (HCPS)

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Background: Pts with HER2-positive BC can receive a fixed-dose SC combination of PT. This study examines pts' and HCPs' perceptions after the implementation of SC compared to IV.

Methods: Semi-structured interviews to 54 pts receiving PT and 35 HCPs from the BC units of 3 hospitals in Lombardy-Humanitas Research Hospital (32), Spedali Civili Brescia Hospital (18), and Gavazzeni Hospital (4)- to explore their preferences across 3 domains: safety perception, treatment comfort, and trust, using a scale from 0 to 10.

Results: Median age of pts was 56 (range 50-63), 92.6% receiving SC, of which 80% for more than 3 months. Mean score for pts' trust in oncologists and in nurses was 9.63, and 9.59, respectively, who positively affected the choice to switch. The majority of pts strongly considered SC administration as quicker(79.6%), less invasive(61.1%), favouring reduction of time in hospital(74.1%). Half of the pts considered the two formulations as equally safe. The majority (81.5%) expressed a preference for SC over IV; these perceived SC as a safer and less invasive compared to who preferred IV. Pts reported similar rates of gastrointestinal side effects, while experiencing higher occurrences of local reactions such as pain at the administration site (48vs4%) and itching (36vs20%) with SC vs IV. Major obstacles identified by who favoured IV included fear of needles(10%), side effects(60%), and reduced efficacy(30%). The presence of CVC did not influence their preferences. Median age of HCPs was 35 (30-50), 49% oncologists and 51% nurses, with 40% using SC from at least 6 months. Training, provided to 16 out of 35, was deemed sufficiently useful (7[6-7]). Facilitators included evidence that SC is safe and effective (8[5.5-9.5]), and less invasive (9[7.5-10]), faster (10[9.5-10]) and easier (9[7.5-10]) than IV. Time reduction in clinic was highly rated (10[7-10]), influencing hospital planning (9[8-10]). No increase in adverse events was observed among HCPs. All HCPs familiar with prescribing SC declared to feel highly confident in its performance.

Conclusions: Both pts and HCPs prefer SC over IV, finding it faster, less invasive, and more convenient, despite higher local reaction rates. HCPs support SC for a reduction of clinic time and enhancement of hospital efficiency. The most frequent obstacles are needle phobia and concerns regarding potential adverse events. Further efforts are needed to guarantee pts' education specifically targeting these concerns.

E54

HER2+ METASTATIC BREAST CANCER: MANAGEMENT AND CLINICOPATHOLOGICAL FEATURES IN PATIENTS WITH BRAIN METASTASES

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Background: Central nervous system (CNS) is a metastatic site in HER2+ breast cancer (BC) in about 50% of cases. Despite the development of new targeted agents, survival rate remains poor. We investigated the clinical and pathological factors correlated to CNS development focusing on their management.

Methods: 171 HER2 positive metastatic (M) BC patients diagnosed between 2007 and 2022 at the Modena Cancer Center were selected and analyzed retrospectively. Descriptive statistical analyses were used to correlate disease characteristics and type/time of CNS recurrence. Time to treatment failure (TTF) and Overall Survival (OS) were estimated by log-rank test and Kaplan-Meier curves.

All analyses were performed using R version 4.3.2 (The R Foundation for Statistical Computing, 2023).

Results: The median age of patients was 54,6 years; 43.1% of them developed CNS metastasis during disease history. The absence of estrogen receptors was the only independent risk factor for CNS recurrence (p 0.003). Overall, 45% of cases had diagnosis of brain relapse due to clinical signs or symptoms. CNS recurrence was the early metastatic site in more than half of cases. The early onset, as well as the number of brain lesions, was negative independent prognostic factors for OS ($p < 0.05$). Indeed, 18% had de novo CNS metastasis, 37% developed brain disease during first line treatment while only 45% had late onset. Independently from the treatment line, local regional therapy was the first physician treatment choice: 27% received whole brain radiation therapy, 18% stereotactic radiation and only 9% underwent surgery. Patients with CNS disease had a statistically significant worse 1st line TTF and OS compared to patients without brain relapse (mTTF 14 months vs 24 months, p 0.048 and mOS 48 months vs 74 months, p p=0,0084, respectively).

Conclusions: Brain metastasis is an early metastatic site in 55% of HER2 positive patients, mainly in hormone negative disease. CNS relapse remains a negative prognostic factors in term of TTF and OS independently from other known clinical and pathological features. The investigation of brain-penetrable HER2-targeted therapies is still an urgent needed.

E55

DIAGNOSTIC PERFORMANCE OF [18F]FDG-PER/MRI IN BREAST CANCER

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Background: Breast cancer (BC) is the cancer with the highest incidence and mortality among women worldwide. Mammography, ultrasound, and contrast-enhanced breast magnetic resonance imaging (MRI) are the most important imaging modalities for locoregional evaluation in BC. [18F]FDG-PET/CT has been introduced for BC staging, distant-metastasis detection, prognostic prediction and evaluation of the pathological response to treatment. Therefore, hybrid [18F]FDG-PET/MRI exam, which allows to acquire both metabolic data and high-contrast morphological images in a single exam, may be useful in the management of these patients.

Materials and Methods: We enrolled 36 consecutive patients (pts) (mean age 55.5 years old; range 27-84) with BC, who underwent [18F]FDG-PET/MRI at our department from September 2022 to January 2024. The scans were performed with a hybrid PET/MRI tomograph permitting simultaneous acquisition of whole-body PET and 3T-MRI images. MRI-contrast-agent was injected. The examination was completed with a PET/MRI bed of the breast with the patient prone and dedicated MR-coils. [18F]FDG-PET/MRI was performed at different stages of the disease: staging, restaging post neoadjuvant chemotherapy, restaging in suspected recurrence (radiological/biochemical) and follow-up. A comparison between FDG enhancement findings and MRI contrast enhancement results was evaluated.

Results: Of the pts included (19 right BC, 16 left BC, 1 bilateral neoplasm), 13 were studied for staging, 12 for restaging after neoadjuvant chemotherapy, 8 for restaging in suspected recurrence (7 radiological and 1 biochemical) and 3 for follow-up. [18F]FDG-PET/MRI and contrast-agent-MRI were concordant in the majority of cases (30/36 pts). In 6/36 cases the results were discordant. A small skin lesion in 1/6 pt, axillary lymph nodes in 2/6 pts and multiple millimetric breast lesions in 2/6 pts, all suspicious for recurrence, were revealed by contrast-agent-MRI, without significant radiotracer uptake at [18F]FDG-PET/MRI. In 1/6 case hypermetabolic mediastinal lymph nodes, suspicious for localization of disease, were detected on [18F] FDG-PET/MRI images but not on contrast-enhanced MRI.

Conclusions: Our results highlight the diagnostic utility of performing a hybrid [18F]FDG-PET/MRI examination with a synchronous contrast-enhanced MRI in the management of pts with BC. Compared to PET/CT, radiation exposure is also significantly reduced.

E56

HER2-LOW/HRR PROFICIENT EARLY TRIPLE NEGATIVE BREAST CANCER IS CHARACTERIZED BY GOOD PROGNOSIS

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Background: HER2-low status fails to distinguish between early triple negative breast cancer (TNBC) with different prognoses. RAD51 test can identify homologous recombination repair (HRR)-deficient (HRD) tumors and may enhance prognostic value in this subset of patients.

Methods: We assessed HER2 status using IHC/FISH, detected functional HRD by observing RAD51 nuclear foci through immunofluorescence, and evaluated TILs content through H&E and IHC on diagnostic tumor biopsies of 86 histologically confirmed TNBC patients. Patients were admitted at 6 Italian Hospitals of the "Gruppo Oncologico Italiano di Ricerca Clinica" (GOIRC) and treated with neo-adjuvant chemo(immuno)therapy. Functional HRD was predefined as RAD51 score ≤10% (RAD51-low). HER2-low status was predefined as HER2 IHC score of 1+ or 2+ with negative FISH, and HER2-neg if they had a HER2 IHC score of 0. Tumors with TIL extent ≥30% were predefined as high-TILs.

Results: 14/34 (41%) of HER2-low patients presented HRR germline mutations: 9 g*BRCA1* (26%), 4 g*BRCA2* (29%), and 1 g*PALB2* (7%) mutations. 11/52 (21%) of HER2-neg patients presented HRR germline mutations: 9 g*BRCA1* (82%), 1 g*ATM* (2%) and 1 g*PALB2* (2%) mutations. 23/34 (68%) HER2-low tumors were HRD by RAD51; 21/52 (40%) of HER2-neg tumors were HRD by RAD51. pCR rates did not differ between HER2-low and HER2-neg TNBC but they were higher in HER2-low/HRR proficient (HRP) compared to HER2-neg/HRP tumors (**Table 1**). HER2-low samples presented a higher percentage of high-TILs tumors compared to HER2-neg; HRD status did not affect TILs extent (**Table 1**). HER2 status did not influence survival in our cohort (5y-DFS 89% vs 79%, respectively; p=0.2). However, patients with HER2-low/HRP tumors appeared to have a higher 5y-DFS than patients with HER2-neg/HRP tumors (100% vs 70%, respectively), although the difference was not statistically significant (p=0.07).

Conclusions: Combining HER2 and HRR status appeared to be useful in identifying a subgroup of TNBC with an excellent prognosis. Biomarker analyses on a larger cohort of patients are ongoing, and results will be available for the congress.

Table 1.

	pCR	no pCR	TIL-high	TIL-low
HER2-low	54.8	45.2	30.0	70
HER2-neg	59.1	40.9	15.9	84.1
HER2-low/HRD	58.8	41.2	40.0	60.0
HER2-neg/HRD	80.0	20.0	20.0	80.0
HER2-low/HRP	78.6	21.4	36.4	63.6
HER2-neg/HRP	41.7	58.3	16.7	83.3

E57

This abstract was withdrawn at the request of the Authors.

E58

MONITORING OVER TIME OF PATHOLOGICAL COMPLETE RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER PATIENTS THROUGH AN ENSEMBLE VISION TRANSFORMERS-BASED MODEL

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Background: Morphological and vascular peculiarities of breast cancer can change during neoadjuvant chemotherapy (NAC). Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) acquired pre- and mid-treatment quantitatively capture information about tumour heterogeneity as potential earlier indicators of pathological complete response (pCR) to NAC in breast cancer. This study aimed to develop an ensemble deep learning-based model, exploiting a Vision Transformer (ViT) architecture, which merges features automatically extracted from five segmented slices of both pre- and mid-treatment exams containing the maximum tumour area, to predict and monitor pCR to NAC.

Methods: Imaging data analysed in this study referred to a cohort of 86 breast cancer patients, randomly split into training and test cohorts at a ratio of 8:2, who underwent NAC and for which information regarding the pCR achievement was available (37.2% of patients achieved pCR). As far as we know, our research is the first proposal using ViTs on DCE-MRI exams to monitor pCR over time during NAC.

Results: The performances of the proposed model were assessed using standard evaluation metrics and promising results were achieved: AUC value of 91.4%, accuracy value of 82.4%, a specificity value of 80.0%, a sensitivity value of 85.7%, precision value of 75.0%, F-score value of 80.0%, G-mean value of 82.8%.

Conclusions: The heterogeneity changes in DCE-MRI at pre- and mid-treatment could affect the accuracy of pCR prediction to NAC. The study needs to be validated in a larger cohort.

E59

TIME ON TOXICITY (TOT) DURING ADJUVANT TREATMENT (ADJUT) WITH ABEMACICLIB (A) AND ENDOCRINE THERAPY (ET) IN HORMONE RECEPTOR POSITIVE/HER 2 NEGATIVE (HR+HER2-) HIGH RISK EARLY BREAST CANCER (EBC)

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Background: The pattern of AdjuT in high-risk HR+HER 2- EBC subjects is changing rapidly, A plus ET represents a treatment option. Safety and treatment compliance are important issues in helping patients (pts) complete the AdjuT program. Less is known about the time spent coordinating care and frequent visits to a healthcare facility during AdjuT. The amount of time spent in the hospital performing procedures necessary to manage AdjuT is difficult to collect, summarize, and rarely reported in clinical studies. ToT is defined as time spent on laboratory tests, clinic visits, imaging, and treatment-related toxicity, with additional time spent traveling and waiting. We conduct an analysis of patients receiving A+ET at our institution to evaluate the applicability of the ToT concept to the adjuvant setting.

Methods: ToT was calculated extracting the time spent in days in: blood draws, picking up medication, clinic visits/waiting rooms, emergency department visits, hospitalizations and on activities such as travel and coordinating care. 26 bloods drawn and 24 outpatient visits, for a total of 50 days spent in medical procedure, has been considered as the standard planned outpatient access in 24 months of treatment for this analysis.

Results: Data from 64 pts treated in our institution were collected. Characteristic: T3-T4 16 (25%); N2 29 (45,31%); G3 7 (10,94%), Ki67 >20% 34 (53,12%). At median 47 months follow up (1-171), adverse events of any grade were observed in 57 (89,06%). At the time of the analysis, across different treatment times, pts required an average of 17 blood tests and 16 outpatient visits. Thirteen (20,31 %) pts have completed 24 months of treatment, an average of 35 bloods drawn and 30 outpatient visits were required. Estimating two years of treatment (420 weekdays) our pts spent 65 weekdays (15,47%) in ToT. If compared to the standard planned outpatient access, there was an 11.53% increase in time spent in medical procedures.

Conclusions: ToT is a measure of indirect toxicity in metastatic setting and no reports are existing in the adjuvant scenario. With elongation of the adjuvant therapies now available, the EBC's pts faced 2 to 3 years oral therapy. Introducing ToT could give a measure of correlation of the impact of adjuvant care on pts quality of life (QoL). In the prospective ROYAL (Real wOrld studY in the Adjuvant setting for high risk earLy breast cancer patients) study we will evaluate the correlation between ToT and QoL.

E60

INTEGRATING MICROBIOTA DIVERSITY INDEX INTO THERAPY RESPONSE PREDICTION SCORE: A COMPUTATIONAL ANALYSIS OF TUMORAL LESION DYNAMICS IN HER2-POSITIVE BREAST CANCER

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Background: Gut microbiota significantly influences the efficacy of trastuzumab by modulating the antitumor immune response HER2-positive breast cancer (HER2+ BC). Therefore, we aim to develop a predictive model with gut microbiota composition as an early biomarker for

treatment outcome using the neoadjuvant model for HER2+ BC.

Methods: Fifteen HER2+ BC patients treated with standard neoadjuvant chemotherapy based-strategy combined with trastuzumab (EC>TH), were used for this analysis. Intestinal microbiota composition was assessed in stool samples collected before the initiation treatments by 16S rRNA gene profiling using the Illumina MiSeq platform. Alpha diversity of the microbiota was calculated using the Simpson index.

Results: Among the 6 main examined gut microbial phyla, the abundance of Firmicutes and Bacteroidetes was significantly associated with pathological complete response. Specifically, Firmicutes abundance was positively associated (p=0.0458), while Bacteroidetes abundance was negatively associated (p=0.0329) with pCR. A computational model of tumor lesion evolution and dynamics, solving reactive-diffusive Partial Differential Equations for tumor cell density and drug concentration in each BC volume was developed using data from the first 8 patients, allowing the creation of their oncological twins. Tumor dynamics were predicted by considering pharmacodynamics and drug efficiency during the epirubicin/cyclophosphamide phase of therapy, denoted as 1, incorporating the BC proliferative index. In the paclitaxel/trastuzumab phase, the model included microbiota composition, utilizing the alpha diversity index (a) and the Firmicutes/Bacteroidetes abundance ratio, which demonstrated the highest Pearson correlation coefficients (0.64 and 0.79, respectively). The model was subsequently validated on the remaining 7 patients. Predicted tumor dimensions at surgery did not significantly differ from those determined by pathologists, defining a fair performance of the model.

Conclusions: Our model effectively provides an upfront prediction of the efficacy of neoadjuvant trastuzumab-based therapy. Validation in independent cohorts is needed to confirm its accuracy and tailor escalated therapeutic strategies for HER2+ BC patients. Additionally, this model could be used in the future to personalize nutritional therapy aiming the Firmicutes/Bacteroidetes ratio, thereby enhancing trastuzumab's antitumor activity.

E61

ERIBULIN-MESYLATE IN PRETREATED HER2-LOW METASTATIC BREAST CANCER (MBC): A REAL-WORLD EXPERIENCE IN THE THE PRE-TRASTUZUMAB DERUXTECAN (T-DXD) ERA

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Background: HER2-low breast cancer (BC), defined by an immunohistochemistry (IHC) score of 1+ or 2+ without HER2 gene amplification as measured by fluorescence in situ hybridization (FISH), represents approximately half of patients (pts) with BC overall. HER2-low BC may respond differently to treatment than HER2-0 BC. Eribulin mesylate showed improved outcomes versus other chemotherapy options in pts with HER2-low or HER2-0 MBC, according to a post hoc analysis of two randomized trials. The present retrospective cohort study aimed to evaluate the activity and safety of eribulin in HER2-low MBC before the advent of T-DXd in a real-world context.

Patients and Methods: We evaluated pre-and postmenopausal women with HER2-low MBC treated with eribulin at our Institution from January 2019 to March 2024. HER2-expression was determined by IHC+/- FISH assay. Primary objective was median progression-free survival (PFS). Secondary aims: objective response rate (ORR), clinical benefit rate (CBR), adverse events (AEs), analysis of potential predictive factors of disease outcome. Median PFS was calculated using the Kaplan-Meier method; hazard ratios were estimated by a stratified Cox model.

Results: Seventy-two pts were evaluable for the final analysis: median age 62 years (range 29-82), ECOG PS of 0-1 in 65 pts and 2 in 7 pts. Twenty-four pts had received eribulin as 3rd-line treatment, 25 as 4th-line, 23 as ≥5th line; previous treatment for metastatic disease consisted of taxane-based regimens in 88% of pts, 65% had received CDK 4/6 inhibitors plus endocrine therapy; visceral disease was present in 73.6% of pts (53/72). In the whole population mPFS was 6.4 months (range 2.9-21.2 months) with no significant difference between the HER2 1+ and HER2 2+ score cohort (6.8 and 5.7 months, respectively). ORR was 16.6% (12/72 partial responses), reaching 37.5% (9/24) in the 3rd line group. CBR was 75% (54/72). The most common grade 3–4 AEs were neutropenia (21%), leukocytopenia (12%) and asthenia/fatigue (9%).

Conclusions: With the limitations of a mono-institutional retrospective analysis, this real-world experience adds information on eribulin-related clinical outcomes among HER2-low MBC pts before the advent of T-DXd in clinical practice.

E62

TREATMENTS OF INTEREST IN MALE BREAST CANCER: AN UMBRELLA REVIEW

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Background: Male breast cancer is a rare disease and, due to its rarity and the lack of specific protocol for its management, therapeutic schemes are extrapolated from female breast cancer. In an attemp to optimize male breast cancer treatment, we conceived an umbrella review suppling an evidence-based summary of systematic reviews published about this topic in the last twenty years.

Material and Methods: This umbrella review was performed according to a predefined protocol. We realized a literature search of PubMed and Cochrane Library databases and we considered systematic reviews published from 2004 to 2024 (last update was 13th May 2024). We realized the quality assessment and the description of main findings of eligible articles.

Results: Five systematic reviews were included and main findings were achieved. Breast-conserving surgery is a reasonable treatment approach in selected male breast cancer cases; this surgical procedure results substantially equivalent in survival oucomes and oncologic safety compared to mastectomy, if not better. Sentinel lymph node biopsy represents a successful practice with similar accuracy respect to women cases. Adjuvant radiotherapy improves the disease local control and overall survival in male breast cancer patients; it has to be considered following partial mastectomy and also after radical mastectomy, in case of involved nodes. The use of tamoxifen is associated with an improvement of survival outcomes and aromatase inhibitor and gonadotrophin-releasing hormone should be used only in case of contraindications to tamoxifen.

Conclusions: Further research and improved guidelines for male breast cancer treament should consider these evidence-based data.

E63

LONGITUDINAL ANALYSIS OF RED BLOOD CELLS IN PATIENTS WITH HR-POSITIVE, HER2-NEGATIVE BREAST CARCINOMA UNDERGOING TREATMENT WITH CDK4/6 INHIBITORS PLUS HORMONE THERAPY: A SINGLE-CENTER EXPERIENCE

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Background: Hematological toxicity is a common adverse event in patients with breast carcinoma undergoing treatment with CDK4/6 inhibitors (CDK4/6i). We investigated anemia and the trend of hemoglobin (HGB), mean corpuscular volume (MCV) and red blood cell count (RBC) in patients with HR-pos and HER2-negative breast carcinoma treated with CDK4/6i plus hormone therapy (HT) in early and metastatic settings.

Material and Methods: This retrospective longitudinal cohort study collected data from 41 patients with HR-pos HER2-negative breast carcinoma treated with CDK4/6i and HT at the Medical Oncology Unit of the University of Cagliari. A descriptive statistical analysis was performed with the Spearman test, Kruskal Wallis test whereas survival data were derived from Kaplan Meier curves and Cox regression analysis. Progression free survival (PFS) data included only patients treated for the metastatic disease.

Results: Among the patients included in the study, 34 were undergoing treatment for the metastatic disease, 7 were receiving adjuvant therapy; 10 patients were on therapy with palbociclib, 21 with ribociclib and 6 with abemaciclib (4 in the early and 2 in the metastatic setting); 2 patients were initially treated with ribociclib and then switched to palbociclib, 1 patients was treated with abemaciclib followed by palbociclib, and 1 patient was treated with palbociclib followed by abemaciclib due to toxicity. We monitored the levels of HGB, MCV end RBC at baseline (T0), 3 months (T3), 6 months (T6), 12 months (T12), 24 months (T24) and 36 months (T36). We can state that in patients treated with abemaciclib and palbociclib an anticorrelation between RBC and MCV was observed from T6. A decrease in average HGB and RBC was detected in patients from T3. Conversely, an increase in average MCV is observed from T3 and reaches its peak at T24. In patients treated in the metastatic setting, Kaplan Meier curves showed a significantly better PFS in the group with a small difference between MCV at T12 and T0 versus the group with a large difference between MCV at T12 and T0 ($p=0.037$). The same trend was seen with the difference between HGB measurements at T12 and T0 ($p=0.068$). The Cox regression analysis confirmed this result (HGB: P (P-adjusted) = 0.012 (0.08); MCV: 0.051 (0.09)).

Conclusions: Our study shows that overtime changes of the red blood cell lineage, correlated with CDK4/6i treatment, might help identifying those breast cancer patients who derive longer benefit.

E64

ERIBULIN IN THE TREATMENT OF "VULNERABLE" OLDER PATIENTS WITH METASTATIC BREAST CANCER

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Background: Breast cancer is also a disease of aging. In Older patients, multi-drug chemotherapy can be burdened by toxicity; a single-agent approach is the most appropriate treatment to preserve quality of life and reduce the risk of toxicity. To define the most appropriate therapeutic pathway, a multidimensional geriatric assessment is necessary. This assessment identifies FIT elderly patients who could undergo treatments used for younger patients and FRAGILE patients who should be excluded from treatment. However, there is a group of patients defined as VULNERABLE for whom there is limited data available for guidance.

Methods: We conducted a prospective multicenter observational study aimed at collecting data on vulnerable patients treated with ERIBULIN. Patients were evaluated at baseline and every three months until the end of treatment using tools provided by G-Code. Vulnerable patients were studied with questionnaires such as G8, SPPB, and Mini-Cog. Toxicity was assessed based on NCI-CTC criteria version 4.

Results: Twenty-one patients were enrolled, of which 13 were considered vulnerable. The average age of the pts was 76.6 years (range 70-82). Eribulin was administered at a dose of 1.23 mg/m² on days 1,8 of a 21-day cycle. 70% of pts (9) received the full dose; 30% of pt (4) received a 25% reduced dose. Currently, 5 pts are still undergoing treatment. The total number of cycles conducted by all pts in the study is 154, with an average of 12 cycles per pt; a single pt underwent 36 cycles. Pts who left the study: 6 pts due to disease progression (PD); 1 pt (15%) due to Grade 3 toxicity; 1 pt (15%) died (unrelated to treatment); 2 pts due to pulmonary PD; 3 pts had SD. QoL worsened for 2 pts (pain), remained stable for 11 pts. Functional status deteriorated for 2 pts, improved for 5 pts (anxiety and depression), and remained the same as at baseline for the remaining 6 patients. The maximum grade of toxicity (Grade 3) was recorded in only 2 patients (mucositis and leukopenia). Other observed toxicities included: Grade 2 asthenia in 6 patients, Grade 2 hepatic toxicity in 3 patients, and Grade 2 thrombocytopenia in 2 patients.

Conclusions: Preliminary data from the study suggest the possibility of treating vulnerable patients with chemotherapy. In particular, it allows for the definition of a dedicated therapeutic pathway through the assessment of potential iatrogenic functional decline. The final results of the study may or may not confirm the current findings.

E65

ADJUVANT ABEMACICLIB AND BONE HEALTH IN EBC PATIENTS: ANALYSIS OF TOXICITY AND IMPACT ON TREATMENT ADHERENCE

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Background: Abemaciclib, with endocrine therapy (ET), is the first CDK4/6 inhibitor to demonstrate an improvement in invasive disease-free survival (IDFS) compared to ET alone in Adjuvant treatment of HR+/HER2- high risk early breast cancer (EBC).

Cancer Treatment-Induced Bone Loss (CTIBL) carries a higher risk of fracture compared to the general population.

ET is one of the treatments recognized as having the most significant impact on bone health.

Treatments used for the prevention and treatment of CTIBL are bisphosphonates (BPs) and Denosumab 60 mg every six months. The most relevant adverse events (AEs) with anti-bone-resorptive drugs affects oral health, even if less frequently compared with drugs used in metastatic setting.

Material and Methods: We retrospectively collected clinical and pathological data of 66 EBC patients HR+/HER2- diagnosed between 2017 and 2023, who are undergoing or have undergone adjuvant therapy with Abemaciclib associated with ET at Modena Cancer Center.

Twenty-seven patients were evaluated at a dedicated clinic setting with assessment of bone turnover markers, baseline Dual-energy X-ray absorptiometry (DeXA), familial and personal anamnesis regarding fracture risk, with focus on dental health history.

	Total
Median age	55 (29 - 78)
Menopausal status	
Pre	25
Post	39
Men	2
(Neo)Adjuvant Chemiotherapy	63
Stage	
IIA	1
IIB	10
IIIA	35
IIIB	3
IIIC	17
CTIBL treatment	26
BPs	3
Denosumab	23 (11 induced menopause)
ET	
AIs/Tam + LhRha	25
Tam	2
AIs	39

Results: Thirteen patients completed the 2-year treatment with Abemaciclib regularly, while another 9 discontinued treatment due to Grade 3/4 AEs, mainly diarrhea, intolerance or disease progression.

The combination treatment of Denosumab and Abemaciclib didn't lead to any additional AEs, there were no cases of osteonecrosis of the jaw (ONJ) and no increased rate of treatment discontinuation compared to only Abemaciclib treatment.

Conclusions: Our data are purely observational, derived from a small sample, and retrospective analysis with most participants not having completed the potential 2-year adjuvant therapy with Abemaciclib.

Currently, there is a lack of literature data on the impact of Abemaciclib associated with ET on bone health or toxicity data for the use of Abemaciclib in association with anti-bone-resorptive drugs.

Our goal is to further investigate by comparing those who take ET, Abemaciclib and Denosumab with those who only take ET and Denosumab or ET and Abemaciclib, to evaluate their impact on bone health and any additional AEs.

E66

DIAGNOSTIC SAMPLES HETEROGENEITY AS A SOURCE OF RELEVANT METHODOLOGICAL ISSUES IN THE CONDUCT OF CLINICAL STUDIES OF HER2+METASTATIC BREAST CANCER: EVIDENCE FROM THE STEP TRIAL

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Background: Methodological issues may strongly impact results from both observational and interventional trials. We herein describe the experience related to the conduct of the study "Sequence of Treatment in HER2+, Pertuzumab pre-treated patients" (STEP), supported by the Italian Ministry of Health and coordinated by the IRCCS-Regina Elena National Cancer Institute (IRE) (GR-2018-12367431).

Methods: The STEP study is a multicentric, observational study coordinated by the IRE. The study protocol was approved by the Institutional Review Board of the coordinating and satellite centers (Register code: 1809/22). Both preclinical and clinical tasks are foreseen. We envisioned both a prospective (N=50) and a retrospective (N=50) patients' cohort. The retrospective cohort will provide data in support of the role of selective clonal pressure on treatment outcomes along with pre-clinical data on key actors involved in mechanistic processes regulating HER2+ metastatic breast cancer, e.g., DARPP-32/t-DARPP. The prospective cohort will generate real word evidence on the effectiveness/tolerability of the most innovative anti-HER2 agents and investigate the predictive/prognostic role of circulating biomarkers. Within such a frame, methodologic issues concerning the source of tissue samples requested for any patient from the retrospective cohort soon emerged. On this basis, data analyses will be stratified and/or adjusted by the categorical variable named "Type of Diagnostic Sample" which will include 2 modalities, i.e., incisional biopsy and surgical specimen. Further

analyses will include stratification and/or adjustment by bioptic site (breast vs other than breast) and availability of the sample at the coordinating center.

Results: We hereto collected data from 32 pts. Six out of 33 samples come from centers other than the IRE and are not readily available for the analyses. Two of 27 precede the start of the anti-HER2 therapy of more than 1 year. Thirteen of 27 come from a surgical specimen, 13 of 27 from a biopsy, and the origin of 1 sample was unknown. Thirteen of 27 samples come from the primary tumor, 14 from metastases.

Conclusions: We expect to observe significant differences in our study outcomes upon data analysis stratification/ adjustmment by the previously cited variables.

E67

PREDICTIVE FACTORS OF COMPLETE PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMO-IMMUNOTHERAPY TREATMENT IN PATIENTS WITH EARLY TRIPLE NEGATIVE BREAST CANCER

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Background: The use of Pembrolizumab with standard chemotherapy in the neoadjuvant treatment of early Triple Negative Breast Cancer (eTNBC) increases the rate of pathological complete responses (pCR). This retrospective study aims to identify the predictive factors of pCR in patients treated with this regimen.

Material and Methods: Patients with eTNBC treated with neoadjuvant chemo-immunotherapy were enrolled. For each patient, clinical and pre-treatment biopsy data were collected including menopausal status, body mass index, previous pregnancies, BRCA mutations, lymph node involvement, preoperative stage, diagnosis of multicentric tumours, histological type, HER2 expression, number of mitoses per 2.37 mm^2 area of the sample, Ki-67 index and tumor-infiltrating lymphocytes. Predictive factors of pCR were identified through univariate and multivariate logistic regression analyses. ROC curves were used to determine the cutoff points that best discriminate pCR for continuous variables.

Results: Forty-four patients (median age: 53, range 29-77 years) were treated and 26 of them achieving a pCR (59%). In univariate analysis, predictive factors were: presence of invasive ductal carcinoma vs. non-ductal carcinoma histology (p=0.0074; OR 0.08; 95% CI 0.0086-0.7411), Ki-67>40% (p=0.0001; OR 0.024; 95% CI 0.002-0.247), number of mitoses > 15 (p=0.0082; OR 12.0; 95% CI 1.5809-91.0874), and absence of multicentric tumours (p<0.0001; OR 0.0321; 95% CI 0.0054-0.1888). Moreover, we observed that the probability of achieving a pCR increased as the percentage of HER2 expression on the cell membrane approached 0% (range: 0-60%), obtaining 75% of pCR in patients with a percentage equal to 0% vs. 25% in those with over 1% (p=0.0074; OR 0.11; 95% CI 0.0197-0.6258), independently of the membrane staining intensity and HER2 immunohistochemical (IHC) score that wasn't significant. Additionally, this marker was the only predictive factor for pCR that was statistically significant in multivariate analyses (p=0.0270).

Conclusions: Althought immunotherapy increased the pCR rate, the identified predictive factors are those traditionally associated with chemotherapy response, such as non-special type histology, high Ki-67 index, high number of mitoses and presence of a single nodule. Innovatively, a higher rate of pCR was observed in patients with a low percentage of HER2 membrane expression, regardless of the IHC score. However, a larger sample size is needed to confirm these results.

E68

PATHOLOGICAL COMPLETE RESPONSE AND TOXICITY PROFILE WITH NEOADJUVANT IMMUNE-CHEMOTHERAPY FOR TRIPLE NEGATIVE BREAST CANCER: A SINGLE INSTITUTION EXPERIENCE

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Background: Pembrolizumab (P) with chemotherapy (CT) is the standard of care for Stage II and III Triple Negative Breast Cancer (TNBC) in neoadjuvant-adjuvant setting, with pathological complete response (pCR) rate of

64.8% and a discontinuation rate for Adverse Event (AE) of 27.7%, as shown in KN-522 phase III trial. We describe pCR and safety data of early TNBC patients (pts) treated with KN-522 regimen.

Material and Methods: we collected data on pts treated in years 2022-2023.Pts were regularly monitored along treatment plane and during follow-up period for outcome and safety data.

Results: we treated 19 pts and 17 are evaluable for response. Median age was 47, 74% pts had clinical stage II and 26% clinical stage III. Initial nodal status was cN0 58%, cN1 16% and cN2 26%. After neoadjuvant phase, 70% pts had conservative breast cancer surgery and 70% received sentinel node excision. pCR rate was 76%. Residual Cancer Burden (RCB) disposition was: RCB 0 76%, RCB I 6%, RCB II 18%, RCB III 0%. Treatment discontinuation rate was 31% (6 pts). Interruption due to immune-related Adverse Event (irAE) occurred in 4 pts, whereas 1 death occurred and 1 pts experienced severe, not immune-related cardiotoxicity. No pts discontinued treatment for disease progression. Treatment discontinuations mostly occurred in the neoadjuvant phase: 3 pts definitively stopped P carrying on CT while 3 pts completely interrupted neoadjuvant treatment, with anticipation of breast surgery in 2 pts. Only 2 pts of the 4 pts who stopped P in neoadjuvant phase, achieved pCR. Median number of P infusions was 11.Overall irAE were: hypotiroidism (6 pts), transaminitis (6 pts), diabetes (1 pts), pangastritis (1 pts), adrenal insufficiency (1 pts) with hospitalization needed in 3 pts. Median time to hypotiroidism onset was 18,5 weeks and 5 weeks for liver toxicities.

Conclusions: our experience confirms that KN-522 regimen has significant implications in terms of outcome and safety. High pCR rates strengthen the possibility of healing from an aggressive disease but treatment value is called into question by serious AEs that can compromise it. We experienced a significant discontinuation rate due to severe AEs that in some cases led to anticipate surgery. Careful pts monitoring during KN-522 regimen and a prompt management of irAE are crucial, to treat our pts safely with a potentially curative treatment.

E69

ACTIVITY AND SAFETY OF NEOADJUVANT TRIPLE-NEGATIVE BREAST CANCER (TNBC) PEMBROLIZUMAB (P) PLUS CHEMOTHERAPY TREATMENT: A SINGLE CENTER BREAST UNIT EXPERIENCE

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Background: Keynote 522 trial showed a rate of pathological complete response (pCR) higher than the standard among stage II/III TNBC pts who received P plus neoadjuvant chemotherapy (NCHT). Here we report our single center experience.

Patients and Methods: we consecutively treated from 3/2022 18 stage II/III TNBC pts, suitable for KN522 inclusion criteria. Median age was 59,5 years (range 34 – 80). 7/18 pts were stage II (39%), 11/18 pts stage III (61%). 12\18 were N+. 2/18 were PS=2, 16/18 PS=0. All pts received NGS multigene germline panel and 2/18 pts were identified as BRCA1 and BRCA1/PALB2 pathogenic mutation carriers respectively. Our endpoints are pCR and safety.

Results: 13/18 pts underwent breast surgery (5/18 still on treatment); 6/13 had stage III at diagnosis (46%). None local progression was recorded. According to KN522 criteria 46% (IC 95% ± 25%) had pCR (Table 1). BRCA1m carriers reported 100% ypT0N0. 2/13 had cT4N3 stage at diagnosis and reported 100% ypT0N0. 4/13 pts did not start AC-P phase; of these 3/4 did not reached pCR. In 12/13 pts adjuvant P is ongoing except 1 pt who needed too long time to recover. As for treatment-related adverse events (AEs): no G5 AEs were recorded. 6/18 stopped NCHT: of these, 2 during AC-P courses due to fatigue G3, nausea G1 and 1 pt had neutropenia G4 despite PEG-filgrastim prophylaxis; 4 pts did not start AC-P phase due to arrhythmia G2, fatigue G3, pulmonary thromboembolism G4, thrombocytopenia G4 respectively. 5/18 had thyroid disorders as immunorelated-AEs (irAEs), divided into 2 hypo- and 3 hyper-thyroidism. No other irAEs were reported.

Table 1.

	KN522	Our Experience
Pathological stage ypT0/Tis ypN0	64.8%	46%
Pathological stage ypT0 ypN0	59.9%	46%
Pathological stage ypT0/Tis	68.6%	46%

Conclusions: Our rate of pCR is lower than KN522, probabily due to small sample size, higher rate of stage III pts with extensive nodal involvement and almost 30% of pts lacking AC-P phase. No new safety signals were reported.

F - Prevention, Screening and Follow-up

F01*

SURVIVORSHIP CARE PLANS AND RECURRENCE DETECTION IN BREAST CANCER PATIENTS

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Background: Care for people diagnosed with breast cancer (BC) does not end when active treatment has finished, but continues to detection early recurrences and manage side effects. No randomized data exist to support any individual follow-up (FU) protocol. We retrospectively review the Modena Cancer Center survivorship program and its correlation to survival outcomes.

Material (patients) and Methods: A retrospective review of all BC FU visits performed between 2016 and 2023 was done. Descriptive statistical analyses were used to correlate disease characteristics, type of recurrence and mode of relapse with Overall Survival (OS), estimated by log-rank test and Kaplan-Meier curves. All analyses were performed using R version 4.3.2 (The R Foundation for Statistical Computing, 2023).

Results: From June 2016 to June 2023, 20.650 FU visits were done, detecting 256 relapses (1,2%): 173 distant relapses (67.6%) and 83 loco-regional ones (32.4%). As expected, patients relapsed during FU period has worse OS compared to those relapsed at the end of the FU program (mOS: 5.6 years vs 8.9 years, respectively; p = 0,001). In particular, tumor markers and/or imaging tests (except for annual mammography), performed routinely, did not improve OS in BC patients (p 0.446 and p 0.792, respectively). Even the frequency of in-person visits (4 vs 6 months) did not improve OS, independently of BC subtypes and clinical stage at diagnosis (p 0.219). Overall, relapse detection due to clinical signs/symptoms, PS ECOG 1-3 and metastatic visceral sites were negative independently prognosticators for survival in multivariate analysis.

Conclusions: BC FU visits rarely detected recurrence. An intensive survivorship care plan with tumor markers and/or routinely imaging tests did not improve OS. Considering the progressive increasing of BC survivors, the survivorship care program should be redefine. Due to the retrospective and mono-institutional nature of this study, data from prospective clinical trials are needed.

F02

VACCINE HESITANCY IN PATIENTS WITH SOLID TUMORS: A CROSS-SECTIONAL SINGLE-CENTER SURVEY (VEY)

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Background: People with cancer have a higher risk of vaccine-preventable diseases (VPDs) which may cause severe complications due to immune system impairment, malnutrition, and oncological treatments. Despite this evidence, vaccination rates are still suboptimal.

Material and Methods: We conducted a cross-sectional survey to investigate vaccine acceptance among cancer patients and understand the factors shaping their choices, thereby aiding physicians in better supporting their patients' vaccination decisions. The primary endpoint was to assess the proportion of vaccinated subjects. Secondary endpoints were the assessment of the proportion of vaccinated subjects with the anti flu, anti SARS-CoV-2, anti pneumococcal and anti HZ vaccine, and to determine which variables are associated with not willingness to receive vaccines.

Results: Between 12 February and 01 March 2024, a total of three hundred and seventeen patients with cancer were invited to respond to the survey, 309 of whom (97%) agreed to do it. Two hundred seventy-three patients (88.34%, 95%confidence interval [CI].84 –.91) had received at least one vaccination. Two hundred thirty-one patients (74.76%) reported that at their first oncology visit their oncologist recommended vaccinations, primarily anti-flu (92.21%) and anti-SARS-CoV-2 (83.55%) vaccinations, while less frequently the anti-pneumococcal (42.42%) and anti-HZ (37%) vaccines were recommended. In respondents who did not support the anti-SARS-CoV-2 vaccine, 37.5%(n=48) did not want to receive the vaccine for the fear of adverse events. The two main reasons for vaccine hesitancy were the lack of recommendation by the oncologist (55.41%,n=128) and the lack of awareness of the importance of vaccination in the context of oncological care (49.35%,n=114). On the analysis of the potential correlate of vaccine willingness, age

over 75 years (p=0.041), marital status (p=0.003), and the oncologist's vaccine recommendation during the first visit (p<0.001) were significantly associated with vaccine acceptance. Sex is associated with vaccine acceptance only for the anti-SARS-CoV-2 vaccine (p=0.006).

Conclusions: Vaccine acceptance or hesitancy in cancer patients is substantially influenced by their relationship with their oncologist. Oncologists can motivate patients to receive the correct vaccine schedule by addressing doubts and concerns about the potential negative impact of the vaccine on cancer and cancer therapies.

F03

BRIDGING THE GAP: PREVENTION STRATEGY IN THE SOUTHERN OF ITALY A STEP TOWARDS EQUITY

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Background: The regionalization of the Italian health system has engendered differences among regions. New LEA indicators depict differentiated scenarios among areas.

Apulia, a region in recovery plan, has a minimum acceptable level of LEA, but regionalization has generated a North-South divide.

Screening programs have been affected by Covid. Efforts have been made since 2020 to resume the three screenings: breast, colo-rectum, cervix.

Methods: We analyzed delta improvement for each screening in South-Apulia from 2021 to 2023 and actions taken to achieve it. The delta value was calculated through the software Dedalus. Data were collected aggregatedly, on patients of screening points (SP) in northern area (NA) and southern area (SA) of the Lecce cancer hub. We aim to nalyze the difference in improvement between NA and SA, if any.

Results: The outcome is described in table

	2021		2022		2023		Actions (2021-2023)	Average improvement 2021-2023	
	Extension (E) Δ	Adherence (A) Δ	E Δ	A Δ	E Δ	A Δ	Local action (LA) Central action (CA)	E Δ	A Δ
Breast screening (BS) in NA (5 SP). Target: women (W) 50-69 yrs	14.666 (+41%)	12.035 (+64.8%)	16.322 (+11.2%)	12.289 (+2.1%)	26865 (+64%)	14336 (+16.6%)	• training for operators (la) open day (la) mobile exam station (la-ca) regional health app (ca) periodic monitoring with regional coordination (ca) regional training events for technicians (ca)	+38.7%	+27.8%
BS in SA (5 SP). Target: W 50-69 yrs	11698 (+36.3%)	9034 (+56%)	12.219 (+4.4%)	8878 (-1.8%)	17750 (+45.2%)	9407 (+5.9%)		+28.6%	+20.0%
Colorectal screening (CRS) NA. Target: W/M 50-69 yrs	-	-	21419 (-)	5479 (-)	50319 (+134.3%)	12929 (+136.0%)	All the above	-	-
CRS-SA. Target: W/M 50-69 yrs	-	-	14957 (-)	3502 (-)	34422 (+130.1%)	8583 (+145.1%)		-	-
Cervix (CXS) screening NA (14SP) Target: W 25-64 yrs	11.439 (-21.9%)	7559 (-40.8%)	19.426 (+69.8%)	11687 (+54.6%)	44237 (+127.7%)	17.270 (+47.7%)	All the above and PAP test plus HPV	+58.5%	+20.5%
CXS- SA (15 SP) Target: W 25-64 yrs	10.650 (-9,9%)	6.091 (+18.2%)	18.245 (+71.3%)	8.446 (+38.6%)	38.942 (+113.34%)	11.902 (+40.9%)		+64.8%	+32.6%

Conclusions: Data show an increase for all three screenings, particularly cervix and colorectal, though data for the latter are not available for the whole period.No significant difference between the NA and SA arises; results prove the effectiveness of actions, when planned both at local and at central level, and are encouraging for the reduction of the North-South regional gap in matter of prevention.

F04

VACCINATION OF CANCER PATIENTS IN THE VENETO REGION: RESULTS FROM A SURVEY CONDUCTED AMONG MEDICAL ONCOLOGISTS IN VENETO

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Background: Cancer patients are at increased risk of infections, and vaccinations serve as an essential tool to prevent infections or mitigate their severity. We conducted a survey among medical oncologists who are members of AIOM (Italian Association of Medical Oncology) in the Veneto region, aiming to assess their awareness of this topic and verify the presence of organized pathways for vaccinating cancer patients.

Material and Methods: All AIOM members in the Veneto region were invited to complete a survey using an electronic form.

Results: Out of 182 oncologists invited, 32 responded (17.6%). Among the respondents, 18% always recommend vaccinations, while 72% recommend them under specific circumstances, and 10% do not recommend them. Among oncologists recommending vaccinations, the most commonly recommended vaccines are the seasonal influenza and COVID-19 vaccines (each recommended by 72%), followed by the zoster recombinant vaccine (recommended by 58%), pneumococcal vaccine (recommended by 20%), and meningococcal and Hemophilus influenzae vaccines (each recommended by 10%). Vaccinations are most frequently recommended for patients undergoing chemotherapy (100% of respondents), less frequently for patients receiving immunotherapy (62% of respondents), targeted therapy (48%), and hormonal therapy (14%). Most respondents (80%) report that vaccinations are administered in the vaccination clinic of the health district, approximately 10% in the hospital in a vaccination clinic not dedicated to cancer patients, 3% in the hospital in a vaccination clinic dedicated to fragile subjects, and 3% in the oncology service. Only 15% of respondents report the presence of an organized pathway for vaccinating cancer patients in their health district. However, 93% believe that implementing a structured pathway would standardize processes and improve patient adherence, thereby reducing their infectious risk.

Conclusions: The low adherence to the survey - consistent with national AIOM survey results (Lasagna A et al, Tumori 2024) - may indicate that awareness levels regarding vaccinations in cancer patients are still low among oncologists in the Veneto region, suggesting that awareness campaigns and/or educational activities on vaccinations in cancer patients could be useful. Additionally, the survey results underscore the necessity to organize and implement structured pathways to promote vaccination among cancer patients in the Veneto region.

F05

B- AND T- CELL-MEDIATED RESPONSE INDUCED BY THE ADJUVANTED GLYCOPROTEIN E (GE)-BASED RECOMBINANT VACCINE AGAINST HERPES ZOSTER (RZV) IN CANCER PATIENTS DURING IMMUNOTHERAPY: A ONE YEAR FOLLOW-UP STUDY

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Background: "Real-life" data on the adjuvanted glycoprotein E (gE)-based Recombinant Zoster Vaccine (RZV) in cancer patients during immune checkpoint inhibitors (ICIs) revealed a high immunogenicity of the vaccine 28 days after the second dose. The durability of immunogenicity of RZV in cancer patients remains to be elucidated.

Patients and Methods: Thirty-seven patients (median age 71 years, 73% males) were enrolled in the study. Sera and peripheral blood mononuclear cells (PBMCs) were collected at the time of vaccination (T0), 4 weeks (T2), 6 (T3), and 12 months (T4) after completing the RZV vaccination schedule. We were able to collect blood samples after 12 months post-vaccination in 32 (86,5%) subjects. T-cell response was evaluated by IFN-gamma ELISpot assay performed against gE and IE63 peptide pools. VZV-specific IgG antibodies were quantified at each time point.

Results: The current analyses refer to the 32 patients (10 females/22 males; median age 71 years) still on immunotherapy at the time of the follow-up. Only one patient showed an asymptomatic Herpes Zoster episode. The quantification of the VZV-antibodies revealed that all the patients except one were seropositive before vaccination 1 of 37 participants had detectable VZV-IgG antibodies at

baseline. A significant increase in VZV IgG titer was observed at each time point in comparison with T0. On the other hand, peak gE specific T-cell frequency was observed at T2 and persisted over 6 months after the complete vaccination schedule. gE-specific T cell response measured, in 25 patients, 12 months post-vaccination were slightly lower than those measured at T3 (20 IQR 10.75-60.5 versus 42.5 IQR 20-120 IFN-?-producing cells/106 PBMCs; p=0.36). Conversely, no variation was observed against IE63 peptide pool. Interestingly, only 20% of the RZV recipients showed negative gE-specific T-cell responses at 12 months post-vaccination versus 8.1% at 6 months post-vaccination indicating a long-lasting gE--specific CMI in more than two-thirds of RZV recipients. The evaluation of B- B-cell-mediated response is under analysis.

Conclusions: RZV-Shingrix induced strong humoral and cell-mediated immune responses for up to 1 year in patients with solid cancer undergoing immunotherapy. Efficacy should be evaluated in prospective long-term studies.

F06

DAPAGLIFLOZIN REDUCES SYSTEMIC PCSK9 LEVELS IN PRECLINICAL MODELS OF SHORT-TERM DOXORUBICIN CARDIOTOXICITY THROUGH NLRP3 INFLAMMASOME/IL-1ß: A FIRST EVIDENCE OF SGLT-2/PCSK9 CROSS-TALK IN CARDIONCOLOGY

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Background: Anthracyclines are an effective and widely used chemotherapy agent in the treatment of multiple solid organ tumors and hematologic malignancies. The use of anthracyclines as a standard cancer therapy is limited by the potential for the development of cardiac dysfunction, arrhythmias, and clinical heart failure. In recent five years, it was demonstrated that proprotein convertase subtilisin/kexin type 9 (PCSK9), a lipid metabolism-related protein, is a key orchestrator of immune infiltration in myocardial and cancer tissues and could regulate cardiac fibrosis and inflammation. PCSK9 is a protein with key roles in hepatic low density lipoprotein (LDL) homeostasis. PCSK9 systemic levels are associated to HOMA score and high insulin levels. Dapagliflozin exerts systemic ant-inflammatory properties and cardioprotective effects in diabetic and non-diabetic patients. We hypothesized that Dapagliflozin, administered during doxorubicin, could reduce PCSK9 systemic levels in preclinical models.

Material and Methods: Female C57Bl/6 mice were untreated (Sham, n=6) or treated for 10 days with doxorubicin i.p at 2.17 mg/kg (DOXO, n=6), DAPA at 12 mg/kg (DAPA, n=6) or doxorubicin combined to DAPA (DOXO-DAPA, n=6). After treatments, plasma levels of PCSK9, IL-1β and CRP were analyzed through selective anti-mouse ELISA methods. Myocardial and liver expression of NLRP3-inflammasome and IL-1β were analyzed through ELISA method in tissue lysates after treatments.

Results: DAPA associated to DOXO reduces significantly systemic levels of PCSK9 (-37,5% vs DOXO group, p<0,001). IL-1β and CRP levels were also reduced (-47,3 and – 28,5 %, respectively; p<0.05 for both). Myocardial and liver IL-1β and NLRP3 inflammasome expression were also reduced in DAPA/DOXO group vs DOXO and control, indicated beneficial metabolic and anti-inflammatory effects of SGLT2i.

Conclusions: DAPA has been shown to reduce systemic levels of PCSK9 in preclinical models of short-term DOXO cardiotoxicity. To the best of our knowledge, this is the first evidence of SGLT-2/PCSK9 crass-talk in cardioncology therefore the overall picture of the study open a new window on the beneficial properties of DAPA against anthracyclines side effects.

F07

IMPACT OF CARDIONCOLOGY AMBULATORY CARE ON CARDIOPROTECTIVE STATEGIES: A SINGLE CENTER EXPERIENCE

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Background: Cardiovascular toxicities related to onco-hematological treatments (CTR-CVT) significantly impact the efficacy of therapy as well as the quality of life and overall survival of cancer patients (pts). Therefore baseline pts risk evaluation is key. Early identification and management

of potential risk factors with cardioprotective strategies (lifestyle modifications or pharmacological therapy) seem to contribute to the prevention and reduction of cardiotoxic events.

Patients and Methods: Since June 2023 a specific cardiological ambulatory for onco-hematological pts candidates to potentially cardiotoxic agents was started. According to ESC 2022 guidelines, all pts were screened for cardiovascular risk, past and programmed therapy, HbA1c, lypidic profile, cardiac troponin and BNP determination, pressure, ECG and echocardiogram with global longitudinal strain measurement. A referring oncologist, hematologist and cardiology team was identified to discuss face-to-face complex cases and implement competence and process.

Results: After ten months, 118 pts were evaluated: 82% have solid tumors (33% breast, 45% GI, 13% lung, 3% GU, 6%other), 18% hematological cancers (57% NHL, 14% HL, 19% LMC, 10% LLC). Cardiotoxic drugs administered were: anthracyclines (31%), anti HER2 (9%), 5-FU (30%), VEGFRis (8%), immunotherapy (13%), TKIs (5%), BTKis (2%), others (2%). Based on HFA-ICOS score, 37% pts were classified as high, 5% intermediate and 58% low risk.13 pts required further cardiological assessments, but only in 2% of cases a change in the proposed therapy was needed.As for the cardioprotective strategy, 111 interventions were carried out: 26% were modification in lifestyle (diet 38%, physical exercises 3%, smoke cessation 35%, weight loss 24%) whereas 74% were pharmacological therapy (betablocker 17%, ACE-I 15%, statins 45%, sartans 8%, others 15%). In 4% pts ≥ 2 lifestyle modifications were proposed; in 13% pts ≥ 2 pharmacological therapies were offered and in 12% pts both lifestyle and pharmacological modifications were prescribed. During this time, no patient developed CTR-CVT.

Conclusions: A specific cardio-oncology service is effective and allows a better risk stratification and cardioprotective strategies prescription with reduction of CTR-CVT in onco-hematological pts.

F08

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR DAPAGLIFLOZIN REDUCES SYSTEMIC H-FABP AND MONOCYTE-TO-LYMPHOCYTE RATIO IN PRECLINICAL MODELS OF ANTRACYCLINE INDUCED CARDIOTOXICITY

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Background: Anthracyclines are an effective and widely used chemotherapy agent in the treatment of multiple solid organ tumors and hematologic malignancies. The use of anthracyclines as a standard cancer therapy is limited by the potential for the development of cardiac dysfunction, arrhythmias, and clinical heart failure. Dapagliflozin exerts several cardiometabolic benefits in patients with and wthout T2DM through SGLT2-NLRP3 mediated pathways. In this study, we highlighted on new beneficial properties of Dapagliflozin in preclinical models of doxorubicin-induced cardiotoxicity.

Materials and Methods: Female C57Bl/6 mice were untreated (Sham, n=6) or treated for 10 days with doxorubicin i.p at 2.17 mg/kg (DOXO, n=6), DAPA at 12 mg/kg (DAPA, n=6) or doxorubicin combined to DAPA (DOXO–DAPA, n=6). After treatments, plasma levels of H-FABP and monocyte-to-lymphocyte ratio were determined through selective quantitative methods.

Results: Dapagliflozin associated to Doxorubicin reduces of 48,7% plasma levels of H-FABP compared to DOXO group ($p<0.001$). Myocardial expression of H-FABP were also reduced, indicating cardioprotective properties of SGLT2i. Moreover, monocyte-to-lymphocyte ratio was strongly enhanced after DOXO therapy, indicating systemic pro-inflammatory properties; notably, Dapagliflozin reduced of 32,8% the monocyte-to-lymphocyte ratio compared to only DOXO treated mice ($p<0.005$).

Conclusions: For the first time, Dapagliflozin demonstrated a significant reductions of monocyte-to-lymphocyte ratio during doxorubicin therapy, indicating new potential pathways of cardioprotection in cancer patients.

F09

COMBINATORIAL IMMUNE CHECKPOINT BLOCKADE INCREASES MYOCARDIAL SECRETION OF H-FABP, NT-PRO-BNP, NLRP-3 INFLAMMASOME, INTERLEUKIN-1ß AND INTERLEUKIN-6: BIOCHEMICAL IMPLICATIONS IN CARDIO-IMMUNO-ONCOLOGY

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Background: Immune checkpoint blockade alone or in combination with chemotherapy or radiotherapy or other immune checkpoint blocking agents have become an integral part of oncology in recent years. Monoclonal antibodies against CTLA-4 or PD-1 or PDL-1 are the most studied ICIs in randomized clinical trials, however, more recently, an anti-LAG3 (Lymphocyte activation gene-3) human monoclonal antibody, Relatlimab, has been approved by FDA for combinatorial treatment with Nivolumab for metastatic melanoma. Moreover, anti PD-L1blocking agent Atezolizumab is actually under study in association with Ipilimumab as innovative therapy for metastatic lung cancer. Myocarditis, vasculitis and endothelitis are rarely observed in these patients on monotherapy, however new combination therapies could expose patients to more adverse cardiovascular events.

Materials and Methods: Human cardiomyocytes co-cultured with human peripheral blood lymphocytes (hPBMCs) were exposed to monotherapy and combinatorial ICIs (PD-L1 and CTLA-4 or PD-1 and LAG-3 blocking agents, at 100 nM) for 48 h. After treatments, cardiac cell lysis and secretion of biomarkers of cardiotoxicity (H-FABP, NT-Pro-BNP), NLRP3-inflammasome and Interleukin 1 and 6 were determined through colorimetric and enzymatic assays.

Results: Both combinations of immune checkpoint inhibitors exert more potent cardiotoxic side effects compared to monotherapies against human cardiac cells co-cultured with human lymphocytes. LDH release from cardiac cells was 43% higher in PD-L1/CTLA-4 blocking agents, and 35.7% higher in PD-1/LAG-3 blocking agents compared to monotherapies. Biomarkers of cardiotoxicity, such as NT-Pro-BNP and H-FABP, were also strongly increased in combination therapy with respect to monotherapies. NLRP3 inflammasome, IL-6 and IL-1β levels were also increased by PDL-1/CTLA-4 and PD-1/LAG-3 combined blocking agents compared to untreated cells and monotherapies.

Conclusions: Data of the present study, indicate that combinatorial immune checkpoint blockade, induce a pro- inflammatory phenotype, thus indicating that these therapies should be closely monitored by the multidisciplinary team consisting of oncologists and cardiologists.

F10

This abstract was withdrawn at the request of the Authors.

F11

BEYOND BRCA: PRELIMINARY RESULTS OF A STUDY FOR THE IMPLEMENTATION OF HEREDITARY CANCER DIAGNOSES

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Background: The presence of genetic variants results in a higher lifetime risk of cancer compared to the general population.

AIOM has implemented the Recommendations for the analysis of BRCA genes in breast, ovarian, pancreatic and prostate cancer and the universal test in colon-rectum and endometrial cancer for the identification of Lynch syndrome; some Italian regions have implemented PDTA in order to increase the diagnosis of BRCA hereditary syndrome.

However, there are numerous other syndromes that predispose to the development of tumours, which may be considered rarer.

Within the Oncology Unit of the ASP of Enna, we conducted a prospective observational study with the aim of increasing the possibility of diagnosing and preventing familial hereditary syndromes in an area without medical genetics units, through the validation of a family history collection tool with online assessment by geneticist.

Patients and Methods: Until now sixty three patients afferent to the Oncology Unit of ENNA and thirty eight healthy volunteers were enrolled.

All of them were administered the form subject to validation; the healthy women were given the questionnaire proposed by Sicilian PDTA relating to the syndrome of hereditary breast and/or ovarian cancers; for cancer patients, the AIOM recommendations were applied.

All questionnaires were shared online with the geneticist-oncologist, who gave indication for onco-genetic counselling.

Results: Among the 63 cancer patients (median age 60 years (range 39-79) there were 51 females and 12 males. Of the 38 healthy volunteers only 4 men (median age 53 range 25-71).

Indication for oncogenetic counselling outside the AIOM recommendations was given in 11/63 cancer patients and in 8/38 healthy volunteers outside the regional PDTA indications. Among the healthy volunteers 1 BRCA mutation carrier lady had a score of zero in the test proposed by the Sicilian PDTA and therefore would not have been indicated for onco-genetic counselling.

Conclusions: The implementation of family history assessment within the Oncology Unit with online evaluation by the geneticist, in an area without physician expert in cancer genetics, is feasible and has led to an increase in the number of indications for onco-genetic counselling, with the possibility of increasing the chances of cancer prevention.

G - Management of Cancer Pain and Supportive Care

G01*

EXPLORING PROGRAMMED DEATH CELL-1 (PD-1) SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) AS PREDICTIVE BIOMARKERS FOR IMMUNE-RELATED ADVERSE EVENTS (IRAES) IN ADVANCED CANCER PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS (ICIS)

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Background: Immune checkpoint inhibitors (ICIs) targeting programmed death cell-1 (PD-1) and its ligand 1 (PD-L1) revolutionized the management of many types of solid tumors. However, a portion of treated patients develops severe immune-related adverse events (irAEs) potentially causing prolonged sequelae. As a result, there is the urgent need for biomarkers to identify which patients have a higher likelihood of developing irAEs.

Material and Methods: We assessed the role of *PD-1* single nucleotide polymorphisms (SNPs) as biomarkers for predicting the occurrence of irAEs in advanced cancer patients treated with ICIs. Selected *PD-1* SNPs were genotyped by TaqMan RT-PCR. To assess the mechanism underlying the predictive value of the identified *PD-1* SNP, we employed peripheral blood mononuclear cells (PBMCs) isolated from two cancer patients, transfected with specific miRNAs and co-cultured with HaCat cells.

Results: Seventy-two patients including 49 (68.06%) non-small cell lung cancer, 9 (12.50%) renal cell carcinoma, 8 (11.11%) head and neck squamous cell carcinoma and 6 (8.33%) melanoma patients were treated with anti-PD-1/PD-L1 therapy. Grade 1-2 and grade 3-4 irAEs were reported in 45 (69.23%) and 6 (9.23%) of the treated patients, respectively. Among selected *PD-1* SNPs, rs10204525 exhibited a significant association with grade 1-2 ($P < 0.005$) and grade 3-4 irAEs ($P < 0.002$). Indeed, patients carrying allele C reported a higher rate of irAEs than those carrying allele T. rs10204525 mapped on the 3'-UTR region of the *PD-1* affecting the binding affinity of specific miRNAs. Specifically, miR-4717 strongly bound to rs10204525 in presence of allele C but not in presence of allele T. The differential binding of miR-4717 to rs10204525, in turn differentially modulated the expression of *PD-1* on PMBCs both under basal conditions and following treatment with IFN-gamma. Moreover, a decreased cell viability, an increased IFN-gamma release and induction of apoptosis of HaCat cells when co-cultured with miR-4717-transfected $PBMCs^{C/C}$ were reported. In contrast, no significant difference when HaCat cells were co-cultured with $PBMCs^{C/T}$ was found.

Conclusions: Our findings have high clinical relevance since identify rs10204525 as an efficient biomarker for predicting the occurrence of irAEs in advanced cancer patients treated with ICIs. We also revealed the biological mechanism underlying the predictive value of rs10204525.

G02*

IMPACT OF EDOXABAN TREATMENT ON ANTINEOPLASTIC THERAPY AND QUALITY OF LIFE (QOL) IN ITALIAN CANCER PATIENTS WITH VENOUS THROMBOEMBOLISM EVENTS (VTE) UNDER CANCER TREATMENTS. THE RESULTS OF THE PHASE IV EDOI STUDY (GOIRC-05-2018)

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Background: The oral factor Xa inhibitor, edoxaban, is effective and safe in cancer-associated VTE treatment. The EDOI study aims to evaluate compliance and QoL in cancer-associated VTE patients treated with edoxaban during antineoplastic care.

Material (patients) and Methods: The EDOI Study (EUDRACT 2018-003833-14) was a multicentre phase IV, open-label, single-arm study conducted from July 2019 to March 2022 in 21 Italian Centers. Patients received orally edoxaban at a dosage of 60 mg/day for 6 up to 12 months. The primary objective was to evaluate the impact of edoxaban-related adverse events (AEs) as adverse drug reactions on antineoplastic therapy in patients' candidates for at least 3 additional months of cancer treatment (expected rate was 10%-15%). The secondary objective was the assessment of QoL, evaluated with validated questionnaires (FACT-G, PACT-Q2, and ACTS). The primary endpoint was reported in terms of rate and 90% Poisson Confidence Intervals, and by cumulative incidence rate using by Aalen Johansen curve. Multivariable Mixed Model for Repeated Measure has been adopted to evaluate the change of QoL scores in the 4 study points, from the enrollment to 1, 3, and 6 months later.

Results: Among 150 enrolled patients, 147 were evaluable. Edoxaban-related AEs that impacted antineoplastic therapy were observed in 7 patients, with a 4.76% rate (90%CI 2.23%- 8.94%; p-value of 0.024), suitable to reject the expected rate of 10%. The cumulative incidence of AEs was 2.7% at 1 month from enrollment. A statistically significant increase ($p<0.05$) was observed for the subscale scores of the Convenience (+5 points) and the Satisfaction (at least +2.5) of the PACT-Q2, and reduction of Burden (at least +1.7 points) of the ACTS at 1 month after the enrollment. Overall QoL measured by FACT-G did not show any reduction for patients over time. A significantly higher mean score was observed for patients who experienced edoxaban-related AEs (+5.89; 95%CI 0.13-11.65; p=0.045).

Conclusions: The results of the EDOI Study demonstrate that edoxaban was well tolerated in cancer-treated patients, showing a low rate of AEs with an impact on antineoplastic therapy, mainly within the first 30 days of administration. Lastly, the edoxaban-related AEs did not result in a lower overall QoL.

G03

THE USE OF SYSTEMIC ANTICANCER TREATMENT NEAR END OF LIFE IN ADVANCED GASTROINTESTINAL TUMORS

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Background: Rate of advanced cancer is rising with an increase in the burden of care and costs. Calibrate type and duration of treatments is crucial to preserve the quality of life of patients and to optimize resources. Systemic Anticancer Treatment (SCAT) is widespread in end of life (EoL) phase, dispite, owing to its doubtfull benefits, guidelines discourage its use. No criteria are available to identify the optimal time to stop SCAT. The factors currently identified as related to an increased likelihood of receiving SCAT in EoL phase are: early age, pancreatic cancer, ECOG PS=2, symptomatic disease and lack of comorbidity. Our study, conducted on population of patients affected by gastrointestinal tumors and treated at Modena Cancer Center, has the aim to identify factors related to likelihood of receiving SCAT at the EoL in a real-world setting.

Material and Methods: Data from 500 patients affected by gastrointestinal tumors and treated in the EoL phase at Modena Cancer Center from July 2008 to June 2020 were retrospective collected. Univariate and multivariate analysis was done.

Results: 50% of patients received SCAT in the 30 days prior to death, 90% present more than 2 metastatic sites, 97% received chemo, 94% received day hospital

treatment, 47% had activated integrated home care, 71% died at home/hospice, 47% were admitted to the hospital before death. Factors related with likelihood of SCAT in the EoL phase were:activated home health care, number of metastatic sites,outpatient care, hospitalization before death and death at home/hospice.

Conclusions: It has been demonstrated that the use of SCAT in the EOL phase worsen QOL and OS and increase heathcare costs. Although discouraged by international guidelines, this practice is still widely used today, as confirmed by our series of patients with GI malignancies. It is of paramount importance to formulate a single definition of end-of-life and find validated criteria to identify the correct time to interrupt SCAT.

G04

A MULTIDISCIPLINARY MANAGEMENT OF IMMUNE-MEDIATED PNEUMONITIS IN CANCER PATIENTS TREATED WITH IMMUNE-CHECKPOINT INHIBITORS

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Background: Immune-mediated pneumonitis (im-PN) is a rare but potentially life-threatening adverse event in the course of immune-checkpoints inhibitors (ICI)-based immunotherapy. A multidisciplinary management may be crucial to avoid worsening of im-PN and to promptly resume ICI therapy.

Material and Methods: We collected a case series of skin cancer (melanoma-MEL, cutaneous squamous cell carcinoma-CSCC), lung cancer (NSCLC), and mesothelioma (MESO) patients (pts), treated with ICI at the Center for Immuno-Oncology of the University Hospital of Siena, Italy, who were diagnosed with im-PN. Clinical and radiologic data were thoroughly collected, as well as bronchoalveolar lavage (BAL) samples; im-PN were graded using CTCAE v.5.0. Radiological patterns were reported according to the *Fleischner Society* classification of drug-related pneumonitis.

Results: From January 2014 to February 2023, 1004 pts with MEL (n=522), CSCC (n=42), NSCLC (n=342) or MESO (n=98) were treated with ICI (619 anti-PD-1 monotherapy; 385 ICI combinations). Among treated pts 24 (2%) developed an im-PN and 14 (58%) were symptomatic. The incidence of im-PN was 58% (n=14) and 42% (n=10) in pts receiving ICI monotherapy or combination(s) respectively. Im-PN were classified grade (G)1 in 10 (42%) pts and G2 in 14 (58%). Prompt steroid treatment led to complete resolution of im-PN in 21 (95%) pts, with a median time to clinical and/or radiological resolution of 14 weeks. Twelve pts resumed ICI therapy once fully-recovered from im-PN, and 2 of them experienced im-PN recurrence that completely resolved with steroids re-treatment. Three distinct radiologic patterns were identified: organizational pneumonia-like in 16 (67%) pts, pulmonary eosinophilia in 7 (29%) pts, and hypersensitivity pneumonitis in 1 (4%) patient. Furthermore, BAL samples analysis performed in 8 (33%) pts showed an inflammatory lymphocytic infiltrate predominantly consisting in foam cell-like macrophages infiltrate in 6 cases. Among the latter, Transmission Electron Microscopy evaluation performed in 2 pts, revealed multilamellar bodies, lysosomes, and lipid vacuoles into the alveolar macrophages, a scenario suggestive for a drug-mediated toxicity.

Conclusions: Im-PN is an uncommon but challenging side effect of ICI therapy, with variable time of onset and non-specific clinical and radiological presentations. A multidisciplinary management is mandatory to optimize the clinical management of im-PN and to rapidly resume ICI therapy.

G05

ACCESS TO THE EMERGENCY DEPARTMENT (ED) OF PATIENTS UNDERGOING TREATMENT WITH CHECK-POINT INHIBITORS (CPI): AN UNMET NEED

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Background: Cancer patients are frequent ED users. The advent of CPI has led to notable progress in the management of different types of tumors, although these drugs are not free from side effects (immune-related adverse events (IRAE) which, in the most serious cases can cause referral to the ED. Knowledge about the effects of these therapies is key to promptly identify patients who may require specific management and hospitalization.

Patients and Methods: We retrospectively analysed the data relating to patients who started therapy with ICIs in the Oncology Department of the S. Croce e Carle Hospital in Cuneo from 2013 to 2021; in detail, we evaluated every access to the hospital ED of these patients starting, from the month following the start of therapy up to six months following the last administration. The presenting symptoms and final diagnosis at discharge were classified as unrelated, potentially related, or definitely related to ICIs, based on a multidisciplinary review of the medical record.

Results: 449 patients were treated with CPI in the selected period and were included in the analysis. There were 457 visits to the ED, relating to 216 patients. Median age was 68 (range 61-74) and the most frequent tumors were lung (42%) and melanoma (20%). 41% of patients were assigned a high priority triage code (red/orange/yellow); the most frequent symptoms were pain (25%), dyspnea (14%), worsening of general conditions (12%), gastrointestinal symptoms (5%) and fever (5%). 55% of patients were admitted after evaluation in the ED; of these, 11% were admitted to an intensive or sub-intensive care unit. In-hospital mortality among hospitalized patients was 19%. For 27 (5.9%) visits to the ED the review confirmed an IRAE as the reason of referral and for 15 (3.3%) the review suggested a possible IRAE. The confirmed IRAEs were pneumonia (12 cases), colitis (5 cases), hepatitis and polymyositis (3 cases each), thrombocytopenia, myasthenia, polyneuropathy and heart failure (one case each). The median time between the start of ICI and admission to the ED for IRAE was 21 (range 9 – 50) weeks.

Conclusions: We found that 9.2% of the patients undergoing treatment with CPI had an access to the ED due to a verified or probable IRAE. Training on CPI-related toxicities and strict collaboration between oncologists and emergency physicians are to be considered mandatory in order to handle patients undergoing this type of treatment.

G06

THYROID ADVERSE EVENTS DURING TREATMENT WITH IMMUNE CHECKPOINT INHIBITORS (ICIS): POTENTIAL PREDICTIVE FACTORS AND RISK OF DEVELOPING MULTIPLE IMMUNE-RELATED ADVERSE EVENTS (IRAES)

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Background: Thyroid toxicities are among the most common AE related to ICI treatment. Data about possible predictors of development of these irAEs are still limited and sometimes controversial. In this study, we retrospectively assessed the prevalence of thyroid irAEs in a cohort of patients with different tumor types treated with ICIs, the potential risk factors correlated to the onset of these events, and the risk of developing a second irAE in patients who had already developed a first thyroid irAE.

Material and Methods: We analyzed 130 patients with different types of cancer at advanced stage of disease, treated with ICIs at our Medical Oncology Unit. Clinical and biochemical data including thyroid function values at baseline and during treatment and any positivity of thyroid autoantibodies were collected. Patients under replacement therapy before starting ICI were excluded.

Results: 41/130 patients (31.5%) developed thyroid AEs. Hypothyroidism was the most frequent thyroid AE (N=39; 30% of all patients); only 2 patients developed persistent hyperthyroidism. 29 patients (22.3%) experienced nonendocrine irAEs. At the uni- and multivariate analysis, an increased risk of thyroid AEs was observed in patients with a pre-existing thyroid disorder, anti-thyroid autoantibodies positivity at baseline, and a family history of endocrinopathy. Previous TKIs treatment and TSH value at baseline were also significantly associated with the occurrence of irAEs at univariate analysis. The risk of developing another AE, was about 3.5-fold greater in those patients who develop a first thyroid AE **(Table).** The median time of occurrence of thyroid AEs was 8 weeks.

Variable	Crude OR	Univariate	p-value	Adjusted OR	Multivariate	p-value
		95% CI			95% CI	
Previous TKI	**3,459**	**1,026 – 11,655**	**0,045**	1,051	0,042 – 26,593	0,976
Personal history of thyroid disease	**45,769**	**13,795 – 151,848**	**0,000**	**29,556**	**5,470 – 159,719**	**0,000**
Family history of endocrinopathy	**15,043**	**5,983 – 37,822**	**0,000**	**13,599**	**2,791 – 66,256**	**0,001**
Antibodies positivity at baseline	**31,448**	**3,912 – 252,829**	**0,001**	**12,272**	**0,911 – 165,291**	**0,004**
TSH at baseline	**1,496**	**1,221 – 1,832**	**0,000**	1,382	0,994 – 1,921	0,055
Others AE	**3,742**	**1,583-8,843**	**0,003**	**3,866**	**1,492 – 10,020**	**0,005**

Conclusions: Our results confirm that thyroid toxicities represent the most common irAEs. We have identified some possible predictors factors of the development of thyroid irAEs that can help clinicians to identify patients who are more likely to experience irAEs, improving their management.

G07

TAILORED TREATMENT AND CLINICAL MANAGEMENT FOR DPYD COMPOUND HETEROZYGOUS: A MULTIDISCIPLINARY TEAMWORK

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Background: Dihydropyrimidine dehydrogenase (DPD), encoded by the DPYD gene, is the rate-limiting enzyme responsible for the catabolism of fluoropyrimidines (FPs). The toxicity profile of FPs is partially determined by the genetic polymorphism in the DPYD gene that drives variable DPD expression. Impaired or abrogated DPD enzyme activity leads to a prolonged FPs half-life and a potential increase in toxicity. To date, FP genetic-based dosing guidelines recommend the evaluation of four variant DPYD. Screening for genotypic DPYD variants and subsequent dose adjustments in individuals with DPYD variant alleles have significantly improved the patient safety of FP treatment. Nonetheless, managing the rare occurrence of double heterozygote variant carriers of the DPYD gene, called 'compounds heterozygous', remains still challenging.

Methods: We enrolled 993 patients diagnosed with solid tumours and candidates for fluoropyrimidine treatment according to the standard of care. All patients underwent preemptive DPYD genotyping for DPYD*2A, DPYD*13, D949V, and IVS10. Additionally, patients were analysed for the DPYD*6 variant allele. Adverse drug reactions (ADRs) were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: The analysis showed that 809 patients were wild-type (82%), while 184 patients were mutated (18%). The most prevalent variant was DPYD*6 while no patients presented the DPYD*13 allelic variant. In addition, we identified 6 carriers of the double-site variant DPYD*6/IVS10 and 1 carrier of the double-site variant DPYD*6/DPYD*2A. Our case series focused on 4 out of 6 compound heterozygous carriers of DPYD*6/IVS10 diagnosed with either colon adenocarcinoma or breast cancer and underwent a FP-based treatment. These patients were treated with a different pharmacogenetic-guided dose reduction of the standard. One of two patients with a 25% dose reduction developed G4 palmo-plantar erythrodysesthesia after one week of treatment, while one of two patients with a 50% dose reduction developed nausea and diarrhoea G3 after the first cycle of therapy.

Conclusions: The management of patients carrying compounds heterozygous DPYD variants should be performed by a multidisciplinary team in order to apply tailored treatment approaches including integrative deep analysis, precision dosing and early detection of ADRs ensuring that therapeutic efficacy is maintained for each case.

G08

END-OF-LIFE DECISIONS AND OPINIONS IN ONCOLOGY CLINICAL PRACTICE: RESULTS OF SURVEY IN HEALTH CARE PROFESSIONALS, PATIENTS, AND CAREGIVERS.

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Background: Issues related to end-of-life decisions (ELDs) generate impassioned debates in the society. Our study aimed at investigating attitudes in the care of cancer patients (pts) at the end of life; ascertaining the opinion of health care professionals (HCPs) as well as of pts and caregivers; verifying the quality of HCPs communication and exploring Law 219/2017 knowledge.

Material and Methods: An anonymous questionnaire was sent to HCPs (physicians, nurses, psychologists and healthcare workers), pts and caregivers at IOV, Padova. A total of 425 questionnaires were collected from 136 HCPs (38 physicians, 56 nurses, 7 psychologists, 16 healthcare workers, 19 not declared), 171 pts and 118 caregivers.

Results: With regard to ELDs, life-sustaining treatment was reported to be withheld by 11.3% of physicians and nurses and to be withdrawn by 19.3%; conversely, it was stated to be started by 46.8%, and not discontinued by 48.4%. Most HCPs (75.7%) were in favor of pt's right to anticipate end of life, and 86.4% of withholding/withdrawing life-sustaining treatments on pt's request, with 62.4% HCPs agreeing on lethal drug doses to be allowed upon pt's request. A majority (80.1 %) disagreed that "life is an unavailable asset and there is no right to die". According to physicians and nurses, palliative sedation was used in 75% of pts. There was little pts use of advance directives (ADs, 6.5%), trustee appointment (10%) and shared care planning (SCP,16%). According to pts and caregivers, in ELDs greater value was given to self-determination (i.e. written ADs, verbal ADs inferred from declarations, SCP), and in second place involvement of family members/trustee. Discussing incurability and life expectancy was stated to always occur by respectively 32.4% of physicians and 21.6% of pts. A consistent number of physicians and nurses reported feeling inadequate to communicate bad news. No difference in responses was found for age, gender and, for HCPs, training in palliative medicine.

Conclusions: With regard to ELDs and opinion of end of life, our study found an attitude to prolonging patient's life rather than withholding or withdrawing life-sustaining treatment still prevails in Italy, though there are signs of change. A discrepancy between what HCPs and pts/caregivers reported regarding communication of incurability and prognosis exists, highlighting the need for education and training in effective communication, also for greater implementation of Law 219/2017.

G09

EFFICACY OF ONCOLOGICAL REHABILITATION POST BREAST SURGERY: A SYSTEMATIC LITERATURE REVIEW

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Background: Oncological rehabilitation following breast surgery is crucial for mitigating post-operative complications and enhancing recovery and quality of life for breast cancer survivors. Despite numerous studies, a comprehensive synthesis of existing evidence is necessary to guide clinical practice. This study presents a systematic literature review of the effectiveness and components of post-breast surgery rehabilitation programs.

Materials and Methods: A systematic literature review was conducted following PRISMA guidelines. Databases searched included PubMed, Scopus, and Cochrane Library, covering studies from January 2000 to December 2023. Inclusion criteria were randomized controlled trials (RCTs), cohort studies, and systematic reviews focusing on post-operative rehabilitation in breast cancer patients. Meta-analyses using random-effects models aggregated data. Statistical tests, including Cohen's d for effect size and I^2 for heterogeneity, assessed the interventions' effectiveness and consistency.

Results: A total of 45 studies met the inclusion criteria, comprising 25 RCTs, 15 cohort studies, and 5 systematic reviews. Meta-analysis revealed that rehabilitation programs significantly improved physical outcomes, such as shoulder range of motion (SMD = 0.85, 95% CI: 0.65-1.05, $p < 0.001$) and grip strength (SMD = 0.78, 95% CI: 0.58-0.98, $p < 0.001$). The incidence of lymphedema was significantly reduced (RR = 0.45, 95% CI: 0.30-0.70, $p < 0.01$). Psychological benefits included decreased fatigue (SMD = 0.65, 95% CI: 0.45-0.85, $p < 0.001$) and anxiety (SMD = 0.60, 95% CI: 0.40-0.80, $p < 0.001$), with improved quality of life scores (SMD = 0.90, 95% CI: 0.70-1.10, $p < 0.001$). Heterogeneity across studies was moderate to high (I^2 = 50%-75%). Effective interventions included physical therapy, strength training, aerobic exercise, and psychosocial support, with an average duration of 12 weeks.

Conclusions: This systematic review confirms that multidisciplinary rehabilitation programs significantly improve physical and psychological outcomes for breast cancer survivors post-surgery. Key components include personalized physical therapy regimens, continuous psychosocial support, and lifestyle modifications. This synthesis highlights the necessity of integrating structured rehabilitation protocols into standard post-operative care. Future research should focus on standardizing rehabilitation protocols and exploring long-term benefits and cost-effectiveness.

G10

THE ROLE OF NUTRITIONAL ASSESSMENT ON WEIGHT LOSS AND MUSCLE STRENGHT IN CANCER PATIENTS: EXPERIENCE AT AOU SAN LUIGI GONZAGA ORBASSANO (TO)

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Background: Nutrition in cancer patients is essential to prevent and minimize negative health outcomes (e.g. muscle loss). ESPEN guidelines recommends to regularly evaluate the nutritional status (weight change, muscle strenght by dinamometry) in order to reduce the risk of malnutrition.

Methods: Patients are referred by oncologists to the dietician and the evaluation includes screening test (MST) and handgrip test (dinamometry).

Results: From May 2021 to March 2024, 466 patients were assessed (table) and re-evaluated. 50% of the sample was affected by lung cancer. At T0 median % weight loss from the last 6 months was 6,4%.

Mean(range)	T_0 (n466)	T_1 (n270)	T_3 (n161)	T_6 (n89)
Weight 6 months before Kg	69,9 (35-140)			
Weight Kg	65,6 (33-126) p<0,001	65,8 (35,5 – 120,5)	67,4 (36,5 - 118)	69,5 (40-120)
% weight loss from T0, T1, T3		0,1 (-10,5 – 21,9)	-1 (-18,5 – 12,9) p < 0,003	-0,8 (-15,8 – 9,5)
BMI	23,2 (14-49)	23,2 (14-47)	23,8 (16-46)	24,5 (15-45)
MST	0 = 23,5%	0 = 51,4%	0 = 63,2%	0 = 62,7%
	1 = 19,1%	1 = 26,4%	1 = 22,3%	1 = 20,9%
	2 = 35,4%	2 = 15,8%	2 = 9,9%	2 = 16,9%
	≥3 = 22%	≥3 = 6,4%	≥3 = 4,6%	≥3 = 0,1%
HAND GRIP Kg	24,8 (7,3-54)	25,9 (7-49)	26,1 (8,7-55,5)	25,5 (7,1-45)

Conclusions: Nutritional evaluation was carried out on the sample after significant weight loss in the previous 6 months. Despite the lack of uniformity in the literature regarding handgrip cut-offs, the patients assessed do seem to be at risk of sarcopenia from T_0. Different nutritional strategies had a significant effect on cancer patients' handgrip strenght. These results suggest that these indicators could be used in the nutritional and functional assessment of the patients. The findings indicate that these indicators could be employed in the evaluation of patients' nutritional and functional needs. The nutritional approach must be tailored to the patient, based on their therapies and potential side effects. In conclusion, nutritional intervention and dietary counselling help to reduce weight loss and improve muscle strenght. Furthermore, the data obtained highlight the need to follow patients with periodic follow-up, in order to strengthen nutritional counselling.

G11

PHYSICAL EXERCISE DURING AND AFTER CANCER TREATMENT: INVESTIGATING A NON-PHARMACOLOGICAL APPROACH TO ADDRESS CARDIOVASCULAR TOXICITY IN CANCER SURVIVORS

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Background: The widespread use of anthracyclines, potent cardiotoxic medications, have underscored the need of acknowledging the impact of cancer therapy on cardiac function. A plethora of studies have been conducted to evaluate the cardiovascular toxicity associated with therapeutic protocols along with the patient's pre-existing risk factors. These study often ended up suggesting the introduction of cardioprotective medications. However, multiple drugs regimens may be not tolerated in the long-term life of cancer survivors who are frequently less keen to adhere to pharmacological treatments.This research aims to analyse the current evidence about the benefits of Physical Exercise (PE) as an alternative intervention that can potentially improve the patient's overall fitness.

Methods: Clinical trials (CT) and randomized clinical trials (RCT) were identified by searching in Medline/PubMed and CHOCRANE Library. The research focuses on physical exercise (PE) in survivors of breast and urogenital cancers, with records screened according to the

PRISMA method. The parameter considered is Peak VO2, an established surrogate marker for cardiovascular risk. The meta-analysis was conducted using means and standard deviations, and the analysis was performed with SPSS software.

Results: The research has yielded 113 records, of which 11 were actually included in the analysis (1 CT and 10 RCT). The overall number of patients enrolled in the research is 849, 223 males affected by prostate or urogenital cancer undergoing Androgen Deprivation Therapy and 626 females affected by breast cancer undergoing anthracycline chemotherapy. The meta-analysis showed a positive effect of PE performed during and/or after cancer treatment on the cardiorespiratory fitness with an increase of Peak VO_2 (Adjusted Mean: 3,109 CI: 0,167-6,05 P-value: 0,03). In addition to the limited number of studies, the analysis is limited by the heterogeneity of exercise performed and duration.

Conclusions: This research highlights that physical exercise during cancer treatment can have a positive effect on cardiorespiratory fitness, as evidenced by the increase in Peak VO2. Despite the limitations, the findings imply the promising potential of this approach, which can be further optimized through risk stratification and personalized interventions. Future research and widespread knowledge on this matter may encourage professionals to systematically include this aspect in the patient care pathways.

G12

NEUROLOGICAL ADVERSE EVENTS OF ICI THERAPY: A SINGLE-CENTER TEN-YEAR EXPERIENCE

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Background: The unique immune-activating mechanism of action of immune checkpoint inhibitors (ICI) can lead to auto-inflammatory events, potentially involving any organ. Among these, different rare immune related adverse events (irAEs) have been also identified, and Neurological irAEs (NirAEs) account for about 2% of them. Due to their rarity and insidious onset, NirAEs may result in potentially life-threatening toxicity. In this scenario, we here report the 10-year experience in the diagnosis and clinical management of NirAEs of the multidisciplinary team at the University Hospital of Siena, Italy.

Materials and Methods: We collected a case series of consecutive patients (pts) with solid tumors treated with ICI and diagnosed with Nir-AEs. Neurological specific antibodies were tested in central and neural/muscular-peripheral toxicities. In the event of laboratory and CNS imaging suspicious for NirAEs, lumbar puncture was utilized to exclude infectious and/or paraneoplastic causes. In pts with signs and symptoms suggestive for myositis, a diagnostic muscular biopsy was performed.

Results: From Jan 2012 to Dec 2022, 1328 cancer pts were treated with ICI. Among those, 24 (1,8%) were diagnosed with NirAEs (19 males and 5 females; median age 67 years). Pts were affected by skin cancer (17), NSCLC (2), mesothelioma (2), other (3), and were treated with anti-PD-1 (16), anti-CTLA-4 (3) or their combination (5). Among the observed NirAEs, 1, 20 and 3 cases were diagnosed as central, peripheral neurotoxicity or both, respectively. The most representative toxicity was muscular/neuromuscular junction involvement, (50%), with single manifestations of myositis (3 pts), myasthenia gravis (2 pts), or both (7 pts). Histological examination of muscle biopsies depicted two main pathological patterns: highly inflammatory (4 pts), or necrotizing (4 pts). NirAEs were Grade (G) 1 (2), G2 (9), G3 (6), G4 (4), or G5 (3), with a median time to onset of 22 weeks (range: 1-145). NirAEs were treated with high doses steroids, immunoglobulins and/or plasma exchange. Treatment led to complete or partial recovery of NirAEs in 11 (46%) and 10 pts (42%), respectively. In 3 cases (12%) NirAEs progressively worsened and pts died thereafter.

Conclusions: Though rare, NirAEs are potentially life-threatening toxicities of ICI therapy. Our long-term experience indicates that a multidisciplinary approach avoids more severe complications, and leds to clinical recovery from NirAEs in the large proportion of pts.

G13

IMPORTANCE OF PROMPT MEDICAL ONCOLOGIST (MO) CONSULTATION AT THE EMERGENCY DEPARTMENT (ED). A PROSPECTIVE STUDY IN A TERTIARY HOSPITAL ON 10,896 ADMISSIONS IN THE FIRST QUARTER OF 2024

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Background: Management of cancer patients at the ED has long been problematic, especially with regard to the intensity of care for patients near the end of life. We sought to investigate the utility of MO consultation at the ED in indicating the best supportive care for cancer patients.

Methods: Consecutive MO consultations with patients presented to the ED from January 1 to March 31, 2024 were recorded. MO indication of best supportive care (BSC) was correlated with overall survival (OS) and 30-day mortality rate (30-DMR). Additionally, 47 clinical and laboratory candidate variables were collected and correlated with OS. Significant variables ($p < 0.005$) selected at univariate analysis were analyzed in a multivariate Cox-regression model.

Results: Out of 10,896 adult ED visits, MO consultation was required in 120 visits (1.1% of cases) well below the 5% prevalence of cancer patient ED visits reported in the literature). The most common cancers for which consultation was required were lung, gastrointestinal, and genitourinary cancer, and most common presenting symptoms were pain (26.4%), dyspnea (24.1%), and neurological symptoms (19.5%). Following MO consultation, BSC was indicated in 37.9% of cases. BSC indication was associated to a significantly higher 30-DMR compared to active treatment indication: 28% vs 19%, HR 2.50 (95%CI: 1.19 to 5.29), p 0.01. Following univariate analysis, alkaline phosphatase (ALP), neutrophils-to-lymphocyte ratio, Charlson comorbidity index, concomitant infection and modified Glasgow prognostic score (mGPS) were selected for the multivariate model and ALP >100 IU/L (HR 5.28, 95%CI: 1.73-16.12, p 0.003) and mGPS score 2 (HR 12.78, 95%CI: 2.89-56.53, p 0.0008) were confirmed to be independent predictors of OS. Among patients eligible to active treatment, those with ALP>100 and/or mGPS=2 had a 30-DMR of 22% vs 6% of patients with ALP<100 and mGPS 0/1.

Conclusions: Early MO consultation is strongly recommended for the appropriate management of cancer patients in the Emergency Room. ALP and mGPS may assist prognostication in this setting.

G14

EXCELLENT (EXERCISE IN EXTENDED ONCOGENE ADDICTED LUNG CANCER IN ACTIVE TREATMENT) TRIAL: PRELIMINARY RESULTS ON IMPACT OF PHYSICAL ACTIVITY (PA) ON EMOTIONAL, METABOLIC AND IMMUNE STATUS

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Background: EXcellenT (NCT05306652) is a prospective randomized trial on PA in oncogene-addicted advanced NSCLC patients (pts) in active treatment with TKIs. These pts are often young, keen to regain their pre-disease QoL and have prolonged survival. Depression may hamper compliance and response to treatment and delay social life recovery. This trial evaluates if tailored PA have an impact on QoL, metabolic and immune status.

Methods: Pts are randomized in an interventional arm of a personalized supervised PA prescription (arm A) or a counseling on home-based exercise (arm B). Depression is assessed by Beck's Depression Inventory (BDI) questionnaires administered at week (wk) 0 and 12. Blood samples are collected at baseline, wk 4 and 12 for metabolic and immune status evaluation. Fatty acid (FA) composition is carried out using gas liquid chromography with flame ionization detection and liquid chromatography-mass spectrometry; immune cell composition through flow cytometry.

Results: Preliminary data on personalized PA influence on depression are available for 22 pts enrolled, FA analysis and immune cells count for 4 and 3 pts, respectively. Pts characteristics are: median age 53 yo, 53% female, 80% ECOG PS 0, 52% pre-diagnosis leisure-time PA; ALK+ 53%, EGFR+ 31%, BRAF+ 13%, RET+ 3%, ROS1+ 16%. In arm A depressive symptoms improved at wk 12 vs wk 0 (BDI mean difference: 6 points [IQR 4-9], p=0.0039). Only a trend to improvement was found in arm B (p=0.1270). The extent of improvement between the 2 time points was more sustained in arm A than arm B (p=0.0237). Plasma analysis showed a significant increase in Mono-Unsaturated Fatty Acids (p=0.0329) whereas FACS analysis highlighted reduction in circulating CD34+ hematopoietic stem cell (p=0.0112, ANOVA, Tukey's multiple comparisons) and parallel increase in mature CD66b+CD10+ neutrophils.

Conclusions: The preliminary analysis of our trial confirms that a tailored PA program can significantly improve depression state, increase mature immune cell precursors and enhance metabolic state. A personalized PA program should be integrated to standard oral therapies to enhance NSCLC pts well-being and not only treat their disease.

G15

VERY HIGH LEVELS OF DIAGNOSIS AND PROGNOSIS AWARENESS IN A POPULATION OF CANCER PATIENTS ATTENDING A DAY HOSPITAL FOR ONCOLOGIC TREATMENT AND A SIMULTANEOUS PALLIATIVE CARE PROGRAM

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Background: Patients' information about cancer diagnosis and awareness of incurability remain poor in Italy. Despite significant improvement, a 2015 multicentric study on Day Hospital (DH) patients (Pts) found that 49% of metastatic Pts though they had a curable disease. Figure was no better in studies on Pts admitted to palliative care programs. This study reports on a series of Pts attending a DH for cancer treatment, who entered a program of Simultaneous Palliative Care (SPC).

Patients and Methods: 100 consecutive Pts (52% female; age 36-89, median 70; cancer diagnosis %: gastroenteric 28, lung 22, breast 19, genitourinary 11, hematologic 7, other 10; treatment %: chemotherapy 47, biologic 21, combined 11, none 17, other 4) attending the Oncology DH at Aosta Hospital from September 2022 to April 2024 entered a SPC program, on the basis of their prognosis and/or symptom burden. During the initial SPC consultation, Pts completed the Integrated Palliative Outcome Scale (IPOS) and were offered to discuss their diagnosis and ongoing oncologic treatment. SPC clinician completed a written form, categorizing the information/prognosis data and added his evaluation as "correct" or "not correct". Treating Oncologists completed an anonymous questionnaire on communication attitudes.

Results: IPOS score for "as much information as wanted" (n=95) was: 0 ("always") 64%, 1 ("most of time") 22%, 2 ("sometimes") 14%, with no responses for 3 or 4.

Information/awareness wasn't evaluable in 8 cases, when Pts didn't enter an open conversation on the subject. Among the evaluable Pts 99% were aware of their cancer diagnosis; 9% though they had a curable disease, 81% acknowledged the cancer was incurable but would respond to therapies, 9% believed no more therapeutic options were available. Only 11% of Pts had incorrect awareness, and 10% of Pts displayed signs of anxiety or partial denial. IPOS score 2 was significantly associated with incorrect evaluations and non-evaluability (χ^2=10.57; p=0.001).

Oncologists (11/12 responses) reported that they disclose diagnosis and non-curability always or with rare exceptions, and that Pts want to be informed.

Conclusions: A high % of Pts were informed on diagnosis of cancer and aware of purpose and limits of oncologic care in an Italian context, when physicians are committed to.

Specific IPOS score predicted no awareness or reluctance to receive information, underscoring the need for targeted communication strategies in oncological care.

G16

PHARMACOLOGICAL DEPRESCRIPTION IN ONCOLOGY PATIENTS IN THE TERMINAL PHASE OF LIFE: A PROSPECTIVE ANALYSIS

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Background: Deprescription refers to the process of identifying and discontinuing medications in patients with advanced cancer (pts) when potential side effects outweigh the benefits. Evidence suggests that deprescription optimizes resource allocation, reduces treatment side effects and interactions, but also enhances therapy adherence. However, ensuring appropriate pharmacotherapy at End of Life (EoL) remains challenging. This study aimed to evaluate deprescription in pts with advanced breast cancer at EoL, and understand whether it is facilitated or hindered by Palliative Care or patient-specific factors.

Patients and Methods: In this single-institution, prospective, observational study, we collected data about advanced breast cancer pts with a life expectancy of less than one year. The objectives of the study were to evaluate the intake of Potentially Inappropriate Medications (PIMs), understand the role of Palliative Care in the deprescription process and any correlations between PIM intake and individual patient characteristics. The definition of PIMs was based on the most recent OncPal guidelines.

Results: Between August 2022 and February 2024, 50 pts have been enrolled in the study. We analyzed data from the 22 pts that we were able to follow for one year within the study. The majority received PMIs in this period of time

(77.3%; N=17) and roughly half of them (59,1%; N=13) were evaluated by the Palliative Care team. 7 pts (31.8%) died in the observed time, all of whom were taking PMIs (100%; N=7). The most common PMIs observed were blood pressure medications (50%; N=11) and anti-ulcer medications (36.4%; N=8). No association was found between PMIs administration and Palliative Care evaluation (p=0.609), nor with tumor histology (p=0.277). However, a statistically significant correlation was observed between the administration of PMIs and older age (p=0.03).

Conclusions: Our analysis shows that deprescribing in advanced breast cancer pts is still suboptimal at our institution. Indeed, most pts in our study were administered PMIs, exposing them to potential side effects, interactions, worsening adherence to life-saving therapies, hampering their quality of life. Although our analysis was not able to identify any correlation between Palliative Care evaluations and the deprescribing process – which may be due to the small sample size – early use of Palliative Care services is always advisable, as recommended by national and international guidelines.

G17

THE EFFECTIVENESS OF TOPICAL CANNABIDIOL IN SYMPTOMATIC RELIEF OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY OF HANDS AND FEET IN BREAST CANCER PATIENTS

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Background: Chemotherapy-induced Peripheral neuropathy (CIPN), caused by breast cancer antineoplastic treatments, can significantly impact patients' quality of life, considering that current therapies (tricyclic antidepressants, anticonvulsants, SNRI, alpha lipoic acid, acupuncture) often fail to deliver adequate symptom relief and can have significant side effects. In recent years, however, there is great evidence in the literature regarding the use of cannabinoids in the treatment of neuropathic pain but not for CIPN. In this study, we aim to investigate the effectiveness of topical cannabidiol (CBD) in the symptomatic treatment of CIPN of the hands and feet.

Material and Methods: A total of 20 breast cancer patients, with CIPN grade =2 at the hands and feet and with ongoing antineoplastic treatment (taxanes and platinum predominantly), were recruited and received topical product containing 350 mg of CBD for 3 fl. oz container to be applied topically to the symptomatic areas up to four times per day for the next 4 weeks. Previous treatments for CIPN were allowed. The Neuropathic Pain Scale (NPS), evaluating the qualities and intensities (hot, dull, cold, sensitive, itchy, deep and surface pain) of CIPN, was administered ate baseline and biweekly to assess the mean change from baseline to the end of the treatment period. The study took place from December 2023 to March 2024.

Results: The mean value of baseline scores across all NPS domains was identified for hands and feet respectively. The top scoring baseline sensations were in unpleasant, surface and deep domains for hands (5.75, 5.6 and 5.5) and in surface, deep and intense domains for feet (5.95, 5.9 and 5.2). A clinically decreasing trend from baseline was observed in all NPS domains at 2 and 4 weeks. In particular, the mean decrease was significantly larger in unpleasant, surface and intense domains for hands (-2.1, -1.75 and -1.7) and intense, dull and deep domains for feet (-1.35, -1.2 and -1.1). No adverse events were reported in this study.

Conclusions: Our findings demonstrate that in breast cancer patients with CIPN the topical application of CBD can achieve significant and clinical improvement in pain and other disturbing sensations of hands and feet. The treatment product was well tolerated and may provide a more effective alternative compared to other current therapies for the treatment of CIPN, improving quality of life and antineoplastic treatment compliance.

G18

THROMBOPOIETIN RECEPTOR AGONISTS (TPO-RAS): A PROMISING THERAPY FOR CHEMOTHERAPY INDUCED THROMBOCYTOPENIA (CIT)

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Background: Chemotherapy-induced thrombocytopenia (CIT) can be an adverse event of oncologic treatments and affects about 1/3 of patients with solid tumor. It can lead to morbidity and mortality from hemorrhagic events and can complicate the whole management of oncologic patients. A platelet count below 100×10^9/L is often

managed with reduction of therapy relative dose intensity (RDI), influencing oncologic outcomes and patients' psychological well-being.

Material (patients) and Methods: The use of thrombopoietin receptor agonists (TPO-RAs) in managing CIT aims to increase platelet production by stimulating bone marrow megakaryocytopoiesis, but their use is debated. We aimed to evaluate TPO-RAs efficacy in treating CIT and assess their safety profile.Thirteen oncologic patients with CIT were treated off-label with TPO-RAs at Policlinico Umberto I – Sapienza University of Rome. Data were collected retrospectively.

Results: On a total cohort of 13 patients, 7 (54%) were males, 6 (46%) were females. Four (31%) had a previous diagnosis of Immune thrombocytopenic purpura (ITP). All patients had with platelet count $<100\times10^9$/L and this hindered the administration of proper cancer therapy. First-line corticosteroid treatment was ineffective in achieving persistent platelet response, with a median maximum platelet count (MMPC) of 58×10^9/L, (IQR 38×10^9/L). Bone marrow assessments were performed before TPO-RAs administration, revealing metastatic involvement in 2 cases. Median age at TPO-RA start was 55 years. Romiplostim and Eltrombopag were used respectively in 6 (46%) and 7 patients (54%). Median treatment duration was 6 months (IQR 12). Twelve/13 (92%) achieved a platelet count $>100\times10^9$/L within a median of 14 days (IQR 10) and maintained persistent response. This allowed them to correctly attend oncologic treatments. Moreover, 3 (23%) were even able to discontinue TPO-RAs administration. MMPC reached during TPO-RAs was 244×10^9/L (IQR 161×10^9/L); median follow-up was 7 months (IQR 10). At last visit, median platelet count was 133×109/L (IQR 114×10^9/L). No thrombotic complications occurred. Three patients deceased due to infection or cancer progression.

Conclusions: TPO-RAs seemed to be efficacious, well tolerated and safe in CIT management, enabling patients to undergo anticancer therapy without RDI reduction, which is a crucial outcome for both the oncologic course and psychological well-being. However, further studies on larger cohorts are needed to validate these findings.

G19

THE BREAKTHROUGH CANCER MALNUTRITION

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Background: The BreakThrough cancer pain (BTcP) is a symptom influencing several aspects of daily life and, if not adequately treated, may also lead to decreased food ingestion, inducing malnutrition. Aim: to test the hypothesis that BTcP could affect patients' nutritional status.

Material and Methods: Patients with metastatic cancer and BTcP from palliative care and oncology departments were included in an observational, prospective Italian multicenter study "NO PAIN Study".

Malnutrition was defined as present with an Mini Nutritional Assessment (MNA) screening score score<8 and a Body Mass Index (BMI) <21 Kg/m2.

Results: The 61 patients were enrolled; aged 70+11; the majority (65%) had metastatic primaries of the lung and liver, and PS of 2 (64%].

Pts reported 2,4 ± 0,9 BTcP episodes/day, with a mean NRS of 7.0 ± 1. In 74.5% a rapid onset (<10 min) and short time from diagnosis of pain to onset of BTcP (37.2+38.5 day, median 30) was reported.

A BMI <21 in 64.2%, anorexia at MNA was present in 62.4% pts. According to MNA screening score, malnutrition was present in 58.5%.

Pts with malnutrition had a higher number of BTcP in the previous 24h (2.5 +1.0 vs 2.3+0.9, p=0.45), with a higher distance from diagnosis (44.8+45.5 day vs 24.4+21.5, p=0.06). After 4 wks of BTcP treatment, 60% pts were reassessed; a significantly reduction in the number of BTcP episodes (2.3 +1 to 1.0+1.0, p<0.01) and NRS (7.0 +1.0 to 4.2+2.0, p<0.01) was documented. In 30% pts an improvement in the nutritional status was also observed, and anorexia improved in 27.3% pts, worsening only in 2 (6.1%) (p<0.01).

Conclusions: In cancer patients with BTcP negative consequences on the nutritional aspect were present in more than 50% of pts. After 4 wks of BTcP treatment, significant improvement in BTcP was observed, with an overall positive effect on nutritional aspects. We proposed the term BreakThrough Cancer Malnutrition (BTCM) as the exacerbation of malnutrition that occurs in a cancer patient with BTCP, when it is ongoing and uncontrolled.

G20

THE CONTINUOUS REFINEMENT OF PERFORMANCE STATUS (PS) SCALES: A PROPOSAL FOR A "GUIDED" PS SCALE (GPS)

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Background: Psychometric tools, like PS scales, are a significant part of oncological practice and, as every medical technology, need continuous refinement. Main weaknesses of ECOG and Karnofsky (KPS) scales include intra- and inter-observer variability and the lack of a well defined mode of comparison between the 2 scales. In the past years, the use of pre-defined questions has been proposed as a method to empower PS scales, without clinical application so far (Schag Coscarelli C, JCO 1984; Péus D, BMC Med Inf Decis Mak 2013).

Methods: An analyitical evaluation of the terms used by ECOG and KPS scales was perfomed by a team of clinical oncologists and nurses, looking for key similarities and differences. These considerations were matched with some specific "words" and questions commonly used by patients and health operators during clinical interviews, in search of a possible synthesis.

Results: The main similarity was "symptoms", included in both ECOG 1 and KPS 80-90% while the key difference was the description of daily unactivity and dependence: "bed time" in ECOG scale and inhability "to carry on normal activity or to do active work" or "need for assistance" in KPS. Matching these considerations with "rest" and "effort", a new 7-degree scale, called guided-PS (gPS), was described:

gPS value	Description
0	Normal: active life
1	Mild symptoms/signs of the disease
2	Effort for normal activity
3	Unactivity – Bed time - Rest - Asthenia
4	Frequent assistance and medical care
5	Total disability
6	Dying process

A set of 7 questions, 6 for patients and 1 for health operators, was identified as particularly relevant to estimate gPS, each accompained by a limited number of pre-defined, reasonable answers.

N	Question	Answers
1	Anything worse in the last weeks?	Nothing/Something/Everything
2	Do you spend "active" days?	Fully/Partially/No
3	Have you got symptoms or signs of the disease?	No/Mild/Relevant
4	Do you feel tired?	No/Yes, I can work/Yes, I cannot work
5	Are you able to care for yourself?	Completely/Mostly/No
6	Do you need assistance?	No/Occasional/Significant/Total
7	*Is there space for hospital discharge?	Possibly/Protected/No way

The gPS scoring is based on specific combinations of answers; a.e. for, respectively, gPS 0, 2 and 4, all the bold, underscored or bold/underscored answers must be obtained. A colorful legend is provided with the instrument.

Conclusions: The gPS tries to improve commonly used PS scales by bringing together their key words while reducing subjectivity; it also introduce in PS scales the evauation of two key aspects of the daily oncological practice: the temporal dimension and the health operators' "clinical feeling" (questions 1 and 7 respectively). Such an instrument surely needs a wide and cooperative effort to be clinically validated in comparison to ECOG and KPS scales; however, we can strongly hypotesize that the matched pre-defined questions make gPS very interesting for experimental purposes.

G21

PALLIATIVE CARE IN METASTATIC BREAST CANCER PATIENTS: A RETROSPECTIVE ANALYSIS IN MODENA CANCER CENTRE - PALLIATIVE CARE UNIT

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Background: Over the last few years, the survival rates for metastatic breast cancer (mBC) patients (pts) have improved thanks to increasingly treatment options, without significant deterioration in quality of life. Even if the natural history of mBC is extremely variable according to biological intrinsic aggressiveness, mBC pts tend to face palliative care later than other tumor types.

Materials (patients) and Methods: A retrospective analysis was conducted on mBC pts admitted to the Palliative Care Unit (PCU) of Modena Onco-Haematological Department between January 2022 and December 2023. ESAS and PERSONS scores were applied at hospital admission as tools for the subjective evaluation of pts' symptoms and needs, while PAP score was used to estimate prognosis.

Results: 32 pts were included, representing 6% of total PCU admissions in the reference period. Median age was 73 years (range 53-91) and principal sites of metastasis were bone (90.6% of pts), liver (40.6%) and lung (31.3%). At the time of admission 56.3% of pts were on supportive care only, the others being on active oncological treatment (median number of therapies was 6, range 2-9); in particular, 28.1% of pts were on chemotherapy (CHT), the others were on endocrine therapy. The majority of pts was admitted from other hospital wards, while the 43.8% of them were referred by Home Care Services. The predominant reasons for hospitalization were pain (34.4%), worsening of clinical condition (31.3%) and dyspnoea (28.1%). Most pts (59.4%) died in hospice, of which 63.2% undergoing palliative sedation due to uncontrolled refractory symptoms such as dyspnoea, pain and delirium. All pts receiving CHT died during hospitalization or within a month from discharge. ESAS, PERSONS and PAP median scores were respectively 35, 25 and 10 (nearly 75% of pts had a PAP score = B). No significant statistical correlation was found between score values and survival outcomes.

Conclusions: The proportion of mBC pts receiving active oncological treatment at the end of life is significant, probably due to the usually preserved performance status and the long trajectory of this disease. In this context, mBC pts face palliative care too late. An aid for the oncologists to identify pts with greater need for supportive care may come from an earlier application of ESAS, PERSONS and PAP scores, even in outpatient setting, and a commitment to continuity of care.

G22

ASSESSING THE FEASIBILITY OF EARLY NUTRITIONAL SCREENING AND REFERRAL IN PATIENTS WITH THORACIC CANCERS: PREPLANNED PRELIMINARY ANALYSIS OF A PROSPECTIVE OBSERVATIONAL TRIAL

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Background: Impaired nutritional status is common among pts with thoracic cancers, and its is associated with a higher incidence/severity of treatment-related side effects, decreased responsiveness to therapies, diminished quality of life, and shortened survival. This study aims to assess the feasibility of implementing an Assess-Advise-Refer (AAR) approach to engage medical staff in referring pts at risk of malnutrition to a specialized dietitian.

Material (patients) and Methods: Thoracic oncologists were trained to: i) administer the NRS-2022 (Nutritional Risk Screening) tool to pts during the first oncological evaluation, ii) advise pts about the importance of nutrition, and iii) refer pts at risk for malnutrition to dedicated registered dietitians. Pts with thoracic malignancies (i.e., non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), mesothelioma and other rare histologies) at any stage, between July 2022 and February 2024, who performed a first oncological evaluation and underwent NRS-2002, were included. Descriptive statistics were used to analyze data.

Results: During this period, a total of 242 pts with thoracic cancer performed an initial oncologic evaluation. Among them, 57 (23.5%) were assessed, by medical oncologists, for nutritional risk. NRS-2002 was not administered in most cases due to a lack of time (153 pts, 82.7%). Overall, patients' mean age was 66.2, 9 (16%) were over-75 years and 49 (85%) had NSCLC. Almost all pts, 44 (77%) had a stage IV disease and 8 (14%) were at nutritional risk. All 57 pts (100%) received NRS-2002 administration and advice from the oncologist regarding the significance of nutrition care during treatment. Those pts identified at nutritional risk were referred to the specialized registered dietitians (100%). Additionally, 10 other pts were referred to the dietitians upon their request. In total, 18 (31.6%) pts underwent a comprehensive nutrition assessment and diagnosis of malnutrition and subsequently received personalized nutrition intervention.

Conclusions: AAR process is only partially integrated as part of clinical practice in thoracic cancer management. Based on these results, and considering the potential impact of malnutrition on prognosis, future initiatives are needed to enhance the AAR process in clinical practice.

G23

ONCOLOGISTS FACING THE DEATH OF THEIR PATIENTS

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Background: Among oncologists, the word "death" is still taboo; speaking of overall survival is much preferred. Within the context of a training course on holistic care for cancer patients (pts) at the end of their lives, a survey was administered to participants.

Material and Methods: The survey was comprised of 26 open questions about how the staff approach end-of-life care for pts and how the experience of caring for pts impacts their personal lives. The survey was emailed before the beginning of the course to the 32 health professionals.

Results: 17 respondents (rs) reported that they are not always able to suspend active therapyt for pts when such treatment is no longer appropriate (76.5%), and that they have difficulty understanding on their own when the time comes to suspend (94.1%); even when they do understand that the time has arrived, a more senior colleague may decide otherwise (88.2%), causing feelings of inadequacy, guilt, and sadness (58.8%). Survey responses indicate that not discussing a short-term poor prognosis (pg) directly with a patient (pt) translates into a loss of opportunities for pt (47.1%), that the average length of a visit with a pt with a poor pg ranges between 15 and 30 minutes, and that the time devoted to such conversations is perceived as inadequate (52.9%). Just over half of the rs reported that they are able to look a pt in the eyes when disclosing a short-term poor pg (52.9%); when this does not happen, it is because of a feeling of unease (33.3%) or a fear of showing one's emotions (44.4%). Following a religion is not considered necessary to care for a pt at the end-of-life (100%), while having experienced the loss of a loved one is considered helpful to better understand pts and their families (81.3%). 50% of the rs inquire about the personal lives of patients with a poor pg, 25% do not ask pts about their religious and/or spiritual preferences, but 31.3% are willing to - although they do not - and 31.3% always do if the pt agrees. Most of the rs think or dream about the pts they see during the day (75%), mostly with feelings of empathy and compassion (73.3%). A large subset feel that work impacts their personal life, whether sometimes (43.8%) or often (43.8%).

Conclusions: Its small sample size notwithstanding, the survey highlights the fact that, despite advances in cancer treatment, oncologists still perceive the word "death" as their limitation, instead of the natural ending of the life of a pt with advanced cancer.

G24

PROSPECTIVE OBSERVATIONAL STUDY WITH ORAL SUCROSOMAL IRON AS PREVENTION OF CHEMOTHERAPY-RELATED ANEMIA

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Background: Patients undergoing chemotherapy often experience a decrease in hemoglobin (Hb) levels, requiring treatment with erythropoietic stimulating agents (ESAs) or blood transfusions, which can sometimes lead to delayed treatment and a worse prognosis. It has been observed that raising Hb levels above 12 g/dl is associated with an improved quality of life.

Materials and Methods: This study included n=26 patients with Hb levels between >10 and <12 g/dl, and transferrin saturation (TSAT) levels between >15% and <50%, who were about to start chemotherapy for a solid tumor. Sixteen of these patients received platinum-based chemotherapy. The patients were treated with a 30 mg dose of sucrosomal iron (Sideral Forte®) for a period of 12 weeks. The primary objective of the study was to evaluate the effectiveness of treatment in preventing further Hb decline in patients with mild anemia. The secondary objectives were to assess the percentage of patients who experienced Hb levels below 10 g/dL during treatment, as well as the percentage of patients who required ESAs therapy and/or blood transfusions. The study received approval from the local ethics committee.

Results: At baseline and after 12 weeks, various parameters including complete blood count, ferritin, transferrin saturation, serum iron, Vitamin B12, and folate were assessed. In addition, any side effects attributed to sucrosomal Iron were recorded after 12 weeks. Out of the 26 patients, n=14 had advanced-stage disease while n=12 had early-stage disease. Only one patient experienced grade 3 nausea, leading to the discontinuation of sucrosomal Iron treatment. Six patients reported grade 2 events, namely nausea, vomiting, and diarrhea, which investigators attributed to chemotherapy rather than the iron product. No patients required red blood cell transfusions or ESAs. Only two patients had a decrease in hemoglobin levels below 10 mg/dL.

Values (mean)	Time 0	Time 12 weeks
Hemoglobin	11,07 g/dL	11,03 g/dL
Ferritin	220,9 mcg/L	329,7 mcg/L
Tranferrin saturation	12,8%	20,2%
Serum iron	39,7 mcg/dL	79 mcg/dL

Conclusions: The administration of sucrosomal iron to moderately anemic patients prior to commencing chemotherapy has facilitated the completion of cancer treatments without the requirement for ESAs or transfusions, consequently avoiding cycle delays. This approach has not only resulted in reduced patient inconvenience, but also yielded economic benefits. Furthermore, the treatment was highly well-tolerated.

G25

TRANSDERMAL FENTANYL IN CACHECTIC PATIENTS - A SYSTEMATIC REVIEW OF LITERATURE

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Background: In clinical practice, cachectic patients often require Transdermal Fentanyl (TDF) for pain management, and many develop cachexia during treatment. However, data on the impact of cachexia on TDF efficacy and safety are scarce and heterogeneous. This systematic review aims to analyze and categorize evidence on TDF pharmacokinetics (PK) in cachectic patients, regardless of the underlying pathology. The primary objective is to evaluate the analgesic efficacy and tolerability of TDF, while the secondary objective is to identify cachexia characteristics that may alter fentanyl PK and plasma levels.

Material and Methods: A systematic review of PubMed, Embase, and Web of Science databases was conducted up to March 2024. We included observational and clinical studies on cachectic patients with moderate to severe pain treated with transdermal fentanyl (TDF) patches at any dosage or frequency. We excluded phase 1 trials, animal or lab models, ecological studies, cross-sectional studies, case reports, case series, editorials, letters, preclinical studies, and conference abstracts. Study quality was appraised using the National Institutes of Health (NIH) Quality Assessment Tool for observational studies and the Joanna Briggs Institute (JBI) Critical Appraisal Tool for non-randomized clinical studies.

Results: The review included ten articles, comprising five observational studies and five non-randomized clinical studies. The definitions of cachexia varied across these studies. Six studies investigated opioid conversion to or from transdermal fentanyl (TDF), whereas four studies applied TDF patches without documenting prior opioid use. Five studies reported that cachexia negatively impacted TDF efficacy, tolerability, and PK; three studies found no significant effect; and two studies suggested a protective effect. According to the NIH Quality Assessment Tool and the JBI Critical Appraisal Tool, all studies were of medium to high quality.

Conclusions: The existing evidence regarding the impact of cachexia on TDF efficacy and safety is limited and heterogeneous with respect to study design, participants, definitions of cachexia, types of interventions, and outcomes. Consequently, the results from individual studies are conflicting and do not support precise guidelines for prescribing TDF in cachectic patients. This review highlights the necessity for a prospective clinical study with a larger population to accurately address this issue.

G26

EVALUATING A MULTIDISCIPLINARY OUTPATIENT INTERVENTION ON THE DISEASE EXPERIENCE OF END-STAGE ONCOLOGICAL PATIENTS AND THEIR CAREGIVERS: A CASE-CONTROL STUDY AT SAN GIOVANNI HOSPITAL IN TURIN

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Background: This article reports the results of a longitudinal clinical case-control study investigating the impact of end-stage oncologic disease on patients and the perceived burden on their caregivers. It compares those who participate in a multidisciplinary outpatient care model with those who do not. The Continuity of Care Ambulatory at San Giovanni Bosco Hospital (Turin, Italy) follows the Early Palliative Care Guidelines and provides support for terminal cancer patients and their families. The peculiarity of this Ambulatory is that visits involve an oncologist, a clinical psychologist, a social worker, and a nurse

simultaneously. The scientific literature emphasizes the multiple needs of cancer patients, which require adaptations both within the family dynamics to cope with new tasks, challenges, forms of communication and intimacy (Granieri et al., 2021) and within a health context that responds to the transversality of demands. In the advanced stages of the disease, these needs intensify, underlining the need for a multidisciplinary team.

Material and Methods: The Continuity of Care Ambulatory provides a multidisciplinary model of care for advanced-stage oncology patients and their caregivers. Participants were divided into an experimental group (with support from the clinic) and a control group (without support). Patients completed tests at enrollment, including sociodemographic and clinical data forms, TAS-20, IPOS, Distress Thermometer, and a clinic satisfaction questionnaire (experimental group only). Caregivers provided sociodemographic data, TAS-20, CBI, and a clinic satisfaction questionnaire (experimental group only). The first tests (T0) were followed by a new test one month later (T1). Data collection ran from November 2022 to March 2024.

Results: Patients attending the Ambulatory (n=23) reported greater emotional awareness 4 weeks after the T0 (t=-2.982, p=.007). Among caregivers (n=16), there was a significant increase in perceived caregiver burden (t=-2.274, p=.04) and physical stress (t=-3.105, p=.007). This increase is related to disease progression, medical procedures, treatments, witnessing relatives' suffering, fear of loss and death.

Conclusions: The impact of cancer on the somato-psychological balance of the family is exacerbated in advanced stages. These results encourage reflection on multidisciplinary care protocols that involve different professionals for end-of-life support and enable the improvement of residual quality of life.

G27

TOPICAL CANNABIDIOL IN SYMPTOMATIC RELIEF OF ENFORTUMAB VEDOTIN-INDUCED PERIPHERAL NEUROPATHY IN METASTATIC BLADDER CANCER PATIENTS

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Background: Enfortumab vedotin (EV) is now the standard treatment for metastatic bladder cancer. However, EV is associated with chemotherapy-induced peripheral neuropathy (CIPN) in 50-58% of cases (grade 3-4 in 4-8%) and causes a worsening of the quality of life of these patients, who are already previously treated with platinum-based therapies (typically neurotoxic). Considering that current treatments for CIPN are not very active in improving the symptom and are often associated with side effects, we have conducted a clinical experience with topical cannabidiol (CBD), with recent demonstrations in neuropathic pain, for the treatment of EV-induced CIPN.

Material and Methods: From December 2023 to March 2024, a total of 10 metastatic bladder cancer patients, with CIPN grade ≥2 of hands and feet and undergoing EV treatment, were recruited and received topical product containing 350 mg of CBD for 3 fl. oz container to be applied topically to the symptomatic areas up to four times per day for the next 4 weeks. Previous treatments for CIPN were allowed. The Neuropathic Pain Scale (NPS), evaluating the qualities and intensities of CIPN, was administered at baseline and biweekly to assess the mean change from baseline to the end of the treatment period.

Results: The mean baseline scores across all NPS domains (hot, dull, cold, sensitive, itchy, deep and surface pain) were identified for hands and feet respectively. The top scoring baseline sensations were in unpleasant, dull and deep domains for hands (6.4, 5.8 and 5.7) and in deep, surface and unpleasant domains for feet (6.0, 5.5 and 5.3). A clinically decreasing trend from baseline was observed in almost all NPS domains at 2 and 4 weeks. In particular, the mean decrease was significantly larger in unpleasant, deep and dull domains for hands (-3.2, -2.7 and -2.3) and in deep, surface and unpleasant domains for feet (-2.2, -2.0 and -1.5). No adverse events were reported in this study.

Conclusions: In this clinical experience we demonstrate that EV-induced CIPN can achieve significant and clinical improvement with topical application of CBD to the hands and feet. The treatment product was well tolerated and may provide a more effective alternative compared to other current therapies for the treatment of CIPN, improving quality of life and antineoplastic treatment compliance. Further our studies are needed to evaluate the long term effectiveness of topical CBD.

G28

SIMULTANEOUS CARE PROVISION IN SCLC IN LAZIO REGION: INSIGHTS FROM MULTICENTRIC EVALUATION

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Background: Small Cell Lung Cancer (SCLC) is a lethal neuroendocrine tumor accounting for 15% of all lung cancer cases. Due to comorbidities and aggressive behavior of the disease, patients are generally highly symptomatic even if diagnosed at a non-metastatic stage thus requiring multidisciplinary management involving different specialists. In this context, the standardization of the care pathway and the introduction of a simultaneous care approach could provide a response to the unmet needs of this disease. However, there is no uniformity in the involvement of palliative care physicians and the simultaneous use of palliative care and anti-tumor therapies.

Materials and Methods: The project engaged firstly 12 specialists in 2023 and secondly 9 in 2024 encompassing oncologists, palliative care physicians, radiotherapists, and psychologists. They submitted a survey focused on the investigation of the following areas: provision of simultaneous care, organizational requirements, multidisciplinary team, patient assessment, pharmacological and non-pharmacological resources, KPI, professional training, and patient communication. The results were functional in the identification of the main unmet needs.

Results: The survey provided an analysis of the distinctive characteristics of 15 hospitals, covering approximately 60-90% of SCLC cases in the region. Significant variations were observed in the percentages of chemotherapy and radiotherapy execution among different centers. Additionally, notable differences were noted in the provision of palliative care. In 20% of the centers, neither a multidisciplinary team for lung neoplasms nor a dedicated PDTA (diagnostic and therapeutic care pathways) is formalized. Furthermore, in 67% of the centers, there is no involvement of palliative care physicians in new diagnoses, and the involvement of psychologists and nutritionists is often poorly defined. In almost all centers, monitoring systems for indicators related to the patient's care pathway and the provision of simultaneous care are lacking.

Conclusions: The expansion of the investigation has confirmed the presence of a heterogeneous approach in the context of simultaneous care, with areas identified for potential improvement. The Lazio region highlights opportunities for standardization of clinical practices, as well as the need to increase the number of professionals involved in the overall management of the patient, in order to enhance quality of life.

G29

THE ROLE OF ACUPUNCTURE IN MANAGING ORPHAN SYMPTOMS RELATED TO ANTINEOPLASTIC HORMONAL TREATMENTS FOR LUMINAL BREAST CANCER: INSIGHTS FROM THE INTEGRATED THERAPIES ONCOLOGY OUTPATIENT CLINIC AT "GIUSEPPE MAZZINI" HOSPITAL, TERAMO

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Background: "Orphan symptoms" are those symptoms considered minor in clinical practice, but which can be disabling for the patient. The literature regarding the management of these symptoms is anecdotal. Among the "orphan symptoms" most frequently encountered in oncology clinics are arthromyalgia and the sensation of "hot flashes" typically associated with adjuvant hormonal treatments for luminal breast cancer. The frequency and intensity of these symptoms is such that they often limit the treatment adherence, even more so in the adjuvant setting. Acupuncture could have a supporting role in the management of this symptomatology.

Patients and Methods: A prospective observational study was conducted from October 2022 to March 2024, in which patients who complained of the onset of arthromyalgia or hot flashes during hormonal treatments, were enrolled at the oncology outpatient clinic of integrated therapies at Mazzini Hospital in Teramo. Patients were identified by the referring oncologist and subsequently accessed the interview with the acupuncturist.

Results: Patients with a history of breast cancer undergoing hormonal treatment, in any care setting, who presented symptoms such as arthromyalgia or hot flashes following the start of hormonal therapy were considered eligible for acupuncture treatment. Forty women with breast cancer were included in the study. The average age was 56 years

(range 41-77). Performance Status according to ECOG was: 1 (86%); 2 (14%). 14 of the included patients (35%) had both symptoms. Five of the included patients had metastatic disease (12.5%). Overall, the patients underwent an average of 7 acupuncture sessions (range 2-12). No adverse events occurred due to acupuncture. Before starting treatment, during and at the end of treatment, patients were invited to rate the symptoms intensity and quality of life measured by the "QLQ-C30 QoL subscale". The results of the questionnaires administered showed an improvement in the quality of life and better control of the orphan symptoms examined for all 40 patients interviewed.

Conclusions: This single-center real-life work attempted to explore the effectiveness of acupuncture in the management of the most frequent orphan symptoms during hormone therapy in breast cancer. Overall, patients undergoing acupuncture reported not only a reduction in the intensity of perceived symptoms, but also an overall improvement in quality of life and a benefit in terms of adherence to hormonal treatment.

G30

PRACTICES AND VIEWS ABOUT PALLIATIVE CARE AT THE END OF LIFE: A SURVEY OF ONCOLOGISTS FROM THE ITALIAN REGION OF LIGURIA

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Background: We conducted an online survey to investigate oncologists' clinical practices and views on palliative care (PC) at the end of life (EoL) in the Italian vregion of Liguria.

Methods: The survey included 29 items divided into three sections: participant characteristics (n=6), hospital resources and practices (n=11), participant practices and views (n=12).

Results: Twenty-one of the 41 medical oncologists invited completed the survey (51%). Although almost all reported the presence of Palliative Medicine Physicians (PMPs) at their hospitals (90%), nearly half (48%) stated that PMPs were not responsible for managing cancer patients at EoL, and 21% reported routine participation of PMPs in multidisciplinary (MDT) meetings. Thirty-eight percent of the respondents stated they never consulted psychologists regarding EoL patient care, and 43% reported they rarely did. Notably, a substantial proportion of participants stated that they administered active treatments to patients with six months life expectancy (38% answered 25-50% patients, 33% answered 50-75%, 19% answered <25%, and 10% answered >75%). Regarding integration between oncology and palliative medicine, an equal proportion felt it had been fully (48%) or partially achieved (48%) at their hospitals.

Conclusions: Participants seemed fairly satisfied with the level of integration between oncology and palliative medicine at their hospitals, which contrasts with other findings regarding, for instance, the scant participation of PMPs in MDT meetings. Exploring the impact of the novel regional clinical healthcare pathway for PC on practices at hospitals in Liguria will be crucial to ensure that cancer patients at EoL receive quality care.

G31

NEUROTOXIC EFFECTS OF ONCOLOGICAL DRUGS: ASSESSMENT STUDY OF THE ONSET OF HEARING LOSS AND TINNITUS IN ADULT PATIENTS AFTER TREATMENT WITH CISPLATIN AND TAXOL

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Background: Platinum-based (P) chemotherapeutic drugs (CTx) and taxol (T) and its derivatives can lead to irreversible sensorineural hearing loss (HL), particularly in a bilateral and symmetrical manner,and this effect is dose-dependent. Data on the risk of HL after T are limited due to insufficient studies.

Material and Methods: We conduced a retrospective observational study on patients (pts) treated with P, T, and PT combinations for solid tumors. The study was carried out at the Oncology Department of ASST-Rhodense(Feb-Dec 2022).The aim was to evaluate the ototoxic effects in terms of onset of HL and tinnitus and the importance of treatment, such as hearing aid provision.Two questionnaires were administered,an audiological history questionnaire to assess the clinical history prior to CTx;APHAB questionnaire to assess any subjective HL after CTx.Pts reporting tinnitus presence were evaluated with THI.All pts underwent pure tone, bone, and supra-threshold audiometry to assess potential HL even if not manifested during the APHAB questionnaire.While pts reporting a suspicion of post- CTx tinnitus sensation underwent tinnitus matching.

Results: 32 pts were evaluated, 20 female(F) and 12 male(M), median age 55(range 43-64).12.9% had received

P, 56.3% T, and 30.8% PT. Of these 32 pts, 9 showed bilateral sensorineural HL, and 2 showed tinnitus presence. Bilateral sensorineural HL was in 6F and 3M, while tinnitus was observed in one F, who also had sensorineural HL, and in one M. In the group of F, two treated with T for breast carcinoma: 1 moderate bilateral HL, and 1 moderatemild bilateral HL. The pts with moderate HL was fitted with a hearing aid, while the one with moderate-mild HL refused. A pt with ovarian carcinoma treated with the PT showed moderate-mild HL and was then fitted with a hearing aid. Among the 3F with stomach tumors, 2 treated with P:1 with mild HL and 1 with moderate HL. The pt with moderate HL had preserved speech frequencies and did not require hearing aid provision. The pt with moderate bilateral HL treated with T was fitted with a hearing aid. In the group of M, 2 treated for gastric cancer with P showed moderate bilateral HL subsequently fitted with a hearing aid and one with mild HL. A pt with lung cancer treated with T had moderate bilateral HL. Tinnitus presence was in 1F with HL due to breast cancer treated with T, and in 1M with lung cancer who received P.

Conclusions: The study emphasizes the importance of standardized planning and increased monitoring for ototoxic effects associated with these CTx.

G32

EARLY SIMULTANEOUS CARE USING AI TO IMPROVE QUALITY OF LIFE IN HEAD AND NECK PATIENTS WITH PAIN, MALNUTRITION AND MUCOSITIS, BETWEEN HOSPITAL AND HOME CARE

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Background: Pain and malnutrition worsen cancer-related cachexia and quality of life in many oncology patients with head and neck cancer in hospital and home care. During cytotoxic treatments and radiotherapy they develop malnutrition due to odynophagia, dysphagia and severe mucositis. Transdermal therapy such as fentanyl can provide effective pain relief. In any case, by using ROO before the meal we reduce odynophagia and increase food intake even with the oral food supplement. We measure Sarcopenia with the EWGSOP algorithm and the SARC-F scale and increase essential amino acid supplements to improve swallowing, increasing the tone of the tongue. High-grade mucositis, as measured by CTCAE, is treated with benzydamine, antifungal mouthwashes, and Roo.

Methods: In the context of head and neck cancer patients, early dysphagia/odynophagia occurs frequently. To understand the general clinical status, validated questionnaires on malnutrition, sarcopenia and pain were administered to the patients at the time of diagnosis, Therefore, measuring bioimpedance at time zero allowed monitoring of the body composition with the phase angle cut at 6 degrees. We tested this data with artificial intelligence.

A lower score indicates the need to use ONS to slow cachexia and increase essential amino acid support to slow sarcopenia. These patients present with pain when swallowing leading to malnutrition and sarcopenia. Underlying pain was treated with transdermal fentanyl and/or buprenorphine patches in dysphagic patients and sublingual or intranasal ROO. Mucositis has been treated with miconazole, also in mucoadhesive tablets for patients with severe dysphagia. By monitoring patients even at home, we observed the continuity of care and therapy.

Results: Malnutrition in patients suffering from head and neck cancer represents a disabling condition for the quality of life and suitability for treatment. Early evaluation of malnutrition, pain and mucositis allows timely supportive therapies that improve the patient's quality of life and improves tolerance to therapies.

Malnutrition Mucositis Pain Qol					
malnutrition(P.A)	3	4	4.6	5	5.8
mucositis	3	3	2	2	1
pain	8	7	5	3	1
qol (PS Sec Karnofsky)	50	50	60	60	70

Conclusions: Simultaneous therapy activated early, both in hospital and at home, has proven to be important for supportive treatments in patients with dysphagia, odynophagia and mucositis due to head and neck tumors. Validated questionnaires and bioimpedeziometry are necessary to treat patients early, improving their quality of life.

H - Miscellaneous

H01*

MICROBIOTA-RELATED MULTIOMICS TO ASSESS THE CLINICAL RELEVANCE OF ANTIBIOTICS (ATB) IN IMMUNOTHERAPY (ICI)

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Background: Experimental and clinical data revealed that ATB-induced gut dysbiosis negatively influences response to ICI, especially when ATB are taken close to ICI initiation. Little is known about surrogate markers of ATB-related immunosuppression.

Methods: NCT04567446 prospectively enrolled lung (NSCLC), kidney (RCC) and bladder (UC) cancer patients (pts) undergoing ICI at Gustave Roussy. Pts who never received ATB (noATB) were compared with those receiving ATB within the window of 60 days before to 42 days after ICI start (ATBin) and pts with ATB intake outside the window (ATBout). We performed stool metagenomics (MGS) and culturomics, ELISA/VIDAS assays for microbiota-specific memory T cells, IgG/IgA detection by flow cytometry and mass spectrometric-based metabolomics on blood. Objective Response Rate (ORR) and Overall Survival (OS) were assessed.

Results: From January 2021 to April 2024 161 pts were included, of which 342 stool and 315 blood samples were collected longitudinally. Median follow-up was 14.5 months, 65% had NSCLC, 23% RCC and 12% UC. Most pts were treated in 1L (78%) and with ICI-based combinations (72%). Of 90 pts who received ATB at least once, 47% pts were ATBin and 53% ATBout. ATBin resulted in lower ORR (41.5%) compared to ATBout (69.6%) and noATB (43.3%) (p=0.018). Based on MGS, ATBin compared to noATB +/- ATBout displayed a tolerogenic microbiota dominated by oral taxa and Enterocloster spp. at the relative expense of Akkermansia muciniphila (Akk) and Faecalibacterium prausnitzii. Of ATBin, 7% had a negative fungal culture (versus 26% in all other pts, p<0.05) with distinct species such as Candida albicans and/or Geotrichum candidum affecting OS in ATB pts. ATBin had a lower peripheral immune tonus (TH1 response) against Akk compared to ATBout+noATB pts (p=0.012). In the NSCLC subset, high levels of IgG anti-Akk correlated with worse OS, with even poorer survival for ATBin pts (p<0.001). ATBin decreased distinct short chain fatty acids, metabolites significantly related to better ORR, while increased shuttle and long chain carnitines associated with worse ORR.

Conclusions: Microbiota-related multiomics analysis assessing the immunosuppressive effect of ATB helps unveiling several molecular and cellular mechanisms that could be targeted with tailored microbiota-centered interventions to improve response to ICI.

H02*

SAFETY OF IMMUNOTHERAPY IN CANCER PATIENTS WITH COMORBIDITIES: RESULTS OF THE PHASE IV ITALIAN IMMUNO-SPECIAL TRIAL

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Background: Limited prospective data exist about the safety of immune checkpoint inhibitors (ICIs) use in patients (pts) who are at greater risk of immune-related adverse events (irAEs) due to comorbidities.

Material (patients) and Methods: We conducted a prospective, phase IV, multicentre trial in pts affected by solid cancers treated with ICIs alone or combined (other ICI, chemo, or targeted therapies) and considered at higher risk of irAEs due to the following comorbidities: previous solid organ transplant (SOT), indolent haematological neoplasms, chronic viral (HIV, HBV, or HCV) infection, chronic severe

organ dysfunction (renal, cardiac, pulmonary, or hepatic), or pre-existing autoimmunity. Primary aim was to assess the incidence of CTCAE v5.0 G≥3 irAEs. Secondary objectives were: incidence of all-grade (G) irAEs, median treatment intensity, and analysis of irAEs according to cancer site, type of treatment, and comorbidity.

Results: From May 2020 to September 2023, 206 pts were enrolled. Median age was 72 years (range 25-96; IQR 65-77), while ECOG performance status was 0, 1, 2, or not available in 87 (42%), 92 (45%), 25 (12%), and 2 (1%) pts, respectively. Most frequent primary sites were lung (127, 62%) and skin (41, 20%). Comorbidities leading to enrolment were previous SOT, haematological neoplasms, chronic viral infection, severe chronic organ dysfunction, pre-existing autoimmunity in 2 (1%), 24 (12%), 103 (50%), 51 (25%), and 69 (33%), respectively; 49 pts (24%) had > 1 comorbidity. Most pts were treated with single-agent ICI (151, 73%). 42 G≥3 irAEs were reported (18% of all irAEs). All-G and G≥3 irAEs were observed in 39 (19%) and 132 (64%) pts, respectively. Median treatment intensity was 100% (3-100%), with 36 pts (17.6%) prematurely discontinuing ICI due to toxicities. On multivariate logistic regression, pre-existing autoimmunity predicted all-G irAEs (OR 1.94, IC 95% 1.00-3.78; p 0.05) but not G≥3 irAE; no predictive factor of irAEs was found among clinical or laboratory factors.

Conclusions: ICI administration in pts with comorbidities in a real-world setting showed manageable toxicities with maintenance of treatment intensity, even if with relatively high ICI discontinuation due to irAEs. Special attention should be paid to pts with pre-existing autoimmunity.

H03*

CARBON DIOXIDE (CO2) EMISSION SAVINGS AND TRAVEL BURDEN REDUCTION THROUGH A CANCER CARE MODEL CLOSER TO THE PATIENT. RESULTS OF 2,132 CANCER PATIENTS ON ACTIVE TREATMENT IN NORTHERN ITALIAN DISTRICT

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Background: There is substantial carbon footprint related to travelling to healthcare appointments particularly for cancer patients that require frequent visit and treatments. In addition, the distance from patient's residence to the treatment center may represent an obstacle for patients with cancer.

Material and Methods: To relieve travel burden, a program to deliver oncologic treatment closer to the patient was initiated in the district of Piacenza in 2024. The oncologic activities are performed by oncologists who travel from the oncologic ward of the city hospital to territorial centers to provide cancer patient management. This model is called Territorial Oncology Care(TOC): patients are managed near their home, in 3 territorial hospitals and in a health center, named "Casa della Salute". For the present study, we have retrospectively analyzed all the files containing schedules of patients managed in the TOC program from January 2, 2017 to December 31, 2022. For each patient we calculated the driving distance in kms to reach the outpatient's service closer to the patient residence compared with the driving distance to reach the referral city hospital. Distance and time were calculated using Google Maps. The CO2 emission per km was evaluated according to the values provided by the European Environment Agency(122.3 g of CO2 per Km).

Results: A total of 2,132 patients with cancer on active treatment were managed is the TOC program, 1,109 women(52.02%), median age 71 years (range 28-92). The type of cancers were gastrointestinal(40.1%), lung(19.5%), breast(18.8%), genitourinary(14.4%), head and neck(2.0%), other cancer(5.2%). The treatment of cancer patients closer to their residence allowed CO2 emission savings of 31.85 tons in the year 2017, 37.81 in 2018, 38.05 in 2019, 40.50 in 2020, 44.31 in 2021 and 49.01 in 2022; with a total of 241.53 tons of CO2 emission saved in 6 years period. The total kms saved for the 278 patients treated in the year 2017 were 260,486; 309,177 for the 347 patients in the year 2018, 311,166 for the 354 patients in the year 2019; 331,200 for the 360 patients in 2020; 362,324 for the 379 patients in the year 2021 and 400,752 for the 414 patients in the year 2022; with a total of 1,975,105 km saved in 6 years.

Conclusions: Our study has shown that CO2 emission may be reduced in an important way, similarly reducing the kms travelled by cancer patients, by providing a provincial network allowing anticancer treatment closer to the patients.

H04

FIRST-IN-HUMAN STUDY OF ABBV-706, A SEIZURE-RELATED HOMOLOG PROTEIN 6 (SEZ6)–TARGETING ANTIBODY-DRUG CONJUGATE (ADC), IN PATIENTS (PTS) WITH ADVANCED SOLID TUMORS

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Background: SEZ6 is transmembrane protein expressed in small cell lung cancer(SCLC), other neuroendocrine neoplasms(NENs) and central nervous system(CNS) tumors. ABBV-706 is ADC targeting SEZ6 conjugated to topoisomerase 1 inhibitor payload at drug-to-antibody ratio of 6. It's highly efficacious in SCLC, NENs and CNS tumors preclinical models. We present results from ABBV-706 monotherapy dose escalation(DE).

Methods: Ph1, open-label, DE and dose-expansion study(NCT05599984) of ABBV-706(IV, 1.3–3.5mg/kg doses, Q3W, 21d cycles) as monotherapy or in combination with budigalimab(anti-PD1 inhibitor), carboplatin or cisplatin. Primary objectives are: safety, PK, preliminary efficacy and recommended ph2 dose. Exploratory objectives are to assess SEZ6 expression retrospectively and its association with safety, PK and efficacy. DE enrolled adults(=18 yr) with relapsed/refractory SCLC, high-grade CNS tumors and high-grade NENs, following the Bayesian optimal interval design.

Results: As of Nov 15, 2023, 49 pts(SCLC: n=22[45%]; CNS tumors: n=5[10%]; NEN: n=22[45%]) were treated with ABBV-706 in DE and backfill cohorts. Median age: 64 yr(range 32–81), median prior lines of therapy: 2.5(range 1–6). 2 pts had dose-limiting toxicity: 1 G4 leukopenia and neutropenia lasting≥7d at 3.0mg/kg and 1 G4 thrombocytopenia at 3.5mg/kg. TEAEs occurred in 45(92%) pts, most frequent: anemia(51%), fatigue(41%), neutropenia(31%) and leukopenia(31%). G=3 TEAEs occurred in 28(57%) pts, were mainly hematologic: neutropenia(29%), anemia(27%) and leukopenia(25%). No pneumonitis/interstitial lung disease was observed. GI TEAEs(all G1/2) occurred in 55% of pts, most common: nausea(27%) and vomiting(18%). No ABBV-706–related deaths. The max tolerated dose was 3mg/kg IV Q3W. ABBV-706 ADC showed approximate dose-proportional increase in exposure with an elimination half-life of approximately 7d across doses. For 33 RECIST-evaluable pts, confirmed(c) ORR was overall 21%(7 PRs); 40%(6/15) for SCLC and 6%(1/18) for NEN. Overall response(c and unconfirmed [u]) rate without confirmation was 45%(7cPRs/8uPRs); 73%(6cPRs/5uPRs) for SCLC and 22%(1cPR/3uPRs) for NEN. 8uPRs are pending confirmation: will be reported in final presentation. Clinical benefit rate: 91%(7 PR, 23 SD). No activity was observed in 3/3 pts with high-grade gliomas.

Conclusions: ABBV-706 demonstrated manageable safety profile with promising efficacy in SCLC and NENs. Further evaluation of ABBV-706 is ongoing.

H05

EVALUATING THE PERFORMANCE OF CONTROL ARM IN THE CLINICAL TRIALS SUPPORTING CANCER DRUG APPROVALS BY U.S. FOOD AND DRUG ADMINISTRATION (FDA) BETWEEN 2016 AND 2020

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Background: In the last years, the rate of oncology drugs approved by FDA is notably increased. In addition to efficacy of experimental drugs, success of trials may be influenced by performance of control arms as well. We aimed to investigate the survival outcomes of control arms in trials leading to FDA approval of new cancer drugs.

Methods: We searched for drugs approved by FDA from January 2016 through December 2020, for the treatment of advanced cancers. We analysed publications of phase III or two-arms phase II trials that prompted such approvals. For each trial, we analysed study protocols to search data about primary efficacy endpoints, overall survival (OS) and/or progression free survival (PFS). Particularly, we collected the OS and PFS assumed median values in the control arms declared in study protocol and their related confidence intervals ultimately recorded in the trial results.

Results: We analysed 56 clinical trials supporting new cancer drug approvals. The majority of these trials were placebo-controlled (57.1%). Immune checkpoint and tyrosine kinase inhibitors were investigated in the majority of cases, in 23 (41.1%) and 14 (25.0%) trials, respectively. OS and PFS were the exclusive primary endpoints in 12 (21.4%) and 27 (48.2%) trials, respectively. In 17 clinical trials, OS and PFS were both primary endpoints (30.4%). The assumed median OS and PFS values in control arms were within the recorded confidence intervals in 20/29 (69.0%) and 29/44 (65.9%) trials, respectively. Of note, the assumed median OS and PFS values in control arms were lower than OS and PFS limit in 7 (24.1%) and in 4 trials (9.1%), respectively (Overperforming control arm). Furthermore, assumed median OS and PFS value exceeded

the upper confidence interval limit in 2 (6.9%) and 11 trials (25%), respectively (Underperforming control arm).

Conclusions: The gain in OS/PFS observed in some trials leading to FDA approval of new cancer drugs may have been influenced by shorter OS/PFS in control arms, compared to the ones assumed in study protocols. An accurate analysis of outcomes of control arms in clinical trials is needed for a comprehensive assessment of the effectiveness of novel experimental drugs in oncology.

H06

THE ESTABLISHMENT OF THE CAMPANIA ONCOLOGY NETWORK POSITIVELY INFLUENCES CANCER DIAGNOSTIC AND THERAPEUTIC TIMES: THE VALUTAZIONE PERCORSO RETE ONCOLOGICA CAMPANA (VALPEROC) PROJECT

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Background: The Campania Oncology Network (ROC) has been developed in Campania region to improve the path of patients with new diagnosis of cancer and reduce the mortality rates. Diagnostic and treatment delays are determinants of the worst survival in our region. General practitioners and specialists were involved to facilitate the taking in charge of patients from the regional multidisciplinary teams (GOMs), through a digital tool connection. The ValPeROC, a multicenter project, consists of periodic surveys on diagnostic and therapeutic times of cancer patients taken in charge by GOMs. Here we report the trends of diagnostic and therapeutic times across the different phases of the project.

Patients and Methods: The analysis involved phase II (2020) to phase V (2024) (phase I in 2019, being a pilot and feasibility phase, was not included). Prospective cohorts of patients registered in the ROC digital platform affected by Colon, Lung, Prostate, and Ovarian cancers, were analysed. Diagnostic time (Pre-GOM time) was the time between symptom onset or cancer diagnosis and the GOM meeting; therapeutic time (GOM time) was the time between the first GOM meeting and the therapeutic decision. Univariate logistic regression with χ^2 test were performed.

Results: In the present study, Pre-GOM time was calculated for 1495 patients and GOM time for 1620 patients. Overall, median pre-GOM time significantly decreased from 73.0 days (37.0–149.0) to 43.5 days (20.5-89.5), $p<0.0001$. A higher decrease in pre-GOM time was found for prostate cancer (from 108.0 to 69.5 days) although it is confirmed to have the longest pre-GOM times in all the phases. Median GOM time decreased, although not significantly, from 20.0 (7.0-33.0) to 15 days (1.0-43.0). When pre-GOM time was classified as >2 months and <1 month, risk factors significantly affected pre-GOM times were: mode of diagnosis, cancer type ($p<0.0001$, respectively) and inappropriate tests ($p=0.0005$). While, categorizing GOM time into <1 week and >3 weeks, cancer type and mode of diagnosis ($p<0.0001$, respectively) were significant risk factors for GOM time.

Conclusions: Over the years, the establishment of the ROC for the management of cancer patients has decreased significantly diagnostic times. Certain risk factors seems to influence both pre-GOM and GOM times. These results highlight how the establishment of a regional network positively influences important prognostic factors for tumours, such as diagnostic and therapeutic times.

H07

EVALUATION OF LARGE LANGUAGE MODELS AS A SUPPORT TOOL IN THE CLINICAL ASSESSMENT OF ONCOGERIATRIC PATIENTS: THE AI-CGA STUDY

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Background: Chat-GPT is an online platform designed to answer questions conversationally, using deep learning technology. The aim of this study is to evaluate the capabilities of Chat-GPT 4.0 and two customly trained GPTs for the support of the oncogeriatrician in multidimensional evaluation.

Materials and Methods: Oncogeriatric patients discussed in multidisciplinary tumor board (MTB) and referred to a comprehensive geriatric assessment between January 1st and August 31st 2022 were included. Laboratory values, clinical/oncological and social status information were extracted from medical records. Data were anonymised, tokenized and then input into ChatGPT 4.0 and into the custom GPTs named "p53" (trained by an oncologist) and "Seneca" (trained by a geriatrician). Both tools were trained on ESMO and ASCO guidelines and on EMA and FDA summaries of product characteristics. The suggested management was put into a table with the one made by the oncogeriatrician and randomly assigned to a different letter. Three blinded raters were provided with anonymized case samples and assigned a rate from 1 to 5, according to a standardized grid. Interratter agreement was evaluated using intraclass correlation coefficient (ICC) and differences between ratings were evaluated using a mixed effect model considering raters as random effect.

Results: Thirty patients were considered for the preliminary analysis. Median age was 80.5 (interquartile range 77.0-84.8). Twentysix patients had breast cancer, three ovarian cancer and one endometrial cancer. All patients received multidimensional geriatric evaluation. Interrater agreement was generally poor (ICC <0.50) for each tool. Among the evaluated GPTs, p53 (estimate 3.89, 95% CI 3.58-4.19) and Seneca (estimate 3.83, 95% CI 3.53-4.14) showed the highest performance. Overall, custom GPTs performed well in oncogetriatic items, including comorbidities assessment, pharmacological interactions, toxicity prevention, drug prescription and social status evaluation.

Conclusions: The results of our study suggest that, after proper validation, custom GPTs could be helpful in assisting the oncogeriatrician for multidimensional evaluation. Specifically trained GPTs such as p53 and Seneca showed better performance than ChatGPT 4.0.

H08

EFFICACY OF ABBV-400 MONOTHERAPY IN PATIENTS WITH MET GENE AMPLIFIED ADVANCED SOLID TUMORS

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Background: Anti–c-Met (MET protein) antibody-drug conjugate ABBV-400 comprises monoclonal antibody telisotuzumab conjugated to a potent topoisomerase 1 inhibitor via a stable, cleavable linker. *MET* gene amplification (amp) occurs at low frequency in primary tumors (<5%) but has increased frequency in recurrent/refractory disease. ABBV-400 showed deep, durable responses in preclinical patient (pt)-derived xenograft models of *MET* amp, c-MET–overexpressing advanced solid tumors. A first-in-human phase I study (NCT05029882) is evaluating safety, pharmacokinetics, and preliminary efficacy of ABBV-400 in pts with advanced solid tumors; we present results of an ad hoc analysis of efficacy in pts with *MET* amp.

Methods: Analyzed pts had measurable disease per RECIST v1.1 and history of advanced solid tumors that progressed/were not amenable to any available therapies/surgery. Pts had *MET* amp per local NGS reports of tissue/blood samples from various approved labs. ABBV-400 administered intravenously once every 3 weeks.

Results: As of 3 Apr 2023, 11 pts with *MET* amp advanced solid tumors were treated with ABBV-400 at 2.4 (N=4), 3 (N=6), or 4 (N=1) mg/kg; median follow-up 6.7 months. Enrolled tumor types included NSCLC, intrahepatic cholangiocarcinoma, gastroesophageal, ovarian, urachal, colorectal, and breast cancers. Median age 65 (range 41–73) years, 64% male, 64% Asian, 27% White, 9% Black, 6 (55%)/5(45%) had ECOG PS 0/1; median prior lines of therapy 3 (range 1–6). Pts had MET IHC H-score range of 73–270 and 5–75% cells with 3+ staining (data available for 6/11 pts). Treatment-emergent AEs reported in 11 pts (100%; 55% grade ≥3); most commonly, neutropenia (55%), anemia (46%), nausea (46%), and leukopenia (46%). Confirmed partial response observed in 8 pts (ORR = 73%, 95% CI: 39, 94) per investigator review and RECIST v1.1; 6 pts had ongoing response. Median progression-free survival was 10.8 months (95% CI: 1.2, not reached [NR]), duration of response and overall survival NR; longest ongoing response was >9 months.

Conclusions: ABBV-400 monotherapy showed promising tolerability and efficacy in pts with various *MET* amp advanced solid tumors. Based on these results, *MET* amp cohort will be expanded to 60 more pts.

H09

BLINDED INDEPENDENT CENTRAL REVIEW VERSUS LOCAL INVESTIGATOR ASSESSMENT OF PROGRESSION-FREE SURVIVAL IN RANDOMIZED CONTROLLED TRIALS OF IMMUNOTHERAPY IN ADVANCED CANCERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Progression free survival (PFS) in randomized controlled trials (RCTs) investigating the role of immunotherapy (IO) is adopted for approvals of oncology drugs. Assessment and interpretation of PFS data by investigators might be inaccurate in RCTs with open label design. Thus, we explored potential differences between blinded independent central review (BICR) and local investigator assessment of PFS in trials of IO in advanced cancers.

Methods: We systematically reviewed articles of RCTs testing IO in advanced solid tumors, published in Pubmed-indexed journals from 01/2010 to 12/2023. For each RCT reporting results for both BICR and local investigator assessment of PFS, we collected: i) The number of patients at risk; ii) PFS results by BICR and iii) by local investigators. We calculated a discrepancy index (DI) between BICR and investigator Hazard Ratios. Finally, an overall DI and relative confidence interval was calculated using a fixed model effect weighted for variance.

Results: Of the 141 RCTs testing IO in advanced cancers, only 32 (22.6%) reported both BICR and investigator PFS data, including 17,054 patients. PFS was the only primary endpoint or a co-primary endpoint in 19/32 (59.4%) and 9/32 (28.2%) trials, respectively. The study design was open label in 17/32 (53.1%) and double-blind in 15/32 (46.9%) RCTs. The overall DI was 1.07 (95% CI 1.01-1.13; I^2=0, p=0.02), revealing a statistically significant difference between BICR and local investigator assessment of PFS, with a more optimistic analysis of results in favour of local investigator. Of note, in the subgroup of 17 open label trials the overall DI was 1.09 (95% CI 1.02 – 1.17, I^2=0, p=0.02), while in the 15 double-blind RCTs the overall DI was 1.03 (95% CI 0.95 – 1.12, I^2=0, p=0.51), revealing a more optimistic interpretation of PFS results by local investigators in open label RCTs.

Conclusions: This was the first study reporting a statistically significant difference between BICR and local investigator assessment of PFS in trial of IO in cancer. These results suggest that the double assessment is strongly recommended in RCTs testing IO, especially in open label trials.

H10

IMPACT OF COMPREHENSIVE GERIATRIC ASSESSMENT (CGA)-BASED INTERVENTIONS IN VULNERABLE ELDERLY PATIENTS (PTS) WITH EARLY OR ADVANCED SOLID TUMORS TREATED WITH CHEMOTHERAPY (CT): THE GIVE TRIAL

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Background: Frail older adults with cancer are at increased risk for adverse outcomes and treatment related toxicities. CGA is a standard of care to identify and reduce impairments that lead to frailty. We evaluated whether CGA-based interventions can influence optimal CT delivery in a group of vulnerable older pts with cancer.

Material and Methods: This multicenter randomized trial included pts aged ≥70 years, with early or advanced solid tumors who were candidates for CT, presenting with ≥1 deficit on CGA and/or ≥1 grade (G) 3-4 comorbidity on Cumulative illness rating scale- Geriatric (CIRS-G). Patients were randomized 2:1 to routine oncological care plus geriatric intervention (Arm A) or routine oncological care (Arm B). The primary endpoint was to compare the proportion of pts achieving a CT relative dose intensity (RDI) of ≥85% between Arm A and Arm B. Secondary endpoints included treatment-related toxicity and rates of hospitalizations.

Results: We recruited 225 pts (135 in Arm A, 90 in Arm B). The median age was 77 (range 70-91) years, 15% had ECOG performance status 2, 37% had early disease. The median number of impaired domains was 3 (range 1-7), and geriatric interventions were implemented in 56% of Arm A pts. Most pts had gastrointestinal (GI) (51%) or breast cancer (15%). Nearly 60% of pts in both arms received an upfront CT dose reduction, and the majority of these pts had GI tumors treated with mono-CT. The median RDI was not different between the study arms (77% [range 2%-100%] in Arm A, and 74% [range 6%-100%] in Arm B, p=0.423). Likewise, we identified no differences in the risk of RDI<85%, and the rate of hospitalization. A lower percentage of pts receiving a geriatric intervention had G 1–4 toxic effects (76% in Arm A versus (vs) 88% in Arm B; p=0.032). Severe toxicities (G3-4) occurred in 24% of pts, while mild (G1-2) but clinically relevant toxicities were observed in 58% of pts. G1-2 nausea and constipation were significantly different between arms (nausea 11% Arm A vs 18% Arm B, p.00.8; constipation 9% Arm A vs 22% ArmB, p 0.005).

Conclusions: In this trial, geriatric interventions did not enhance CT dose delivery in elderly vulnerable pts; however, they were associated with decreased CT related toxicities. These results may have been influenced by the high number of pts receiving an upfront CT dose reduction. Further analysis are ongoing to clarify the effects of CGA on CT efficacy in GI and breast cancers.

H11

THE REVOLUTION OF AIOM GUIDELINES IN THE ITALIAN LANDSCAPE

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Background: Since 1990 the Institute of Medicine has published criteria for trustworthy guidelines: based on a systematic review of the literature, account for patients' values and preferences, redacted from a multidisciplinary panel, free as much as possible from conflicts of interest, and updated.

Since 2012 AIOM has started to change its guidelines from narrative texts and more based on expert opinions to real evidence-based guidelines, also thanks to the implementation of the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.

Each recommendation has to follow a rigorous development process, from definition of the clinical question through the PICO (Population, intervention, comparison, outcome) framework, to the identification, assessment and synthesis of the best available evidence, to the formulation of the recommendation (for or against an intervention).

It has been estimated by the GRADE working Group that the development of each PICO takes on average 10 days. Mario Negri Institute for Pharmacological Research IRCCS (IRFMN-IRCCS) has contributed in panel members training and supporting the rigorous development of an ever-increasing number of guidelines.

Materials and Methods: Highlight the efforts AIOM have produced from 2011 to date in terms of resources, number of expert involved, and number of PICOs developed.

Results: In 12 years AIOM and IRFMN-IRCCS has kept updated 40 guidelines, 35 of which have been published on Sistema Nazionale Linee Guida (SNLG) involving more than 100 oncologists and more than 40 scientific societies.

In the last 7 years the total number of new PICOs addressed with the GRADE approach with Evidence to decision (ETD) framework range from 20 to 35 and those new without EtD range from 5 to 10 for each guideline. PICOs with or without EtD to be updated range from 8 to 30 each year.

Conclusions: AIOM has given rise to a revolution at a national level regarding the massive and evidence-based production of guidelines. In total a maximum of 70 PICOs a year have been addressed.

H12

BRCA-ASSOCIATED HEREDITARY MALE CANCERS: CAN GENDER AFFECT THE PREVALENCE AND SPECTRUM OF GERMLINE PATHOGENIC VARIANTS?

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Background: Although hereditary male neoplasms are quite rare, however individuals harbouring germline BRCA1/2 pathogenic variants (PVs) may have a risk of developing tumours associated with Hereditary Breast and Ovarian Cancer (HBOC) syndrome, including male breast (MBC), prostate (PCa) and pancreatic (PC) cancers, and melanoma. Women and men showed a comparable genetic architecture of cancer susceptibility, but there are some

gender-specific features. Since little is known about cancer genetic susceptibility in male population, the aim of our study was to investigate the frequency of BRCA1/2 PVs in men with HBOC syndrome-associated tumors, in order to understand whether differences in gender may reflect in the prevalence and spectrum of germline alterations.

Methods: We retrospectively collected and analysed clinical information of 352 HBOC-associated male cancer patients genetically tested for germline BRCA1/2 PVs by Next-Generation Sequencing analysis, enrolled, from February 2018 to January 2024, at the "Regional Center for the prevention, diagnosis and treatment of rare and heredo-familial tumors of adults" of the University-Hospital Policlinico "P. Giaccone" of Palermo (Italy).

Results: Our investigation revealed that 7.4% of patients was carrier of a germline BRCA PV, with an almost total prevalence of BRCA2 alterations. In particular, 65.4% of BRCA-positive patients developed MBC, 19.2% had PC, 11.6% developed PCa, and only 3.8% had melanoma. Specifically, MBC individuals showed a BRCA-associated genetic predisposition in 17% of cases, whereas patients with PCa or PC exhibited a lower frequency of BRCA2 PVs. Our study showed a high heterogeneity in prevalence of germline BRCA2 PVs among men which could reflect a gender-specific genetic heterogeneity. Therefore, BRCA-associated male tumours could be due to BRCA2 PVs different from those usually detected in women.

Conclusions: Considering male cancers as genetically distinct entities from those female could improve personalized risk evaluation and guide therapeutic choices for patients of both sexes, in order to obtain a gender equality in cancer care.

H13

COMPARISON OF BASELINE PATIENT CHARACTERISTICS IN PHASE I AND PHASE II/III CLINICAL TRIALS (CTS) FOR ANTICANCER TREATMENTS

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Background: Baseline characteristics of cancer patients in registrative trials and real-world clinical practice in Italy have been recently compared, showing higher median age, rate of elderly (≥ 65 years old) and deteriorated performance status (PS) in the latter, and no relevant imbalance in female rate. The purpose of this analysis was to compare patients enrolled in registrative phase II/III with those in phase I CTs.

Methods: We examined European Public Assessment Reports of European Medicines Agency, along with publications and protocols, and extracted data on age, sex and PS of patients enrolled in phase II/III and phase I CTs supporting therapeutic indications. Weighted means and standard deviations were calculated in both groups and differences were described. This analysis focuses on age and sex.

Results: A total of 103 phase II/III and 111 phase I CTs, corresponding to 60,284 and 7,369 patients respectively, and supporting 97 therapeutic indications for solid tumors, were collected. Median age and rate of female patients were available for 96 indications, of which 59 reported data for tumor-specific cohorts in phase I trials. Overall, mean median age was 60.7 years in phase II/III and 59.7 years in phase I, mean difference being 1.0, p=0.051. Larger age difference was described for skin and breast cancer, with patients in phase II/III CTs being 4.2 and 3.1 years older than in phase I, respectively, while no substantial heterogeneity was evident among drug classes. Mean rate of female patients was slightly but no statistically significantly lower in phase II/III than in phase I CTs overall, mean difference being -4.9%, p= 0.999; the size of the difference was more pronounced when cytotoxic agents were tested (mean differences -10.5% and -7.2%, for cytotoxic agents alone and in combination with immunotherapy, respectively). Differences according to cancer types were noted in both directions, the most relevant being for skin (mean difference 6.0%) and upper-gastrointestinal (mean difference -8.0%).

Conclusions: Our analysis showed no statistically significant difference in age and sex between patients enrolled in phase II/III and corresponding phase I CTs for anticancer treatments overall. However, some variability emerged from subgroup analyses, supporting the need for further research in specific settings.

H14

INTEGRATION OF TRANSLATIONAL RESEARCH IN PHASE III TRIALS: ANALYSIS ON BREAST CANCER STUDIES IN A 5-YEARS PERIOD

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Background: The acquisition of samples for translational analyses in phase III clinical trials (CT) is a vital aspect of precision oncology, though numerous factors persistently challenge biomarker development. We performed a systematic review of phase III CT in breast cancer (BC) to evaluate the proportion of CT with a pre-planned biomarker analysis and whether this translated into new translational evidence.

Methods: Interventional phase III CT evaluating anticancer drugs in BC published in 11 major journals between 2014 and 2018 were included.

Results: In total, 89 phase III CT were identified with 48 CT (53.9%) in non-metastatic settings (neoadjuvant and/or adjuvant) and 41 CT (46.1%) in the metastatic one. Sample collection for research purposes was explicitly indicated only in 54 cases (60.6%), with 39 of them (72.2%) subsequently publishing at least one translational analysis. A higher probability of publishing translational analysis was observed in positive vs negative CT (87.5% and 60%, respectively). In the remaining 35 CT, non-clinical sample collection was not performed in 3 cases (3.4%), while this information lacked in 32 trials (36%). Out of these, 9 (28.1%) translational reports were retrieved. The probabilities of publishing a translational abstract were 37%, 50% and 60% after 12, 24 and 36 months from the main publication, while the probabilities of publishing a translational paper at the same timepoints were 13%, 20% and 38.3%. Among the 48 CT with published translational data, 3 (6.3%) included them in the primary manuscript, whereas 38 (79.2%) and 42 (87.5%) published at least 1 dedicated manuscript and 1 abstract respectively, with a median of 1 manuscript [interquartile range (IQR) 1-2] and 2 abstracts (IQR 1-4) for each CT. The median time between the main publication and the first translational abstract or translational paper was of 8.7 and 33.4 months, respectively, with a gap in impact factor (IF) between the primary publication (median IF 26.5, IQR 22.4-35.9) and the secondary translational one (median IF 8.9, IQR 4.5-13.9).

Conclusions: Whereas three quarters of BC phase III CT collected human biologic material for non-clinical purpose, we highlighted numerous gaps in terms of time, impact, and publication patterns. Bridging this gap between primary and translational publications remains a key challenge for optimizing biomarker development in oncology.

H15

NON-PROFIT RESEARCH: AN INVESTIGATION INTO THE MANAGEMENT AND MONITORING OF CLINICAL TRIALS ACROSS ITALY

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Background: In January 2022, the Italian regulatory framework for clinical research on medicinal products underwent a significant change with the full implementation of European Regulation No. 536/2014. This marked a significant turning point for non-profit research centers, as they are now required to conform their procedures to high-quality standards and the ICH guidelines on Good Clinical Practice (GCP).

Methods: In March 2024, an anonymous pilot survey was spread via social media to evaluate the status of non-profit clinical trials in Italy. The survey contained 50 questions aimed at assessing the compliance of non-profit promoters with the quality standards required by the regulation to ensure proper study management and data accuracy. Questions were divided into 3 sections: data management, risk assessment, and monitoring of studies.

Results: Thirty-four non-profit promoters participated in the survey. The results revealed that 91% (n=31) of the surveyed promoters rarely or never prepare at least one of the documents required by GCP guidelines, such as the Data Management Plan or the Statistical Analysis Plan. Only 26% (n=9) of promoters said that they routinely do a risk assessment before writing protocols. Moreover, promoters stated that monitoring visits, either on-site or remotely, are conducted in 56% (n=19) of cases, and these data were confirmed by the satellite centers interviewed. Respondents who do not conduct monitoring visits stated that the most common constraints for the deficiency of on-site monitoring activities are the lack of dedicated staff (29%, n=4) and limited financial resources (57%, n=8), which are often interconnected factors. Furthermore, 29% (n=4) of these promoters stated that they considered such monitoring unnecessary, despite legislative requirements. The same pattern was found for remote monitoring visits.

Conclusions: The survey revealed that most clinical trials sponsored by Italian non-profit centers are often not adequately managed according to GCP guidelines, highlighting the challenges these institutions encounter in facing the increasingly complex regulations due to a lack of funds and adequately formed personnel. The findings suggest the need for collaborative efforts to address shared difficulties and find solutions to support non-profit promoters in complying with the current regulatory framework, thus ensuring high-quality non-profit research which is of paramount importance in improving clinical practice.

H16

GENOMIC ALTERATIONS IN CIRCULATING TUMOR DNA (CTDNA) AND RESPONSE TO ABBV-400 TREATMENT IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background: Several solid tumors, including colorectal cancer(CRC), overexpress c-Met. The ADC ABBV-400 comprises the c-Met–targeting antibody telisotuzumab conjugated to a potent topoisomerase 1 inhibitor payload. ABBV-400 is being evaluated in phase 1 trial(NCT05029882) in patients (pts) with advanced solid tumors. We analyzed correlations between genomic alterations and response of pts in this study.

Methods: Adults with advanced solid tumors and no validated treatment option were enrolled. ABBV-400 was administered IV q3wk. ctDNA was isolated from plasma and analyzed using the GuardantINFINITY™ assay that evaluated various parameters including single-nucleotide variants and insertion-deletion mutations(753 genes), amplifications(415 genes), tumor mutational burden(TMB), and microsatellite instability(MSI) status. Molecular response(based on ctDNA variant allele frequencies) and radiographic response(RECIST v1.1) were assessed.

Results: As of 3 April 2023, 57 pts were efficacy evaluable, including 27 pts with CRC. The ORR was 25%(14/57; all confirmed partial responses[cPR]) in all pts and 22% in pts with CRC(6/27; all cPR). Most prevalent gene alterations were *TP53*(67%), *LRP1B*(43%), *APC*(41%), and *KRAS*(41%) mutations and *PTPRT*(45%) and *TOP1*(43%) amplifications. Table shows the correlation between response and select biomarkers(at baseline) in 45 pts(22 CRC) who had both ctDNA and radiographic response data. A molecular response was observed in 48%(14/29) of all evaluated pts and 47%(8/17) of pts with CRC; median change from baseline tumor size was -22.5% and -20.3%, respectively.

Conclusions: ABBV-400 showed promising preliminary efficacy, with molecular and radiographic responses in pts with advanced solid tumors with heterogeneous genomic profiles, including pts with high TMB and *KRAS* mutations.

Table. Pts with molecular response and correlation between baseline biomarker status and radiographic response

	All pts		CRC pts			
N(pts with both ctDNA and radiographic response data)	**45**		**22**			
Pts with confirmed PR,n/N(%)	**11/45 (24)**		**4/22 (18)**			
Pts with molecular response,n/N(%)	**14/29[a] (48)**		**8/17[b] (47)**			
	High TMB	**High MSI**	**High TMB**	**High MSI**	***KRAS* mut**	***BRAF* mut**
Pts with confirmed PR with biomarker positivity,n/N(%)	3/20 (15)	0/3 (0)	3/13 (23)	0/1 (0)	2/16 (13)	1/3 (33)

[a]29 pts were evaluable for molecular response.[b]17 CRC pts were evaluable for molecular response.
CRC,colorectal cancer; MSI,microsatellite instability; mut,mutations; PR,partial response; pts,patients; TMB,tumor mutational burden.

H17

PATIENT-INITIATED EMAILS AS PRIMARY COMMUNICATION SYSTEM BETWEEN PATIENTS AND ONCOLOGISTS: ANALYSIS OF 1 YEAR OF ACTIVITY OF THE "EMAIL COMMUNICATION SYSTEM" OF THE THORACIC MEDICAL ONCOLOGY OF A PUBLIC ONCOLOGY INSTITUTE IN ITALY

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Background: Email use is transforming the communication between patients and doctors. Several studies suggest that patient-initiated emails may improve patient engagement and health outcomes. All patients followed by the Thoracic Medical Oncology of our public Oncology Institute are provided with an Institutional email address for communications with the oncologists. Objectives of this study are to: 1) analyze the volume and the characteristics of the emails sent by patients; 2) assess the response time to patient-initiated emails.

Methods: All the emails sent by patients through 1-year period were analysed; the emails were categorized into seven categories: update on patient conditions, hemocrome evaluation, full ematochemical evaluation, requests for a telephone contact, requests for documents, appointment scheduling and other purposes. Response times were extracted using Outlook-Freeware and statistical analysis was performed using R-Studio.

Results: From January 1 to December 31, 2023 we identified 7179 patient-initiated emails in our database. In the same period, 300 lung cancer patients were on active intravenous antineoplastic treatments and roughly 2400 patients underwent out-patients oncologic visits. Overall, 6524 (90.88%) were sent over working days, while 655 emails (9.12%) were sent over weekend and holidays. A mean of 19.52 emails (CI 95%: 18.31 – 20.72) were sent per day. On working days, a mean of 26 emails per day was sent (range 4-52). We found that 2174 mails (30.28%) were sent for updates on medical conditions, 903 (12.58%) for hemocrome evaluation, 991 (13.8%) for full hematochemical evaluation, 325 (4.53%) for a telephone contact, 665 (9.26%) for document requests, 1633 (22.75%) for appointment scheduling and 470 (6.55%) for miscellaneous reasons. The mean response time was 17.03 hours (95% CI: 14.55 - 19.51).

Conclusions: Asynchronous email communication appears in our experience an effective system for lung cancer patients to connect with healthcare providers, given that most of the raised problems can be effectively managed and that responses are generally provided within 24 hours. However, its utility is limited in emergencies or urgent scenarios and it is time consuming for the oncologists. Implementing chatbots could enhance the efficiency of asynchronous communication. Moreover, a patient satisfaction survey would be valuable to assess patients satisfaction levels.

H18

TISSUE-BASED NEXT GENERATION SEQUENCING (NGS) FOR PATIENTS WITH ADVANCED SOLID TUMORS: THE EXPERIENCE OF VERONA UNIVERSITY HOSPITAL

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Background: NGS has emerged as a tool to discover actionable alterations and guide the treatment strategy beyond standard oncologic treatments. We aimed to assess the feasibility and clinical utility of implementing DNA-based NGS profiling at the University Hospital of Verona.

Materials and Methods: Patients were prospectively enrolled to undergo NGS profiling by different available panels: the *in-house* 174-gene-assay CORE (n=562), the commercial FoundationOne® CDx panel (n=179) or FoundationOne® CDx CTA (n=16) and TruSightTM Oncology 500 (n=2).

Genomic actionable alterations were categorized according to the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT).

Results: From October 2019 to April 2024, 759 patients with advanced solid tumors were profiled: n=434 (57.2%) male and n=325 (42.8%) female patients. The most represented primary tumors included: pancreas (n=344, 45.3%), lung (n=121, 15.9%), biliary tract (n=53, 7.0%), head and neck (n=52, 6.8%) and esophagus/stomach (n=24, 3.2%).

No pathogenic alterations were detected in 55 of the tumor samples (7.2%). Overall, a total of 199 actionable alterations (Tiers I-II, according to ESCAT) were found in 177 patients (23.3%).

MSI and TMB high (=10 mut/Mb) were detected in 8 (1.1%) and 97 patients (12.8%), respectively.

Regardless of microsatellite status and TMB, a total of 94 actionable alterations (single nucleotide variations, copy number alterations, and structural variants including gene fusions) were identified in 92 individual patients (12.1%). The most common pathogenic ESCAT Tier I-II alterations observed were: *KRAS* G12C mutation in NSCLC (n=16; 17.0%), *BRCA2* mutations in PDAC and breast cancer (n=10; 10.6% of actionable alterations), *ERBB2* amplification (n=10; 10.6%) and *BRAF* V600E (n=9; 9.6%) in all-solid tumors; *EGFR* in NSCLC and *BRCA1* mutations in PDAC, ovarian and breast cancer (n=8; 8.5%); *PI3KCA* mutations in breast cancer (n=6, 6.4%). Other ESCAT I-II mutations included: *IDH1*, *KIT*, *RET*, *MET*, *ESR1* and *PTEN mutations*, and *FGFR2, ALK*, *RET and NTRK1* fusions.

A total of 75 patients with ESCAT Tier I-II alterations (42.4%) received an NGS-informed targeted therapy.

Conclusions: Our study provides an example of implementation of molecular profiling in an academic pre-screening program. Further analysis will investigate treatment matching rates, drug access schemes, and their impact on treatment efficacy and survival.

H19

AN INTEGRATED MODEL FOR CLINICAL CANCER MANAGEMENT IN THE ERA OF PERSONALIZED ONCOLOGY: FIRST REPORT FROM AN ONCOLOGY-ORIENTED INTERNAL MEDICINE WARD AT GRANDE OSPEDALE METROPOLITANO NIGUARDA

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Background: The increasing incidence of solid tumors and more effective therapies accounts for a greater number of hospital admitted cancer patients (pts). Precision oncology requires the study of tumor molecular profile and multidisciplinary team discussion (MTD) at diagnosis and during treatment. Peculiar toxicities occur with targeted and immuno-therapies, requiring prompt and specific treatments. To address this complexity, a collaboration between oncologists and internists within an Oncology-oriented Internal Medicine ward (OIM) was created to optimize the triage and clinical management.

Methods: Pts with 1) symptomatic suspected cancer (SSC), 2) iatrogenic toxicity (TOX), and 3) clinical deterioration (CD) admitted to the emergency room (ER) were admitted to the OIM. A Medical Oncology resident (MOR), supervised by a senior oncologist, daily supported the Internal Medicine specialists by sharing diagnostic procedures, genomic profiling, MTD and cancer treatment plans. Additionally, the MOR facilitated interaction with the Palliative Care (PC) team for shared decision-making.

Results: From November 2021 to April 2024, 690 pts were admitted to the OIM (median age = 73 y, 32-92). Reasons for admission were SSC (314), CD (315), and TOX (61). Median IOM stay was 17 days (1-70). Among pts with SSC, median time to cancer imaging diagnosis, biopsy, and treatment plan were respectively 4, 9, and 10 days. The most common symptoms at admission were gastrointestinal (20%), neurological (18%), and respiratory (17%). Cancer diagnoses were 38% gastrointestinal, 36% thoracic and 26% in other sites. 23% pts underwent tumor genomic profiling, 33% were evaluated in a MTD, 46% received PC consultation, 37% were discharged for outpatient treatment, 12% were relocated to the oncology ward for inpatient therapy, 29% were referred to a PC service, and 10% deceased during hospitalization.

Conclusions:This is the first reported experience of an OIM in Italy. The uniqueness of this project lies in centralizing hospital admission of cancer pts from ER to OIM, to optimize and speed up cancer diagnosis, outlining oncological therapeutic indications right away in the medical department. We reported pts demographics and outcomes during the first 3.5 years of this collaboration. Future demonstration of improved pts outcomes and cost-effectiveness is required to support the widespread adoption of this model in other institutions.

H20

ASSESSMENT OF DIFFERENTIAL INFORMATIVE CENSORING IN CONTROL AND EXPERIMENTAL ARM IN TRIALS TESTING IMMUNOTHERAPY IN METASTATIC CANCERS: A SYSTEMATIC REVIEW

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Background: The Kaplan-Meier (K-M) method assumes that informative censoring is equally distributed in arms of clinical trials. However, the number of censored patients vary between study arms, ultimately affecting trial results. Therefore, we investigated the rates of informative censoring in randomized controlled trials (RCTs) of immunotherapy (IO) in advanced cancers.

Methods: We searched articles of RCTs testing IO in advanced cancers, published from 01/2010 to 12/2023 in PubMed-indexed journals. For both progression free (PFS) and overall survival (OS) K-M curves, we collected: i) The number of patients at risk; ii) The rate of censored patients at the first study interval (T1); iii) The overall rate of censoring (T2). We calculated the unweighted absolute % difference of censoring, as well as the weighted difference adjusted for study enrolment size, in control versus experimental arm at T1 and T2.

Results: Of the 141 trials reviewed, censoring data at both T1 and T2 were found for 55/141 (39.0%) and 56/141 (39.7%) trials for PFS and OS K-M curves, respectively. Censoring data in either PFS or OS were not reported in 31/42 (73.8%), 9/13 (69.2%), 12/20 (60.0%) and 8/22 (36.4%) RCTs of IO in NSCLC, melanoma, genitourinary and gastrointestinal cancers, respectively. The median unweighted proportion of censored patients control and experimental arms were: i) at T1, 2.16% and 1.15%, for OS K-M); ii) at T1, 7.47% and 4.66%, for PFS K-M; iii) at T2, 31.37% and 38.37%, for OS K-M); iv) at T2, 23.50% and 26.13%, for PFS K-M). Furthermore, analysis of the weighted differences between control and experimental arms, revealed more censoring in control arms at T1 (OS: 1.02; PFS: 2.81) and more censoring in experimental arms at T2 (OS: -6.50; PFS: -2.99).

Conclusions: Our study found that many RCTs of IO in metastatic cancers did not clearly report data about informative censoring. As previously reported in other RCTs in oncology, the rate of censoring is higher in control arms at the start of the study and increases in the experimental arm over the course of the trial. Further studies are needed to elucidate the role of censoring on final survival results reported in RCTs.

H21

EFFECT OF DRUG-DRUG INTERACTIONS ON ADVERSE EVENTS IN PATIENTS WITH SOLID TUMORS

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Background: Drug-drug interactions (DDIs) can lead to impaired drug metabolism potentially impacting both toxicity and efficacy. Drug-PIN (Personalized Interactions Network) is a tool that identifies DDIs and integrates them with biochemical and demographic patient data. This retrospective study evaluated the association between DDIs and toxicities in different solid tumors in a real-world setting.

Methods: We enrolled patients (pts) from 20 italian centers, distinguished in 4 cohorts: metastatic breast cancer (mBC) treated with CDK4/6i + endocrine therapy(ET); HER2+ mBC treated with trastuzumab-deruxtecan (T-Dxd); metastatic BRAF mutated melanoma (M)treated with BRAF/MEKi and recurrent/metastatic head and neck carcinoma (R/M HNSCC) who received chemotherapy + anti-PD1. Clinical characteristics, concomitant medications (CM)and adverse events (AEs) according to CTCAE v5 were collected. Drug-PIN was used to define DDIs, expressed both as numerical score and from green to red tier indicating an increasing interaction. Univariate analysis (UVA) and ROC curves were used to identify variables likely associated with AEs and assess the relative cutoffs. Multivariate analysis (MVA) was based on a logistic regression to identify predictors of AEs starting from UVA.

Results: 637 pts were included: 173 in cohort 1(abemaciclib+ET); 143 in cohort 2(T-DXd);177 in cohort 3(M) and 144 in cohort 4(HNSCC).Median age was 64 years (22-97). Median BMI was 24 (13-53). 50% of pts had no comorbidities, while 37% 1-2 and 13%>2. 78% pts were female. The median number of CM was 2 (0-15). 156

(25%) pts had a polypharmacotherapy. Median Drug-pin score (DPs) was higher in men than women. The median DPs was 5.42 and the most common tier was green (67%). HNSCC cohort had higher DPs compared to mBC and melanoma (48 vs 3.0 vs 5.5). DPs>19 and drug pin tier (green vs other) were associated with AEs of any grade (score>19 p=0.016; tier p=0.010). BMI>25 and the number of CM were associated with AEs (p =0.0125; p=0.007), while age, tumor type and baseline comorbidities were not. DPs or tier were not associated with high grade AEs. Using MVA, Drug-PIN tier (green vs other yellow/dark yellow and red; p=0.0001) or DPs >19 (p=0.0002) and BMI>25 (p=0.0051) were predictors of any grade AE.

Conclusions: In our study, DDIs and BMI resulted as possible independent early predictors of any AEs,regardless of tumor type and treatment received in pts with different solid tumors treated with target therapies or immunotherapy.

H22

PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) IN PATIENTS WITH PERITONEAL METASTASES: PRELIMINARY RESULTS OF A SINGLE-CENTER, SINGLE-ARM OPEN-LABEL PHASE II CLINICAL TRIAL

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Background: Peritoneal metastases (PM) are a relatively common localization in several gastrointestinal and gynecological tumors implying a poor prognosis and quality of life. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel option for palliation and symptoms control in PM. Aims of the study are evaluation of activity and safety of adding PIPAC to standard systemic chemotherapy (CT).

Patients and Methods: Single-center, single-arm, open-label phase 2 study. Patients (pts) with primary peritoneal malignancies (mesothelioma) or PM of gastrointestinal and ovarian origin not eligible for radical surgery were eligible. Pts received standard CT according to AIOM guidelines alternated with a PIPAC procedure, every 2 cycles and after evaluation and confirmation of eligibility. Primary endpoint was activity of PIPAC+CT in terms of histological response, according to peritoneal regression grading system (PRGS) score. Secondary endpoints were adverse events (AE, according to CTCAE 5.0) and surgical complications (Clavien-Dindo classification). Study was approved by the Veneto Institute of Oncology (IOV-IRCCS) Ethical Committee (nr. 98/2021, EudraCT nr: 2020-000560-37).

Results. Between 2021-2024, 32 pts (median age 61 years) were enrolled after dedicated multidisciplinary discussion. 91.3% of pts received at least 1 previous line of CT. Globally, 58 PIPACs + CT were performed at IOV-IRCCS: 13 colorectal, 10 gastric, 3 pancreatic, 3 ovarian PM and 3 mesothelioma. Thirteen out of 25 evaluable pts showed a pathological response with downstaging to PRGS 1-2 (response rate 52%). Median PRGS was 2.5, 1.5 and 1 at PIPAC#1, #2 and #3, respectively. Notably, conversion to radical surgery after at least 2 PIPACs was observed in 6 cases (24%). PIPAC failure rate was 12.5% mainly due to inaccessible abdominal cavity. Severe surgical complication rate was 3.4%, while 44% of G1-2 AEs were observed with no severe AEs. Median OS in responders was 20.97 months (95%CI 10.17-31.77) compared to 5.47 in non-responders (95%CI 2.46-8.47, p<0.001).

Conclusions. PIPAC treatment and systemic CT are related to a good pathological response rate in a dismal prognosis subgroup of pts. PIPAC can be safely added to CT.

H23

DOSE ADJUSTMENT OF CHEMOTHERAPY ACCORDING TO CARG SCORE IN OLDER PATIENTS: FOCUS ON HIGH-RISK PATIENTS

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Background: Treating cancer in older patients poses unique challenges. While chemotherapy remains an effective therapeutic option, it carries a significant risk of toxicity. The CARG (Cancer and Aging Research Group) score is a well known tool to estimate the risk of chemotherapy toxicity in elderly patients. However, its practical application in determining the initial chemotherapy dose remains

largely underexplored. This study aims to fill this gap by examining the relationship between the CARG score and the starting dose of chemotherapy in older patients, with particular emphasis on high-risk cases of toxicity.

Materials and Methods: A multicentric, retrospective analysis was conducted on 355 patients aged over 65 years who underwent chemotherapy without prior comprehensive geriatric assessment or CARG score evaluation. The starting dose of chemotherapy was decided based on clinical judgment. Patients were categorized into high, medium, and low-risk groups based on the CARG score. Toxicities, treatment delays, hospitalizations, dose reductions, and treatment suspensions were analyzed for each group.

Results: Among high-risk patients (19%), starting chemotherapy at a reduced dose resulted in a significantly lower incidence of G3-G4 toxicities (OR 0.2, 95% CI 0.07-0.56; $p < 0.01$), delays (OR 0.1, 95% CI 0.03 – 0.36; $p < 0.01$), hospitalizations (OR 0.15, 95% CI 0.03 – 0.62; $p < 0.01$), and dose reductions (OR 0.17, 95% CI 0.06-0.51; $p < 0.01$) compared to starting with a full dose.

Conclusions: The study underscores the importance of individualized chemotherapy dosing in elderly patients, based on risk stratification using the CARG score. This approach can lead to a reduction in adverse outcomes particularly in high-risk groups. Urgent research is needed to validate these findings in prospective studies.

H24

IMMUNE CHECKPOINT INHIBITOR THERAPY INCREASES SYSTEMIC SDF-1, CARDIAC DAMPS FIBRONECTIN-EDA, S100/CALGRANULIN, GALECTINE-3, AND NLRP3-MYD88-CHEMOKINE PATHWAYS

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Background: Immune checkpoint inhibitors (ICIs) have significantly changed the oncology clinic in recent years, improving survival expectations in cancer patients. ICI therapy have a broad spectrum of side effects from endocrinopathies to cardiovascular diseases. In this study, pro-inflammatory and pro-fibrotic effects of short-term ICIs therapy in preclinical models were analyzed.

Materials and Methods: Firstly, in a human *in vitro* model, human cardiomyocytes co-cultured with hPBMC were exposed to ICIs (with CTLA-4 or PD-1 blocking agents, at 200 nM) for 72 h. After treatment, production of DAMPs and 12 cytokines were analyzed in the supernatant through colorimetric and enzymatic assays. C57/Bl6 mice were treated with CTLA-4 or PD-1 blocking agents (15 mg/kg) for 10 days. Before (T0), after three days (T3) and after treatments (T10), ejection fraction, fractional shortening, radial and longitudinal strain were calculated by using bidimensional echocardiography (Vevo 2100, Fujfilm). Fibrosis, necrosis, hypertrophy and vascular NF-kB expression were analyzed through Immunohistochemistry. Myocardial expression of DAMPs (S100- Calgranulin, Fibronectin and Galectine-3), MyD88, NLRP3 and twelve cytokines have been analyzed. Systemic levels of SDF-1, IL-1β, and IL-6 were analyzed before, during and after ICIs therapy.

Results: Radial and longitudinal strain were decreased after 10 days of ICIs therapy. Histological analysis of NF-kB expression shows that short-term anti-CTLA-4 or anti-PD-1 treatment increased vascular and myocardial inflammation. No myocardial hypertrophy was seen with the exception of the pembrolizumab group. Myocardial fibrosis and expression of galectin-3, pro-collagen 1-α and MMP-9 were increased after treatment with all ICIs. Both anti-CTLA-4 or anti-PD-1 treatments increased the expression of DAMPs, NLRP3 inflammasome and MyD88 and induced both *in vitro* and *in vivo* the secretion of IL-1β, TNF-α and IL-6. Systemic levels of SDF-1, IL-1β and IL-6 were increased during and after treatment with ICIs.

Conclusions: Short therapy with PD-1 and CTLA-4 blocking agents increases vascular expression of NF-kB, systemic SDF-1, IL-1ß, IL-6 levels and myocardial NLRP3, MyD88 and DAMPs expression in preclinical models. A pro-inflammatory cytokine storm was induced in myocardial tissues and in cultured cardiac cells after ICIs therapy.

H25

ELECTRONIC VS. PAPER-BASED INVESTIGATOR SITE FILE: MODERNIZATION OR TRADITIONALISM IN CLINICAL TRIALS DOCUMENT MANAGEMENT?

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Background: The importance of correct management of clinical trials documentation in terms of quality, organization and conservation has become a central focus. Even European Regulation 536/2014 has emphasized the need to maintain and archive a permanent file of the clinical trial. The introduction of technology has led to the implementation of new electronic document management methods, starting with the Investigator Site File (ISF). Our work aimed to understand the perspective of Clinical Research Coordinators (CRC) regarding the activation status of proposed new electronic systems, with their advantages and disadvantages.

Methods: In April 2024, the CRC Working Group of the Italian Association of Medical Oncology (AIOM), in collaboration with the Italian Group of CRC (GIDMcrc), released a survey, consisting of 20 multiple-choice questions divided into 3 areas: personal data, electronic ISF (e-ISF) use and benefits/barriers.

Results: A quote of 114 CRC has completed the survey: most of them works in the oncology area (46.5%, n=53), while Scientific Institute for Research, Hospitalization and Healthcare were the most represented (n=65, 59%). Only 31% (n=35) of respondents confirmed the use of eISF in a small number of studies (61%, n=25), not exceeding 3. Mostly still involve a mixed paper and electronic document management (84%, n=56). Furthermore, 60.5% (n=69) of respondents confirm that studies in the activation phase do not involve the use of eISF. However, the majority of CRCs (75.4%, n=86) are favourable to the introduction of eISF, especially for recovering office space (88%, n=78) and minimizing document storage costs (58.4%, n=2). Among the barriers encountered by centers for the activation of eISF, there is particularly little availability of staff in online document management activities (46%, n=49).

Regarding the management of paper ISF, only 34.2% (n=39) believe it is easier document management with paper ISF (65%, n=26) and less workload (30%, n=12), also thanks to the support of the CRA in managing the ISF during on-site monitoring visits (65%, n=26). The main obstacle was identified in logistic aspects: limited space for document storage (78%, n=87), long-term archiving (79.5%, n=89) and office material consumption (70%, n=78).

Conclusions: Although the implementation of eISF in clinical trials is not yet widespread, this survey highlights a positive perception by CRC that using eISF is associated with an improvement in workload and document management.

H26

CORRELATION BETWEEN DIFFERENT PHENOTYPIC SPECTRUM AND GERMLINE MONOALLELIC MUTYH PATHOGENIC VARIANTS: WHAT ELSE?

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Background: Inherited biallelic pathogenic variants (PVs) in MUTYH gene are responsible for an autosomal recessive syndrome, called MUTYH-associated polyposis (MAP), which significantly increases the risk of developing, beyond colorectal cancer (CRC), also breast, ovarian, pancreatic, bladder, duodenal, and skin cancers. However, several studies recently reported an increased genetic susceptibility to cancer also for carriers of germline monoallelic MUTYH PVs. Therefore, our study was aimed to evaluate the spectrum of tumors associated with heterozygous PVs.

Patients and Methods: We retrospectively collected and analyzed all clinical information of 52 patients with germline MUTYH PVs enrolled from Genuary 2018 to February 2024 at the "Sicilian Regional Center for the Prevention Diagnosis and Treatment of Rare and Heredo-Familial Tumors" of the Section of Medical Oncology of University Hospital Policlinico "P. Giaccone" of Palermo. The investigated patients, selected based on criteria established by current guidelines, have been genetically tested by analysis with NGS-based multi-gene panel.

Results: Overall, the mutational analysis revealed that 32 (61.5%) out of 52 patients harboured germline PVs in MUTYH gene, whereas 20 (38.5%) subjects were carriers of variants of uncertain significance (VUSs). Among patients harbouring PVs, 15 (46.8%) out of 32 showed breast, 6 (18.8%) ovarian, 6 (18.8%) pancreatic and 5 (15.6%) colorectal cancer. In particular, only 3 CRC individuals were affected by MAP, as two of them carried biallelic PVs, while

one patient harbored 2 compound heterozygous variants. Also, among patients carrying VUS, breast cancer was the major observed tumor (11 out of 20 patients, 55%), followed by ovarian cancer (5, 25%), pancreatic cancer (2, 10%) and CRC (2, 10%).

Conclusions: Although germline monoallelic MUTYH PVs are not thought to confer a meaningfully increased risk of cancer, however investigating the impact of these variants on phenotypic spectrum could increase diagnostic power and provide new strategies for clinical management of mutation carriers.

H27

REPORTING OF PARTICIPANT RACE AND ETHNICITY IN CLINICAL TRIALS LEADING TO US FOOD AND DRUG ADMINISTRATION (FDA) DRUG APPROVALS BETWEEN 2014 AND 2023

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Background: Clinical trials are the cornerstone for generating solid evidence to support guideline recommendations and new drug approvals. However, the lack of diversity in clinical trials' participants creates racial/ethnic data gaps that affect the generalizability of the study findings. Therefore, reporting the enrollment of participants from underrepresented minorities is essential to understand the overall applicability and safety of new investigational drugs.

Material and Methods: In this cross-sectional study, we assessed the reporting of race and ethnicity of participants enrolled in clinical trials leading to FDA approvals. We searched "Drugs@FDA" for approval notifications in solid tumors between 2014 and 2023. We then identified the clinical trials leading to approvals and retrieved the manuscripts and supplementary materials. We evaluated the reporting of race/ethnicity in the entire decade and two consecutive time intervals: 2014-2018 and 2019-2023.

Results: A total of 260 clinical trials were identified: 85 (32.7%) were phase 1 or 2, and 175 (67.3%) were phase 3. Overall, only 37 (14.2%) clinical trials reported data on both race and ethnicity (R+E) of the participants, while 152 (58.5%) clinical trials on either race or ethnicity (R or E). No differences were found between early and late phase trials. In addition, the subgroup analyses by time interval showed an improvement in reporting R+E with a decreasing number of clinical trials reporting R or E. However, the number of clinical trials that did not report any racial/ethnic data was similar between the two 5-year intervals (Table).

Conclusions: The majority of clinical trials leading to FDA drug approvals from 2014 to 2023 partially reported racial/ethnic data of enrolled participants, limiting the ability to confidently apply the safety and effectiveness results in the real-world population, especially in underrepresented minorities. Thus, further strategies to improve the reporting of participant racial/ethnic data are needed.

Clinical Trials	2014-2018 (n, %)	2019-2023 (n, %)	Total (n, %)
Phase 1 and 2	33	52	85
R+E	2 (6.1)	9 (17.3)	11 (12.9)
R or E	21 (63.6)	28 (53.8)	49 (57.6)
None	10 (30.3)	15 (28.8)	25 (29.4)
Phase 3	75	100	175
R+E	7 (9.3)	19 (19)	26 (14.9)
R or E	44 (58.7)	49 (49)	93 (53.1)
None	24 (32)	32 (32)	56 (32)

H28

RETROSPECTIVE RESEARCH: A PILLAR IN THE KNOWLEDGE PRODUCTION PROCESS

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Background: Retrospective studies play an important role in the clinical studies. The European Institute of Oncology (IEO) formalized an organizational model which adheres to both the General Data Protection Regulation (GDPR) and the European regulations on Artificial Intelligence. Clinical

Data Platform (CDP) was needed for improved data and knowledge management purposes. It is a centralized Health Data Lake containing clinical and research data of the IEO. The valuable data collected in 30 years of activity of the Institute are available on a single platform to researchers and medical staff.

Methods: The Clinical Trial Office (CTO), with the Information Systems Technology (SIS), started a project to implement retrospective study datasets using the CDP. Users no longer need to search for data in different Institute applications but could consult the CDP, which centralizes data in a single repository, through data pre-processing pipelines. Structured data is easily extracted, while unstructured data is standardized using AI models. Notebooks, like Python and R, are integrated into the platform for reporting and complex analysis. The platform has a high level of security guaranteed by numerous data management measures. The CTO liaises with the Principal Investigator (PI) to define which info are needed to extract from the CDP for the study purpose. After the requirements approval by CDP-Steering Committee, a technical analysis of the study dataset is performed. The study dataset is created in a dedicated area on the CDP and made available for data verification by CTO and PI through a web app. Then the dataset is made available for statistical analyses through the notebooks on the CDP. When the study is concluded and the purposes of the study archived, the dataset is historicized.

Results: The Data Products of 20 retrospective studies are currently being analyzed and developed on the CDP. Natural Language Processing models will be required for some of these studies to identify, extract, and standardize certain information reported in the medical reports, such as therapy lines. Dashboards could also be created for data exploration and analysis.

Conclusions The adoption of the mentioned organizational model allows: an in-depth evaluation of each project according to evaluation standards; the awareness of the real dimension of retrospective studies; ethical, legal, and security guarantees to better address the challenges of Big Data.

H29

EARLY CARDIAC WASTING IN LOCALLY ADVANCED HEAD AND NECK CANCER AND IN CARDIAC AUTOPSIES IN A CHEMOTHERAPY-NAIVE CONTEXT. A RETROSPECTIVE "REAL-LIFE" STUDY

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Background: Cardiac wasting is a detrimental consequence of cancer that has been largely overlooked for decades, often being misinterpreted as drug-induced cardiotoxicity. The translation of basic knowledge regarding cancer-driven cardiac wasting into clinical practice remains a significant challenge.

Methods: We conducted a retrospective clinical study involving 42 chemo-naive patients with locally advanced head and neck cancer (HNC). Based on body weight, patients were categorized as either cachectic or non-cachectic. Echocardiographic measurements, including left ventricular mass (LVM), left ventricular wall thickness (LV-WT), interventricular septal (IVS) thickness, and left ventricular ejection fraction (LV-EF), were analyzed. Additionally, we retrospectively examined 28 cardiac autopsy specimens from patients who either died of cancer before beginning chemotherapy or were diagnosed with cancer at autopsy.

Results: Significant differences in LV-WT and IVS thickness were observed between cachectic and non-cachectic patients. LV-WT was 9.08 ± 1.57 mm in cachectic patients compared to 10.35 ± 1.57 mm in non-cachectic patients (p=0.01). IVS thickness was 10.00 mm (8.50-11.00) in cachectic patients versus 11.00 mm (10.00-12.00) in non-cachectic patients (p=0.035). However, LVM and LV-EF did not differ significantly between the two groups. Multivariate logistic regression analysis identified LV-WT as the only variable that maintained a statistically significant difference between cachectic and non-cachectic patients (p=0.035, OR=0.240).

Secondary analysis of autopsy specimens revealed no significant change in heart weight, but there was a notable reduction in LV-WT, specifically 7.50 mm (6.00–9.00) compared to 9.50 mm (7.25–11.00) (p=0.043) between specimens with myocardial fibrosis and those without. This finding was confirmed by multivariate logistic regression analysis (p=0.041, OR=0.502). Moreover hitopathogical analysis confirmed severe atrophy and significant reduction in cardiomyocites cross section areas (CSA).

Conclusions: Subtle changes in heart structure and function occur early in patients with HNC and can be detected through routine echocardiography. These findings may inform the selection of cancer treatment regimens for patients with HNC and other tumor types. Histopathological analysis provided conclusive evidence of cardiomyocyte atrophy, fibrosis, and edema occurring in the early stages of cancer. To our knowledge, this is the first clinical study to examine the direct relationship between tumor progression and cardiac remodeling in HNCs and the first pathological study conducted on human cardiac autopsies from selected chemo-naive cancer patients.

H30

ELECTRONIC MEDICAL RECORDS AND SOURCE DOCUMENTS FOR CLINICAL TRIALS IN ITALY: A GAP IN COMPLIANCE WITH EMA GUIDELINES FOR COMPUTERIZED SYSTEMS?

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Background: Over the past decade there has been a significant shift from paper-based to digital management of medical records, driven by the increasing reliance on digital information technology. This shift has led to the widespread adoption of Electronic Medical Records (EMRs). The ongoing digitization process is expected to fully replace paper-based documentation in the near future. In response, the European Medicines Agency's "Guideline on computerised systems in clinical trials" has established essential criteria for validated EMR systems to safeguard data integrity and security. These guidelines also define the required standards for electronic source documents in clinical trial settings.

Methods: In January 2024, the Italian Group of Data Managers (GIDMcrc) shared an online survey within professionals engaged in clinical research in Italy. The survey aimed to evaluate the characteristics of medical records and source documents (SD) existing in different experimental sites.

Results: The survey was completed by 82 professionals, with 90.2% of them being study coordinators. The respondents primarily hailed from university or public hospitals (47.5%), private IRCCS (26.8%) and public IRCCS (20.4%). A majority of sites use a mixed digital-paper system for SD (70.7%), while only 8.5% have adopted fully digital SD. Only the 57.3% of responders have implemented an organized EMR: 20.0% stated validation according to EMA guidelines, 53.8% reported lack of validation, while for 26.2% this information is unknown. Despite the presence of EMR, Source Data Verification (SDV) is conducted using paper-certified copies in 73.4% of responding sites. In 47.5% of cases the EMR is integrated with other e-systems (e.g. laboratory or pharmacy systems), but the majority of respondents (71.2%) are unaware of whether tests are conducted by IT technicians.

Conclusions: This survey underscores the significant variability among Italian experimental sites in terms of their level of digitalization. While most sites have implemented EMRs, they often lack validation in accordance with EMA guidelines. Moreover, there is a prevalence of hybrid electronic/paper SD systems over fully electronic. Furthermore, in many cases paper-certified copies are produced for SDV. These findings indicate that digitalization is an ongoing process, necessitating further investment and time to reach EMA's standards of quality and achieve full implementation.

H31

PRESS RELEASES OF INDUSTRY-SPONSORED CLINICAL TRIALS IN ONCOLOGY: CHARACTERISTICS OF CONTENT AND TIME ELAPSING BEFORE AVAILABILITY OF RESULTS

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Background: Pharmaceutical companies issue press releases (PRs) to reach not only the scientific community but also the media and shareholders. PRs anticipate a result achieved with the drug, which could impact clinical practice and finances. The absence of detailed data in the PR does not allow critical evaluation of the results. The purpose of this analysis was to describe the characteristics of PRs of industry-sponsored studies in oncology, and delays in the availability of results.

Methods: PRs published between 2018 and 2022 about solid tumors, archived on the websites of the top 20 oncology pharmaceutical companies, were screened. Information about PR content, presence of study results, time between PRs and presentation at scientific meeting, full paper publication and approval by regulatory agencies were collected. Each PRs was analysed by 2 readers; in case of disagreement, a third reviewer adjudicated the discrepancy.

Results: Out of 159 identified PRs, 157 were eligible. The most represented tumors were lung cancer (44, 28%), breast cancer (33, 21%) and prostate cancer (22, 14%). Most PRs (127, 81%) were referred to phase III trials. 141 (90%) were focused on the primary endpoint of a specific trial. In most cases (117, 74.5%), PRs announced that the study met its primary endpoint. Among these 117, PRs included specific results in 15 (13%), while the remaining

102 (87%) contained only generic sentences on the study positivity, without numeric details. Of note, 100 (86%) contained words or sentences supporting the clinical relevance of the results (with a similar proportion - 84% - among those not reporting any numeric detail). Out of the 117 PRs announcing the positivity of the primary endpoint, 117 presentations at meeting (100%) and 113 full paper publications (97%) were found. Median time elapsed between PR and meeting presentation was 3.1 months. Median time elapsed between PR and full paper publication was 8.0 months. After a median follow-up of 48 months, 92 / 117 treatments (79%) were approved by FDA and 87 / 117 (74%) were approved by EMA. Median time to approval by FDA and EMA were 10.0 and 15.9 months, respectively.

Conclusions: Most PRs in oncology announce for the first time the positivity of a clinical trial, without providing detailed results. The time elapsing between PR, the availability of detailed data for the scientific community and any approval by regulatory agencies for use in clinical practice is not negligible.

H32

A RISK MANAGEMENT FRAMEWORK TO IMPROVE CANCER DRUGS PRESCRIPTION, COMPOUNDING AND ADMINISTRATION IN LUNG CANCER PATIENTS CARE IN ITALY

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Background: The objectives of the study were: a) to identify through a proactive approach the risks that could negatively impact patient safety or organizational aspects related to the different phases of cancer drugs prescription, compounding and administration for lung cancer patients in the Day Hospital (DH) service of a public Oncology Institute in Italy; b) to manage the risks by identifying appropriate mitigation strategies.

Methods: A team of multi–health care professionals (oncologists, pharmacists, nurses and health management specialists) used a modified Delphi approach to identify the processes (DH Outpatient Visit, Antiblastic Manipulation Unit Compounding and DH Administration), the main activities performed and the related risk factors. Each risk event was first adequately described, and then evaluated considering its weight on patient safety and organizational concerns. The severity of the harm and the probability of occurrence were assessed by applying a semi-quantitative risk matrix, with a five-point scale, according to the International risk management standards ISO 31000-2018. The risk magnitude was calculated by multiplying the likelihood and consequences scores. The team then identified and adopted multiple improvement actions to reduce the risks to a more acceptable level.

Results: Nine activities and 19 correlated potential risks were identified for patient safety (53%) and organizational area (47%). The highest risk levels were identified in the organizational area and, specifically, in: a) DH Outpatient Visits, for excessive waiting times due to delays in check-in or lab test results or problems with the prescription software; b) DH administration, for long patient waiting times due to unavailability of chemotherapy chairs or lack of dedicated nursing staff. Conversely, the risk levels for patient safety area were overall lower, due to the control measures already in place. After the implementation of the mitigation measures, a new semi-quantitative risk analysis was performed. Risk levels for organizational areas changed from 44.4 to 0% high level, 44.4 to 67% moderate level and 11.2 to 33% minor level. Risk levels for safety area have not modified for high level (10%), while changed from 50 to 10% moderate level and 40% to 80% minor level.

Conclusions: A risk management framework applied to cancer drugs prescription, compounding and administration could improve both organizational and safety objectives.

H33

MINIMUM REQUIREMENTS FOR PHASE I STUDIES IN ITALY: ARE THEY STILL RELEVANT OR DO THEY NEED A REVISION?

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Background: The Italian Medicines Agency AIFA's Determination 809/2015 sets all the requirements that clinical units and laboratories must meet to conduct phase I studies. Almost 10 years later, stakeholders are wondering

whether it is time to update the law to reflect the changes occurred in the world of clinical research.

Methods: In April 2024, the Italian Group of Clinical Research Coordinators (GIDMcrc) shared an online survey within clinical research professionals. The survey aimed to evaluate the characteristics of certified clinical units and laboratories and the opinion of professionals regarding critical issues and necessary changes to the law.

Results: Questionnaires were collected from 48 respondents: mostly study coordinators (50%,n=24) and study nurses (25%,n=12). The majority of respondents (79.2%, n=38) work in facilities that have self-certified both clinical units and laboratories. In all cases the certification involved the analysis laboratory, in 47.4% microbiology (n=18) and in 34.2% pathological anatomy labs (n=13). These facilities conduct phase I trials exclusively on patients (68.7%,n=33), encompassing both profit and non-profit studies (72.9%, n=35), with a focus on oncology (52%,n=25). The self-certification process typically spans a duration of 12 months, primarily influenced by staff training (average impact rating of 7.1 on a scale ranging from 1=minimum impact to 10=maximum impact), followed by the need to recruit new professionals (rated 6.1). The majority of respondents stated that the law should be updated (average score 7.9): most urgent issues to be modified are requirements on the clinical trial quality team requirements (6.7), on standard operating procedures (6.2) and on the professionals' certification in accordance to the Decree of 30 Nov 2011 (6.2). Regarding to the application of the minimum requirements for phases I also to the other study phases, the average score of the respondents was equal to 6.1 (1-10 scale).

Conclusions: The efforts of the already certified structures seem to have focused on the hiring of new staff and their training; at the same time, these are the aspects on which the experts request the majority of updates compared to what is foreseen by the legislation, with regard to the areas of emergencies and the clinical trial quality team. Given the widespread idea that the Italian phase I minimum requirements could be extended to cover all other phases, these updates requires particular attention.

H34

CREATION OF POINTS (PHASE ONE ITALIAN NETWORK TRANSFER & SHARE) - A NETWORK OF ITALIAN PHASE I CLINICAL TRIAL (CT) UNITS THROUGH THE DEVELOPMENT OF AN AIFA'S DIGITAL PLATFORM

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Background: Phase I CT Centers play a pivotal role in the development of new drugs and therapies, providing rapid access to innovative drugs, particularly for unmet medical needs. According to global ranking, Italy records a reduced number of phase I studies compared to all other phases. Although smaller than phase II and III, lately in Italy the number of phase I CTs has been rising, mainly for anticancer agents. The following project focused on the creation of POINTs, a network of Phase I Centers, through the project and implementation of a platform by AIFA.

Methods: Starting 2019, leading representatives of phase I Units self-certified to AIFA, met to define critical issues in CTs management and suggest potential solutions. Main outcomes were set, and for each one the output and suitable key performance indicators (KPI) identified. A project work was generated by AIFA and in one of the packages a survey was submitted to each phase I Unit in November 2023. The methodology adopted in the development of this project package includes: definition of critical issues arising from "inspection deviations" analysis, development of a questionnaire to gather results on the perception of this initiative, performing a gap analysis between the critical issues found in inspections (severity and type of GCP deviations) and the actual needs expressed in the questionnaire by the phase I Centers. Here we report the preliminary results of the survey.

Results: At the end of 2023, a total of 107 phase I CT Units were self-certified, of which 82 (76.6%) joined the network. Since activation, 15 (18.3%) Units had conducted >20 profit CTs, 44 (53.7%) 20 or less, and 23 (28%) none. Moreover, 23 Units (28%) had conducted no-profit CTs. Finally, 73 (89%) phase I CT Units employed a CT Center for their activities. The current analysis of the national context reveals a significant gap between the northern and southern regions in terms of research and development; the data obtained confirms that cooperation among Centers could promote sharing of best practices, data, training, skills, allowing these Centers to benefit from the experience and resources of more advanced Centers to reduce the existing geographical gap in access to innovative therapies.

Conclusions. Phase I CTs Units have progressively expanded during the last decades in Italy but the rate of Units with low number of trials is still high. Hopefully, the national POINTs network will contribute to overcome current limitations.

H35

CONDUCTING CLINICAL TRIALS WITHIN A DEDICATED STRUCTURE – 10 YEARS OF CLINICAL TRIAL OFFICE IEO

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Background: The Clinical Trial Office (CTO) aims to optimize the management of Clinical Trials at the European Institute of Oncology (IEO) and to disseminate the culture of clinical research according to Good Clinical Practices (GCPs). The IEO CTO was founded in 2013 and it celebrated its 10th anniversary since its establishment (13/12/2013) in 2023; this abstract aims to show the results achieved during the first decade of activity.

Methods: Data from 2014 to 2023 were prospectively collected within a database for management of clinical studies, which included all the necessary information to map the status of a clinical study from the selection to the closure. The CTO adopted several quality indicators for monitoring its activity such as the number of drop out or the center's attractiveness or the number of patients enrolled.

Results: A total of 1262 studies activated were identified in 10 years from the database, 871 interventional and 391 non-interventional, equally distributed between profit (686) and non-profit (576). The drop-out indicator, which allows monitoring premature withdrawal of eligible enrolled patients from a clinical study, decreased from 2.2% in 2014 to 1.6% in 2023. The center's attractiveness indicator evaluates the total number of pre-study visits (PVT) with a positive outcome; comparison with previous years shows a greater number of studies with positive PVT (72 in 2023 compared to 64 in 2022). The CTO IEO indicators also includes the number of patients enrolled in clinical studies. In 2023, 6326 patients were enrolled in a total of 728 ongoing trials, compared to 2692 patients in 2014 for a total of 418 ongoing trials. Patient enrollment in clinical trials is growing after the decrease caused by the COVID-19 pandemic restrictions in 2020.

Conclusions: The presence of an infrastructure focused on and dedicated to clinical research within an oncological center determines greater attractiveness of the center to sponsors and scientific community; furthermore, the conduct of clinical trials within the CTO, with dedicated figures and constant monitoring of trial-related activities, has led to an increased number of activated clinical trials and enrolled patients over the past 10 years of activity, allowing IEO to efficiently respond to an increasingly complex and diverse demand for services.

H36

COMPLEXITY FACTORS IN PHASE I STUDIES FOR SOLID TUMORS: A MONOCENTRIC ANALYSIS FROM THE PHASE I CLINICAL TRIAL UNIT AT NIGUARDA CANCER CENTER

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Background: In the last ten years there has been notable progress in oncology clinical trials (CTs), leading to the introduction of new study designs, endpoints, integration of predictive biomarkers, and molecular tumor profiling for patient selection. Moreover, the increased quality standards and the regulatory changes in phase I cancer trials over the past two decades have resulted in a significant rise in study-related procedures requiring dedicated professionals to handle this complexity. To better highlight which factors impact the complexity, we conducted a descriptive single-center analysis of a pool of phase I CTs.

Material and Methods: We retrospectively analyzed data from a set of 32 phase I clinical trials conducted at Niguarda Cancer Center from 2018 to 2023 for solid tumors in adult patients.

Results: The predominant phase I study design was escalation/expansion type (n=27, 81.8%), with 34.4% (n=11) including also a phase II part in the study protocol. Despite the majority of studies was biomarker-driven (n=27, 81.8%), only 24.2% (n=8) involved a molecular pre-screening. The average number of Investigational Medicinal Products (IMPs) was found to be 3.9 per trial (median = 4, min = 1, max = 9). Furthermore, stratifying the studies based on the number of tumor histologies as inclusion criterium, it was observed that 34.4% (n=11) involved more than 10 histologies. The mean number of cohorts planned per study was 7.3 (median = 6, min = 2, max = 26). Comparing across trienniums (2018-20 vs. 2021-23), a rise in the average number of IMPs (3,4 vs 4,3) and in the average number of cohorts planned per CTs (6,1 vs 8,2) was observed.

Conclusions: Our analysis provides insight into factors that contribute to trial complexity and documents that the complexity factors of phase I CTs are increased number of histologies, cohorts and IMPs. Despite a large portion of CTs was biomarker-driven, only a small fraction of them included molecular pre-screening, leaving the molecular patient identification as per clinical practice. Moreover,

comparison of studies across years shows an increasing trend of these complexity factors over time, underscoring the importance of a team dedicated to phase I CTs. Although it's a monocentric and exploratory analysis, these data suggest an increasing complexity in phase I trials that should be investigated in the near future by broadening the sample size with other clinical trial centers.

H37

EMPOWER PROJECT. COMMUNICATION MANAGEMENT, HUMAN RESOURCES AND OPERATIONS MANAGEMENT: AN INNOVATIVE NATIONAL PILOT EXPERIENCE OF TRAINING IN MEDICAL ONCOLOGY UNITS

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Background: The field of medical oncology is rapidly changing requiring more diversified knowledge, skills and competency to ensure optimal cancer care and to promote a more sustainable healthcare system. With the aim of establishing an effective education in communication management, human resources and operations management, we developed the Empower national pilot project.

Material and Methods: Six italian medical oncology units were involved, representing different realities and contexts (university hospitals and community hospitals), located in the north, center and south of Italy. Rather than involving the entire team, 34 change agents were selected and participated in a 6-month training course. The course included an initial alignment phase; an intensive training; a group coaching to put new knowledge into practice.

Results: The main topics addressed during the phase of coaching were: problematic communication with patients and family members (bad news, aggressive patient), management of conflicts between colleagues, through dual and group strategies; the use of time management and feedback management tools; the formulation of an improvement project, using the Lean A3 Report technique. The methodologies were discussed theoretically; a benchmark was carried out between centers on common problems; a focus and a structured analysis of the problems identified by each center were carried out; different improvement projects were therefore set up in terms of resources and time. Conclusions. The Empower project was well received by the participants, who appreciated the possibility of training in areas not covered during oncology education, its practical format and the transferability of training contents. The next step, to confirm the feasibility and explore the effectiveness of the course, will be the involvement of a greater number of units and the start of shared paths at national level to give answers to the requests emerged during the project.

H38

LOOKING FOR PROXIMITY CARE IN ONCOLOGY: EXPERIENCE OF THE ASL OF MEDIOCAMPIDANO

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Background: In Italy the current system for cancer patients management is concentrated mainly at hospital while territorial resources are underused. Although Ministerial Decree 77/2022 defines the new standards of territorial care, it does not provide a univocal guidance model in the oncology field. A large part of the oncology patient's needs could be satisfied in the extra-hospital context.

Methods: Starting from 2018, a project has been developed in the Mediocampidano ASL for the dehospitalization of cancer patients through the transfer to extra-hospital health facilities (EHHF) of some activities that had until then been concentrated in the hospital oncology unit (HOU). Based on a principle of proximity care, from 2018 to 2023 the first visits and follow-ups were progressively reorganized at 5 EHHF, in addition to the hospital one. Each territorial outpatient clinic is entrusted to an oncologist of the HOU that is the reference specialist for general practitioner and the population of a geographical area. An electronic data base allows access to clinical data from all the structures of the network. Between 2018 and 2019, on-the-job training was carried out aimed at territorial nursing staff. The management of vascular access, blood tests, the administration of simultaneous care, and the removal of elastomeric chemotherapy pumps have been progressively delocalized. Since 2018, outpatient treatment settings (oral-SC-IM drugs) have been implemented in the HOU through shared medical-nursing management and in February 2023, an outpatient clinic was established in a territorial facility for the prostate cancer management.

Results: Between 2018 and 2023, a progressive reorganization of outpatient activities was carried out in 5 EHHF. The results achieved in 2023 were: 75% of follow up visits and 48% of first visits carried out outside of hospital. The territorial outpatient clinic for prostate cancer treatment established in February 2023 took on 52 patients in the first 10 months. Access to hospital for services which are carried out at 3 territorial nursing clinics, has been minimised. Patients demonstrated excellent adherence to the project.

Conclusions: Based on our experience, we believe an innovative model of proximity to cancer care is feasible. A single governance, task shifting logic, professional enhancement and empowerment, shared clinical data, represent key elements in the creation of a system that improves access to care and patients' quality of life.

H39

ENHANCING COMMUNICATION SKILLS IN BREAKING BAD NEWS

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Background: Effective communication of bad news in oncology is pivotal for patient well-being. However, many oncologists feel inadequately trained in this area. This preliminary study evaluates the impact of a structured communication training program on the delivery of bad news by oncologists to cancer patients.

Materials and Methods: This preliminary study involved 20 oncologists from diverse cancer centers. Participants were randomly assigned to either the intervention group, receiving a comprehensive communication skills training based on the SPIKES protocol, or the control group, receiving no additional training. The training included workshops, role-playing, and feedback. Validated questionnaires (CSAS and CARE Measure) were administered to oncologists and a subset of patients before and three months after the intervention. Statistical analyses included paired t-tests and chi-square tests.

Results: Of the 20 oncologists, 18 completed the study (intervention: 9, control: 9). The intervention group showed significant improvements in CSAS scores (pre: 31.8 ± 5.2; post: 37.6 ± 4.4; $p < 0.01$) compared to controls (pre: 32.4 ± 5.3; post: 32.9 ± 5.1; $p = 0.72$). CARE Measure scores also increased significantly in the intervention group (pre: 33.9 ± 5.8; post: 39.5 ± 5.1; $p < 0.01$), with no significant change in controls (pre: 34.1 ± 5.6; post: 34.3 ± 5.9; $p = 0.89$).

Conclusions: This preliminary study indicates that structured communication skills training improves oncologists' ability to deliver bad news, as evidenced by enhanced communication and empathy scores. Future research with larger cohorts and long-term follow-up is warranted to confirm these findings and assess patient outcomes.

H40

DIGITAL TELEMONITORING FOR CANCER CARE: ARE THE PATIENTS SATISFIED?

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Background: Telemedicine has shown to improve quality of care of patients with cancer, allowing medical and nurse staff to maintain a continuous link with them and to monitor adverse events (AEs) in real-time.

As part of a telemedicine development project, the European Institute of Oncology (IEO) has used the Cureety platform since July 2023to tele-monitor AEs related to oncological oral therapy in patients treated at IEO.

We present data regarding patient satisfaction about the use of Cureety.

Methods: This report included patients with solid tumors treated with oncological oral therapy at IEO, Milan, and registered on the Cureety platform (from July 2023 to April 2024). One month after the start of monitoring, patients are asked to complete a questionnaire to analyze their satisfaction with the use of Cureety, consisting of four questions. Data about patients' satisfaction are reported.

Results. In April 2024, 81 patients were registered on the platform and completed the questionnaire about satisfaction. Of these, approximately 50% received a diagnosis of primary breast cancer.

As far as the first question ("Are you satisfied with the Cureety platform for remote monitoring?") is concerned, none of the patients were "not at all satisfied" while 63% of them were "very satisfied" with the platform.

Messages about treatment management received were considered useful by 32.1% of the patients and very useful by 60.5%. Furthermore, 67.9% were "very satisfied" with "the response times of your care team" and 29.6% were satisfied.

Overall, on a scale from 1 (unlikely) to 10 (very likely), 72.8% of the patients would consider it very likely to recommend the Cureety app to another patient. No score lower than 6 was registered.

Conclusions: This report shows that patients are satisfied with their experience with the Cureety. This user-friendly

platform allows to immediately communicate any AEs, with the timeliness of the feedback received from the staff.

Moreover, over 60% of patients rated the feedback received as very helpful, suggesting a high level of appreciation for the assistance provided through the platform.

H41

BRIDGING THE DIVIDE: HEALTHCARE MIGRATION OF SOUTHERN ITALIAN CANCER PATIENTS TO THE NORTHERN REGIONS

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Background: Disparities in healthcare access and infrastructure between Northern and Southern Italy have led to a significant phenomenon of healthcare migration, particularly among cancer patients. While the Northern regions boast advanced oncological centers, patients from the economically disadvantaged South often seek treatment there, necessitating a comprehensive understanding of this migration pattern's implications.

Materials and Methods: This study conducts a systematic literature review, synthesizing data from published studies and reports on healthcare migration of cancer patients within Italy. Statistical analysis, including meta-analysis techniques, is employed to examine demographic characteristics, cancer types, treatment modalities, and outcomes of migrant patients compared to native Northern patients.

Results: The literature review identifies a considerable proportion of cancer patients in Northern Italian centers originating from Southern regions, particularly from areas with limited healthcare resources. Across included studies (n=15), approximately 35% (n=875) of patients were migrants from Southern Italy. Migrant patients exhibit distinct demographic profiles, with a higher proportion of advanced-stage cancers (pooled odds ratio = 1.67, 95% CI: 1.45-1.92) compared to native Northern patients. However, meta-analysis results show no significant difference in survival outcomes between migrant and native Northern patients (pooled hazard ratio = 0.98, 95% CI: 0.88-1.09), indicating the efficacy of care provision in Northern centers. Subgroup analysis by cancer type reveals similar survival outcomes across different malignancies, suggesting consistent quality of care.

Conclusions: Healthcare migration of cancer patients from Southern to Northern Italy underscores the disparities in healthcare accessibility within the country. While migration offers Southern patients access to superior oncological services, it also highlights the need for equitable healthcare distribution across regions. Policy interventions should aim to address structural inequalities, enhance healthcare infrastructure in Southern Italy, and promote regional collaboration to ensure equitable cancer care delivery nationwide. This study emphasizes the importance of understanding healthcare migration dynamics to inform targeted interventions and optimize oncological services for all Italian cancer patients.

H42

CORRELATION BETWEEN VITAMIN D3 LEVELS AND RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN CANCER PATIENTS: A PROSPECTIVE SERIES

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Background: Vitamin D3 is a secosteroid hormone that plays a crucial role in regulating immune responses, particularly in preventing excessive inflammation. This vitamin also affects cells in the tumor microenvironment. Immune checkpoint inhibitors (ICIs) are a novel class of therapies that effectively stimulate the immune system, leading to significant clinical responses in various types of cancer. The recent discovery of a direct involvement of the vitamin D endocrine system in modulating anti-tumor immune surveillance provides an opportunity to investigate the impact of circulating vitamin D3 levels and supplementation on the clinical benefits and reduction of toxicities associated with ICI treatment in cancer patients.

Materials and Methods: A prospective study was conducted on cancer patients undergoing systemic therapy with immune checkpoint inhibitors. Patients were assessed for vitamin D3 levels before treatment initiation and after 12 weeks, in addition to routine blood examinations. For patients with vitamin D3 levels below 20 ng/mL (indicative of vitamin deficiency), supplementation was offered in the form of 2 monthly oral doses of 50,000 IU of vitamin D3. A correlation analysis was performed to evaluate the relationship between vitamin D3 levels (>20 vs <20 ng/mL) and clinical response based on RECIST criteria. Additionally, survival and progression-free survival analyses based on vitamin D3 levels were planned.

Results: Among the 72 patients included in the study, 62 had their vitamin D3 levels assessed prior to starting ICI therapy. The main histologies observed were lung cancer (56%), renal cell carcinoma (14%), and bladder cancer

(11%). The mean vitamin D3 level was 21.6 ng/mL, with a median of 18.7 ng/mL (range: 4.6-56.6 ng/mL). The overall response rate (ORR) was 40.7% in patients with vitamin D3 levels >20 ng/mL, compared to 34.4% in those with levels <20 ng/mL. When comparing patients with sufficient and insufficient vitamin D3 levels (>30 vs <30 ng/mL), the ORR was 60% and 35.7%, respectively (p=0.15). After 3 months of supplementation with oral vitamin D3, less than 40% of patients achieved sufficient vitamin D3 levels.

Conclusions: Approximately two-thirds of cancer patients assessed for vitamin D3 levels in this study had levels below 20 ng/mL. Patients with sufficient vitamin D3 levels demonstrated a higher overall response rate. Ongoing research is needed to determine the correlation between vitamin D3 levels and survival outcomes.

H43

BREAKING BARRIERS TO CLINICAL TRIAL ACCESS

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Background: Clinical trials (CTs) are essential for advancing patient care. However, numerous obstacles, including limited physician and patient awareness, hinder widespread participation (Unger et al., 2016). Trialing, a clinical trial search and patient referral platform, was launched in Spain in 2022 to address some of these challenges. It has quickly gained traction within the Spanish oncology community, with over 2,200 users (more than 1,800 oncologists and hematologists) and nearly 9,000 monthly trial views. A major challenge in Spain was the uneven geographical distribution of clinical trials, with many regions offering very few. With its recent expansion into Italy, Trialing aims to enhance access to clinical trial opportunities for patients there as well. This study provides an overview of the medical oncology and radiotherapy clinical trial landscape in Italy, including an analysis of their geographical distribution.

Methods: The data for this study were sourced from Trialing, which compiles information from public repositories, primarily clinicaltrials.gov. This data is manually checked, curated, and supplemented by collaborating institutions to ensure it is up-to-date. Our analysis focuses on the number and landscape of recruiting clinical trials (CTs) and their geographical distribution across Italy.

Results: As of May 10th, 2024, there were 431 oncology CTs open for recruitment in Italy. The most common primary tumor types were NSCLC (80 / 19%), non-Hodgkin lymphoma (69 / 16%), breast cancer (58 / 13%), colorectal cancer (42 / 10%), and gastroesophageal tumors (29 / 7%). There are 641 oncology centers registered in Italy, of which 221 (34%) currently offer clinical trials (CT). Based on the number of CTs, we categorized 72% of centers as small (<10 CTs), 18% as medium (11 to 40 CTs), 7% as large (41 to 100 CTs), and only 3% as giant (> 100 CTs). Only 1 of the 20 administrative regions in Italy offers more than 50% of the CTs currently available, while 40% of the regions have < 10% of them.

Conclusions: Similar to Spain, Italy has a substantial number of oncology CTs, though they are heavily concentrated in certain areas. The success of Trialing in Spain suggests it has the potential to significantly improve clinical trial participation in the Italian oncology community by addressing these geographical and awareness barriers.

H44

HARMONIZATION OF CANCER PATIENT DATA AT THE MODENA ONCOLOGY CENTER

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The evolution of treatments has revolutionized the therapeutic strategy in the treatment of early and metastatic cancers in the last 10 years. The analysis of a unique database may allow the identification of any parameters to be able to propose Real Word Evidence studies in the future aimed at creating a platform with data, standardized and anonymized according to the computer language.We conducted a retrospective cohort study in all patients (pts) treated with solid tumors starting from the year 2001 at the Modena Oncology Center (COM). The protocol has been approved by the local ethic committee in January 2024. The main objective is the creation of a database through the collection of demographic and clinical parameters in order to evaluate the actual outcome of pts treated in normal clinical practice. Local data sources databases were used. Individual pts has been identified by a unique ID code. The IT Service executed pts extraction queries and was responsible for their anonymization. The data has been standardized using a dedicated application. The analysis, mapping and ETL of the local e -chart (COMNet) data has been performed on docker platform hosted on a shared virtual server accessible via VPN to ensure maximum data confidentiality. Data from 33,000 patients were evaluated. The results highlight an increase in clinical data entry and digitalisation over the last 2 decades. An increase

in the use of cancer drugs is observed after 2010, due to the availability of new therapies. In addition, a parallel increase in clinical instrumental controls is observed, visible in the increase of measurement and observation information. The lack of data on visits, prior to 2010, highlights the change in the method of clinical data collection due to the evolution of the medical record and the progressive digitalisation of the paper data collected in the decades-long history of the COM. The harmonization process highlighted numerous inconsistencies related to missing dates on information entry or diagnosis of conditions related to pts clinical data stored in the COMNet platform. The analysis of the harmonised data revealed the criticality of data fragmentation due to the incompleteness of the digitalisation process and the presence of different and unconnected software platforms. The objective of achieving greater interoperability and having an integrated view of the information will be one of the guidelines of the re-engineering process of the COMNet platform.

H45

EMPOWERMENT, PAIN CONTROL, AND QUALITY OF LIFE IMPROVEMENT OF EARLY TRIPLE NEGATIVE BREAST CANCER PATIENTS THROUGH PAIN NEUROSCIENCE EDUCATION: A PROSPECTIVE COHORT STUDY PROTOCOL

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Background: The treatment of early triple negative breast cancer (eTNBC) have improved patients' prognosis, but often leads to adverse events and sequelae affecting quality of life (QoL). Pain Neuroscience Education (PNE) is a promising non-pharmacological intervention in this field. Preliminary data showed the beneficial effect obtained by PNE in breast cancer survivors. However, there are still gaps in knowledge on its optimal use in eTNBC.

Materials (patients) and Methods: This prospective pilot study will enroll 30 consecutive patients diagnosed with eTNBC at the IRCCS Humanitas Research Hospital. They will be given a web link to monthly complete pain questionnaire, and those with numerical rating scale (NRS)≥4 will be invited to join the study. The PNE program will consist of 10 weekly sessions to be started within 4 weeks of the onset or worsening of pain syndrome. The evaluation of QoL, perceived pain, and disability will be carried out at baseline, about 5 weeks after the start, at the end, and 6 months after the PNE end. This evaluation will be conducted using validated questionnaires measuring: i) the overall QoL (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer–Specific 23), ii) pain (NRS), iii) migraine and headache (Headache Impact Test -6 and MIgraine Disability ASsessment questionnaires), and iv) anxiety and depression (Hospital Anxiety and Depression Scale scale). A blood sample will be collected before and at the end of PNE to evaluate inflammatory serum biomarker levels. The primary objective is to evaluate whether PNE leads to clinical improvement in QoL and pain.

Expected Results: We anticipate that the PNE program will enhance coping strategies, reduce disability, and improve the patients' QoL, thus improving the knowledge about the feasibility of administering a PNE protocol to eTNBC patients. In addition, the measurement of inflammatory markers will allow obtaining more comprehensive data.

Conclusions: To our knowledge, this study is the first to test PNE intervention in eTNBC patients under treatment. The project outcomes will directly benefit the target audience and will provide medical oncologists with a standardized approach to improve QoL and pain and, as a result, improve patient outcomes. If successful, it will be validated in an enlarged multi-centric cohort, leading to a potential widespread implementation of the PNE program as a standard pain management tool for eTNBC patients.

H46

ASSOCIATION BETWEEN PERIPHERAL BLOOD BIOMARKERS AND CLINICAL OUTCOMES IN PATIENTS WITH MSI-HIGH SOLID TUMORS TREATED WITH IMMUNE-CHECKPOINT INHIBITORS

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Background: Recently, immune checkpoint inhibitors (ICIs) have been approved for treating MSI-high solid tumors like colorectal and endometrial cancers, significantly improving outcomes with favorable tolerability. Various prognostic and predictive biomarkers, such as NLR, PLR, Hb, and Na levels, have been studied across different cancers. Our study aims to assess the correlation between these peripheral blood biomarkers and clinical outcomes in an unselected population with MSI-high tumors.

Material and Methods: This is a monocentric retrospective study of a real-world population of MSI-high colorectal and endometrial cancers treated with ICIs between September 2019 and April 2024. We examined clinical parameters, peripheral blood biomarkers (NLR, PLR, Hb, Na), and outcomes (PFS, OS) of 40 pts treated with ICIs across different treatment lines.

Results: Overall, 27 patients (67.5%) had colorectal cancer, while 13 patients (32.5%) had endometrial cancer. Among the endometrial cancer patients, 6 received dostarlimab (46.15%), and 7 received pembrolizumab (53.8%). All colorectal cancer patients received pembrolizumab (100%). Median PFS during immunotherapy was 20.28 months, while median OS was not reached. Baseline Hb levels < 11g/dL were associated with poorer OS compared to Hb levels >= 11 (p=0.023). Patients with PLR >= 200 at the second cycle of immunotherapy had worse OS (p=0.04). A significant association was observed between baseline NLR < 6 and better OS (p=0.01). Similarly, NLR values < 6 at the third cycle were associated with better PFS and OS (p=0.002 and p<0.001, respectively). However, the low sample size in the NLR>=6 arm (N=6 pts) limits its clinical significance. We recalculated the NLR cutoff based on the median NLR of our population (median NLR= 2.8), showing no significant difference in OS between patients with basal NLR < 2.8 and NLR >= 2.8. No differences were observed between baseline Na levels and PFS or OS.

Conclusions: Low baseline hemoglobin levels are linked to poorer survival in MSI-high solid tumor patients. However, the small sample size and lack of a validated NLR cutoff hinder establishing its prognostic value, unlike in other cancers. Further analyses are needed to identify the most effective prognostic and predictive biomarkers in MSI-high tumors.

H47

TACKLING INEQUITIES IN CLINICAL TRIALS IN SPAIN: A DIGITAL APPROACH

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Background: Clinical trials (CT) are fundamental in advancing patient care. Regrettably, the accessibility of clinical trials remains uneven, partly due to a lack of trial awareness among physicians and patients. Trialing is a user-friendly platform poised to address some of these challenges, offering up-to-date CT information, streamlining the identification of suitable trials and facilitating patient referral. It started operations in Spain in 2022 and it has recently expanded to Italy. Drawing from key insights from Spain, we offer a glimpse into the platform's potential impact in Italy.

Methods: We present data from Trialing. These data originate from public repositories, mainly clinicaltrials.gov, are manually checked and curated, and are supplemented by data from collaborating institutions, to ensure that it is updated. We leverage the platform's database to report key user, site, and referral metrics.

Results: There are 2218 users (1851 oncologists or hematologists). On average, every month there are ~5000 clinical trial searches and ~8800 trials viewed on our platform. As of May 10th, there were 569 CTs recruiting in Oncology in Spain. The most common tumor types were NSCLC (22%), breast cancer (16%), non-Hodgkin lymphoma (15%), colorectal cancer (9%) and urothelial carcinoma (8%). Of 561 oncology centers in Spain, 146 (26%) offer ≥ 1 CT; 58% offer <20 (small), 19% between 21 and 75 (medium), 9% between 76 and 150 (large), and 14% > 150 CTs (giant). Only 2 of the 17 administrative regions in Spain offer > 50% of the CTs available, while more than half of the regions have < 10% of CTs. Through Trialing: (i) 100% of giant, 91% of large, 96% of medium, and 41% of small centers receive referral requests; (ii) oncologists working in 66% of small, 83% of medium, 82% of large and 100% of giant centers use Trialing to refer patients to other centers. The most common tumor type for patient referral were NSCLC (24%), colorectal cancer (12%), and breast and pancreatic cancer (7% each).

Conclusions: The distribution of CTs in Spain is highly concentrated, with many regions having a minimal subset of available CTs. Trialing, which has become widely used in Spain, provides updated CT information and offers patients access to them, thus improving treatment equity. The acceptance of Trialing in the Spanish oncology community suggests that it can be replicated in other countries with similar challenges, like Italy.

H48

ARTIFICIAL INTELLIGENCE AND BONE METASTASIS: A SYSTEMATIC REVIEW

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Background: Bone is one of the most frequent sites of metastasis, especially for breast, prostate, and lung cancers. In recent years, artificial intelligence (AI) has spread to the medical field as an aid in decision-making, diagnosis, and treatment. The aim of this systematic review was

to evaluate the potential of using AI in clinical, radiological, and pathological fields of bone metastases.

Material and Methods: We included studies that evaluated the use of AI applications in patients affected by bone metastases. Two reviewers performed on 31 December 2023 an electronic search on PubMed, Scopus, and Cochrane library, and extracted these data from the included studies: authors, AI method, interest area, main modalities used, and main objectives. The analysis included the assessment of nuclear medicine, clinical research, radiology, and molecular biology.

Results: In this review we included 59 studies, which analyzed the role of AI in diagnosis or prognosis in patients with bone metastasis. Six studies (10,2%) were specific for spine metastasis. The study involved nuclear medicine (N=26 [44.1%]), clinical research (N=17 [28,8%]), radiology (N=12 [20,4%]) or molecular biology (N=4 [6,8%]). When primary tumour was reported, prostate cancer was the most common (N=13 [22%]), followed by lung (N=7 [11,9%]), and breast (N=3 [5,1%]), kidney (N=3 [5,1%]).

AI models with deep neural networks using image features from bone scintigraphy with 9mTc-MDP showed great time efficiency, accuracy, specificity, and sensitivity in the diagnosis of bone metastasis. Computed tomography (CT) widespread adoption allows for routinely performed exams making it an ideal candidate for computer-aided detection (CAD) systems under AI. Magnetic Resonance Imaging (MRI) offers a sensitivity and specificity of 70–100% for the detection of bony metastases. The combination of MRI and Positron Emission Tomography (PET)/CT parameters has the possibility of predicting early metastatic disease if analyzed by AI models. Clinical prediction AI models have been developed for evaluating disease-free survival and overall survival in cancer patients.

Conclusions: The diagnosis and management of tumors in the musculoskeletal system are extremely complex, requiring a multidisciplinary approach. Appropriately trained AI models may be very useful in merging information to achieve an overall improved specificity and sensitivity in the diagnosis and treatment of bone metastasis.

H49

THE MANAGEMENT OF THE VALIDATION PROCESS OF A SOFTWARE USED IN A ANTIBLASTIC DRUG UNITS ACCORDING TO THE SPECIFICATIONS OF THE EUROPAEN MEDICINE AGENCY (EMA). A GUIDE TO RISK ASSESSMENT

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Background: A modern antiblastic drug unit ("UFA") should operate under complete computerization of galenic preparation operations. It's also strongly recommended to maintain the conformity to Ministry of Health Recommendation 14. Regarding preparations to be used in the conduct of clinical trials, the Italian Medicines Agency (AIFA) requires that the process of preparation of galenic preparations be computerized and that the related software undergo a complete validation process as described in the European Medicines Agency (EMA) document "Guidelines on Computerized Systems and Electronic Data Management in Clinical Trials". We describe the steps necessary for conducting a proper validation activity starting from a complete risk assessment.

Materials and Methods: Validating a software means verifying that it works consistently according to the specifications for which it is built and the process it handles. A software validation process cannot be separated from an initial assessment of the risk associated with the process it handles and the characteristics of the software itself.

Process of risk analysis: This step is mainly divided into three parts: risk evaluation based on the Good Automated Manufacturing Practices (GAMP version 5) classification [R1], risk evaluation based on the risk for patients' rights, safety and wellbeing (including privacy risks) [R2] and risk evaluation based on reliability and credibility of data [R3]. Each part has a score from 1 to 3 (higher means greater risk). The tables are shown below:

GAMP CATEGORY

	RISK	VALUE
CATEGORY 5	HIGH	3
CATEGORY 4	MEDIUM	2
CATEGORY 3	LOW	1

IMPACT OF A POTENTIAL ERROR ON THE PROTECTION OF PATIENTS' RIGHTS,SAFETY AND WELLBEING (INCLUDING PRIVACY RISKS)

RISK	VALUE
HIGH	3
MEDIUM	2
LOW	1

IMPACT OF A POTENTIAL ERROR ON THE RELIABILITY AND CREDIBILITY OF DATA RISK – VALUE.

RISK	VALUE
HIGH	3
MEDIUM	2
LOW	1

The overall risk is determined by the sum of the 3 risk values described on a scale ranging from 1 to 9, the score of 3 represents a low overall risk, 4 to 6 a medium risk, 7 to 12 a high risk.

Each level of risk corresponds to a higher level of complexity of the required validation protocol.

Results: A software for an the antiblastic drug unit because of the nature of the process it handles scores no less than 7 (2 or 3 [R1], 3 [R2],2 or 3 [R3]) according to the features of the software.It's highly recommended to perform a full Installation, Operational and Performance Qualification protocol based on the risks and the specific features of the software.

H50

A COMPARISON OF BASELINE CHARACTERISTICS IN THREE GROUPS OF INDIVIDUALS SUFFERING FROM ADVANCED CHRONIC DISEASES (ONCOLOGICAL, RENAL, AND PULMONARY)

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Nearly 57 million people worldwide are estimated to require palliative care (PC) annually but only 14% receive it. Many initiatives have lately been developed to promote PC integration: the most significant obstacles are clinicians' reduced awareness and the difficult identification of patients in need. We aim to verify if combining PC needs identification (NECPAL) and prognostic (PaP Score) tools can be a valuable screening method for detecting advanced chronic disease patients with short term prognosis and likely in need of PC. The study, financed by the Italian Ministry of Health and the Emilia Romagna Region (NET-2018-12367032) and approved by the local Ethics Committee, is ongoing. This is a descriptive sub-study assessing baseline patient characteristics to compare three distinct populations affected by advanced chronic disease, enrolled in four Italian centers. Statistical analysis was performed to compare baseline demographic and disease-related data, NECPAL and PaP Score, Edmonton Symptom Assessment System, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) and the Borg Scale. We enrolled 187 patients: 102 with advanced tumors (48 non-small cell lung cancer, 23 gastric and 31 pancreatic adenocarcinoma), 35 with chronic renal failure and 50 with chronic respiratory failure (39 obstructive pulmonary disease (COPD) and 11 idiopathic pulmonary fibrosis). Except for age, there are no statistically significant differences between the groups' baseline characteristics. Cancer patients is on average younger (71 years) than the non-oncologics (78-79 years). The ECOG-PS slightly differed, with the oncologic population having a better one. A similar trend was noted in a general high prevalence of comorbidity but particularly in nearly the whole non-oncologic population. Results are consistent with trend and characteristics of non-oncological chronic diseases, known for a variable and slow progression, with unpredictable exacerbations accelerating the deterioration of functional status. As a result, these patients may present poorer conditions than those with cancer, often characterized by relative initial clinical stability and a rapid decline approaching death.

H51

THE TREE OF IDEAS

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Background: The subjective experience of those who experience oncological disease goes beyond physical disorders and requires a biopsycho-social approach inserted in the context of a more humanized and humanizing treatment process. To better interpret the patients' experience we have tried to give them a voice and welcome needs, desires and proposals to facilitate the doctor-patient-health facility relationship.

Methods: In collaboration with a voluntary assciatin ACTO(alliance against ovarian cancer) we set up in the area in front of the U.O. area of Medical Oncology of the P.O. S Elia a space, in which "The tree of ideas" was placed, a cardboard tree with related branches. Patients, caregivers and healthcare workers were invited to give their own contribution of ideas and proposals through messages written on adhesive leaves to be placed on the branches of the cardboard tree. Narration of oneself through "handwriting" is a effective tool - scientifically proven - which allows emotions to flow freely, to promote the motor activity of the

fingers, to solicit greater attention to what one is thinking and to induce a more elaborate connectivity between the different neuronal areas than otherwise happens in typing on a keyboard or in verbal production.

Results: It was deemed useful to divide what was written on the leaves into three areas:

- area of Humanization of Care (requests for improvement of the doctor-patient relationship, treatment paths and the active involvement of the patient in these paths);
- area Services (requests to strengthen those services aimed at making hospital access and pathways more fluid in order to guarantee continuity of assistance);
- area structures (requests to upgrade dedicated spaces and diagnostic tools whose lack forces migration to other structures).

Conclusions: The greatest requests include needs relating to the strengthening of the humanisation of care (43%) and the increase of Services (43%).This experience aims to offer food for thought on the need to increasingly consider the patient as a whole person, to bring out hidden emotions and discomforts in order to improve the quality of life. The subjective experience of those who experience oncological disease goes beyond physical disorders and requires a biopsychosocial approach inserted in the context of a more humanized and humanizing treatment process.and to improve the ability to listen as a fundamental basis for improvement

I – Brain Tumors

I01*

A NOVEL MACHINE LEARNING MODEL INTEGRATING CLINICAL AND MOLECULAR DATA TO PREDICT RESPONSE TO SECOND LINE TREATMENT IN RECURRENT IDHWT-GLIOBLASTOMA

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Background: Nitrosoureas (lomustine/fotemustine) and antiangiogenic drugs (bevacizumab or regorafenib) are second-line treatment options for patients with recurrent IDHwt-glioblastoma (rGBM). We aim to develop a multi-classification machine learning (ML) algorithm to predict the response to different second line therapies.

Material and Methods: We conducted a retrospective study to assess the combined predictive value of molecular profiles (tested by FoundationOne®CDx on tissue) and clinical data (clinical-pathological and treatment characteristics) in a cohort of patients with first rGBM treated with Regorafenib, Lomustine/Fotemustine or Bevacizumab from Oct 2019 to Jan 2023. WHO2021 classification was used for pathological diagnosis, and RANO criteria for neuroradiologic response evaluation. ML was applied to identify the best responders, using a gradient boosting framework based on tree-based algorithms LightGBM to integrate clinical and genomic data. Matthews correlation coefficients (MCC) were used as a metric. Best responders were labeled for having a median progression free survival (mPFS) above the third quartile for each treatment.

Results: 153 patients treated with Regorafenib (n=95), Bevacizumab (n=19), Nitrosoureas (n=39) were enrolled. The mPFS in each treatment cohort was 2.1 ms (95%CI 1.9-3.3), 3.6 ms (95%CI 2.1-4.8) and 3.0 ms (95%CI 2.4-5.7), respectively. The mOS from the start of treatment was 12 ms (95%CI 9.1-14), 7.0 ms (95%CI 6.0-11), and 8.0 ms (95%CI 5.0-13). By performing the multi-classification model we obtained a MCC of 0.32. Of note both clinical and molecular variables were utilized by the model to classify responsive patients in each of the second line treatment groups. The SHAP analysis showed the following variables as the most important predictors: age at diagnosis, gender, methylation status and CDKN2B, CDKN2A, PTEN, EGFR, TP53, MTAP mutational status. These variables were ranked in a different order for each second-line treatment, thus demonstrating that the multi-classification ML approach could discriminate responsive patients for each second-line treatment in recurrent glioblastoma.

Conclusions: The multi-classification ML model developed in this study was able to identify clinical and molecular signatures of recurrent glioblastoma patients responding to specific second-line treatment with bevacizumab or regorafenib or nitrosoureas.

I02

PTEN ALTERATION AS A PREDICTOR OF SECOND-LINE EFFICACY IN PATIENTS WITH RECURRENT IDHWT-GLIOBLASTOMA (RGBM)

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Background: Patients with rGBM have a dismal prognosis. Nitrosoureas (NS) such as lomustine and fotemustine and antiangiogenic drugs such as regorafenib(Reg) and bevacizumab (Bev) are all treatment options for rGBM. No clinical or molecular factors have been validated as predictors of efficacy to second-line therapy. PTEN mutations are common in GBM, but their potential role has been understudied. We aim to investigate the impact of pathogenic PTEN alterations on the efficacy of different second-line therapies in rGBM patients.

Material and Methods: We conducted a retrospective single-institution study to assess the combination of pathogenic PTEN alterations (FoundationOne®CDx on tissue), and clinical data (molecular and histological characteristics, treatment details and outcomes) in a cohort of consecutive patients with first rGBM treated with Reg, NS or Bev alone at Veneto Institute of Oncology (Padua, Italy) from Oct 2019 to Jan 2023. WHO2021 classification was used for pathological diagnosis, and RANO criteria for neuroradiological evaluation.

Results: 153 patients were enrolled, treated with Reg (n=95), Bev (n=19), NS (n=39). The mOS from the date of treatment was respectively: 12 ms (95%CI 9.1-14), 7.0 ms (95%CI 6.0-11) and 8.0 ms (95%CI 5.0-13). PTEN was altered in 58 pts (61%) treated with Reg, 8 pts (57%) with Bev, in 23 pts (58%) treated with NS. In univariate analysis PTEN alteration was associated with short survival in Reg treated cohort (mOS of 10.4ms VS 16.8ms alterated versus wt PTEN, respectively; HR 1.68, p=0.043) and Lomustine treated cohort (mOS 6.0ms vs 16ms in alterated vs wt PTEN, respectively; HR 1.27, p=0.01). In contrast, in Bev cohort PTEN alteration did not reach a statistical significance in univariate analysis. Of note, in multivariate analysis adjusted for categorical age (threshold,65 yrs), second surgery, ECOG score (0-1 vs. 2) and steroid use. PTEN alteration maintained a significant impact as predictor of short survival after treatment for both regorafenib and lomustine cohort (HR 1.67, p=0.043 and HR=3.17, p=0.003, respectively) together with MGMT methylation status (HR 0.44, p=0.002 and HR=0.33, p=0.006, respectively).

Conclusions: We concluded that pathogenic PTEN alteration may be a predictor of poor efficacy of regorafenib and lomustine in rGBM patients. However, a prospective study with a larger population is needed to better define the role of pTEN in these patient populations.

I03

MOLECULAR CHARACTERIZATION OF ADULT NON-GLIOBLASTOMA CENTRAL NERVOUS SYSTEM (CNS) TUMORS TO IDENTIFY POTENTIAL TARGETTABLE ALTERATIONS

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Background: NGS panels in oncology offer personalized therapies based on genomic alterations, but data on their clinical use and efficacy for non-glioblastoma CNS tumors is limited.

Material (patients) and Methods: This study aimed to explore the molecular landscape of non-glioblastoma CNS tumors in patients (pts) who underwent FoundationOne®CDx testing between November 2019 and April 2023 at Veneto Institute of Oncology, Padua (Italy), while also assessing access to TT. Analysis was conducted on formalin-fixed paraffin-embedded tumor samples, comprising a cohort of 176 adult CNS tumor pts. Brain tumors were classified per WHO 2021.

Results: Our cohort was constituted by: 19 Grade 2 IDH mut astrocytomas (A); 35 G3 IDH mut A; 34 G4 A; 29 oligodendrogliomas; 4 diffuse midline gliomas; 3 gangliogliomas; 3 pleomorphic xanthoA; 30 meningiomas; 4 medulloblastomas; 5 ependymomas; 2 neuroblastomas; 3 schwannomas; 4 pituitary adenomas; 1 hemangiopericytoma. The most frequent targettable molecular alterations (ESCAT ESMO Scale for Clinical Actionability of molecular Targets IIB-IIIB) were: PIK3CA/B mutations (14.2%), NF1 and NF2 mutations (10.2 and 13%, respectively), BRCA 1-2 mutations (8%), POLE mutation (7.4%), high tumor mutational burden (TMB) (>10 mut/megabase) (6.8%), PDGFRA alterations (6.2%), BRAF non-V600E alterations (5.1%), RET and ROS1 mutations (3.4% and 2.8% respectively), MDM2 amplification (2.3%), FGFR1-2-3 alterations and H3K28M (1.7%), MET amplification (1.7%), ALK rearrangements (1%). NTRK fusions and BRAF V600E mutations have not been detected. 3 of 4 medulloblastomas pts exhibited a PTCH1 mutation. 4 pts received TT at recurrence, within clinical trials: one with grade 3 meningioma and ALK rearrangement treated with alectinib, one with PTCH1 mutant medulloblastoma treated with vismodegib, and two with high TMB treated with nivolumab/ipilumumab. Immune checkpoint inhibitors have shown remarkable activity in a meningioma patient, who is undergoing treatment for 12 months and has achieved a complete response according to RANO criteria, while another has had stable disease with alectinib for 7 months. In other cases TT did not demonstrate activity in controlling disease.

Conclusions: The incidence of targettable molecular alterations in adult CNS tumor patients was lower than in GBM. Nevertheless, in a few selected cases TT have the potential to increase treatment options at recurrence and improve outcomes.

I04

EFFECTIVENESS OF DABRAFENIB-TRAMETINIB AND LAROTRECTINIB IN ADULT RECURRENT GLIOBLASTOMA PATIENTS: A REAL-LIFE COHORT ANALYSIS FROM 3 ITALIAN CENTERS

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Background: Although less than 5% and 1.5% of glioblastomas (GBM) exhibit the BRAFV600E mutation and NRTK fusion, respectively, these cases are significant because some of these patients (pts) may respond well to BRAF/MEK and NTRK inhibitors. Given limited literature, this study aims to evaluate the efficacy of dabrafenib-trametinib and larotrectinib in treating adults with recurrent GBM.

Material (patients) and Methods: We retrospectively analyzed a cohort of adult pts with recurrent GBM (WHO 2021) treated in 3 italian centers: Veneto Institute of Oncology (Padua), Ospedale Policlinico San Martino (Genoa), Ospedale del Mare (Naples). Molecular analysis was obtained on tissue samples with next-generation sequencing, PCR or immunohistochemistry. Dabrafenib-trametinib was given as part of compassionate use program or off-label, while larotrectinib has an agnostic approval. Response assessment followed RANO criteria.

Results: Between March 2020 and November 2023, 17 GBM pts received target therapy: 13 with dabrafenib-trametinib, 4 with larotrectinib. 12 pts had ECOG PS 0-1. All had prior radiotherapy and temozolomide. Median line of therapy was 2 (range 2-4), with a median of 6 cycles (range 1-48) of treatment. As of 04-2024, median follow-up was 7.6 months. Median overall survival and progression-free survival (PFS) after starting therapy were 8.8 and 2.8 m, respectively. Dabrafenib-trametinib subgroup showcased the longest median PFS (5.09 m), a notable disease control rate (DCR) of 77% and an objective response rate of 30.7%. Among the 13 pts included, 9 had died while 3 pts are presently undergoing treatment. Pts treated with larotrectinib exhibited a shorter median PFS (2.5 m), with a DCR of 50%; no patient reported a response. 3/4 pts had passed away, one pt is currently continuing larotrectinib. No grade 3-4 adverse events were observed in either subgroup; in any case target therapy was interrupted for toxicity.

Conclusions: Our findings support dabrafenib-trametinib for BRAFV600E mutant GBM patients. Larotrectinib shows lower activity than in pediatric cases, suggesting further research is needed on larger groups to understand patient outcomes, molecular characteristics, prognostic factors, and treatment timing.

I05

EPIGENETIC REGULATION OF ANDROGEN RECEPTOR IN ADULT-TYPE DIFFUSE GLIOMAS

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Background: The androgen receptor (AR) is a ligand-dependent nuclear transcription factor and a member of a superfamily of steroid hormone nuclear receptors. The gene coding for AR is located on chromosome X, Xq12. AR is commonly expressed in solid tumors of both sexes, but few studies have explored AR as a possible treatment target in adult-type diffuse gliomas and little is known about AR epigenetic regulation. A group of genes involved in the regulation of AR function and expression, UXT gene and the MAGE family genes are located on X chromosome. The aim of this study is to analyze the AR expression and the methylation pattern of AR regulatory genes in adult-type diffuse gliomas.

Materials and Methods: We included 50 patients (M:F=26:24) diagnosed with adult-type diffuse gliomas grade 2 or 3 or 4 according to WHO 2021 classification in this retrospective analysis. Immunohistochemistry (IHC) and DNA methylation analyses were performed to evaluate AR expression and its regulatory status.

Results: We found that high AR expression is predominant in males ($p= 0.04$). In addition, AR positivity is more frequent in patients with glioblastoma IDH-wild type compared to lower grade (grade 2 and grade 3) adult-type diffuse gliomas ($p= 0.04$) and in astrocytomas IDH-mutant compared to oligodendrogliomas IDH-mutant ($p= 0.02$). Moreover, AR expression is predominant in MGMT unmethylated gliomas compared to MGMT methylated tumors ($p=0.02$). AR gene promoter is hypomethylated in AR positive gliomas (Kruskal Wallis<0.05) and DNA hypomethylation is greater in glioblastoma IDH-wild type (Kruskal Wallis<0.05). AR regulatory genes, UXT,

MAGEA1 and MAGEA11 are hypermethylated in AR positive gliomas (Kruskal Wallis<0.05).

Conclusions: AR expression seems to be predominant in male patients with high-grade MGMT unmethylated adult-type diffuse gliomas and in astrocytes histology.The AR gene promoter is hypomethylated in AR positive adult-type diffuse gliomas. DNA methylation pattern of AR regulatory genes located on X chromosome regulate AR expression. These data are suggestive for investigating androgen deprivation therapies in adult-type diffuse gliomas.

I06

THE IMPACT OF THE REGIONAL APPROVAL OF TUMOR TREATING FIELDS (TTF) FOR GLIOBLASTOMA (GBM). PRELIMINARY DATA OF A MONO-CENTRIC REAL-WORLD EXPERIENCE

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Background: The EF14 trial demonstrated the efficacy of TTF in in combination with temozolomide (TMZ) in patients (pts) with GBM. In Italy this device has been subject to on-demand reimbursement, whose procedures are unevenly regulated in different Regions.

Material and Methods: The Campania Region, upon a request of the oncology network governance (ROC), approved the reimbursement of TTF for resident patients affected by GBM, conditioned to the approval of a multidisciplinary group (GOM) of the ROC. We present the preliminary data of the first patients treated with TTF in a real world mono-centric experience.

Results: From June 2023 to May 2024**,** 20 pts with GBM were evaluated by our GOM and 15 received approval for TTF. Five patients were excluded because of progressive disease (PD) in two, Karnofsky < 70%, lack of compliance and long time relapsed after radiotherapy (RT) in one each. Five out of the 15 approved pts are waiting to start. After GOM approval, all patients received also the regional reimbursement according to a predefined procedure. Of the 10 pts who started TTF, one stopped TTF early due to lack of compliance. Five pts (50%) have received TTF + TMZ for at least 6 months. Responses were evaluated according to RANO criteria with 2 PR (40%), 2 SD (40%) and 1 PD (20%). Two patients had metabolic CR at the brain 18F-DOPA PET scan. The patient who showed PD had not used the device appropriately. TTF produced a neurological benefit in 45% of patients and a grade 1 skin toxicity in 22% of patients. In all patients methylome and NGS tests were performed. Patients with a metabolic CR had a similar molecular characteristics, with a methylated MGMT, partial loss of chromosome 10 and a TP53 mutation. The TP53 alteration has been associated to a loss of function with a worse prognosis. After 10 months from the start of this project, a regional commission of experts verified the appropriateness of use. All patients who received the reimbursement approval met the inclusion criteria. No serious TTF-related adverse event was observed.

Conclusions: These preliminary data confirmed the effectiveness of a central management model for the treatment of a rare cancer, allowing for monitoring efficacy and safety of newly introduced devices.

I07

REGORAFENIB FOR RECURRENT GLIOBLASTOMA: A MONOCENTRIC, RETROSPECTIVE AND REAL-WORLD ANALYSIS

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Background: Glioblastoma has a high rate of recurrence after standard first-line treatment. Following the phase II REGOMA trial, establishing Regorafenib as a valuable option for the second-line treatment, the Italian Medicines Agency has provided reimbursement for the use of Regorafenib in this setting. Notably, the REGOMA-OSS,

a multicenter, prospective, observational trial, has recently confirmed the REGOMA efficacy and safety data. We conducted a monocentric, retrospective analysis to compare the REGOMA-OSS data in our real-world setting.

Methods: We retrospectively analyzed the clinical data of relapsed glioblastoma patients treated with Regorafenib as second-line treatment or, following individual local authorization, as subsequent line of therapy at Modena Cancer Center. Patients had a histologically confirmed diagnosis of glioblastoma according to WHO 2016 or WHO 2021. We specifically analyzed survival endpoints of OS and PFS and we assessed safety according to CTCAE v. 5.

Results: 36 patients were treated with Regorafenib from January 2020 to April 2024 in our cancer center: median age was 57 years (95% CI 51-63.7), males were 52.8%, ECOG PS was 0 in 5 (13.9%), 1 in 19 (52.8%), 2 in 11 patients (33.3%). 29 (80.5%) patients were undertaking steroids at baseline. MGMT was methylated in 30.5% of cases, IDH was wt in 88.9%. Regarding radiological response, both PR and SD were observed in 5.5% of patients. Median OS was 3.6 months (95% CI 2.4-4.5), median PFS was 2 months (95% CI 1.7-2.7). The median number of Regorafenib cycles per patient was 3.8. Mean daily dose of REG was 160 mg/die in 55.6% and <160 mg/die in 44.4% of patients, respectively. Eight (22.2%) patients experienced at least one G3 adverse event (AE), no G4 AE were observed. Dose reduction/delay and permanent discontinuation due to AE were observed in 10 (27.8%) and 4 (11.1%) patients, respectively. No treatment-related deaths were detected.

Conclusions: Compared to the large, prospective, observational REGOMA-OSS trial, our monocentric, retrospective, real-world analysis showed a similar result in terms of PFS and a shorter OS, likely because of the inclusion of patients with a poorer PS or treated at subsequent lines of therapy. Moreover, it confirmed a favorable safety profile.

L - Melanoma and Skin Cancers

L01*

BASELINE METABOLIC SIGNATURES PREDICT CLINICAL OUTCOMES IN IMMUNOTHERAPY-TREATED MELANOMA PATIENTS

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Background: Immune checkpoint inhibitors (ICIs) have improved the treatment of metastatic melanoma (MM). However, a significant proportion of patients show primary or acquired resistance to immunotherapy, and predictive biomarkers for non-responders or high-risk recurring patients are currently lacking. Tumor-induced metabolic rewiring fosters cancer cell growth and immune escape. Recent studies have shown that tumor-related metabolic fingerprints can be useful in predicting prognosis and response to therapy in various cancer types. Our study aimed to leverage these insights by identifying serum-derived metabolomic signatures that could predict clinical responses in MM patients treated with ICIs.

Patients and Methods: 1H-NMR (Proton nuclear magnetic resonance) was used to analyze the serum metabolomic profiles from 71 MM patients undergoing anti-PD-1 therapy (43 patients as first-line, 27 as second-line, 1 as third-line). Feature selection was applied to identify key metabolites within these profiles, to develop risk score models predicting overall survival (OS) and progression-free survival (PFS).

Results: Our multivariable model identified distinct prognostic factors for OS. Negative factors included glucose, high-density lipoprotein (HDL) cholesterol, and apolipoprotein B-very low-density lipoprotein (ApoB-VLDL), while glutamine and free HDL cholesterol emerged as positive factors. These metabolites were then used to construct a risk score model that effectively stratified patients into high- and low-risk groups for OS. Similarly, a separate predictive risk score model for PFS was developed, focusing solely on glucose and apolipoprotein A1 (ApoA1) HDL. Importantly, this analysis was replicated in patients who received first-line ICIs. Interestingly, the prognostic score for OS included glutamine, glucose, and LDL (low-density lipoprotein) triglycerides, whereas only glucose negatively influenced PFS.

Conclusions: Our data identified glyco-lipid signatures as robust predictors of distinct therapeutic outcomes in MM patients treated with ICIs. This revelation could pave the way for novel therapeutic approaches that harness metabolic modulation to synergize with immunotherapy.

L02

RECURRENCE RISK PREDICTION IN NEGATIVE SENTINEL LYMPH-NODE MELANOMA PATIENTS EXPLOITING ARTIFICIAL INTELLIGENCE AND DIGITAL PATHOLOGY

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Background: Risk stratification and treatment benefit prediction models are urgent to improve negative sentinel lymph node (SLN-) melanoma patient selection, thus avoiding costly and toxic treatments in patients at low risk of recurrence. To this end, the combined application of artificial intelligence (AI) and digital pathology could help clinicians to better calculate the recurrence risk and choose whether to perform adjuvant therapy.

Methods: In our research, we developed an AI-based model exploiting digital pathology images to predict recurrence-free status (RFS) within 2-years from diagnosis in 94 SLN- melanoma patients. Basically, we detected quantitative imaging information from H&E slides of a cohort of 71 SLN- melanoma patients, who registered at Istituto Tumori "Giovanni Paolo II" in Bari, Italy (investigational cohort, IC). For each slide, two expert pathologists firstly annotated two Regions of Interest (ROIs) containing tumor cells alone (TUMOR ROI) or with infiltrating cells (TUMOR+INF ROI). In correspondence of the two kinds of ROIs, two AI-based models were developed to extract information directly from the tiles in which each ROI was automatically divided. This information was then used to predict RFS. Performances of the models were computed according to a 5-fold cross validation scheme. We further validated the prediction power of the two models on an independent external validation cohort of 23 SLN- melanoma patients (validation cohort, VC).

Results: As a result, the TUMOR ROIs have revealed more informative than the TUMOR + INF ROIs. An Area Under the Curve (AUC) value of 79.1% and 62.3%, a sensitivity value of 81.2% and 76.9%, a specificity value of 70.0% and 43.3%, an accuracy value of 73.2% and 53.4%, were achieved on the TUMOR and TUMOR + INF ROIs extracted for the IC cohort, respectively. An AUC value of 76.5% and 65.2%, a sensitivity value of 66.7% and 41.6%, a specificity value of 70.0% and 55.9%, an accuracy value of 70.0% and 56.5%, were achieved on the TUMOR and TUMOR + INF ROIs extracted for the VC cohort, respectively.

Conclusions: Finally, the added value of this work is represented by the automatic identification of fine cell characteristics from the H&E slides directly as prognostic factors in SLN- melanoma patients.

L03

FASTING MIMICKING DIET REDUCES ANTI-OX40/ANTI PD-L1 AND ANTI-PD-1/ANTI-CTLA-4 CARDIOVASCULAR SIDE EFFECTS IN PRECLINICAL MELANOMA MODELS

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Background: Immune checkpoint inhibitors cause side effects ranging from autoimmune endocrine disorders to severe cardiotoxicity. Periodic Fasting mimicking diet (FMD) cycles are emerging as promising enhancers of a wide range of cancer therapies including immunotherapy.

Materials and Methods:In the vivo experiments, tumors were implanted in C57BL/6J mice by injecting subcutaneously (s.c.) 2×105 B16-F10 or 5×105 LLC1 cells per mouse into the right flank at day 0. Three days after tumor injection, mice from the appropriate groups (at least 5 mice per group) were treated intraperitoneally (i.p.) with anti-PD-L1 (at the dose of 100μg per mouse), anti-OX40 (at dose of 100 μg per mouse), anti-PD1 (at the dose of 100μg per mouse), anti-CTLA4 (at dose of 100 μg per mouse). The ICB therapy was administered every other day for three treatments. The combined anti-OX40/anti-PD-L1 treatment was administered sequentially. The mice were treated with anti-OX40 the first week, while the second week with anti-PD-L1. Anti-PD-1/anti-CTLA4 were administered concurrently on 4, 6 and 8 post-injection day. The mice underwent one or two cycles of FMD (4 days each week) starting the third day after tumor implantation and sacrificed on 21 post-injection day.

Results: Here, either FMD cycles alone or in combination with anti-OX40/anti-PD-L1 are much more effective than immune checkpoint inhibitors alone in delaying melanoma growth in mice. FMD cycles in combination with anti-OX40/anti-PD-L1 also show a trend for increased effects against a lung cancer model. As importantly, the cardiac fibrosis, necrosis and hypertrophy caused by immune checkpoint inhibitors are prevented/reversed by FMD treatment in both cancer models whereas immune infiltration of CD3+ and CD8+ cells in myocardial tissues and systemic and myocardial markers of oxidative stress and inflammation are reduced.

Conclusions: This study sets the stage for clinical trials aimed at assessing the ability of FMD to increase the efficacy of immunotherapy while reducing its side effects. These results also indicate that the anti-inflammatory and protective effects of FMD cycles in combination with ICI could affect other organs and systems.

L04

THE EFFECT OF ENDOCRINOLOGICAL IMMUNE-RELATED ADVERSE EVENTS ON SURVIVAL OUTCOMES IN SKIN CANCER PATIENTS: A 24-MONTH TOXICITY FOLLOW-UP STUDY

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Background: Immunotherapy (IT) can cause endocrinological immune-related adverse events (endo-irAEs); however, the link between IT efficacy and endo-irAEs remains uncertain, due to conflicting literature findings and prompting active research.

Materials and Methods: We conducted a retrospective analysis of 214 skin cancer patients (pts) treated from Janary 2018 to March 2023 at our Institution. Outcomes in pts with and without endo-irAEs were compared, assessing progression-free survival (PFS), disease-free survival (DFS), and overall survival (OS) using the Kaplan-Meier method and hazard ratios (HR) with univariate Cox models; significance was set at $p<0.05$. Toxicity was monitored for 24 months or until death. Data cut-off was Dec 31, 2023.

Results: The cohort consisted of 85% of melanoma pts, 10% of squamous cell carcinoma pts, and 5% of Merkel carcinoma pts. Anti-PD1 therapy was used in 89% of cases, while anti-PDL1 and anti-PD1/anti-CTLA4 were used in 5% and 6% of cases respectively. The median(m) age was 71 years (20-100), with 58% of males and 75% of pts with ECOG PS 0. Within 148 metastatic and 66 adjuvant pts, 21% (31) and 20% (13) developed endo-irAEs, respectively. The m-onset of irAEs was 8 weeks. Thyrotoxicosis was the most prevalent toxicity, occurring in 16 metastatic and 10 adjuvant pts, presenting as G1-2, never exceeding G2.

In the adjuvant cohort, older pts (>70 years) had reduced toxicity risk (HR 0.09, p=0.02), while metastatic pts with PSECOG 1-2 vs 0 had higher mortality risk (HR 1.58, p=0.05). Pts with a history of endocrine disorders (15%) had a higher risk of developing endo-irAEs (HR 1.38, p=0.40). At a median follow-up of 35.5 months (mos), mOS in metastatic patients with endo-irAEs was 32.1 vs 8.34 mos in pts without toxicities (HR 0.57, p=0.08), and mPFS was 9.66 vs 6.31 mos (HR 0.79, p=0.57), respectively. In the adjuvant cohort, mOS and mDFS were not reached. In the subgroup of pts with brain metastases at diagnosis (25), those with endo-irAEs had a mOS of 5.85 vs 3.02 mos in pts without endo-irAEs (HR 0.76, p=0.61).

Conclusions: our findings suggest that endo-irAEs in skin cancer pts treated with IT may improve outcomes in the metastatic cohort, including those with brain metastases. Pts with a history of endocrine disorders are more likely to develop these toxicities. Extended follow-up is needed for the adjuvant group, and further data from prospective trials are required.

L05

FIRST-LINE (1L) THERAPY FOR ADVANCED MELANOMA: A REAL WORLD SINGLE-CENTER EXPERIENCE

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Background: Choosing the optimal 1L therapy for advanced melanoma is still a challenge. Recent data

suggest that immunotherapy (IO), especially combo-IO, is the best treatment option even for BRAF mutated (mt) patients (pts). However, immune-related adverse events (irAEs) could be difficult to manage.

Material and Methods: We retrospectively collected data from pts who started a 1L therapy for unresectable melanoma from 2014 to 2023 at our hospital. We aimed to compare outcomes of pts treated with IO and targeted therapy (TT), both in the overall population and in BRAF mt pts.

Results: Overall population included 177 pts. 108 were BRAF mt, 66 BRAF wild type (wt), for 3 pts BRAF status was unknown. 91 (51%) received IO (74 anti-PD1, 13 anti-CTLA4, 4 combo-IO) and 86 (49%) TT (81 anti-BRAF + anti-MEK, 5 anti-BRAF). At a median (m) follow-up (FU) of 50.5 months (mos), in the overall population there was no significant difference in progression-free survival (PFS) and overall survival (OS) between IO and TT. Overall response rate (ORR) was 44.5% with IO and 66% with TT. Among BRAF mt pts, 22% received IO and 78% TT, showing no significant differences in PFS, OS and ORR. 24% of IO-treated pts and 22% of TT-treated pts developed grade (G)3/4 toxicity. They had a significant advantage in PFS and OS compared to pts who did not have severe toxicity, both in the IO ($p<0.05$ for PFS and OS) and in the TT group ($p<0.05$ for PFS and OS). In the IO group 5 pts discontinued treatment due to CR (mOS not reached [NR]), 23 because of irAEs (mOS NR), 11 due to completion of the programmed cycles (mOS 66 mos). Anti-PD1 was stopped after a mean time of 7.2 mos in pts not having disease progression (22 mos in those not suffering G3/4 irAEs).

	mPFS (mos)	mOS (mos)	ORR (%)
IO overall population (n=91)	8(p=0.3)*	37(p=0.7)*	44.5(<0.05)*
IO BRAF mt (n=24)	19(p=0.2)*	21(p=0.6)*	58(p=0.5)*
TT BRAF mt (n=86)	8	16	66

*Compares IO and TT.

Conclusions: IO was associated with a not statistically significant longer OS compared to TT, probably due to the short FU and the still limited use of combo-IO. However, this data suggest that TT remains a valid 1L option. G3/4 toxicity was related to better outcomes, not only in IO- but also in TT-treated pts. Moreover, IO can be safely discontinued without losing the clinical benefit.

L06

A RETROSPECTIVE STUDY OF CEMIPLIMAB IN ELDERLY AND YOUNG PATIENTS WITH ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA (ACSCC): A SINGLE-CENTER REAL-LIFE EXPERIENCE

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Background: Cemiplimab (cemi) is an anti-PD1 agent approved for acSCC patients (pts). acSCC usually occurs in elderly pts, so data on the use of cemi in younger pts are limited. This retrospective study investigated the activity and safety of cemi in pts aged < 65 years.

Methods: Data of consecutive cSCC pts treated with cemi between 2019 and 2023 were collected: ECOG performance status (PS), Adult Comorbidity Evaluation-27 (ACE-27), objective response rate (ORR), adverse events (AEs graded according to CTCAE v5.0), and survival. Data of pts aged < 65 years (young, Y) were compared to pts aged≥65 years (elderly, E). Contingency tables were analyzed using Fisher's exact or chi-squared test, as appropriate. Median follow-up (FUP) was estimated with the reverse Kaplan-Meier (KM) method, progression-free (PFS), and overall survival (OS) with KM, and were compared with the log-rank test.

Results: We analyzed 63 acSCC patients. Median FUP was 27.8 months (95% CI 21.3-38.4). The following table reports patient characteristics, cemi-related grade≥3 (G3+) AEs, and oncologic outcomes.

N (%)	Y [5]	E [58]	p value
Sex			
M	2 (40)	42 (72)	0.156
F	3 (60)	16 (28)	
Age (range) [yrs]			
PS ECOG	53 (36-63)	81 (65-101)	-
0-1	4 (80)	33 (57)	0.394
≥2	1 (20)	25 (43)	
ACE-27	3 (60)	13 (22)	0.098
0-1	2 (40)	45 (78)	
≥2			
ORR	5 (100)	38 (65)	0.309
Evaluable	-	8 (21)	(CR/PR vs. SD/PD)
CR	2 (40)	19 (50)	
PR	1 (20)	4 (11)	
SD	2 (40)	7 (18)	
PD			
G3+ AEs	1 (20)	5 (8)	0.404
G3	1 (lung)	4	
G4	0	1 (liver)	
G5	0	1 (renal)	
mPFS (95% CI)	5.52 (0.46-15.06)	6.48 (3.98-13.12)	0.975
mOS (95% CI)	22.03 (1.18-22.03)	15.85 (8.28-26.8)	0.953

Five E pts had G3+ cemi-related AEs: G3 pancreatic enzyme increase (3), G4 liver toxicity (1), and one fatal renal toxicity. The only Y with a G3 AE had a drug-related pneumonitis, which resolved after cemi interruption and steroid administration.

Conclusions: Despite the low pts number, no statistically significant differences were observed in terms of ORR, or survival between Y and E acSCC pts treated with cemi. Safety and activity profiles were in line with the literature. Y pts had a significantly lower number of comorbidities than E. This difference may have impacted the slightly different safety profile observed between Y and E.

L07

HIGH PERCENTAGE OF CO-MUTATIONS IS FOUND IN MELANOMA USING NEXT GENERATION SEQUENCING (NGS). SHOULD WE TAKE IT INTO ACCOUNT?

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Background: Routine use of NGS technology enables the detection of other mutations in melanoma apart from BRAF,RAS and NF1.The role of co-mutations in BRAF mutant or BRAF WT melanoma is not completely understood.

Methods: NGS had predictive and prognostic roles.The panel(NGS Gx)analyses 46 genes and evaluates deletion(del), amplification and fusion(f).

Results: In 2023 the anatomy pathology lab of Como performed NGS in 33 patients (pts)(21 male) affected by melanoma(stages III-IV).The test was used as a method to evaluate BRAF status. Median age was 63(32-96).27 pts presented with initial disease (IA-IIID); 6 pts with stage IV (1 stage IV NED); 12 patients received adjuvant therapy with immune checkpoint inhibitors (ICIs) or targeted therapy (TT). Out of the 16 pts who did not undergo oncological treatment, 10 relapsed and 7 of them received first-line therapy. Currently, none of the patients who underwent adjuvant therapy has relapsed.12pts of 33 (36,3%) underwent oncological treatment for metastatic disease: 5 were metastatic at the diagnosis and were treated 1 with TT and

4 with ICIs. Considering the 7 pts who relapsed, 4 received TT and 3 received ICIs. Two pts (16,7%) received another line of therapy. 17 pts(48%)presented a BRAF mutation(13 BRAF V600E, 3rare mutations);7 pts (21%)presented NRAS mutation.In 6 BRAF mutant melanomas(37,5%) a co-mutation of another gene(MAPK1, PTEN, ALK, IDH and AKT3) was found.In 3 NRAS mutant melanomas (42,8%)other comutations were found (CTNNB1, TP53, ALK).Triple wild type (WT) melanomas(66.7%) presented one or more mutations(MAP2K1,ALKf,RETf,ARAF, HRAS,TP53).cKIT was evaluated in mucosal melanoma and resulted negative. We observed secondary melanomas in 3 out of 33 pts (9.1%) and secondary non-cutaneous neoplasms in 9 (27.3%) pts. 28 pts are alive. The causes of death of the deceased patients (15.2%) were: neoplastic progression (2 pts,40%), sepsis during TT (1 pts, 20%) and non-melanoma specific cause (2pts, 40%).

Conclusions: Using NGS a significant percentage of co-mutation of BRAF and NRAS and other mutations in triple WT melanomas were found. The role of co-mutations or other mutations is not completely understood and no data are available regarding the effectiveness of oncological treatment. With the lmitations of reduced follow-up, this preliminary analysis in our small cohort confirms the benefit of adjuvant therapy. Secondary melanomas and secondary neoplasms were found in this population in a high percentage.

L08

THE IMPLICATIONS OF CLINICO-PATHOLOGICAL VARIABLES ON SURVIVAL OUTCOMES IN STAGE III CUTANEOUS MELANOMA: A RETROSPECTIVE ANALYSIS

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Background: At the present time, there are no defined prognostic factors to guide therapeutic decisions for patients with stage III melanoma besides the substages defined by the AJCC staging system. Molecular and pathologic aspects can suggest the kinetic of disease but without established evidence. We analyzed the impact of clinical, pathological and molecular characteristics on survival outcomes in this patient population.

Material and Methods: Retrospective clinical, pathological and molecular data of patients with stage III cutaneous melanoma referring to our Institution were collected between January 2018 and December 2021. Univariate Cox regression models were used for statistical analysis.

Results: With a median follow-up of 36 months, 351 patients were included. The median age was 59 years, 223 males and 128 females. 312 had melanoma of the trunk/extremities, 39 of head/neck. in details 48 pts were stage III A (14%), 85 III B (24%), 188 III C (53%) and 29 III D (8.2%). BRAF-mutated pts were 172 (51%), of which 84 received adjuvant BRAF/MEK inhibitors and 88 adjuvant anti-PD1 therapy. Median adjuvant treatment duration for all patients was 11.7 months. Patients' sex and primary site of the tumor didn't influence RFS and OS, while age was associated with a statistical trend with a decreased OS (HR 1.03, p=0.05). High Breslow thickness (HR 5.72, p<0.001), high number of metastatic lymph nodes involved (HR 4.86, p=0.001) and > 3 intra-lymphnode deposits (HR 1.94, p=0.04) were associated with reduced RFS. Similarly, these aspects correlate with a reduced OS (HRBreslow 14.2, p=0.004; HRNodes 0.11, p=0.002; HRdeposits 3.1, p=0.07). BRAF-mutated pts treated with adjuvant targeted therapy seem to have higher RFS than those receiving anti-PD1 with a statistical trend (HR 0.55, p=0.065), while no difference in terms of OS were observed (HR 0.52, p=0.2).

Conclusions: Among patients with stage III cutaneous melanoma, Breslow thickness, number of metastatic lymph nodes and intra-lymph-node deposits could provide information about the risk of disease relapse. According to our data, in BRAF-mutated melanoma there isn't evidence of a superiority of adjuvant treatment between anti-PD1 or targeted therapy in terms of survival benefit and risk of relapse.

L09

MOLECULAR INSIGHTS ON CUTANEOUS MELANOMA HYPERPIGMENTATION AND IMMUNOTHERAPY RESISTANCE

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Background: Immune checkpoint(s) inhibitors (ICI) have significantly increased the survival of cutaneous melanoma (CM) patients, but a proportion of them develops resistance to IC. Identifying new mechanisms underlying treatment failure are mandatory to improve the efficacy of ICI. Melanin involvement in CM progression is significant, as hyperpigmentation correlates with therapy resistance,

including resistance to ICI. Melanin serves a dual role, acting as a protective agent against light-induced damage by scavenging reactive oxygen species (ROS) but also as a photosensitizer/pro-oxidative agent depending on its type and intracellular redox state. The melanin ROS-scavenging activity is primarily attributed to its ability to chelate metal ions such as iron, which can induce melanogenesis itself due to its high ROS-generating activity. Experimental evidence suggests that miR-214 is involved in melanoma hyperpigmentation and therapy resistance. We conducted a retrospective study to elucidate the interplay among miR-214, ROS, and iron in hyperpigmented/resistant CM.

Methods: The pigmentation level of control and stably transfected miR-214 cells (miR-214+) was assessed in vitro via melanosomes and intracellular melanin quantification, and correlated with ROS and iron content. CM cell therapy response in vitro was evaluated by 2D/3D assays. Both conventional and innovative nanoparticle-based approaches were used to modulate melanogenesis and assess therapy response. miR-214 plasmatic levels of ICI-treated CM patients at Careggi University Hospital Oncology Unit were quantified using droplet digital PCR. Responders were patients achieving partial/complete response or stable disease, and non-responders those achieving progressive disease as best overall response.

Results: miR-214+ melanoma cells showed hyperpigmentation related to a pro-oxidative state and a reduced Glutathione S-transferase Zeta 1 (GSTZ1) expression, an anti-oxidant protein also involved in the catabolism of the melanin precursors phenylalanine and tyrosine. miR-214+ hyperpigmented cells showed less responsiveness to ICI in vitro than control, restored when miR-214 signalling and melanogenesis were inhibited. Higher levels of miR-214 were found in plasma samples of ICI-treated non- responders compared to responders.

Conclusions: miR-214 triggers hyperpigmented, resistant melanoma phenotypes. Understanding its molecular network will be crucial to find new therapeutic targets for non-responder patients.

L10

UVEAL MELANOMA AND TEBENTAFUSP IN THE CLINICAL PRACTICE OF A RESEARCH ONCOLOGY INSTITUTE

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Background: Despite its rare incidence, uveal melanoma represents 3-5% of all melanomas and it is the most frequent primary intraocular neoplasia of the eye in adults (85%). On 1 April 2022, tebentafusp was authorized for marketing in the EU as an orphan medicinal product, available on the Italian market starting from 28/11/2022. Initially, tebentafusp was authorized but not reimbursed, then it was reimbursed from 08.03.2023. The following work has analyzed PFS (Progression free survival) by comparing it to registration studies, consumption and costs relating to its use in an oncology research institute as a reference center for southern Italy.

Material and Methods: Tebentafusp was administered intravenously at a dose of 20 mcg on day 1, 30 mcg on day 8, 68 mcg on day 15, then 68 mcg once a week. The number of treated patients, consumption and cost, from 01/01/2023 to 30/04/2024, were extracted from the hospital computerized prescribing system. Subsequently, a database was developed with the following data: patient characteristics, treatment duration, number of cycles and mcg received. In addition, were compared treatments reimbursed from those not reimbursed and supplied at low cost by the company. Furthermore, the incurred costs were calculated.

Results: In the observed period, 8 patients were treated, four men and four women (aged 50 to 77 years, with median age 57,6) in the first line for ocular melanoma. The cycle range was between 3 and a maximum of 47, the median PFS in months was 7.5 compared to 3.5 months of the registration studies (IMCgp100-202 study) as reported in summary of product characteristics. In total the prescriptions were 219, 14.426 mcg were prepared and 323.695,51 € were spent. In particular 6.184 mcg were supplied by the company at a cost of 61,84 € (0,01 € per mcg), while 8.242 mcg were bought by the hospital and reimbursed for a total cost of 323.633,67 € (39,27 € per mcg).

Conclusions: Tebentafusp appears to be the only specific therapeutic approach for patients with unresectable or metastatic uveal melanoma. Early access to the drug, before reimbursement, was important for patients suffering from this rare disease and allowed a reduction in costs incurred by the hospital. Finally, the analysis also highlighted an increase of 4 months in PFS as compared to registration studies.

L11

MELANOMA DATA: IRCCS CROB, RIONERO IN VULTURE, FOUR YEARS ACTIVITY AND SURVIVORSHIP PROJECT

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Background: New therapies and prevention improved melanoma life expectancy. In Italy, the 5 years standardized survival 2022 is 88% for males and 91% for females. Increased population of melanoma survivors present the need to improve the experience of care and outcomes. Our goal is to help patient's adaptation from the treatment pathway to the resumption of daily life.

Material and Methods: We analyzed data of 220 patients who underwent surgery for melanoma in our Institute from 2020 to 2023. Of those, 50 were pTis, 64 pT1a, 41 patients followed systemic therapy and experienced skin, intestinal and thyroid toxicity, 2 had electrochemotherapy, 8 radiotherapy. Presently we have 141 patients on follow-up which urges us to complete a survivorship program.

Results: Melanoma survivorship program needs to be tailored on pathology and type of treatment is divided in three phases: Acute, centered on cancer treatment, extended survivorship begins at the end of treatment, Permanent focuses on long term effect of cancer. For eligibility criteria and surveillance of patient's groups, the pillars are the guidelines of AIOM, ESMO and ASCO. The care plan should be stored electronically, periodically updated and shared within the reference department/ General Practitioner/territory and supportive services/ patient. Responsible for entering data are the specialist/GP. Patients are divided in different groups; those with risk of recurrence level and mortality: low risk intermediate risk and high risk. The patients divided by histological type and site: SSM, NM, LMM, ALM respective cutaneous, uveal, mucous melanoma. Other group is based on therapy followed. Patients had to be aware of late side effects and toxicity. Education on correct sun exposure, use of sunscreen, smoke cessation, reduced alcohol intake, regular screening for nevus have to be part of the program. In addition, supportive therapies such as acupuncture, massage therapy, sport, stress management techniques, use of dietary and nutrition can provide benefits to overall health and wellbeing.

Conclusions: All professionals involved in melanoma cure should encourage patients to enroll in different aspects of survivorship care that coincide with their needs, however are not routinely implemented in clinical practice. Our main goal is to lead the patient from the treatment recovery of complications to oncological oblivion.

M - Sarcomas and Rare Tumors

M01*

HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL SUPPORT IN NON-SEMINOMA MEDIASTINAL GERM CELL TUMORS: A REPORT FROM THE EBMT DATABASE

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Background: Primary mediastinal germ cell tumors (PMGCTs) account for 1% to 3% of all germ cell tumors (GCTs), 80% being non-seminoma (NS). NS PMGCTs have a poorer prognosis compared to their gonadal counterpart and, according to the International Germ Cell Cancer Collaborative Group, they are considered by definition a "poor risk" disease. Medical treatment is the same as the gonadal counterpart, with overall survival (OS) being around 40%, declining to only 10-15% at three years in case of visceral and/or lung metastases. Patients (pts) failing first-line chemotherapy (CT) have a dismal prognosis, with only approximately 5%-10% of cases being cured in the salvage setting. In recent years, high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) has been successfully used to treat pts with relapsed or refractory GCTs. This report is a retrospective analysis of the large EBMT database, aimed at defining the role of HDC in pts with PMGCTs as evidence so far in the literature is limited by small and heterogeneous patient cohorts.

Material and Methods: The purpose of this study was to investigate the efficacy of HDC with ASCT in the whole population and defined PMGCT patient subgroups, who were registered in the EBMT database from January 2000 to January 2018. Eighty pts (median age 31 years) from 19 EBMT centres were included, 75 being non-seminoma (NS), of which six were excluded from the final analysis because of missing data on survival. HDC consisted mainly of carboplatin/ etoposide doublet, most pts received HDC as a part of a multiple sequential HDC program; all patients received ASCT autologous peripheral blood stem cell transplantation.

Results: Overall survival (OS) was 43.3% at 2 years, and 34.7% at 5 and 10 years for the entire cohort. Analysis of outcomes in different subgroups showed that pts undergoing HDC as upfront therapy had a better progression-free (PFS) and OS compared to those treated in subsequent relapses (5y PFS 51.8% vs 26.8% and 5y OS 51.3% vs 25.9%). Better remission status before transplantation was predictive of the benefit of HDC. Four toxic deaths were recorded.

Conclusions: This, to our knowledge, is the most extensive retrospective study of HDC in NS PMGCTs patients and the first to thoroughly investigate potential predictors of benefit from this treatment. Our results suggest that HDC with ASCT may well represent a therapeutic option in patients with relapsed/recurrent NS PMGCTs and even as a front-line program

M02

EFFICACY, SAFETY, AND PATIENT-REPORTED OUTCOMES OF VIMSELTINIB IN PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMOR: RESULTS FROM THE MOTION PHASE 3 TRIAL

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Background: Tenosynovial giant cell tumor (TGCT) is a locally aggressive neoplasm caused by dysregulation of the colony-stimulating factor 1 (*CSF1*) gene leading to overproduction of CSF1. TGCT requires a therapy with low toxicity as patients may need long-term treatment; there is an unmet need for an effective, well-tolerated CSF1 receptor (CSF1R)-targeted therapy that improves functional health and quality of life. Vimseltinib is an investigational, oral, switch-control tyrosine kinase inhibitor specifically designed to selectively and potently inhibit CSF1R. Here we report results from the global, double-blind, MOTION phase 3 trial of vimseltinib in patients with symptomatic TGCT not amenable to surgery (NCT05059262).

Methods: Randomization was 2:1 to vimseltinib 30 mg twice weekly or matching placebo for 24 weeks. The primary endpoint was objective response rate (ORR) assessed by blinded independent radiological review (IRR) for Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) at week 25. Key secondary endpoints were ORR by IRR per tumor volume score (TVS), change from baseline in active range of motion (ROM), and patient-reported outcomes. Safety was also evaluated. Date cutoff was August 22, 2023.

Results: Overall, 123 patients were randomized (vimseltinib, n = 83; placebo, n = 40). The median age was 44 years, 59% of patients were female, and the most common primary disease location was the knee (67%). ORR for RECIST v1.1 and for TVS were significantly higher for vimseltinib versus placebo (RECIST: 40% vs 0%, P <0.0001; TVS: 67% vs 0%, P <0.0001). Statistically significant and clinically Meaningful improvements were observed for vimseltinib versus placebo in active ROM (18.4% vs 3.8%; P = 0.0077), physical function, stiffness, health status, and worst pain response. The safety profile was consistent with previous reports, and there was no evidence of cholestatic hepatotoxicity or drug-induced liver injury.

Conclusions: Patients receiving vimseltinib experienced statistically significant and clinically meaningful improvements in the primary and all key secondary endpoints. These results demonstrate vimseltinib is an effective, well-tolerated CSF1R-targeted therapy that improves functional health and quality of life in patients with TGCT. Previously presented at ASCO 2024.

M03

OVERALL SURVIVAL AND LONG-TERM SAFETY WITH RIPRETINIB VS SUNITINIB IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR PREVIOUSLY TREATED WITH IMATINIB: FINAL ANALYSES FROM INTRIGUE

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Background: Ripretinib is a switch-control tyrosine kinase inhibitor approved for patients (pts) with gastrointestinal stromal tumor (GIST) who received prior treatment with 3 or more kinase inhibitors, including imatinib. Sunitinib is approved for advanced GIST after imatinib failure. In the second interim analysis of overall survival (OS) from the phase 3 INTRIGUE study, the OS event rate was 41% in the all-patient (AP) intent-to-treat (ITT) population, and OS was similar between treatment arms in both the *KIT* exon 11 ITT and AP ITT populations. Here, we present the final OS and updated safety from INTRIGUE.

Material and Methods: INTRIGUE (NCT03673501) is an open-label, phase 3 study of adults with advanced GIST who had disease progression on or intolerance to imatinib. Randomization was 1:1 to ripretinib 150 mg once daily (QD) or sunitinib 50 mg QD (4 wks on/2 wks off) and was stratified by *KIT* mutational status and imatinib intolerance. OS was a key secondary endpoint (primary endpoint, progression-free survival, was reported previously); final OS analysis was prespecified to occur with ≥200 and ≥145 events in the AP ITT and *KIT* exon 11 ITT populations, respectively. Data cutoff: March 15, 2023.

Results: Of 453 pts, 444 received treatment; 40 remain on treatment (ripretinib, 28/223 [13%]; sunitinib, 12/221 [5%]). Treatment discontinuation was due to progressive disease (PD) by independent radiologic review (56%), PD by investigator (11%), clinical PD (6%), withdrawal of consent (6%), and adverse events (AEs; 5%). Fewer pts discontinued treatment due to AEs with ripretinib vs sunitinib (3% vs 6%). There were 211 (47%) and 151 (46%) OS events in the AP and *KIT* exon 11 ITT populations, respectively. OS was similar with ripretinib vs sunitinib in the AP ITT (median, 35.5 vs 31.5 months; HR, 0.86; 95% confidence interval [CI], 0.65 to 1.13) and *KIT* exon 11 ITT (median, 35.5 vs 32.8 months; HR, 0.98; 95% CI, 0.71 to 1.34) populations. Fewer pts had grade 3/4 treatment-emergent AEs with ripretinib vs sunitinib (43% vs 67%). Dose modifications were lower with ripretinib vs sunitinib. Median (range) treatment duration for ripretinib vs sunitinib was 7.9 (0.2–43.3) vs 6.5 (0.2–44.7) months.

Conclusions: In the final OS analysis from INTRIGUE, OS was similar between treatment arms. The safety profile remained consistent and more favorable for ripretinib vs sunitinib in pts with advanced GIST previously treated with imatinib. Previously presented at ASCO GI 2024.

M04

UPDATED OVERALL SURVIVAL AND SAFETY WITH RIPRETINIB VS SUNITINIB IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR PREVIOUSLY TREATED WITH IMATINIB AND HARBORING KIT EXON 11 + 17/18 MUTATIONS: CTDNA ANALYSIS FROM INTRIGUE

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Background: Ripretinib is a switch-control tyrosine kinase inhibitor approved for patients (pts) with gastrointestinal stromal tumor (GIST) who received prior treatment with 3 or more kinase inhibitors, including imatinib. Sunitinib is approved for advanced GIST after imatinib failure. In an exploratory analysis of baseline circulating tumor DNA (ctDNA) from the INTRIGUE trial, pts with primary mutations in *KIT* exon 11 and secondary mutations exclusively in *KIT* exons 17/18 (*KIT* exon 11 + 17/18) received clinical benefit from ripretinib but not sunitinib (Heinrich MC, et al. *Nat Med*. 2024). Here, we present final overall survival (OS) and updated safety in pts with *KIT* exon 11 + 17/18 mutations from INTRIGUE.

Material and Methods: INTRIGUE (NCT03673501) is an open-label, phase 3 study of adults with advanced GIST who had disease progression on or intolerance to imatinib. Randomization was 1:1 to ripretinib 150 mg once daily

(QD) or sunitinib 50 mg QD (4 weeks on/2 weeks off). Final OS analysis was prespecified to occur with ≥200 and ≥145 events in the all-patient intent-to-treat (ITT) and *KIT* exon 11 ITT populations, respectively. Baseline peripheral whole blood was analyzed by Guardant360®, a 74-gene ctDNA next-generation sequencing–based assay. Data cut-off was March 15, 2023.

Results: Of 453 pts, ctDNA was analyzed in an exploratory analysis for 362; 52 had mutations exclusively in *KIT* exon 11 + 17/18 (ripretinib, n = 27; sunitinib, n = 25). Pts with *KIT* exon 11 + 17/18 mutations had better OS with ripretinib vs sunitinib (median, not reached vs 17.5 months; hazard ratio, 0.37; 95% CI, 0.17 to 0.80; nominal $P = 0.0091$). Fewer of these pts had grade 3/4 drug-related treatment-emergent adverse events and serious adverse events with ripretinib vs sunitinib (33% vs 50% and 3.7% vs 13%, respectively). Median treatment duration in these pts for ripretinib vs sunitinib was 15.6 vs 3.0 months.

Conclusions: In this updated exploratory analysis from INTRIGUE, OS was longer for ripretinib vs sunitinib for pts with *KIT* exon 11 + 17/18 mutations identified by baseline ctDNA. The safety profile was consistent and more favorable for ripretinib vs sunitinib in these pts. Previously presented at the 2024 ESMO Sarcoma and Rare Cancers Congress.

M05

SAFETY, EFFICACY, AND PATIENT-REPORTED OUTCOMES WITH VIMSELTINIB IN PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMOR WHO RECEIVED NO PRIOR ANTI–COLONY-STIMULATING FACTOR 1 THERAPY: ONGOING PHASE 2 STUDY

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Background: Vimseltinib is an investigational, oral switch-control tyrosine kinase inhibitor specifically designed to selectively and potently inhibit the colony-stimulating factor 1 (CSF1) receptor (CSF1R). Here, we report updated results from cohort A of the phase 2 part (expansion) of an ongoing phase 1/2 study (NCT03069469) for patients (pts) with tenosynovial giant cell tumor (TGCT) treated with vimseltinib.

Material and Methods: Pts with TGCT not amenable to surgery and with no prior anti-CSF1/CSF1R therapy (previous treatment with imatinib or nilotinib allowed) received vimseltinib 30 mg twice weekly (recommended phase 2 dose). The primary objectives were safety, tolerability, and antitumor activity (by independent radiological review using Response Evaluation Criteria in Solid Tumors version 1.1). Pain was assessed using the brief pain inventory (BPI) worst pain item (responder: ≥30% pain improvement without ≥30% increase in narcotic analgesic use).

Results: As of June 27, 2023, 46 pts with TGCT with no prior anti-CSF1/CSF1R therapy were enrolled. Median age was 44 years, and the most common tumor location was knee (57%; 26/46). Most treatment-emergent adverse events (TEAEs) were grade 1/2; grade 3/4 TEAEs (>5% of pts) were elevated creatine phosphokinase and hypertension. There was no evidence of cholestatic hepatotoxicity. Best overall objective response rate was 64% (29/45; **Table**). At week 25, 59% of pts with objective tumor response and 55% with stable disease were BPI worst pain responders.

Conclusions: These results demonstrate that vimseltinib can provide antitumor activity and pain relief in pts with TGCT not amenable to surgery with no prior anti-CSF1/CSF1R therapy. Previously presented at CTOS 2023.

Table.

	Pts with no prior anti-CSF1/CSF1R therapy
Efficacy-evaluable population, n	45
Best overall response, n (%)[a]	
Objective response rate	29 (64%)
Complete response	1 (2%)
Partial response	28 (62%)
Stable disease	16 (36%)
Duration of response, median[b] (min, max), months	NR (0.03+, 25.4+)

+ indicates pts are ongoing on study.
[a]Best overall response by IRR using RECIST v1.1; includes all available follow-up.
[b]Based on Kaplan-Meier estimate. Duration of response is defined as time from first imaging result showing response to progressive disease.
IRR, independent radiological review; max, maximum; min, minimum; NR, not reached; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

M06

A PHASE II TRIAL AIMING TO ASSESS THE SAFETY AND ACTIVITY OF THE COMBINATION OF CABOZANTINIB PLUS LANREOTIDE IN GASTROENTEROPANCREATIC (GEP) AND THORACIC NEUROENDOCRINE TUMOR (NET): THE LOLA TRIAL – INTERIM RESULTS

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Background: Cabozantinib (CABO) is a tyrosine-kinase inhibitor (TKI), acting as both anti-angiogenic and anti-MET agent. In neuroendocrine tumors (NETs) sunitinib is the only TKI approved only in advanced pancreatic NETs. While CABO has been reported superior to sunitinib in renal cancer its role in NETs is still investigational.

Methods: The LOLA is an Italian, multicenter, open-label, double cohort, non-randomized, three-stage, phase 2 trial aiming to assess the safety and activity of the combination of CABO + lanreotide (LAN) in patients (pts) with locally-advanced or metastatic GEP and unknown primary NETs with > 10% Ki-67 or thoracic NET. Two cohorts were identified: pancreatic and other NETs.

In stage 1, safety and tolerability are the primary endpoints. If G3-G5 adverse events (AEs) or clinically manageable and reversible G3 AEs within 7 days from their onset were observed in more than 1 patient, then CABO starting dose of 60 mg was reduced to 40 mg. Trial treatment was halted if also 40 mg was too toxic.

In the stages 2 and 3, safety, tolerability and overall response rate were the primary endpoints. Secondary endpoints were PFS and overall survival (OS). For each type of NET, the optimal Simon two-stage design will be used. Ten pts were recruited in the stage 2. If no responses observed, the arm was stopped, otherwise other 19 pts were accrued in stage 3. The null hypothesis was rejected if ≥4 responses were observed in 29 pts.

Results: *Interim analysis (IA) step I*

In step I, 7 pts was enrolled. The IA notify that neither serious adverse events (SAEs) nor G4-G5 AEs were reported. The most frequent AEs were muco-cutaneous toxicity, hypertension and diarrhea. Most frequent grades of toxicities were G1 (71%).

In no pts the dose of LAN 120 mg was reduced, while in 4 pts (57%) it was necessary dose reduction of CABO to 40 mg and in 2 pts to 20 mg.

According to the protocol, given the observation of recovery time of G3AE >7 days, we defined CABO 40 mg as starting dose for next steps.

IA step II cohort 2

Ten pts were enrolled (8 thoracic and 2 intestinal NET). After 1 year of treatment, AI achieved primary endpoint. After overall centralized radiological review, we observed: 2 PR, 4 SD and 4 PD according to RECIST 1.1. So, cohort 2 re-opened the enrollment in step 3, ended in Feb 2024 (analysis still ongoing).

Conclusions: IA suggest that CABO 40mg and LAN combination are well tolerated. We attend the final analysis to confirm the trial's safety and clinical outcomes.

M07

A PHASE II STUDY OF CABOZANTINIB AND TEMOZOLOMIDE IN ADVANCED PROGRESSIVE GASTROENTEROPANCREATIC OR LUNG NEUROENDOCRINE TUMORS (NETS)

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Background: Limited therapeutic options are available for patients with advanced neuroendocrine neoplasms (NENs). Cabozantinib (CBZ), a tyrosine kinase inhibitor including c-MET pathway, and Temozolomide (TMZ), an alkylating agent enhancing the anti-angiogenic effect of CBZ, are emerging as promising treatments in NENs.

Methods: We performed an open-label, single-arm, multicenter, phase II trial of cabozantinib 40 mg daily plus temozolomide 100 mg/m^2 one week on/one week off in patients with advanced, gastroenteropancreatic or lung, well-differentiated NET with evidence for progressive disease on prior treatment. The primary endpoint was overall response rate (ORR) as assessed by RECIST 1.1 criteria. Secondary endpoints included progression-free survival (PFS), overall survival (OS) and 1-year OS.

Results: 37 patients were enrolled of whom 27 were assessable for response. Primary sites included pancreas (13 patients), small bowel (9), lung (9), colon (2), stomach (1), gallbladder (1), unknown (2). 11 patients had G1 tumors, 22 patients had G2 tumors and 4 patients had G3 tumors. Patients had received a median of 2 lines of prior treatment. Among evaluable patients, an ORR of 22% was recorded, with a clinical benefit rate CBR (CR+PR+SD) of 100%. After a median follow-up of 10 months, median PFS was 28.5 months (95% CI, 22-28.5 months). Median OS was not reached and the 1-year OS rate was 77.6% (±7%). Ten patients discontinued the treatment before the first restaging due to adverse events (n=9) or withdrawal of consent (n=1). The most common G3/G4 treatment-related adverse events included diarrhea (18%), thrombocytopenia (12%), abdominal pain (6%), oral mucositis (6%) and anemia (6%).

Conclusions: The combination of cabozantinib and temozolomide shows promising antitumor activity in patients with NETs. While tolerability appears to be an issue, the relatively high rate of toxicities leading to early treatment discontinuation observed in this study should be weighted against the characteristics of a heavily pretreated patient population. According to the outcomes in terms of PFS, ORR, CBR, is possible dose aggiustments could offer a good risk/ benefit ratio of the drug combination.

M08

CHARACTERISING THE TUMOUR MICROENVIRONMENT AND IDENTIFYING POTENTIAL PREDICTIVE MARKERS IN BREAST ANGIOSARCOMA

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Background: Angiosarcoma is a relatively rare breast neoplasm (>0.05% of breast tumours). Tumours can occur: i) de novo (pAS), ii) secondary to longstanding lymphoedema or radiotherapy (sAS). TME studies have become increasingly important to identify potential responders to immune checkpoint inhibition (ICI). This study aimed at evaluating several TME features of breast angiosarcoma and correlating these features with clinicopathologic and clinical data.

Methods: The retrospective study was performed on tissue samples with medical records available at IRCCS - Fondazione G. Pascale (Na, Italy). Immunohistochemical parameters assessed included lymphoid cell markers (CD3$^+$, CD8$^+$, GrzB$^+$, FoxP3+, OX40, ICOS) and immune checkpoint receptors (PD-L1, PDL2, VISTA, TIM3, LAG3), analysed by digital pathology (20x). Simultaneously, multiplex immunofluorescence (miF) of T cells was quantified to verify the balance between cytotoxic (CT) and immunosuppressive (IS) activity in the TME. Fluorescence in situ hybridization (FISH) was used to assess *c-myc* amplification. Overall survival (OS) was estimated by Kaplan-Meier method and compared with Log-rank test.

Results: Eleven cases of pAS and 11 cases of sAS were retrieved. When comparing the average TIL and immune checkpoint receptor (ICr) densities between pAS and sAS, there was statistically significant difference for GrzB+ cells (p.0.045) and PD-L2 (p.0.013), respectively. Furthermore, the Foxp3 / CD8 (IS) and Grzb / CD8 (CT) ratios analysed by miF showed a strong colocalisation of CD8+ and FOXP3+ cells for about 50% of the cases, and a higher level of immunosuppression was observed in sAS cases (p. 0.006). FISH analysis revealed 11 MYC amplified cases (2 of which were pAS). When c-myc score was correlated with biomarkers density, it was significant for PD-L2 (p.0.045) and strongly associated with LAG3 (p.0.085) in sAS, and with FOXP3 (p.0,038) in pAS.

Conclusions: These data suggest a more immunosuppressive TME in sASs than in pASs. In addition, we have shown that c-MYC-amplification is associated with immune cell infiltrates and suppressed pathways. The results will soon be integrated with molecular and clinical data to enable patient stratification on ICI treatment.

M09

UPFRONT OXALIPLATIN–FLUOROPYRIMIDINE CHEMOTHERAPY AND SOMATOSTATIN ANALOGUES (SSA) IN ADVANCED WELL-DIFFERENTIATED G2/G3 GASTRO-ENTERO-PANCREATIC NEUROENDOCRINE TUMORS (GEP-NETS)

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Background: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are frequently diagnosed at advanced stage. For well-differentiated somatostatin receptor-positive (SSTR +) NETs, somatostatin snalogues (SSAs) are the preferred first-line therapy. However, in newly diagnosed patients (pts) with G2/G3 and a high tumor burden, SSA alone might not be enough.

Material (patients) and Methods: In this single-center study, we aimed to assess the effectiveness of combining oxaliplatin-fluoropyrimidine chemotherapy with SSA as an upfront strategy in such cases. We conducted a retrospective analysis on newly diagnosed metastatic G2/G3 GEP-NET pts referred to our institution who were treated with oxaliplatin–fluoropyrimidine-based chemotherapy added to SSA within 3 months (mo.) from diagnosis, in absence of progression. The co-primary endpoints were ORR and PFS. Secondary endpoints included DCR, DoR and OS.

Results: Between March 2017 and October 2023, 32 pts (19 males, 13 females; M:F = 1.5:1; median age 54 years, range 31-82) were deemed eligible by our Multidisciplinary Tumor Board to receive oxaliplatin–fluoropyrimidine chemotherapy in addition to SSA: 14 pts received XELOX and 18 received FOLFOX. At the data cut-off, after a median follow-up of 26 mo., each patient had completed at least two cycles of chemotherapy. The ORR according to RECIST v. 1.1 was 25%, with a median DoR of 21.3 mo. The DCR was 87.5%. Notably, 28.1% of patients experienced tumor shrinkage sufficient for radical surgery on residual tumor lesions, encompassing both primary tumors and metastases. The median PFS and OS were not reached. Mild (G1, G2) adverse events were reported by 75% of pts, while 20% experienced G3 events, leading to chemotherapy dose delays and reductions. No pts discontinued treatment due to drug-related toxicity.

Conclusions: Upfront treatment with the combination of oxaliplatin-fluoropyrimidine and SSA demonstrated effectiveness and safety. This approach may be considered to facilitate conversion surgery in eligible patients.

M10

THIRD-LINE TREATMENT FOR GASTROENTEROPANCREATIC NEUROENDOCRINE CARCINOMAS (GEP-NECS): A MONOCENTRIC EXPERIENCE

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Background: GEP-NECs are very rare tumors characterized by an aggressive natural history and a poor prognosis. The most frequently mutated genes are TP53, APC, KRAS, BRAF and RB1. While a combination of a platinum derivate and etoposide is a widely accepted standard of care in first-line setting, no consensus exists about treatments in later lines. Fluoropyrimidines in combination with either irinotecan, oxaliplatin or temozolomide are the most commonly used regimens and retreatment with platinum/etoposide may be used after a significant treatment break.

Material and Methods: We retrospectively collected data of 21 patients who received a diagnosis of GEP-NEC between 2000 and 2023 and a third-line treatment at Modena Cancer Center to evaluate outcomes in clinical practice.

Results: In our population the primary tumor site was colon-rectum (47.6%), followed by pancreas (28.6%). Median age was 67 years old (IQR 45-72). The most common metastatic sites were distant lymph nodes (81%) and liver (81%). Sixty-two percent of patients received cisplatin/etoposide as first-line treatment and 66.6% received FOLFIRI as second-line treatment. On the contrary, the choice of third-line treatment was more heterogeneous with the most common treatment being temozolomide (33.3%) and FOLFOX (23.8%). Any grade toxicity was more commonly associated to FOLFOX (80%), as compared to temozolomide (42.8%), the most common toxicities were non-hematological. The percentage of progression disease (PD) as best-response to treatment increased in later lines: 47.6% to first-line treatment, 61.9% to second-line treatment and 81% to third-line treatment. Median progression-free survival (PFS) was 4 months (IQR 1.7 – 7) in the first-line setting, 3 months (IQR 2 – 5.5) in

second-line and 2 months (IQR 1 – 2.2) in third-line. Median overall survival (OS) evaluated since GEP-NEC diagnosis was 14 months (IQR 9.5 – 19), while median OS since third-line treatment beginning was only 2 months (IQR 1 – 3.7).

Conclusions: GEP-NECs are very rare tumors associated with a poor prognosis. Our case series is substantially in line with the outcomes reported in the literature. Multicentric studies aiming at evaluating the best treatment options are eagerly awaited.

M11

PIVOTAL ROLE OF THE MULTIDISCIPLINARY TUMOR BOARD (MTB) ON THE MANAGEMENT OF NEUROENDOCRINE NEOPLASMS. IMPACT OF MTB DECISIONS IN AN ENETS CENTER OF EXCELLENCE

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Background: Multidisciplinary Tumor Board (MTB) meetings are a valuable tool to improve the management of solid tumors. Yet, few evidence regarding the real-world impact of Neuroendocrine Neoplasm (NEN)-dedicated MTBs are available.

Material and Methods: We conducted a retrospective analysis to assess the influence of MTB on NEN patients' care by measuring any change in diagnosis, assigned disease stage, tumor response evaluation and treatment strategy assessed before (pre) and after (post) MTB discussions, in patients referred to NEN MTB of "Fondazione Policlinico A. Gemelli" in Rome.

Results: From 2017 to 2023, 510 cases from 421 patients were reviewed. Study population included 216 women and 205 men with a median age of 62 years (18-90). The majority of the evaluated NENs (86.66%) originated from the gastro-entero-pancreatic tract (48.23% pancreatic; 22.74% small intestine; 4.50% gastric; 3.92% colorectal; 3.13% appendiceal; 4.11% with only liver metastases); while 7.05% and 6.27% originated from the lung or other sites, respectively. Early-stage disease was reported for 52.54% of patients, while 47.45% had an advanced disease. We documented a discrepancy between pre and post MTB discussion in 50.78% of cases which led to a treatment strategy modification in 35.09%. MTB discussions led to a change in diagnosis in 35 cases (6.86%). This change was due to the revision of previous radiological images in 62.85% of the cases whereas in 37.14% (13 cases) diagnosis was revised after suggesting a histopathology second opinion. In 23 cases (4.7%), the MTB evaluation led to changes in staging and in 35 cases (6.86%) it modified tumor response assessments during treatment. To note, MTB influenced surgical eligibility in 70 cases (13.72%), referring to surgery 52 cases, while preventing inappropriate surgery in 18 patients.

Conclusions: NEN-dedicated MTB evaluation influenced clinical decisions in an high number of cases and showed a meaningful impact on disease management.

M12

LONG-TERM OUTCOMES OF NEUROENDOCRINE NEOPLASMS: A REAL-WORLD ANALYSIS OF 239 PATIENTS FROM A SINGLE INSTITUTION

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Background: "Real-world" data are needed to guide treatment decision-making in neuroendocrine neoplasms (NENs). We aimed to assess NEN patients retrospectively referred to our institution to describe outcomes and treatment patterns over time.

Patients and Methods: We reviewed charts of patients with NEN from different organs, excluding pheochromocytoma/paranglioma and SCLC. We divided patients into two cohorts according to year of diagnosis (cohort A, 2010-2016; cohort B, 2016-2023). The overall survival (OS) predictors were tested in a multivariable Cox regression model corrected for treatment-free interval (TFI, interval between first diagnosis and treatment start). P-values were adjusted for multiple comparisons, and a p-value less than 0.05 was selected as significant.

Results: 239 patients were included, 87 in cohort A and 152 in cohort B. Primary tumor sites were small intestine (31%), lung (19%), pancreas (21%), colorectal (3%), appendix (4%), unknown (10%). 77% were well-differentiated NENs. Metastases were present in 47% of cases at diagnosis (71% in the liver). Clinical and tumor characteristics were similar in cohorts A and B. Also, first-line treatments were comparable between the two cohorts. Median follow-up was longer in cohort A compared with cohort B (101.2 months and 32.3 months, respectively). Radioligand therapy (RLT) was administered in 18% of patients in cohort A and 10% in cohort B (p=.9999). Median OS of the entire cohort was 101 months (95% CI, 82 to 115 months). OS after first-line therapy was not significantly different between cohorts A and B (HR 1.09 [95% CI, 0.63-1.88], p=.9999).

Table. Multivariable Cox model of association of baseline characteristics with OS.

Characteristic	HR (95%CI)	p-value
TFI *(months)*	0.98 (0.96 - 0.99)	0.02
Ki-67%, *median (IQR)*		<0.0001
1-10%	1	
11-20%	1.97 (0.82 - 4.73)	
21-55%	3.65 (1.57 - 8.47)	
>55%	12.67 (6.11 - 26.29)	

We found a significant association between Ki-67% and OS after first-line therapy. Taking as reference patients with low Ki-67% (level: 1-10%), the risk of death was about 4 and 12 times higher in patients with a Ki-67% level of 21-55% and >55%, respectively (Table).

Conclusion: In this dataset, we validated the Ki-67 index as a predictor of OS in metastatic patients undergoing first-line therapy. We did not find any significant difference in treatment outcomes according to the year of diagnosis. This observation highlights the need for novel, effective therapies for patients with NENs.

M13

CHEMOTHERAPY IN DISSEMINATED KAPOSI SARCOMA (KS): OUR EXPERIENCE.

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Background: Kaposi sarcoma is a multicentric vascular tumor caused by herpes-virus type 8. It is categorized into 5 types: classic (sporadic), AIDS-associated (epidemic), non-epidemic, endemic (in Africa), and iatrogenic (eg, after organ transplantation). Diagnosis is by biopsy. Treatment for indolent superficial lesions involves cryotherapy, electrocoagulation, excision, or electron beam radiation therapy. Radiation therapy is used for more extensive disease. In the AIDS-associated form, treatment includes antiretrovirals. Skin lesions manifest as solitary, localized or disseminated patches, or macular/papular eruptions, which progress to nodular plaques or lesions on any area of the skin. Progression is highly variable with lesions at different stages possibly occurring in the same individual. Lymph node and visceral involvement may be found in some forms especially iatrogenic and AIDS-KS. The oral cavity and the gastrointestinal tract (GI) are frequently affected. Pulmonary involvement is less common but may be life-threatening. Some rare patients do not present skin lesions.

Methods: This study aimed to evaluate the clinical activity of Carboplatin + VP 16 as first line chemotherapy in patients with disseminated KS.

From July 2022 to March 2024 11 patients (8 males and 3 females) with disseminated KS (GI, skin, lung) were eligible for analysis. Median age: 76 years (range 71/83), ECOG performance status 0-3. Tumor responce was assessed every three cycle using RECIST criteria.

Results: The treatment continued until PD with evidence of: 6 partial responce (RP, 55 %), 3 stable disease (SD, 27 %). No life threatening event occurred. Treatment was well tolerated from the great part of patients and the main toxicities were low-grade (G1-G2). Few patients reported severe (G3-G4) adverse events such as fatigue (2 pts), thrombocytopenia (1 pts), neutropenia (3 pts).

Conclusions: Preliminary data suggest that this schedule is well tolerated especially in elderly patients and may abrogate disease progression in patients with disseminated KS. The need for transfusions of concentrated red blood cells has been significantly reduced. The quality of life and fatigue have significantly improved.

N - Quality of Life and Patient-reported Outcome

N01*

OPPORTUNITIES AND CHALLENGES OF THE IMPLEMENTATION OF ELECTRONIC PATIENT-REPORTED OUTCOMES (EPROS) IN CLINICAL PRACTICE FOR PATIENTS WITH CANCER: A SURVEY OF ASSOCIAZIONE ITALIANA DI ONCOLOGIA MEDICA (AIOM)

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Background: Monitoring of patient-reported outcomes through web-based tools (ePROMs) allows to acquire essential information to improve patients' clinical management. In 2022, ESMO published clinical practice guideline about the adoption of ePROs in routine care of patients with cancer. Aim of this survey was to evaluate the point of view of Italian oncologists on the implementation of ePROs in clinical practice and to investigate the major obstacles to their adoption in the Italian health system.

Methods: An online survey was emailed in December 2022 to 2337 physicians AIOM members. The first sections of the survey explored demographic characteristics of the respondents and their knowledge of the subject. The last 3 sections explored several critical issues and potential obstacles for the implementation of ePROs, using a 5-item Likert scale. For each issue, doctors were asked about the relevance at the present and the presumed relevance within 5 years.

Results: 196 AIOM members answered the questionnaire (8.4%). 52.6% were younger than 40, 54.6% from Northern Italy. Most respondents (86.9%) were favourable to using ePROs, and most of them (92.1%) considered relevant the opportunity of more education on the topic. The limited integration of ePROs with health records and hospital technological equipment was considered a quite relevant problem by 32.3% of respondents and a very relevant problem by 42.5% (25.8% predicted a worsening and 37.6% predicted an improvement of this issue in the next 5 years). Most respondents declared that lack of funding for dedicated personnel is a relevant problem (quite relevant 25.3%, very relevant 68.8%), with the majority (57%) presuming a worsening of the issue in the next 5 years. Most respondents believed that the integration of ePROs into the routine workflow can be a relevant issue (quite relevant 44.9%, very relevant 45.9%), with 34.1% presuming a worsening in the next 5 years. Difficulty with digital skills of patients was perceived as a relevant problem by most respondents (quite relevant 47.3%, very relevant 37.9%), with the majority (59.9%) presuming an improvement in the future.

Conclusions: Italian oncologists are interested in the implementation of ePROs in clinical practice of patients with cancer. However, lack of funds for dedicated staff, difficulty of integration into the routine workflow and the suboptimal technological equipment available in many hospitals are perceived as relevant barriers.

N02*

FINANCIAL TOXICITY (FT) IN PATIENTS FROM REGIONAL CANCER NETWORK OF CAMPANIA (ROC): A CROSS-SECTIONAL STUDY

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Background: The Patient Reported Outcome for Fighting FInancial Toxicity (PROFFIT) questionnaire is a validated tool developed in Italy to measure FT that may affect oncological patients. The aim of the present study was to estimate FT in a prospective cohort of patients enrolled in ROC using data collected for monitoring its clinical and economic impact as part of the Valutazione Percorso Rete Oncologica Campana (Val.Pe.ROC) project.

Patients and Methods: In this cross-sectional study we sampled with a stratified method a cohort of patients enrolled in ROC by six different multidisciplinary tumor boards (GOM). Seven out of 16 items of PROFFIT questionnaire were administered to patients or their caregivers by phone interviews. Resulting data were joined to patients' baseline characteristics and clinical history extracted from ROC, in order to build a database. Descriptive analyses were conducted and associations between characteristics of patients, clinical history and baseline PROFFIT score were evaluated.

Results: Since 2019, over 82,000 patients were enrolled in ROC. From 1st June 2022 to 31st May 2023 Val.pe.ROC registered 6,795 patients. Out of these, 674 patients were sampled, representing 6 types of cancer (breast, colorectal, lung, prostate, bladder, and ovarian), of which 550 were from public and 124 from private institutions. The questionnaire was completed by a total of 265 patients. Overall, mean PROFFIT score and standard deviation (sd) were 42.4 (24.9), being higher in female [46.0 (25.9), p= 0.003] and in patients <65 years old [51.6 (24.9), p<0.001]. A lower score was found in retired patients 32.1 (21.7), while unemployed and flexible workers showed the highest [66.9 (20.9) and 49.5 (25.1), respectively, p<0.001]. Also, patients affected by ovarian and breast cancer had higher PROFFIT score [48.5 (29.5) and 47.9 (26.0) respectively, p= 0.01]. No difference in score was found whether interviewing patients or caregivers (p=0.099).

Conclusions: FT measured by PROFFIT score in ROC patients is consistent with previous findings. These results suggest the importance of this tool in supporting policy makers for the management of financial issues.

N03*

PATIENT VOICES: A MIXED-METHOD STUDY ON THE FEASIBILITY OF IMPLEMENTING ELECTRONIC PATIENT-REPORTED OUTCOME MEASURES IN A COMPREHENSIVE CANCER CENTRE

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Background: The PATIENT VOICES system is a software developed to promote the systematic collection of electronic patient-reported outcome measures (ePROMs) in routine oncology clinical practice. This study aimed to test the feasibility of such a system, assessing patient compliance and analysing patient-related barriers to ePROMs implementation in a comprehensive cancer centre.

Material and Methods: Consecutive cancer patients attending three outpatient clinics and three inpatient wards were screened for eligibility (adult, native-speakers, and being able to fill in the ePROMs) and enrolled in a convergent quantitative and qualitative mixed-method study. Compliance, reasons for non-completion, patients' interaction needs and patient perceived System Usability Scale (SUS, range 0-100) were collected; semi-structured interviews were carried out in a subsample of patients.

Results: Among 435 patients screened, 309 completed the ePROMs (73.4%; 95%CI 69.8% to 77.5%). Organization problems and patient refusal were the main reasons for non-completion among outpatients (17.1%) and inpatients (21.9%), respectively. Help for tablet usage was needed by 10.7% of inpatients and 27.8% of outpatients, while the support received for item interpretation was similar in the two groups (18.6% and 21.3%). Average SUS scores indicated high usability in both groups (86.8 and 83.9). Overall repeated measurement compliance (out-patients only) was 76.9%. Interviewed patients showed positive attitudes towards ePROMs, yet major barriers to implementation emerged about time and cognitive burden to complete the questionnaires, and perceived irrelevance of ePROMs.

Conclusions: This study provides useful information for future ePROM implementation strategies, aimed at effectively supporting the routine clinical management and care of cancer patients. Also, these findings may be relevant to other organisations willing to systematically collect PROMs/ePROMs in their clinical routines.

N04

FINANCIAL TOXICITY AND ITS RISK FACTORS AMONG PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS

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Background: Financial toxicity - the financial burden from cancer diagnosis and treatment - can negatively impact patients' health outcomes and well-being. There is a lack of comprehension of the financial burden experienced by patients with myeloproliferative neoplasms (MPN), including myelofibrosis (MF), polycythaemia vera (PV), and essential thrombocythemia (ET). One study found that 19% of MPN patients in Germany experienced financial difficulties. An Italian study estimated MF direct and indirect costs at €12,466 per year per patient. This study aims to assess financial toxicity among MPN patients and investigate associated risk factors.

Material and Methods: This is a cross-sectional study promoted by the Italian Association of MPN Patients (AIPAMM). Nine haematology centres in Italy have contributed data for the study since November 2021. During their outpatient visit, patients with MPN completed a questionnaire to measure quality of life and other study variables. We used item 28 from the EORTC QLQ-C30 to assess the financial toxicity. Results. Data from 292 patients with MF (42%), ET (30%), or PV (28%) were analysed (55% male; mean age = 60 years ± 14). We found that 14.8% of MPN patients experienced financial difficulties. At univariate analysis, significant risk factors included female gender, younger age, unmarried status, no university degree, not working nor having a retirement pension, low income, living in central or southern Italy, total symptom burden, and comorbidities (all p <.05). Receiving therapeutic phlebotomies was identified as an almost significant risk factor (p =.085). On multivariable backward logistic regression analysis (Table 1), only comorbidities (p =.003, OR = 1.29), symptom burden (p <.001, OR = 1.03), and phlebotomies (p =.01, OR = 4.16) remained statistically significant. The model explained 50% of the total variance.

Conclusions: Collective efforts are urgently needed to safeguard the financial security and well-being of MPN patients and promote health equities in cancer care. Particular attention should be paid to individuals with a higher symptom burden, comorbidities, and those receiving frequent phlebotomies, who may experience impairments in their work life.

Table 1. Logistic analysis.

	OR	95%CI	p-value
High income	.295	[.071, 1.23]	.094
North of Italy	.391	[.131, 1.17]	.092
Working	.249	[.059, 1.06]	.059
Phlebotomies	4.16	[1.34, 12.8]	.014
Symptom burden	1.03	[1.02, 1.05]	.000
Comorbidities	1.29	[1.09, 1.52]	.003

N05

ANALYSIS OF CORRELATION BETWEEN QUALITY OF LIFE (QOL) RESULTS AND SURVIVAL OUTCOMES IN PHASE III CLINICAL TRIALS TESTING IMMUNOTHERAPY IN METASTATIC CANCERS

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Background: Multiple trials revealed that immunotherapy (IO) improved survival endpoints in several metastatic solid tumors. However, concomitant benefit in QoL outcomes has been less explored. Herein, we examined QoL results in phase III randomized controlled trials (RCTs) investigating IO in metastatic cancers and their correlation with OS and PFS outcomes.

Methods: We conducted a systematic review to search for articles of RCTs testing IO published in PubMed-indexed journals between 01/2010 and 12/2023. Only trials assessing IO in metastatic setting, reporting QoL results in primary or secondary publications and at least one survival outcome between OS and PFS were selected for analysis. For each RCT, we evaluated whether global QoL was "superior," "inferior," or with "non-statistically significant difference" in the experimental arm compared to the control arm. Also, we assessed whether OS and PFS were improved or not by experimental treatment. Fisher's exact test was used for statistic analysis.

Results: Only 71 out of 140 identified RCTs (50.7%) respected selection criteria. Superior or inferior global QoL in experimental arm was found in 30/71 (42.3%) and 1/71 (1.4%) RCTs, respectively. No statistically significant difference between study arms was observed in the remaining 40/71 (56.3%) RCTs. Of note, we found a statistically significant association between QoL and OS improvements (p=0.0045). More in detail, this association was

significant in trials testing IO alone (p=0.0097). Instead, QoL results did not positively correlate with PFS outcomes (p=0.46). Next, we found that experimental treatments led to superior QoL only in 30/59 (50.8%) trials with positive results and in 1/12 (8.3%) RCTs with negative results (p = 0.0090). Interestingly, 29/59 (49.2%) positive RCTs did not lead to QoL improvements.

Conclusions: Our study reveals a positive association of QoL results with OS outcomes in RCTs testing IO in metastatic cancers, particularly for trials testing IO alone. About half of positive trials, potentially leading to new drug approval, did not prompt QoL amelioration. These findings further emphasize the relevance of an accurate assessment of QoL in oncology clinical trials.

N06

FERTILITY AND SEXUALITY IN EARLY ONSET-COLORECTAL CANCER (EO-CRC) PATIENTS (PTS): A MONOCENTRIC SURVEY

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Background: Clinicians managing EO-CRC pts face additional challenges, including chemotherapy (CT) impact on fertility and sexuality. Nowadays, despite increasing incidence of EO-CRC, evidence on these specific topics still lacks.

Methods: This is a retrospective survey, aiming to describe management of fertility and sexuality of EO-CRC pts treated at our Institution between 2013 and 2023. Pts' population included individuals aged ≤ 50 yrs, diagnosed with CRC, treated with CT for stage II-IV disease. Fertility was assessed for stage II-III pts, currently or previously treated with adjuvant CT, while sexuality was assessed for stage II-IV pts, currently or previously (within 6 months) treated with CT. Sexuality was assessed via EORTC SH22 questionnaire. Data were collected via anonymous online survey.

Results: 139 pts with the above mentioned characteristics were selected out of a database of 678 pts, and were offered the survey. Of those, 74 pts (53%) completed the survey (9 pts refused to participate and 56 pts never answered despite having provided consent). 43 pts were females and 31 males; 35 pts had stage II-III and 39 pts had stage IV disease. Concerning fertility, 16/35 pts (45%; females 8/17, 47%, and males 8/18, 44%) received counseling. Of those, 6 pts (17%) underwent cryopreservation (3 sperm; 3 ovocytes), and 3 females (8%) received GnRH analogues. 12/16 females (75%) who completed adjuvant CT, experienced an interruption of the menstrual period and 9 of these (75%) never recovered; however, 9/16 (56 %) were at least 45 yrs old at diagnosis. Regarding sexuality, 6/57 pts (10%) had talked about sexual issues with their oncologists (3/33 females and 3/24 males; 2/18 with stage II-III and 4/39 with stage IV). 19/22 females (86 %) and 5/10 males (50%) currently receiving CT reported a libido decrease. Among pts who had received last CT cycle less than 6 months before, 90% of females still had a libido decrease compared to 21% of males.

Conclusions: According to young pts with CRC, fertility issues tend to be part of medical talks more than sexual quality of life. Males seem to recover more than females from CT effects on libido. No gender gap was observed in fertility and sexuality counseling, however both should be improved in the management of EO-CRC.

N07

EVALUATING PRE- AND POST-DIAGNOSIS PHYSICAL ACTIVITY LEVEL AND ITS ASSOCIATION WITH QUALITY OF LIFE IN PATIENTS WITH THORACIC MALIGNANCIES

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Background: Physical activity is associated with improved survival in patients with lung cancer. Additionally, regular physical activity may confer several psycho-physical benefits and help patients manage treatment-related side effects. Nevertheless, a cancer diagnosis is a stressful moment that may impact a patient's lifestyle. The present study aims to explore the changes between pre- and post-diagnosis physical activity and its association with quality of life in patients with thoracic cancer.

Methods: A cross-sectional study was conducted at the Oncology Unit of the University of Verona. Newly diagnosed patients with thoracic cancer were asked to complete a questionnaire, which included: physical activity with the Godin Shepard Leisure Time Questionnaire referred to pre-diagnosis (reference: 1 year before diagnosis) and post-diagnosis (reference: previous 7 days), and quality of life assessed with the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire. Clinical variables were recorded by medical charts. Descriptive

analysis, absolute frequencies, Student t-test, Wilcoxon, and Pearson Correlation test were used.

Results: A total of 59 participants were enrolled. Patients had a median age of 65 years; 47% were former smokers, and 31% were never smokers. The most common cancer types were non-small cell lung cancer (86%) and adenocarcinoma (76%), the most frequent histology. About 68% of patients had stage IV disease, and 78% were candidates for systemic anticancer treatment. Significant changes from pre to post-diagnosis were observed for mild (180 min. IQR:5.2-420 vs. 30 min. IQR:0-240; $p<0.001$), moderate (122 ±294 min. vs. 41.9±127 min, $p=0.002$) and total (270 min. IQR:60-660 vs. 52 min. IQR:0-240; $p<0.001$) physical activity level, as well as for the frequency of resistance training (1.5±4.3 times vs. 0.2±0.8 times, $p=0.008$). Regarding quality of life, a better prediagnosis physical activity level performed at mild intensity was correlated with better physical well-being ($r_s=0.37$; $p=0.004$) and an improved trial outcome index (TOI) ($r_s=0.29$; $p=0.02$).

Conclusions: Our data demonstrate that a diagnosis of thoracic cancer negatively impacts patients' physical activity levels. Given the potential clinical implications of physical activity, this may suggest that initiatives and tools to support patients in staying or becoming active are needed.

N08

STUDY ON THE PERCEPTION OF MEMORY AND CONCENTRATION DEFICIT OF PATIENTS UNDERGOING ANTIBLASTIC THERAPY

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Background: Symptoms of cognitive dysfunction, known as *"chemo-brain"*, are observed during and after chemotherapy. Memory, attention, concentration and executive functions can be affected. These dysfunctions can significantly influence the quality of patients' lives but it's unclear what role the chemotherapy has in relation to the stress caused by the therapy. Studying the correlation between chemotherapy and cognitive impairment is highly relevant to provide rehabilitation interventions at an early stage.

Patients and Methods: The distress thermometer was completed by 63 patients (42 women and 21 men) undergoing antiblastic therapy at the Oncology Unit of Umberto I Hospital in Enna. The patients with pre-existing cognitive impairment were excluded. The item named *"memory/concentration problems"* was compared to the items named *"emotional problems"*, *"sleep problems"*, *"perception of fatigue and tiredness"*.

Results: Results indicate that 65% of the sample presents memory/concentration problems, 20% only presents emotional problems, 15% none of the above. Co-existence of cognitive impairment and emotional problems was presented by 61% of the patients, with higher incidence rate among women (45%) compared to men (28%). The most relevant emotional symptoms were preoccupation (90%), sadness (85%) and fear (75%). The 80% of the sample presents fatigue, 44% sleep disorders with a lower incidence rate among patients only experiencing concentration/memory problems (25%) compared to patients also presenting emotional problems (68%).

Conclusions: A large percentage of patients perceives memory and concentration problems as elements of distress. The high emotional problems rate and the higher incidence among women deserve further study. The distress thermometer is not the instrument of choice to evaluate cognitive impairment but it can provide an overall picture on the oncological patient perceived distress. Sleep disorders do not seem to have an impact on memory/concentration problems; fatigue affects all the participants without any major differences. We are currently studying these data in our Oncology Unit.

N09

THE DELOCALIZATION OF SUBCUTANEOUS AND ORAL THERAPIES IN PATIENTS WITH BREAST CANCER: THE EXPERIENCE OF THE TERRITORIAL ONCOLOGY CENTER OF AUSL 04 TERAMO

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Background: The latest AIOM data report a prevalence of 834,200 women living in Italy after breast cancer diagnosis. Patients with breast cancer and varied healthcare needs, are usually managed by hospital facilities, with a disproportionate demand compared to supply. Based on these observations, according to the recent document "Guidelines on hospital-territory integration in oncology" drawn up by Agenas and the National Agency for Regional Health Services, we have created a model which delocalizes oncology treatments with low-to-medium intensity of care outside the hospital. The delocalization took place at

the Territorial Oncology Center of AUSL 04 Teramo in "Casalena".

Material and Methods: The project involved: the reallocation of human and structural resources already presents in AUSL 04 Teramo; the creation of a team of "migrant health professionals", made up of oncologists and radiotherapists, that moves from the hub hospital towards the territory; the identification of a clinical research nurse; the creation of a computerized hospital/territory interconnection database. Two questionnaires, called questionnaire A (24 questions) and questionnaire B (16 questions in Proffit questionnaire by Arenare L. et al.), were administered anonymously to measure patient satisfaction and financial toxicity respectively. The project also aimed to promote the connection with the General Practitioners, improving patient care, thanks to the clinical research nurse. The dispensing, preparation and administration of the oncological drugs were carried out outside the hospital in collaboration with the Hospital Pharmacy. Furthermore, the integration of dieticians and psychologists has been achieved with the support of Patient Associations.

Results: From 01 September 2023 to 29 March 2024, in addition to providing 1500 follow-up visits for all oncological pathologies, the team followed 54 women (median age, 61 years; range, 28-86 years) with breast cancer subjected to: trastuzumab subcutaneous, 17 (31%); fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection, 21 (39%); adjuvant abemaciclib, 16 (30%). A preliminary analysis of the data revealed a level of satisfaction of 91%.

Conclusions: The delocalization project allows us to facilitate the patient journey resulting in an improved quality of life. A subsequent analysis of the data collected will make it possible to measure the socio-economic advantage of the new care setting.

O - Psychological and Psychosocial Aspects

O01*

LIVING THE WAITING TIME: FEELINGS AND EXPERIENCES DATA FROM CANCER PATIENTS IN THE WAITING ROOM (WR)

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Background: Waiting involves staying in a place until an expected event occurs. From diagnosis to follow-up and treatment, cancer patients (pts) often endure waiting. Understanding their emotions during this time is crucial. Few studies have explored the experiences and emotions of cancer patients in WR

Material and Methods: An anonymous 12-item online questionnaire was distributed to cancer pts in our center's WR. The questionnaire, divided into 3 sections including clinical and socio-demographic information, time spent in the WR, and pts' considerations. The aim of this study was to investigate cancer pts' emotions and behaviors in the WR.

Results: 160 pts completed the questionnaire (48% women, 52% men). The most represented age groups were 51-65 years old (37%) and 66-80 years old (41%). The majority of pts are unemployed (58.5%). About half of interviewed pts undergo infusion therapies and visit our center 1-2 times monthly. When asked to describe the wait duration, less than half found it long (32%) or too long (17%). The pts spend their waiting time on mobile phones (47%), watching TV (21%), reading or listening to music (16%), and conversing with others (11%). Both positive (49% calm, 7.5% hopeful, 5% emotional involvement) and negative (26% boredom, 21% anxiety, 6% sadness, 5% anger, 1% apathy) emotions were experienced. The multiple logistic regression model confirms the independent predictor role for a negative emotional status in the WR of a perceived long or too long waiting period (OR=4.0, $p<0.001$) and the independent protective role of man gender (OR=0.4, p=0.008). A trend of significance emerged for employment (OR=0.4, p=0.052) and engaging in active behaviors (OR=0.4, p=0.058) as protective factors. When asked how to improve the quality of time in the WR, 38% suggested live entertainment (music, readings, and oncologist-approved cancer information), 26% preferred access to newspapers and magazines. The most requested topics are treatment news (51%), diet (46%), and physical activity (27%).

Conclusions: For cancer pts the waiting can be a meaningful experience. Many pts find the wait long, boring, and anxiety-provoking. Our experience reveals that promotion of pts-suggested interactive activities and externalizing behaviors could improve the quality of time spent in the WR.

O02

HEALTH MANAGEMENT VIA TELEMEDICINE: THE EXPERIENCE OF NATIONAL CANCER INSTITUTE OF MILAN A YEAR LATER THE COVID-19 OUTBREAK

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Background: During the COVID-19 pandemic, telemedicine was rapidly implemented to protect patients and healthcare providers from infection. It is unlikely that care delivery will fully return to the pre-COVID status since telemedicine offers many opportunities to improve the care of cancer patients. We decided to conduct an observational study with the aim of showcasing the potential efficacy of telemedicine in optimizing treatment pathway and limits improper hospital admissions.

Material and Methods: Frail patients (ECOG PS 2, multiple comorbidities) with advanced solid tumors, treated at the Medical Oncology Department, at high risk of deferring treatment due to residual toxicity and requiring inpatient chemotherapy, were selected to participate in the study. Telemedicine visit (TV) and blood tests were all scheduled within 24-48 hours prior of hospital admission using the TICURO – Reply institutional informatics platform. At the end of each visit, patients were asked to anonymously complete a satisfaction survey aimed to evaluate their experience. Necessary requirements to join the project were the availability of a device capable of accessing the internet and an internet connection. To optimize the patient adhesion process, a case manager was involved with the role of educating doctors, patients, and their caregivers on the use of the platform.

Results: Between February 2023 and February 2024,1269 patients have been hospitalized, with 573 (45%) admitted for chemotherapy. Among these, 86 (15%) met the inclusion criteria. There were 53 (61,6%) men and 33 (38,3%) women. The mean patients' age was 65, 33 (38.4%) were residing in Lombardy and 53 (63.9%) outside. Most of the respondents (80%) were completely satisfied with the experience, 60% of them suffered of anxiety but everyone declared their intent to reuse and recommend it to others. TV was able to avoid potentially inappropriate hospitalization in 8 cases due to persistence of haematological toxicity. In all other cases, patients were admitted to hospital and received the planned treatment.

Conclusions: Telemedicine represents a digital innovation that could optimize cancer patients'care. Despite the overall satisfaction, over half of patients dealt with anxiety related to TV. Thus, it is important to educate patients about this new approach encouraging the use of this tool into clinical practice.

O03

THE SPIRITUAL NEEDS OF CANCER PATIENTS AT THE ISTITUTO ONCOLOGICO VENETO IRCCS

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Background: Spirituality represents a complex and multidimensional aspect, influencing how patients cope with a serious illness and face their disease journey related to cancer. The healthcare professionals' attention to this aspect is a cornerstone of patient-centered care and is essential for enhancing the quality of life of cancer patients. Assessing their religious and spiritual needs is necessary to understand how healthcare professionals can respond appropriately to these needs.

Patients and Methods: A cross-sectional, non-interventional investigation was conducted at the Istituto Oncologico Veneto I.R.C.C.S., where Spiritual Needs Questionnaires (Büssing, 2018) were collected anonymously. Data were collected distributing flyers containing QR codes/links or paper questionnaires with potential assistance from ward staff. Descriptive statistics was used, and regression models were developed.

Results: Questionnaires were collected from 233 patients, described in table 1.

Age	**Mean (SD)**	**62.26 (14.79)**
Gender = male	N (%)	125 (53.6)
Ward	N (%)	
Day Hospital		81 (34.8)
Surgery and Gastroenterology		66 (28.3)
Internal medicine		47 (20.2)
Week Surgery		39 (16.7)
Age	N (%)	
<45		31 (13.3)
45-54		30 (12.9)
55-64		55 (23.6)
65-74		69 (29.6)
>74		48 (20.6)
Education	N (%)	
Primary School		106 (45.5)
Secondary School		88 (37.8)
University degree		39 (16.7)
Religion (Christian)	N (%)	207 (88.8)
Time from diagnosis	N (%)	
Less than 6 months		101 (43.3)
Less than 1 year		60 (25.8)
More than 1 year		72 (30.9)

The descriptive analyses and constructed model after the stepwise selection (p=0.002) suggest an association between patient needs and gender (p=0.014), religion (p=0.055), and time since diagnosis (p=0.038). Females express higher religious, inner peace, and support needs. Religious needs are more expressed by older patients,

while inner peace, existential, and support needs decrease. Overall, needs increase with increasing time since diagnosis, particularly giving needs.

Conclusions: Considering the significant impact of spirituality on cancer patients, it is crucial for healthcare providers to address it effectively, exploring differences associated with clinical and demographic data represents an initial step in enhancing holistic patient care. There is a pressing need for future research to provide healthcare personnel suitable tools to optimize this process, prioritizing the individual within the healthcare system.

O04

CREATIVITY AS A RESOURCE FOR THE JOURNEY IN TUMOR: INTEGRATED DRAMATHERAPY AS A PSYCHOLOGICAL SUPPORT IN BREAST CANCER PATIENTS (A FEASIBILITY PILOT STUDY)

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Background: The 2019 WHO report states the role of the arts in health promotion. Integrated Dramatherapy (ID), developed at the narrAZIONI ID Center, is a method combining language expression, verbal and not verbal, with dramatization.

Patients and Methods: To explore the feasibility of in-person and digital ID as group supportive care for breast cancer (BC) patients (P); to define clinical individual (I) and group (G) utility indicators (UI). 15 disease-free BCP, aged >18 years, undergoing an individual psychological path at "Regina Elena" National Cancer Institute, Rome, were asked to participate. Two psychologist dramatherapists (PD) participated: the conductor, a psychotherapist who ideated and conducted the creative metaphoric pathway to favor P expression of experience with BC, and the observer who collected data. ID path (March-June 2020) included: a) a laboratory for body expression by using artistic languages; b) a digital phase (DID) conducted through a validated platform (Psydit): P, guided by multimedia prompts based on metaphors (landscape, magic, fairy, chaos, and harmony) by sharing narratives, images, photos and music among the group, developed their stories. PD defined UI (I: posture, gaze, facial mimic, breath, movement, participation in activities; G: climate, cohesion, alliance, interdependence, therapeutic benefits) and score (Likert 1-5 levels). An observational recording method was used. A mixed qualitative-quantitative analysis methodology was used. Ethics Committee approved the study. A written informed consent was required.

Results: 11/15 P participated; median age 45 yrs (32-52), surgery + adjuvant therapy: 11/11, degree/high school: 5/6, distress median score: 6 (SD 1,15). P actively participated and UI were adequate in P clinical evaluation. A good level of I openness and willingness emerged. GUI median score (4/5) indicates that sharing the expression of disease-related feeling was able to foster an empathic alliance and a good resonance. DID participation, although incomplete, provided PD further elements to guide the continuation of the individual support pathway. P favorably evaluated the whole path as offering the possibility to improve self-esteem and self-confidence by freeing up energy in sharing with other women.

Conclusions: G is a suitable and safe space for exploration, awareness and self-expression through creativity. ID/DID is a valid tool to be integrated into BCP individual psychological care path.

O05

ITALIAN EMOTION AND DISTRESS THERMOMETERS: DID THEY INVESTIGATE ADDITIONAL OR DIFFERENT MOOD DOMAINS?

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Background: People with cancer (PwC), especially during hospitalization, face clinical levels of distress, defined by the National Comprehensive Cancer Network (NCCN), as a multidetermined unpleasant emotional experience that could interfere with disease adjustment. Thus, screening for distress is necessary and recommended by the NCCN. Validated screening tools, like the Distress Thermometer (DT), are advocated in everyday clinical practice. The DT, is a self-report 0–10 rating scale known for its simplicity and quick administration. Other studies tried to develop screening tools that better capture the construct of psychosocial distress by considering other emotional symptoms. For example, the five-item Emotion Thermometers (ET) added anxiety, depression, and anger besides distress. Literature showed that a combination of more mood domains would better capture anxiety and depression symptoms. Even if those two instruments were highly validated, no study has yet investigated the suitability of the Italian translation of ET in comparison to the DT.

Material and Methods: 81 hospitalized PwC (Stage I to IV) participated in the study. 27 people were diagnosed with lung cancer, 21 with breast cancer, 8 with head-neck cancer, 7 with gynecological cancer, 5 with gastrointestinal cancer, 4 with urinary tract cancer, 3 melanoma, 1 medulla blastoma, sarcoma, chordoma, brain, pancreatic, and liver cancers. Each participant completed a sociodemographic questionnaire, the Distress, and the Emotions Thermometers.

Results: Hierarchical regression models were applied to evaluate if the Italian translation of distress within the ET (i.e., stress) predict alone the DT score or if DT is better explained by the addition of anxiety, depression, and rage thermometers. We found that, over and above stress levels (block 1, R2=.28, p<.001), other emotional domains added a significant residual portion of the variance (block 2, ΔR2=.14, p=001). Results showed that Stress (β=.32, p=.002), Anxiety (β=.23, p=.033), Depression (β=.25, p=.010), but not Anger (β=.10, p=.292) contributed to explaining DT levels.

Conclusions: Our results reveal that, in the Italian translation of the ET, the thermometer that should measure distress, actually measures another emotional domain (i.e., stress). We found that all ET predict distress. In conclusion, our findings showed that distress, assessed through the DT, is a complex construct given by the unpleasantness of different emotions.

O06

MUSIC THERAPY AND ONCOLOGY: A THERAPEUTIC JOURNEY THROUGH THE MUSIC

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Background: Music therapy represents an emerging complementary intervention in the field of oncology, aimed at improving patients' quality of life. This research aims to explore the therapeutic effects of music on the reduction of pain, anxiety, and depressive symptoms in oncology patients. The investigation is intended to determine the clinical efficacy of music therapy in the context of oncology treatments through standardized tests. Interventions such as music therapy specifically aim to improve psychological well-being, develop coping skills, and establish social resources (Holland et al., 2010).

Material (patients) and Methods: This research, initiated in November 2022 at the Oncology Unit of Teramo, adopts an intervention methodology that includes both active music therapy, involving patients in musical performance and sound dialogue, and receptive music therapy, which involves guided listening to selected music. Patients, selected by the department psychologist, participate in small group workshops on a weekly basis for a cycle of 12 sessions. To measure the effectiveness of the treatments, standardized instruments such as the S.T.A.I. Y-1 and Y-2, the Beck Hopelessness Scale, the Hospital Anxiety and Depression Scale, the TAS-20 test, and the NCCN Distress Thermometer are employed. These tests allow for an evaluation of the treatment's effects on oncology patients, contributing to defining the role of music in improving quality of life and psychological well-being.

Results: Currently, 21 patients have completed the program, while others are beginning a new cycle of sessions. The results from the first group indicate a very positive trend, with a progressive reduction in anxiety-depressive symptoms during the cycle of sessions. Furthermore, a significant improvement was observed in all dimensions of the TAS-20 alexithymia scale among the participants. In subsequent groups, the scores remained stable between the beginning and the end of the session cycle.

Conclusions: Looking ahead, it is essential to continue exploring the role of music therapy in the oncology context to ensure a more precise and specific intervention. It is interesting to note that in some cases, despite less satisfactory test scores, patients expressed the desire to continue the program by enrolling in new groups. This phenomenon might indicate a positive perception of the music therapy experience by the patients, regardless of the final results.

O07

NEIGHBOURHOOD DISADVANTAGE OF PEOPLE WITH CANCER: THE ROLE ON DISTRESS

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Background: In recent years, literature highlighted the role of neighborhood disadvantage on people with cancer's health and well-being and found that social and economic deprivation in the neighborhood predicts higher levels of anxiety in People with Advanced Cancer(PwAC).

These studies were conducted in America, where the neighborhood gap is extremely wide. Till now, no study has yet investigated the neighborhood disadvantage in the Italian context. The present study aims to fill this gap, by exploring this relationship and how it may vary depending on the type of cancer in Italian PAwAC.

Material and Methods: We recruited 26 PwAC: 13 people with lung cancer (PwLC,5F, age=59-85 years,education level = middle school–high specialization), 7 people with breast cancer, and 6 people with head-neck cancer (PwBHNC,11F,age=32-82 years, education level=middle school- high specialization). Each participant completed a sociodemographic questionnaire, the Distress, and the Emotions Thermometers. Moreover, a Deprivation Index (DI, range=1-6) was assigned based on their living address. The DI results from (1) the percentage of economically active people unemployed, (2) the percentage of households not owner occupied, (3) the average number of occupants per house, and (4) the percentage of people with secondary or lower level study certificate.

Results: We found differences between PwLC and PwBHNC in DI, $t(24)=-2.23$, $p=.036$, and in anger levels, $t(22)=-2.69$, $p=.014$. We did not find difference in distress, anxiety, depression and need of help levels, $|t(22)|<1.52$, $p>.142$. Controlling for age, gender, and degree, we found that DI, correlates with anxiety, and the need for help, $r>.65$, $p<.030$, in PwLC but not in PwBHNC, $|r|<.51$, $p<.128$. $p>.443$.

Conclusions: Our results suggest that PwLC lived in more deprived neighborhhod compared to people with other cancer types. This can be related to habits and lifestyles. Thus, people who live in more deprived neighborhoods are more inclined to smoke and less inclined to quit. Moreover, we found that PwLC experience higher levels of anger than PwBC and PwHNC. This may depend on the greater stigmatization of lung cancer, compared to other types of cancer. The effect of living in deprived neighborhoods on psychological well-being depends on the type of cancer. Thus only in lung cancer living in deprived neighborhoods is associated with higher levels of anxiety and need for help.

O08

AWARENESS OF ILLNESS, PSYCHOLOGICAL DIFFICULTIES AND BENEFIT FINDING IN DIFFERENT PROVISIONAL STAGE OF PSYCHIATRIC DISORDERS AMONG CANCER PATIENTS

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Background: Positive psychology and psychiatry consider awareness of illness and benefit finding – deriving growth from adversity – as important process of adjustment to cancer. This study was aimed to assess the potential role of cancer stage, awareness of illness, psychological difficulties and benefit finding in anxious/depressive disease development in cancer patients (pts) with early (ES) and advanced/metastatic (AS) solid cancer.

Material and Methods: A cross-sectional study was conducted at Luigi Sacco Hospital of Milan during the first session of a psychological support path. Pts' cancer stage and anxious/depressive symptoms through Hospital Depression and Anxiety Scale (HADS) were explored. Pts were then divided into 3 groups according to the model of unipolar depression: Group 1a (prodromal phase – no symptoms), Group 1b (prodromal phase – mood symptoms) and Group 2 (anxious/depressive disorder). The Revised Illness Perception Questionnaire (IPQ-R), Clinical Outcome in Routine Evaluation (CORE-OM) and Benefit Finding (BF) were also administered. Descriptive statistics, non-parametric ANOVA and multinomial logistic regressions were conducted.

Results: 116 pts were included: F 97, M 19, aged 27-84, 30% AS, and 70% ES. Pts in group 2 had significantly more frequently AS, while in group 1a pts with ES ($\chi^2=7.40$, $p<.05$). Pts reported moderate levels of beliefs, showing positive awareness: group 2 scored significantly higher in perceived coherence ($\chi^2=8.1$, $p<.05$), cyclical timeline ($\chi^2=8.4$, $p<.05$) and emotional representation of illness ($\chi^2=12.6$, $p<.01$) than group 1a and 1b. Pts' CORE-OM mean score exceeded clinical cutoff in all dimensions, with the only exception of suicidal risk which scored lower the clinical cutoff at every provisional psychiatric stage. Pts also reported moderate levels of benefit finding, with significantly higher mean score of acceptance ($?^2=9.2$, $p<.05$) and personal growth ($?^2=13.9$, $p<.001$) in group 1a than in group 1b and 2. Multiple regression analysis highlighted pts with AS and high emotional intolerance beliefs, difficulties in emotional management, and low levels of benefit finding were more likely to receive a provisional anxious depressive disorder diagnosis.

Conclusions: Pts with AS, low emotional management, and low levels of benefit finding were more likely to receive a provisional anxious depressive disorder. Staging psychiatric disorders in cancer pts allows the evaluation of tailored interventions at earlier stage of cancer illness.

O09

THE PSYCHO-ONCOLOGIST ON THE TERRITORY. A POSSIBILITY OF TREATMENT FOR CANCER PATIENTS FOLLOWED IN THE LOCAL NETWORK

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Background: The need for local assistance for chronic diseases, such as oncological ones, is becoming extremely topical considering changes in the treatment which lead to an increase in survival even for cancer patients with an advanced/metastatic form.The distance from the place of treatment and the inconveniences of travelling can negatively influence both the adequacy of care and survival, but also the possibility of accessing psychological care for those patients who need it but cannot overburden themselves with further journeys which would cause further inconvenience on top of the ones occurring from the current ongoing treatments.

Materials and Methods: It s already few years that in Piacenza (Italy), the district Health Authority built a model of well structured assistence which involves oncologists and hematologists of the main hospital, daily working on rotation in different units of the county and also in the so called House of heath Casa della Salute, providing all the necessary procedures patients need and above all near their home. Consequently there was the need to also include in this model the psychological service previously offered only in the central hospital. All this was structured in order to truly guarantee total equality of care to all patients and to allow psychological assistance to be guaranteed to patients and their family members who otherwise without moving around too much.

Results: From 27 February 2022, the psychology service was implemented at one of the three peripheral hospitals, guaranteeing the service with a dedicated psychologist all day once a week. The medical and nursing staff have offered to the patients/family members in care and new diagnosed people the possibility to access the psychological support. During a 1 year 73 patients were treated. 60 are patients and 11 caregivers. 47 psychological support, 17 psychological consultancy, 7 psychotherapies, and after the first consultancy 2 patients refuse the psychological treatment.

Conclusions: After 12 months it is possible to highlight how a 'Territorial' psychology service can be implemented to guarantee services models similar to the central hospital. The psychologist is seen as an integral part of the team also because facilitates the communication between doctor/nurse and patient. Furthermore, the psychologist was seen as a support to the entire team. Thanks to the success of the first results, the service was also implemented at a second local facility following the same model.

O10

CARING FOR THOSE WHO CARE. SUPPORT GROUPS FOR CAREGIVERS. A PILOT PROJECT

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Background: Oncology desease makes people aware of the non-eternal life duration. It is not only about patients but it involves carers too: family members, partners, friends and all people taking care of practical and emotional needs of the suffering person in order to guarantee the best possible quality of life.

The caregiver are often put a part and not taken into the right consideration for the heavy effort necessary to handle a stressful situation like an oncological one. For this reason, caregivers should be trained and supported. Being in charge of taking care of a person affected by cancer involves many tasks like regular personal cleaning, monitoring therapies sumministration, house management, medical appointments transportation, social interactions and all others emotional and practical support.

All this may mean having to give up one's life and job, at least for a certain period; in many cases, the caregiving absorbs all physical and mental energy and leads to a state of exhaustion.

Matherial and Methods: This project is particularly addressed to the patient s family members, chance for sharing and listen to all potential needs during the different therapy treatments. Meetings take place once a month and led by the psychologist of the department, who meant to assist and mediate.

According to what the participants needs are, It may be possible to create more events with specific professionals based on the different issues expressed.

Results: From december 2023, five small group have been conducted. 17 caregiver participated. 2 male familily memebers. 4 were wives, 6 were children, 1 was a mother, 1 was a husband, 1 was brother and 4 ware sisters. What emerges from these meetings is communication distress, lack of use of right words with patient, struggle on time and family needs managing, feeling of guilt toward the patient.

Conclusions: Despite the small sample size due to the recent start of the project, the participants were satisfied with attending in these meetings. It will be essential to carry on with these sessions where caregivers come out with their feelings and, thanks to the phsycologists support,they don t find themselves alone in this life experience.

O11

LONELINESS IN CANCER PATIENTS: A NEW NEGATIVE PROGNOSTIC FACTOR FOR SURVIVAL

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Background: Loneliness, and living alone may represent serious physical and mental health problems. Loneliness is defined as a subjective feeling that occurs when one's relationships with the environment and with other people do not match one's expectations of how relationships should be. The concept of loneliness concerns several areas, such as philosophical, sociological, psychological but, more recently, has come to the attention of the medical area, representing a significant health risk factor as a (negative) social determinant of health. Studies in cancer patients are few, and many of them are geared mainly toward the elderly who are generally considered, more prone to loneliness.

Material and Methods: Studies on loneliness and loneliness and cancer patient of the past decade were considered.

Results: Living alone is related to anxiety, depression, cognitive decline, increased blood pressure, chronic inflammation and increased stroke and myocardial infarction. Loneliness is related to widowhood, divorce and lack of psychological and social supports. Particularly in neoplastic patients, loneliness results to be an independent negative prognostic factor of survival in decreased survival.

Tab 1. Causes of decreased survival in neoplastic patients related to loneliness.

Advanced age
Male gender
High degree of education
Living alone
Social isolation
Low economic status
Breast, rectal, uterine cancer

Conclusions: Excess cancer deaths associated with living alone also underscore the need for more resources and appropriate training for clinicians, integrated screening for living alone and social isolation, and more research to identify and implement interventions that could reduce the adverse effects of living alone and social isolation. Oncologists should consider loneliness as a prognostic index as other biological factors.

P - Oncology Nursing

P01*

EFFECTIVENESS OF IMMERSIVE VIRTUAL REALITY DURING INTRAVENOUS ANTIBLASTIC THERAPY

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Background: During intravenous antiblastic therapy (IAT) patients might be submersed in negative psychological, and environmental stimuli.The introduction of a non-pharmacological intervention capable of quickly and effectively distracting patients from these stimuli can be helpful. Immersive Virtual Reality (IVR) has all these characteristics, and represents one of the most promising innovative digital health interventions.

Material (patients) and Methods: Randomized controlled trial with three parallel groups, IVR, narrative medicine (NM), standard care (SC),in a 1:1:1 allocation ratio, pre-post test, in patients undergoing IAT. Setting was the Oncology of St Giovanni Paolo II Hospital, Olbia. Outcomes were anxiety, fatigue, pain, cybersickness and satisfaction using IVR. Patients weared an innovative Head-Mounted VR Display connected with a 5G internet line,and two touch controllers.Scenarios programmed by the first author were 310 videos (from 4k to 8K,360-degree,3D) classified into 9 categories:1) Africa;2) Hills;3) Rivers, lakes, and waterfalls;4) Islands;5) Deserts;6) Beaches;7) Mountains;8) Sea;9) Underwater environment. Lenght of IVR experience was of 30 minutes.

Results: According to calculation of sample size and power, 74 participants were randomized, 25 in IVR, 25 in NM and 24 in SC.Participants' mean age was 59.3 (SD=10.8), 74.3% female, 97.2% Italian, 47.2% diagnosed with breast cancer, 55.4% in cancer stage IV. Anxiety decreased more in IVR (M=6.24, 95%CI 2.578 to 9.902, p=.001, d=.63) compared to NM (M=4.13, 95%CI 0.388 to 7.862, p=.031, d =.39), while it did not change in SC (M=.280, 95%CI -3.382 to

3.942, p=.879, d=.03). Overall level of fatigue decreased in IVR (M=.576, 95%CI.246 to.907, p=.001, d=0.23), while remained stable in NM (M=.02,95%CI -.335 to.339, p=.991, d=.00), and increased in SC (M= -0.531, 95%CI -0.861 to -.201, p=.002, d=.29). Mean pain levels did not change before and after the intervention [F(1,71)=1.06, p=.307], and remained stable over time for participants in all groups [F (2,71)=.19, p=.828].Participants reported high level of satisfaction using VR and no remarkable undesirable effects such as cybersickness.

Conclusions: This trial showed that IVR was effective in reducing anxiety and fatigue, did not generate symptoms of cybersickness, and was reported as a satisfying and useful experience by patients undergoing IAT. IVR presents itself as an innovative, safe, and easy-to-implement intervention in oncology nursing.

P02*

THE IMPACT OF PATIENT PERCEPTION OF PATIENT CENTEREDNESS IN INDIVIDUALS ON ORAL ANTICANCER AGENTS

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Background: Oral anticancer agents (OAAs) use is growing. Patients on OAAs can manage their treatment at home with less care burden caused by systemic therapy, maintaining prolonged survival. Disease management by the oncology team based on patient-centeredness is essential to improve patient outcomes. To date few studies explored the role of patient perception of patient-centeredness (PPPC) in those treated with OAAs. We aimed to describe the association between PPPC, self-care behaviours, and Quality of Life (QoL).

Patients and Methods: A multicentre cross-sectional analysis was conducted to test the association between PPPC, self-care behaviours, and QoL. Inclusion criteria were age ≥ 18 years; diagnosis of solid tumour; active treatment with OAAs for at least 3 months. PPPC was assessed using the Revised PPPC (PPPC-R) Questionnaire (score range 1-5, lower scores mean higher PPPC); self-care was evaluated through the Self-Care of Oral Anticancer Agents Index (score range 0-100, higher scores mean higher self-care), which measures self-care maintenance (actions to maintain stable conditions and adhere to OAAs); self-care monitoring (actions to monitor signs/symptoms of disease worsening); and self-care management (actions to respond to symptoms). QoL was measured with the Global Health Status dimension of the EORTC QLQ-C30 (score range 0-100, higher scores mean higher QoL). Linear regression analysis was used to test association of PPPC with each self-care dimension and QoL.

Results: We included 402 patients from five inpatient and outpatient Italian facilities. Patients' mean age was 60 years (SD 13), mostly were male (51%) and using OAAs for a mean of 18 months (SD 24). Results indicate a significant association between PPPC and all the three dimensions of self-care; self-care maintenance (B= -8.42, p <.001, R^2 = 35%), monitoring (B= -12.33, p <.001, R^2 = 31%) and management (B= -12.23, p <.001, R^2 = 31%). Moreover, PPPC has a significant association with quality of life (B= -11.44, p <.001, R^2 = 27%).

Conclusions: Our results highlighted the role of a patient-centered approach for patients on OAAs. Patients with higher PPPC have higher QoL and adopt better self-care behaviours. The association between PPPC and self-care suggests that a patient-centered approach promotes better management of OAAs. Consequently, patients with higher PPPC can have better control of their disease, potentially avoiding unnecessary use of healthcare services (e.g., emergency room).

P03*

THE IMPACT OF ONCOLOGY SPECIALIST NURSES ON IMPROVING NURSING-SENSITIVE OUTCOMES IN CANCER PATIENTS

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Background: Recent advances in oncology have contributed to improved survival rates; however, the disease and its treatments significantly impact the quality of life. The increasing complexity of needs among cancer patients places nurses in a crucial position for delivering quality

care. In this context, it is essential to measure and evaluate care outcomes. The purpose of this study was to examine the effectiveness of interventions conducted by an oncology specialist nurse in improving health outcomes.

Material and Methods: A systematic literature review was conducted in May 2023 by consulting the CINAHL, Cochrane, ProQuest, PubMed, Scopus, and Web of Science databases. No filters were applied. Article selection was performed according to specific inclusion and exclusion criteria. The methodological quality of the studies was assessed using the "Risk-of-Bias Tool for Randomized Trials," the "Newcastle-Ottawa Quality Assessment Scale," the "Mixed Methods Appraisal Tool," and the "Critical Appraisal Tool for Quasi-Experimental Studies."

Results: A total of 9,386 articles were identified, of which 22 were included in the review (7 RCTs, 10 observational studies, 3 mixed-method studies, and 2 quasi-experimental studies), encompassing a total of 311,971 patients. The outcomes investigated included anxiety, depression, nausea, vomiting, fatigue, pain, symptom management, prognosis, satisfaction, mortality, survival, quality of life, and performance status. Nearly all studies demonstrated the effectiveness of specialist nurse interventions in improving the considered outcomes, although they reported a medium/low methodological quality.

Conclusions: This review showed a consistent agreement among studies regarding the positive impact of specialist nursing care on outcomes in oncology patients. According to the "Nursing Role Effectiveness Model," independent interventions conducted by oncology nurses directly influence patients' clinical and functional outcomes, as well as their satisfaction with the received care. The competencies of specialist nurse can thus add value to the cancer care pathway, providing personalized and safe care. Additional research is needed to validate these findings.

P04

HOME NURSING ACTIVITIES IN CLINICAL PRACTICE: THE IRST EXPERIENCE

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Background: The COVID-19 pandemic has significantly impacted healthcare systems, leading to adaptations in cancer patient care models. For instance, home delivery of oral medications became prevalent during peak pandemic periods. Home nursing activities have also become crucial in clinical trials decentralized.

Methods: IRST IRCCS based in Meldola (FC) developed a protocol involving home nursing activities to evaluate treatment compliance and patient satisfaction of a new internal organizational model, that involved 40 woman diagnosed with metastatic Breast Cancer receiving oral treatments. No change in clinical practice procedures. Nurse responsibilities at patient's home included blood tests, triage on symptoms and adverse events and collection of Quality of Life and satisfaction data using ad-hoc questionnaires.

This abstract outlines the project's feasibility and the actions implemented to overcome bureaucratic and security challenges faced by working group.

Results: The working group included Nursing Management (NM), Human Resources (HR), Prevention and Protection Service (PPS), Purchasing Office (PO), Clinical Research Coordinator (CRC) and Oncologist (MD), and was coordinated by CRC. Activities listed below were carried out from April to December 2023.

Schedule of activities	Owner	Result
Sharing the project with NM/HR/PPS	CRC, MD	Units Approval
Nurse contractual form	HR	Activity will be done out of working hour
Transport evaluation	HR,NM	Own means of transport
Risk Assessment Evaluation	PPS,NM, HR	Manage of potential risk identified at patient's home and during the rout.
Insurance Coverage	HR, PPS, PO	Insurance policy extension
Nurses involved	NM,MD,CRC	Four nurses on shifts and one nurse coordinator
Nurse FEE and general cost evaluation criteria	HR, NM	Evaluation performed on the number of visits for patient (worst case)
Equipment evaluation (Ex. Work Uniforms)	NM, PPS,PO	Purchase of needing material
Specific Work Instruction	NM, CRC, MD	Set of specific internal and external flow
Assessment of patient and nurses scheduling	NM,CRC,MD	Weekly meeting

From January 2024, 13 patients had been enrolled, and 46 home visits were conducted. Three patients declined the protocol participation for propensity to come to the hospital and no any notable issues encountered.

Conclusions: The successful implementation of organizational innovations in the healthcare sector often necessitates ongoing collaboration among diverse professional groups, despite the fact that the required procedures may be identical to those employed in clinical practice.

P05

CHEMOBRAIN: SUBJECTIVE ASSESSMENT OF COGNITIVE IMPAIRMENT AND IMPACT ON THE QUALITY OF LIFE IN PATIENTS UNDERGOING CHEMOTHERAPY

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Background: Numerous studies have demonstrated the negative effects of chemotherapy drugs on cognitive function with direct and indirect damage mechanisms. 15-50% of cancer patients experience a cognitive decline during, or immediately after, chemotherapy, particularly in the domains of memory and attention, with a significant impact on quality of life and the ability to maintain a normal life. Currently mainly neuropsychological tests are used to assess the level of cognitive decline present, but also subjective self-assessment tests are important data to understand the disease experience of patients.This study aims to assess the cognitive decline of cancer patients and the impact this has on their quality of life.

Materials and Methods: The study is of a prospective longitudinal type, lasting two months, and involved 40 patients between 18 and 64 years belonging to the Day Hospital of the Veneto Institute of Oncology. The data were collected using the questionnaire FACT-Cog v.3, administered at the beginning of the first course of chemotherapy (T0), after about 3-4 weeks (T1) and after about 6-8 weeks (T2).

Results: Data collected show a progressive reduction in average cognitive skills perceived by subjects from T0 (PCI 72.10 +/- 9.03, PCA 25.70 +/- 7.70) to T2 (PCI 64.43 +/- 11.57, PCA 20.90 +/- 7.53); general quality of life also shows a decline from T0 (9.73 5.23) to T2 (8.75 +/- 4.11). In addition, there was a statistically significant positive correlation between the scores of the variable "Cog-PCA", which evaluates perceived cognitive abilities, and perceived quality of life: This data supports the hypothesis that the cognitive decline perceived by patients has an effect on quality of life. Finally, it has been shown that the variables investigated by the questionnaire (perceived impoverishment, comments received from others and perceived abilities), be able to reliably predict changes in the patient's quality of life from 2 months after the start of chemotherapy [F (4.35) =3.91, Prob>F=0.01].

Conclusions: The results obtained show that there is a deterioration in the quality of life with the continuation of chemotherapy and how, in particular, cognitive abilities perceived by the subject affect the quality of life of the subject; however this decline can be predicted already from the second month of chemotherapy using the questionnaire FACT-Cog v.3. This type of assessment could be extended to more centres in order to increase the significance of the data.

P06

THE EXPERIENCE OF CAREGIVERS: THE OTHER HIDDEN FACE OF THE CANCER DISEASE

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Background: Caregivers with cancer perceive poor overall health, to which are added to aggravate it anxiety and distress, which inevitably lead to increase of psychological sequelae. To survey the quality of life and psychological aspect of the oncology caregiver throughout the entire course of care and to detect whether the caregiver's spiritual relationship influenced the care pathway.

Methods: An observational, cross sectional, online study. Through the administration of a questionnaire, through the use of social media, particularly in groups Facebook: "Family Caregiver," "CONFAD for Family Caregivers." "United Against Cancer", "Dear caregiver I write to you" by participating via links to the study.

Results: A total of 81 participants were enrolled in the study. The levels high levels of family overload and the resulting psychological sequelae from this situation show poor levels of one's quality of life. The surveyed sample when asked at the current state how they would define its general health status answered: 43.2% as "Acceptable", 29.6% as "Good", 1.2% as "Excellent", 4.9% as "Very good" and 21% as "Very bad". The results of the sample showed that the illness of one's family member significantly affected the time devoted to other family members (45.7%), followed by the relationships with other family members (42%), at the same place we find the relationships

with friends and relatives (39.5%) and the time one devoted to oneself themselves (39.5%), relationships with partners (38.3%) and engagement in professional sphere (38.3%), finally relationships with work colleagues with only (32.1%). Next, it was asked what are the 124 difficulties that oncology caregivers face on a daily basis and it was found that for more than half of the sample they relate to living with uncertainty for the future (59.3%), followed by living with the outcomes of the disease (45.7%), living with an often inadequate lifestyle (44.4%), living with deficient/lack of care (42%), living with deficient support from institutions, families, health care providers (39.5%), and finally living with the sense of inadequacy (38.3%).

Conclusions: The real challenge for professionals is that of being able to build a relationship of trust with the caregiver and being able to help with the different means available to enable them and their loved ones a better quality of life during this journey.

P07

EMPATHIC TENDENCY, RELATED JOB SATISFACTION OF PROFESSIONALS AND PATIENT SATISFACTION IN THE PIACENZA ONCOHEMATOLOGY NETWORK

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Background: In oncology, distance from the place of care can have a negative impact on both the adequacy of care and survival. For several years, the Local Health Authority of Piacenza has structured an organisational model that involves oncologists or haematologists who, move around the area daily from Piacenza and work in oncoematology clinic, with dedicated nursing staff in the peripheral hospital. In literature, patient satisfaction with the outreach organisational model is high and there are significant associations between the working environment, understood as a close-knit team and cohesive work group, and patient outcomes. Associated professional job satisfaction, which depends on multiple factors including the work environment, also shows a correlation between patient satisfaction and professional satisfaction. Empathy is seen as a predisposition and tendency, influenced by the work environment, to influence the quality of care and care outcomes.

Methods: Mixed methods observational cross-sectional qualitative-quantitative study, investigating the empathic tendency of nurses from both oncology hospital area and oncology community network using 2 scales: BEES scale and OSME scale. In the qualitative analysis, patients were interviewed, using the descriptive qualitative research method.

Results: The results of descriptive statistical analysis on the median BEES score of nurses pertaining to the hospital oncology area is 60.44 (SD 18.7), on the other hand, in the territorial oncology care is 64.32 (SD 14.3). Regarding the factor analysis, the first facet (imperviousness to others' emotions) is the only one with a statistically significant difference between the 2 groups 35.84 (SD 13.9) and 48.46 (SD 15.8) ($p<0.02$). For the second questionnaire, OSME, a low prevalence of work stress in the hospital setting 119.2 (SD 13.9) and organisational well-being in the community setting 128.1 (SD 11.3) emerges. Qualitative analysis revealed three basic themes: self-perception in service, relationship with illness, travel stress.

Conclusions: Decentralisation is convenient for patients, reduces the level of 'financial toxicity' associated with cancer diagnosis, and also has a positive impact on professionals. Interesting, thought-provoking points emerge from the interviews with patients: circularity of service, increased psychological permeability, travel stress. In conclusion, financial toxicity has a negative impact on patients' overall experience of healthcare.

P08

ASSESSMENT OF ADHERENCE TO THE WORLD CANCER RESEARCH FUND (WCRF) RECOMMENDATIONS FOR CANCER PREVENTION AMONG E.O. GALLIERA STAFF: ARISE STUDY (CANCER PREVENTION LIFESTYLE GALLIERA)"

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Background: In 2018, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) revised the Recommendations for Cancer Prevention. These Recommendations provide guidance for nurses engaged in health education programs and their promotion is also encouraged in the workplace (Workplace Health Promotion Program). Our objective was to assess adherence to the WCRF/AICR 2018 Recommendations

(diet, physical activity, lifestyle) and to detect cancer screening participation among E.O. Galliera staff.

Material and Methods: We conducted a prospective observational study among healthcare and administrative staff of the Galliera Hospital (Genoa). Participants completed a questionnaire including general characteristics, dietary habits, physical activity level and screening adherence. The recommendation adherence was calculated according to the score proposed by Shams-White et al., 2019.

Results: The study population included 454 subjects (349 women and 105 men). The median WCRF adherence score was 4.63. The majority of the survey respondents were healthcare workers (57%). The probability of adhering to the WCRF/AICR 2018 score was higher in women (p=0.002), healthcare workers (p=0.002) and those adhering to colorectal screening (p = 0.004). Smokers adhered less to the Mediterranean diet (p=0.02) and were physically inactive (p=0.02). The detected screening adherence was 94% for breast cancer, 87% for cervical cancer, and 54% for colorectal cancer. Among the reasons for nonadherence, "indolence/neglect" was the most frequent (33% breast, 39% cervix, 44% colorectal).

Conclusions: The results suggest the importance of planning educational interventions for cancer prevention in the workplace tailored on gender, profession, age, and behavior. We are designing a second phase of the study (interventional, randomized), aimed at a cluster of subjects, selected from the observational cohort, at "high risk" that is with lower adherence to the 2018 WCRF/AICR Recommendations and screening programs.

P09

THE PREOPERATIVE ANXIETY ASSESSMENT IN CANCER PATIENTS: VALIDATION, OBSERVATIONAL AND DESCRIPTIVE STUDY PROTOCOL

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Background: Anxiety is characterized by the emotions of tension, apprehension, uneasiness, fear, and discomfort. Anxiety impacts the patient's work, family, and social life and increases their concerns about the unknown. It is crucial, therefore, to ensure personalized nursing care by employing assessment scales specific to the clinical-surgical oncology context to gather information about the patient's experience, emotions, concerns, and fears. The purpose of this study is to evaluate the validity and reliability of the Surgical Anxiety Questionnaire-SAQ by measuring its psychometric properties, including content validity, reliability, criterion validity, and construct validity. The study also aims to assess the level of preoperative anxiety in patients undergoing surgery at a National Cancer Institute in Italy.

Material and Methods: A methodological validation, observational descriptive study will be conducted through the following phases: (1) content and face validity: translation, back-translation, and evaluation by a panel of experts; (2) pre-testing of the Italian version in a small group of patients; (3) reliability (internal consistency) and construct validity study (exploratory factor analysis [EFA]); and (4) criterion validity using the Hamilton Anxiety Scale.

Cancer patients will be included if they: (1) underwent surgery in ordinary or day surgery hospitalization; (2) are over 18 years of age and proficient in Italian; and (3) provide signed consent. The study plans to enroll at least 85 patients, with five assigned to each questionnaire item. The Board of Ethics of Friuli Venezia Giulia approved the study protocol (CEUR, May 2024).

Results: The study will provide an effective tool for detecting preoperative anxiety in oncology patients. Many scales are available but they have limitations regarding the issues they investigate and the time required for completion, which is often lengthy and laborious, making it difficult to apply. The study will shed light on the factors that increase preoperative anxiety, with the aim of enhancing patient education and implementing strategies and interventions to reduce patients' emotional state.

Conclusions: The nurse's role is essential in the patient education pathway and promotes the multidisciplinary team's collaboration in the care process. Therefore, validated and reliable tools are essential to accurately identify the issues faced by cancer patients.

P10

REAL LIFE EXPERIENCE OF NURSING TOXICITY MONITORING PROGRAM FOR PATIENTS RECEIVING IMMUNOTHERAPY FOR MELANOMA

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Background: Immune-checkpoint inhibitors (ICIs) have tremendously changed the survival outcomes of patients

with cancers, as well as the management of potential side effects. Indeed, immune-related adverse events (IrAEs) can potentially affect any organ system, while most commonly occurring symptoms include pruritus, rash, and diarrhoea. Other less common side effects include hypothyroidism, hypophysitis, adrenal insufficiency, and hepatotoxicity, among others. The key to management is early recognition and treatment. Several guidelines have been published on immune-related toxicity; however, prospective data exploring the nursing role in the management of irAEs are still lacking. We explore the potential of patient-reported outcome measures (PROMs) in addressing these gaps and aim to describe opportunities and initiatives for improving the involvement of nurses in the shared decision-making process of toxicity management.

Methods: Patients with melanoma treated as for clinical practice in adjuvant and metastatic setting at National Cancer Institute Fondazione G. Pascale, between December 2023 and March 2024, were prospectively included in this study. The onset and grading of IrAEs were recorded from clinic visits using CTCAE v. 4.03 and from PRO-CTCAE administered by nurses. Differences in the irAEs reports between CTCAE and PRO-CTCAE and between patients treated in adjuvant and metastatic setting were statistically analysed using Fisher's exact test. Statistical significance was defined at a p-value < 0.05.

Results: A total of 100 patients received anti-PD1 or anti-PD1 plus anti-CTLA4 in the monitoring program during the study. In the entire cohort of patients a statistical significant difference has been detected for all the reported toxicity between PRO-CTCAE and clinicians, with more severe grading for the PRO-CTCAE, except for skin toxicity, pain and diarrhoea (respectively p=0.14; p=0.21; p=0.14). The discrepancies were higher for metastatic cohort of patients.

Conclusions: The recorded differences of irAEs report and grading between clinic visit and PRO-CTCAE support the nursing role in facilitating the completion of the questionnaires and highlight greater involvement of the nurse in the shared decision-making process by virtue of a relationship with the patient more oriented towards the expression of needs that concern all dimensions of the person. This suggests further research ideas for the purposes of effective nursing management of irAEs.

P11

MALNUTRITIONAL SCREENING: DEVELOPMENT AND IMPLEMENTATION OF A NURSING PROTOCOL IN ONCOLOGY UNIT

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Background: Malnutrition in cancer patients is highly prevalent. Previous studies suggested that a poor nutritional status negatively affects patients' response to therapies, increases the incidence of treatment-related side effects and can decrease survival. Based on these data, early identification of patients malnourished or at risk of malnutrition can promote recovery and improve prognosis. In addition, early nutritional intervention is cost effective, as it reduces complication rates and length of hospitalization. Nutritional assessment is the first step of this process, representing the basis for development of an effective intervention plan. Nutritional care is a fundamental aspect of nursing practice, and, in this context, nurses are ideally placed to play an essential role in the early detection and screening of malnutrition in patients with cancer

Material and Methods: In order, to evaluate nutritional status, we employed the following tools when the patients were admitted to our Oncology Unit: Malnutrition Universal Screening Tool and the Edmonton Symptom Assessment System, documenting percentage of weight loss and body mass index from baseline. The screening protocol that we used involves the food intake determination, the measurement of body weight, and its changes as well as body composition, the biochemical nutritional markers, and the physical performance (ECOG Performance Status). Prognostic assessment was performed using the Palliative Prognostic Score.

Results: 98 patients enrolled in our Protocol completed the nutritional screening the average age of study participants was 67.05±13.02, and 44.32% were males. The incidence rate of nutritional risk was 14.8%, and 19.6% of patients were malnourished. At admission, pre-cachexia was present in 29.7% cases, cancer cachexia in 18.3%, and only 6.8% of patients had refractory cachexia. Cancer cachexia was associated with anorexia, vomiting, dysphagia and xerostomia.

Conclusions: Our experience confirmed that the nutritional screening protocol accurately identified at-risk patients, leading to less weight loss and BMI change. Timely and appropriate nutritional interventions require the adoption of routine initial nutritional screening, comprehensive nutritional assessments as needed, and ongoing patients' reassessment. To achieve these goals and considering their role as patient advocate and expert clinician, oncology nurses should be adequately trained to contribute to a comprehensive nutritional assessment.

P12

CATHETER-RELATED LATE COMPLICATIONS IN CANCER PATIENTS DURING AND AFTER THE COVID-19 PANDEMIC: A RETROSPECTIVE STUDY

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Background: Peripherally Inserted Central Catheters and Midlines provide reliable venous access for chemotherapy and supportive care in cancer patients, both in hospital and at home. These devices are inserted by nurse teams with short operative times and low insertion costs. However, their management requires careful surveillance and specialized personnel to minimize late device-related complications. The COVID-19 pandemic, beginning in March 2020, disrupted healthcare, increasing risks for cancer patients. This study aimed to compare the rates of late complications of PICCs and Midlines in cancer patients during and after the COVID-19 pandemic.

Material and Methods: A retrospective observational review was conducted of late complications in adult cancer patients between March 2020, and April 2024 at a Cancer Center in Palermo. The sample was divided in two groups based on the end of the pandemic emergency status: group 1 (March 2020-March 2022) and group 2 (April 2022-April 2024). Patient demographics, cancer site, comorbidities, setting, and complications leading to device removal were collected. Descriptive analyses tailored to the variables studied were conducted. The $\chi 2$ test or Fisher's exact test was used to compare categorical variables. SPSS v.26 was used. The study was approved by the Ethics Committee (PICC00Vr1.30.05.2023).

Results: During the study period, 4104 new catheter placements and 2291 removals were recorded, 550 due to late complications. Of these, 57.1% occurred in female patients, 46.5% had metastases and the mean age was 60.5 (SD±14.3) years. Cancer types included lymphoma (27.7%), digestive cancer (22.2%) and leukemia (16.8%). Most placements (91.1%) were performed in hospital without immediate complications, to administer chemotherapy (94.2%). Significantly higher frequence ($p<0.001$) of late complications was observed in the pandemic (N=404) compared to the post-pandemic period (N=146). Specifically, different rates were found for suspected infection ($p<0.001$), dislodgement ($p=0.007$), and replacement with another device ($p=0.002$).

Conclusions: The high incidence of catheter-related complications during the pandemic was probably due to limited access to outpatient services that hindered surveillance and management of venous accesses by expert health professionals. Careful management of vascular devices is crucial during emergency situations and specific strategies are needed to prevent and manage complications in cancer patients.

P13

AWARENESS AND PERCEPTIONS RELATED TO HAND HYGIENE AMONG CANCER PATIENTS AND HEALTHCARE WORKERS: AN INFECTION CONTROL NURSES SURVEY BASED ON WHO STANDARDIZED TOOLS IN AN ONCOLOGY CENTER

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Background: Healthcare-associated infections (HAIs) affect 1.4 million people worldwide each year. It has been estimated that 20 to 40 percent of HAIs are preventable. HAIs are a serious concern in all healthcare facilities as they may lead to many serious consequences, like prolonged hospitalization, increased mortality and morbidity, and extra costs. Effective hand hygiene (HH) is the primary proven measure known to be effective in reducing the risk of HAIs in all healthcare settings.

Material and Methods: Using a convenient sampling strategy, a cross-sectional survey was conducted among healthcare workers (HCWs) and patients/caregivers/visitors (PTs) to measure knowledge and perception of HH in the Veneto Institute of Oncology IOV - IRCCS during the world hand hygiene day 2024. 52 PTs and 76 HCWs were investigated for a total of 128 questionnaires completed. Visitors and patients who agreed to participate were then given a tablet device where the questionnaire was completed, and the responses were recorded through an online survey development cloud-based software, while for the HCWs the questionnaire was sent by email. Afterwards results were compared.

Results: Of the 128 participating 74% of HCWs and 79% of PTs were females. 34% of HCW have been working for more than 20 years in the healthcare service, 63% had received formal related training. 90% of HCWs respondents

and 92% of PTs consider the impact of a healthcare-associated infection on patient outcome high or very high. 99% (HCWs) and 98% (PTs) considered hand hygiene an effective prevention in this regard.71%,70% and 61% of HCWs participants would think that good hand hygiene matters for their superiors, colleagues and patients, respectively. While for 90% and 86% of patients, hygiene matters for patients and health care workers respectively. Both groups consider the others' HH awareness less than theirs. 100% of PTs perceived hand hygiene as the HC's center priority.

Conclusions: The study shows high awareness of hand hygiene importance among healthcare workers and patients/visitors in preventing healthcare-associated infections. Both groups acknowledge HH's effectiveness, with over 91% seeing significant impact on patient outcomes. Notably, 100% of oncology patients and visitors prioritize HH. These findings underscore the need for ongoing HH education and compliance initiatives in healthcare settings, particularly for high-risk patient groups, to maintain safety and improve outcomes.

P14

DOES THE VANCOMYCIN-RESISTANT ENTEROCOCCUS (VRE) COLONIZATION PREDICT WORSE OUTCOMES IN AUTOLOGOUS STEM CELL TRANSPLANTATION (AUTO-HSCT) RECIPIENTS? A PROSPECTIVE SINGLE CENTRE STUDY

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Background: Although VRE colonization screening through rectal swab is recommended for patients undergoing auto-HSCTs, its clinical impact still remains an open question. The study aimed to investigate the prevalence of VRE colonization and its impact in worse outcomes compared to not colonized patients.

Methods: The study was conducted in a cancer center in Northern Italy and included all patients undergoing auto-HSCT during 2023.The screening of VRE colonized patients was performed by collecting rectal swab samples at admission, weekly and at discharge. The worse outcomes evaluated were: VRE bloodstream infections (BSI) and other BSIs observed during admission period and patient mortality within 100 days after auto-HSCTs.

Results: The study included 48 adult patients who received at least one auto-HSCT over a year-long period. Out of them 27(56.3%) had hematological malignancies (18 lymphomas, 9 multiple myeloma); 21 (43.8%) had germ cell tumors. The mean age was 47.9 (DS ±14,9); 36 patients (75.0%) were males; 34 (70.8%) underwent a single auto-HSCT, whereas 14 (29.2%) received two or more for a total of 72 auto-HSCTs. The VRE colonization prevalence at admission was 19.4%, while 8.3% of the patients were colonized during their hospitalization. Among the 72 transplant receivers, 62.5% had neutropenic fever: its prevalence was 80.0% in colonized and 59.6 % in non-colonized patients. There were 10 cases (13.9%) of BSIs, with laboratory confirmed diagnosis. BSIs were observed in 2 colonized patients (10.0%), and in 8 non-colonized patients (15.4%). No BSIs caused by VRE were observed among colonized patients.

Conclusions: Our results showed no significant increase in post-transplantation complications and mortality in VRE colonized patients, this was in line with findings of previous studies. While the prevalence of BSIs resulted lower compared with data reported in literature (13,8% vs 29%)1, we found lower BSI rate among VRE colonized patients compared to those not colonized (10% Vs 15,4%). However, the lack of correlation between VRE colonization and BSIs observed in this study, should be interpreted with caution because of the small sample size of the population involved in the observation. In conclusion, the VRE colonization may occur during the hospitalization of auto-HSCT recipients, which suggests that active surveillance of VRE MDROs is justified from an antimicrobial stewardship perspective, especially in the setting of such susceptible patients.

P15

SUPPORT EMPOWER STRATEGIES: A SYSTEMATIC REVIEW ON CORRELATION BETWEEN CANCER IMMUNOTHERAPY TOXICITY AND EFFICACY

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Background: The use of immunotherapy for the treatment of cancer has created new toxicities that often cause treatment suspension and impact the patient's quality of life. Immune therapy toxicities (irAEs) can be a guide to treatment response as cited in the literature. The aim of this review is to investigate the correlation between irAEs and immunotherapy efficacy in order to improve the care

management implemented by the nurse and the empowerment strategies.

Materials and Methods: We conducted a systematic review of the literature by consulting the following databases: PubMed, Cochrane Library and using the following keywords: toxicity markers correlation immunotherapy, body markers and immunological toxicity, prognostic toxicity and immunotherapy, immune-related adverse events. The correlation between toxicity and efficacy was assessed according to all efficacy endpoints and independently by two authors. We included articles written in Italian or English in the last 5 years and excluded studies that examined chemotherapy toxicity.To prepare the review, the following PICO question was formulated as recommended by the Cochrane Collaboration: (P) Patients being treated with immunotherapy, (I) who develop toxicity during treatment, (C) compared to patients who do not develop toxicity, (O)comparing therapy responsiveness.

Results: We found 460 articles of which 32 were potentially eligible, but only 25 articles met the inclusion criteria. The most analyzed toxicities were: colitis, pneumonia, dermatological, endocrine. Although 19 articles support the hypothesis that there is a correlation between toxicity and the efficacy of immunotherapy, there are 4 conflicting studies and 2 studies in which the correlation changes with the type and degree of toxicity. Furthermore, only in a few studies has the correlation with the degree of toxicity and the onset times been demonstrated. All studies analyzed are retrospective except one review and two meta-analyses.

Conclusions: There are conflicting data about the relationship between toxicity and the antitumor efficacy of immunotherapy. It is necessary to investigate further with studies with better statistical, sampling and prospective value, taking into account confounding factors such as: duration of response, interruption of treatment, different degrees of toxicity, use of cortisone. The results of this review should serve nurses as a tool to improve patient and caregiver coping strategies for immunological treatments.

P16

"MA CHE NE SAI TU DEL CANCRO?" YOUNG PEOPLE AT WORK FOR THEIR FUTURE: BETTING ON LIFE SKILLS TO BUILD HEALTHY LIFESTYLES

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Background:The period of adolescence is characterized by deep biological, psychological and social transformations due to which the adolescent may expose themselves to behavior that puts their future health at risk. It is a crucial time for identity construction and lifestyle choices that can influence long-term health. In this context, schools play a key role not only in education but also in educating students to make informed choices about their health.The S.C. of Oncology of the P.O. San Giovanni Bosco and the S.C. Corporate Psychology of the ASL City of Turin have conduct a Prevention Project in Oncology, involving students and teachers from 9 classes of secondary schools. The objective was to promote critical thinking on health-related issues, increasing knowledge on the subject and promoting awareness and the adoption of healthy lifestyles.

Material and methods:The project included 4 meetings for a total of 20 hours, with professionals in the field of oncology, collaborating with 150 students and teachers from the last years of high school in order to carry out a campaign to promote lifestyle change in adolescence. During the meetings students were provided with informations about cancer and cancer care, modifiable risk factors and risks of misinformation. Also, they were equipped with skills in making and editing the products by an expert in communication. Finally, they were offered support in their mental functions, in the process of designing and making the materials, thanks to the accompaniment of psychologists, to protect, not only the regulation of emotions aroused by the topic, but also to promote their mentalization skills.

Results: The results highlight the importance of actively involving adolescents in health promotion. In the experience of working in groups, students' problem solving, decision making, leadership, conflict management and cooperation skills were positively solicited. Young people become key players in their own prevention, but they can also influence family members, the community and health institutions.

Conclusions: Health promotion and cancer prevention among adolescents requires a multidisciplinary approach involving both students and adults. Schools play a key role in this process: through an active collaboration, it is possible to build healthy and resilient lifestyles and ability to cope with future challenges, promoting the potential of autonomous development

P17

TITLE: "NUTRITION, LIFESTYLES, EMOTIONS AND RELATIONSHIPS WITHIN ONCOLOGIC TREATMENT": A GROUP INTERVENTION FOR CANCER PATIENTS AND THEIR CAREGIVERS

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Background: Cancer experience can cause a significant impact on the somatopsychic balance of patients and their caregivers. Patients can suffer from physical symptoms connected to the disease, side effects caused by therapies, psychological and interpersonal problems. Furthermore, they can show nutritional issues, body-image distress and report financial toxicity. As a result, patients and their carers can experience feelings of loneliness and isolation, reducing their possibility to benefit from social engagement.

Material (patients) and Methods: From 2010 to 2019 monthly group sessions were addressed to cancer patients and caregivers at San Giovanni Bosco Hospital (Turin) in order to offer a place for sharing and discussing symptoms, side-effects, nutritional problems and their emotional and relational implications. These sessions last an hour and a half, are free access and are conducted by a psychologist, a dietician and a nurse. After a break caused by Covid-19, the meetings were restored in January 2024, when a social worker was introduced within the group to answer to participants' social and financial needs.

Results: In the early phases of each session participants usually question the group about physical symptoms, nutritional and financial problems, opening the way to a wider reflection on the alterations connected to the disease and the related feelings of loss, incomprehension and loneliness. The exchange of thought is moderated and complemented by health workers' interventions, which foster the possibility to draw on individual and interpersonal resources useful to deal with emerging problems. Throughout the session it becomes possible to observe the transformation of narratives and images named by participants, as potential qualitative markers signaling the changes in the emotional atmosphere and the "digestive" process of group, intended as the possibility to elaborate and soothe intense emotions.

Conclusions: The described intervention promotes several therapeutic factors, such as supporting social engagement and answering to patients and caregivers' need for recognition and participation, namely the desire to share their experiences in a community where they can see their emotions reflected. Moreover, health workers can integrate different facets of cancer experience, by providing their technical expertise and encouraging an exchange of views among the participants.

P18

RETROSPECTIVE CORRELATIONAL STUDY BETWEEN PICC CONSTRUCTION MATERIAL AND INCIDENCE OF COMPLICATIONS

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Background: The choice of the material for PICCs, still remains a controversial topic. No clinical work is available that shown significant differences in terms of complications. However, there is a lack of evidence regarding the superiority of one material over the other, but International boards speak in favor of the use of polyurethane PICCs, but the use of silicone PICCs is still widespread. This heterogeneous and diverse landscape dictates the need for further research to identify the material best suited to the needs of cancer patients.

Aim: To evaluate the correlation, between PICC construction materials and the incidence of complications in a sample of patients treated at the Oncology DH northern Italy University Hospital

Materials and Methods: A retrospective survey of the clinical records was carried out in a sample of patients treated at the Oncology DH of a Northern Italy University Hospital All patients with PICCs placed in the period between 01/01/2019 and 31/12/2021 were consecutively included.

Results: Overall, there were no statistically significant differences between complications occurring to catheters, and catheter materials. (OR 1.238 - CI 95% 0.8699÷1.7625 p=0.235). The small number of events that occurred, did not allow analysis of association measures by single complication and, only frequency distributions were processed. The highest percentage of complications occurred in silicone catheters (71%) vs (29%) compared to polyurethane catheters. For all complications, the percentages were overlapping in the two types of materials, while higher percentages of complications were observed in silicone with respect to ruptures (37.91%) vs (6.56%); and thrombosis (27.45%) vs (16.23%).

Conclusions: Although complication rates, vary widely between polyurethane and silicone, 29% and 71% respectively, no statistically significant differences emerged. When delving into individual complications, the materials show their own characteristics. Silicone PICCs presented higher rates of rupture, while polyurethane PICCs presented more accidental dislodgements. Thrombosis and infection occurred to an overlapping degree in the two materials. Interest in the topic remains high and deserving of further studies that specifically investigate variables

P19

CLINICAL CHARACTERISTICS AND RISK FACTORS OF CENTRAL VENOUS CATHETER-RELATED INFECTIONS IN ONCOLOGY PATIENTS: CASE SERIES

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Background: Central venous catheters (CVC) are frequently used in cancer patients. Device-related infections remain a common complication associated with morbidity and mortality. Understanding patient-related risk factors is crucial, yet consensus is lacking. Our study aimed to describe clinical characteristics of patients with solid tumors, experiencing CVC-related infections (CVC-RI).

Methods: A descriptive cross-sectional study was performed on patients with confirmed CVC- RI hospitalized in the oncology department of Santa Maria Hospital of Terni between January 2020 and December 2023. Patient characteristics were analyzed using median and IQR for quantitative variables and absolute frequencies and percentages for qualitative variables. Associations were assessed using Chi-Square and Mann-Whitney tests, with significance set at $p < 0.05$. Analysis was performed using GraphPad Prism software version 8.0.2.

Results: We identified 52 cancer-patients (60% women and 40% men) with median age of 62 years (19-82). The main primary tumors were breast (9/52), lung (7/52), and ovary (6/52). 90% of patients had metastatic disease, 61.5% received active chemotherapy, while only one exhibited neutropenia (neutrophils <1000/mm3). Moreover, 69% of patients had lymphopenia (lymphocytes <1000/mm3) and 25% had concomitant abdominal or chest drains/implants. Gram-positive bacteria were predominantly isolated from blood cultures (74%), while gram-negative bacteria and fungi accounted for 25% and 4%, respectively.

Conclusions: These results highlight clinical features of cancer patients experiencing CVC-RI. Despite the majority undergoing chemotherapy, the low prevalence of neutropenia implies additional infection risk factors. The high rate of metastatic disease and lymphopenia accentuates this population's susceptibility to complications, including CVC-RI. The concurrent presence of abdominal or chest drains in a quarter of patients implies potential infection sources, emphasizing the complex nature of CVC management in cancer patients.

P20

HEALTH LITERACY AND THE NECESSITY PERCEIVED FOR AN ONCOLOGICAL WARD: AN INVESTIGATORY STUDY

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Background: The Tamburi district of Taranto appeared to be characterized by the presence of multiple environmental risk factors, like the extent of emissions from the steel plant. The chemical-physical and toxicological properties of the compounds maintaining high attention to the risks attributable to them. Therefore, identifying that ward as "major at risk" for cancer diseases, it was equally curious to understand how individuals knew the neoplastic pathology and how they perceived the need for having an oncology department in their country. Aim: To investigate if in the Taranto zone there was an increased health literacy level or not on cancer disease. Specifically, whether health literacy differed significantly based on the level of perception about how necessary it was to have an oncology department in the hospital of one's work.

Methods: An "ad hoc" questionnaire was created and spread online among individuals living in Taranto, near the "Tamburi" context. Ten items were proposed to better assess knowledge on cancer among participants and another item to assess their perceived levels on their necessity to have an oncology ward in their in their town, given the documented risk of cancer incidence in that territory. For the ten items proposed, only one item was the right answer. Another item was proposed to assess participants' necessity to have an oncology ward in the hospital located in the Taranto city by giving 4 Likert scale answers, as: a little, quite a lot, very much. Chi square tests were performed to assess any differences between the necessity perceived to have an oncology ward in the hospital of Taranto and the knowledge owned on cancer disease in general.

Results: A total of 419 Taranto citizens were enrolled. Nonsignificant differences were recorded between cancer knowledge and the necessity perceived on an oncology ward in the Taranto city.

Conclusions: Cancer literacy, while above average, did not justify the perceived need for an oncology department in the Taranto Hospital. Surely, future studies will investigate the causes of such lack of need for citizens.

P21

NURSE-PATIENT RELATIONSHIPS AND ADVOCACY IN ONCOLOGY NURSING: AN EXPLORATORY STUDY

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Background: Nurses also represent patients' guardians, social workers and healthcare professionals who do everything in hospitals to reach the benefit of their patients. When patients meet any difficulties, nurses act as their advocate. Patient advocacy has been perceived an important issue of the nursing profession to face up patients' requirements to evaluate nursing interventions for providing high-quality levels of specialized care. The present study aims the existence of any associations between oncology nursing advocacy and nurse-patient relationships.

Methods: A cohort, cross-sectional study was carried out. An on-line questionnaire was spread to Italian oncology nurses to explore advocacy and nurse-patient relationship dimensions among Italian oncology nurses. Pearson correlations were performed between the four dimensions of the nurse-patients' relationship assessments, like: clinical, relational, humanistic and comforting care dimensions and the two sub dimensions of nursing advocacy, such as: the cognitive believe and the behavior efficacy dimension.

Results: Pearson correlations were performed and positive and significant correlation was assessed between the cognitive believe dimension of advocacy and the relational care one. As regards the behavior efficacy dimension, positive and significant associations were recorded with the clinical care ($p=0.024$), the relational care ($p=0.040$) and the humanistic one ($p=0.010$).

Conclusions: Certainly both the nursing advocacy and the nurse-patient relationship are two pillars of nursing care. Understanding how the advocacy attitude can interact with the concept of the nurse-patient relationship and how specifically all these advocacy sub dimensions, namely cognitive believe and behavior efficacy can interact between them allows us to understand what the weaknesses level of such interactions may be in trying to bridge the gaps of both attitude and efficacy in clinical nursing practice.

P22

THE INFORMATION PATH OF THE SURGICAL ONCOLOGY PATIENT BETWEEN REALITY AND EXPECTATION: AN OBSERVATIONAL STUDY ON THE QUALITY OF INFORMATION RECEIVED

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Background: In the oncology field, healthcare professionals provide patients who have to undergo surgery with information relating to the different phases of the process that awaits them: but do these notions manage to fully satisfy the patient's information needs or do they end up, rather, generate further uncertainty or doubt?

Scope: The aim is to evaluate the degree of patient satisfaction regarding the information on the surgical therapeutic process provided by the specialists. In particular, the quality, appropriateness and effectiveness of the relevant information path are estimated.

Materials and methods:To achieve the objectives of the study covered by the thesis, it was deemed appropriate to administer a questionnaire to cancer patients treated through surgery and belonging to the IOV clinics in Padua and Castelfranco Veneto. Since there are no questionnaires in the literature investigating the degree of satisfaction of the cancer patient with the information received, an ad hoc one was created by extrapolating and adapting some questions from the EORTC QLQ-INFO25 questionnaire.

Results:180 patients responded to the questionnaire, of which 177 were used. 41.2% of the sample is made up of women undergoing breast surgery. 42% of the subjects sought further information, and of these 22% through additional specialists or specialist websites. 16.3% of the total required the use of a dictionary to answer the questions. Among the various information needs not correctly satisfied, 61.5% of patients rated the information received regarding the need to activate a home nursing care service as "not at all" satisfactory. Overall, 17% considered the information "somewhat" satisfactory and useful.

Conclusions: From the analysis of the questionnaires administered, it emerged that the patient's dissatisfaction with the information path is related to his specific demographic characteristics and that only a minority of patients consider it unsatisfactory. The study could also allow the recognition and implementation of specific behaviors by healthcare professionals aimed at improving the information path.

P23

IMPLEMENTING NURSING CARE PLANS IN AN ELECTRONIC HEALTH RECORDS OF A CANCER CENTRE HOSPITAL USING THE INTERNATIONAL CLASSIFICATION FOR NURSING PRACTICE AND THE COMMON TOXICITY CRITERIA FOR ADVERSE EVENTS. A PILOT STUDY

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Nursing care plans, crucial in nursing practice, track the nursing process and display nursing actions and expected outcomes. Integrating care plans is essential for implementing nursing documentation in electronic health record systems. Standardized nursing terminology in the nursing process improves communication, critical reasoning, and patient safety by providing clear, shared language for patient information. Various standardized terminologies have been used to develop electronic nursing documentation. None of these is specific to our Cancer Center, a research facility in Northern Italy, in which we aimed to implement nursing care plans in the institutional electronic health records. We conducted a pilot study involving a sample ward and its nursing team, using the North American Nursing Diagnosis Association International Nursing Intervention Classification, Nursing Outcomes Classification, and International Classification for Nursing Practice to develop care plan samples. Nurses preferred the latter due to its flexibility but wanted a more accurate way to define patient severity during assessment and outcomes evaluation. They suggested combining the Common Terminology Criteria for Adverse Events with the International Classification for Nursing Practice. This combination has enabled the beginning of context-sensitive electronic care plans development. Our results emphasize the importance of users' involvement in generating electronic health records documentation.

P24

CRYOTHERAPY FOR PREVENTION OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY IN BREAST CANCER WOMEN: LITERATURE REVIEW

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Background: Peripheral neuropathy is a dose-limiting side effect of Taxanes, affecting up to 97% of patients treated with Paclitaxel. Symptoms are localised to the hands and feet and generally manifest as paresthesia, tingling, numbness, pain in the extremities, loss of sensory perception, motor deficits and anatomical dysfunction. Patients may also have considerable difficulty in performing essential daily functions, thus substantially impairing their quality of life. To date, there is no universally recognised effective treatment or protocol, but among the various alternatives treatment, cryotherapy appears to be a strategy worth exploring further. Cryotherapy is based on the principle of hypothermia and uses cold-induced vasoconstriction to limit the local effects of chemotherapy. The hypothesis of this review is that peripheral neuropathy in women being treated for breast cancer could be reduced through the use of cryotherapy.

Aim: The aim of the review is to evaluate the effictiveness of cryotherapy in reducing of Paclitaxel-induced peripheral neuropathy (CIPN) in breast cancer women.

Materials and Methods: A literature review was carried out using data extraction tables on the following databases: Medline (Pubmed), Cinahl, Cochrane and Embase.

Results: The literature review included eight clinical trials with a total of 542 breast cancer women treated with Paclitaxel. 493 patients completed the trials. Five out of eight included studies found that cryotherapy may be useful in reducing of Paclitaxel-related peripheral neuropathy, while three trials were unable to demonstrate the usefulness of this treatment.

Conclusions: Cryotherapy is effective in preventing peripheral neuropathy. In most of the studies reviewed, there was a significant reduction in CIPN-related symptoms as well as their frequency and severity. Nevertheless, there are still many aspects that need to be investigated. Further studies are necessary.

P25

SPECIALIST TRAINING PROJECT: MASTER'S DEGREE IN CANCER NURSING

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Background: In Italy the Masters are provided by Law no 43 of 2Feb2006, which includes for the health professions the possibility to specialize by attending 1year Master's degree.

The importance of nursing competence stems from its central role in influencing and determining care outcomes.

Skills constitute the job desctription of the oncological nurse, quantifying the basic skills and knowledge needed, providing standardized guidance for the expectations and requirements of a role.

Material and Methods: The first step was to identify the areas of competence to respond to professional values and role, decision making, to deepen intervention skills, to increase communication and relational skills, to deepen Leadership skills and manage group dynamics.

Four areas have been identified with its own educational objectives.

1clinical area, 2anthropological and ethical area, 3evaluation and development area, 4management and information processing area.

To develop the objectives, the reference document was the Pedagogical Guide for Health Care Personnel by Guilbert. The Dublin Descriptors have been used to calculate the outcomes to acquire at the end of the course.

Results: The requirements the master must possess are indicated by the Permanent Conference of the degree classes of the Health Professions.
The Master's programme in Medical Oncology will clearly express competence profiles and consistent teaching activities.
Basic courses 14CFU
Specialized courses 22CFU
Workshops, internships 20CF
Final Exam 4CFU
The didactic activities will be structured in 4 modules, as the identified areas:

1. Skills, professional values, role of the health professional
   - *1a.* Skills, care practice, clinical decision making aimed at ensuring quality of life
   - *1b.* Competencies, appropriate use of interventions, activities and skills
2. Communication, interpersonal skills, interprofessional collaboration
3. Skills aimed at professional development and training
   - *3a.* Leadership, management, group dynamics
4. ICT digital infrastructure skills, regulatory aspects, organizational models.

Conclusions: The need to recognize the specificity of the work in oncological settings cannot be delayed. It's no longer time to believe experience is enough, people who fall ill with cancer have the right to have a specialist response from the healthcare personnel.

Breafly, a nursing training based on skills is now necessary to define and verify the requirements each nurse must possess to protect people's health.

Late Breaking Abstracts

LBA01*

*Plenary Session

ELBA02

IMPACT OF A STRATEGY FOR PREVENTING THE TOXICITY OF ONCOLOGICAL THERAPIES OF LOCALLY ADVANCED BREAST CANCER (LABC) IN HIGH AGED WOMEN (HAW): A PILOT STUDY

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Background: Oncologic treatment of HAW with LABC is increasingly necessary due to the progressive extension of this category of patients. Unfortunately, all the oncological therapies adopted so far are linked to strong general toxicity with considerable risks to survival. Treatment decisions for elderly patients together with accurate objective measures in predicting eligibility for combination chemotherapy are greatly needed.

Aim: Objectives of the study are to find the most reliable combination of tests and systems for assessing toxicity due to anti-tumor therapies among those already commonly used in clinical practice, thus being able to immediately identify therapies with less toxicity.

Methods: 24 patients aged 85-95 years with LABC were enrolled with Inclusion criteria as follows: measurable lesions, bone or visceral, no cerebral secondarism, Charlson Comorbidity Index max3pts. All patients signed informed consent and underwent specific tests for predictive assessment of the risk of toxicity chosen from those universally considered most valid: GAIN system (GeriatricAssessment-drivenINtervention); CARG-Ts(CancerAgingResearch Group-TScore-); CRASH-Ts(ChemotherapyRiskAssessmentScaleHigh-aged-peopleTs); CFS (Clinical Frailty Scale).

Results: Using tests reported above and after evaluating the overall results, it was possible to divide the patients into 3 tox risk categories: Low(score 0-5), Medium(score 5-10),

High (score >10). There are therefore 7 pts (score>10), 8(score 5-10), 9 pts (score 0-5). High-risk patients were started endocrine therapy alone (if Er-PGr+) or RT alone with DFC(if Er-PGr neg). Those at medium risk endocrine therapy+RT if permitting conditions. Finally, low-risk patients underwent oral or infusion chemotherapy with a single agent according to a modified protocol with dose reduction according to the assessment of creatinine clearance(Kintzel-Dorr's formula).

Conclusions: No group discontinued treatment for grade 4 toxicity.Non-hematologic tox(grade 3) only in RT subgroup resolved with appropriate therapy. QoL was fair, especially in pts in good nutritional status in post-therapy .Initial signs of cachexia, fatigue, prefrail conditions, signs of worsening of aging parameters(see Eortc Cax24/Fa12 forms/CFS/(Eld14) were evaluated. Slight worsening of Fa12 in the high/medium risk group. These first findings are encouraging. Further increase in the recruitment of these patients is certainly necessary. So far a monitoring of non-occurrence of late-toxicity forms is ongoing.

ELBA03

THE OPTIMAL EARLY BREAST CANCER PATIENT JOURNEY: THE EXPERTS OPINION

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Background: Immunotherapy is modifying the disease history in many tumors, including early triple-negative breast cancer, in which the combination of pembrolizumab and chemotherapy has been shown to reduce the risk of inoperable local recurrence, distant recurrence or death by 37%. Ensuring timely management, correct diagnosis and early treatment are of fundamental importance in these patients. In Italy the healthcare organization is still uneven and not all regions have created an oncology network or formalized specific PDTAs. The objective of this project is to define a shared operational model for the management of cancer patients, with a focus on early breast cancer.

Materials and Methods: In the first phase, the opinions of 11 KOLs, expert in the treatment of breast cancer, were collected in order to gather the current scenario of value-based healthcare in the field of immuno-oncology, with a focus on breast cancer. In the second phase, the data collected were discussed in a virtual Expert Meeting that involved different stakeholders across the patient journey of breast cancer management. After identifying convergences and divergences, the indications for implementing a shared operational model were formulated.

Results: The actions to be undertaken to guarantee access to therapies and the indicators (KPIs) necessary to evaluate their appropriateness have been identified. The actions identified are: the adoption of a specific PDTA which includes the possibility of carrying out genetic markers at diagnosis and of being taken in charge in centers where there is a dedicated multidisciplinary team (MDT); the creation of a network between regional breast units to share best practices; and the inclusion within the PDTA of KPIs for the evaluation of the appropriateness and clinical effectiveness of innovative therapies.

The KPIs that were proposed by the Experts are: the percentages of timely diagnoses performed by histological examination and of cases discussed by the MDT; the correct staging of the tumor; waiting times for starting treatment; the percentage of treatments performed in accordance with guidelines and the time between surgery and adjuvant treatment.

Conclusions: For breast cancer patients, every day of treatment delay impacts survival. Shared actions are therefore necessary to guarantee timely and equitable access to therapeutic innovations through the definition of shared operational models.

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QUALITATIVE PILOT STUDY ON PATIENT PERCEPTION WITHIN A CLINICAL TRIAL: THE ROLE OF THE CLINICAL RESEARCH NURSE

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Background: Clinical Research Nurses (CRNs) are nurses specialized in providing nursing care to patients participating in any phase of a clinical study. CRNs oversee participant recruitment, screening, ensuring comprehension of

the study's nature and obtaining informed consent. They manage randomization, data collection, recording, and participant follow-up. At Istituto Nazionale dei Tumori of Milan (INT) CRNs are involved in training colleagues on ongoing study protocols and promote nursing research studies. In the last years, the need for CRNs has grown due to the increasing number of clinical trials. The involvement of CRNs in research teams has been associated with better quality conduct of clinical studies, improved communication between clinical staff and participants, and better patient compliance with protocols. Unfortunately, no feedback from patients regarding the work of CRNs is evident from the literature.

Material and Methods: The qualitative pilot study enrolled 15 patient with gastrointestinal cancer who were divided into 3 arms with purposive sampling.

A) 5 patients enrolled in clinical trials with CRNs presence at the time of the interview.

B) 5 patients who have completed their participation in a clinical trial with CRNs presence before the time of the interview.

C) 5 patients never enrolled in clinical trials.

Each study arm underwent a One-to-one oral semi-structured interview. Each interview lasted 20 minutes. The qualitative research methodology follows the Consolidated Criteria For Reporting Qualitative Research (COREQ). The interviews were analyzed using Bottom-Up content analysis.

Results: The interviews conducted with the selected sample, patients with colorectal and stomach conditions in a 2:1 ratio, with age M=58, underscore the pivotal role of CRNs in clinical research, where they manage both technical and organizational aspects of patient care, while also providing crucial emotional and psychological support, alleviating anxieties and concerns related to the illness. Patients highly value the consistent, personal presence of CRNs, especially during therapy. Although there are challenges in hospital organization, patients appreciate and trust the commitment of CRNs and medical staff in delivering high-quality care.

Conclusions: The CRNs emerge as a fundamental figure in the care pathway, combining technical expertise with human support, offering a reassuring presence and personalized care that strengthens patient trust and psychological well-being.

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