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Plenary Session

01*

MODIFIED FOLFOXIRI PLUS PANITUMUMAB (MFOLFOXIRI/PAN) VERSUS MFOLFOX6/PAN AS INITIAL TREATMENT OF UNRESECTABLE RAS/BRAF WILD-TYPE METASTATIC COLORECTAL CANCER (MCRC) PATIENTS: RESULTS OF THE PHASE III RANDOMIZED TRIPLETE STUDY BY GONO

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Background: The association of a chemotherapy doublet (FOLFOX/FOLFIRI) with an anti-EGFR monoclonal antibody (cetuximab or panitumumab) is an upfront option for the treatment of *RAS* and *BRAF* wt mCRC patients. Phase II studies investigating FOLFOXIRI with an anti-EGFR reported promising activity results and an acceptable safety profile with lower doses of 5FU and irinotecan. The added value of intensifying the upfront chemotherapy when combined with a targeted agent in a molecularly selected population is not established.

Methods: TRIPLETE is a prospective, open label, phase III trial in which untreated patients with unresectable *RAS* and *BRAF* wt mCRC were randomized to receive mFOLFOX6/pan (arm A) or mFOLFOXIRI (irinotecan 150 mg/sqm, oxaliplatin 85 mg/sqm, L-leucovorin 200 mg/sqm, 5-fluoruracil 2400 mg/sqm 48 h infusion)/pan (arm B) up to 12 cycles, followed by 5FU/LV/pan until disease progression. The primary endpoint is ORR. Secondary endpoints include safety profile, R0 resection rate, PFS and OS. Under the assumption of an ORR of 60% in arm A, to detect a $\geqslant$ 15% increase in arm B, a sample size of 432 cases provided approximately 90% power to a two-sided χ^2 test for heterogeneity at the 0.05 significance level. Clinical trial info: NCT03231722

Results: 435 pts were enrolled (arm A/B: 217/218) in 67 Italian sites. Main pts' characteristics were (arm A/B): median age 59/59, ECOG PS 0 80%/84%, left-sided 88%/88%, synchronous metastases 88%/87%, prior adjuvant 2%/6%, resected primary 43%/51%, liver-only 37%/39%. Main grade $>$ 2 adverse events were diarrhoea 7%/23%, stomatitis 7%/7%, neutropenia 20%/32%, febrile neutropenia 3%/6%, fatigue 2%/7%, skin rash 29%/19%. 160 (73%) out of 218 patients in arm B and 165 (76%) out of 217 patients in arm A achieved RECIST response (OR 0.87, 95%CI 0.56-1.34, p=0.526). No differences in early tumor shrinkage (arm A/B 58%/57%, p=0.878) and deepness of response (median arm A/B: 47%/48%, p=0.845) were reported, nor in R0 resection rate (arm A/B 29%/25%, p=0.317). At a median follow up of 26.5 mos, 305 (arm A/B: 157/148) PFS events were collected, with no significant difference between arms (median PFS: 12.7 vs 12.3 months, HR: 0.88, 95%CI 0.70-1.11, p=0.277).

Conclusions: The intensification of the upfront chemotherapy backbone in combination with panitumumab in molecularly selected and mostly (88%) left-sided mCRC patients does not provide any benefit in terms of treatment

activity at the price of a non-negligible increase in gastrointestinal toxicity.

02*

FIRST LINE AVELUMAB IN PD-L1+VE METASTATIC OR LOCALLY ADVANCED UROTHELIAL CANCER (AUC) PATIENTS UNFIT FOR CISPLATIN (CIS): THE ARIES TRIAL

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Background: Avelumab (ave) was approved as maintenance therapy after platinum-based first line (1L) therapy for patients (pts) with aUC based on ph. 3 Javelin Bladder 100 study (NCT02603432), showing significant overall survival (OS) improvement. Here we tested the activity of ave as 1L of therapy in pts with aUC and PD-L1+ve expression.

Methods: ARIES is a single-arm, multi-site, open-label phase II trial. Enrolled pts had aUC, were cis-unfit (at least one of: ECOG-PS=2, CrCl <60 mL/min, grade ⩾2 peripheral neuropathy/hearing loss, progression within 6-mos before the end of neo/adj chemo), had not previously received chemo for aUC and PD-L1⩾5% (SP263) centrally assessed. Pts received ave 10 mg/Kg IV Q2W until progression, unacceptable toxicity and withdrawal, whichever occurred first. The primary endpoint was the 1-year OS. Key secondary endpoints were median-OS, -PFS, ORR, DOR and safety. The outcome based on PDL1 expression >10 has also been investigated.

Results: A total of 198 eligible cis-unfit pts have been tested for PD-L1 and 71 (35.6%) have been found positive. Among enrolled patients (N=71), median age was 75 y, 35 (49.3%) had visceral disease, and 22 (31.0%) had ECOG-PS=2; 50 (70.4%) had CrCl <60 mL/min and 9 (12.7%) progressed within 6-mos from the end of neo/adj chemo. At the cut-off data (Feb 2, 2022), median follow up was 10.0 mos and 14 patients are still on treatment. The median OS was 10.0 mos (95% CI, 5.5-14.5), and 43.0% of patients were alive at 1-year. The ORR for all patients was 24.0%; complete response, 8.5% (n=6); partial response, 15.5% (n=11). Clinical benefit was 43.6% (n=31). Median PFS was 2.0 mos (95% CI, 1.7-2.3). Among the 17 pts who had tumour response 13 had DOR > 1y and 5 > 2y. A total of 67 patients have been evaluated for CPS and among these 56 (83.6%) have been classified as high expression. The median OS was 11.0 mos (95%CI, 0.1 – 22.9) for those with high CPS and 7.0 mos (95%CI 2.8 – 11.2) for low CPS (p=0.13). The median PFS was 2.0 mos for both high and low CPS (p=0.34). Five (7.0%) grade 3 ave-related adverse events, and no treatment-related death were reported.

Conclusions: Ave is active and safe in pts with cis-unfit, PD-L1+ve aUC and poor baseline characteristics.

03*

THE HOBOE MULTICENTER RANDOMIZED PHASE 3 TRIAL IN PREMENOPAUSAL PATIENTS (PTS) WITH HORMONE-RECEPTOR POSITIVE EARLY BREAST CANCER (EBC) COMPARING TRIPTORELIN PLUS EITHER TAMOXIFEN (T) OR LETROZOLE (L) OR ZOLEDRONIC ACID + LETROZOLE (ZL): 8YR EFFICACY ANALYSIS

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Background: At 5yr analysis HOBOE showed that in premenopausal EBC pts receiving triptorelin, ZL combination was better than T in terms of DFS, with worse compliance. Subsequently, a EBCTCG metanalysis, including HOBOE data, has shown that aromatase inhibitors slightly reduce risk of recurrence with no effect on mortality.

Patients and Methods: Women operated for an ER/PgR positive EBC with last menses within 1 year from randomization were eligible. Previous adjuvant and/or neoadjuvant chemo was allowed. Triptorelin 3.75 mg every 4 weeks for 5 years or up to the age of 55 was given to all patients. Pts were randomly assigned 1:1:1 to (T) tamoxifen 20 mg/die, (L) letrozole 2.5 mg/die or (ZL) zoledronic acid 4mg iv every 6 months + letrozole 2.5 mg/die. Primary end-point was disease-free survival (DFS) including locoregional or distant recurrence, second breast or non-breast invasive cancer and death without cancer as event. Analyses were based on intention to treatment. Pairwise comparisons with Bonferroni-Holm correction were allowed if the overall log-rank test was statistically significant.

Results: From March 2004 to August 2015, 1065 pts were randomized (T: 354, L:356, ZL: 355). Median age was 45. 67.7% had a pT1 tumor, 54.7% had negative axillary nodes and 62.6% had received chemo. After 8.6 years median follow-up, there were 81, 57, and 47 DFS events and 8yr DFS probability was 0.78, 0.86 and 0.90 in the T, L and ZL arms, respectively (overall Log-rank test P=0.001). Two pairwise comparisons were statistically significant: ZL vs T (HR 0.54, 95% CI 0.38-0.78, P<0.0007) and L vs T (HR 0.64, 95% CI 0.46-0.90, P=0.009); the ZL vs L comparison showed no statistically significant difference (HR 0.84, 95% CI 0.57-1.24, P=0.38). A statistically significant interaction was found between treatment and HER2 expression in the ZL vs T comparison: the HR was 0.41 (95% CI 0.27-0.61) in HER2-negative pts and 1.84 (95% CI 0.60-5.66) among those HER2-postive (P for interaction = 0.005). There was no interaction between treatment and body mass index. Overall, 72 deaths were reported (30 with T, 22 with L, 20 with ZL). No statistically significant difference was evident in overall survival analysis (overall Log-rank test P=0.25).

Conclusions: At 8yr update HOBOE shows that, in premenopausal EBC pts, both the ZL+triptorelin and L+triptorelin combination are more effective than T+triptorelin in terms of DFS.

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A - Thoracic Cancers

A01*

REAL-WORLD OUTCOMES OF PATIENTS WITH ADVANCED LUNG ADENOCARCINOMA TREATED WITH FIRST-LINE CHEMO-IMMUNOTHERAPY IN ITALY

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Introduction: The combination of chemo-immunotherapy (CT-IT) with cis/carboplatin, pemetrexed and pembrolizumab is the current standard of care as first-line (1L) treatment for patients with advanced lung adenocarcinoma (LUAC), according to KEYNOTE-189 study. Real data on efficacy and safety of combo therapy are still limited. Our study sought to evaluate the real-world clinical outcomes of CT-IT in this setting of patients in Italy.

Methods: This is a retrospective-prospective study including patients diagnosed with advanced LUAC who received 1L CT-IT from September 4th, 2018 in 42 Italian Centers.

Results: 642 patients were enrolled at the time of data cut-off (January 31st, 2022). Median age was 66 years (Range, 27-85). The majority of patients was men (64.2%) and current or former smokers (85.6%). ECOG-PS was 0/1 in 581 patients (90.5%), and 2 in 55 patients (8.4%); 280 patients (43.6%) had more than three metastatic sites. A PD-L1 tumor proportion score (TPS) of 1% or greater was reported in 44.7% of the patients. Among these, PD-L1 TPS was ⩾ 50% in 29/642 patients (4.5%). KRAS mutation was the most frequent molecular alteration in the study population (37.1%). Median treatment duration was 7.6 months (95% Confidence Interval [CI], 6.7–8.6). 447 (69.6%) patients completed the induction phase with all three drugs; 451 (70.3%) patients started the maintenance phase. Overall response rate (ORR) was 42.7% (95% CI, 39.6–51.7) in the overall population. ORR was 39.7% (95% CI, 34.2–45.3) in PD-L1 < 1%, 45.7% (95% CI, 39.5–52.0) in PD-L1 1–49% and 34.5% (95% CI, 17.9–54.3) in PD-L1 ⩾ 50%, respectively. 269 (41.9%) patients experienced progression of disease (PD) and the most frequent site of PD was lung (25.9%). After a median follow-up for surviving patients of 10.2 months (95% CI, 9.1–11.5), median progression-free survival was 10.1 months (95% CI, 8.7–11.5) and median overall survival was 15.2 months (95% CI, 13.4–20.4). 246 (38.3%) patients discontinued one or more drugs. The most frequently discontinued drug was pemetrexed (n=218, 33.9%), and the most common reason for pemetrexed discontinuation was toxicity (n=99, 15.4%). Adverse events (AE) of grade 3 (G3) or

higher occurred in 85 (13.2%) patients and most common ⩾ G3 AE was neutropenia (8.2%).

Conclusions: Our findings support the effectiveness and safety of 1L CT-IT in advanced LUAC patients. Our results were in line with the KEYNOTE-189 registration study.

A02*

IMPACT OF TP53 MUTATIONS IN ROS1 POSITIVE NSCLC RECEIVING LORLATINIB: FINAL RESULTS OF THE PFROST TRIAL

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Introduction: Lorlatinib demonstrated activity in crizotinib-refractory ROS1+ NSCLC, especially in absence of acquired ROS1 mutations. Other molecular events affecting sensitivity to lorlatinib are under investigation. In the prospective PFROST trial evaluating lorlatinib at crizotinib failure, response rate (RR) exceeded 40%, median progression-free survival (PFS) was 8.9 months and median overall survival (0S) was not reached. Here, we present final results of the trial focusing on the role of molecular events in modulating activity of lorlatinib.

Methods: In the PFROST trial, tissue or plasma samples collected at baseline and at lorlatinib failure were analysed using NEOSelect and NEOliquid, two NGS assays covering 39 cancer-related genes. All patients received lorlatinib 100 mg once daily orally until disease progression, unacceptable toxicity or patient refusal to continue. Clinical outcomes were analysed according to molecular characteristics, long-term survival and impact of brain metastases (BM).

Results: With a median follow-up of 36.0 months (data cut-off February 2022), in the whole population (N=22) median PFS and OS were 8.9 months (95% CI: 2.2-15.6) and 30.4 months (95% CI: 10.6-50.2). Among patients with baseline BM (N=15), median PFS and OS were 8.5 months (95% CI: 4.3-12.7) and 30.4 months (95% CI: 0-62.4), while in patients without BM (N=7), median PFS and OS were 12.6 months (95% CI: 0-41.9) and 34.2 months (95% CI: 13.6-54.8). At lorlatinib failure, patients with BM progressed mainly outside the brain. AII but one patient had baseline tissue or plasma samples for NGS analyses. Mutations in TP53 gene were detected in 11 (52.3%) patients, including 4 cases who harbour a concomitant ROS1 mutation (N=2, G2032R; N=1, V2054A; N=1, S1861I). ROS1+/TP53+ co-mutated patients were mainly females (54.5%), never smokers (54.5%), with median age of 57 years and PS of 1 (63.6%). In this subgroup, RR was 27.3%, median PFS was 8.5 months (95% CI: 0.8-16.2) and median OS was 14.6 months (95% CI: 0-31.1), while in ROS1+/TP53- patients, RR was 50%, median PFS was 26.3 months (HR: 2.30, 95% CI: 0.78-6.75) and median OS was 30.7 months (HR: 2.75, 95% CI: 0.84-8.96).

Conclusions: In the PFROST study, presence of TP53 mutations identified a subset of ROS1+ individuals at high risk of progression and death for which more potent and aggressive strategies are needed.

A03*

CABINMET: CABOZANTINIB IN MET DEREGULATED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: *MET*-deregulated NSCLC represents an urgent clinical need because of unfavorable prognosis and lack of specific approved therapies. Clinical data suggested a potential activity of cabozantinib, a multi-target tyrosin-kinase inhibitor (anti-MET and anti-VEGF) in

patients harboring *MET* amplification or exon 14 skipping mutation, including individuals pretreated with crizotinib or with brain metastasis. The CABinMET study aimed at investigating activity of cabozantinib, in patients harboring *MET* alterations.

Material (patients) and Methods: Patients with pretreated advanced NSCLC and evidence of a *MET* deregulation where centrally tested for amplification in FISH (ratio *MET/CEP7* >2.2) or locally tested for *MET* exon 14 skipping mutation in PcR. Patients were treated with cabozantinib 60 mg/daily orally and analyzed in two separate cohorts (mutated and amplified). The primary endpoint was objective response.

Results: From September 2018 until now, 43 patients were screened in 21 active centers across Italy and a total of 18 patients (10 in cohort A - *MET* mutant and 8 in cohort B - *MET* amplified) were enrolled onto the study. Median age in cohort A was 74 years (61-79) with prevalence of female patients (60%). Among patients included in cohort A, 9 patients had classic exon 14 skipping mutation, while 1 patient had activating intron 14 mutation (C.3082+3A>G). According to statistical design, cohort A was early closed for no evidence of at least 2 responses in the first 10 patients included. No patients are still on treatment into this cohort, 2 patients discontinued study treatment for toxicity, 3 for death and 5 for progression. Median PFS and OS were 3.6 months (95% CI: 1.8-5.4) and 4.8 months (95% CI: 0.7-9.0), respectively. Cohort B has enrolled 8 patients, mostly man (90%) and is currently open to recruit. No unexpected toxicity was observed in both cohorts.

Conclusions: Cabozantinib has lack of efficacy in *MET* mutant NSCLC. *MET* amplified cohort is still recruiting.

A04*

MOLECULAR PREDICTORS OF IMMUNOTHERAPY EFFICACY IN LUNG SQUAMOUS-CELL CARCINOMA (LSCC): RESULTS FROM THE RANDOMIZED PROSPECTIVE SQUINT TRIAL

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Background: Immunotherapy as single agent or in combination is the standard of care for metastatic non-small-cell lung cancer (NSCLC), including LSCC. The randomized, prospective, phase II SQUINT trial was designed to assesses the efficacy of nivolumab plus investigator-choice platinum-based chemotherapy (N-CT) versus the combination of nivolumab and ipilimumab (NI) in patients with advanced/metastatic LSCC.

Material and methods: All eligible patients were randomly assigned to either NI (Arm A) or N-CT (Arm B). Nivolumab at the dose of 360 mg was administered every 3 weeks in combination with ipilimumab at the dose of 1 mg/kg every 6 weeks or investigator's choice platinum doublet (Arm B). The primary endpoint was overall survival (OS) at 12 months. Availability of an adequate tumor tissue obtained before trial enrolment was mandatory. Comprehensive genomic profiling of tumor samples was analyzed using the Vela Diagnostics' OncoKey SL 525 Plus Panel. This next-generation sequencing (NGS) assay covers 525 cancer-related genes and can also be used to assess pathogenic single-nucleotide variants (SNV) and multiple-nucleotide variants, gene fusions, splice variants, copy number variants (CNVs), MSI, TMB, and ten oncogenic pathogens.

Results: From September 2017 to February 2022, a total of 91 patients were enrolled in the study, including 45 subjects assigned to NI and 46 to N-CT. With a median follow-up of 18 months, 1-year OS rate was 59.4% with NI and 56.7% with N-CT. Median OS and median PFS were 14.7 and 3.8 months in the NI arm and 12.9 and 6.3 months in the N-CT arm. Response rate was 24.4% with NI and 34.8% with N-CT. In the NI arm median OS was 13.9, not reached and 16.3 months in PD-L1 negative, PD-L1 low and PD-L1 high, respectively. In the N-CT arm median OS was 12.1, 13.8 and 11.7 months in PD-L1 negative, PD-L1 low and PD-L1 high, respectively. Biomarker analyses are ongoing and results are pending at the time of this analysis.

Conclusions: Results of the SQUINT trial showed no difference between NI and N-CT for any clinical end-point. Correlative biomarker analyses will be presented at the meeting.

A05*

EFFICACY, SAFETY AND BRAIN METASTASES CONTROL OF FIRST-LINE TREATMENT STRATEGIES FOR ANAPLASTIC LYMPHOMA KINASE-POSITIVE NON-SMALL CELL LUNG CANCER: A NETWORK META-ANALYSIS

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Background: In recent years, several inhibitors were introduced for ALK-positive NSCLC patients. Most of them have been compared with crizotinib but head-to-head comparisons among the others are lacking. Here, we systematically reviewed literature and performed a network meta-analysis of first-line systemic therapeutic options used for the treatment of ALK-rearranged NSCLC.

Methods: We searched randomized controlled trials (RCTs) published in Pubmed, Embase, and Cochrane Library until April 01, 2022. Trials investigating first-line treatments of ALK-rearranged NSCLC were eligible if reported the following outcomes: Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), or adverse events of grade 3 or higher (Grade $\geqslant$ 3 AEs). Subgroup analysis was conducted according to central nervous system (CNS) metastases.

Results: A total of 2443 patients from 9 RCTs were included. Patients received eight different treatments: alectinib (300 mg and 600 mg), brigatinib, ceritinib, crizotinib, ensartinib, lorlatinib, and chemotherapy.

Compared with chemotherapy, TKIs significantly prolonged PFS with lorlatinib followed by alectinib (either, 300 mg and 600 mg) yielded the most favourable PFS (p-score 0.98, 0.78 and 0.77, respectively). Nevertheless, to date, only alectinib significantly prolonged OS compared with chemotherapy. Interestingly, all the TKIs but crizotinib and ceritinib reduced risk of CNS progression. Lorlatinib appears superior at reducing risk of CNS progression (p-score 0.98). On the other hand, ceritinib showed the highest rate of AEs followed by lorlatinib and brigatinib (p-score 0.08, 0.12 and 0.24, respectively).

Conclusions: In our network meta-analysis, alectinib and lorlatinib resulted the therapeutics with the highest probability to be the best first-line options for ALK-rearranged NSCLC patients ensuring prolonged disease control.

A06*

ACTIVITY OF OSIMERTINIB IN NSCLC WITH UNCOMMON EGFR MUTATIONS: RETROSPECTIVE OBSERVATIONAL MULTICENTER ITALIAN STUDY (ARTICUNO)

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Background: In 10-20% of patients (pts) with *EGFR* mutated NSCLC, an assorted group of uncommon mutations can be detected. These mutations confer variable sensitivity to 1st and 2nd generation TKIs, overall resulting in lower therapeutic activity. Data of Osimertinib (Osi), a 3rd generation TKI, are limited and strongly warranted.

Methods: This is a retrospective multicenter study of pts with advanced NSCLC with any uncommon *EGFR* alteration and treated with Osi since August 2017. Investigators collected response in terms of overall response rate (ORR) and disease control rate (DCR) by RECIST 1.1 criteria. Survival outcomes were estimated by Kaplan-Meier method.

Results: As of April, 2022, 65 pts were identified in 18 institutions in Italy. Pts characteristics: 62% female, median age 68 (31-87) years, 86% ECOG PS 0-1, 63% smoking history, 92% caucasian, 95% adenocarcinoma. A large group of pts presented compound mutations (37%, N=24) (**Table 1**). In 88% (N=57) Osi was used in TKI-naïve setting and in 80% as first treatment. ORR and DCR were 45% (CI 95%, 32-58%) and 78% (CI 95%, 66-88%) in the evaluable population (N=60), and 49% (CI 95%, 34-64%) and 78% (CI 95%, 63-88%) in TKI-naïve (excluded ins20) cohort (N=49), respectively. With a median follow up of 13 months, mPFS and mDOR in TKI-naïve were 11 months (CI 95%, 7-18) and not reached (CI 95%,11-n.r.), respectively.

Table 1. *EGFR* mutations and outcome in ARTICUNO study.

Major uncommon mutation (single or compound*)	**N (%)**	**ORR%(95%CI) DCR%(95%CI) mPFS(months,95%CI)**
G719X	19 (29)	50 [26-74] 89 [65-99] 11 [5-15]
L861X	15 (23)	50 [23-77] 86 [57-98] 9 [5-14]
S768I	11 (17)	55 [23-83] 91 [59-100] 17 [7-24]
OTHERS (minor mutations or Ins20)	**27 (42)**	**Best Response**
L858R+dnT790M (N=2), L833V+L858R, Del19+L747Q, I740_K745dup, V738_I744ins, EGFR-KDD, D770_N771insSVD	8 (12)	CR/PR
V738_A743del, Del19+A750P, Del19+S751V, Del19+P753S+aqT790M, Del19+L858R, V769_D770insASV, A767_V769dup	7 (11)	SD
Y801C, R831C, A702S, V765M, A702_K728del, G709T, E709_T710delinsD (N=2), D770_N771insSVD, A767_V769dup	10 (15)	PD
E868Q, V769_D770insASV	2 (3)	NE

*Regrouped and re-counted for each major uncommon mutation.

Conclusions: In this widest known dataset, major uncommon mutations were the most frequent, largely occurring as compound. Notably, one third of our cases presented heterogeneous minor uncommon mutations. Osimertinib showed relevant activity, overall comparable with data of Afatinib and Osi in a Korean trial. ARTICUNO study is still ongoing and more data will be presented.

A07

DURABILITY OF EFFICACY WITH SELPERCATINIB IN PATIENTS (PTS) WITH RET FUSION+ NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: Selpercatinib, a first-in-class highly selective and potent CNS-active RET kinase inhibitor, is approved in multiple countries for treatment of *RET* fusion+ NSCLC. In prior reports, follow-up was limited and duration of response (DoR) and progression-free survival (PFS) were ongoing and immature.

Patients and methods: Updated analysis of selpercatinib in pts with *RET* fusion+ NSCLC in LIBRETTO-001 (NCT03157128) was conducted with a 15-month (mo) interval between the preceding and current analyses. Primary endpoint was objective response rate (ORR, RECIST 1.1) by independent review committee (IRC). Secondary endpoints included DoR, PFS, clinical benefit rate (CBR; CR+PR+SD ⩾16 weeks), OS and safety.

Results: Efficacy results from treatment naïve pts (N=69) and pts previously treated with platinum chemotherapy (N=247) are shown (Table). Despite a median follow-up (f/u) of ~24 mo in the treatment naïve and platinum chemotherapy pretreated populations, median DoR (mDoR) and PFS (mPFS) estimates are still not mature. Among all NSCLC pts, 26 had measurable CNS metastases at baseline per IRC. Selpercatinib treatment resulted in a CNS ORR of 84.6% (95%CI=65.1–95.6), with a CNS mDoR of 9.4 mo (95%CI: 7.4–15.3) at a median f/u of 25.8 mo. In the safety population (NSCLC pts with ⩾1 dose, N=356), the most common adverse events (AEs in ⩾25% pts) were dry mouth, diarrhea, hypertension, increased ALT/AST, peripheral edema, constipation, rash, headache and fatigue. In total, 34 pts (9.6%) discontinued treatment due to AEs, including 11 pts (3.1%) due to drug-related AEs per investigator.

By IRC	Prior Platinum Chemotherapy		Treatment Naïve	
% (95%CI)	30Mar20 N=218	15Jun21 N=247	30Mar20 N=48	15Jun21 N=69
ORR	56.9 (50.0–63.6)	61.1 (54.7–67.2)	85.4 (72.2–93.9)	84.1 (73.3–91.8)
CBR	84.4 (78.9–89.0)	85.4 (80.4–89.6)	93.8 (82.8–98.7)	92.8 (83.9–97.6)
mDoR, mo (95%CI)	17.5 (12.1–NE)	28.6 (20.4–NE)	NE (12.0–NE)	20.2 (13.0–NE)
Censoring,%	69.4	60.9	75.6	55.2
Median f/u, mo	12.0	21.2	9.8	20.3
12mo DoR	69.1 (58.1–77.8)	73.1 (64.9–79.7)	65.0 (42.8–80.3)	66.1 (51.6–77.3)
mPFS, mo (95%CI)	19.3 (16.5–NE)	24.9 (19.3–NE)	NE (13.8–NE)	22.0 (13.8–NE)
Censoring,%	66.1	55.9	70.8	53.6
Median f/u, mo	13.6	24.7	10.8	21.9
12mo PFS	69.7 (62.2–75.9)	70.5 (64.1–76.0)	67.6 (49.5–80.3)	70.6 (57.8–80.2)

Conclusions: With longer follow-up and additional patients, selpercatinib demonstrates durable efficacy and intracranial activity regardless of line of therapy. The safety profile of selpercatinib remains consistent with prior reports.

A08

RATIONALE AND DESIGN OF A SINGLE-ARM, PHASE 2, MULTI-CENTER STUDY OF CHEMO-IMMUNOTHERAPY FOLLOWED BY HYPO-FRACTIONATED RT AND MAINTENANCE IMMUNOTHERAPY IN PATIENTS WITH UNRESECTABLE STAGE III NSCLC: THE DEDALUS TRIAL

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Background: Lung cancer is the leading cause of death from cancer worldwide. The standard approach for unresectable PD-L1 positive stage IIIA/B/C non-small cell lung cancer (NSCLC) is platinum-based concurrent or sequential chemo-radiotherapy (c/sCRT), with 60-66 Gy over 6 weeks, followed by the anti-PD-L1 antibody durvalumab as maintenance therapy for responding patients. Moving forward on developing the best combination of chemoradiation and durvalumab, this single-arm, phase 2, Italian, multi-center, open-label study aims to assess the safety and efficacy of a regimen of induction chemo-immunotherapy followed by de-intensified, hypo-fractionated RT given concurrently with durvalumab followed by durvalumab maintenance in patients with unresectable, stage III NSCLC.

Material and methods: 45 patients with unresectable stage III NSCLC, PD-L1 all comers, ineligible for cCRT and candidate to sCRT followed by durvalumab will be enrolled. After 3 cycles of cisplatin/carboplatin plus etoposide plus durvalumab, responders (SD, CR, PR) will be receiving hypo-fractionated thoracic RT (45 Gy over 3 weeks) plus durvalumab, followed by durvalumab maintenance up to 12 months or progression. This pilot study is designed to obtain preliminary estimates upon which we will base our sample size calculations in a future, larger study.

Results: Primary endpoint is safety, defined by the incidence of grade 3 and 4 possibly related adverse events within 6 months from the initiation of treatment. The secondary objectives are PFS and OS (median and 12 months) and quality of life. Exploratory objectives consist of radiomic and molecular analyses: the correlation of radiomic signatures extracted form baseline and post-RT TC-scans with PFS; molecular alterations detected on tumor tissue specimens obtained at the first diagnosis will be then monitored on cell-free DNA in plasma specimens in a longitudinal series of liquid biopsies at 3 different time-points (at baseline, after the end of radiotherapy and at progression).

Conclusions: The DEDALUS study explores the safety and efficacy of a new sequential approach in patients with

unresectable stage III NSCLC, by a) potentiating chemotherapy effects through the concomitant use of durvalumab upfront, b) de-intensifying RT with concurrent durvalumab administration for responding patients and c) keeping maintenance durvalumab as per PACIFIC regimen. This study is active and recruiting in 3 Italian centers (ClinicalTrials.gov Identifier: NCT05128630).

A09

OSIMERTINIB IN UNTREATED EGFR-MUTANT NON-SMALL CELL LUNG CANCERS: OVERALL SURVIVAL AND BUDGET IMPACT ANALYSIS IN REAL-WORLD

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Background: The observational prospective multicenter FLOWER study reported effectiveness and safety of osimertinib (O) for untreated *EGFR*-mutant (m) advanced non-small cell lung cancer (aNSCLC) patients (pts) in the real-world (RW) (Lorenzi et.al, Oncologist, 2021). Herein, we report updated (upd) outcome and cost-effectiveness (CE) data.

Patients and methods: Median time to treatment discontinuation (mTTD) and overall survival (mOS) were reported with an upd follow-up (FUP). The monthly budget impact (BI) of O was calculated by multiplying the 28-days cost/pt by mTTD and the incremental CE ratio (ICER) as the ratio between difference in costs and effectiveness, taking as comparison RW data of an overlapping population receiving gefitinib (G) or erlotinib (E). The difference (BI-gap) between real-BI calculated on RW mTTD and theoretical-BI calculated on FLAURA trial data was estimated.

Result: At data cut-off (February 2022), 91 pts (out of the overall population of 126) from 6 Italian centres were included. Pts features and outcome were previously presented. After a mFUP of 21 months (mo), 47(51.6%) pts discontinued O. Upd mTTD was 23.2 (95%CI,17.4-29.0) and mOS 30.2 mo(95%CI,-inf,+inf). At progression, tissue biopsy was performed in 14(43.8%), liquid in 13(40.6%) and both in 5(15.6%) pts. 1(3%) histological transformation was detected. NGS was performed in 10(21.2%) cases. *MET* amplification (amp) was found in 9(28.0%), *EGFR plus MET* amp in 1(3.1%), *HER2* amp in 1(3.1%) and other complex mutations in 5(15.6%) pts. 22 (24.2%) pts received second-line treatment (trt): 7(31.8%) an EGFR-/MET-TKIs combination, 12(54.5%) chemotherapy alone, 2 (9.1%) in combination with atezolizumab and 1(4.5%) with EGFR-TKI. Response rate was 50%, median progression-free survival (mPFS) 7.3 mo (95%CI, 5.2-9.4). The monthly BI/pt was 3.921€, 1.864€ and 2.190€ for O, E and G, respectively. The ICER in terms of cost per life-year-gained was not available due to the lack of events for OS analysis (41% maturity). Considering TTD as a surrogate of OS, the ICER for O was 7.173€ and 6.898€ compared to E and G, respectively. A BI-gap of 17.725€ and 10.165€ considering mPFS and mTTD from FLAURA trial, was observed.

Conclusions: We confirm effectiveness of O as first-line trt in *EGFR*-m aNSCLC pts. BI of O is in line with previous data and the ICER calculated on TTD lower than the Italian willingness-to-pay threshold. The BI-gap suggests TTD as a more reliable measure for BI estimation compared to PFS.

A10

CABOZANTINIB (C) PLUS ATEZOLIZUMAB (A) AS A FIRST- OR SECOND-LINE THERAPY FOR PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC) AND PREVIOUSLY-TREATED EGFR MUTANT ANSCLC

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Background: COSMIC-021 (NCT03170960) is a phase 1b study evaluating C+A in advanced solid tumors; C+A demonstrated clinical activity in a pt cohort with aNSCLC

previously treated with an immune checkpoint inhibitor (ICI; Neal. ASCO 2020). Outcomes of C+A in first- or second-line aNSCLC (cohort 8 [C8]) and previously-treated EGFR mutant aNSCLC (C9) are presented.

Methods: Pts with PD-L1+ (⩾1% of tumor tissue), stage IV, nonsquamous NSCLC, ⩽1 prior line of systemic therapy, no prior ICI, and no EGFR, ALK, ROS1, or BRAF V600E mutations were eligible for C8. C9 enrolled EGFR mutant, stage IV, nonsquamous NSCLC pts previously treated with ⩾1 EGFR-TKI (no limit on prior therapies). Pts received C 40 mg PO QD + A 1200 mg IV Q3W. Primary endpoint: objective response rate (ORR) per RECIST v1.1 by investigator; other endpoints: safety, duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Results: The study enrolled 29 pts in C8 and 30 in C9; baseline characteristics (C8, C9): median age 65y, 62y; male 55%, 40%; ECOG PS1 76%, 87%; liver metastasis 21%, 17%; 0/1/⩾2 lines of prior therapy 79%/21%/0, 33%/23%/43%. As of Nov 30, 2021, median follow-up was 19.9 mo in C8 and 26.2 mo in C9, with 9 (31%) and 1 (3%) on study treatment. Clinical activity was observed in both cohorts and in C8 irrespective of PD-L1 expression level (Table). Treatment-related adverse events (TRAEs) of any grade (C8, C9) included diarrhea (38%, 20%), aspartate aminotransferase increased (31%, 17%), nausea (21%, 20%), and decreased appetite (17%, 20%); grade 3/4 TRAEs occurred in 41% and 27%, and 1 grade 5 TRAE occurred in C8 (drug hypersensitivity).

Conclusions: C+A demonstrated clinical activity in first- or second-line PD-L1-positive aNSCLC and more modest activity in previously-treated EGFR mutant aNSCLC; AEs were manageable.

	C8*			C9
	All pts (N=29)	PD-L1+ 1%-49% (n=17)	PD-L1+ ⩾50% (n=11)	(N=30)
ORR,% (95% CI)	28 (13–47)	24 (7–50)	36 (11–69)	7 (1–22)
Best response, n (%)				
Complete response (CR)	1 (3)	0	1 (9)	0
Partial response (PR)	7 (24)	4 (24)	3 (27)	2 (7)
Stable disease (SD)	15 (52)	10 (59)	4 (36)	17 (57)
Progressive disease	2 (7)	1 (6)	1 (9)	7 (23)
Disease control rate (CR+PR+SD),% (95% CI)	79 (60–92)	82 (57–96)	73 (39–94)	63 (44–80)
Median DOR, mo (95% CI)	NE (2.8–NE)	7.4 (2.8–NE)	NE (NE–NE)	15.2 (NE–NE)
Median PFS, mo (95% CI)	4.7 (2.8–8.4)	4.7 (2.8–8.4)	7.5 (1.5–NE)	2.7 (1.5–3.5)
Median OS, mo (95% CI)	14.7 (5.1–20.5)	12.0 (3.3–20.5)	15.7 (1.6–NE)	6.1 (3.9–11.8)

*PD-L1 level unknown in 1 pt in C8.

A11

CRIZOTINIB IN ROS1+ NSCLC: LONG-TERM OUTCOME OF PATIENTS WITH BRAIN METASTASES INCLUDED IN THE PHASE II METROS TRIAL

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Background: Crizotinib has a well-established role in *ROS1*+ non-small cell lung cancer (NSCLC). Few data exist on the intracranial activity of the drug in *ROS1*+ patients with brain metastases (BMs). The METROS trial

was a multicentric phase II trial aiming at investigating the efficacy of crizotinib in pretreated patients with NSCLC and *MET* deregulation (amplification or exon 14 mutations) or *ROS1* rearrangements. The study confirmed the efficacy of the drug in *ROS1*+, with modest activity in the *MET*-deregulated cohort (Landi L et al., Clin Cancer Res 2019). Here we present long-term survival outcomes of *ROS1*+ cohort, according to presence of BMs.

Material and Methods: Patients with *ROS1*+ NSCLC received crizotinib 250 mg BID orally until disease progression, unacceptable toxicity, withdrawal of consent, or death. Progression-free survival (PFS) and overall survival (OS) were analyzed in the whole population and according to presence of BMs at baseline.

Results: A total of 64 ROS1+ patients were analyzed in the METROS trial, including 26 in the study cohort and 38 in the expansion cohort. Overall, 17 patients presented BMs at baseline. Characteristics of patients with or without BMs were similar in terms of median age (50 and 58 years) gender (male/female: 12/5 and 30/17) PS (0/1: 9/8 and 28/19), previous therapies (1/⩾2 13/4 and 33/14). With a median follow-up of 54.4 months (data cut-off February 2022), in the whole population median PFS and OS were 13.8 months (95% CI: 7.4-20.2) and 40.5 months (95% CI: 27.9-53.1), respectively. Among patients with BMs, the brain was among the sites of progression in all patients. Among patients without BMs, intracranial progression was observed in 16 individuals (34.0%). Median PFS was 6.8 months (95% CI: 0.1-13.5) in patients with BMs versus 17.4 months in those without BMs [95% CI: 7.9-26.9, HR: 1.94 (95% CI: 0.99-3.40)]. Median OS was 16.4 months (95% CI: 15.5-17.3) in patients with BMs versus 42.8 months (95% CI: 28.6-57.0) in patients without BMs [HR: 1.63 (95% CI: 0.81-3.30)].

Conclusions: At a median follow-up >4 years, crizotinib confirmed its marked activity in *ROS1*+ NSCLC. Patients with BMs had higher risk of disease progression and death, highlighting the need for brain-penetrant drugs in the management of the disease.

A12

SAFETY OF SUNITINIB IN PATIENTS WITH TYPE B3 THYMOMA OR THYMIC CARCINOMA IN THE STYLE TRIAL

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Background: Activity of sunitinib (S) in patients (pts) with thymic malignancies after progression to standard chemotherapy showed promising results especially in pts with thymic carcinoma (TC). Here we report data of safety and tolerability of S in B3 thymoma (T) and TC pts treated into the prospective STYLE trial.

Methods: In this multicentric phase II trial, involving centers of the Italian Collaborative Group for ThYmic MalignanciEs (TYME) network, pts with advanced type B3 T or TC were enrolled in two cohorts and analyzed separately according to two Simon two-stages design (H0:p<5%, H1:p>25%, alpha=5% one-sided, power=85%, stage 1:12 pts, stage 2:23 pts). Primary endpoint was ORR, safety a secondary one. S was administered 50mg daily for 4weeks (w), followed by a 2w rest period, until disease progression or unacceptable toxicity. Alternate schedule (50 mg for 2w and 1w rest period in a 6w cycle) or two dose reductions were allowed in case of toxicity.

Results: From 03/2017 to 01/2022, 12 pts in T cohort and 32 in TC cohort were included (enrollment in T cohort was interrupted at a preplanned interim analysis for futility). At data cut-off, 11 pts in T (91.7%) and 26 in TC (81.2%) discontinued treatment. Median treatment duration was 5.4 months (m) in T (2.9-17.2) and 9.1 m in TC (4.6-11.3). At the final analysis on 23 TC, ORR was 21.7% (90%CI 9.0%-40.4%). In the intention to treat analysis DCR was 91.7% (95%CI 61.5%-99.8%) in T and 89.7% (95%CI 72.7%-97.8%) in TC. Shift to alternate schedule occurred in 58.3% of pts in T and 43.8% in TC, dose reduction in 8 (66.7%) and 13 (40.6%) pts, respectively, with 33.3% and 9.4% of pts requiring a further dose reduction. The main reason for dose adjustment was adverse event (AE) occurrence; 91.7% of pts in T and 93.8% in TC experienced at least one AE. Grade 3 treatment-related AEs were reported in 3 T (25%) and 17 TC (53.1%). The most common any grade AEs were: fatigue (58.3% T/46.9% TC), hypertension (41.7% T/34.4% TC), neutrophil count decreased (33.3% T/43.8% TC), platelet count decreased (33.3% T/46.9% TC), mucositis (41.7% T/34.4% TC), diarrhea (33.3% T/28.1% TC). Serious AEs were reported in 3 (6.8%) pts.

Conclusions: In this trial safety of S was consistent with previously reported data. Due to AEs, many schedule and

dose adjustments were required, suggesting the need for an alternative dosing regimen that, improving treatment compliance, may make S more effective in both cohorts. Further investigation are needed.

A13

THE EUROPEAN PROGRAM FOR ROUTINE TESTING OF PATIENTS WITH ADVANCED LUNG CANCER (EPROPA) 1-YEAR ACTIVITY

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Background: The Women Against Lung Cancer Europe (WALCE) Association promoted the European Program for Routine testing of Patients with Advanced lung cancer (EPROPA) with the aim of increasing the detection of targetable drivers and optimizing patients' access to biomarker-driven clinical trials.

Methods: From January 2021 to February 2022, 24 centers sited at 6 different European countries (Greece, Slovenia, Romania, Slovakia, Italy, Portugal) joined EPROPA. A targeted next-generation sequencing (NGS), using the Ion Torrent platform (ThermoFisher Scientific) has been performed. Molecular reports have been discussed within molecular tumour board (MTB) to assess clinical trials eligibility.

Results: Among 205 NSCLC patients registered to EPROPA, 121 (59%) were over 65 years/old, 72 (35%) aged between 50-65 years/old and 12 (6%) <50 years/old. About half of patients (99/48%) were females, and 158 (77%) were never/former smokers. The majority of analyzed samples were adenocarcinoma (169/82%), 19 (9%) squamous cell carcinoma and 18 (9%) other histological subtypes. 85 (41%) patients received molecular profiling by EPROPA for a newly diagnosed metastatic disease since NGS was not available at their center, while 121 (59%) had previously received non-NGS molecular profiling and were on anticancer treatment. A median turnaround time of 10 (8-12) days was reported for providing the NGS molecular report. A targetable oncogenic alteration was identified in 117 out of 205 (56%) analyzed samples, including: KRASp.G12C (18), KRAS p.G12V (3), other KRAS mutations (25), EGFR activating mutations (25), EGFRex20ins (6), ERBB2 mutations (7), ALK (7), ROS1 (4), RET (5), and NRG1 (1) rearrangements, METex14skipping (6), MET amplification (1), FGFR mutations (2) and amplification (1) and molecular alterations within the homologous recombination repair genes (6). A total of 82/117 (70%) patients harboring driver alterations received a targeted therapy either in clinical practice or in clinical trials. A clinical trial was proposed by the MTB to 64/117 (55%) of patients, but only six of them were enrolled since worsening of clinical status and/or their medical oncologist's decision.

Conclusions: These preliminary results confirm the feasibility of the program in the real-world scenario, supporting the implementation of NGS-based molecular characterization of advanced NSCLC samples in highly specialized centers in order to reduce the unequal access to tests, drugs and clinical trials.

A14

THE ITALIAN NSCLC PRECISION MEDICINE KNOWLEDGE DATA BASE: BIOMARKERSATLAS.COM

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Background: In the era of precision medicine, an increasing number of predictive biomarkers have to be tested in advanced non-small cell lung cancer (NSCLC) patients. In this scenario, the necessity to qualify each mutation changed the paradigm of "one gene- one biomarker" and encouraged the widespread diffusion of Next Generation Sequencing (NGS) platforms in the clinical practice. To shed light in this complex scenario, the development of a knowledge-based system may be helpful for both molecular pathologists and thoracic oncologists to avoid leaving any patient behind.

Methods: Our aim was to build a real-world mutation knowledge-based database (https://biomarkersatlas.com/) focused on molecular actionable alterations in NSCLC patients able to support the healthcare personnel in routine

practice. We identified the mutation subtypes and technical platforms from ten Italian institutions in order to cover all clinically relevant genomic alterations found in advanced NSCLC. Moreover, five different categories (sex, age, smoking status, tumor histotype, and Programmed death ligand 1 expression) were also collected from included NSCLC patients and matched with their own molecular hallmark.

Results: The knowledge-based database covers (last access 04/28/2022) n=62 unique DNA-based molecular alterations detected in different genes (n= 35 EGFR, n=20 KRAS, n=5 NRAS and n=2 BRAF) derived from n=608 advanced NSCLC patients. In addition, n=44 aberrant transcripts in ALK (n=26), ROS1 (n=8), RET (n=10) genes were observed. Overall, clinical data were available in n=313 cases. Briefly, n= 141 (45.1%) male and n= 172 (54.9%) female; n=4 (1.3%) <40 years, n=68 (22.5%) 40-60 years, n=205 (67.9%) 60-80 years, n=25 (8.%) >80 years; n=217 (88.2%) adenocarcinoma; n=5 (2.0%) squamous cell carcinoma, n=10 (4,1%) not otherwise specified subtype and n=14 (5.7%) other histological subtypes; n=74 (35.9%) never smoker, n=35 (17.0%) current smoker, n=21 (10.2%) former (<10 p/y) and n=76 (36.9%) former (>10 p/y) smokers; n=107 (64.1%) of patients received target therapy, n=40 (23,9%) chemotherapy, n=8 (4,8%) immunotherapy and n=12 (7,2%) chemo-immunotherapy, respectively. Moreover, each mutation reported in the biomarkers ATLAS was connected to pubmed indexed references and clinicaltrials.gov. (Figure 1)

Conclusions: Our data aims to confirm the feasibility of the italian NSCLC Precision Medicine Knowledge Data Base to guide decision making for NSCLC patients in real world practice.

A15

CLINICAL OUTCOME AND IMMUNOLOGICAL SIGNATURE IN PATIENTS WITH THYMIC EPITHELIAL TUMORS

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Background: Thymic epithelial tumors (TETs) are complex diseases, characterized by the association with paraneoplastic syndromes, which are either autoimmune diseases (AD) or clinical manifestations of immunodeficiency, such as Good Syndrome (GS). Etiopathogenesis of immune dysregulations in TETs patients (pts) is still not totally explained. The aim of this study was to evaluate differences in immune cell phenotype and expression of cytokines, chemokines and growth factors, as well as clinical outcome in patients with TETs and GS with or without autoimmune disorders (AD).

Methods: Consecutive patients with TETs and GS were recruited at Rare Tumors Coordinating Center of Campania Region (CRCTR – Naples, Italy), from May 2019 to June 2020. The immunophenotype from peripheral blood (monocytes, neutrophils, eosinophils, CD4+T cells, CD8+T cells, B-cells, NK cells and NKT- cells, T regulatory cells) was analyzed with the 8-color immunophenotyping kit and Treg detection kit (CD4/CD25/CD127); the expression levels of cytokines, chemokines, and growth factors were analyzed with pre-formed kits by Bioplex multiplex. D'Agostino-Pearson normality test, two-tailed test and log-rank test was used for statistical analysis.

Results: Twenty-four pts, 12 female and 12 male, 22 with thymoma and 2 with thymic carcinoma were enrolled. We observed a statistically significant higher number of leucocytes, attributable to T lymphocytes ($p = 0.023$), B lymphopenia ($p = 0.003$) and decrease of T regulatory cells ($p = 0.009$) in TET pts with AD, as compared with TET pts without AD. Moreover, TET pts with AD showed significantly higher circulating levels of IL-15 ($p = 0.032$), VEGF ($p = 0.007$), IP-10 ($p = 0.013$), GM-CSF ($p = 0.042$), IL-6 ($p = 0.031$), and MIP-1α ($p = 0.017$) with respect to TET pts without AD. The median OS for TETs patients with GS and GS plus AD were 131 and 76 months, respectively ($p = 0.024$).

Conclusions: Our preliminary data contribute to a better characterize TETs and GS pts with or without AD. Significant differences in the immunological profile and clinical outcome characterized these two groups of patients. Additional studies are needed to better understand the immunophenotypic alterations in TETs pts, in order to provide additional insights in this complex disease potentially useful in its clinical management.

A16

LONGITUDINAL MONITORING OF RADIOMIC AND BLOOD IMMUNE-INFLAMMATORY DESCRIPTORS AS A NON-INVASIVE APPROACH TO PREDICT ICI EFFICACY IN ADVANCED NSCLC PATIENTS

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Background: Clinically suitable biomarkers to foresee the response to immune checkpoint inhibitors (ICIs) can be achieved by tracking tumor heterogeneity and its evolution during treatment. Thus, we explored whether the longitudinal monitoring of radiomic features (RFs) and blood immunophenotypes may predict ICI benefit in advanced NSCLC.

Methods: We prospectively enrolled NSCLC patients undergoing ICI-based regimens in our 5-year AIRC granted project. Peripheral blood (PB) and CT-scans were acquired at baseline (T0) and at first disease assessment (T1). On PB samples we computed the Lung Immune Prognostic Index (LIPI) and analysed by flow-cytometry circulating CD3+, CD8+, CD4+, NK and Tregs as the expression of PD-1, Granzyme B [GnzB], Perforin [Perf] and Ki67. From CT-images, 851 RFs were extracted through a dedicated software (SlicerRadiomics). Time-dependent changes in PB parameters were expressed as percentage delta immune variation (ΔI= [T1 value – T0 value/T0 value]*100), while ΔRFs as (T1–T0)/T0. Primary endpoints were PFS and tumor response per RECIST (v.1.1). CR/PR or SD ⩾ 6 months defined clinical benefit (CB), while SD < 6 months or PD non-responders (NR).

Results: Our preliminary data on 58 NSCLC underlined a significant increase in the overall number of PB CD3+, CD8+ and NK cells in CB group, with a remarkable proliferation (Ki67+) and cytotoxic activity (GnzB+, Perf+) of CD8+ lymphocytes. Mean Δ variations of NK, CD8+Ki67+ and CD8+GnzB+Perf+ phenotypes were, respectively, -20%, -0.4% and -41% in NR *vs* +22%, +170% and +65% in CB ($P<0.05$, Mann Whitney), which also exhibited a more pronounced Tregs counterbalance. Strikingly, cases displaying concomitant rise of all these meaningful PB immune feature had a significantly prolonged PFS compared to the counterpart (HR=0.49, $P<0.01$). In addition, we found that following ICIs most patients preserving good LIPI or experiencing LIPI improvement belonged to CB ($P<0.05$, Fisher exact) and presented a longer PFS.

Pre-processing and Z-score standardization narrowed ΔRFs to 657, among which 11 were differentially regulated in CB *vs* NR ($P<0.05$, Mann Whitney). Distinct ΔRFs principal components, largely embodied by wavelet-HLL_firstorder_Maximum and -HLL_firstorder_Skewness, showed, respectively, direct and inverse correlation with ΔI CD8+Ki67+.

Conclusions: Dynamic monitoring of immunophenotypic and radiomic cues may implement our current prognostic and predictive models in advanced NSCLC treated with ICIs.

A17

CRIZOTINIB IN ANAPLASTIC LYMPHOMA KINASE (ALK) REARRANGED NON-SMALL-CELL LUNG CANCER (NSCLC): REAL WORLD DATA FROM THE ITALIAN SPECIALK TRIAL

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Background: For years crizotinib has been the standard of care in ALK positive NSCLC, being the first ALK inhibitor entered in clinical practice. Indeed, clinical trials demonstrated the superiority of crizotinib over chemotherapy in both first and second line treatment, thus highlighting the importance to guarantee to every ALK positive patient the proper treatment. The SPECIALK is an Italian, multicentre, observational and retrospective trial aiming at investigate the clinical impact of crizotinib in a real-life population of ALK positive NSCLC.

Material e methods: We retrospectively collected data of ALK positive NSCLC patients receiving crizotinib 250 mg bid in any line of therapy at 19 Italian centers. Treatment was given according to 648 Legislative Decrete (April 2013 -February 2015), Italian Name Patient Use program (December 2010 - April 2013) or thereafter in clinical practice (until December 31st, 2017). The efficacy of treatment was assessed in term of response rate (RR), progression-free survival (PFS) and overall survival (OS)

in the overall population and according to clinical characteristics, including the presence of brain metastases (BMs) or the smoking history.

Results: Overall, 179 individuals were included onto the study. Patients had a median age of 58 years and were mainly female (54.2%) with adenocarcinoma histology (95.5%) and received the drug as second line therapy (66.5%). Response rate was 59.8% (95% CI: 52.6-66.9), including a 5.6% of complete response. Median PFS was 11.3 months (95% CI: 9.4-13.2) and median OS was 52.8 months (95% CI: 34.0-71.6), with a 5-years OS rate of 51.2%. Thirty-seven patients presented BMs at the time of start crizotinib. Median PFS and 5-years OS rate were 8.8 months (95% CI 2.7-15.0) and 27.8% in patients with BMs and 12.8 months and 51.2% in those without BMs. Regarding to smoking habit, 114 patients (63.7%) were never smokers and 65 (36.3%) former/current smokers. Median PFS were longer in never smokers (13.3 (95% CI 10.7-15.9) and 7.7 months (95% CI 6.1-9.3)), whereas the 5-years OS rate was similar in the two groups (45.8% and 49.3%). Therapy was generally well tolerated, with an overall incidence of grade 3 or worse adverse events of 9.5%.

Conclusions: Real world data confirm that crizotinib is an effective and well tolerated agent in ALK+ NSCLC, supporting its usage when second or third generation ALK inhibitors are not available or contraindicated.

A18

OSIMERTINIB IN EGFR-MUTANT ADVANCED NSCLC: THE ATLAS MULTICENTRE COHORT STUDY

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Background: The FLAURA trial introduced Osimertinib as first line treatment for advanced NSCLC patients harbouring common EGFR mutations. This study evaluated real-world clinical features and survival outcomes from patients with EGFR-mutant advanced NSCLC who received Osimertinib in Italy.

Materials (patients) and methods: Clinical, pathological and molecular data of patients receiving first line Osimertinib for advanced NSCLC, harbouring EGFR exon 19 deletions and exon 21 L858R point mutations, were retrospectively collected across six different Italian institutions participating to ATLAS.

Results: Between January 2019 and December 2020, a total of 90 patients were included. Median age at diagnosis was 68 years, female were 68.9%, never-smokers were 60%, and brain metastases at diagnosis were 17.8%. Among the 90 EGFR-mutant patients, 60% had exon 19 deletions and 40% for L858R point mutation. The overall median progression-free survival (mPFS) was 23.2 months (24.1 months for exon 19 deletion and 17 months for L858R, p: 0.09). Seven patients (7.7%) experienced grade $\geqslant$ 3 toxicity, with only 4 patients (4.4%) definitely discontinuing treatment due to toxicity. 20 patients (22.2%) continued Osimertinib beyond progression, only 7 of them (35%) received locoregional treatment on site of progression. 18 out of 90 (20%) patients underwent re-biopsy after progression, only 10 of them had an identified mechanism of resistance (5 MET amplification, 1 MET exon 14 alterations, 1 both, 1 EGFR A776S, 1 PI3KCA and 1 phenotypical switch to small-cell lung cancer). Among 21 patients (21%) receiving a second-line therapy 4 (19%) were enrolled in clinical trials with MET inhibitors. Median overall survival (mOS) of the entire series was 24.2 months (95% IC 21.7-NA). mOS in patients with EGFR exon 19 deletion was not reached versus 19.2 months for patients with L858R point mutations (p: 0.008).

Conclusions: The outcomes of EGFR mutated NSCLC treated with Osimertinib in the first line setting was consistent with those reported in the literature. Such data highlight the need of better define the role of second line options for these patients and the urgent need of novel treatment strategies after progression.

A19

TISSUE AND BLOOD IMMUNE PROFILING TO PREDICT ICI EFFICACY IN ADVANCED NSCLC PATIENTS

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Background: The rousing success of Immune-checkpoint inhibitors (ICIs) leaves uncovered multiple drawbacks on the current clinical translation of cancer-immune interplay. The simultaneous analysis of tumor-immune microenvironment (TIME) and peripheral blood (PB) immunophenotypes may unveil immune profiles exploitable as new prognostic tools in ICI treated NSCLC.

Methods: We prospectively enrolled NSCLC patients undergoing ICI-based regimens in our 5-year AIRC granted project. PB was explored quantifying effector (NK, CD8, PD1, Granzyme B [GnzB], Perforin [Perf], Ki67) and suppressor (CD4+CD25+FOXP3+ Tregs) phenotypes (flowcytometry), soluble PD-L1 (sPD-L1) and Lung Immune Prognostic Index (LIPI). TIME was defined by PD-L1 expression and density of infiltrating lymphocytes (TILs). We separately assessed TILs organized in clusters and the fraction of lymphocytes located proximal to cancer cells (immune efficient, IEff) or within fibrotic tissue (immune excluded, IEx). PB and TIME features were correlated with tumor response: CR/PR or SD $\geqslant$ 6 months defined clinical benefit (CB), while SD $<$ 6 months or PD non-responders (NR).

Results: Our preliminary data on 58 patients showed that TIME from CB patients disclosed a significant 2.5-fold, 2.6-fold and 3.3-fold increase in CD3+ (P=0.05), CD8+ (P=0.017) and PD-1+ (P=0.03) TILs, respectively compared to TIME from NR. Raised CD8+ and CD4+ clustering and lower IEx CD3+ and CD4+ density were distinctive of CB group ($P<0.01$). TIME from ECOG PS 2 patients displayed a significant reduction of CD8+ clusters, while smoking status was coupled by prominent IEff TILs ($P<0.05$, Mann-Whitney).

We found direct correlation between TIME and PB in CD4/CD8 and CD8/CD3 numerical ratios, while the number of PB Tregs matched directly with IEx and inversely with IEff CD8+ lymphocytes. The prognostic power of individual PB immunophenotypes, sPD-L1 and LIPI was integrated in a multiparametric score. Specifically, we identified low PB NKs, CD8+PD1+, CD8+Ki67+, CD8+GnzB/Perf+ cells, high sPD-L1 and intermediate/poor LIPI as putative risk factors. Stratifying patients in low- (0-1 risk factor) and high-risk (2-4 risk factors) groups, we observed that 92% of low-risk NSCLC cases belonged to CB (Fisher exact test, $P<0.005$ vs high-risk).

Conclusions: Intersecting tissue with circulating events implicated in tumor-immune cross talk might disclose new paths to guide clinical decision in the era of immunotherapy.

A20

IMMUNE-RELATED ADVERSE EVENTS (IRAES) IN ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC): POTENTIAL ROLE OF PREDICTIVE MARKERS

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Introduction: Immune checkpoint inhibitors (ICIs) are widely used in aNSCLC. They are generally well tolerated, but their toxicity requires prompt and multidisciplinary management while markers predicting the irAE risk are missing.

Methods: We retrospectively reviewed clinico-pathological data, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) at baseline of aNSCLC patients (pts) treated with single-agent ICIs at Veneto Institute of Oncology between 2014 and 2021. We evaluated the impact of clinical variables and circulating biomarkers on irAEs development by logistic regression. Median progression-free survival (mPFS) and median overall survival (mOS) were estimated using Kaplan-Meier method.

Results: A total of 448 pts were enrolled: most pts were males (280, 62.5%) and former/current smokers (365, 81.5%), median age at diagnosis was 69 years (IQR 62.72-75.03). The majority had adenocarcinoma (293, 65.4%) and were PD-L1 positive (248, 55.6%). Most pts presented with <=2 metastatic sites (n=340, 75.9%). ICI was administered as first-line in 159 (35.5%).Baseline NLR was >=3 (high) in 257 pts (57.4%). At the time of analysis, median follow up was 8.9 months (IQR 3.2-18.9). Three hundred thirty-four pts (74.6%) experienced progression and mPFS was 5.7 months (95% CI 4.8-6.7); 355 deaths were registered and mOS was 9.5 months (95% CI 7.9-11.1). One hundred ninety-six patients (43.8%) developed irAEs, mainly grade 1–2 (79.1%). In multivariate logistic regression analysis, low NLR (OR=2.52, 95% CI: 1.50-4.22; p<0.001), <=2 sites of metastasis (OR=2.59, 95% CI: 1.45-4.64; p=0.001) and a PD-L1 >=50% (OR=2.78, 95% CI: 1.09-7.07; p=0.032) resulted to be independent predictors of irAE development. Low NLR evaluated at the time of onset of first irAE was also associated with higher risk of recurrence/development of further irAEs (OR=3.07, 95% CI: 1.13-8.29, p=0.027). IrAE occurrence confirmed as favorable prognostic factor (HR for PFS=0.30, 95% CI: 0.24-0.38; p<0.001; HR for OS=0.27, 95% CI: 0.21-0.34; p<0.001).

Conclusions: PD-L1 expression, NLR value and number of metastatic sites are potential predictors of risk for irAE. Studies concerning predictive markers for irAE could help in personalizing clinical management and follow-up in pts treated with ICIs.

A21

PROGNOSTIC FACTOR OF ROS1 REARRANGEMENTS CONCOMITANCE IN PATIENTS WITH EGFR-MUTATED LUNG ADENOCARCINOMA

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Background: EGFR mutations are the most common gene alterations in non-small cell lung cancer (NSCLC) patients (pts), with a prevalence of 10%-20% of the Caucasian population with adenocarcinoma, according to literature. However, certain tumors are characterized by co-occurring mutations and represent a rare molecular subtype; in particular pts with ROS1 rearrangements concomitant with EGFR represent less than 1% of cases. The aim of this work was to describe if the co-occurrence of ROS1 rearrangements and EGFR mutation may influence patients' outcome when compared with isolated EGFR mutation, in the setting of metastatic NSCLC.

Material and Methods: We retrospectively reviewed a total of 17 EGFR-mutated pts with advanced NSCLC, treated at our Institution between January 2020 and December 2020. EGFR analyses was performed by next-generation sequencing (NGS), ROS1 rearrangements were confirmed by FISH (after immunohistochemistry screening). Progression free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier method and $P<0.05$ was considered for statistical significance. Data cut-off date was April 20, 2022.

Results: The genetic details of 17 EGFR mutations are as follows: exon 19 deletions (n=7, 41.2%), L858R mutation in exon 21 (n=5; 29.4%), exon 20 insertions (n=5; 29.4%). Concomitant ROS1 fusions were identified in 7 pts (41%). Median age was 69 years (38-85). First line treatments were as follows: chemotherapy in 2 pts (11.8%) (with exon20 insertions), immunotherapy in 1 (5.9%) (PD-L1 90%) and TKI in 14 pts (82.3%), respectively. In the TKI group, 2 pts (EGFR+ROS1) (14.3%) were treated with crizotinib and 12 pts (85.7%) were treated with EGFR-TKIs which included gefitinib (n=2; 16.7%) and osimertinib (n=10; 83.3%). Median follow-up time was 21.6 months (mo) (20.4-24.9). The Median OS (mOS) were 13.4 mo (10.6-18.4) and 7.4 mo (5.1-19.1) in mutants of single EGFR and concomitant ROS1 fusion gene, respectively (p=0.8). Subgroup analysis considering only first line treatment with EGFR-TKI showed a median PFS of 7.6mo (6.7-16.1) and 5.3mo (0.7-18.6) (p=0.6) and a mOS of 13.9 (9.8-17.5) and 5.6 months (0.6-18.7) (p= 0.7), respectively.

Conclusions: Although not statistically significant, our observations suggest that concomitant alteration of ROS1 might worse patients' outcome and decrease EGFR-TKIs efficacy. The increase of sample size, longer follow-up and prospective studies, could help to achieve statistical significance in the future.

A22

CLINICAL TRIALS INCLUSION IN LUNG CANCER PATIENTS: A REAL-WORLD MULTICENTER ANALYSIS

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Background: One of the major need in the oncology field is to include patients into clinical trials and, more specifically, to enroll cancer patients truly reflecting the real world population. However, critical barriers concerning study design, health system and logistics can limit patients' enrollment.

Patients and methods: From April to October 2021, we prospectively collected data of lung cancer patients receiving new treatment indication in four Italian Oncological Institutions, in order to evaluate study inclusion rates and factors limiting clinical trials participation.

Results: Overall, 397 patients were included in the analysis. Median age was 70 years (range 31-91). Patients were predominately males (250, 63%), former or active smokers (302, 76%), affected by NSCLC (349, 88%), with locally advanced/metastatic disease (373, 94%). ECOG Performance Status (PS) $\geqslant$2 patients were 13% (52) of the entire population and 72% (286) presented with at least one major comorbidity. 374 patients (94%) were candidate to active anticancer therapy, for adjuvant/neoadjuvant (6%), first (64%), second (19%) or third (11%) treatment line.

Among them, 309 (83%) received standard treatment as per clinical practice, 15 (4%) targeted therapies within expanded access programs and 58 (15%) were included in experimental trials. Median age of patients enrolled in clinical studies was 62 years (range 45-83). The majority of trials were phase II (27, 47%) and III (22, 38%), more than half (38, 66%) were sponsored trials and had a superiority (37, 64%), open-label (39, 67%) design, not requiring re-biopsy (39, 6%) nor placebo-containing (41, 71%). Targeted therapy ± other drugs (19, 33%), immunotherapy ± other drugs (17, 29%) and antibody-drug conjugate therapy (9, 16%) were the most common experimental treatments. Main obstacles to recruitment were: unavailability of studies at home/near institutions (167, 54%), disease/molecular characteristics not satisfying inclusion criteria (37, 12%), poor PS (22, 7%), presence of relevant comorbidities or non-permissive medical history (10, 3%), patient's refusal (5, 2%) related to studies requiring re-biopsy or placebo-containing.

Conclusions: Proposing inclusion and enrolling patients in clinical trials remains an important goal in thoracic oncology, especially in consideration of the many novelties in the therapeutic area. Efforts to recognize and face inclusion limitations are paramount in order to provide high-quality care to our patients.

A23

EFFICACY OF CHEMOTHERAPY AFTER IMMUNOTHERAPY: RESULTS OF THE MULTICENTRE RETROSPECTIVE OBSERVATIONAL ARTIMINO 2 TRIAL

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Background: Limited evidence is available concerning the efficacy and safety of chemotherapy after previous immunotherapy in advanced NSCLC patients.

Materials and Methods: We retrospectively collected data on consecutive, stage IIIB-IV, ECOG performance status (PS) 0-2, NSCLC patients treated with single agent or combination chemotherapy after progression on a previous immunotherapy regimen. Baseline characteristics, outcome measures and toxicities were recorded. An exploratory analysis on the predictive value of the neutrophil-to-lymphocyte (N/L) ratio was performed.

Results: One-hundred patients were included in the analysis. Median age was 67 (range 39-81) years, M/F 66%/34%, ECOG PS 0/1/⩾2 47%/51%/2%, adeno/squamous carcinoma 77%/23%, with median of 50% (range 0-100) PD-L1 expression. Previous immunotherapy consisted on a single agent treatment in 83% of cases with a prevalence of pembrolizumab use and median N/L ratio of 4. Only 33% of cases received chemotherapy after immunotherapy. Platinum doublets (mostly carboplatin) were delivered in 31% while single agent chemotherapy in 69% of cases (vinorelbine 25%, taxanes 25%, gemcitabine 8%) with a median of 4 (range 1-16) cycles delivered. Overall response rate was 21% with a median clinical benefit of 55%. Median time to progression was 4 (range 1-17) months and median overall survival was 5 (range 1-22) months. Comparison of low vs high N/L ratio subgroups did not show any significant difference in terms of survival.

Conclusions: A minority of advanced NSCLC patients received chemotherapy after immunotherapy. Chemotherapy showed modest clinical efficacy after progression on immunotherapy while no safety issues were recorded. N/L ratio failed to predict chemotherapy benefit in this setting.

A24

RISK MANAGEMENT IN THE ACTIVITY OF A LUNG CANCER MULTIDISCIPLINARY TEAM (MDT) OF A COMPREHENSIVE CANCER CENTER: RESULTS OF A PROSPECTIVE ANALYSIS

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Background: Objective of the present study was to highlight the sources of harm that could negatively impact on decision making or affect the planning process of a Lung Multidisciplinary Team (MDT), in order to define the level of risk of each factor, evaluating the likelihood and severity of harm and suggesting risk mitigation measures.

Methods: The members of the lung MDT described and identified the main processes and sub-processes of the entire multidisciplinary pathway of patients with lung cancers. For each sub-process, the MDT identified one or more risk factors. Then the MDT members used a risk matrix table to describe scales of "probability of occurrence" and "severity of consequences" to rate risks associated with MDT activity, according to the phases of risk

assessment and treatment of the international risk management standards ISO 31000/2018. A semi-quantitative matrix was built with a five-level scale for the likelihood (L) and consequences (C) to graduate the risks as product of (L) x (C). Risk grading could be very low (light green, 1-2 points), low (green, 3-4 points), moderate (yellow, 6-12 points), high (orange, 15-16 points) or very high (red, 20-25 points). Mitigation strategies have been then identified to reduce risks to an acceptable level.

Results: The MDT members identified three main processes of the multidisciplinary pathway of patients, including outpatient specialistic visit, MDT discussion and MDT program implementation and eight related sub-processes. For each sub-process, the MDT identified one or more risk factors: four (25%) were related to outpatient specialistic visit, 7 (43.75%) to the MDT discussion and 5 (31.25%) to MDT program implementation. Overall, two risk factors were assigned to the low-risk level (12.5%), eleven to the moderate risk level (68.75%), 1 (6.25%) to the high risk level and two (12.5%) to the very high risk level. After the development of mitigation measures, a new semi-quantitative risk analysis performed after 3 months showed a reduction in almost all hazardous situations: two risk events (12.5%) were assigned to very low level, 6 (37.5%), to low level, 7 (43.75%) to moderate level, 0 to high level and 1 (6.25%) to very high level, respectively.

Conclusions: An interdisciplinary risk assessment analysis is applicable to the MDT activity using an ad-hoc risk matrix. If the hazard is identified and monitored, the risk could be reduced and managed even in a short time.

A25

PREVENTION OF HEPATIC TOXICITIES ASSOCIATED WITH ANAPLASTIC LYMPHOMA KINASE INHIBITORS IN THE TREATMENT OF NON-SMALL-CELL LUNG CANCER BY ADMINISTRATION OF URSODEOXYCHOLIC ACID: ANALYSIS FROM THE MONOISTITUTIONAL ANALYSIS

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Background: ALK gene rearrangement is a driving mutation underlying the development of NSCLC, and has been identified in 5–6% of NSCLC cases. The selective ALK-inhibitors showed therapeutic activity in in patients with non-small cell lung cancer (NSCLC). Hepatotoxicity is reported relatively frequently in clinical practice and may cause either a dose reduction or treatment interruption. Ursodeoxycholic acid, a unique bile acid protects the liver from injury.

Methods: An analysis was performed on two groups of patients: already on treatment with ALK inhibitor and with liver toxicity G1 and G2 (group 1), in prophylaxis at the start of treatment with ALK inhibitor (group 2). Patients were enrolled in the program between February 2018 and February 2022.

Results: Overall, 35 patients with ALK-positive NSCLC gene rearrangement were analyzed in group 1 and 45 patients in group 2. Based on clinical trial experiences, each patient's liver function was assessed at baseline before treatment and monitored every two weeks during the first two months, then monthly. Liver metastases were known in 3 patients in group 1 and 4 patients in group 2 at the time of taking the ALK inhibitor. In group 1 25 patients developed liver toxicity ranging from G1 to G2 and started ursodeoxycholic acid at a dose of 450 mg / day. In group 2 40 patients started treatment with an ALK inhibitor and ursodeoxycholic acid at a dose of 450 mg / day simultaneously. The rate of reduction in liver toxicity from G2 and G1 to G0 was 78% in the evaluable group 1 population (n = 32). In group 2 only 9% of patients developed grade <G2 liver toxicity (evaluable population n = 41).

Conclusions: Alterations in liver enzyme levels are one of the most common problems encountered in everyday clinical practice. In the real world, ursodeoxycholic acid at a dose of 450 mg / day has shown excellent efficacy in the management of liver toxicity associated with ALK inhibitors.

A26

DEVELOPMENT OF AN IMMUNE-BASED PREDICTIVE TOOL FOR PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE IMMUNOTHERAPY

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Background: First-line treatments for metastatic non-small cell lung cancer (mNSCLC), apart from oncogene-driven treatments in patients (pts) whose tumour is oncogene-addicted, are mainly based on immunotherapy (IT) and chemo-immunotherapy (CT-IT). Even if such treatments did revolutionize the treatment landscape, responses may be very variable. Understanding the pts' prognosis at baseline is then crucial and might be important for more tailored treatments, such as the implementation of CT-IT in pts with a high PD-L1 expression.

Material and Methods: We tested several immune-based biomarkers in all pts starting a first-line treatment with IT at our centre from September 2019 to January 2022. We considered four biomarkers associated with sensitivity to IT: 1) high serum levels of interleukin-2; 2) high serum levels of interleukin-6; 3) low serum levels of tumour necrosis factor-alpha; 4) low CD4/CD8 ratio. We evaluated these biomarkers before the start of IT, then at the time of the first evaluation and at the moment of disease progression. For this first analysis, we focused on the baseline evaluation. We identified three different classes of pts: Group 1) pts with no biomarkers of sensitivity to IT at baseline; Group 2) pts with 1 or 2 biomarkers; Group 3) pts with 3 or 4 biomarkers. We calculated and compared the overall survival from the start of the first-line treatment with the Kaplan-Meier method.

Results: We included 97 pts. 95 pts were treated with pembrolizumab, whereas only 2 were treated with atezolizumab. 25 pts were in group 1, 32 in group 2, and 40 in group 3. The median overall survival was 6.84 months (95%CI 4.71-8.97) in Group 1, 12.3 months (95%CI 11.37-13.18) in Group 2, and 20.3 months (95%CI 17.59-23) in Group 3 and the difference is statistically significant (log-rank $p < 0.001$).

Conclusions: The clinical outcome of IT in mNSCLC is extremely variable and PD-L1 expression alone is known to be not sufficient to determine the outcome of IT monotherapy. Our immune-based score seems to give a good stratification of the clinical benefit deriving from IT and might be useful in clinical practice to identify those pts who, regardless of PD-L1 expression, might benefit from more intensive therapeutic approaches, such as first-line CT-IT.

A27

BUDGET IMPACT ANALYSIS OF CEMIPLIMAB FOR FIRST-LINE (1L) ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) WITH PROGRAMMED CELL DEATH-LIGAND 1 (PD-L1)= 50% IN ITALY

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Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer related death among men and the second among women worldwide. Cemiplimab monotherapy demonstrated significant survival benefit versus chemotherapy in the first-line treatment of advanced NSCLC with PD-L1 ⩾50%. This study aims to assess the budget impact of adding cemiplimab monotherapy to the Italian clinical practice since the European Commission recently approved its use.

Material (patients) and methods: The budget impact model simulates the average management cost of an NSCLC patient over a 3-year time horizon considering the establishment of a competitive dynamic due to the introduction of cemiplimab in the clinical practice. Acquisition, administration, monitoring and adverse event costs as well as treatments duration were considered. Eligible population to the treatments were estimated in approximately 4.700 patients. Also, we assume an incremental uptake in the market shares of cemiplimab (10%; 20%; 35%), assuming a reduction in acquisition prices during the three-year time horizon. This assumption was based on real world data provided by Policlinico Agostino Gemelli regarding the analysis of a case study on melanoma in which a second entrant got into the market.

Results: The results of our model indicates incremental savings in terms of average management cost per patient equal to -3.268,90 € for the year 1, 10.001,93 € for year 2 and -11.361,35 € for year 3. These savings derived mainly due to the establishment of the competitive dynamic. Furthermore, the number of additional patients to be treated with the same amount of health care resources is incremental and reaches its peak during the third year of the analysis.

Conclusions: This tool demonstrates that the addition of cemiplimab monotherapy in the Italian clinical practice could lead to a reduction in expenditure treating the same number of patients, maximizing the allocative efficiency of the National Health System resources. Furthermore, the model is flexible enough to test other monotherapies that could soon enter the market, thus being a useful tool for policy-makers in order to optimize the use of the resources.

	Y1	Y2	Y3
Average management cost per patient – "Reference case"	€ 41.231,51	€ 41.231,51	€ 41.231,51
Average management cost per patient – "Projected Scenario"	€ 37.962,62	€ 31.229,58	€ 29.870,16
Differential	-3.268,90 €	-10.001,93 €	-11.361,35 €
Number of extra patients treated with the same economic impact for the NHS	**373**	**1.143**	**1.298**

A28

MACADAM (MESOTHELIOMA CLINICAL DATA PLATFORM): A REFERENCE DATABASE AS A TOOL FOR LARGE SCALE COLLABORATIVE RESEARCH

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Background: Electronic Medical Records (EMR) and administrative claims (AC) are non-negligible source of information for the constitution of observational databases. Those last are a fundamental source of information in rare cancers, fostering novel investigations. Pleural Mesothelioma (PM) is a rare cancer, strictly tied to asbestos fiber exposure. PM has a dismal prognosis. Despite the progresses in the cure achieved in the last years, only few therapeutic options are currently available. Hereby we describe the constitution process of a EHDEN (European Health Data Excellence Network) database for PM in a center at high volume for this elsewhere rare cancer.

Methods: Patients (pts) diagnosed with PM and who underwent at least one procedure (either diagnostic or therapeutic) at Azienda Ospedaliera SS Antonio e Biagio in Alessandria (AOAL), were identified using a code-identification system based on ICD 9 CM code 163 specific for PM. Data regarding demographics, histology and clinical course were obtained from electronic medical records (EMR). Data regarding procedures were obtained through administrative claims. An extraction transform load (ETL) process was structured through data ingestion, data lake configuration and data mapping execution. Data retrieved were standardized to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). The database obtained, as well as the ETL process are monthly updated and implemented. The process was validated by the EHDEN consortium.

Results: 867 PM pts, diagnosed from 01/2016 to 11/2021, have been identified at AOAL using the ETL procedure tied to EHDEN consortium. Data have been provided in a readily exploitable OMOP CDM format. In the same period from our internal research records we identified 594 patients (68% of the whole number of PM patients accessing AOAL).

Conclusions: We demonstrate that data retrieval from both AC and EMR of PM pts is feasible at a single institution at high volume for PM, with standardization to the OMOP CDM. The ETL procedures allowed the identification of additional cases. Our results pave the way to novel collaborative networks in PM that are crucial for large scale observational studies and translational research in this rare tumor. The ETL process starting from EMR and AC is applicable also to other rare diseases.

A29

SMARCA-2 AND SMARCA-4 EXPRESSION IN NSCLC: NEW PROGNOSTIC OR PREDICTIVE FACTORS FOR IMMUNOTHERAPY? A SINGLE INSTITUTION EXPERIENCE

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Background: SMARCA2 and SMARCA4 (SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily A, Member 2 and 4) are important ATPase catalytic subunit in the SWI/SNF gene complex. Deficiency in these 2 genes with loss of the relevant protein expression have been associated with peculiar histological features, aggressive behavior and poor prognosis in many tumors, including NSCLC. However, relationship between SMARCA-4 and SMARCA-2 deficiency and response to Immune Checkpoint Inhibitors (ICIs) in NSCLC remains unclear.

Patients and Methods: We retrospectively assessed SMARCA-4 and SMARCA-2 protein expression by immunohistochemistry (IHC) (SMARCA-2:clone BRM/D9E8B; SMARCA-4:clone EPNCIR111A) on biopsy or surgical specimens from 32 NSCLC patients (pts) treated with ICIs (anti PD-1/PD-L1) in first or second line setting in our institution. Pts with complete or partial protein loss were considered "SMARCA-deficient", while pts with completely preserved expression as "SMARCA- proficient". Associations among SMARCA-4 and SMARCA-2 expression, overall survival (OS), progression free survival (PFS), response and PD-L1 expression was assessed.

Results: Out of 32 eligible pts,19 (59.4%) died after a median follow-up of 18.9 months. 18(56.3%) were male, 26 (81.3%) were adenocarcinoma, 9 (28.1%) had PD-L1 expression >50%, 14 (43.8%) PD-L1 1-49% and 10 (32.3%) were PD-L1 negative. SMARCA-2 deficiency was found in 21 pts (65.7%) [complete loss in 9 (28.1%) and partial retention in 12 (37.5%)], while 11 (34.4%) preserved the protein expression. As only 1 pts (3.1%) showed

SMARCA-4 deficiency (concurrent with SMARCA-2 partial expression),analysis was limited to SMARCA-2. Kaplan–Meier curves confirmed that OS and PFS were similar between SMARCA-2 "loss" and "partial retention". OS was significantly higher in SMARCA-2 deficient than proficient NSCLC [p= 0.03; HR (95%CI): 2.64 (1.04-6.70)]. A trend toward improved PFS in SMARCA-2 deficient tumors was observed (p=0.07), while no relation was unveiled with PD-L1 expression (p= 0.51) nor response to ICIs (p= 0.28).

Conclusions: Our data suggested an improved OS in SMARCA-2 deficient NSCLC upon ICI therapy, which turned out somewhat independent of PD-L1 expression. As SMARCA-2 deficient tumors generally bear poor prognosis, a positive effect of ICIs in this subgroup of pts can be speculated. Larger and prospective studies are needed to evaluate the role of SMARCA-2 as a new predictive factor for immunotherapy.

A30

AN INTEGRATED IMMUNE-METABOLIC SCORE PREDICTS OUTCOME IN ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH IMMUNOTHERAPY

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Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment. However, optimal patient selection remains a challenge. 18F-labeled 2-deoxy-D-glucose Positron Emission Tomography/Computed Tomography (18F-FDG PET/CT) is an essential tool for the initial staging and response assessment in many tumors. New PET-based volumetric imaging parameters such as tumor metabolic volume (MTV) and total lesion glycolysis (TLG) represent three-dimensional parameters that can provide information on both tumor volume and metabolic activity.

Methods: This retrospective observational study evaluated clinical, biological and PET-FDG parameters in advanced NSCLC patients receiving ICIs at the Oncology Institute of Southern Switzerland (IOSI) from January 2016 to December 2020. PFS and OS were estimated by Kaplan-Meier analysis and differences in survival curves by log-rank test. The protocol was approved by the Ethic Committee. The objective was to assess the role of PET-FDG together with clinical and biologic characteristics, as possible biomarkers that could predict the outcome of advanced NSCLC patients with high PD-L1 expression treated with ICI single agent in first-line.

Results: Between January 2016 and December 2020, 48 patients with advanced NSCLC were treated with first line single-agent pembrolizumab. Median age was 70 (43-87 years); male/female: 29/19; adenocarcinoma 65%; stage III/IV: 9/39. With a median follow-up of 27 months (IQR, 25-39 months), 32 patients (66%) had cancer progression or relapse and 25 (52%) died. Median PFS and OS were 5.4 and 17.6 months, respectively. 39 patients had baseline 18F-FDG PET/CT available. MTV and derived neutrophil to lymphocyte ratio (dNLR) were independent prognostic factors of PFS and OS. A prognostic score, which integrates MTV and dNLR, was able to stratify our population into three risk groups: Low (L: MTV $\leqslant$ 17.5 cm3 and dNLR $\leqslant$ 3), Intermediate (I: MTV $>$ 17.5 cm3 or dNLR $>$ 3) and High (H: MTV $>$ 17.5 cm3 and dNLR $>$ 3). Median PFS in L/I/H risk was 24.6/6.6/2.1 months, respectively ($p = 0.0003$); median OS in L/I/H risk was not reached/27.1/7.2 months, respectively ($p < 0.0001$).

Conclusions: A model integrating baseline MTV and dNLR can distinguish 3 risk groups among ICI-treated patients with advanced NSCLC. An external validation of these results is ongoing in NSCLC patients treated at University Hospital of Parma.

A31

PEMBROLIZUMAB (PEMBRO) ALONE OR PEMBRO PLUS CHEMOTHERAPY (CHT) IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): CLINICAL PREDICTORS OF RESPONSE AND SURVIVAL

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Background: In Italy, Pembro and Pembro-CHT are indicated in first-line for advanced NSCLC. Apart from PD-L1, no other factors for selecting Pembro vs. Pembro-CHT are known. Our aim is to evaluate the impact of different clinical factors on the outcomes of Pembro vs. Pembro-CHT.

Material (patients) and methods: We retrospectively collected data from 91 Pts treated with Pembro and 55 Pts treated with Pembro-CHT, selected solely on the basis of

PD-L1 expression as per Italian prescribing indications. We compared objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). We evaluated sub-groups based on gender, performance status (ECOG-PS), measurable tumor burden, number of metastatic sites (N#MTS), use of corticosteroids (CTS) or proton pump inhibitors (PPI). Since Pts progressing on Pembro can receive platinum-based CHT, we focused on OS to evaluate the global benefit of combining Pembro and CHT in first-line.

Results: We included 91 Pts (Pembro) and 55 Pts (Pembro-CHT). Median follow up was 10.6 months for Pembro and 5.9 months for Pembro-CHT. The outcomes are reported in table 1 and include OS for sub-groups of interest. No significant difference in PFS or OS was observed between Pembro and Pembro-CHT, with the exception of female Pts (15 of 18 of whom are currently alive in Pembro-CHT group).

88 Pts treated with Pembro and 51 Pts treated with Pembro-CHT were evaluable for ORR and DCR, the latter being higher with Pembro-CHT. Notably, 12 Pts (13.6%) in Pembro group experienced early death (ED) before the first response assessment, whereas no ED occurred with Pembro-CHT.

Conclusions: Pembro and Pembro-CHT achieved similar OS among most sub-groups apart from female Pts. Pembro-CHT achieved better DCR and might be associated with fewer rapid progression and early death. Longer follow up and enrichment of Pembro-CHT group will provide more robust data.

	Pembro	Pembro-CHT	p
PFS (months)	5.7	5.4	0.40
OS (months)	14.4	12.5	0.99
Males	13.9	10.5	0.16
Females	14.6	Not reached	0.04
High tumor burden (⩾62 mm)	10.1	12.4	0.87
Low tumor burden (<62 mm)	23.5	10.5	0.30
N#MTS 1-2	23.3	Not reached	0.70
N#MTS ⩾ 3	7.7	9.5	0.56
PS ECOG 0-1	22.6	13.9	0.61
PS ECOG 2	2.7	1.5	0.20
No CTS or ⩽ 10mg/die	22.8	13.9	0.35
CTS > 10mg/die	2.9	Not reached	0.08
No use of PPI	22.6	12.4	0.26
Use of PPI	8.9	13.9	0.33
ORR	27.3%	25.5%	0.84
DCR	61.4%	82.4%	0.01

A32

IMPACT OF 1-YEAR NUTRITIONAL COUNSELLING ON THE QUALITY OF LIFE (QOL) OF ONCOGENE ADDICTED ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC) PATIENTS TREATING WITH TIROSIN-KINASE INHIBITORS AGENTS (TKIS)

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Background: According to our preliminary data presented at AIOM Congress 2021, nutritional counseling (NC) improved QoL in oncogene addicted aNSCLC patients (pts) treated with tyrosine kinase inhibitors (TKIs). Here we present an update with 1-year follow-up results.

Material (patients) and methods: In oncogene addicted aNSCLC pts (EGFR mutated or *other*), NC including evaluation of QoL (T0) was performed before starting TKIs therapy. The Edmonton Symptom Assessment System (ESAS), a numeric rating scale (0-10) of 9 symptoms (pain, fatigue, nausea, depression, anxiety, drowsiness, lack of appetite, illness, dyspnoea) and an optional 10th symptom (constipation or diarrhoea, mostly) was used. Enrolled pts underwent 3- (T3), 6-(T6) and 12- months (T12) follow-up visits. The change in QoL was defined as the difference of the median score (*mscore*) for each symptom in T0 and T3 (D1), T0 and T6 (D2) and T0 and T12 (D3); data were analysed using *Kolmogorov- Smirnov* test.

Results: A total of 49 pts were consecutively enrolled with median age (range) 67y (35-84); male/female 12/37; molecular alterations in EGFR/ *other* 32/17. Firstly, NC resulted in a positive effect on the optional 10th symptom in D1= -1 ($p= 0.02$) and in D2= -0.5 ($p= 0.02$). A not statistically validated trend in fatigue improvement was evident in D1= -0.5 ($p= ns$) and in D2= -1 ($p= ns$). Perception of illness was not influenced by NC al 3- and 6-months follow-up, in D1= 0 ($p= ns$) and D2=0 ($p= ns$), respectively. The correlation between pain, nausea, depression, anxiety, lack of appetite and NC remains unclear. An impairment in dyspnoea and drowsiness was disclosed. The role of NC appeared to be prominent in D1 and D2.

Conclusions: Despite the small sample size worthy of validation on a larger scale, NC improved ESAS QoL and

its use should be encouraged in the multimodal therapeutic strategy of oncogene addicted aNSCLC pts.

A33

HIGH-DOSE IFOSFAMIDE FOR ADVANCED THYMIC EPITHELIAL TUMORS (TETS): A TYME NETWORK STUDY

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Background: Patients (pts) with advanced thymoma (TM) and thymic carcinoma (TC) progressing to standard, platinum-based chemotherapy, have limited and poorly active treatment options. Referral centers of the Italian Collaborative Group for ThYmic MalignanciEs (TYME) network prospectively evaluated activity of high-dose ifosfamide in this subset of patients

Methods: We performed a prospective muliticenter study in pts with advanced TETs, progressing at least to one line of platinum-based chemotherapy.

Pts received Ifosfamide (1g/m^2/day) and sodium-2-mercaptoethanesulfonate (1g/m^2/day), as continuous infusion, via a portable pumps for 14 consecutive days.

Treatment was administered every 4 weeks until progression or unacceptable toxicity, up to a maximum of 6 cycles.

The primary endpoint of the study was the overall response rate (ORR) by RECIST 1.1. The secondary endpoint was Progression Free Survival (PFS). All CT scans were revised by a referral center radiologist.

Results: 17 pts (12 TC/ 5 TM; 8 stage IVA/ 9 stage IVB, 6 females/ 11 males) were enrolled from October 2020. Median age was 60 years (range 35-82). All patients had RECIST tumor progression at the time of study entry.

The median number of previous systemic treatment was 2 (range 1-5). Eleven pts were pretreated with an immune checkpoint inhibitor (ICI) and 12 pts with an anti-angiogenic drug. All pts were evaluable for response: ORR was 23.5% (95%CI, 6.8% - 49.9%; 4/17) and disease control rate was 70.6% (95%CI, 44.0%-89.7%; 12/17). Among the 12 pts with TC, 2 reached a partial response (PR), 5 stable disease (SD) and 5 had a progressive disease (PD) as best response; among the 5 pts with TM, 2 PR and 3 SD were observed. In the whole patients' cohort, the mean best tumor shrinkage from baseline was +6.8%, ranging from a mean value of +13.9% in TC and -12.8% for pts with TM. The median PFS for all pts was 4.5 months (95%CI 4.0-6.5): 4.1 mo. (95%CI, 3.4-6.4) for pts with TC and 6.55 mo. (4.2-NA) for those with TM.

Conclusions: preliminary results showed antitumor activity of ifosfamide in pts with tets. Recruitment is currently ongoing.

A34

APPLICATION OF NEXT GENERATION SEQUENCING (NGS) IN LIQUID BIOPSY FOR OPTIMIZING MOLECULAR CHARACTERIZATION OF HOSPITALIZED PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Molecular characterization of tumor samples has become pivotal in the management of patients affected by NSCLC, due to the availability of effective targeted agents. However, this approach requires non-negligible amount of tumor tissue and is potentially time-consuming. Some patients experience the first detection of lung neoplasm after hospitalization through the First Aid Department and might suffer from performance status worsening while waiting for the analyses, potentially resulting in inability to start antineoplastic treatments.

The primary aim of this ongoing study is to evaluate the performance of "up-front" NGS analysis through liquid biopsy of hospitalized patients with newly detected lung neoplasm compared to conventional diagnostic procedures. Secondary aims include response assessment and longitudinal monitoring through liquid biopsy of patients with oncogenic alterations at baseline.

Patients and methods: We aim to enroll 30 consecutive patients, irrespective of smoking history, with new

clinical and radiological finding of symptomatic, locally advanced or metastatic lung neoplasm. Liquid biopsy from peripheral blood is performed at baseline, in parallel with conventional biopsy, when feasible. Additionally, liquid biopsies are repeated during treatment and at progression in patients with any molecular alteration at baseline. *Oncomine™Lung cfTNA Research Assay* or *Oncomine™Lung cfDNA* panels are employed for processing plasma samples in NGS.

Results: Between January and May 2022, we recruited 18 hospitalized patients. Liquid biopsy NGS identified five *EGFR* activating mutations, one *ALK* rearrangement, five *KRAS* mutations and one *ERBB2* mutation. Median time to results of liquid biopsy was 8 days (5-15) compared to 17 (8-34) by conventional biopsy. Liquid biopsy and conventional biopsy were consistent in all cases with the exception of one patient who was wild type at liquid biopsy and harbored *EGFR* exon 19 deletion at tissue biopsy. Four patients with actionable oncogenic drivers at liquid biopsy (one *ALK* rearrangement, two *EGFR* mutations and one *ERBB2* mutation) could not undergo conventional biopsies due to clinical contraindications.

Conclusions: Front-line liquid biopsy might improve the management of symptomatic, hospitalized patients with lung cancer, potentially leading to early start of targeted therapy. Enrollment and longitudinal monitoring of oncogenic drivers with liquid biopsy are ongoing.

A35

IMMUNOBLOOD: A PROSPECTIVE STUDY EVALUATING THE DEVELOPMENT OF ANTI-CHECKPOINT INHIBITOR ANTIBODIES IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER TREATED WITH IMMUNOTHERAPY

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Background: Immunotherapy has radically changed the treatment of patients with locally advanced or metastatic-non-small cell lung cancer (NSCLC). PD-L1 expression is generally associated with efficacy of immunotherapy, with PD-L1 overexpressing (PD-L1 >50%) NSCLC patients deriving the greatest benefit. However, a consistent proportion of positive cases do not respond to treatment, while some PD-L1 negative patients gain a significant survival benefit. Mechanisms underlying these different outcomes remain largely unknown. The development of antibodies directed against immune checkpoint inhibitors (ICIs) could affect sensitivity and tolerability to treatment. Aim of the present study was to investigate whether patients receiving ICIs develop antidrug antibodies and if this event impact on drug efficacy and/or toxicity.

Material and methods: Patients with advanced NSCLC candidate for immunotherapy were included. Serial blood samples were collected at baseline and every cycle until disease progression. Levels of antidrug antibodies (ADA) assessed in plasma using enzyme immunoassay (ELISA) were correlated with response, duration of response, progression-free survival (PFS), overall survival (OS).

Results: From May 2021 to February 2022, a total of 50 patients were enrolled, including 11 patients receiving single agent ICIs (pembrolizumab = 7, nivolumab = 2, atezolizumab = 2), 3 patients ICIs combination (nivolumab – ipilimumab =2, atezolizumab – bevacizumab = 1), and 36 patients platinum-based chemotherapy plus ICI (35 = pembrolizumab; 1= nivolumab). Overall, 108 blood samples at different timepoints were collected and analysed; among them, 83 were from patients treated with chemio-immuno, 22 from patients treated with single agent immunotherapy and 3 for patients receiving nivolumab-ipilimumab combination. No ADA were detected in plasma samples at baseline and in early timepoints, in patients treated with immunotherapy as single agent as well in patients treated with the combination of chemo-immunotherapy.

Conclusions: Development of ADA was not an early event during immunotherapy and chemo-immunotherapy. Investigations in patients with long time exposure to immunotherapy are ongoing and will be presented at the meeting.

A36

ACTIVITY-BASED COSTING ANALYSIS OF LIQUID BIOPSY AND FFPE NGS APPROACH IN NSCLC DIAGNOSTIC PATH

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Background: Molecular analysis from solid specimens drawn from patients affected by Non-Small-Cell-Lung-Cancer (NSCLC) may be influenced by scarcity or low quality of the biological material. Liquid biopsy (LB) could help both in case of therapeutic resistance and in diagnostic definition. In solid tissue (ST) and liquid analyses NGS is nowadays the most useful approach to evaluate a complete biomarker panel using less material with less time consuming. Here we propose an Activity-Based

Costing (ABC) analysis aimed at comparing the genomic profiling by NGS of ST and LB as first step of cost-effectiveness analysis in NSCLC in our Institution real-life diagnostics.

Material and methods: At the Molecular Diagnostics Laboratory of Istituto Tumori, a business process analysis has been evaluated from the biospecimen pick-up to the final report ready to be handled to real-life patients. FFPE tissue and LB procedures have been considered. ABC analysis for each activity included the actual timing involving both personnel and machineries in reference to the gross costs of salaries, depreciation and maintenance, and reagents.

Results: LBs were usually analyzed as a monitoring tool for response to therapies, especially when ST were not available. In our Institute Real-Life more than 22% of NGS determinations in NSCLC regards plasma analysis with a sensitivity rate of 70%, in terms of informative results. Our ABC analysis evidenced that fully automated NGS analysis is more expansive than manually ones, even if the latter consists of a longer wet time. Indeed, it has to be highlighted that load of costs derived from reagents were confirmed in both methodologies (93% and 86% in FFPE and LB respectively). To make our analysis more reliable, the costs related to manually-prepared libraries for NGS analyses have been compared both for STs and LBs (644,47 € and 537,96 €, respectively). Even though LB procedure seems to be cheaper the need to associate a FFPE analysis when possible should be always highlighted to avoid a false negative result: the absence of peculiar mutations in plasma is considered a non informative analysis.

Conclusions: LB is a procedure with numerous benefits and some disadvantages. In the contest of our Institute, the direct costs of conducting LB are lower than the cost of conducting ST. The present study highlighted that due to the lower costs of this test in our hands, it could allow to perform it more frequently during patients follow-up, when appropriate.

A37

IMPACT OF KRAS MUTATIONS ON CLINICAL OUTCOMES OF PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER RECEIVING ANTI PD1/PDL1 THERAPY

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Background: To evaluate the impact of KRAS mutations on response and survival outcomes in mutated vs wild type KRAS advanced non squamous non small cell lung cancer patients treated with immune checkpoint inhibitors alone or in combination with chemotherapy.

Patients and methods: We retrospectively identified 119 patients, most of which (58%) were wild type. For each patient we evaluated overall survival (OS), progression free survival (PFS) and disease control rate (DCR). An exploratory analysis was performed among mutated patients to investigate the impact of specific KRAS mutations on response and survival outcomes.

Results: After a median follow-up of 10.3 months, the median OS was 14.9 months (95% CI 7.6 – 22.7) in wild type KRAS patients vs 14.7 months (95% CI 8.0 – 19.5) in mutated KRAS patients; p-value=0.529. No differences were also detected between two groups in terms of PFS and DCR. Patients with pG12C KRAS mutation reported survival and response outcomes that were not statistically different from those of patients with other KRAS mutations.

Conclusions: Our data confirmed that KRAS mutational status is not associated with survival and response outcomes in advanced non squamous NSCLC patients treated with immunotherapy alone or combined to chemotherapy.

A38

PROGNOSTIC NUTRITIONAL INDEX AND CLINICAL OUTCOME IN PATIENTS WITH ADVANCED NSCLC FOLLOWING EGFR-TKIS: A PRELIMINARY REPORT

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Background: There is increasing evidence that the nutritional and immunological status is closely related to clinical outcome of patients (pts) with advanced non small cell lung cancer (NSCLC). The prognostic nutritional index (PNI) has been deeply investigated as a reflection of pre-treatment immuno-nutritional status. Few data are available for EGFR positive advanced NSCLC, expecially for pts treated with Osimertinib (OSI) in first line setting.

Methods: Eligible advanced NSCLC pts with sensitive EGFR mutation positive (exon 19 deletion or L858R in exon 21) were included in order to describe baseline PNI and clinico-pathological features. The PNI was calculated as 10 x serum albumin value (g/dl) + 0.005 x pheripheral lymph (x mm3). Data collection provided clinical

outcomes as Response Rate (RR) and Progression Free Survival (PFS).

Results: Between January 2020 and April 2022 15 advanced NSCLC pts with sensitive EGFR mutation positive consecutively treated with OSI as first line setting were enrolled and analyzed. The optimal cut-off value of PNI for PFS was 45. Based on this cut-off value, 9 pts were categorized as PNI high group (> 45) and 6 pts as PNI-low group. Higher RR and longer PFS were observed both in PNI high group respect to PNI low group. Significantly higher proportion of pts presenting with EGFR exon 19 sensitive mutation tended to be categorized as PNI high group. More data will be presented at the meeting.

Conclusions: This pilot investigation suggests that low prognostic nutritional index is an easy obtainable index and correlates with worse clinical outcome following osimertinib treatment, even in a population usually at good prognosis due to oncogene addiction and suitable effective target therapies. The assessment of PNI index would be useful in locating pts at major risk of treatment failure for which additional research would be expected (e.g combination treatment; additive nutritional support) in order to lower this risk.

A39

MODULATION OF FIRST-LINE COMBINATION IMMUNE CHECKPOINT INHIBITORS (ICIS) AND PLATINUM-BASED CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC) TREATMENT IN CLINICAL PRACTICE

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Background: Advanced NSCLC treatment radically changed with first-line ICIs introduction, as single agent or combined with chemotherapy. Patients frequently require careful management due to impaired clinical conditions. We evaluated safety, activity, efficacy of combined ICIs/platinum-based chemotherapy in clinical practice.

Methods: Clinical parameters, age, performance status (PS), comorbidities evaluated by Cumulative Illness Rating Scale (CIRS), distinguished patients in fit or unfit to conventional treatment, treated with standard doses/schedules, pembrolizumab 200 mg added to cisplatin (75 mg/mq) or carboplatin (AUC 5) plus pemetrexed (500 mg/mq) or carboplatin (AUC 5) plus paclitaxel (175 mg/mq), d1 every 3 weeks, or modulated doses/schedules, respectively.

Results: From 02/2019 to 04/2022, 27 patients were treated, 15 (56%) adenocarcinoma, 10 (37%) squamous cell carcinoma, 2 (7%) large cell neuroendocrine carcinoma. Metastatic sites were: lymph nodes 89%, lung 44%, bone 44%, central nervous system 33%, pleura 22%, liver 15%. Median age was 68 years (50-83), young 37%, young-elderly 41%, old-elderly 22%; PS 0 4 (15%), 1 11 (41%), 2 12 (44%); CIRS stage, 9 (33%) stable, 6 (22%) intermediate, 12 (44%) secondary; male/female, 22 (81%)/5 (19%); 44% smokers, 37% former smokers. Prevalent comorbidities were: hypertension (48%), dyslipidemia (19%), chronic lung disease (22%), heart disease (15%), prostatic hypertrophy (15%), thromboembolism (11%), diabetes (11%), thyroid disorders (11%). PDL1 expression was <1% in 20 (74%), 1-50% in 7 (26%); all *EGFR*, ALK, ROS1 negative; 1 dMMR and HER2 amplified tumor. According to clinical parameters, 4 (14.8%) patients were fit, 23 unfit (85.2%): 3 (11%) received reduced-dose chemotherapy, 19 (70%) modulated schedule, 1 modulated doses and schedule. Among 16 evaluable patients (59%), objective partial response was reported in 11 patients (68.8%), stable disease 4 (25%), progression disease 1 (6.2%). Limiting toxicity syndromes were reported in >50% patients. At median follow-up of 7 months, median PFS and OS were 7 (1-24) and 24 (1-24) months, respectively.

Conclusions: Most metastatic NSCLC patients suitable for first-line ICIs/platinum-based chemotherapy combinations were elderly, unfit for recommended doses and/or schedules. Proper treatment modulations were tolerable in unfit patients treated in clinical practice, and guarantee consistent activity and efficacy. Updated safety, activity, efficacy data will be presented.

A40

INFLAMMATORY AND IMMUNE-NUTRITIONAL STATUS AS AN INDEX OF BENEFIT OR NOT IN ADVANCED NON-SMALL CELL LUNG CANCER TREATED WITH IMMUNE CHECK-POINT INHIBITORS: A PRELIMINARY REPORT

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Background: Literature data suggest prognostic nutritional index (PNI), peripheral blood neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) would be able to predict the benefit of immunotherapy treatment in many solid tumors. The present work aims to describe the immune-inflammatory and nutritional status through these indices in patients affected by advanced non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors.

Methods: The data of 30 advanced NSCLC patients consecutively treated - between January 2020 and january 2022 - with immune checkpoint inhibitor alone or in combination to platinum chemotherapy according to PDL1 expression level were retrospectively analyzed. PNI, NLR, PLR were calculated at baseline, before any treatment was started. PCR was collected at baseline too. Clinico-pathological characteristics of the patients together with efficacy outcomes were also reported. Depending on PNI, NLR and PLR together with PCR value two main group were identified: High Expression Group (HEG) and Low Expression Group (LEG) were identified.

Results: Due to the limiting number of patients we chose to evaluate only Response Rate (RR), as efficacy outcome, with special interest in fast progression and any possible correlation with HEG or LEG. 12 patients were allocated to LEG and 18 patients to HEG. Interestingly, higher Progression Disease (PD) rate (45%) was registered in patients allocated to LEG, while - on the contrary - lower PD rate (25%) was encountered in HEG group. In the latter group 3 rapid progressions - described as fast clinical deterioration associated to impressive radiological progression – were described. Interestingly, all 3 patients showed elevated PCR values at baseline, KRAS G12C mutation and due to high PDL1 expression were receiving anti PD1 alone.

Conclusions: Our work confirm feasibility of PNI, NLR and PLR as low cost and easily collecting indices in daily clinical practice in the treatment of advanced NSCLC patients. Low number of patients enrolled and short follow up time doesn't allow further considerations but suggest this indices particularly useful in discovering patients at major risk to benefit less from immunotherapy, especially if administered alone.

A41

INTRA- OR EXTRA-THORACIC DISEASE INVOLVEMENT IN ADVANCED NSCLC: INSIGHTS INTO RISK STRATIFICATION AND TREATMENT EFFICACY IN THE ERA OF IMMUNE CHECKPOINT INHIBITORS WITH CHEMOTHERAPY IN FIRST LINE TREATMENT

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Background: The combination of chemotherapy and immune checkpoint inhibitors is already considered a new standard strategy for first-line treatment of advanced non-small cell lung cancer (NSCLC) non oncogene- addicted with PD-L1 1-49% expression. To date, the effectiveness of the combination in this real-world population has no clear correlation with disease characteristics.

Methods: A retrospective efficacy analysis was performed on data from non oncogene-addicted NSCLC patients with PD-L1 expression of 1-49% who were treated between March 2020 and December 2021. Treatment efficacy was correlated to localizations of the disease.

Results: Overall, 60 patients non oncogene-addicted NSCLC with 1-49% PD-L1 expression received chemotherapy and immune checkpoint inhibitors in the Oncology Department of San Giovanni Addolorata, Rome. Median age was 65 years (range, 34–88), most patients were female (54%) and never or former smokers (78%). Lung and intrathoracic lymph node metastases were present in 12 patients (20%), hepatic and abdominal lymph node metastases were present in 30 patients (50%). Bone metastases with localizations greater than 4 sites were present in 35 patients (58%). The objective response rate (ORR) was 63% [95% confidence interval (CI), 51–79] in the evaluable population (n = 55). The disease control rate (DCR) was 68%. After a median follow-up of 15.2 months, the median progression-free survival was 11.9 months (95% CI, 4.7 – NA). In patients with measurable, non-symptomatic brain metastases (n = 6) the intracranial ORR was 78% and the intracranial DCR 99%. Patients with only intrathoracic localizations of disease showed better ORR (80%), DCR (72%) and PFS (18 months) data. Overall, patients with liver disease (10%) experienced less treatment efficacy and experienced grade 2 or higher treatment-related adverse events (TRAE). The most common G3 TRAEs were neutropenia (9%), thrombocytopenia (5%), increased liver enzyme levels (5%).

Conclusions: In this real world experience, the combination of chemotherapy and immune checkpoint inhibitors confirmed lasting systemic activity, with manageable toxicity. However, it was found that some subgroups of patients, especially with liver disease and extrathoracic localizations of disease, benefit from treatment less.

B - Gastrointestinal Cancers

B01*

FOLFOXIRI/BEVACIZUMAB (BEV) COMBINED WITH NIVOLUMAB (NIV) AS FIRST-LINE (1L) THERAPY IN METASTATIC COLORECTAL CANCER (MCRC) PATIENTS (PTS) WITH RAS/BRAF MUTATIONS, REGARDLESS OF MICROSATELLITE STATUS: RESULTS OF PHASE II NIVACOR TRIAL (GOIRC-03-2018)

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Background: FOLFOXIRI/BEV represents a standard approach in the 1L setting of pts with mCRC, especially RAS/BRAF mutated (mut). The NIVACOR study (NCT04072198) aims to evaluate NIV added to FOLFOXIRI/BEV as first-line therapy in mCRC RAS/BRAF mut pts, regardless of MSS/MSI status.

Methods: This is a single-arm, multicenter, open-label, phase II trial in a first-line setting. Pts received NIV 240 mg flat dose, FOLFOXIRI (IRI 165 mg/m2, OXA 85 mg/m2, leucovorin 200 mg/m2, and 5-FU 3,200 mg/m2 IC for 48 h) plus BEV 5 mg/kg IV q14 days for 8 cycles and then, maintenance with BEV/NIV until PD or unacceptable toxicities. The primary endpoint was the ORR according to RECIST 1.1. All images are reviewed by Independent Data Monitoring Committee. According to Fleming's design with alpha and beta levels of 0.05 and 0.2 respectively, in a sample size of 73 pts (comprehensive of a 10% drop-out rate), at least 56 responses were necessary to not reject the alternative hypothesis of an ORR=0.80.

Results: From October 2019 to March 2021, 73 pts were enrolled in 9 Italian centers. The median age was 60(51-65) and 50.7% were male; the main primary tumor side was right (50.7%). The molecular characteristics were: 87.7% RAS mut, 16.2% BRAF mut, and 4.5% both RAS and BRAF mut; 10/62(16.1%) MSI, 52/62(83.9%) MSS, and 11 pts not assessed. Liver metastases were present in 56.2%. The median (m) follow-up was 14.3 months (mo) (IQR 11.5-16.5) on December 31, 2021. The median duration of treatment was 12(8-17) cycles. The ORR was 76.7%, with 7(9.6%) CR and 49(67.1%) PR; 15(20.6%) was SD with a DCR of 97.3%, and 2(2.7%) were not evaluable. The mDoR was 8.4 mo (95%CI, 7-NE). The mPFS was 10.1 mo (95%CI, 9.4-NE) and 12-mo PFS was 53.4%. At data cut-off, 65(89.1%) pts are still alive. In the MSS subgroup, the ORR was 78.9% with a mDoR of 7.59 mo (95% CI 6.21-11.43), DCR of 96.2%, and mPFS of 9.8 mo (95% CI 8.18-15.24). The surgery of the primary tumor, metastases, or both was performed on 6(8.2%), 9(9.6%), and 5(6.9%) pts, respectively. The main grade 3-4 toxicities were: neutropenia (G3 21.9%, G4 15.1%), diarrhea (G3 17.8%, G4 1.4%), hypertension and fatigue G3 each in 6.8%, and febrile neutropenia G4 (4.1%).

Conclusions: The primary endpoint was met. These results show the preliminary efficacy and safety of NIV plus FOLOXIRI/BEV as 1L therapy in mCRC RAS/BRAF mut. The promising activity was observed also in MSS subgroup pts. These data support the conduction of a phase III randomized-controlled study.

B02*

PROSPECTIVE EVALUATION OF EMERGENT RAS AND BRAF MUTATIONS IN PRE-TREATED METASTATIC COLORECTAL CANCER PATIENTS CANDIDATE TO ANTI-EGFR RE-TREATMENT: PRELIMINARY FINDINGS FROM THE PARERE STUDY

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Background: Retreatment (re-tx) with anti-EGFRs is a promising strategy in RAS/BRAF wild-type (wt) anti-EGFR pre-treated metastatic colorectal cancer patients (mCRC pts), provided that no mechanisms of acquired resistance to anti-EGFRs are found in circulating tumor DNA (ctDNA). The phase II single arm CHRONOS study showed a 31% prevalence of RAS/BRAF mutations (mut)

in ctDNA of pts candidate to re-tx with panitumumab. We are now conducting a phase II randomized study, PARERE, to compare panitumumab followed by regorafenib versus the reverse sequence as treatment strategy in anti-EGFR pre-treated chemorefractory pts with RAS/BRAF wt ctDNA. Here we show initial results from the molecular screening.

Methods: mCRC pts with RAS/BRAF wt tumours who achieved ⩾ 6 months benefit with a previous anti-EGFR based tx and received at least one subsequent anti-EGFR free tx lasting ⩾ 4 months were eligible. ctDNA was analyzed with the Next Generation Sequencing Ion Torrent™ Oncomine™ cfDNA Colon assay, enabling parallel profiling of 14 genes.

Results: 101 pts were screened and ctDNA was successfully assessed in 91 cases (90%). Among them, 25 (28%) harboured KRAS/NRAS/BRAF V600E mut, with co-mut of KRAS and BRAF V600E genes in 2 pts (8%). Within the RAS/BRAF wt cohort (n=65), mut in at least another gene were found in 49 cases (75%). In particular, TP53, APC, PIK3CA, FBXW7, GNAS, EGFR, AKT and SMAD4 mut occurred in 39 (60%), 24 (36%), 8 (12%), 7 (11%), 2 (3%), 1 (1%), 1 (1%) and 1 (1%) cases, respectively. No mut in ERBB2, CTNNB1 and MAP2K genes were detected. The overall Limit of Detection (LOD) was 0.07% [95% CI: 0.06-0.09%] and the median variant allele fraction (VAF) of RAS/BRAF genes was 0.32% [95% CI: 0.23-1.70%]. No difference in the median anti-EGFR free interval was found between the group with RAS/BRAF wt and RAS/BRAF mut ctDNA (13.8 [95% CI: 12-18.3] and 16.9 months [95% CI: 10.6-24.6], respectively, p=0.70).

Conclusions: This is the largest series of pts prospectively screened for anti-EGFR re-tx. Around one out of 3 pts bear RAS or BRAF mutations in their ctDNA. Anti-EGFR free interval is not a valuable surrogate of ctDNA mutational status, thus supporting liquid biopsy as a selection tool for clinical trials in this setting and for the use of anti-EGFR re-tx in the real life.

B03*

METASTATIC COLORECTAL CANCER (MCRC) PATIENTS (PTS) TREATED WITH UPFRONT CHEMOTHERAPY (CT) + BEVACIZUMAB (BEV) WITHIN TRIBE AND TRIBE2 STUDIES: A FOCUS ON PRIMARY TUMOR RESECTION (PTR)

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Background: Management of primary tumor in mCRC pts still remain an intricate and complex issue for oncologists, especially in case of asymptomatic pts and during therapy with antiangiogenic drugs. The present analysis focused on the role of PTR in a pooled analysis of two randomized phase III studies (TRIBE and TRIBE2).

Patients and methods: We conducted a pooled-analysis including pts enrolled in the phase III TRIBE (NCT00719797) and TRIBE-2 (NCT02339116) studies that compared upfront FOLFOXIRI + BEV to FOLFIRI or FOLFOX + BEV, respectively. Association between PTR and adverse events experienced during 1st-line therapy was analyzed by $\chi 2$ test or Fisher's exact test, as statistically appropriate. Survival curves were estimated with Kaplan-Meier method and compared by log-rank test.

Results: Overall, 1175 pts were included. Of them, 680 (58%) underwent PTR before starting therapy. Pts with resected primary tumor had more frequently received adjuvant CT ($p < 0.001$); moreover, they had more often a metachronous disease ($p < 0.001$), a right sided colon cancer ($p = 0.001$), an ECOG PS 0 ($p = 0.025$), and a liver only metastatic disease ($p = 0.006$).

Pts who underwent PTR compared to those with an intact primary experienced a better progression-free survival (PFS) and overall survival (OS): 11.5 vs. 10.0 months ($p < 0.001$) and 28.2 vs. 22.4 ($p < 0.001$), respectively.

In multivariate analysis, PTR was confirmed as an independent prognostic factor for better PFS ($p = 0.05$) together with triplet CT + BEV ($p < 0.0001$), ECOG PS 0 ($p < 0.0001$), RAS/BRAF wild-type cancer ($p = 0.01$) and liver-only metastatic disease ($p = 0.02$).

Considering adverse events during 1st-line CT + BEV, pts with a resected primary tumor more often experienced diarrhea ($p = 0.028$), whereas anemia ($p = 0.044$), perforation ($p = 0.008$), and gastrointestinal and surgical serious adverse events ($p < 0.0001$) were less frequent observed. No statistically significant differences were noted in incidence of bleeding ($p = 0.427$).

Conclusions: Baseline PTR was associated with lower incidence of serious gastrointestinal and surgical adverse

events during upfront CT plus BEV and impacted positively on prognosis of mCRC pts.

B04*

AN IMMUNE-RELATED GENE EXPRESSION PROFILE PREDICTS THE EFFICACY OF ADDING ATEZOLIZUMAB TO FIRST-LINE FOLFOXIRI/BEVACIZUMAB IN METASTATIC COLORECTAL CANCER: A TRANSLATIONAL ANALYSIS OF THE PHASE II RANDOMIZED ATEZOTRIBE STUDY

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Background: AtezoTRIBE demonstrated that adding atezolizumab (atezo) to first-line FOLFOXIRI/bevacizumab (bev) prolongs PFS of mCRC patients, with a clinically modest benefit among proficient mismatch repair (pMMR) mCRC patients. We investigated the predictive role of an immune-related pan-cancer 27-genes signature (IO score) measuring immune components of tumor microenvironment, in order to identify a pMMR subgroup able to benefit from immunotherapy.

Methods: AtezoTRIBE phase II trial randomized 1:2 mCRC patients, unselected for MMR status, to receive FOLFOXIRI/bev (control arm A) or FOLFOXIRI/bev/atezo (experimental arm B). Gene expression was measured using RT-qPCR by DetermaIO™ on RNA purified from FFPE blocks of pre-treatment tumor samples (142/218 enrolled patients [65%]). IO score was calculated according to the pan-cancer algorithm. The predefined IO cut-point (0.09) was applied to dichotomize tumors as IO^+ or IO^-. To identify patients deriving maximal benefit from arm B, an exploratory optimized IO cut-point (IO^{OPT}) was calculated by using a method based on maximizing the log-rank statistics to compare the two groups, then tumors were dichotomized as IO^{OPT+} or IO^{OPT-}.

Results: IO score was successfully determined in 122 (86%) cases, with 33 (27%) IO^+ tumors. IO^+ and IO^- mCRC were similar in terms of baseline characteristics and clinical outcome (mPFS:14.4 vs 13.6 mos; HR:0.84 [95%CI:0.53-1.33], p=0.468). A higher PFS benefit from arm B among IO^+ (HR:0.39 [95%CI:0.15-1.02]) than IO^- tumors (HR:0.83 [95%CI:0.50-1.35]) was reported (p for interaction=0.066). In the pMMR group (n=110), a similar PFS trend was observed (IO^+[n=30]: HR:0.47 [95%CI:0.18-1.25]; IO^- [n=80]: HR: 0.93 [95%CI:0.56-1.55]; p for interaction=0.139). In the overall population, the computed IO^{OPT} cut-point was 0.277, with 16 (13%) IO^{OPT+} tumors. Compared to IO^{OPT-}, IO^{OPT+} tumors were more frequently TMB-high (p=0.007), had a longer mPFS (14.8 vs 13.3 mos; HR:0.50 [95%CI:0.28-0.87], p=0.053) and derived higher PFS benefit from arm B (IO^{OPT+}: HR:0.10 [95%CI:0.02-0.52]; IO^{OPT-} HR:0.85 [95%CI:0.54-1.33]; p for interaction=0.004). Similar results were observed among pMMR group, with a computed IO^{OPT} cut-point of 0.304 and 12 (11%) IO^{OPT+} tumors.

Conclusions: IO score with the predefined cut-point may help to predict benefit from the addition of atezo to first-line FOLFOXIRI/bev in mCRC, even within pMMR tumours. Exploratory IOOPT cut-points should be validated in independent mCRC cohorts.

B05*

ROLE OF GERIATRIC ASSESSMENT AND ONCOLOGICAL MULTIDIMENSIONAL PROGNOSTIC INDEX (ONCO-MPI) IN OLDER PATIENTS WITH METASTATIC COLORECTAL CANCER IN A REAL-WORLD SETTING

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Background: About 50% of colorectal cancers occur in patients (pts) older than 70 years. International oncological societies suggest using geriatric tools to evaluate older pts to optimize treatment. Comprehensive Geriatric Assessment (CGA) is a multidimensional assessment of older subjects, classifying pts as fit, vulnerable or frail. Oncological multidimensional prognostic index (oncoMPI) is a CGA-based score which also considers tumour characteristics, classifying pts in high-, intermediate- and low-risk group. We

investigated the role of CGA and onco-MPI in older pts with metastatic colorectal cancer (mCRC) in a real-world setting.

Methods: Consecutive mCRC pts aged ⩾70 years evaluated at Istituto Oncologico Veneto from 2010 to 2020 were retrieved from a prospectively maintained database. Pts' demographics (age, gender), CGA (ECOG PS, comorbidity and their severity according to CIRS, medications, pain and caregiver presence, BMI, ADL and IADL, MMSE and the 15-items Geriatric Depression Scale) and tumor characteristics (primary tumor location, *RAS*/*BRAF* status, presence of synchronous metastasis, number of metastases, total lines and regimens of chemotherapy) were analysed. Onco-MPI was calculated by a validated algorithm from the CGA domains, as previously described. We used Pearson's chi-squared test to verify if onco-MPI and first-line decision-making were statistically and reciprocally correlated.

Results: A total of 488 mCRC pts were included, 287 males. Mean age was 76.1 years, ECOG PS was < 2 in 84%. According to CGA, 52% of pts were classified as fit, 28% vulnerable and 20% frail. According to onco-MPI score, 9%, 54% and 37% of pts were low, medium and high risk, respectively. Median overall survival (OS) was 22.7 months. The following factors were significantly associated with OS: ECOG PS (0-1 vs > 1, HR 2.4), CGA (fit vs frail, HR 2.4), onco-MPI score (low vs high risk, HR 1.7), number of metastases (1 vs > 1, HR 2.1), chemotherapy administration (none vs at least first-line, HR 0.63), first-line regimen (monotherapy vs doublet, HR 0.7). Chemotherapy administration correlated with onco-MPI scores (with a Pearson's test p-value < 0.0001) providing a survival gain in all the risk subgroups.

Conclusions: CGA and onco-MPI confirmed their prognostic role in older pts with mCRC. Notably, CGA-derived onco-MPI may help drive decision-making in clinical practice and standardize subgroups of the heterogenous population of older pts in clinical trials.

B06*

GUIDELINE APPLICATION IN REAL WORLD: MULTI-INSTITUTIONAL BASED SURVEY OF ADJUVANT AND FIRST-LINE PANCREATIC DUCTAL ADENOCARCINOMA TREATMENT IN ITALY. FIRST ANALYSIS OF THE GARIBALDI TRIAL

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Background: Information about the adherence to Scientific Societies Guidelines in the 'real world' therapeutic management of patients (pts) with Pancreatic Ductal Adenocarcinoma (PDAC) are lacking. The aim of this national, observational, multicenter, prospective survey is improving the knowledge on this topic relative to recommendations provided by the Italian Association of Medical Oncology (AIOM 2017).

Material and Methods: Since December 2017, consenting pts who had to be treatment-naïve, > 18-year, with pathological diagnosis of PDAC were enrolled and grouped in 3 settings: 1) receiving adjuvant therapy after resection (GROUP A); 2) receiving primary chemotherapy (GROUP B); 3) metastatic (GROUP C). Participating institutions were selected to adequately represent different geographical and expertise areas (high-volume with >50 pts treated /year; medium-volume with 25-50 pts treated /year; low-volume with <25 pts treated /year). AIOM guidelines changed in November 2019. Accordingly, here we present the results of pts accrued until October 31 2019.

Results: 832 pts of 924 (90%), enrolled in 44 Italian centers, were considered eligible for primary analysis. Median age was 69 (range 36-89; 24% >75-year); 48% female; 93% ECOG PS 0-1; group A: 16%, group B: 31%; group C: 54%; 72% Nord, 13% Centre, 15% South. Nutritional and psychologic counseling were provided to 20% and 8% of pts, respectively.

In group A, guidelines adherence was 91%; 22% of pts received FOLFIRINOX, 15% gemcitabine+capecitabine, 54% gemcitabine; median CA19.9 was 29 (range 0-7300; not reported 16%); median survival was 33.4 mo.

In group B, guidelines adherence was 98%; 55% of pts received nab-paclitaxel+gemcitabine, 27% FOLFIRINOX, 12% gemcitabine, 3% clinical trial; median CA19.9 was 336 (range 0-20220; not reported 9%); median survival was 18.1 mo.

In group C, guidelines adherence was 96%; 71% of pts received nab-paclitaxel+gemcitabine, 8% FOLFIRINOX, 16% gemcitabine, 4% clinical trial; liver metastases were reported in 76% and lung in 23% of pts; median CA19.9 value was 760 (range 0-1374500; not reported 9%); median survival was 10.0 mo and 1-y OS 41%.

Conclusions: The GARIBALDI data show a very high rate of adherence to guidelines and OS in line with the literature. Data are more representative of Northern Italy. CA19.9 testing should be enhanced; nutritional and psychologic counseling represent an unmet need. Enrollment is ongoing.

B07

IRINOTECAN IS SUPERIOR TO OXALIPLATIN IN KRAS G12C-MUTATED COLORECTAL CANCER AND SHOULD BE PREFERRED IN COMBINATION STRATEGIES WITH KRAS G12C INHIBITORS. A MULTICENTER PROPENSITY SCORE-MATCHED RETROSPECTIVE ANALYSIS

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Background: KRASG^{12}C inhibitors have recently become available, yet limited activity has been observed when used as monotherapy in colorectal cancer (CRC). Given their good safety profile, combination strategies with other targeted agents or chemotherapy are being considered to increase therapeutic efficacy.

Patients and methods: A multicenter retrospective analysis was conducted to assess the efficacy of standard first-line chemotherapy in KRASG^{12}C mutated metastatic CRC patients. KRASG^{12}D-mutated patients were used as control group. Only patients treated with first-line FOLFIRI or FOLFOX +/- bevacizumab(bev) were included. Primary and secondary outcome measures were progression free survival (PFS) and objective response rate (ORR), respectively. Both an unmatched and a propensity score (PS) matched analysis were conducted.

Results: 86 patients were included: 51 KRASG^{12}C-, 35 KRASG^{12}D-mutated. Median(m) age was 63 years (range 34-83), 49 were male, 37 female. Liver metastasis were present in 71% of patients, 51% had 2 or more metastatic sites. FOLFIRI, FOLFIRI-bev, FOLFOX and FOLFOX-bev was the first-line for 15, 36, 10 and 25 patients, respectively. In KRASG^{12}C-mutated patients a statistically significant benefit in PFS was demonstrated for FOLFIRI+/-bev vs FOLFOX+/-bev: Hazard Ratio(HR) 0.52 (95%CI 0.28-0.98), p 0.04. The benefit was even more pronounced in the PS-matched analysis, with PS estimation based on age, gender, receipt of bevacizumab, histological grade, performance status, metachronous vs synchronous metastasis, number of metastatic sites, presence of peritoneal metastasis: HR 0.24 (95%CI 0.08-0.71), p 0.01. No difference in ORR was seen: 48% vs 47%, p 0.87, respectively. Also mPFS was not numerically different: 11.7 vs 11.6 months, however 12-, 18-, 24-month PFS rates were 48% vs 46%, 43% vs 18% and 32% vs 5% for FOLFIRI+/-bev vs FOLFOX+/-bev. In the KRASG^{12}D-mutated group, no significant differences were observed between FOLFIRI+/-bev vs FOLFOX+/-bev for both PFS and ORR, p 0.09 and 0.45, respectively.

Conclusions: Irinotecan (i.e. FOLFIRI+/-bev) was significantly superior to oxaliplatin (i.e. FOLFOX+/-bev) in KRASG^{12}C-mutated CRC patients, with a subset of patients (32%) achieving a long-lasting (> 2 years) PFS. Irinotecan should be the preferred chemotherapy to be used in combination strategies with KRASG^{12}C inhibitors.

B08

VARIATIONS IN CIRCULATING LEVELS OF ANGIOPOIETIN2 OVER TIME ARE PREDICTIVE OF RAMUCIRUMAB-PACLITAXEL THERAPY OUTCOME IN ADVANCED GASTRIC CANCER: RESULTS OF PROSPECTIVE STUDY

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Background: The combination of Paclitaxel and Ramucirumab is the second-line therapy of choice in the treatment of advanced Gastric Cancer (GC). However, to date no biomarkers are available in GC to predict the outcome of antiangiogenic therapy.

Methods: The present prospective study included 35 patients undergoing second-line therapy with Ramucirumab and Paclitaxel. Analysis of the levels of selected angiogenic biomarkers was performed on serum samples at multiple time points. The population was divided into "control-disease (CD) group" and "progressive-disease (PD) group". The levels of the different markers were measured at baseline, at the beginning of the third cycle of therapy and at the time of disease progression. All VEGF family members as well as Angiopoietin2 (Ang2) and its receptor were considered.

Results: The aim of our study was to identify possible predictive markers and to evaluate whether variations in a given marker over time could be predictive for therapeutic outcome. Patients with longer PFS presented higher baseline levels of VEGFs and Ang2 compared to those with

Table 1. Differences between serum biomarker levels at T3 and T0 times.

	delta T0-T3		
*Biomarkers	CD patients (n=17)	PD patients (n=18)	p^
VEGFC	590.29±1732.78	−1687.01±2898.69	0.02
Ang2	2018.43±1209.89	920.96±1892.42	0.05
PLGF	−29.87±31.52	−33.76±24.16	0.41
VEGFD	−264.51±168.37	−181.57±162.14	0.30
VEGFA	−240.38±234.89	−290.93±168.11	0.26
sVEGFR1	16.73±83.97	−2.44±9.49	0.41
sVEGFR2	109.61±704.49	335.98±884.00	0.36
VEGFR3	20138.10±8857.56	24898.74±11633.47	0.17
sTie2	585.91±827.08	541.21±1343.28	0.52

*Concentration *pg/ml* Mean±DS;
^Wilcoxon rank-sum (Mann–Whitney) test.
Abbreviation: CD, Control Disease; PD, Progression Disease; $_{?T0\text{-}T3}$, T_0-T_3 delta.

shorter one. Although the basal levels of the markers examined were not predictive of response, the results indicate that the decreases of Ang2 and VEGFC, both involved in angiogenesis and lymphangiogenesis, measured at the beginning of the third cycle are associated with a lower risk of progression and therefore a longer PFS. In addition, there was a significant increase in VEGFC and Ang2 at the progression time, which could suggest the activation of alternative pathways such as VEGFC/VEGFR3 and Ang2/Tie2 that may counteract the blockade of VEGFR2 by Ramucirumab.

Conclusions: The results of these analyses showed that a greater change in VEGFC and Ang2 levels measured at the beginning of the third cycle of therapy corresponded to a lower risk of progression and thus to a longer PFS.

B09

LANDSCAPE OF GERMLINE PATHOGENIC VARIANTS (PV) IN PANCREATIC CANCER (PC)-PREDISPOSING GENES AND THEIR IMPACT ON OUTCOMES IN PC PATIENTS

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Background: Despite the lack of a validated surveillance program for high-risk individuals, international guidelines recommend multigene germline (MGP) testing for PC pts. However, the implementation of this recommendation is hampered by the uncertainty around its clinical utility, particularly for genes other than BRCA1/2. Preliminary data showed a high prevalence of CDKN2A PV in Italian PC pts, regardless of familial status, and BRCA1/2 PVs were found only in pts<74yo. A comprehensive analysis by MGP in unselected Italian PC pts is lacking.

Methods: We evaluated the prevalence and impact on outcomes of PVs in 51 PC susceptibility genes in a real-life retrospective series of 422 Italian PC pts. Characteristics of pts with PV were compared to WT pts using Student's t-test or chi square test. Cox proportional hazard regression models were performed to estimate hazard ratios (HR) and 95% confidence interval.

Results: PVs were found in 17% of pts (70/422). The most frequently altered genes were BRCA1-2 (4.5%, all<70 yo), CDKN2A (4.5%), ATM (2.1%), CHEK2 (1,7%) and COL7A1 (1,2%). Overall, mean age was 67 yo, median follow-up was 9.8 months (0.02–156), and 22% were resectable PC at diagnosis. When compared with WT (N=352) pts, PVs carriers were associated with younger age at diagnosis (64 yo vs 67; P=0.02), positive family history (FH) for PC (26% vs 10%; P<0.001), melanoma (10% vs 4%; P=0.034), breast and ovarian cancer (29% vs 13%, P=0.001), and with personal history of other tumors (32% vs 13%, P<0.001). Of note, 46% of pts carrying PVs in CDKN2A, BRCA2 and ATM had no FH. Compared to WT, overall pts carrying any PVs showed a trend for better OS (HR 0.78; 0.59-1.04; P=0.090). This trend may be explained by the group with ATM PVs (N=9) that seem to confer a better prognosis (HR 0.33; 0.10-1.02; P=0.054); no significant differences were observed between pts with

PVs in other genes and WT pts. Overall, median OS was 11.5 months (10.3-13.3).

Conclusions: Overall, a high PV frequency was found in our PC cohort (17%), with a 4.5% rate for CDKN2A and for BRCA. ATM PVs were associated with improved survival. Since 50% of pts carrying PVs had no FH, they would have been missed by traditional referral. These findings may have a great impact on PC pts management as well as on high-risk family member genetic counselling and follow-up.

B10

THE ROLE OF THE PRE-TREATMENT INFLAMMATORY BIOMARKERS IN THE PREDICTION OF THE EARLY RESPONSE TO PANITUMUMAB IN METASTATIC COLORECTAL CANCER

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Background: The systemic inflammation is a critical component of the development and progression of several types of cancer. Neutrophil-lymphocyte (NLR) and lymphocyte-monocyte ratio (LMR) are simple, inexpensive, and reliable predictors of the systemic inflammatory response to the therapy in different malignant tumors, including colorectal cancer.

Methods: Metastatic colorectal cancer (mCRC) receiving first line treatment with panitumumab plus chemotherapy at our Institution between 1st January 2016 and 1st February 2021 were retrospectively analyzed. NLR and LMR were divided into two groups (high and low) based on the cut off points with the estimation of the prognostic accuracy of NLR for the early treatment response as the primary end-point of this study.

Results: Complete data for the purpose of the study was available in 54 patients. The ROC analysis showed a fair prognostic accuracy of NLR for early response (AUC=0.76, 95%CI: 0.62-0.89). The Youden Index identified 2.72 as the optimal cut-off for NLR to 'classify' early treatment response, with a sensitivity of 75% (95%CI: 55.1%-89.3%) and a specificity of 76.9% (95%CI: 56.4%-91.0%). According to this cut-off, 27 patients belonged to NLRLow group (NLR$<$2.72) and 27 belonged to NLRHigh group (NLR$\geqslant$2.72). A slightly lower prognostic accuracy was found for LMR (AUC=0.71, 95%CI: 0.57-0.85). The optimal cut-off for LMR according to Youden Index was 2.81 (sensitivity: 42.3%, 95%CI 23.4%-63.1%; specificity: 92.9% 95%CI: 76.5%-99.1%). In the univariable Proportional Hazard Cox model, no effect of NLR on PFS was found (NLRHigh vs. NLRLow HR=1.3; 95%CI:0.7-2.4, p=0.414). Patients with higher levels of LMR showed a trend towards higher PFS (LMRHigh vs. LMRLow HR=0.4; 95%CI:0.2-1.1,p=0.066). No association was found between NLR (or LMR) and skin toxicity.

Conclusions: Our preliminary results suggest that NLR and LMR may be used as prognostic biomarkers of early treatment response in mCRC patients treated with panitumumab. Ultimately, these biomarkers are only the tip of the iceberg of a much more complex biology, concerning the complex and dynamic relationship between the tumour, its micro-environment and the immune system of the host.

B11

CLINICOPATHOLOGIC FEATURES, TRANSCRIPTOMIC LANDSCAPE AND TREATMENT IMPLICATIONS OF THE IMMUNOSUPPRESSIVE CD73/NT5E IN BILIARY CANCER (BTC)

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Introduction: Despite the improved outcome with the addition of the anti-PD-L1 durvalumab to standard treatment, the vast majority of BTC do not benefit from chemo-immunotherapy. Immunosuppressive microenvironment is a dominant feature of BTC, involved in tumour progression and drug resistance. Here, we investigated the biological role and treatment implications of the adenosine-producing enzyme CD73 in a clinically-annotated cohort of BTC.

Methods: Immunohistochemistry for CD73, CD4/CD8 and FOXP3, whole-exome and transcriptomic sequencing were performed on resected specimens of 80 BTC (Illumina Platform). Spatial Transcriptomics was performed by using Visium Spatial Gene Expression-10x Genomics. Tumor growth was assessed in 2D and 3D

culture by using MTS assay and spheroid growth analysis. Survival and correlation analyses were performed.

Results: High CD73 expression (CD73high) was associated with older age (p=0.01), gallbladder subsite (p=0.03), and nodal involvement (p=0.04). CD73high tumours were significantly enriched in FOXP3+ T lymphocytes (p<0.001). CD73high status was independent predictor of poorer prognosis at the multivariate analysis (p=0,03), with ECOG PS =2 (p=0,001) and the pathological stage (p=0,025) and was associated with a remarkably shorter RFS in patients treated with adjuvant chemotherapy (p=0,011). Transcriptomically, CD73high tumours were significantly enriched in upregulated EMT, TNF-alfa/NFKB, hypoxia and G2/M checkpoint signaling pathways and p53, BMI1, MEL18, EGFR and K-RAS genes. In in vitro models, siRNA-mediated depletion and CRISPR-CAS9 gene KO of CD73 sensitized both BTC 2D and 3D culture to cisplatin/gemcitabine treatment. The pharmacological inhibition of CD73 by AMCP improved the sensitivity of BTC cell lines to cisplatin/gemcitabine treatment. Finally, spatially resolved transcriptomics of CD73high revealed a critical role of CD73 in tumor immunity and therapeutic response.

Conclusions: We showed that CD73high BTC display aggressive biological features, poorer prognosis and resistance to standard chemotherapy. The therapeutic targeting of this adenosinergic ectonucleotidase by clinically-available compounds has the potential to enhance the efficacy of conventional treatment in BTC.

B12

DNA DAMAGE REPAIR (DDR) GERMLINE MUTATIONS (GMS) IN PANCREATIC DUCTAL ADENOCARCINOMA (PDAC): A MONO-INSTITUTIONAL RETROSPECTIVE STUDY

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Background: GMs in DDR genes, in particular BRCA1/2,are associated with increased cancer risk, among which PDAC. Their identification is crucial, not only for clinical relevance but also for family implications. However, there are few data regarding the epidemiology and the prognostic role of DDR GMs in PDCA pts. The aim of our study is to determine the prevalence of DDR GMs, their correlation with clinicopathological features and their prognostic role.

Methods: Unselected PDAC pts, assessed by BRCA1/2 GM analysis or multigenic panel at our Institution, were retrospectively analyzed. We divided the overall population into 3 groups based on GMs: pts with pathogenic variants (PVs), pts with variants of uncertain significance (VUS) and pts with no alterations. Clinicopathologic characteristics were collected. The incidence of DDR GMs variants and their association with OS were evaluated. Uni and multivariate analyses for OS were performed.

Results: From 2019 to 2021, 200 PDAC pts were tested for DDR GMs: all pts were evaluated for BRCA 1/2,140 pts were tested for DDR GMs. 25 pts (12.5%) had PVs, 45 (22.5%) VUS and 130 (65%) no GM.BRCA 1-2 PVs were found in 10 pts (5%). Out of 91 pts with metastatic disease, the rate of PVs BRCA1/2 was 8.8%. Among 140 pts tested with multigenic panel, PVs included: 7 (5%) ATM, 5 (3.6%) MUTYH, 1 (0.7%) TP53, 1 (0.7%) BARD1 and 1 (0.7%) MSH6. The most frequent VUS were: CHECK2 (5%), APC (3.6%), ATM (3.6%), BRCA2 (3.6%). Regarding cancer family history, a statistically significant difference was reported between the 3 group (76% in PV, 82% in VUS, 60% in no GM; p 0.01). No difference was found concerning age (p 0.69),stage at diagnosis (p 0.31),platinum-exposure (p 0.27).Out of 189 evaluable pts, mOS was 23 months. A significant difference in OS was observed in the 3 groups (30 months in PVs, 14 months in VUS, 24 months in no GM, p 0.0006). No factor, including the presence and the kind of GM, age, stage and family history,was significantly associated with OS at the multivariate analysis.

Conclusions: In our study, we observed a high incidence of DDR GMs PV (12.5%),beyond BRCA 1/2, regardless age, stage and family history. Despite retrospective nature of our analysis, small population and single-institution evaluation, our findings confirmed the importance of genetic testing for BRCA1/2 and, where available, a multigenic test in all PDAC pts due to the therapeutic implications and cancer risk prevention in patients relatives. The prognostic role of DDR GM and the impact of VUS remain unclear

B13

ADVANCED BILIARY TRACT CANCERS: EXTENDED MOLECULAR PROFILING AND REAL-LIFE ACTIONABILITY IN A MONOCENTRIC CASE SERIES

Niger M.[1], Nichetti F.[1], Vingiani A.[2], Pircher C.[1], Agnelli L.[2], Conca E.[2], Tamborini E.[2], Perrone F.[2], Damian S.[1], Duca M.[1], Proto C.[1], Corti F.[1], Provenzano L.[1], Franza A.[1], Raimondi A.[1], Morano F.[1], Pruneri G.[1], Di Bartolomeo M.[1], Pietrantonio F.[1], De Braud F.[1]

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Background: Biliary Tract Cancers (BTC) have poor prognosis and limited therapeutic options. There is

mounting evidence for biomarker-directed therapy for BTC, with several potentially actionable molecular targets reported in up to 47% of patients and significant biological differences between intrahepatic (ICC) and extrahepatic (ECC) cholangiocarcinoma and Gallbladder cancer (GBC). ESMO recommends the use of tumour multigene sequencing for CCA.

Methods: This was an retrospective, monocentric study aimed at assessing real-life feasibility of expanded sequencing and clinical actionability of the results for patients (pts) affected by advanced BTCs. Clinical and molecular data of patients admitted at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan from January 2016 to March 2022 were reviewed. Molecular profiling was performed either via the 50 genes "Hotspot Cancer Panel, Ion Torrent®" or the FoundationOne®CDx panel; FGFR2 testing was also performed via fluorescence in situ hybridisation. Molecular alterations were classified according to ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) and correlated with targeted treatments administrated and efficacy endpoints.

Results: Amongst the 263 samples with adequate tissue, 181 (68%) were ICC, 48 (19%) were ECC and 34 (13%) were GBC. Actionable targets as per ESCAT I-II were found in 27% of pts (N=68, including 27 IDH1 mutation, 33FGFR2 fusions, 3 MSI-H, 5 $BRA^{F}V^{60}0E$ mutations); ESCAT III alterations were found in 14% of pts (N=37, 4 ERBB2 mutations, 6 ERBB2 amplification, 7 BRCA1/2 mutations, 20 PIK3CA mutations). Among pts with ESCAT I-III alterations, 44 patients (16%) were actually started on targeted therapy (9 ivosidenib, 30 FGFR2 inhibitors, 1 PD-L1 inhibitor, 3 BRAF+MEK inhibitor, 1 ERBB2 inhibitor) in ⩾ 2 line. Among pts treated with matched targeted therapy with adequate follow up, median overall survival of targeted therapy was 10.4 months (95%CI 7.8 - 18.2) and median progression free survival was 4.1 (95%CI 2.3 – 5.8months.

Conclusions: Expanded sequencing for BTCs is feasible and can improve treatment strategy.

B14

LABORATORY PARAMETERS PLUS EARLY TOXICITY TO ASSESS PROGNOSTIC GROUPS IN PROSPECTIVELY STRATIFIED, RAS WILD TYPE, ANTI-EGFR RESISTANT, METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH SECOND-LINE FOLFIRI-AFLIBERCEPT IN THE PHASE 2 DISTINCTIVE TRIAL – A GISCAD STUDY

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Background: The prognostic role of early adverse events during treatment and haematologic parameters became of interest in various tumors. Here, we present the results of a pre-planned interim analysis of the phase 2 DISTINCTIVE trial (NCT04252456) on prognostic groups assessed by combining toxicity occurring during the first 4 cycles and laboratory values in anti-EGFR resistant RAS wild type (wt) metastatic colorectal cancer (mCRC) patients (pts) receiving second-line FOLFIRI-aflibercept.

Material (patients) and methods: RAS wt mCRC pts progressing after oxaliplatin-based chemotherapy + anti-EGFR receive second-line FOLFIRI-aflibercept. Primary endpoint is overall survival (OS) according to VEGFR2 levels. Secondary endpoints are OS, progression free survival (PFS), response rate, safety (CTCAE v.4.03) and angiogenic factors levels. Clinical and laboratory data are collected at baseline and during treatment. Statistical analysis is performed with MedCalc (survival distribution: Kaplan-Meier; survival comparison: log-rank test; multivariate analysis: logistic regression; cut off: ROC curves).

Results: Globally, of 73 pts enrolled (04/2018-06/2020), 44 were eligible for interim analysis. Multivariate analysis showed the independent role of baseline red blood cells count (RBC) and occurrence of early any-grade diarrhoea for PFS (Exp(b) 0.2431, p=0.0157 and Exp(b) 0.3659, p=0.0134, respectively). Based on these findings, we separated pts in 2 prognostic groups: favourable prognosis ($RBC > 3.81x10^6/\mu L$ + early diarrhoea) and unfavourable prognosis ($RBC = 3.81x10^6/\mu L$ and/or no early diarrhoea). The favourable group had a significantly longer PFS (10 months [95% CI: 8.4-14.2] versus 4 months [95% CI: 2.6-5.4], p=0.0002, HR=0.20) and OS (not reached versus 10 months [95% CI: 6.4-11.9], p=0.0058, HR=0.19).

Conclusions: Our findings showed the prognostic role of the combination of laboratory parameters and early toxicity in RAS wt anti-EGFR resistant mCRC pts receiving FOLFIRI-Aflibercept. These promising results need confirmation in the final analysis of the study and they might represent a useful tool to identify a subgroup of pts who are more likely to benefit from this treatment.

Funding

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B15

COMPARATIVE ANALYSIS OF REGORAFENIB AND TRIFLURIDINE/TIPIRACIL IN LATER-LINE REFRACTORY METASTATIC COLORECTAL CANCER: A REAL-LIFE MULTICENTER RETROSPECTIVE STUDY

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Background: Regorafenib (REG) and Trifluridine/tipiracil (FTD/TPI) have been shown to prolong survival for patients (pts) with refractory metastatic colorectal cancer (mCRC). Our analysis aimed to compare the efficacy and safety profiles of these agents in daily clinical practice.

Materials and methods: Clinical data of pts diagnosed with mCRC who received REG and/or FTD/TPI between July 2012 and March 2022, were retrospectively collected from 12 institutes in Lazio Region. Overall survival (OS), progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), and adverse events (AEs) were compared between the two groups. Results. 765 pts were included. Of these, 315 (41.1%) received FTD/TPI alone, 314 (41%) REG alone, 69 (9%) FTD/TPI followed by REG, and 67 (8.7%) the reverse sequence. M/F=440/325; median age was 68 (42-86); median duration of follow-up was 30.3 months (mos) (95% CI=26.3-37.0). The prevalent ECOG PS was 2 (54.6%). For the time being, we focused on pts who received TAS or REG alone (N=629). Drug dose reductions due to grade 3-4 AEs were carried out in 23.4% in FTD/TPI-treated pts (the reduction to 30 mg/m2 was the most prevalent in 16.1% of the events) vs 45.2% of REG-treated pts (the reduction to 120 mg occurred in 26.3% of the cases) (p=<0.00001); 2 pts discontinued therapy in the FTD/TPI group vs no one of the other group. The most common grade 3/4 AEs related to FTD/TPI were haematologic: neutropenia (48.6%) and anemia (28.9%); on the other hand, these were non-haematologic like hand-foot syndrome (19.7%) and fatigue (17.1%) (p=<0.00001). The median PFS and OS of the FTD/TPI group were both longer than the REG group: 3.2 vs 3 mos (HR=1,03; 95%CI=0,86-1,24; p=0.71) and 5.9 vs 5 (HR= 0,91; 95%CI=0,75-1,11; p=0.37), respectively. The ORR did not differ significantly showing slightly higher in the FTD/TPI-treated group (REG 2.3%, FTD/TPI 3%); to mention 1 complete response achieved using REG. The DCR was modestly in favor of the FTD group (REG 22.8%, FTD/TPI 26.9%; p=0.28).

Conclusions: Our real-world analysis showed similar effectiveness of FTD/TPI and REG with no relevant PFS and OS differences between the two groups. Despite a statistically non-significant best ORR, treatment with FTD/TPI, although worse tolerated up to the discontinuation in sporadic cases because of hematologic toxicities, could allow a modest improvement in OS and DCR. In conclusion, we suggest that prospective clinical trials directly comparing REG and FTD/TPI are needed.

B16

CORRELATION OF EARLY TOXICITY WITH EFFICACY OF SECOND-LINE FOLFIRI-AFLIBERCEPT IN PROSPECTIVELY STRATIFIED, RAS WILD TYPE, ANTI-EGFR RESISTANT, METASTATIC COLORECTAL CANCER PATIENTS – AN INTERIM ANALYSIS OF THE PHASE 2 DISTINCTIVE STUDY – A GISCAD TRIAL

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Background: The correlation of early toxicity with efficacy in the specific population of RAS wild type (wt) metastatic colorectal cancer (mCRC) patients (pts) resistant to first-line anti-EGFR and treated with second-line anti-angiogenic agents has not been fully explored. We report the safety results of a pre-planned interim analysis of the prospectively stratified, biologically enriched, phase 2 DISTINCTIVE study (NCT04252456).

Material (patients) and methods: Oxaliplatin + anti-EGFR treatment resistant RAS wt mCRC are treated with second-line FOLFIRI-aflibercept. Primary endpoint is overall survival (OS) according to VEGFR2 levels. Secondary endpoints are OS, progression free survival (PFS), response rate, safety and angiogenic factors levels. Safety is assessed before each treatment cycle according to CTCAE v.4.03; in this analysis, we focused on the first 4 treatment cycles. Statistical analysis is performed with MedCalc (survival distribution: Kaplan-Meier; survival comparison: log-rank test; multivariate analysis: logistic regression).

Results: Overall, 44/73 pts enrolled (04/2018-06/2020) were eligible for interim analysis. Any-grade toxicity in the first 4 cycles occurred in 90.9% of pts; only 18.1% of adverse events (AEs) were grade 3-4. The most common any-grade AEs were diarrhoea (52.3%), fatigue (45.4%), neutropenia and nausea/vomiting (13.6% each), hypertension and fever (11.4% each); other AEs (excluding bleeding, proteinuria and thromboembolic AEs) were reported in 43% of pts. The most frequent grade 3-4 AE was neutropenia (4.5%), followed by fatigue, diarrhea and proteinuria (2.3% each). Our analysis showed a statistical significant correlation between longer PFS and early occurrence of any-grade diarrhoea (10 months [m] [95%CI:8.4-11.9] vs 4.2 m [95%CI:2.6-5.4], p=0.0021, HR=0.26) and the absence of early AEs classified as "other" (9.8 m [95% CI: 3.1-14.2] vs 5.8 m [95% CI: 4-8.5], p=0.0372, HR=0.44). At multivariate analysis, only diarrhoea maintained an independent role (Exp(b) 0.1849, p=0.0002).

Conclusions: Early safety data on second-line FOLFIRI-aflibercept in RAS wt oxaliplatin+anti-EGFR pretreated pts were consistent with tolerability shown in previous trials. We found a promising significant correlation between early occurrence of diarrhea and improved PFS. If confirmed in the final analysis, these findings might allow to identify pts with improved benefit from this treatment.

Funding

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B17

CIRCULATING TUMOUR DNA AS A MARKER OF MINIMAL RESIDUAL DISEASE AFTER RADICAL RESECTION OF COLORECTAL LIVER METASTASES

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Background: Prognostic tools to estimate the risk of relapse of liver-limited metastatic colorectal cancer (LL-mCRC) patients undergoing resection with curative intent are needed. Circulating tumour DNA (ctDNA) as a surrogate of postsurgical minimal residual disease (MRD) is a promising marker in localized CRC. We explored the role of post-operative ctDNA as a marker of MRD in radically resected patients with LL-mCRC.

Patients and Methods: 76 LL-mCRC patients were included. DNA from tumour tissue was sequenced and one somatic mutation was then assessed by ddPCR in plasma samples collected after surgery to identify the persistence of ctDNA. Relapse-free (RFS) and post-resection Overall Survival (OS) were compared between patients with positive vs negative post-operative ctDNA.

Results: CtDNA was found in 39 (51%) out of 76 LL-mCRC patients. At a median follow-up of 77 months, 33 out of 39 ctDNA-positive and 20 out of 37 ctDNA-negative patients experienced disease relapse (p=0.008). CtDNA-positive patients reported significantly shorter RFS than ctDNA-negative ones (median RFS 12.7 vs 27.4 months, (HR: 2.09, p=0.008). In the multivariable model

including other prognostic covariates this association was still significant (p=0.045), a trend toward shorter OS among ctDNA-positive patients was reported (HR 1.65, p=0.183).

Conclusions: The detection of postsurgical ctDNA is an independent negative prognostic marker and identifies patients at high risk of relapse after liver metastases resection. Assessing an individual somatic mutation has lower sensitivity than tissue-informed techniques searching for multiple alterations.

B18

COMPARISON OF PACLITAXEL + RAMUCIRUMAB (PAC/RAM) FOLLOWED BY FOLFIRI VERSUS THE REVERSE SEQUENCE IN UNRESECTABLE OR METASTATIC GASTROESOPHAGEAL AND GASTRIC ADENOCARCINOMA (GA) PATIENTS (PTS) AFTER FRONT-LINE PLATINUM + FLUOROPYRIMIDINE THERAPY

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Background: Combination of platinum and fluoropyrimidine represents the standard first-line therapy for advanced gastroesophageal and gastric adenocarcinoma (GA). The recommended second-line choice is Paclitaxel + Ramucirumab (PAC/RAM); however, patients (pts) can have controindications due to platinum-related neuropathy, presence of thromboembolic venous disease or a short interval between taxane-based chemotherapy (CHT) for local advanced or oligometastatic GA and recurrence of disease. In this retrospective monocenter study we assessed varied sequencing of second-line and third-line therapies comparing PAC/RAM followed by fluoropyrimidine + irinotecan (FOLFIRI) versus the opposite sequence.

Material and Methods: GA pts who received at least 3 lines of therapy, including PAC/RAM and FOLFIRI, were retrospectively collected. Two cohorts of pts were analyzed: Cohort A: RAM/PAC second-line followed by FOLFIRI third-line; Cohort B: FOLFIRI second-line followed by RAM/PAC third-line. Primary endpoint was overall survival (OS) from start of second-line therapy and from the diagnosis of advanced GA; secondary endpoints were progression free survival (PFS) from start of second-line and Response Rate (RR). PFS and OS analyses were performed using Kaplan-Meier method, and survival curves were compared using the log-rank test. RR was evaluated according to RECIST criteria and compared in the two groups using Fisher's exact test.

Results: A total of 100 advanced GA pts who received PAC/RAM followed by FOLFIRI or the reverse sequence as second and third-line therapy respectively were enrolled (71 pts in Cohort A; 29 pts in Cohort B). No difference was observed in median OS (mOs) from the start of second-line therapy (Cohort A=9.8 months vs. Cohort B=9.8 months, HR 0.95 95% CI 0.58-1.56, p=0.84) or mOS from metastatic disease diagnosis (Cohort A=20.6 months vs. Cohort B=19 months, HR 0.97 95% CI 0.59-1.60, p=0.91). PFS (Cohort A=5.7 months vs. Cohort B=6 months, HR 0.86 95% CI 0.52-1.42, p=0.55) and RR (Cohort A=61.9% vs Cohort B=65%, p=0.82) were similar between the two cohorts.

Conclusions: Our study, even though its retrospective nature and the small number of pts enrolled, suggests similar efficacy of one sequence versus the other, with similar survival outcomes.

B19

ASSOCIATION BETWEEN MALNUTRITION AND TREATMENT COMPLIANCE AND OUTCOMES IN PATIENTS UNDERGOING PERIOPERATIVE CHEMOTHERAPY FOR RESECTABLE GASTRIC (GC) OR GASTRO-OESOPHAGEAL JUNCTION CANCER (GEJC)

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Background: Perioperative treatment with FLOT chemotherapy (CT) proved to significantly improved survival in GC or GEJC patients (pts). Due to disease-related symptoms, including nausea and dysphagia, many pts present weight and fat-free mass loss at diagnosis which is often under-estimated when evaluated only with body mass index (BMI). The Nutritional Risk Index (NRI) has been developed as a valid tool to assess the nutritional status. Aim of our study was to determine if the presence of baseline malnutrition is associated with dose limiting toxicity (DLT), treatment compliance and outcomes in GC or GEJC pts undergoing perioperative treatment.

Patients and methods: In this observational retrospective study, we collected data from pts with resectable GC or GEJC undergoing perioperative FLOT CT between April 2018 and February 2022 at our Institution. Baseline

malnutrition risk was defined by the presence of a NRI <97.5 within 15 days prior to the start of CT. DLT was defined as a toxicity leading to dose reduction, delay,or definitive interruption of treatment.

Results: A total of 31 pts were eligible for our analysis. At diagnosis all pts had a normal or increased BMI (median BMI: 25.2; range 18.8–34.5) but 45% had a weight loss of ⩾5% compared to the usual weight. Twelve patients (38.7%) resulted at malnutrition risk by NRI at baseline. The prevalence of DLT was higher in pts at malnutrition risk compared to well-nourished pts (33.3% vs 5.3%, p=0.038). Pts at malnutrition risk had a not statistically significant reduced compliance to perioperative treatment: 83.3% vs 100% completed the pre-operative phase (p=0.06) while 41% vs 63% completed the postoperative treatment (p=0.11). Patients with pre-treatment malnutrition had a significantly shorter disease free-survival (DFS: 27.4 vs 33.1 months, p=0.03) and a trend toward decreased overall survival (35.1 vs 41.9 months, p:0.73).

Conclusions: Early assessment of malnutrition risk by NRI is associated with increased DLT and shorter DFS in patients undergoing perioperative CT for GC and GEJC. Future studies are required to evaluate, in larger series, the impact of specific and early nutritional interventions on treatment compliance and patient outcomes.

B20

EFFICACY OF IMMUNE CHECKPOINT INHIBITORS IN ADVANCED ESOPHAGEAL SQUAMOUS CELL CARCINOMA: A PATIENT-LEVEL META-ANALYSIS WITH KMSUBTRACTION DERIVED PD-L1 SUBGROUPS

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Background: The use of immune checkpoint inhibitors (ICI) improved the survival outcomes of patients with advanced esophageal squamous cell carcinoma (ESCC) in both first- and second-line settings. The efficacy of immunotherapy is evident in patients with high PD-L1 expressing tumors, but it remains unclear in patients with a low PD-L1 expression.

Materials and Methods: Randomized controlled trials (RCTs) investigating the efficacy of anti-PD1-based regimens versus chemotherapy alone for advanced ESCC were selected. We adopted a graphical reconstructive algorithm to estimate time-to-event outcomes from reported overall survival (OS) Kaplan-Meier (KM) plots and to retrieve KM curves of the unreported subgroups through KMSubtraction. After deriving individual patient survival data (IPD), we conducted IPD meta-analyses of studies grouped by the treatment line and the scoring system of PD-L1 expression, to compare survival outcomes with immunotherapy-based regimens versus chemotherapy. Subgroup analyses were conducted to compare outcomes in patients with low and high PD-L1 expression.

Results: The IPD meta-analysis of CHECKMATE648 and ESCORT-1ST showed a hazard ratio (HR) benefit for OS with CTLA-4/PD-1 dual immunotherapy [0.792; 95% confidence interval (CI), 0.665 – 0.943; P<0.001] or chemo-immunotherapy (0.735; 95% CI, 0.665-0.943; P<0.001) compared with chemotherapy alone. In the TPS<1 subgroup, immunotherapy and chemo-immunotherapy showed no OS benefit compared to chemotherapy (respectively, HR 1.000; 95% CI, 0.789 – 1.267; P = 0.997; HR 0.926; 95% CI, 0.753 – 1.139; P = 0.469).

Conclusions: Overall, the addition of ICI to chemotherapy reduces the risk of death in patients affected by advanced ESCC. However, our results suggest a lack of survival benefit of ICI-based regimens in first line setting compared to chemotherapy alone in the TPS < 1 subgroup.

B21

MICRORNA EXPRESSION PROFILE IN PATIENTS WITH METASTATIC PANCREATIC CANCER

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Background: A lot of studies in Literature documented that benign and malignant conditions in the context of pancreatic pathology can be discriminated by different miRNA expression profiles, while there is a paucity of data that can demonstrate a different miRNA expression profile in relation to the prognosis of the patients. The aim of this study is to demonstrate that miRNAs could be used as a tool to predict the possible course of the disease itself at the time of diagnosis as they are expressed differently in relation to survival characteristics.

Patients and methods: We retrospectively collected data about clinical and biologic parameters of 118 patients whose diagnosis and treatment of metastatic pancreatic cancer took place in the University Hospital of Ferrara in the period between 2013 and 2019.From this broader

case series, two subgroups were then selected:- the "poor survivors" (9/118), patients whose survival was less than 6 months from the date of diagnosis of the metastatic disease; - the "long survivors" (8/118), patients with survival longer than 18 months from the date of onset of metastases.

The two subgroups were well matched for age, ECOG PS (0-1), comorbidity, histotype, metastatic disease. We performed the RNA extraction from the histological samples of the primary tumor of the patients of the two subsets; subsequently we carried out the NGS sequencing through the Illumina platform: 1654 miRNAs were tested on both clusters under analysis.

Results: Through the NGS analysis we obtained a list of 39 miRNAs with significant difference of expression in the two subsets. miRNAs overexpressed in the poor survivor group were: hsa-miR-122-5p, hsa-miR- 181b-5p, hsa-miR-222-5p, hsa-miR- 223-3p, hsa-miR- 223- 5p, hsa-miR- 302b-5p, hsa-miR- 3127-3p, hsa-miR- 3153, hsa-miR- 371b-5p, hsa-miR-340 -3p, hsa-miR-4472, hsa-miR-483-3p, hsa-miR-511-3p, hsa-miR-511-5p, hsa-miR-514a-5p, hsa-miR-5692b, hsa-miR-592, hsa-miR-6073, hsa-miR-6507-3p, hsa-miR-758-5p, hsa-miR-885-5p.

Conversely, miRNAs overexpressed in the long survivor subset were: hsa-miR-133a-3p, hsa-miR-133b, hsa-miR-152-5p, hsa-miR-184, hsa-miR-187-3p, hsa-miR-3200-3p, hsa-miR-370-5p, hsa-miR-4284, hsa-miR-4297, hsa-miR-5006-3p, hsa-miR-501-3p, hsa-miR-504-5p,hsa-miR-549, hsa-miR-5699-5p, hsa-miR-769-3p, hsa-miR-769-5p, hsa-miR-8071, hsa-miR-875-3p.

Conclusions: Patients with different survival also have a different profile of molecular expression, suggesting a possible role of miRNAs as a prognostic factor.

B22

EXPLORING TROP2 AND NECTIN4 IMMUNOHISTOCHEMICAL EXPRESSION IN METASTATIC COLORECTAL CANCER: A SUBGROUP ANALYSIS OF THE TRIBE2 STUDY

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Background: Trop2 and Nectin4 are two transmembrane proteins overexpressed in many epithelial cancers with minimal or absent levels in cellular membrane of adult somatic tissues, thus emerging as appealing therapeutic targets. Indeed, sacituzumab govitecan, an anti-Trop2 antibody–drug conjugate (ADC), and enfortumab vedotin, an anti-Nectin4 ADC, were recently approved for the treatment of triple-negative breast cancer and urothelial carcinoma, respectively. In metastatic colorectal cancer (mCRC), the role of Trop2 and Nectin4 has been poorly investigated.

Methods: Available chemo-naïve tumour samples of patients randomized in the phase III TRIBE2 study comparing upfront FOLFOXIRI/bevacizumab (bev) *versus* (*vs*) FOLFOX/bev, were assessed for Trop2 and Nectin4 expression (exp). Immunohistochemistry (IHC) exp levels were categorized based on a histochemical score (H-score) accounting for both the staining intensity and the percentage of stained cells at different intensity levels.

Results: Out of 679 patients enrolled in the TRIBE2 study, 386 tumours were assessed for Trop2 exp. Overall, 90 (23%), 115 (30%) and 181 (47%) were classified as high, medium and low, respectively. High Trop2 tumours were more frequently *BRAF* mutated (p=0.005) and right-sided (p=0.03) compared to medium and low ones. Patients with low Trop2 tumours achieved longer progression-free survival (PFS) (12 *vs* 9.9 months, HR: 0.81, 95%CI: 0.66-1.00, p=0.05) and overall survival (OS) (27.3 *vs* 21.3 months, HR: 0.76, 95%CI: 0.60-0.95, p=0.01) than those with high/medium Trop2 tumours. The prognostic value of Trop2 exp levels was confirmed in the multivariate analysis in terms of both PFS (p=0.02) and OS (p=0.03). An interaction effect was shown between Trop2 exp and treatment intensification with higher benefit from FOLFOXIRI/bev in the medium/high Trop2 cohort ($p_{interaction}$=0.04).

Overall, 251 tumours were assessed for Nectin4 exp and 14 (5%), 67 (27%) and 170 (68%) were classified as high, medium and low, respectively. High Nectin4 tumours were more frequently left-sided (p=0.01). No prognostic impact was observed based on Nectin4 exp and no interaction effect was reported between Nectin4 exp groups and treatment arm.

Conclusions: In mCRC, exp levels of Trop2 and Nectin4 are heterogeneous, suggesting a target-driven development of anti-Trop2 and anti-Nectin4 ADCs. Medium/high Trop2 exp is associated with worse prognosis and higher benefit from chemotherapy intensification.

B23

MICROSATELLITE INSTABILITY AND HER2 STATUS IN RADICALLY RESECTABLE LOCALLY ADVANCED ESOPHAGO-GASTRIC ADENOCARCINOMA

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Background: Peri-operative systemic chemotherapy significantly improved the prognosis of patients with resectable locally advanced gastric cancer (LAGC) and is currently recommend by international guidelines. Several biomarkers, including human epidermal growth factor receptor-2 (HER2) and mismatch repair (MMR) or microsatellite instability (MSI) are crucial for treatment decision in metastatic setting but, currently, they do not guide the choice of NAC in clinical practice. Our aim was to evaluate correlations between MSI and HER2 status and clinical outcomes in resectable LAGC treated with perioperative chemotherapy.

Methods: We conducted a retrospective cohort study of resectable LAGC patients treated with NAC and surgery +/- adjuvant chemotherapy from 2006 to 2018, for whom endoscopic pre-NAC and surgical post-NAC samples were available. Determinations of HER2 and MMR status were carried out on endoscopic pre-NAC and surgical samples. Pathologic complete response (pCR) rate, overall survival (OS) and event-free survival (EFS) were estimated and evaluated for association with histologic downstaging and MSI status using Cox proportional hazard models. For dMMR cases, a custom Next-Generation Sequencing (NGS) 26 tumor-genes panel was performed.

Results: We selected 76 with a median age at diagnosis of 61 years. Fifty-nine patients received NAC, while 17 were treated with adjuvant chemotherapy alone. Overall, dMMR/MSI-H counted for 8% of cases, entirely consistent between endoscopic and surgical samples. Six percent of tumors were HER2 positive on endoscopic tumor samples. Tumor downstaging was observed in 52.5% of the population, with 3 pCR (5.1%), but none of them occurred in MSI-H cancers. According to MSI status and pCR, EFS and OS were better for MSI-H patients and MSS achieving pCR compared to MSS without pCR [EFS NR vs NR vs 30.0 months (95% CI 16.8 – NR.), p= .08; OS NR vs NR vs 39.6 (95% CI 27.6 – NR) p= .10]. In the entire population, EFS and OS were analyzed according to MSI status with a better outcome for MSI-H patients [EFS NR vs 48.0 months (95% CI 25.2 – 229.4), p= .121; OS NR vs 62.4 (95% CI 28.8 – 229.4) p < .143]. The most common alteration in MSI-H cases was TP53 mutation.

Conclusions: Our work confirms the positive prognostic effect of MSI-H in the curative setting of LAGC, not correlated with the rate of pathologic tumor response to NAC. Prospective ad-hoc trial focused on dMMR/MSI-H and more in-deep molecular profiling are strongly needed in resectable LAGC.

B24

INTENSIVE MULTIMODAL TREATMENT OF OLIGO-METASTATIC COLORECTAL CANCER (OMCRC): A RETROSPECTIVE SINGLE CENTRE EXPERIENCE

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Background: The management of omCRC patients (pts) includes the association of systemic treatments and loco-regional approaches that improve survival. Whether a repetitive use of loco-regional treatments in this setting affects clinical outcomes, however, is poorly investigated. We conducted a retrospective single centre analysis to explore survival in pts with omCRC treated with an intensive multimodal approach.

Patients and methods: Patients with omCRC treated at our centre between January 2015 and December 2020 were included in the analysis if they had undergone to surgery of the primary tumor, systemic treatment for metastatic disease, and at least two different loco-regional procedures for metastases (e.g., surgery, TARF, or STRT). Multiple procedures performed in the same time have been considered once. Objectives of the study were median overall survival (mOS) from diagnosis of metastatic disease and survival rate at 4 years.

Results: We enrolled 21 pts (Table 1). The median age was 68 years (range 41-81). Thirty-three percent of pts had right-sided CRC, while 67% left-sided. A mutation of RAS was identified in 40% of cases analyzed, while the remaining were RAS/BRAF wild type. The MMR/MSS status was tested in 8 pts and were all pMRR/MSS. The majority of pts (81%) have undergone to 1-2 lines of systemic therapies, while only 19% were treated with ⩾3 lines.

Table 1. Patient characteristics (n=21).

	N	%
Median Age		
68 yrs		
Primary site		
Right	7	33
Left	14	67
***RAS/BRAF* status (n=20)**		
RAS mutated	8	40
RAS/BRAF wild type	12	60
MMR/MSS status (n=8)		
pMMR/MSS	8	100
Systemic treatments		
1-2	17	81
⩾3	4	19
Number of loco-regional treatments		
2	8	38
⩾3	13	62
Number of patients undergoing loco-regional procedures		
Surgery (liver, lung, other sites)	16, 8, 3	76, 38, 14
STRT (liver, lung, other sites)	3, 8, 1	14, 38, 5
TARF (liver)	4	19

Sixty-two percent of pts experienced ⩾3 loco-regional procedures (range 3-6), prevalently involving liver (76%) and lung (38%) resections, and STRT of lung metastases (38%). At a median follow-up of 47.5 months, the mOS was still unreached and the 4-yr survival rate was 90%.

Conclusions: Intensive multimodal treatments allowed impressive survival in our pts with omCRC, particularly involving left-sided and RAS/BRAF wild type tumors, and is feasible in advanced age. Since the majority of pts experienced at most 2 lines of therapies, it is conceivable that the concomitant intensive use of loco-regional procedures extends the benefit of early lines of systemic treatments and should be considered whenever is possible.

B25

VIVA TRIAL: A RANDOMIZED PHASE II STUDY OF ADJUVANT REGORAFENIB PLUS DURVALUMAB IN STAGE IV COLORECTAL CANCER PATIENTS ACHIEVING THE NO EVIDENCE OF DISEASE STATE

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Background: The improvements in the systemic control of metastatic colorectal cancer (CRC) motivate doctors and patients (pts) to pursue the no evidence of disease state (NED) via locoregional treatments independently of the line of treatment and the classical guidelines indications. Standard treatments for the stage IV NED condition include surveillance despite a relapse rate of approximately 80-90% or perioperative/adjuvant FOLFOX for those pts who have never received chemotherapy before. Early-phase trials have shown a potential synergic effect of the VEGFR tirosin-kinase inhibitor Regorafenib combined with anti PD-1 agents in advanced gastrointestinal cancers. Our study explores the efficacy of low dose Regorafenib plus Durvalumab in stage IV NED CRC.

Materials and Methods: VIVA is a multicentre, open-label, phase II trial that randomizes pts with metastatic CRC achieving the NED state after completion of any treatment, to observation versus the combination of Regorafenib 90 mg d1-21 q28 plus Durvalumab 1500 mg q28 for 1 year.

The NED state can be achieved in any line of treatment and it is defined as:

a) R0 resection for surgery,
b) the complete ablation defect covering the lesion on CT scan for radiofrequency,
c) the erogation of ⩾ 60 Gy for stereotactic radiotherapy,
d) complete response to antineoplastic treatments on CT scan.

In all these cases CEA and CA 19.9 must be within normal limits at the time of randomization. dMMR/MSI pts were not eligible.

The primary objective is the efficacy of adjuvant regorafenib and durvalumab versus control. The primary endpoint is DFS. Secondary endpoints are 18-months DFS, overall survival, and toxicity. Tumor assessment will be performed every 12 weeks. Crossover to the experimental arm is allowed in case of relapse. 172 pts are to be accrued to meet the ambitious primary endpoint of a 40% reduction in DFS event rate, corresponding to a median DFS increase from 6 to 10 months.

Results (trial in progress): The run-in phase is ongoing on the first 6 pts randomized to the experimental arm using a starting dose of 60 mg/die of Regorafenib (and fixed 1500 mg of Durvalumab), to be escalated after 2 months to 90 mg/die if < 2 patients report serious adverse events.

B26

IDENTIFICATION OF NEW POTENTIAL DRUGGABLE TARGETS IN GASTROINTESTINAL STROMAL TUMOR (GIST) THROUGH RNA SEQUENCING ANALYSIS

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Background: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract with an incidence in the European countries of 10-15 cases per million inhabitants. Imatinib, a tyrosine-kinase inhibitor is the standard treatment for GISTs; however, many patients develop resistance to this drug and to sunitinib, regorafenib and repretinib (used as second, third and fourth lines of treatment) and so identification of new potential pharmacological targets remains an unmet clinical need. microGISTs are benign GISTs that already harbour driver mutations but very rarely progress to a clinical tumor; the progression of this type of tumor can be thought as sequential steps from microGIST to low risk, high risk and development of metastases.

Methods: The aim of this study was to identify novel potential druggable targets in GISTs. RNA-seq was carried out on 24 GIST samples (8 microGIST, 8 low risk (LR) and 8 high risk (HR) GIST) to compare mRNA levels. Selected deregulated genes were validated in RT-PCR. The role of a specific gene of interest was explored through shRNAs mediated known-down in 3 GIST cell models (GIST882, GIST 48, GIST T1). Silencing was tested by Western Blot; survival and cell cycle were analyzed. Different treatments on infected cells were tested and cells viability was evaluated through CellTiter-Glo Assay (CTG).

Results: RNA-seq showed 513 significantly deregulated genes in LR and HR GISTs compared with microGIST. 18 were validated and 10 maintained the significant difference. Based on enriched functional analysis, TOP2A, upregulated in HR GIST vs LR and microGIST ($p<0.05$). was selected to be validated in functional studies in GIST882, GIST 48, and GIST T1. Two different shRNAs were used to infect the cells and compared with a pLKO Control Vector. WB confirmed TOP2A knowndown; both TOP2A shRNAs induced a changed in the cell morphology compared with the negative control which did not promote any change. Moreover, inhibition of TOP2A slowed cell growth. Finally, suppression of TOP2A conferred resistance to doxorubicin and to SN38 (two TOP inhibitors) as showed by increased IC50 in shRNAs infected cells versus controls.

Conclusions: TOP2A may represent a novel druggable target in GIST; further studies will be needed to better understand its role in the carcinogenesis process.

B27

THE IMPACT OF THE MULTIDISCIPLINARY TEAM (MDT) IN THE MANAGEMENT OF COLORECTAL CANCER (CRC)

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Background: The management of CRC is complex, particularly in metastatic disease, where it is crucial the definition of disease burden, the assessment of radiological response and the identification of the right timing for potential radical surgery or loco-regional treatments. A correct CRC evaluation and the subsequent choice of the most appropriate treatment strategy, need, therefore, a MDT involving surgeons, oncologists, radiologists, radiation oncologists, endoscopists, gastroenterologists and pathologists. Based on such considerations, we investigated the impact of the MDT meeting in the management of CRC at our Institution.

Methods: We retrospectively evaluated all the cases discussed at our MDT meeting between September 2019 and September 2021. We collected data, both pre- and post-MDT meeting, regarding radiology evaluation (disease control vs progression), surgical assessment (yes vs no) and radiotherapy evaluation (yes vs no). Primary endpoint was the overall rate of discrepancy in evaluation between pre- and post-MDT meeting.

Results: Between September 2019 and September 2021, 696 cases were presented at our MDT meeting. The median age was 65 years (24-86), 391 (56%) patients were male and 553 (79%) patients had metastatic disease at

diagnosis. After MDT meeting, a total of 214 decisions were modified, for an overall discrepancy rate of 31%. In particular, among 377 cases discussed for radiology evaluation, 110 decisions (29%) were modified after a central imaging review: 80 cases initially evaluated as progressed disease before MDT meeting were defined stable after MDT meeting, for a discrepancy rate of 73%. Regarding the 246 cases discussed for surgical assessment on primary tumor and/or metastatic sites, treatment strategy changed in 86 cases (35%). More specifically, 16 cases (19%), evaluated unresectable before MDT meeting, were then considered resectable after MDT meeting. Finally, among the 71 cases discussed for radiotherapy evaluation, treatment strategy changed in 18 cases (25%).

Conclusions: Our analysis demonstrates a significant rate of discrepancy in radiology and/or surgical evaluation between pre- and post-MDT meeting. Our results show that a MDT allows a considerable modification in CRC management, maximizing the treatment strategy, in particular avoiding unnecessary changes in therapy and allowing surgery where possible.

B28

TARGETING FGFR PATHWAY IS NOT AN ACTIVE THERAPEUTIC STRATEGY IN PATIENTS WITH METASTATIC ESOPHAGEAL-GASTRIC JUNCTION/GASTRIC CANCER RESISTANT TO TRASTUZUMAB

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Background: Trastuzumab remains the only targeted agent approved for the first-line treatment of patients with HER2-overexpressing advanced esophageal-gastric/ gastric cancer (EGJ/GC) in combination with chemotherapy, However, patients invariably progress under this treatment. In preclinical models, we identified the overexpression of Fibroblast Growth Factor Receptor (FGFR) 3 as a molecular mechanism potentially responsible for trastuzumab resistance in GC, providing the rationale for the inhibition of this receptor as a potential second-line strategy in this disease.

Methods: In this Simon's two-stages phase 2, single arm, open-label study, adult patients with advanced EGJ/GC refractory to first-line trastuzumab-containing therapies received a starting dose of 13.5 mg oral pemigatinib – an oral inhibitor of FGFR1, 2, and 3 – once daily (21-day cycle; 2 weeks on, 1 week off). The primary endpoint was the 12-week progression free survival rate. We measured the expression of HER2 and FGFR1-3 by IHC, and performed Next Generation Sequencing (NGS) on tumor and plasma DNA samples collected at the enrollment.

Results: Between November 2019 and February 2021, eight patients were enrolled in the first stage of the trial. Only one patient achieved a stable disease after 12 weeks. The trial was, thus, discontinued before the second stage. Two out of six evaluable tumor samples had an overexpression of FGFR3, in another patient we have reached a mutation of FGFR1. NGS analysis did not reveal any relevant FGFRs gene amplification. HER2 amplification was lost in six out of eight patients. Three patients had an high Tumor Mutational Burden and two of them are significantly long survivors.

Conclusions: These results do not support the therapeutic activity of targeting FGFR in patients with advanced EGJ/GC refractory to trastuzumab-containing therapies. The combination of treatments targeting HER2 and FGFRs remains a strategy to be potentially explored.

B29

FLIBER - SERUM CYTOKINE LEVELS AS PREDICTORS OF THE EFFICACY OF AFLIBERCEPT IN COMBINATION WITH FOLFIRI IN METASTATIC COLO-RECTAL CANCER PATIENTS (MCRC)

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Background: The results of the VELOUR trial showed that the addition of aflibercept to irinotecan-based chemotherapy in patients with metastatic Colo-Rectal Cancer (mCRC) refractory to oxaliplatin-based chemotherapy yielded an advantage in both progression-free and overall survival. In the randomized phase II AFFIRM study involving mCRC patients treated with oxaliplatin-based chemotherapy with or without aflibercept, patients receiving aflibercept with IL-8 levels $\leqslant$ vs. $>$ 19 pg ml−1 presented a median progression free survival of 9.3 (7.52–11.10) vs. 4.1 (2.33– 8.54) months. In the phase IV FLIBER trial, we aimed to explore the predictive value of IL-8 levels and other cytokines in mCRC patients receiving FOLFIRI plus aflibercept.

Patients and methods: This phase IV, single arm trial includes mCRC patients who are resistant to or have progressed after an oxaliplatin-containing regimen and are planned to start aflibercept in combination with FOLFIRI as per standard clinical practice and decision by their treating oncologist. A serum cytokine panel including IL-8 is assessed at baseline, after 2 months of treatment and at radiologic progression. Serum samples are processed locally and then stored at -80 °C until analysis. The primary end point of the study is progression free survival (PFS), with the objective to estimate the difference in PFS between the two groups defined on the basis of their baseline IL-8 levels (>= vs. < than the median). Secondary endpoints include Radiologic Response Rate (rRR), Overall Survival (OS) and Safety profile. A total of 124 patients is required according to study design.

Results: A total of 103 patients with mCRC have been enrolled since June 2018 to March 2022 at 13 participating centers (45 F; 58 M). A total of 101 patients are assessable for cytokines, with a total of samples taken equal to 236. Median (interquartile range) duration of treatment was 12.9 (8.6; 26.0) weeks. Overall radiological response rate was 21.3% (95% CI: 12.7 to 32.3%). The most common grade 3-4 adverse events were hypertension (14.6%), diarrhea (8.7%), neutropenia (7.8%), fatigue (6.8%) and oral mucositis (6.8%). Median progression free survival was 5 months (95% CI: 3.7 to 7.5 months). Median overall survival was 10 months (95% CI: 8.5 to 14.4 months). Evaluation of cytokines is pending.

Conclusions: FOLFIRI + aflibercept is a safe and effective treatment for mCRC who are resistant to or have progressed after an oxaliplatin-containing regimen.

B30

CONCOMITANT RAS AND BRAF MUTATIONS IN METASTATIC COLORECTAL CANCER PATIENTS AS PROGNOSTIC AND PREDICTIVE FACTOR

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Background: RAS and BRAF alterations are both prognostic and predictive factors in metastatic colorectal cancer. Recent literature has described cases of RAS and BRAF mutations (mut) coexistence in colorectal cancer. This association appears to be related to poor median overall survival (mOS), median progression free survival (mPFS) and treatments responses. The aim of this study was to evaluate outcomes in patients (pts) harboring BRAF plus RAS mut.

Material (patients): We retrospectively collected data from 152 pts affected by BRAF mut metastatic colorectal cancer affering from 2007 to 2021 to the Medical Oncology Units of: University Hospital of Cagliari, Businco Hospital of Cagliari, Istituto Oncologico Veneto (Padua) and Istituto Nazionale Tumori (Milan). All pts received first line (1st L) treatment and 82% received a second line (2nd L) treatment. All pts had more than one metastatic site. Statistical analysis were performed with MedCalc package. Survival distributions were assessed by Kaplan-Meier curves.

Results: Median age was 64 y.o., 74 were male and 78 female. All pts were treated with 1st L chemotherapy plus antiangiogenic and 106 (70%) pts were treated with 2nd L encorafenib plus cetuximab. 152 pts were included in the outcomes analysis. 40 (26%) had BRAF+RAS mut, 84 (55%) had BRAF V600E single mut, and 28 (19%) had BRAF non-V600E single mut. Among the 40 BRAF+RAS mut, 26 (17%) had BRAF+KRAS mut and 14 (9%) had BRAF+NRAS mut. BRAF+KRAS showed worse median overall than BRAF+NRAS (11 versus 26 months [mo], p = 0.02). Subsequently, we compared mOS and mPFS in both BRAF+RAS mut and BRAF V600E single mut treated with encorafenib-cetuximab.

No differences were showed between mutated BRAF+RAS and single BRAF V600E in terms of OS (16 vs 13 mo, respectively) and PFS (4,8 vs 4,2 mo, respectively).

Conclusions: The results of this study, although retrospective, show that concomitant BRAF and RAS mutations are not common but they could relate to different prognosis

than patients with single mutation. The study also showed that double mutations are responsive to encorafenib plus cetuximab therapy. Further studies are needed to better understand and characterize this setting.

B31

BASELINE LDH SERUM CONCENTRATION AS PROGNOSTIC INDICATOR IN SECOND-LINE TREATMENT FOR ADVANCED GASTRIC AND GASTROESOPHAGEAL JUNCTION CANCER: THE LINE STUDY

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Background: Ramucirumab single agent or plus chemotherapy (CT) is the first antiangiogenic agent showing survival benefit in pretreated advanced gastric (GC) and gastroesophageal junction (GEJ) cancers. To date no biomarker can predict the activity of anti-VEGFR2 therapy. This multicenter study aimed to retrospectively assess the prognostic role of baseline lactate dehydrogenase (LDH) levels, an indicator of tumor hypoxia and angiogenesis, in advanced GC and GEJ patients (pts) in second-line setting.

Methods: Statistical analyses were performed on a cohort of consecutive GC and GEJ cancer pts treated with second-line therapy at IRCCS CRO of Aviano, Mauriziano Hospital of Torino and University Hospital of Udine, Italy, from 2010 to 2021. LDH levels prior to second-line start were classified as low-normal or high and standardized according to the upper limit of the reference range. ROC analysis identified a cut-off to define patients with poor PFS. Normalized LDH values were sorted according to the ROC cut-off. The association with survival outcomes was tested through the Kaplan-Meier method and compared using the Log-Rank test. The prognostic impact in second-line setting of LDH levels was assessed with Cox regression analysis.

Results: 164 patients were enrolled. Median age was 66.5 years, 91.46% had an ECOG PS $\leqslant$ 1 and 67.68% was diagnosed with *de novo* metastatic disease. Ramucirumab alone or with paclitaxel was the choice regimen for 53.66% of pts, while 46.34% received CT-based schemes. Median second-line PFS and OS were 3.9 and 6.8 months, respectively. 47.85% of pts had high normalized LDH values. ROC analysis detected a cut point of 0.83. Univariate analyses identified high normalized LDH (HR 2.08, 95% CI 1.42-3.03, $p<0.0001$), an ECOG PS >1 (HR 3.72, 95% CI 1.19-7.21, $p<0.0001$) and synchronous metastatic disease (HR 1.56, 95% CI 1.06-2.28, $p=0.023$) as poor prognostic factors. At multivariable model, normalized LDH level higher than the cut-off confirmed its independent prognostic impact in OS (HR 1.68, 95% CI 1.12-2.52, $p=0.012$), along with an ECOG PS >1 (HR 2.58, 95% CI 1.31-5.09, $p=0.006$). Subgroup analyses showed no significant heterogeneity in survival outcomes according to normalized LDH levels between pts treated with ramucirumab or CT-based regimens.

Conclusions: Elevated LDH levels prior to second-line treatment start and ECOG PS >1 are independent prognostic indicators of worse outcome in advanced GC and GEJ cancer pts. Prospective evaluations are awaited.

B32

PROGNOSTIC VALUE OF A RISK SCORE SYSTEM FOR METASTATIC MUCINOUS COLORECTAL CANCER PATIENTS: AN EXPLORATORY STUDY

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Background: In metastatic colorectal cancer (MCRC), mucinous histology has been associated with poor response rate and prognosis. However, data are controversial (Catalano et al, 2020) and outcome is quite heterogeneous. The aim of the present study was to assess prognostic factors in mucinous MCRC and construct an exploratory

prognostic risk score model to predict patient (pt) overall survival (OS).

Patients and methods: the study population included 221 MCRC pts with mucinous histology (according to the World Health Organization classification, 2010), from 8 institutions, who were treated with at least one line of chemotherapy. Prognostic factors associated with OS were identified using univariate and multivariate Cox proportional hazards analyses. The prognostic score was based on regression coefficients in the multivariate Cox regression analysis, rounded to the ratio nearest the integer value.

Results: pts were male/female 125/96, median age 66 years (range, 27-87), right-/left primary tumour 47%/53%. Univariate analysis showed that age, primary tumour resection, lymph node, peritoneal and bone involvement, number of metastatic sites, performance status (PS), tumour grading, and neutrophil/lymphocytes ratio (NLR) were significantly related to death, but not sex, site of the primary tumour, previous treatment, liver or lung metastasis, RAS/BRAF and microsatellite instability status, CEA and haemoglobin levels. PS (2 vs 0, 1 vs 0), tumour grading (3 vs 1-2), NLR (>3 vs =3), peritoneal and bone (yes vs no) involvement were found as independent prognostic factors for OS. Three different risk categories were defined: low (0-2), intermediate (3-6) and high (9-16). The proportion of patients assigned to the 3 categories was 43.1%, 47.4% and 9.5%, respectively. The median OS for patients included in the high-risk group was 9.3 months (95% confidence interval, CI: 4.6-13.3; Hazard Ratio, HR: high vs low risk: 5.92; 95% CI: 2.06-16.3, p < .0001); for the intermediate-risk group, it was 21.4 months (95% CI: 16.5-28.0; HR intermediate vs low risk: 1.96; 95% CI: 1.36-2.82, p = .0002); and for the low-risk group, it was 38.9 months (95% CI: 26.8-50.6).

Conclusions: This prognostic system can be easily obtained with the use of commonly available data. It may allow to define populations of mucinous MCRC patients with different risk and to help clinicians in treatment decisions. The prognostic score derived from this exploratory set should be further validated externally for confirmation.

B33

MOLECULAR CHARACTERIZATION AND CLINICAL RELEVANCE OF MGMT-SILENCED ADVANCED PANCREATIC CANCER

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Background: The identification of clinically actionable molecular targets of pancreatic carcinoma (PC) is key to improving patient outcome. We hypothesized that O6-methylguanine-DNA methyltransferase (MGMT) silencing may occur in a subset of PC patients and represent a new biomarker for temozolomide (TMZ)-based treatments.

Methods: We performed a bioinformatic analysis of genomic, transcriptomic, methylation and clinical data in The Cancer Genome Atlas (TCGA) and the Clinical Proteomic Tumor Analysis Consortium 3 (CPTAC-3) cohorts to explore the prevalence, molecular correlates, and prognostic impact of MGMT silencing in PC patients. A real-world Italian cohort of PC patients profiled for MGMT status at Fondazione IRCCS Istituto Nazionale Tumori of Milan (INT) was used to validate the results. In TCGA and CPTAC-3, MGMT promoter hypermethylation prediction was computed according to the MGMT-STP27 model on HM-450K platform methylation data. In the INT cohort, MGMT silencing was defined by combined lack of MGMT expression by immunohistochemistry plus promoter methylation by pyrosequencing.

Results: MGMT promoter hypermethylation was consistently identified in 6% (11/178), 4% (3/69) and in 7% (5/69) TCGA, CPTAC-3 and INT PC patients, respectively, and was significantly associated with reduced MGMT mRNA expression. In TCGA, MGMT silencing was more frequently found in non-ductal PC subtypes (p=0.040) with wild-type KRAS status (p=0.045), and enriched in ATM (p<.001) and GNAS (p<.001) mutations. No survival differences were observed between MGMT-mehtylated and not-methylated cases in all 3 cohorts. In the INT cohort, 4 unselected patients were treated with TMZ as late line of therapy, with no benefit.

Conclusions: Our preliminary data suggest that MGMT silencing is found in a small but non-neglibile fraction of PC patients, especially in non-ductal, KRAS wild-type tumors. Deeper investigation is needed to exploit this molecular feature as a new target in this population.

B34

REAL-LIFE OUTCOMES OF ELDERLY PATIENTS RECEIVING FIRST-LINE PLATINUM-BASED CHEMOTHERAPY FOR UNRESECTABLE OR METASTATIC BILIARY TRACT CANCER (BTC)

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Background: To date, little is known about the efficacy of platinum-based chemotherapy (CT) in elderly patients with unresectable or metastatic biliary tract cancers (BTC). Elders are often excluded from clinical trials due to comorbidities or performance status, and are treated with platinum-free CT regimens in daily practice. Real-life data are warranted to assess the safety and outcomes of first-line platinum-based CT in this population.

Methods: This retrospective, observational study evaluated the efficacy of first-line platinum-based CT in elderly patients with unresectable or metastatic BTC treated at Istituto Nazionale dei Tumori of Milan between Jan 2017 and Jan 2022. Patients were categorized into three age groups (< 70 group A, 70–74 group B, ⩾75 group C) and respective treatment outcomes were evaluated.

Result: Overall, 235 patients were retrospectively reviewed, of whom 179 (76%) were < 70 years, 34 (14%) 70-74 and 26 (11%) ⩾ 75. Sixteen (47%) group B and 20 (77%) group C patients had a Charlson comorbidity index ⩾ 10. Median PFS for group A, B and C patients was 5.5, 6.3 and 5.1 months (p=0.53), respectively, while median OS was 19.7, 17.8 and 14.9 months (p=0.16), respectively. Forty-five (25%) patients in group A, 9 (26%) in group B and 8 (31%) in group C achieved a partial response (p=0.83); furthermore, 69 (38%) patients in group A, 13 (38%) in group B and 6 (23%) in group C achieved disease control (p=0.60). Regarding safety, 5 patients (3%) in group A, 1 (3%) in group B and 2 (8%) in group C discontinued treatment due to grade ⩾3 toxicity (p=0.43).

Conclusions: In elderly patients with unresectable or metastatic BTC, use of first-line platinum-based CT is associated with similar survival benefit and toxicity profiles to younger patients. Our data do not support routine treatment de-escalation in this population.

B35

EVOLUTION IN BEYOND FIRST-LINE TREATMENT OF ADVANCED GASTRIC CANCER (AGC) IN THE LAST DECADE: A REAL-WORLD OBSERVATIONAL STUDY FROM MODENA CANCER CENTER

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Background: The treatment paradigm for AGC has changed over the years improving survival. Multiple lines of therapy are associated with better outcomes, although only around 40% of patients manage to receive beyond first-line (1L) treatment.

Methods: Retrospective analysis of medical records of patients with AGC treated at Modena Cancer Center from 2010 to 2020 was conducted. Kaplan-Meier analysis was used to investigate the association between lines of treatment received and overall survival (OS). The impact of variables on the possibility to receive beyond 1L therapy was assessed through multiple logistic regression analysis with a p-value <= 0.05 as significant. Tested variables were age, body-mass index, ECOG performance status (PS), number of metastases and age at diagnosis; period of diagnosis (2010-2015 vs 2016-2020); progression-free survival (PFS) > 6 months and best response during 1L.

Results: 185 patients were included: 104 diagnosed from 2010 to 2015 and 81 from 2016 to 2020. Patient's characteristics at diagnosis (age, gender, ECOG PS, histotype, HER2 status, number of metastatic sites) were similar in the two groups. FOLFOX was the most common regimen used in 1L setting in both groups. Between 2010 and 2015 39% of patients received a second-line (2L) treatment, mostly with FOLFIRI; whereas 17% received a third-line (3L), mainly with paclitaxel. Between 2016 and 2020 53% of patients underwent 2L and the most common regimen was the combination of paclitaxel and ramucirumab. 25% received a 3L, mainly with FOLFIRI. Median OS was 5.8 months for patients treated with 1L chemotherapy, 16.4 months for 2L, and 21.5 months for 3L. PFS longer than 6 months at 1L (p=0.0002) and period of diagnosis (p=0.05) were the only variables to impact on the possibility to receive beyond 1L treatment.

Conclusions: Our data confirm that between 2016 and 2020 patients with AGC were more likely to receive 2L and 3L treatment. Patients who undergo beyond 1L therapies have longer OS. Continuum of care and support strategies in AGC are crucial to improve clinical outcomes and survival.

B36

BORDERLINE RESECTABLE AND LOCALLY ADVANCED PANCREATIC ADENOCARCINOMA: TREATMENTS AND OUTCOMES IN A MULTI-INSTITUTIONAL ITALIAN REGIONAL REALITY

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Background: Surgery is the only curative treatment for pancreatic adenocarcinoma (PC) but only 15-20% of patients (pts) have a resectable disease at diagnosis. We aimed at describing the treatment strategies adopted in two high-volume hub Italian centers, analysing pts characteristics affecting therapeutic decisions and evaluating outcomes.

Methods: We retrospectively analysed a cohort of 178 consecutive pts with borderline resectable (BRPC) or locally advanced PC (LAPC) starting a primary systemic treatment between January 2010 and June 2021 in the centers of IRCCS CRO of Aviano and ASUFC Academic Hospital of Udine. Only pts receiving either a chemotherapy (CT) triplet with fluorouracil, irinotecan and oxaliplatin (FFX) or gemcitabine-based doublets (GbD) were considered. The association of clinico-pathological and treatment characteristics with the probability to reach surgical resectability was tested with uni-/multivariate logistic regression.

Results: Pts had a median age at diagnosis of 69 years, 25-75% IQR [59;74]. According to NCCN guidelines, 46% had BRPC and 54% LAPC. FFX was used in 33% of pts, while 67% received GbD, for a median CT duration of 3.5 months (m) [3;6]. RT was administered after CT in 36% of pts (67% with concomitant CT). Partial response (PR) was reached in 33% of pts, 36% showed a stable disease (SD). CA19.9 serum level significantly reduced during treatment in 67% of pts, in 32% of cases reaching normality range. Overall, surgical resection was performed in 26% of pts (in 53% of pts reaching a PR), 45% of BRPC pts, 13% of LAPC pts. Adjuvant CT was administered in 45% of pts. Among pts undergoing surgery, 64% experienced disease relapse, 73% with distant metastases. Median DFS was 8 m [6;33], median PFS in not-resected pts was 6 m [4;11], median OS was 18 m [12;26]. Median DFS was numerically longer in BRPC pts than in LAPC pts (9 m [7;44] vs 6 m [4;16]). 65% of pts received other CT lines. Age >/= 65 (OR 0.31, p=0.011), stage II (OR 2.88, p=0.034), BRPC (OR 3.94, p=0.008) and PR (OR 7.35, p<0.005) were significantly associated with surgery probability at uni- and multivariate analysis.

Conclusions: Non-metastatic non-resectable PC represents a modern challenge for oncologists and primary treatment strategies must be based on an accurate radiological disease definition and multidisciplinary clinical evaluation. FFX and GbD both represent valid options as primary CT according to literature data.

B37

CAN DIFFERENT SELECTION STRATEGIES INCREASE DIAGNOSTIC POWER FOR THE IDENTIFICATION OF LYNCH SYNDROME-ASSOCIATED COLORECTAL CANCER PATIENTS?

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Background: Lynch syndrome (LS) is an inherited genetic condition associated with increased predisposition to colorectal cancer (CRC) and other tumors and is caused by germline mutations in *Mismatch Repair* (*MMR*) genes, such as *MLH1*, *MSH2*, *MSH6, PMS2*, or in *EPCAM* gene. The identification of LS carriers is currently based on germline testing of subjects with MMR-deficient (dMMR) tumors or fulfilling clinical criteria, but the most efficient strategies to select patients who should be offered genetic testing are yet not well defined.

Patients and Methods: In order to assess the most suitable selection mode to identify LS-related CRC patients, we retrospectively collected and analyzed all clinical and molecular information of 854 CRC patients, recruited from 2013 to 2021 at the University Hospital Policlinico "P. Giaccone" of Palermo (Italy), 100 of which were selected based on revised Bethesda guidelines, Amsterdam criteria II, or tissue MMR deficiency, and genetically tested for germline variants in LS-susceptibility genes.

Results: Our study showed that 32 out of 100 CRC patients harboured germline likely pathogenic/pathogenic variants in *MMR* genes. The analysis of tissue microsatellite instability (MSI) status according to the revised Bethesda guidelines has been to be the best selection approach. In particular, more than half of *MMR*-mutated patients (56.3%) was selected by revised Bethesda guidelines, 28.1% by Amsterdam criteria II, and 15.6% by tissue

MMR deficiency analysis. However, the use of different selection approaches as complementary strategies is useful to identify LS carriers, reducing underdiagnosis of this syndrome. A certain number of LS carriers would have been lost without using multiple selective approaches which may improve the detection rate of LS individuals, including unaffected family members, who may benefit from the screening programs, active surveillance strategies, or cancer risk-reducing surgery interventions, where necessary.

Conclusions: These findings could have a strong clinical impact on the choice of the best therapeutic option by clinicians, by allowing for the selection of subgroups of CRC patients affected by LS who may benefit from immunotherapy.

B38

BUTYRATE, A POSTBIOTIC OF INTESTINAL BACTERIA, AFFECTS PANCREATIC CANCER AND GEMCITABINE RESPONSE IN IN VITRO AND IN VIVO MODELS

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Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer. The excessive stromatogenesis accompanying the growth of this tumor is believed to contribute to chemoresistance which, together with drug toxicity, results in poor clinical outcome. Many studies are showing that gut microbiota and their metabolites are implicated in cancer pathogenesis, progression and response to therapies. In this study we tested butyrate, a product of dietary fibers' bacterial fermentation, whose anticancer and anti-inflammatory functions are known.

Material and methods: Human pancreatic cancer cell lines BxPC-3 and PANC-1 were untreated (CTRL) or treated with gemcitabine (GEM), butyrate (BUT), or gemcitabine+butyrate (GEM+BUT) to investigate by flow cytometry any impact on cell growth, cell cycle and apoptosis. Moreover, BxPC-3 cells were subcutaneously injected in nude BALB/c mice, which were randomly assigned to the following experimental groups: CTRL (control), GEM (50mg/kg gemcitabine intraperitoneally once a week), BUT (800mg/kg sodium butyrate for five consecutive days/week by gavage.), GEM+BUT (50mg/kg/week gemcitabine i.p. and 800mg/kg sodium butyrate for five consecutive days/week by gavage). After four weeks of treatment, blood was collected for obtaining serum employed for biochemical analyses of hepatic and renal markers, as well as for metabolomics. Fresh fecal pellets were also harvested. Upon sacrifice, tumors and intestines were explanted and formalin-fixed for histological analyses.

Results: *In vitro*, beside slowing proliferation, butyrate enhanced gemcitabine effectiveness against BxPC-3 and PANC-1, mainly inducing apoptosis. Moreover, when administered to mice, alone or combined with gemcitabine treatment, butyrate markedly reduced the cancer-associated stromatogenesis, preserved intestinal mucosa integrity and affected fecal microbiota composition by increasing short chain fatty acids-producing bacteria and decreasing pro-inflammatory microorganisms. Furthermore, serum analysis showed butyrate to ameliorate some markers of kidney and liver damage, whereas a metabolomics approach revealed a deep modification of lipid metabolism, which may affect tumor progression or response to therapy.

Conclusions: Such results support that butyrate supplementation, in addition to conventional therapies, can interfere with pancreatic cancer biology and response to treatment and can alleviate some damages associated to cancer itself or to chemotherapy.

B39

THE IMPACT OF SECOND-LINE TREATMENT AFTER FIST-LINE CISPLATIN PLUS GEMCITABINE IN ADVANCED BILIARY TRACT CANCERS: A MONO-INSTITUTIONAL RETROSPECTIVE STUDY

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Background: Advanced biliary tract cancers (ABTCs) have a poor prognosis. The standard of care first-line chemotherapy is cisplatin plus gemcitabine. ABC-06 is the only phase III randomized trial for second-line therapy and it showed an improvement in overall survival (OS) with FOLFOX versus active symptoms control (ASC). Herein, we provide a retrospective analysis of patients (pts) treated with second-line therapy at our Institution investigating the impact of treatment regimen and possible prognostic or predictive factors.

Methods: ABTCs pts receiving second-line treatment after a first-line regimen with cisplatin-gemcitabine were included in the study. The following variables were collected: gender; age (<65 years vs ⩾65 years); baseline ECOG PS (0-1 vs ⩾2); second-line regimen (FOLFIRI vs FOLFOX); comorbidities (yes vs no); number of comorbidities (0-1 vs ⩾2); number of metastatic sites (1 vs ⩾2). Univariate and multivariate analysis for progression free survival (PFS) and OS were performed.

Results: 51 pts affected by ABTCs receiving second-line treatment between January 2016 and May 2021 were included. The median age was 70 years (38-82), 39% were males, 70% were aged ⩾65 years, ECOG PS was 0-1 in 86% of pts; 39% had ⩾2 comorbidities; 60% had ⩾2 metastatic sites. Second-line regimen included FOLFIRI (55%), FOLFOX (29%), capecitabine (4%) and experimental drugs (12%). The overall population median PFS and OS at second-line were 3.5 months (median follow-up 11.4 months) and 8.8 months (median follow-up 22.6 months), respectively; 4% achieved a partial response and the disease control rate was 39%. At the univariate and multivariate analysis, no variable was associated with PFS. At the univariate analysis, second-line regimen FOLFIRI (p=0.03) and single metastatic site (p=0.06) were associated with improved OS; at the multivariate analysis only the second-line regimen was confirmed associated with OS (p=0.02). Out of 43 evaluable pts, the median OS according to treatment (FOLFIRI vs FOLFOX) was 11.3 months versus 5.4 months (p=0.019, HR 0.46, 95% CI: 0.18-0.88).

Conclusions: Despite the retrospective analysis and the small sample size, we confirm the importance of second-line chemotherapy in ABTCs patients. Our results show that FOLFIRI regimen after a platinum-containing fist-line, was independently associated with improved OS. Given that the ABC-06 trial compared FOLFOX to ASC, a randomized trial of FOLFOX vs FOLFIRI as second-line would provide further information.

B40

PATTERN OF DISEASE PROGRESSION IN BRAF V600E-MUTANT METASTATIC COLORECTAL CANCER (MCRC) TREATED WITH ENCORAFENIB AND CETUXIMAB (EC): A SINGLE INSTITUTION ANALYSIS

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Background: EC combination is the new standard of care (SOC) for previously treated *BRAF* V600E-mutant mCRC. Despite the superiority compared to the previous SOC, efficacy is disappointing in terms of duration of response. We have investigated whether the new patterns of response and progression to novel drugs, reported by others, may apply to EC combination.

Methods: This is an observational, retrospective study. Pts affected by *BRAF* V600E mutant mCRC treated with EC at our Institution within a compassionate use program were included. The primary objective of the analysis was to describe the pattern of disease progression (PD) to EC. The secondary objective was to assess the efficacy of subsequent treatments. Primary endpoint was the rate of dissociated response at PD. Secondary endpoints were DCR, mPFS and mOS from start of subsequent therapy.

Results: Between Nov 2019 and Apr 2022, 33 pts received EC. At a median follow-up of 3.2 m, 25 PD events (76%) were observed. The predominant pattern of PD was a mixed response (80%) with part of the disease showing tumor shrinkage or stability, and part progressing, due to appearance of new lesions (10%) increase of some lesions (20%) or both (70%), thus accounting for a PD, according to RECIST criteria. Eighteen pts (72%) received a further treatment: 14 pts (78%) chemotherapy rechallenge (50% FOLFIRI, 36% mFOLFOX6 and 14% 5FU monotherapy), 3 pts (17%) regorafenib and 1 pt stereotactic body radiation therapy. Out of 15 pts evaluable for response, 73% showed PD as best response (with evidence of increase involving all tumor sites, including those previously controlled on EC); DCR was 27%. Median PFS and mOS of further treatment line were 2.5 m (95%CI 1.2-8 m) and 8.4 m (95% CI 1.6-11.4 m), respectively.

Conclusions: This real life analysis shows that the predominant pattern of PD to EC treatment is a dissociated response and that pts may benefit from subsequent therapy. However, we hypothesize that, due to selective pressure of targeted treatment, part of the disease is still controlled at the time of PD and therefore, stopping targeted therapy and switching to another line of treatment, may cause an hyper progression.

B41

SAFETY AND FEASIBILITY OF TYROSINE KINASE INHIBITORS (TKI) IN RECURRENT HEPATOCELLULAR CARCINOMA (HCC) PATIENTS (PTS) AFTER LIVER TRANSPLANTATION (LT): A SINGLE-CENTRE ANALYSIS

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Background: Few data are available for treatment of recurrent HCC after LT. Retrospective studies and case series focused mainly on TKI.

Material and methods: TKI-treated LT pts at Pisa Oncology department were retrospectively studied for safety and clinical outcome. Adverse events of special interest (AESI) included bleeding, liver rejection and immunosuppressive drug change (IDC).

Results: A total of 14 pts were included. Main characteristics are reported in Table 1. Median TKI overall survival was 29.5 mo (5.6-32.3 mo). As first line 13 pts began sorafenib (sor) post LT. Sor starting dose was 400 (range 300-800) mg. Median progression free survival (mPFS) was 5.1 months (mo). Best response (BR) was partial response (PR) in 7.7%, stable disease (SD) in 46.1% and progressive disease (PD) in 38.5%. Main adverse events (AEs) of all grades were diarrhoea (38%), Hand-Foot Syndrome (HFS 30%) and weight loss (30%); AESI were bleeding in 7.7%, biochemical rejection in 7.7%, and IDC in 23%. Due to AEs 6 pts required dose reduction and 2 discontinued sor. Ten pts received TKI as 2nd line (in 80% regorafenib (rego)) and seven pts as a 3rd line (in 71.4% cabozantinib (cabo)). Median rego starting dose was 80 (range 40-160) mg. BR was 18.1% PR, 27.2% SD and 54.6% PD. mPFS for rego was 6.2 mo. Main all grades' AEs were 63% HFS, 45% diarrhoea, and 45% asthenia; AESI were bleeding in 18.2%, biochemical rejection in 9%, and IDC in 45.5%. Rego was reduced in 36.3% pts and discontinued in 9% for AEs. Median cabo starting dose was 40 (range 20-60) mg. BR was 28.6% PR, 42.8% SD and 14.3% PD. mPFS was 5.2 mo. AEs of all grades were 71% asthenia, 42% HFS and 42% diarrhoea; AESI were 14.3% bleeding and 14.3% IDC. Cabo was reduced in 42.8% of pts due to AEs.

Table 1. Baseline characteristics.

Baseline characteristics (n=14)	N (%)
Male	13 (92.2%)
Aetiology of liver disease before LT	
HBV	2 (14.3%)
HCV	2 (14.3%)
Dysmetabolic	2(14.3%)
Mixed	7 (50.0%)
TKI pre-LT	1 (7.1%)
HCC recurrence pattern	
Liver only	3 (21.4%)
Intra- and extra-hepatic	1 (7.1%)
Extrahepatic only	10 (71.4%)
Relapse free survival from LT, median (range)	13.7 (8.2-46.6) months
Immunosuppressive regimen	
Combination	4 (28.6%)
Monotherapy	10 (71.4%)
Alpha-fetoprotein before TKI, median (range)	2.6 (1.2-408.0)

Conclusions: TKI treatment seemed to be feasible and active after LT, generally at reduced doses. Careful monitoring of these pts during treatment should be performed, with a particular focus on AEs and dose of immunosuppressive drug.

B42

ADJUVANT THERAPY (AT) IN PATIENTS (PTS) WITH RADICALLY RESECTED AMPULLARY ADENOCARCINOMA (AA): A MONOCENTRIC RETROSPECTIVE ANALYSIS

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Background: The role of AT in AA is not clearly defined and previous evidence is poor and controversial. Hence, we retrospectively analyzed radically resected AA pts at our Institution, investigating the impact of AT on survival.

Methods: Radically resected AA pts were retrospectively included in the analysis, divided into two groups: pts receiving AT and pts undergoing only postoperative observation (PO). The following variables were collected: gender; age ($\leq$ 65 vs $>$ 65 years); baseline ECOG PS (0 vs $\geq$1); histologic subtype (pancreatobiliary vs intestinal); tumor stage (T1-2 vs T3-4); nodal status (N0 vsN+), margin status (R0 vs R+); radiotherapy (yes vs no), AT regimen [Gemcitabine (GMZ)-based vs fluoropyrimidine (FP)-based treatment)]. The objective of the analysis was to evaluate the impact of AT on overall survival (OS). Univariate and multivariate analyses were performed.

Results: From 2007 to 2021, a total of 69 pts with radically resected AA were identified: 41 (59%) pts received AT, 28 (41%) PO. Tumor characteristics were: 31 (45%) pancreatobiliary, 26 (38%) intestinal, 9 (13%) mixed subtype and 3 (4%) not available. Out of 41 pts receiving AT, 27 (66%) pts were treated with FP-based AT, 14 (34%) with GMZ-based AT; 16 (23%) pts received also RT. In the overall population, median OS was 59.8 months. At the

univariate analysis, there was a statistically significant association of T status with OS (p 0.03), confirmed at multivariate analysis (p 0.03). Further variables (ECOG PS, AT, nodal status and histologic subtype) were not associated with survival. Among the 41 pts receiving AT, median OS was 58.7 months. At the univariate analysis, AT regimen was significantly associated with OS (p 0.02), and it was confirmed at the multivariate analysis. In particular, median OS was 59.8 and 28.3 months in pts receiving FP- and GMZ-based AT, respectively [HR 0.26, (95% CI: 0.09-0.78), p = 0.001].

Conclusions: Among pts with radically resected AA, AT, compared with PO, was not associated with a significant survival benefit. However, among pts receiving AT, FP-based regimen seems to significantly improve OS in comparison to GMZ-based regimen, independently of histologic subtype. Our findings, from a retrospective and limited case series, add to controversial literature data and miss to clarify the real impact of AT in radically resected AA pts. A randomized trial of AT vs PO would provide further information in this setting.

B43

IMPACT OF NEW-ONSET DIABETES IN ADVANCED PANCREATIC CANCER PATIENTS UNDERGOING FIRST-LINE CHEMOTHERAPY

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Background: Metastatic pancreatic adenocarcinoma (mPDAC) is one of the most aggressive cancers, with limited therapeutic options. There is growing interest regarding the impact of systemic metabolic alterations on patients (pts) prognosis and treatment tolerability.

Methods: The aim of this monocentric, retrospective study was to investigate the prognostic role of new-onset diabetes in mPDAC pts who received first-line chemotherapy (1L-CT). Data records of mPDAC pts who underwent 1L-CT at Fondazione IRCCS Istituto Nazionale dei Tumori di Milano with available pre-treatment blood tests were reviewed. New-onset diabetes was defined as fasting hyperglycemia (⩾126 mg/dL) first occurring within 30 days before the start of 1L-CT and persisting thereafter. Pts with (group A) and without (group B) new-onset diabetes were compared in terms of overall survival and treatment tolerability. OS was defined as the time elapsed between the start of 1L-CT and death or last follow-up.

Results: Among 130 evaluable pts, 19 (15%) developed new-onset diabetes before 1L-CT start. Of these, 64 (49%) pts received full-dose, standard of care (SoC) FOLFIRINOX or Gemcitabine-NabPaclitaxel, with no difference according to diabetes occurrence (p=0.94). Median OS was 3.8 months in group A and 8.2 months in group B (HR 2.16, 95% CI 1.3 - 3.54, p<0.01). Treatment-related grade ⩾3 toxicities were experienced more frequently from pts in group A than in group B (68% vs 36%, p=0.02).

Treatment had to be permanently stopped due to G⩾3 CT-related toxicities in 6 (32%) and 20 (18%) pts of group A and group B, respectively (p<0.01).

Conclusions: Our analyses suggests that new-onset diabetes in mPDAC pts may be associated with poorer prognosis and reduced treatment tolerability. Prospective validation of these results is needed to confirm the need to achieve an optimal glycaemic control in this population.

B44

TEN YEARS OF SURGERY FOR GASTRIC CANCER IN OCTOGENARIANS PATIENTS: A SINGLE INSTITUTION EXPERIENCE

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Background: The gastric cancer (GC) prognosis in elderly patients (pts) is poor, and the 5-year relative survival is less than 25%. The aim of our study is to review the surgical outcomes of late elderly (≥80years) GC pts.

Material and methods: Retrospective review of a consecutive series of 40 late elderly GC pts undergoing surgery at a single institution between 2011 and 2021.

Results: Males and females were equally distributed (20 vs 20), the median age was 84 (range 80-93) years. Eight (20.0%) stages I, 7 (17.5%) stages II, 16 (40.0%) stages III and 9 (22.5%) stages IV were collected. Histologically, late elderly GC pts recorded an high prevalence of intestinal type adenocarcinoma (14;35.0%), whereas signet ring cell carcinoma account for only 11 (27.5%) pts. Tumor location was in the lower third for 22 (55.0%), in the middle third for 15(37.5%) and in the upper third for 3 (7.5%) pts. Thirty-four (85.0%) pts received curative resection, 5(12.5%)pts had noncurative resection or bypass surgery, 2(5.0%) pts had explorative laparoscopy only for peritoneal metastases. Surgical treatment included subtotal gastrectomy for 20 (50.0%) pts, D1 lymph node dissection for 3 (7.5%) pts, D2 for 17 (42.5%) pts, total gastrectomy for

7 (17.5%) pts with D2 for 6 (15.0%) pts, partial gastrectomy for 7 (17.5%) pts with D2 for 5 (12.5%) pts. All pts had elective surgery and laparoscopy was performed in 16 (40.0%) pts. Thirty (75.0%) pts had an ASA score=3. The median Charlson Comorbidity Index (CCI) was 7.5 (range 6-12). The overall post-operative complication rate was 25%, including anastomotic leakage in 3 (7.5%) pts, and in-hospital death in 4 (10.0%) pts. Pts were divided in two groups according to CCI index, 6-7 vs 8-12 score, there was no difference in complications neither in mortality. ASA score was not associated with complication rate (ASA 1-2 vs ASA 3+ p=0.68). During the follow-up period,30 pts died. The median overall survival was 10.5 months (range 0-119), and cancer specific mortality occurred in 10 pts.

Conclusions: With a careful pre-operative selection, advanced age does not represent a contraindication to surgery in GC pts. Larger series are needed to investigate factors predicting adverse events.

C – Breast Cancer

C01*

DOSE-DENSE CHEMOTHERAPY IN ADJUVANT TREATMENT OF PATIENTS WITH EARLY-STAGE BREAST CANCER: END-OF-STUDY RESULTS FROM A RANDOMISED, PHASE 3 TRIAL OF THE GRUPPO ITALIANO MAMMELLA (GIM)

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Background: The GIM 2 trial compared in a 2x2 factorial design the dose dense (DD, every 2 weeks) schedule to the standard interval one (every 3 weeks) and the addition of fluorouracil (F) to epirubicin-cyclophosphamide (EC) and paclitaxel (P) as adjuvant chemotherapy for node-positive breast cancer. In the primary analysis (Del Mastro, Lancet 2015), disease-free survival (DFS) and overall survival (OS) were significantly improved with the DD schedule, while no benefit was observed with the addition of F. Here, we report the end-of-study analysis.

Methods: This was an open-label, phase 3 trial, done in 81 Italian centres. Operable, node positive, breast cancer patients were randomly allocated in a 1:1:1:1 ratio to receive either EC-P or FEC-P DD or standard-interval EC-P or FEC-P The primary endpoint was DFS, comparing FEC-P vs. EC-P, and DD vs. standard-interval schedule. Secondary end points included OS and safety.

Results: 2091 patients were randomized; 88 patients were enrolled in centres providing only standard-intensity schedule. After a median follow-up of 15.11 years (IQR 8.40-16.33), 343 of 1002 patients (34.2%) and 409 of 1001 patients (40.9%) in the DD and control arm experienced a iDFS event, with 15-year iDFS of 61% (95% CI 58-64) and 53% (95%CI 49-56), respectively (Hazard Ratio [HR] 0.77, 95% CI 0.67-0.89; $p<0.001$). 198 (19.8%) and 254 (25.4%) OS events were registered, with 15-years OS of 76% (95%CI 73-79) and 69% (95%CI 65-72) in the DD and control arm, respectively (HR 0.72, 95%CI 0.60-0.87, $p<0.001$). Addition of F did not significantly improve iDFS (HR 0.89, 95%CI 0.78-1.03, p= 0.11) and OS (HR 0.89, 95%CI 0.74-1.06, p=0.20).

In hormone receptor-positive (N=1611), the 15-years OS was 76% (95% CI 72-79) with the DD and 71% (95% CI 67-74) with the standard schedule. For hormone receptor-negative (N=335), 15-years OS was 76% (95%CI 68-83) with the DD and 63% (95%CI 54-71) with the standard schedule. Only 4 cases of myelodysplasia/leukemia were observed.

Conclusions: The final analysis confirmed an improved DFS and OS with the use of DD as compared with the standard schedule. The DD should be considered the standard adjuvant chemotherapy schedule for node-positive breast cancer patients.

C02*

CIRCULATING TUMOR DNA (CTDNA) AND SERUM THYMIDINE KINASE 1 ACTIVITY (TKA) MATCHED DYNAMICS IN PATIENTS (PTS) WITH HORMONE RECEPTOR–POSITIVE (HR+), HUMAN EPIDERMAL GROWTH FACTOR 2¬–NEGATIVE (HER2-) ADVANCED BREAST CANCER (ABC) TREATED IN FIRST-LINE (1L) WITH RIBOCICLIB (RIB) AND LETROZOLE (LET) IN THE BIOITALEE TRIAL

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Background: Independent early dynamic assessment (baseline [D0] and day 15 of first cycle [D15]) of both TKa and ctDNA was prognostic and predictive in pts with HR+, HER2− ABC treated with RIB+LET enrolled in the BioItaLEE trial (NCT03439046). Here we performed a combined analysis of these two biomarkers.

Methods: Overall, early dynamics were assessable for both biomarkers in 241/287 pts (84.0%). Methods applied for ctDNA and TKa evaluation were previously reported. For ctDNA, samples were defined as wild type (WT) if no mutations were observed at D0 and D15, ctDNA positive (+) if with or negative (-) if without a primary target mutation at D15. Samples were TKa+ or TKa- if TKa levels were above or below the limit of detection at D15. Three main study groups (GRs) were identified: WT/TKa- (GR1, n=126), WT/TKa+, ctDNA-/TKa-, ctDNA-/TKa+, ctDNA+/TKa- (GR2, n=96) and ctDNA+/TKa+ (GR3, n=19). The association between biomarkers and PFS (progression-free survival) was estimated using Kaplan-Meier analysis and multivariate Cox models with 95% confidence intervals (CIs) adjusted for clinical variables.

Results: Median follow-up was 26.9 months. In multivariate Cox models both TKa dynamics and mutational tumor burden at D15 were independently predictive of PFS. Hazard ratios (HRs) were 0.37 (95% CI: 0.23-0.60; p<0.0001) for WT vs ctDNA+ and 0.56 (95% CI: 0.32-1.00; p=0.0506) for ctDNA- vs ctDNA+. For TKa, HR was 0.49 (95% CI: 0.30-0.80; p=0.0040) in TKa- vs TKa+. Interestingly combining the two variables further improve prediction of outcome. HRs for TKa- vs TKa+ were 0.17 (95% CI: 0.09-0.32; p<0.0001), 0.28 (95% CI: 0.13-0.59; p=0.0009) and 0.44 (95% CI: 0.23-0.86; p=0.0169) in WT, ctDNA- and ctDNA+ pts, respectively. Considering the 3 study GRs, median PFSs (95% CI) were not reached (27.89, NE), 19.58 (13.83, 23.39) and 6.65 (2.83, 12.16) months in GR1, GR2 and GR3, respectively, p<0.001. At multivariate Cox models, HRs of GR1 and GR2 compared with GR3 were 0.17 (95% CI: 0.09-0.32; p<0.0001) and 0.37 (95% CI: 0.20-0.67; p=0.001) respectively.

Conclusions: These findings suggest that combining the early dynamic assessment of both ctDNA and TKa may improve outcome prediction in pts treated with RIB+LET. Pts with ctDNA+/TKa+ are strongly enriched for non-responders. TKa and ctDNA capture different features of tumor biological activity and their combination warrants further evaluation in relation to other treatments, settings, and diseases.

C03*

PRECOCIOUS MODULATION OF PERIPHERAL BLOOD LYMPHOCYTES PREDICTS LONG-TERM OUTCOMES IN PATIENTS WITH HORMONE-RECEPTOR POSITIVE HER2-NEGATIVE ADVANCED BREAST CANCER TREATED WITH CDK4/6 INHIBITORS (PALMARES)

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Background: Cyclin-Dependent Kinase 4/6 inhibitors (CDK4/6i) in combination with endocrine therapies (ETs) are the mainstay of treatment for patients (pts) with Hormone Receptor-positive (HR+), Human Epidermal growth factor Receptor 2-negative (HER2-) advanced breast cancer (aBC). CDK4/6i treatment modulates several peripheral blood cell counts (PBC). However, the prognostic role of these modulations has never been investigated.

Materials and Methods: This was a multicenter, retrospective-prospective Italian study aimed at investigating the association between baseline or early on-treatment modifications (2 weeks after therapy initiation) of

neutrophils, monocytes, lymphocytes or platelets, and the progression-free survival (PFS) of pts with HR+HER2- aBC treated with ETs plus the CDK4/6i palbociclib (pal), ribociclib (ribo) or abemaciclib (abe). Multivariable Random Forest and Cox Regression models were used to assess the independent association between immune variables and patient PFS.

Results: 638 HR+ HER2- aBC pts treated with ETs plus CDK4/6 inhibitor-based therapy as any line of treatment between January 2017 and May 2021 in six Italian Institutions were included in this study. 82.9% of pts received palbo, while 11.6% and 5.5% were treated with ribo and abe, respectively. We found an independent association between baseline lymphocyte counts, or their early on-treatment modulation, and PFS. Pts with high baseline lymphocytes had significantly longer median PFS (mPFS) when compared to pts with low lymphocytes [mPFS 22.3 vs. 12.5 months, respectively; adjusted Hazard Ratio (aHR): 0.78; 95% confidence intervals (CIs): 0.66-0.92; p=0.0144]. Moreover, pts with high baseline lymphocytes and a lower decrease of lymphocyte counts 2 weeks after treatment initiation had significantly better PFS when compared to pts with lower baseline lymphocytes and a higher decrease of lymphocytes (mPFS 24.6 vs. 11 months, respectively; aHR: 0.82; 95% CIs 0.73-0.93; p=0.0037). Baseline and on-treatment changes of other PBC were not independently associated with PFS.

Conclusions: Baseline and on-treatment modifications of peripheral blood lymphocytes are independent predictors of PFS in HR+/HER2- aBC pts treated with ETs plus CDK4/6i. This study paves the way for implementing strategies to boost antitumor immunity in HR+ HER2- aBC pts treated with ETs plus CDK4/6i.

C04*

VIP - VALIDATION OF ITALIAN PRO-CTCAE, A FICOG PROSPECTIVE MULTICENTER STUDY: RESULTS OF THE BREAST CANCER COHORT

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Background: Italian PRO-CTCAE has been recently made available (https://healthcaredelivery.cancer.gov/pro-ctcae/countries-pro.html). VIP (NCT04416672) is promoted by FICOG (Federation of Italian Cooperative Oncology Groups) to study its psychometric properties in Italian patients (pts) with several types of cancer, treated with different classes of anticancer drugs. Results of the breast cancer cohort are reported here.

Methods: A PRO-CTCAE list including 76 items describing 48 symptoms (according to Dueck et al. JAMA Oncol 2015) was given to breast cancer pts on active anticancer treatment at baseline and after 2-6 weeks. Convergent validity with EORTC breast cancer specific module (QLQ B23) and Hospital Anxiety and Depression Scale (HADS) was assessed by Pearson correlation. Known-groups validity was tested with Mann Whitney test using ECOG performance status (PS 0 vs >0) as anchor. Responsiveness was investigated for 27 PRO-CTCAE core items using the Jonckheere-Terpstra test and the Patients' Global Impression of Change (PGIC) scale as anchor.

Results: 303 pts (median age 55), were enrolled from May 2019 to June 2021; 212 (70%) answered both planned questionnaires, with a 3wk median interval; 133 (44%) reported at least one symptom as frequent, severe, and/or interfering with daily activities. Convergent validity: 70/76 items were associated ($p<0.05$) with BR23 functional score and correlation was particularly strong (rho >0.5) for "feeling that nothing can cheer you up", "sadness or unhappiness" and "decreased sexual desire"; 71/76 items were associated with BR23 symptom scale and correlation was stronger for nausea, pain and fatigue. Very strong correlations were also found between "anxiety", "feeling that nothing can cheer you up" and "sadness or unhappiness" items and the anxiety and depression scores of HADS (rho ranges from 0.52 to 0.69 and 0.44 to 0.62, respectively). Known-group validity: scores of 6/76 items ("irregular menses", "missing menses", "decreased sexual desire", "unable to have orgasm", "took too long to have orgasm", "pain during vaginal sex") were significantly worse among pts with worse PS. Responsiveness: mean change scores of the core PROCTCAE items decreased monotonically among the three PGIC groups, worse vs no change vs improved.

Conclusions: PRO-CTCAEs show good psychometric properties in terms of convergent validity, known-group validity and responsiveness in Italian breast cancer pts on active anticancer treatment.

C05*

HER2-LOW POSITIVE STATUS AND BREAST CANCER HETEROGENEITY: FROM REAL WORLD TO GENE EXPRESSION DATA

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Background: HER2-low breast cancer (BC) as defined by Immunohistochemistry (IHC) score 2+ with negative in situ hybridization or IHC score 1+, is associated with low pathological complete response (pCR) and favorable survival, especially in hormone receptor (HR)-negative cases. As these findings came from clinical trial, we first questioned whether HER2-low predictive/prognostic value was also relevant in the real world; then, we analyzed whether primary tumor gene expression data differed according to HER2 status.

Methods: Data for non-metastatic BC patients treated with neoadjuvant chemotherapy and surgery were retrieved from our institutional prospectively-maintained registry. Gene expression profile was analyzed in two different cohorts used as training and testing datasets.

Results: A total of 287 HER2-low and 75 HER2-zero cases were identified. HER2-low cases were more likely HR-positive ($p<0.0001$), well-differentiated ($p=0.0393$), and less proliferative ($p<0.0001$). pCR occurred in 11% and 28% of HER2-low and HER2-zero cases, respectively ($p=0.0002$). At a median follow-up of 60 months [IQR 37-88 months], 118 events were registered. No difference in prognosis was reported, specifically 3-year disease-free survival in HER2-low and -zero was 0.78 (0.73, 0.83) and 0.79 (0.70, 0.90) $p=0.8386$, respectively. Comparative analysis of gene expression profiles of 125 samples with available microarray mRNA measurements confirmed *ERBB2* as the most differentially expressed gene among tumors with different HER2 protein expression by IHC. Beside to this expected result, we found the existence of two additional differentially expressed probes (fold-change HER2-low *vs* HER2-zero>1 and Wilcoxon test adjusted $p<0.05$), namely *ORMDL3* and *PGAP3*. The latter was also confirmed in the testing dataset represented by other 95 cases. Finally, by using filtering analysis and non parametric approaches, we identified specifically deregulated genes in each IHC HER2 category (HER2=0, HER2-low and HER2 3+) as well as those shared by HER2 3+ and HER2-low, most of which impinging on cell-cell adhesion, immune response and signal transduction.

Conclusions: Our results confirm that patients with HER2-low breast cancer are poorly responsive to neoadjuvant chemotherapy. Although preliminary, transcriptomic findings suggest that HER2-positive BC which is currently defined by IHC categories is instead a continuum of diseases in which important differences and exploitable communalities can be considered for therapeutic purposes.

C06

HRD/TIL-LOW HIGH-RISK BREAST CANCER IS CHARACTERIZED BY GOOD PROGNOSIS (THE RADIMMUNE TRIAL)

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Background: Early stage tumor-infiltrating lymphocytes (TIL)-low Triple Negative Breast Cancers (TNBC) are characterized by bad prognosis. The RAD51 test can identify Homologous Recombination Repair (HRR)-deficient (HRD) tumors and may add prognostic value in this subset of patients, potentially guiding post-neoadjuvant treatments in order to improve survival.

Methods: We quantified functional HRD detecting RAD51 and BRCA1 nuclear foci by immunofluorescence, content of TIL by H&E and IHC and expression of immune markers on diagnostic tumor biopsies of 148 high-risk BC patients, namely histologically confirmed TNBC or early onset BC ($\leqslant$ 35 years old) or gBRCA1/2-mutated BC. Patients were admitted at 6 Italian Hospitals of the "Gruppo Oncologico Italiano di Ricerca Clinica" (GOIRC) and at the Bordet Institute in Brussels and treated with (neo)adjuvant chemotherapy based on anthracyclines, taxanes and cyclophosphamide. Functional HRD was predefined as RAD51 score $\leqslant$10% (RAD51-low).

Results: RAD51 was successfully scored in 123/148 (83%) samples. 43/123 (35%) patients presented HRR mutations: 35 gBRCA1 (28%), 6 gBRCA2 (5%), and 2 gPALB2 (2%) mutations. 99/123 (81%) tumors were HRD by RAD51: 41/43 (95%) HRR-mutated and 58/80 (72%) HRR-WT tumors. 39/80 (49%) HRR-WT tumors presented BRCA1-low nuclear foci, surrogate of lack of BRCA1 function likely due to epigenetic silencing. pCR rates, TIL extent and PD-L1 Combined Positive Score (CPS) did not correlate with HRD status. DFS did not differ between HRD and HRR proficient (HRP)-tumors. Instead, patients with HRD tumors had a statistically significant higher 5y-OS than patients with HRP-tumors (88% vs 59%, $p=0.032$). Within TIL-low tumors, the 5y-OS benefit was greater in HRD vs HRP

Table 1. Incidence of eBC, Q: quarter.

	Q1 19	Q2 19	Q3 19	Q4 19	Q1 20	Q2 20	Q3 20	Q4 20
Incidence eBC per 100.000	16.1	15.2	15	16.5	15.7	10.8	11.3	11.5

(92% vs 49%, p=0.004). In support, HRD/TIL-low tumors showed lower PD-L1 CPS compared to others (p=0.0011); no statistically significant differences were found in CD3+ and CD20+ TIL.

Conclusions: The RAD51 test is able to identify HRR-altered tumors, beyond gBRCA1/2 mutations, and to select a cohort of HRD/TIL-low patients with good prognosis in a platinum-free (neo)adjuvant chemotherapy setting. Biomarker analyses on a larger cohort of patients are ongoing. Results will be available for the congress.

C07

EPIDEMIOLOGY AND CHOICE OF TREATMENT IN THE ADJUVANT SETTING OF HORMONE RECEPTOR POSITIVE HER2 NEGATIVE (HR+/HER2-) BREAST CANCER (BC), EVIDENCE FROM ADMINISTRATIVE DATABASES, WITH A FOCUS ON THE SARS-COV2 PANDEMIC

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Background: Real-world evidence through secondary use of data (SUD) in oncology is gaining increasing interest, to better understand cancer epidemiology and provide insights into treatment patterns in daily practice. This study evaluates incidence of HR+/HER2- early BC (eBC) and its management in clinical practice through SUD and gauge the impact of the SARS-COV2 pandemic.

Methods: This observational retrospective analysis integrates administrative databases for healthcare resources consumption (pharmaceuticals, hospitalizations, diagnostic tests and specialist visits databases) from a sample of Italian Local Health Units, based on 15 million inhabitants across Italy. Patients with ⩾1 hospitalization discharge diagnosis for BC, with surgical intervention and HR+ status (determined by coding for HR+ status or by presence of endocrine therapy) between 01/2010-06/2021 were included. Patients with at least one prescription of anti-HER2 monoclonal antibodies were excluded. Patients were classified by menopausal state through prescription for the gonadotropin-releasing hormone analogues (GnRHa). Incidence was calculated during all study period.

Results: Incidence rate has a slight upwards trend, as expected, ranging from 53.9 in 2013 to 62.7 in 2019 per 100,000 health-assisted subjects. Incidence in 2020 is 49.2 per 100,000 (table 1 for quarter split). As for adjuvant therapies, 31,836 patients were included in the analysis of which 5343 (16.8%) were classified as premenopausal. Mean age was 64.5 years. Most patients (78.8%) were treated with only adjuvant endocrine therapy (ET). 16.5% of the sample received adjuvant chemotherapy (CT). CT treatment was more prescribed in premenopausal patients. CT treatment was started within 12 weeks of surgery for 3.9% of the sample. Most patients (12.7%) started it between 12 weeks and 24 weeks.

Conclusions: SUD can provide lots of information with the right queries. The analysis confirms the slight increase in incidence observed by national registries and provides an estimate of the impact of SARS-COV2 with a 22% reduction of breast surgery in 2020. Administrative data can be used to assess clinical variables (e.g. premenopause through GnRHa prescription), and could be further explored for disease stage through axillary dissection, and recurrence through prescription of therapies used in metastatic setting.

C08

ADJUVANT DENOSUMAB (DEN) IN EARLY BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS WITH RESPECT TO DISEASE-FREE SURVIVAL IN D-CARE AND ABCSG-18 TRIAL

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Background: Adjuvant therapy with DEN showed efficacy in reducing the risk of clinical fractures in women with early breast cancer, but survival benefit appears less

clear. We undertook a systematic review and meta-analysis to assess DEN efficacy and safety compared to placebo as adjuvant treatment in addition to standard-of-care anticancer therapy.

Methods: We performed a meta-analysis from the ABCSG-18 and the D-CARE trials, that randomised between adjuvant therapy with DEN and placebo in patients with early breast cancer. Primary end-point was disease-free survival (DFS). Due to trials heterogeneity, a random-effect model was chosen to calculate HR and RR in the overall population. Subgroup analysis involved previous therapy, menopausal status, hormone-receptor status and HER2 status. Secondary end-points were distant recurrence-free survival (DRFI) and safety for osteonecrosis of the jaw (ONJ) and atypical femur fracture.

Results: We analysed data from 7929 women, 4509 in D-CARE and 3420 in ABCSG-18 trial. Median follow-up was respectively of 67.2 months and 73 months. Overall, 1402 DFS events were reported. DFS was not significantly improved with DEN versus placebo (HR 0.93, 95%CI 0.73-1.18, p=0.54; RR 0.93, 95%CI 0.76-1.13, p=0.46). Exploratory subgroup analyses suggested a trend in benefit in patients who underwent adjuvant therapy, ER+ or PR+ and HER2-. DEN effect was similar both in premenopausal (RR 0.96, 95%CI 0.81-1-13) and postmenopausal women (RR 0.94, 95%CI 0.84-1.05); in postmenopausal women RRs were significantly different between the ABCSG-18 (RR 0.84, 95%CI 0.71-0.98) and the D-CARE trial (RR 1.09, 95%CI 0.92-1.30). No benefit was observed in DRFI (RR 1.01, 95% CI 0.90-1.13, p=0.83). In patients treated with a 60 mg twice-yearly schedule, no events of osteonecrosis of the jaw or atypical femur fracture were confirmed, while in the group assigned to intensive schedule 131 patients had ONJ or atypical femur fracture (RR 32.41, 95% CI 12.01-87.50).

Conclusions: Adjuvant treatment with DEN failed to show a significant improvement in DFS and DFIS in women with early breast cancer. Safety data shows no role for intensive administration schedule in adjuvant setting.

C09

HER2-EXPRESSION DISCORDANCE BETWEEN BIOPSY AND SURGICAL SPECIMEN IN A COHORT OF EARLY BREAST CANCER PATIENTS: RATE OF CONVERSION FROM HER2-0 TO HER2-LOW SUBTYPES

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Background: It is well known that breast cancer may display intratumor heterogeneity of human epidermal growth factor (HER2) expression. Novel antibody-drug conjugates (ADCs) such as trastuzumab deruxtecan (T-DXd) have proven to be effective in the HER2-low disease in the advanced setting and are now being tested in the (neo)adjuvant setting as well. Retesting HER2 on the surgical sample if the initially tested core biopsy is negative is no longer mandatory according to the ASCO/CAP HER2 testing guidelines. We conducted a study aimed to determine the rate of conversion from HER2-negative (defined as IHC 0) to HER2-low status (defined as IHC 1+ or 2+ without gene amplification) between diagnostic biopsy and surgical specimen in a cohort of patients (pts) with invasive early breast carcinoma.

Patients and methods: This retrospective observational study enrolled 101 pts with HER2-negative primary invasive early breast cancer (stage I-III) with paired core needle biopsy and surgical specimen, treated at the Oncology Department of Udine Hospital (Italy) from 2019 to 2020. HER2 test was conducted according to ASCO/CAP 2018 guidelines. Pts that received a neoadjuvant treatment were not included in the study.

Results: The median age of the population was 66 years and 80% of pts were post menopausal at diagnosis. The most frequent hystotipe was ductal adenocarcinoma (50%). As expected, luminal subtype was the most common (80%) while about 20% of pts had a triple-negative disease. The majority of pts (about 62%) had a T1 tumor and around 75% were N0 at diagnosis. 67% of pts received an anti-hormone adjuvant therapy, while an adjuvant chemotherapy was performed in 20% of cases. The agreement between preoperative core needle biopsy and paired tumor specimens regarding the assessment of HER2 expression has been around 97%, as in only 3 cases we observed a conversion from HER2-negative to HER2-low status.

Conclusions: Patients with HER2-low breast cancer are currently treated as HER2-negative patients. In the next future this is probably going to change as the new anti HER2 ADCs have shown promising clinical activity against the HER2-low disease. Our retrospective analysis

has shown that 3% of initially tested HER2-negative tumors turned out to be HER2-low after retesting HER2 expression on the surgical specimen. If confirmed by larger prospective studies, this data could expand the number of pts who may possibly benefit from novel ADCs in the (neo)adjuvant setting.

C10

THE ROLE OF LIQUID BIOPSY FOR THE CHARACTERIZATION OF HORMONE RECEPTOR-POSITIVE (HR+) HER2LOW METASTATIC BREAST CANCER (MBC)

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Background: About 50% of BC presented with HER2-low expression. There is a paucity of markers apt to characterize this novel subtype, defined by HER2 immunohistochemistry score of 1+ or 2+ with negative in situ hybridization assay. The aim of this study was to explore the role of liquid biopsy–based biomarkers for the characterization of HER2-low metastatic breast cancer (mBC).

Methods: A cohort of 79 patients (pts) with HR+ HER2-negative mBC was prospectively enrolled in the CRO-2018-56 study and characterized, for ctDNA through droplet digital PCR (ddPCR) and next generation sequencing (NGS) before treatment start (BL). *ESR1* epigenetic status was defined by assessing the methylation of its main promoters (promA and promB). Associations were tested through Mann–Whitney *U* test and Fisher exact test, matched pairs variations through Wilcoxon signed rank test, and survival was analyzed by log-rank test.

Results: In the total population, HER2 0 mBC patients (pts) 49% while HER2-low were 51%. No significant association with the number of metastatic sites and metastatic lesions was detected for HER2-low (P= 0.87 and P=0.78 respectively). Pts with low expression of HER2 showed a comparable outcome in terms of PFS at first line (PFS at 12 months 81% vs 70% P= 0.3822) and OS (OS at 12 months 91% vs 97%, P= 0.37). At BL, ctDNA-detected *ESR1* and *PIK3CA* mutations (muts) were respectively found in 11% and 21% of pts in the HER2 0 cohort and in 8% and 31% of pts in the HER2-low cohort. No differences in distribution were observed (P=1 for *ESR1* and P=0.8 for *PIK3CA*). ACTB short fragments (ACTB_s) weren't significantly different in pts with HER2-low disease (P = 0.95). Moreover, in HER2-low mBC the median methylation for promA was 56% vs 62.3% and for promB resulted 42.9% vs 55% with no significant differences (P = 0.782 and P= 0.406).

Conclusions: The present study characterized a prospective cohort of HER2 low and HER2 score 0 MBC, showing no significant differences for endocrine resistance biomarkers on a mutational and epigenetic standpoint. Since novel antibody drug conjugates are gaining momentum as a viable treatment strategy in luminal-like MBC, highlighting biomarkes linked to intrinsic endocrine resistance will be of pivotal importance for tailoring therapeutic sequences.

C11

IMPACT OF ANTI-HER2 THERAPY ALONE AND IN ASSOCIATION WITH WEEKLY PACLITAXEL ON THE OVARIAN RESERVE OF YOUNG WOMEN WITH HER2-POSITIVE EARLY BREAST CANCER

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Background: The potential gonadotoxicity of anti-HER2 agents remains largely unknown and limited conflicting evidence exists for taxanes. Anti-Mullerian hormone (AMH) is an established biomarker of ovarian reserve that may aid in quantifying anticancer treatment-induced gonadotoxicity.

Materials and methods: The present biomarker analysis of the NeoALTTO (NCT00553358) randomized phase III neoadjuvant trial included premenopausal women aged ⩽45 years at diagnosis of HER2-positive early breast cancer with available frozen serum samples at baseline (i.e. before anticancer treatments), at week two (i.e. "biological window" of anti-HER2 therapy alone), and/or at the time of surgery (i.e. after completing paclitaxel plus anti-HER2 therapy, before starting adjuvant chemotherapy).

Central AMH testing was performed with the Roche Elecsys® AMH Plus assay (LoD=0.001 g/ml). AMH levels during anti-HER2 therapy alone and then combined with paclitaxel were assessed as a measure of treatment-related acute gonadotoxicity. The impact of different anti-HER2 agents, patients' age, and baseline AMH levels on treatment gonadotoxicity were also investigated.

Results: The present analysis included 130 patients with a median age of 38 years (IQR: 33-42 years).

AMH values at the three time-points differed significantly from each other ($p<0.001$). At baseline, median AMH levels were 1.29 ng/mL (IQR 0.56-2.62 ng/mL). At week two, a small but significant reduction in AMH levels was observed (median value: 1.10 ng/mL, IQR 0.45-2.09 ng/mL, $p<0.001$). At surgery, there was a larger significant decline in AMH levels (median value: 0.01 ng/mL, IQR 0.01-0.03 ng/mL, $p<0.001$).

While the type of anti-HER2 treatment (trastuzumab and/or lapatinib) did not appear to impact the results, age and pre-treatment ovarian reserve had a major influence on treatment-induced gonadotoxicity risk.

Conclusions: This NeoALTTO biomarker analysis showed for the first time that anti-HER2 therapies alone had limited gonadotoxicity, but the addition of weekly paclitaxel resulted in marked AMH decline with possible negative implications for subsequent ovarian function and fertility. While further data are needed regarding the actual impact on fertility outcomes, these data highlight the importance of oncofertility counselling among all premenopausal women with HER2-positive breast cancer receiving systemic treatment.

C12

AXILLARY LYMPH NODE MANAGEMENT IN EARLY BREAST CANCER PATIENTS WITH POSITIVE SENTINEL LYMPH NODE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED TRIALS

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Background: Omitting axillary lymph node dissection (ALND) in patients with early breast cancer and 1 or 2 positive sentinel lymph nodes (SLNs) is still debated especially in those undergoing mastectomy. We aim to provide updated evidence on this topic.

Methods: This is a systematic review and meta-analysis of randomized trials evaluating the omission of ALND in patients with positive SLN. Included studies compared ALND vs. no ALND in breast cancer patients with tumors ⩽5 cm and up to 2 positive SLNs. In the no ALND group, patients could receive sentinel lymph node dissection (SLND) only or SLND and complementary axillary radiotherapy (SLND + AR). We assessed differences in overall survival (OS), disease free survival (DFS), axillary recurrence rate (ARR) and surgical outcomes (lymphoedema and neuropathy) in ALND vs. SLND alone group and ALND vs. SLND + AR group. Pooled hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using random effects models.

Results: Of 3,638 identified records, 7 records (6 studies) were included in our meta-analysis. All six studies were randomized non-inferiority trials with a total of 4789 included patients. Four trials evaluated ALND compared to SLND alone (N=2890). By hypothesizing a non-inferiority margin of 1.25 in survival endpoints, we found that SLND alone is non-inferior to ALND in both OS (HR 0.81, 95% CI 0.62-1.05) and DFS (HR 0.91, 95% CI 0.75-1.09). However, the non-inferiority could not be demonstrated for ARR (HR 1.18, 95% CI 0.64-2.15). Compared to ALND, SLND alone resulted in lower incidence of lymphoedema (OR 0.35, 95% CI 0.15-0.81) but no significant reduction in neuropathy (OR 0.31, 95 CI%, 0.08-1.22). Two trials compared ALND versus SLND + AR (N=1899).

In this comparison, the non-inferiority of SLND + AR could not be demonstrated in OS (HR 0.90, 95% CI 0.52-1.58), DFS (HR 0.99, 95% CI 0.66-1.49) and ARR (HR 1.35, 95% CI 0.63-2.89).

Conclusions: SLND is non-inferior compared to ALND in terms of OS and DFS, with lower rates of post-surgical lymphoedema. SLND + AR could be inferior compared to ALND in the survival endpoints evaluated. We were not able to perform subgroup analysis on patients undergoing breast conserving surgery or mastectomy.

C13

RISK ASSESSMENT OF DISEASE RECURRENCE THROUGH SERUM METABOLOMICS ANALYSIS IN ELDERLY PATIENTS WITH EARLY BREAST CANCER (EBC)

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Background: Risk stratification based on prognostic features is crucial for deciding the appropriate adjuvant treatments in eBC, especially in elderly patients (pts). Metabolomics studies metabolites in biological samples. Cancer can impair metabolism, so the pattern of altered metabolites could reproduce a "signature" that could indicate its presence. This analysis aimed to identify a "metabolic signature" that could differentiate elderly eBC pts from elderly pts with advanced breast cancer (aBC) and to investigate the prognostic role of the metabolic model in terms of disease recurrence (DR).

Material and methods: Serum samples of elderly BC patients enrolled in three onco-geriatric trials coordinated by the Medical Oncology of Prato were retrospectively analyzed via proton nuclear magnetic resonance (NMR) spectroscopy. Three NMR spectra were acquired for each fasting serum sample analyzed (NOESY1D, CPMG and Diffusion-edited). A Random Forest (RF) classifier was built. The ability of metabolomics to predict BC relapses was also assessed using Kaplan–Meier curves with calculation of the hazard ratio (HR) and p-value assessed by Log-Rank test.

Results: Serum samples of 140 women with eBC and 27 with aBC were collected between 2008 and 2018. In the aBC cohort, median age was 79 years (95% CI, 70-88); 25.91% of pts had a hormone receptor positive HER2 negative (HR+HER2-) breast cancer (BC), 29.62% a HER2 positive (HER2+) BC, 11.11% a triple negative (TN) one; in 33.33% of cases these data were missing. In the eBC cohort, median age was 76 years (95% CI, 70-91); 30.71 of pts had a HR+HER2- BC, 48.57% a HER2+ BC, 11.42% a TN one; in 3.57% of cases these data were missing. In this cohort, 39.28% of pts had a tumor stage pT2 BC and 56.42% a tumor stage pT1 BC; in 4.28% of cases tumor stage was unknown. Using NOESY1D spectra, the RF classifier discriminated early FFDR pts from aBC pts with a sensitivity, specificity and accuracy of 81.48%, 66.66% and 70% respectively higher than other spectra. Therefore, we tested the NOESY1D spectra of each relapsed eBC pts on the RF models already calculated. If metabolomics model classified the sample as relapsed, it was considered at "high risk" of DR. Our analysis showed that pts classified as "high risk" had a higher risk of DR (HR 3.39, 95% CI 1.59-7.24, p=0.00084).

Conclusions: This retrospective analysis suggested that a "metabolic signature" identified employing NMR spectral profiling is able to predict the risk of DR in elderly pts with eBC.

C14

IMMUNE CHECKPOINT INHIBITORS ADDITION TO CHEMOTHERAPY IN METASTATIC TRIPLE NEGATIVE BREAST CANCER ELDERLY PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The therapeutic approach for metastatic Triple Negative Breast Cancer (mTNBC) has been challenging for decades, given its typically aggressive natural history and the lack of possible actionable targets. The introduction of cancer immune therapy is reshaping clinical practice in the management of this disease; nevertheless, when dealing with special populations characterized by higher heterogeneity, it is still controversial whether treatment with Immune Checkpoint Inhibitors (ICIs) can improve the therapeutic efficacy obtained with standard chemotherapy. Due to the epidemiological transition, older patients, burdened by vulnerability and frailty, will

constitute an ever-increasing proportion of cancer patients. Therefore, this analysis aimed to determine the efficacy of this emerging therapy in older patients with mTNBC, also focusing on the subgroup expressing PD-L1.

Methods: We systematically searched PubMed, Embase, Web of Science, and Cochrane CENTRAL for eligible trials of ICIs addition to chemotherapy compared to chemotherapy alone for mTNBC patients aged =65 years. Progression-free survival (PFS) and overall survival (OS) were measured as primary outcomes. Sub-analyses based on PD-L1 expression were also performed.

Results: Three randomized controlled trials investigating involving 471 older patients were included. The addition of ICIs (atezolizumab and pembrolizumab) to chemotherapy resulted in a better PFS compared with chemotherapy alone in the overall population (hazard ratio [HR]: 0.70 [0.55-0.89], p= 0.004) and in the PD-L1 positive patients (HR: 0.62 [0.46-0.83], p= 0.001). In contrast, the use of ICIs did not significantly improved OS in the overall population (HR: 0.82 [0.65-1.04], p= 0.334) or in PD-L1 positive patients (HR: 0.75 [0.54-1.03], p= 0.573).

Conclusions: ICIs + chemotherapy significantly improves PFS in older patients with mTNBC, especially in PD-L1positive subgroup, while no statistically significant association was found with OS. Further studies are needed to investigate the efficacy and safety of ICIs + chemotherapy in frail and vulnerable population.

C15

EXPERIENCE AND SATISFACTION WITH A NURSE-DRIVEN GENETIC COUNSELING PATHWAY OF ITALIAN WOMEN WITH UNINFORMATIVE BRCA TEST RESULT

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Background: Several models of genetic counseling (GC) have been proposed to tackle the increasing volume of individuals requiring access to *BRCA* testing. Few data are available on patient satisfaction and retention of information with nurse-driven GC. We evaluated experience, satisfaction, and retention of information in women with uninformative *BRCA* test result and not considered at high-risk due to their personal/family history of cancer who underwent a geneticist-supervised nurse-driven GC.

Material and methods: Women who received an uninformative *BRCA* test result between May 2017 and September 2019 were administered a questionnaire exploring satisfaction with GC and retention of information provided.

Results: Of 424 eligible women, 345 (281 breast cancer patients and 64 healthy women) completed the interview. Overall, 324 women (93.9%) positively valued their experience with GC and 331 (95.9%) considered it helpful with 55.6% of them feeling reassured for themselves and their family. Information on the clinical implications of the test result was correctly retained and women acted accordingly. Overall, 286 women (82.9%) reported their test result as normal/negative and none described the test result as suggestive of the presence of inheritance. Only 78 (22.6%) recognized that despite a normal *BRCA* test result a low probability of a hereditary syndrome remains. When asked about the risk of breast, ovarian and other cancer associated to *BRCA* mutations compared to the general population, 66% of women thought that *BRCA* mutation carriers have a greater risk of both breast (66.4%) and ovarian (66.1%) cancer, around one in three did not express an opinion and a few reported no difference or a lower cancer risk in *BRCA*mutation carriers than in the general population.

Conclusions: A geneticist-supervised nurse-driven GC for women with uninformative *BRCA* test result is associated with great patient satisfaction and an adequate retention of information concerning the management of their personal and familial cancer risk. The design and implementation of nurse-driven GC models may contribute to an efficient and timely access to *BRCA* genetic testing.

C16

This abstract was withdrawn at the request of the Authors.

C17

MACHINE LEARNING SURVIVAL MODELS TRAINED ON CLINICAL DATA TO IDENTIFY HIGH RISK PATIENTS WITH HORMONE RESPONSIVE AND HER2 NEGATIVE BREAST CANCER

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Background: For early-stage endocrine-positive and HER2 negative breast cancer patients, the benefits resulting from adding chemotherapy to adjuvant endocrine therapy is controversial. Nowadays, several genomics tests are available, nonetheless these are expensive examinations which require to be performed in equipped laboratories. Therefore, new reliable and less expensive prognostic tools need to be explored. The aim of this work was to devise a survival model able to identify high risk patients for which adjuvant chemotherapy in addition to an endocrine treatment should be envisaged.

Methods: In this work, we developed different machine learning survival models trained on both clinical and histological data belonged to 145 breast cancer patients referred to Istituto Tumori "Giovanni Paolo II" of Bari. Particularly, inclusion criteria were (a) patients with an invasive breast cancer without metastasis *ab initio*, (b) patients who did not undergo chemotherapy, and (c) patients eligible for genomic tests according to the criteria defined by the decree of the Ministry of Health (May 2021), in other words, not high or low risk of recurrence patients with an early-stage endocrine-positive and HER2 negative breast cancer. Thus, with the purpose of identifying high-risk patients, we compared the well-known Cox survival regression model with three machine learning model, namely, Random Forest, Gradient boosting and Component-wise gradient boosting, in terms of time-dependent metrics evaluated within a cross-validation scheme.

Results: The experimental results showed that the Component-wise gradient boosting model outperforms the Cox regression model, achieving 10-years C-indexes equal to 0.73 and 0.60, respectively. Furthermore, survival models estimated by means of machine learning algorithms were able to discriminate, more accurately, high-risk from low-risk patients, identifying a major group of patients for which additional chemotherapy could be spared.

Conclusions: Considering that the EP test has declared a C-index equals to 0.75, our preliminary results obtained including only clinical features are promising. In our future

works, we will involve radiomic features extracted from medical images. Actually, the combined use of clinical data already collected within routine investigations could reduce the time and costs of genomic tests.

C18

EARLY PREDICTION OF NEOADJUVANT CHEMOTHERAPY RESPONSE BY MEANS OF A TRANSFER LEARNING APPROACH PERFORMED ON BREAST DCE-MRIS

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Background: The dynamic contrast-enhanced MR imaging plays a crucial role in evaluating the effectiveness of neoadjuvant chemotherapy (NAC) even since its early stage through the prediction of the final pathological complete response (pCR). Main purpose of this study was the development of a completely automatized support tool for an early prediction of pCR by means of a radiomic analysis performed on both pre-treatment and early-treatment exams.

Methods: In accordance with both MR images availability, 134 cases of study were identified from the I-SPY1 TRIAL public database, enrolling only patients with breast tumors of at least 3 cm in size and who received NAC with an anthracycline-cyclophosphamide (AC) regimen alone or followed by taxane. First, over 40.000 low-level features, i.e., related to local structure of the image, were automatically extracted by a pre-trained convolutional neural network (CNN). Next, an optimal set of features with statistically significant discriminating power was identified and then used to design an SVM classifier.

Results: The experimental results showed that by combining the optimal features extracted from both pre-treatment and early-treatment exams with some clinical features, namely, ER, PgR, HER2 and molecular subtype, an accuracy of 91.4% and 92.3%, and an AUC value of 0.93 and 0.90, were achieved on the fine-tuning dataset and the independent test, respectively.

Conclusions: Overall, the low-level CNN features have an important role in the early evaluation of the NAC efficacy by predicting pCR. The proposed model represents a first effort towards the development of a clinical support tool for an early prediction of pCR to NAC.

C19

This abstract was withdrawn at the request of the Authors.

C20

CORRELATION BETWEEN CLINICOPATHOLOGIC FEATURES AND ONCOTYPE DX RECURRENCE SCORE IN PATIENTS WITH ER+/HER2- EARLY BREAST CANCER: A MONO-INSTITUTIONAL SERIES

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Background: In ER+/HER2- early breast cancer (EBC), the 21-gene recurrence score (RS) assay (Oncotype DX) has been prospectively validated as a tool providing both prognostic and predictive information useful for tailoring adjuvant chemotherapy administration. We aim to evaluate the association between standard clinicopathologic features and RS in a mono-institutional series.

Methods: We selected all consecutive ER+/HER2- EBC patients that performed the Oncotype DX assay at San Raffaele Hospital from January 2017 to April 2022. The following clinicopathologic features were evaluated: tumor size (T1b-c vs T2), nodal status (N0 vs N1), grade (G1 vs G2 vs G3), ER status (⩾ 90% vs < 90%), PgR status (⩾ 90% vs 20-89% vs < 20%), Ki67 index (⩽ 20% vs 21-30% vs > 30%). Patients were assigned to low- (RS 0-25) or high-risk (RS 26-100) RS category according to the TAILORx and RxPONDER cutpoints. The correlation between clinicopathologic features and RS category was assessed using Chi-Square.

Results: We identified 232 patients. Median age: 56 (range 27-91), female: 98%. The distribution of clinicopathologic features according to low and high RS category is summarized in the table.

Grade, PgR and Ki67 were significantly associated with RS category. At an exploratory analysis, the combination of factors appeared to be more informative. For instance, all patients with PgR ⩾ 90% and Ki67 ⩽ 20% (n=27) have a low RS, whereas all patients with PgR < 20% and Ki67 > 30% (n=9) have a high RS.

	RS 0-25 (%)	RS 26-100 (%)	p-value
Tumor size			
T1b-c (n=144)	114 (79.2)	30 (20.8)	
T2 (n=88)	69 (78.4)	19 (21.6)	0.89
Nodal status			
N0 (n=146)	109 (74.7)	37 (25.3)	
N1 (n=86)	74 (86)	12 (14)	0.04
Grade			
G1 (n=15)	15 (100)	0 (0)	
G2 (n=178)	152 (85.4)	26 (14.6)	
G3 (n=39)	16 (41)	23 (59)	< 0.00001
ER			
⩾ 90% (n=213)	171 (80.3)	42 (19.7)	
< 90% (n=19)	12 (63.2)	7 (36.8)	0.079
PgR			
⩾ 90% (n=66)	62 (93.9)	4 (6.1)	
20-89% (n=117)	96 (82.1)	21 (17.9)	
< 20% (n=49)	25 (51)	24 (49)	< 0.00001
Ki67			
⩽ 20% (n=94)	90 (95.7)	4 (4.3)	
21-30% (n=106)	81 (76.4)	25 (23.6)	
> 30% (n=32)	12 (37.5)	20 (62.5)	< 0.00001

Conclusions: No individual clinicopathologic feature appeared to be precisely and robustly predictive of RS risk-category. The combination of PgR and Ki67 might be more informative for identifying patients with very low probability to have an informative test, but reproducibility of these findings in non-reference labs might be low. These findings could improve the tailoring of test prescription to maximize the cost/effectiveness.

C21

STAGING STRATEGIES OF NEWLY DIAGNOSED TRIPLE-NEGATIVE BREAST CANCER (TNBC): COMPARISON BETWEEN CT SCAN AND 18F-FDG-PET/CT

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Background: An accurate radiologic staging of patients with newly diagnosed TNBC plays a pivotal role to determine the optimal management and to minimize unnecessary treatments. According to the 2019 ESMO and the 2020 Italian (AIOM) guidelines, a thoracic and abdominal computed tomography (CT) scan can be considered for staging of patients with clinically positive axillary nodes, large tumors, aggressive biology, and

suspects of metastases. Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan can be used when conventional methods are inconclusive or, for the ESMO guidelines, can replace traditional imaging in high-risk patients. Our retrospective single-center study aimed to compare PET/CT and CT scan in loco-regional staging of TNBC patients.

Methods: Initial TN stage was determined by mammography and breast ultrasound (US). In candidates to neoadjuvant chemotherapy (NACT), breast MRI was performed as well. All patients included in the analysis underwent a thoraco-abdominal CT scan or a whole-body PET/CT according to clinicians' preference. Rates of up- or downstaging using different imaging techniques were evaluated and reported in Sankey diagrams.

Results: A total of 127 consecutive TNBC patients were enrolled. 85 out of 127 patients (67%) were staged with CT scan, whereas 42 (33%) with PET/CT. Among those who underwent CT scan, 7/85 (8%) were upstaged after mammography and breast US and 3/85 (4%) downstaged. Among patients who were studied with PET/CT, 9/42 (21%) upstaged and none downstaged. When locoregional staging included breast MRI, the rate of upstaging in the CT scan group was halved to 2% and decreased to 19% for PET/CT.

Conclusions: CT scan and PET/CT may present different accuracy in local staging of newly diagnosed TNBC. In our analysis, PET/CT upstaged a higher rate of TNBC patients (21%) compared to CT scan (4%). Even in presence of MRI, PET/CT scan showed a higher rate of upstaging, and this could be due to a more accurate evaluation of locoregional lymph nodes (in particular supraclavicular nodes) or false positive results. These findings could have an impact on subsequent treatment management and patient outcomes and thus deserve further research

C22

This abstract was withdrawn at the request of the Authors.

C23

CDK 4/6 INHIBITORS FOR METASTATIC BREAST CANCER: A MULTICENTER REAL-WORLD STUDY

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Background: CDK 4/6 inhibitors (inh) have redefined the standard of care for patients (pts) with HR+/HER2- advanced breast cancer (aBC). Assessing efficacy and safety of CDK4/6 inh in real-world practice is of outmost importance.

Methods: This observational multi-institution retrospective/prospective study included HR+/HER2- aBC pts receiving CDK 4/6 inh + endocrine therapy (ET) in two Italian centers (IOV, INT). Progression-free survival (PFS) was calculated from initiation of CDK 4/6 inh therapy to disease progression or death, whichever occurred first. For pts receiving treatment after progression to CDK 4/6 inh, PFS-2 was calculated as time from progression to CDK4/6 inh to subsequent progression or death.

Results: From October 2015 to January 2021, 444 pts received CDK 4/6 inh (66% palbociclib, 16% ribociclib 17% abemaciclib) + ET: 273 (69%) as 1st line, 122 (31%) as 2nd line. At a median follow up of 31 months, median PFS was 24.9 months (95%CI 20.7-29.1) for 1st line pts and 13.1 months (95%CI 9.4-16.9) for 2nd line pts.

Among 273 1st line pts, 170 (62%) had endocrine-sensitive BC; of these, 42% had *de novo* metastatic disease and 56% did not have visceral involvement. In 1st line endocrine-sensitive aBC pts, median PFS was 35.9 months (95%CI 22.4-39.4); absence of visceral metastases was significantly associated with longer PFS (mPFS 50.1 vs 18.3 mos, HR 0.38, 95% CI 0.24-0.61, $p<0.001$), even after adjustment for baseline performance status, while *de novo* metastatic BC and previous ET therapy were not significantly associated with PFS.

Out of 444 pts, 49% required at least a dose reduction. Pts requiring dose reductions presented a longer PFS than those treated at full dose, both in 1st line (35.4 vs 16.9 mos, $p<0.001$) and in 2nd line (23.7 vs 8.1 mos, $p<0.001$) and after adjustment for other relevant prognostic factors (visceral involvement, performance status, endocrine sensitivity) at multivariate analyses.

Out of 222 pts discontinuing CDK 4/6 inh due to disease progression, 94% received subsequent treatment, mostly chemotherapy (61%). Median PFS2 following 1st or 2nd line CDK 4/6 inh was similar (5.32 vs 4.4 mos).

Conclusions: Our results confirm effectiveness and safety of CDK 4/6 inh in a real-world cohort of HR+/HER2- aBC pts. Good prognosis subgroups (e.g., no visceral involvement) are well represented in real-world cohorts and are associated with prolonged PFS.

C24

BIOMARKERS OF EFFECTIVENESS AND TOLERABILITY IN PATIENTS WITH HR+ HER2-METASTATIC BREAST CANCER TREATED WITH 4/6 CYCLINE-DEPENDANT KINASE INHIBITORS. THE INDACO STUDY: PRELIMINARY RESULTS FROM A FEASIBILITY ANALYSIS

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Background: Cyclin-dependant kinase 4 and 6 (CDK4/6) inhibitors combined with aromatase inhibitors or fulvestrant in hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer represent the newest frontier of endocrine therapy in HR+/HER2- advanced breast cancer. The identification of biomarkers of proven predictivity, both in terms of clinical effectiveness and tolerability, represents a key topic to a cancer reaserch agenda.

Methods: The INDACO is a multicentric, prospective, observational study. Sample size calculations and enrollment capacities of the centers involved defined a minimun enrollment target of 100-120 patients. This study aims to the identification of serum and tissue biomarkers related to the activity of CDK 4/6 inhibitors. Endpoints for effectiveness are: 1-year progression free survival (PFS) (primary endpoint), objective response rate, clinical benefit and survival rate at 24 months. Biomarkers are measured in serially collected sera and tissue samples. The QIAGEN kit is

used for extraction purposes, following RNA purification and cDNA synthesis. miRNA profiling is performed by qRT-PCR (Applied Biosystem). MicroRNAs (miRNAs) profiles are assessed throughout an Agilent platform. We also evaluate circulating tumor DNA (ctDNA) in serum samples. The ctDNA isolation is performed using the QIAGEN Circulion Nucleic Acid kit. ctDNA assessment is based on the use of an Illumina Nextseq 500 platform.

Results: Thus far, 105 patients have provided data and samples to the INDACO study. Analyses have been run with feasibility purposes on tumor tissues from a set of 7 patients distinguished into 2 groups based on PFS, i.e., responders (PFS?6 months) and non-responders (PFS =6 months). RNA sequencing highlighted 74 differentially regulated genes. A differential analysis of the gene expression profiles identified 152 genes, of which 80 down-regulated and 72 up-regulated. A functional annotation analysis was carried out using the Gene Ontologies database. The expression profile of 2,549 microRNA was analyzed using RNA from tumor material. Nonparametric tests detected 10 miRNAs differentially expressed between the two groups.

Conclusions: Results from feasibility analyses are encouraging. Enrollment accomplishment is expected within the next 6 months. Results on biomarkers will be available shortly after.

C25

USING OF THE CTS5 SCORE TO IDENTIFY YOUNG BREAST CANCER PATIENTS WITH A LOW PROBABILITY OF FUTURE PREGNANCIES

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Background: The incidence of breast cancer (BC) in young women (⩽40 years) is significantly increasing in the last years. A significant proportion of young BC patients have not completed their family at the time of diagnosis. Infertility is an important long-term effect of cancer treatment. More frequently young BC patients are favorable to fertility preservation. The Clinical Treatment Score post-5 years (CTS5) estimates the residual disease recurrence risk in hormone receptor-positive (ER+) BC patients who have been treated with five years of adjuvant endocrine therapy. This retrospective analysis aimed to determine the accuracy of the CTS5 to identify early high risk BC patients at diagnosis who could be candidated to extended adjuvant endocrine therapy (ET).

Materials and methods: From a database of 2900 BC patients referred to the Breast Unit of Polytechnic University of Marche-Ospedali Riuniti of Ancona between 2013 and 2020, we identified 107 patients with ⩽ 40 years old at diagnosis. We excluded: patients treated with neoadjuvant chemotherapy; metastatic BC; in situ BC; ER- BC.

Results: 53 patients were availble for CTS5 analysis. Median age was 38 (26-40). 34% were nulliparous while 26.4% had a previous pregnancy. 69.8% wished to preserve fertility (major part with GnRHa). However only 24.5% of patients manteined the desire of pregnancy at the end of the therapies. CTS5 score were low, intermediate and high in 56.6%, 22.6% and 20.8%, respectively. The number of pregnancies before diagnosis were similar in the 3 subgroups. 81.8% and 83.3% of patients with high/intermediate CTS5, decided to preserve fertility while only 60% of patients with low CTS5 decided to preserve fertility. However, 30%, 33% and 0% of patients, respectively with low/intermediate/high CTS5 score, manteined the desire of pregnancy at the end of therapies. Patients with high CTS5 score were significantly associated with KI-67⩾20% (p=0.008), high tumor size (p<0.0001), grading 3 (p=0.002), pN+ (p=0.0001), using of mastectomy (p=0.0003) and adjuvant chemotherapy (p=0.001).

Conclusions: This discrepancy between the desire to preserve fertility at diagnosis and decline/absence of desire for motherhood at the end of treatment could justify the increased use of CTS5 at diagnosis (not only after the end of the first 5 years) to identify early the young high-risk BC patients candidates for ET of longer duration with low future probability of pursuing pregnancy.

C26

ITALIAN CURRENT USE AND UNDERSTANDING OF BREAST CANCER MULTIGENE SIGNATURES IN CLINICAL PRACTICE: RESULTS FROM THE PROCURE PROJECT

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Background: Several Breast Cancer Multigene Signatures (BCMS) are available to profile early breast cancer (eBC) but knowledge regarding their value in clinical practice is scarce. Here we present results on the use of BCMS in Italy from the PROCURE Project, which aim was to develop a European consensus on the utility of BCMS.

Materials (patients) and methods: The Delphi questionnaire developed by the Scientific Committee was administered twice to oncologists, pathologists, and surgeons across Europe. The questionnaire included 5 sections: 1) Panellists' profile and experience with BCMS, 2) Current clinical practice in eBC and use of BCMS, 3) Panellists' opinion on the utility of the BCMS in eBC according to patient profiles, 4) Agreement with a set of recommendations on the use of BCMS in clinical practice and 5) Identification of unmet needs and future applications of BCMS.

Results: 133 panellists from 11 European countries completed both rounds of the survey, being 22 of them from Italy. As in the overall sample, most of the Italian panellists were oncologists (86%) working in teaching hospitals (82%), and with more than 5 years of experience using BCMS (95%), a higher percentage compared to the whole sample (73%).

Regarding their clinical practice, 59% of Italian panellists reported the existence of hospital/country policies to regulate the use of BCMS, which is significantly low compared to the other European countries (85%). This is in line with the fact that Italian panellists give great importance to their own experience when deciding adjuvant therapy (41%).

In Italy, 27% of the panellist reported that BCMS are not available in their hospitals which represents the highest percentage across European countries. When available, they use BCMS mostly in selected cases (73%) and the main reasons are to predict the benefit from chemotherapy (59%) and to assess the risk of distant recurrence within 10 years in order to avoid chemotherapy (47%). They also use them to discuss treatment options with the patient (41%), which is something less relevant in other regions (25%).

Conclusions: Italian panellists that participated in the PROCURE study had an extensive experience in the management of BC patients. However, there is a need to expand the use of BCMS and improve clinicians' knowledge, as suggested by the fact that 27% of hospitals do not have access to BCMS and the misconception among experts regarding the predictive value of these tests.

C27

AN EVIDENCE BASED AND DIGITAL ASSISTED INTEGRATIVE APPROACH TO BREAST CANCER PATIENTS INSIDE AN ITALIAN BREAST CENTER

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Background: Breast cancer survivors have physical and psychological issues that need to be addressed through safe, rational and evidence based tools by health care providers. Unfortunately, many of these issues regarding quality of life, body weight, sleep, mood and sexuality remain unsolved, pushing a number of patients towards "natural" therapies, often misleading and alternative to mainstream cancer care.

Integrative resources and digital health devices can be reliable means in order to give answers to many of those needs, by combining lifestyle counseling, body-mind activities and complementary evidence-informed therapies alongside and beyond lifesaving anticancer treatments.

Material and Methods: In our model at Fondazione Policlinico Gemelli, every breast cancer patient waiting for surgery or candidate to neoadjuvant chemotherapy undergoes a preliminary psycho-oncological distress evaluation and a brief lifestyle interview, a few days after being diagnosed. Anthropometric measurements, body composition analysis and individual levels of physical activity are recorded by a nutritionist. Patients are given evidence based recommendations about the advisable diet during the treatments and basic information about the integrative resources to treat symptoms and side effects (acupuncture, mindfulness-based protocols, qigong, massage therapy and classes of music/art therapy).

After this first assessment, a personalized physical activity program is proposed and monitored through a smartphone based digital health platform (Pinktrainer®).

Results: Between January 2019 and December 2021, the Center for Integrative Oncology at Fondazione Policlinico Gemelli has carried out 2,271 lifestyle counselings, 2,897 acupuncture treatments, 1,664 physiotherapy sessions, 6,115 psycho-oncological consultations. Moreover, 102 breast cancer patients completed the mindfulness based stress reduction (MBSR) protocol and 969 patients participated in qigong, art therapy and music therapy classes.

Between January 2021 and December 2021, 90 breast cancer patients used a Pinktrainer® supervised program of physical activity.

Conclusions Our integrative model, even by the means of digital health devices, aims to deliver a person-centered approach within the same breast center where the anticancer treatments are provided, in order to improve symptoms management, adherence to oncological protocols and overall quality of life.

C28

EFFICACY AND SAFETY OF NAB-PACLITAXEL PLUS ATEZOLIZUMAB AS FIRST-LINE TREATMENT OF PD-L1-POSITIVE METASTATIC TRIPLE-NEGATIVE BREAST CANCER (TNBC): RESULTS OF THE MULTICENTER, REAL-WORD 'ANASTASE' STUDY

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Background: The addition of atezolizumab to nab-paclitaxel represents a new first-line treatment option for PD-L1-positive unresectable locally advanced or metastatic TNBC, based on the results of the phase III IM130 trial. However, 'real-world' data concerning efficacy and safety of this combination are limited. Thus, the aim of the 'ANASTASE' study was to collect data on nab-paclitaxel plus atezolizumab in patients (pts) enrolled onto the Italian expanded access protocol.

Methods: A retrospective analysis of PD-L1-positive metastatic TNBC pts, treated with first-line nab-paclitaxel plus atezolizumab at 29 Institutes, was conducted. Outcomes were objective response rate (ORR), clinical benefit at 6 months (mo.), progression-free- and overall-survival (PFS/OS), and treatment-related adverse events (AEs). Descriptive statistics was adopted. Kaplan-Meier curves were compared with Log-Rank analysis.

Results: Data from 51 pts were gathered (median age 51 years, interquartile range [IQR] 45-63 years). Forty pts (78.4%) received neoadjuvant/adjuvant chemotherapy, including a taxane-based regimen in 80% of cases; median disease free-interval was 20 mo. (IQR 13-50). Overall, 31.4% of pts had one metastatic site and 11.8% >3 metastatic sites. Median number of treatment cycles was 5 (IQR 3-8 cycles); 8 pts (15.7%) were still on treatment at time of analysis. The ORR was 41.2% (95% Confidence Interval [CI] 27.7-54.7%): namely, 5.9% complete response and 35.3% partial response; 33.3% of pts had a progressive disease; clinical benefit rate at 6 mo. was 49%; median duration of response was 12.8 mo. (95% CI 3.7-21.8 mo.). At median follow up of 20 mo. (IQR 16-24 mo.), median PFS was 6.8 mo. (95% CI 3.5-10 mo.); median OS was not reached (at 24 mo. 48.1% of pts were alive). No significant difference in terms of ORR and PFS according to stage at diagnosis, BRCA status, number and type of metastatic sites was reported. Most common AEs of any grade included: neutropenia (50.1%), anemia (31.4%), vomiting (31.4%), fatigue (25.5%), nausea (25.5%), liver toxicity (23.5%) and peripheral neuropathy (15.7%). Most common potential immune-related AEs of any grade included: skin rash (11.8%), pneumonitis (9.8%), hepatitis (3.9%) and thyroiditis (3.9%).

Conclusions: PD-L1-positive metastatic TNBC pts treated with first-line nab-paclitaxel plus atezolizumab substantially derived, in a 'real-word' context, similar PFS and ORR than those reported in the IM130 study, without unexpected adverse events.

C29

ONCOROSA TREKKING. THE MOUNTAIN AS A CURE FOR AFTER TREATMENT WOMEN WITH BREAST CANCER

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Background: In the literature, there is no evidence on the application of mountain therapy in cancer patients. It's showed that the mountain environment is therapeutic to cure and improve the well-being of individuals with different problems. The aim of our project is to offer in women with breast cancer after surgery/chemotherapy/radiotherapy the opportunity to live an experience in the natural environment of the mountain in order to counter the effects of psychological distress. Mountain Therapy is an original therapeutic, rehabilitative and socio-educational approach aimed to secondary prevention, treatment and rehabilitation in people with different problems, pathologies or disabilities; designed to take place through work on group dynamics, in the cultural, natural and artificial environment of the mountains.

Table 1. EORTC QLQ-C30.

Functions	Media T0	Media T1	Improvement
Physiological function	76,89	81,33	+4,44
Function of role	73,33	85,56	+12,22
Emotional function	61,11	83,33	+22,22
Cognitive function	77,78	91,11	+13,33
Social function	74,44	86,67	+12,22
Quality of life	53,33	73,33	+20,00
Fatique	41,48	27,41	-14,07
Nausea	6,67	2,22	-4,44
Pain	25,56	16,67	-8,89
Dyspnea	20,00	8,89	-11,11
Insomnia	26,67	20,00	-6,67
Lack of appetite	11,11	0,00	-
Constipation	13,33	0,00	-
Diarrhea	4,44	0,00	-

Table 2. Distress Thermometer.

T0 (start)	T1 (End)
7	2
7	3
7	2
8	3
7	2
7	0
7	3
7	3
6	0
8	2
8	2
7	2
6	4
7	0
8	0

Material and Methods: We administered at the start (T0) and at the end (T1) of the experience three self-evaluation questionnaires (Nccn distress thermometer, EORTC-QLQ-C30, Hospital anxiety and depression scale HADS).

Results: 19 female breast cancer patients answered at T0; 15/19 at T1.

Conclusions: Montain Therapy project although is an experimental small experience showed an improved of well-being and levels of psychological distress in breast cancer patients. The Questionnaires showed a distress reduction and improvement of physiological, emotional, cognitive, social and physiological functions. The main finding was the improvement in anxiety and depression levels. Has been highlighted also a reduction in symptoms as diarrhea, insomnia, dyspnea, pain and fatigue (**EORTC QLQ-C30)**. We need to confirm the data obtained amplifying the sample to a better scientific validation.

Table 3. HADS.
Mild (M); Borderline abnormal (BA), Normal (N); Abnormal (A).

T0		T1	
Anxiety	**Depression**	**Anxiety**	**Depression**
M	N	N	N
M	N	N	N
M	M	M	N
N	M	N	N
M	N	N	N
N	N	N	N
BA	M	M	N
BA	M	M	M
N	N	N	N
BA	M	N	N
A	A	N	N
A	A	N	N
M	N	N	N
BA	N	M	M
BA	N	N	N

C30

DEVIL'S CLAW (HARPAGOPHYTUM PROCUMBENS) IMPROVES AI-ASSOCIATED ARTHRALGIA IN EARLY BREAST CANCER PATIENTS

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Background: Aromatase inhibitors are recommended as adjuvant hormone treatment for postmenopausal women with early breast cancer. However many patients (about 50%) experience adverse effects including AIA (aromatase inhibitor-related arthralgia - pain and stiffness) witch even leads to non-adherence with therapy and early treatment interruptions. Despite the efforts of the last 20 years with drugs (omega-3 fatty acids, NSAID, vitamin D, duloxetine, codeine) and techniques (physical activity, yoga, acupuncture), the treatment of AIA is a challenge for oncologists. In order to find new approaches, we investigated the role of Devil's claw as treatment of AIA, studying his effects on a BPI-SF scale (Brief Pain Inventory – short form).

Material and methods: From February 2021 to November 2021, we recruited 34 early breast cancer patients reporting AIA. Inclusion criteria are: early breast cancer with oestrogen e/o progesterone receptors positive, postmenopausal status, ECOG PS 0-2; at least 4 weeks of treatments with aromatase inhibitors; at least a period of scheduled 8 weeks of aromatase inhibitor adjuvant therapy; at least a pain severity score $\geqslant$4 at BPI-SF and no previous palliative treatments allowed.

All patients received a supplement of Devil's claw (1000 mg/day) for 8 weeks. BPI-FS, evaluating pain severity (PS), pain interference (PI) and stiffness severity (SS), was collected at baseline and at 2, 4, 6, 8 weeks.

Results: Among 34 patients (median age 60), the median score of PS, PI and SS at baseline was 4.9, 4.2 e 5.3 respectively. At 8 weeks, participants experienced significant improvements of AIA with a progressive reduction of median score of PS (4.5 at 2 week, 3.9 at 4 week, 3.6 at 6 week, 2.9 at 8 week – 40% reduction from baseline) and PI (4.4 at 2 week, 3.7 at 4 week, 3.7 at 6 week, 3.6 at 8 week – 12% reduction from baseline). Lastly SS median score was stable for 2 week with a 37% reduction at 8 week (5.3 at 2 week, 3.9 at 4 week, 3.5 at 6 week, 3.3 at 8 week).

Conclusions: At the current state of knowledge, this is the first experience with Devil's claw, with well-know anti-arthritic properties, for treatment of AIA. Our research points out a correlation between Devil's claw use and improvement of AIA symptoms. In fact, all 3 BPI-SF outcomes evaluated are significantly improved and emphasize the use of Devil's claw as an effective option for the treatment of AIA.

C31

TRASTUZUMAB DERUXTECAN (T-DXD) IN HER2 POSITIVE (HER2+), ADVANCED BREAST CANCER (ABC): A SINGLE INSTITUTION, REAL WORLD EXPERIENCE

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Background: According to recent published clinical trials,T-DXd should be considered the standard option as second and further lines of treatment in HER2+ ABC. However, real world data are lacking.

Materials and methods: We retrospectively identified all consecutive HER2+ ABC patients, who received T-DXd at our center between 2019 and 2022. We collected: patients (pts) demographics, tumor characteristics, preliminary efficacy and toxicities.

Results: A total of 18 pts were included. Pts characteristics were: median age 64 years (range 41-83); median PS 0 (range 0-2),PS 2 11% (2pts); HR+ tumors 78% (14 pts); de novo ABC 33% (6 pts); recurrent disease 67% (12 pts). Median number of metastatic sites was 3 (1-7) and liver involvement was observed in 8 pts (45%). Stable brain metastasis at baseline were reported in 3 pts (17%). Median previous lines were 3 (range 2-7) and included Pertuzumab (78%) and TDM1 (100%). The median number of cycles administered was 7,5 (range 1-31). Among the 17 evaluable pts, ORR was 41%. No CR were recorded. A DCR (PR + SD for 6 months) of 76.5% was reported while the preliminary mPFS was 6.5 months (range 1-24). At the time of this analysis 8 pts (45%) were still on treatment. AEs of any grade occurred in 66% of pts. The primary reason for discontinuation was PD. Grade 1-2 toxicities were: fatigue (67%, 12 pts); nausea (38%, 7 pts); neutropenia (28%, 5 pts); vomiting (16%, 3 pts); diarrhea (5.5%, 1 pt) and hyperbilirubinemia (5.5%, 1 pt). No G4 AEs were reported, while we observed G3: anemia (5.5%, 1 pt), fatigue (5.5%, 1 pt); ALT increase (5.5%, 1 pt) and vomiting (5.5%, 1 pt), the latter, resolved with treatment delay and dose reduction. No cases of ILD, decreased left ventricular EF, prolonged QT interval or infusion related reaction were noted in our pts.

Conclusions: In our real-world experience, T-DXd showed a preliminary efficacy and a safety profile consistent with that reported in RCTs. Nearly all AEs were G1-2 and easily manageable. G3-4 AEs were uncommon and no new safety concerns were identified. All grade nausea occurred in a lower percentage of pts (38%) than in DestinyBreast01 (77%). Furthermore severe (G3-4) nausea and vomiting were uncommon in our cohort. Overall, this may be due to the antiemetic prophylaxis that approximately all pts of our cohort received and that should be considered when administering T-DXd.

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C32

IMPACT OF 21-GENE TEST ON ADJUVANT TREATMENT CHOICE IN PATIENTS WITH RE+, HER2- EARLY BREAST-CANCER: MODENA CANCER CENTER EXPERIENCE

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Background: In hormone receptor positive (HR+), HER2 negative early breast cancer (EBC) the adjuvant treatment strategy may included chemotherapy (CT) added to endocrine treatment (ET) in selected cases. 21-gene BC assay, recently reimbursed in clinical practice in Emilia Romagna, is a useful multi-gene test able to predict the benefit of CT base on a quantitative recurrence score. The aim of this study

Characteristic	Total	RS0-10	RS11-25	R>25
Median age	56 years			
Risk score distribution				
RS<10	7			
RS: 10-25	20			
RS > 25	16			
Menopausal status				
Post	31	4	15	12
Pre	12	3	5	4
N distribution				
N0	26	6	8	12
N+	17	1	13	3

was to evaluate how multi-gene test changes the therapeutic adjuvant choice of a multidisciplinary BC team.

Methods: We retrospective collected clinical and pathological data of patients with ER+, HER2 negative EBC diagnosed from 07/07/2021 (data of 21-gene RS reimbursed by Emilia Romagna Health Care System) to 31/12/2021 who underwent 21-gene assay in Modena Cancer Center. Treatment recommendations from multidisciplinary BC team before knowing the results of RS and post-RS were collected.

Results: From 07/07/2021 to 31/12/2021 220 new cases of BC have been diagnosed in Modena Cancer Center, 73% of these were ER+, HER2 negative EBC. Physicians requested the RS test in 27% of cases. Overall, RS 0-10 was found in 7 cases (16%), RS 11-25 in 20 (46%) and RS>25 in 16 patients (37%) respectively. Considering nodal status, only 7 cases (9%) of N+ patients had an high risk RS compared to 28% in N0 women. Independently from menopausal status, one-third of patients had RS > 25. The matching percentage of treatment recommendations pre-RS and post-RS was 63%, in the half of the cases the therapeutic decision change from CT to ET alone, mainly in N0 population (80%) and post-menopausal woman (68%).

Conclusions: In daily clinical practice, the use of 21 gene test RS change physician's treatment choice in 37% of cases, reducing by 50% the use of chemotherapy. Our real life experience confirmed the utility of RS test in the adjuvant decision making process of ER+, HER2 negative EBC.

C33

RISK OF DRUG-INDUCED INTERSTITIAL LUNG DISEASE IN PATIENTS WITH METASTATIC BREAST CANCER TREATED WITH ANTIHER2 REGIMENS: A NETWORK META-ANALYSIS

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Background: Interstitial Lung Disease (ILD) is a pulmonary disorder caused by several conditions, including drug toxicity, which may cause a wide range of pathological processes, from inflammation to interstitial fibrosis. The advent of new antibody-drug conjugates, such as trastuzumab deruxtecan (T-Dxd), has significantly increased the awareness towards drug-induced ILD, but the differential risk magnitude among the available treatments is still unknown. The aim of this network meta-analysis (NMA) was to provide first preliminary data on the risk of ILD across anti-HER2 regimens.

Methods: After a systematic literature review, a Bayesian NMA using a Markov-Chain Monte Carlo simulation was performed using STATA software (Stata Corp, version 17). Treatments were classified as: Trastuzumab (T) + chemotherapy (CT), T/Pertuzumab (P)+CT, Everolimus (Eve)/T+CT, T-DM1, T-DM1/P, T-DM1+Atezolizumab (Atezo) and T-Dxd. Outcomes were reported with corresponding 95% credible intervals (CrIs). Treatments were ranked using the surface under the cumulative ranking curve (SUCRA).

Results: The main trials included in the NMA were BOLERO-1, BOLERO-3, CLEOPATRA, KATE2, MARIANNE and DESTINY-Breast03. Within the experimental arm, ILD of any grade was detected in 10.5% of patients for DESTINY-Breast03, 4.5% and 3.6% respectively for BOLERO-1 and BOLERO-3, 0.7% in KATE2, 0.5% in CLEOPATRA and 0.3% in MARIANNE.

In terms of tolerability, T-DM1 ranked first (SUCRA 80.1%), followed by TDM1/P/T + CT (SUCRA 77.5%). Instead, T-Dxd and Eve/T + CT were the most prone to ILD development (respectively SUCRA 18.7% and 11.1%). NMA showed no significant differences between T+CT and T-DM1 or T-DM1+Atezo, while a significantly lower risk ratio was observed for T+CT when compared to T/P+ CT (RR 0.04, 95%CrI 0.01-0.34), T-Dxd (RR 0.03, 95%CrI 0.00 - 0.56) and Eve/T+CT (RR 0.02, 95%CrI 0.00 - 0.08).

Conclusions: The present analysis showed how drug induced ILD could differentially affect anti-HER2 treatments for MBC patients. Moreover, TDM1 seems to be associated to a lower risk of ILD. Further investigations are needed to understand the underlying pathological mechanisms causing drug induced ILD and to identify predictive biomarkers to allow an early identification of patients at higher risk.

C34

CLINICO-PATHOLOGICAL CHARACTERISTICS OF HER2 POSITIVE METASTATIC BREAST CANCER (MBC) PATIENTS EXPERIENCING A RADIOLOGIC COMPLETE RESPONSE (RCR): A NATIONWIDE EXPERIENCE

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Background: According to current literature, approximately 6% of patients (pts) with HER2 pos MBC experience a rCR to first line therapy, although figures are often derived by small and/or dated cohorts. Aim of this study was to define the characteristics of HER2 pos MBC experiencing rCR in a nationwide cohort of pts.

Methods: Pts were extracted from the GIM14 study and classified according to the best radiologic response at first line of therapy assessed with RECIST 1.1 criteria and according to time-to-treatment-failure (TTF). rCR was determined by complete response (CR) with a TTF $>$ 12 months. Association with the different variables was tested through logistic regression.

Results: A total of 783 pts from GIM14 had HER2 pos MBC. Radiologic response was described for 593 pts: 56 (9.44%) had a rCR with TTF $>$12 months and 12 (3.14%) a CR with TTF $<$12 months, 223 pts (37.42%) had partial response, 163 (27.35%) were stable and 135 (22.65%) had progressed. Visceral metastases (mets) were present in 436 pts (57.14%) and 390 pts (50.19%) had only one site of distant mets. Taxanes were the main chemotherapy (CT) agents used (445 pts, 73.07%) and 353 pts (51.76%) received the combination Trastuzumab-Pertuzumab. Median follow-up was 65.6 months. At multivariable analysis, hormone receptors status (p=0.0083), non-visceral mets (p=0.017), mets in 1 site (p=0.044) and CT with taxane/anthracyclines (p=0.0065) were significantly associated with rCR. HER2 score was significantly associated with rCR at univariable (p=0.029) but not at multivariable analysis (p=0.16). Type of anti-HER2 regimen and disease-free interval or *de novo* disease, were not associated with rCR. Among pts with rCR, 71% and 42% were respectively progression free after 2 and 5 years. Instead, at the same time points, rate of progression free pts without rCR were respectively 30% and 16%.

Conclusions: This study evaluated the characteristics of HER2 pos MBC pts experiencing a rCR. Novel anti-HER2 agents are gaining momentum as increasingly effective therapeutic strategies and these results will pave the way to new trials focused on liquid biopsy-based assessment of minimal residual disease for treatment de-escalation.

C35

TRASTUZUMAB-DERUXTECAN (T-DXD) IN PATIENTS WITH HER2 POSITIVE METASTATIC BREAST CANCER (MBC): THE MODENA CANCER CENTER REAL WORLD EXPERIENCE

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Background: T-DXD has showed impressive results in advanced, heavily pretreated, HER2 MBC. At 2021 ESMO congress, Destiny-Breast 03 trial showed a reduction of approximately 70% in the risk of disease progression and objective responses with T-DXD compared with T-DM1. Here we present the Modena Cancer Center experience with T-DXD since its clinical practice availability.

Patients and methods: This is a retrospective analysis of 15 MBC patients treated with T-DXD from April 2020 to April 2022 at our institution, of which 13 are evaluable for the analysis. T-DXD was administered according to producer indication, with standard premedication (desamethasone 8

mg, palonosetron 0.25 mg and clorfenamine 10 mg). The adverse events graduated according to CTCAE v 4.0 were analyzed too.

Results: 13 HER2+ve MBC female patients have received T-DXD at our Institution and are evaluable for the analysis.

The median age was 58 years old (range 40-81), three patients were older than 70.

10/13 (77%) had triple positive BC. 7/13 (54%) patients had visceral disease, and all of them showed brain dissemination too. All patients were heavily pretreated with a median of 4 previous lines of therapy, and T-DM1 in all cases; two patients had received 8 previous treatments for metastatic disease. Pertuzumab was comprised in the treatment of 8/13 (61%) patients.

At data collection (30/04/2022), one patient discontinued treatment due to AE, all the other are still on treatment, for at least four months. 2/13 (15%) patients showed complete response, 8/13 (62%) partial response and 3/13 (23%) stable disease. Disease control was achieved also in patients with brain metastases, two of them without needing local treatment.

The most frequent adverse event was nausea, in most cases grade 2, but 2/13 (15%) patients experienced nausea G3. Grade 3 hematologic toxicity was observed in 3/14 patients (23%).

Grade 2 Interstitial Lung Disease (ILD) was observed in one patient after fourteen months of treatment and led to treatment discontinuation. In our experience, ILD manifested with cough without expectoration, mild dyspnea and pathognomonic imaging at CT scan.

Conclusions: In our real world experience, among patients with HER2-positive MBC previously treated with T-DM1, T-DXD was effective and well tolerated, with manageable toxicities even in elderly patients. 76% of patients achieved an objective response, including those with brain metastases. Only one case of ILD was documented.

C36

BREAST CANCER IN ITALY: STAGE AND REGION DISTRIBUTION

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Background: Describe breast cancer in Italy by age, geographical area, stage and sites of metastases. In addition, incident and prevalent cases by region are provided.

Material and methods: This population-based study included all female patients with histologically confirmed breast cancer diagnosed in Italy between 2013 and 2019 in the eight participating Cancer Registries. Cases were described by geographic area (north, center, south), age group (<50, 50-69 and 70+) and site of metastases. In addition, the study also provided an estimate of the cases of metastatic breast cancer per single region.

Results: Of the total 5,731 cases, the number of unknown stage cases (eliminated from our analyses) was 545 (10.5% of cases); therefore, the study was conducted on 5,186 cases. Overall, 333 (6.5%) of tumors were metastatic at diagnosis but the distribution by geographical area was different: 5.1% in the north, 7.4% in the center and 7.8% in the south. Related to age, 5.6% were diagnosed before the age of 50 and 5.6% within the screening target group (50-69 years), while in elderly women the percentage rose to 8.1%. As regards the site of the metastases, 27.1% developed metastasis to the bone, 12.4% to the liver, 8.6% to the lung and 2.6% to the brain; in 34.9%, multiple sites were already present at the beginning of the cancer.

Table. Distribution of number of cases by stage and area.

Stage	North		Center		South		Italy	
	n.	%	n.	%	n.	%	n.	%
I	1,231	51.5	721	47.5	660	51.5	2,612	50.4
II	785	32.9	518	34.1	379	29.6	1,682	32.4
III	251	10.5	166	10.9	142	11.1	559	10.8
IV	121	5.1	112	7.4	100	7.8	333	6.4
Total	*2,388*	*100*	*1,517*	*100*	*1,281*	*100*	*5,186*	*100*

Overall, 3,520 cases of *incident* metastatic Breast Cancer are estimated in Italia every year (520 in Lombardy in northern Italy, 350 in Lazio in the center, followed by 330 in Campania in the south), and finally they are out of 52,000 *prevalent* cases.

Conclusions: A greater possibility of treating and living with the disease for a long time now requires careful monitoring of these tumors.

C37

CAPECITABINE AND VINORELBINE COMBINATION IN METASTATIC BREAST CANCER: DESCRIPTIVE ANALYSIS OF TWO CENTERS EXPERIENCE

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Background: In metastatic breast cancer (mBC), capecitabine (cape) and vinorelbine (vino) are known effective drugs and they have been successfully used in combination in the past, especially in the pre-CDK4/6i era. No literature data are available comparing the combined regimen (concCV) with the administration of single drugs in direct sequence (seqCV).

Methods: We retrospectively analysed a cohort of 188 consecutive mBC patients (pts) treated with concCV or seqCV between January 2010 and December 2016 in the centers of IRCCS CRO of Aviano and ASUFC Academic Hospital of Udine. Only pts receiving the two drugs in direct sequence were considered for the seqCV regimen. For pts receiving the concCV regimen, data on eventual maintenance therapy (MT) with either endocrine therapy (ET) or single-agent chemotherapy (CT) were collected. Pts receiving a new CV regimen were considered only if CV had been reintroduced at disease progression (PD) immediately after MT. The association of CV regimen with survival outcomes was explored by the Kaplan-Meier method. PFS for the concCV regimen was compared to the sum of PFS for single drugs of the seqCV regimen.

Results: Pts had a median age of 51 years (yrs) [44;60] at diagnosis and 57 yrs [49;66] at metastatic disease. Disease was de novo metastatic in 20% of pts. At diagnosis, 90% of pts had luminal-like BC, 10% had a triple negative BC. Disease recharacterization with a metastatic lesion biopsy was performed in 51% of pts, with a phenotype change in 18% of cases. Median number of treatment lines in the advanced setting was 5 [4;7], median line for CV regimen was 2 [2;3]. ConcCV was used in 138 pts (73%), while 50 pts (27%) received seqCV (in 82% of them cape was the first drug). MT was offered at disease control in 67 pts (36%), with a median duration of 8 months (m) [6;14]. ET (i.e. aromatase inhibitors in 49% of cases, fulvestrant in 13%, or other drugs) or single-agent CT (cape in 12%, vino in 10%) were used as MT. CV was reintroduced after MT at PD in 18 pts (27%). Overall, mPFS was 11 m [6;22] and mOS was 24.5 m [13.5;45.3] from CV start. In concCV pts, mPFS was 10 m [5;19] (mPFS2 was 18 m [9;31] with CV reintroduction) and mOS was 27.3 m [13.7;52.6]. In seqCV pts, total mPFS was 11 m [7;20] and mOS was 19.3 m [13.3;37.4].

Conclusions: According to our retrospective data, concCV and seqCV seem to be comparable in terms of survival outcomes, with the limits of a reduced sample size and unbalanced treatment arms.

C38

ALBUMIN AND CREATININE RATIO AS MUSCLE WASTING IN PATIENTS TREATED WITH CDK4/6 INHIBITORS IN METASTATIC LUMINAL-LIKE BREAST CANCER

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Background: Body composition is an established risk factor for development oand an unfavorable prognostic factor with higher incidence of recurrence, progression and cancer related deaths in breast cancer. The albumin (as a measure of visceral proteins) and creatinine (as a measure of the muscle wasting) ratio is a sample biomarker representative of muscle mass composition. Based on these premises, we evaluated albumin-creatinine ratio (ACR) in luminal-metastatic breast cancer (MBC) treated with CDK4/6 inhibitors.

Materials and methods: A retrospective cohort of 72 consecutive luminal-MBC pts treated with CDK4/6 inhibitors between 2018-2022 were analyzed at the Unit of Medical

Oncology of Crotone and Saronno, Italy. Prognostic factors in terms of PFS were tested both in uni- and multivariate models by Cox regression with 95% confidence interval (95% C.I.). Differences in survival were tested by log-rank test and represented by Kaplan-Meier survival curves. The attrition rate (AR) between 1st and 2ndL was calculated.

Results: Overall, 72% of patients received ET-CDKi at 1stL, 65% were hormone-sensitive, 26% had a bone-only disease, and 72% were aged ⩾65. At a median follow-up of 28 months, median PFS was 22 months at 1stL and 11 months at 2ndL. By univariate analysis, high ACR<4 showed a worse mPFS1 (HR 6.33, 95%C.I. 1.72-23.23, P=0.019), confirmed by multivariate analysis (HR 6.35, 95% C.I. 1.65-24.10, p=0.007) and conducted with potential confounders (age, hormone-sensitivity, metastatic sites, ECOG PS, MLR). ACR was not associated with number of metastatic sites (P=0.890) or bone-only disease (P=0.982). First dose level of reduction occurred in 28% of patients and AR between 1stL and 2ndL was 19%.

Conclusions: Our real-world data demonstrated that high AC<4 during ET-CDKi in 1stL luminal-MBC is associated with poor prognosis in terms of PFS. Further analysis, expanding cohort and including body composition measured through CT scan and BMI evaluation, is necessary to better refine the role of muscle mass and visceral fat in that population.

C39

SEQUENCE OF TREATMENTS AFTER CDK4/6 THERAPY IN ADVANCED BREAST CANCER (ABC), A GOIRC MULTICENTER RETRO/ PROSPECTIVE STUDY. PRELIMINARY RESULTS IN THE RETROSPECTIVE SERIES OF 116 PATIENTS. GOIRC-04-2019

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Background: The sequence of treatments in aBC after a CDK4/6 inhibitor (i) based therapy (tx) is not yet defined. Fulvestrant (FUL), everolimus (E) and chemotherapy (CT) are the current treatment options. Neither of these options has proven to be superior to the others. We conducted a retro/prospective, observational, non-randomized study, to evaluate the impact of subsequent treatments options after a 1st or 2nd line of CDK4/6i tx in real-world clinical practice. Preliminary result in the retrospective series are presented.

Methods: All pts who met the criteria to receive CDK4/6i tx plus aromatase inhibitors (AIs) or FUL, from market availability, were enrolled. 400 pts will be included; 200 pts will be collected retrospectively and 200 prospectively.

Results: 116 pts receiving CDK4/6i tx have been enrolled. Characteristics of pts are as follow: M/F 1/115; ductal carcinoma 70%, lobular carcinoma 23%; de novo metastatic 28.4%; in the relapse group 59% pts are endocrine sensitive; 2,6% primary endocrine resistant and 6% secondary endocrine resistant; 65% received adjuvant (adj) endocrine tx, 41% adj CT, 46% adj radiotherapy. In pts receiving 2nd line CDK4/6i; prior tx were as follow: 34,5% taxanes, 43% other CT, 23.5% AIs, 11% E, 8% FUL. 31% had bone only disease. 37% had 1 sites of metastasis; 50,4% received CDK4/6i tx in 1st line, 25,9% in 2nd line; 24% in 3rd or later lines. The subsequent treatments in the 26 pts who progressed after 1st line CDK4/6i tx was: 3.8% AIs, 7.7% FUL, 76.9% CT, 11,5% E. In the 21 pts who progressed after a 2nd line CDK4/6i tx: 9.5% FUL, 19% E, 71.4% CT. Progression free survival (PFS) after 1st line CDK4/6 tx was 27 months (mo) and 17 mo after 2nd line CDK4/6 tx. Median PFS in the group who received 1st line CDK4/6i was 6 mo in pts receiving CT and 3 mo in pts reated with FUL/E whereas, for pts receiving 2nd line CDK4/6i tx, was 7 mo in CT and 4 mo with FUL/E.

Conclusions: The sequence of treatments after a CDK4/6i tx is far to be defined. In this preliminary analysis conducted in pts treated mainly in the years 2017-2019, CT represents the main choice after CDK4/6i failure. These data show the picture of the initial approach in the daily practice in a lacking information scenario. The increasinge skill in the management of the CDK4/6 tx has changed in the last 5 years and we proceed to complete the enrollment in order to evaluate the difference in the choice of the sequence of the tx in the prospective part of the study.

C40

IMPACT OF FIRST LINE THERAPIES ON THE METASTATIC SPREADING OF LUMINAL-LIKE METASTATIC BREAST CANCER

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Background: The pattern of metastatic spreading in Luminal-like metastatic breast cancer (mBC) is a current field of research, but few data are available on the evolution of distant involvement after first line (1L) therapy. We aimed to describe the trend in metastatic sites after progression to a 1L.

Material (patients) and methods: This study retrospectively analysed 717 consecutive Luminal-like mBC patients (pts) treated at the Oncology Departments of Aviano and Udine, in Italy, between 2008 and 2020, with endocrine therapy (ET) (alone or in combination with cyclin-dependent-kinases 4/6 inhibitors [CDK4/6i]) or chemotherapy (CT) (alone or with ET maintenance). Data were collected at baseline of 1L (BL1) and at disease progression (PD1). McNemar and Fisher tests were used to explore pairwise differences and associations between newly identified metastatic sites and 1L treatments.

Results: Overall, bone involvement was 71.2% at BL1 and 76.4% at BL2, of which 30.9% had bone-only disease at BL1 and 21% at PD1. Lung involvement was observed in 21.7% of pts at BL1 and 32.3% at PD1, liver 21.4% at BL1 and 31.6% at PD1. Central nervous system (CNS) metastases (mts) were detected in 2.4% of pts at BL1 and 3.5% at PD1. In the overall population, at paired nominal data test, metastatic sites were consistently increased at PD1 (liver $P < 0.0001$, bone $P = 0.0001$, CNS $P = 0.0039$, bone-only $P < 0.0001$, lung $P < 0.0001$, nodes $P < 0.0001$), as expected. Notably, a similar trend was observed across all 1L treatments, apart for CNS mts in the ET cohort, bone and CNS mts in both the ET+CDK4/6i and CT subgroups, bone-only and CNS disease in CT-ET maintenance group, where no significant pairwise changes were highlighted. Analysing newly identified metastatic sites at PD1, pts treated with ET+CDK4/6i had a higher risk of developing new CNS mts ($P = 0.018$, expected frequency [EF] 1.1 pts vs observed frequency [OF] 3 pts), while pts treated with CT-ET maintenance had a higher risk of developing new lymph node mts ($P = 0.014$, EF 32.5 pts vs OF 45 pts).

Conclusions: The present study suggests the potential impact of 1L treatment strategies on the evolution of metastatic spreading in Luminal-like MBC. Based on these results, future studies will be designed to develop new personalized monitoring strategies.

C41

THE ROLE OF DENOSUMAB AND ALENDRONATE IN POST-MENOPAUSAL OSTEOPENIC EARLY BREAST CANCER PATIENTS: A PROSPECTIVE EVALUATION OF THE PAIN CONTROL

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Introduction: Bisphosphonates and denosumab are the first choices in treating and preventing osteoporosis for patients with postmenopausal breast cancer in endocrine therapy. However, the effectiveness of denosumab on pain relief has been poorly studied.

Materials and Methods: We prospectively evaluated 50 Caucasian breast cancer patients on adjuvant hormone therapy at Palermo University Hospital to compare the impact of alendronate versus denosumab on pain relief. Patients were assessed at baseline (T0) and after 18 months (T1) to evaluate the presence of vertebral fractures and lumbar and femoral T-Score trends. A pain assessment was also made.

Results: At follow-up (T1), we observed a non-significant improvement in the femoral and lumbar T-score in the two groups. A significant change in the mean NRS score in the alendronate cohort was noted (3.88 ± 1.3 vs. 3.02 ± 1.2; $p = 0.004$). We also noted a statistically significant difference in the mean T-score between the alendronate and the denosumab groups (3.52 ± 1.2 vs. 4.36 ± 2.2; $p = 0.01$). Patients in the alendronate group showed a reduction in pain of 22.2%, while patients in the denosumab group of 8.4%. Finally, at T1, we observed a negative correlation between the lumbar and femoral T-score scores and NRS in both groups.

Conclusions: We demonstrated that alendronate acts more effectively on pain relief than denosumab, possibly through an inhibitory action on both osteoclasts and bone nociceptors.

C42

THE PROGNOSTIC POWER OF 18-FDG PET TO ASSESS THE DURATION OF RESPONSE IN METASTATIC BREAST CANCER (MBC) PATIENTS IN CDK 4/6 INHIBITORS (CDK4/6 I) THERAPY

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Background: Clinical guidelines for follow-up and staging of breast cancer (BC) involve mammography, ultrasound, and breast magnetic resonance imaging (MRI) as primary methods of evaluating local disease, whereas computed tomography (CT) of the chest and abdomen and bone scans are appropriate for early detection of distant metastases. Despite the low specificity and sensitivity of 18F-FDG PET in the initial diagnosis of BC, its use in restaging is more promising in detecting axillary and bone marrow metastases than CT or bone scintigraphy. Moreover, changes in 18F-FDG uptake during treatment with new agents as CDK4/6 inhibitors in luminal BC could predict the responsiveness in patients (pts). In our study, we investigated the role of PET in monitoring the response in mBC treated with CDK 4-6 inhibitors compared to CT/bone scans.

Patients and Methods: This study includes 36 pts with mBC in CDK 4/6i therapy from 2018 to 2022. 17/36 pts performed CT and bone scans, 19/36 pts underwent 18F-FDG-PET before and after initiation of therapy. Median progression-free survival (mPFS) was estimated by the Kaplan-Meier method and the log-rank test provides a statistical comparison of the two groups.

Results: In our cohort, mPFS was 9.6 months. Regarding survival outcomes for pts performed 18F-FDG-PET, our analysis showed a significant difference in mPFS compared to pts assessed by CT/bone scans (12.8 versus 8.1 months, 95% CI: 1.34-18.7, p=0.009). We conducted further analysis within subgroups based on bone and lymph node metastases. The mPFS was 9.1 vs 8.1 months (p=0.06) in pts with bone metastases who underwent 18F-FDG-PET or CT/bone scintigraphy respectively, not statistically significant. Instead, in pts with lymph node metastases, 18F-FDG-PET significantly predicts the progression of disease (mPFS 18.3 vs 23.8, p=0.03). Interestingly, in 18-FDG-PET group 2/19 pts (10%) had a partial response, and 7/19 pts (37%) had stable disease after 4 months of CDK4/6i therapy with a median duration of response (DoR) of 12.2 months.

Conclusions: Our data suggest a potential role of 18F-FDG-PET in detecting lymph node involvement with more sensitivity in monitoring DoR. However, an accurate selection for 18F-FDG-PET is required, cause of its high cost which precludes extended application to the general population. Further prospective studies with larger samples, evaluating glucose metabolic profiles with PERCIST, are needed to confirm our hypothesis.

C43

GENETIC COUNSELING AND TESTING FOR BRCA-RELATED CANCER: ONE-YEAR EXPERIENCE OF ASL TO4 GROUP

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Background: pathogenic mutations in breast cancer susceptibility BRCA1 and BRCA2 increase risk for cancer, especially for breast and ovarian cancer in women. Interventions reduce risk in mutation carriers.

A major barrier to genetic counseling in Piedmont is the limited workforce of genetic providers, who are located in Academic center. In October 2019, Regional resolutions ordered establishment of first level genetic counseling clinic working groups within Oncology departments in response to this unmet need of general population.

Aim of this paper is reported ASL TO4 one-year experience as first level genetic counseling working group.

Patients and Methods: In 2020 we created a clinic working group for genetic counseling for healthy people with strong family history of breast and ovarian cancer or known potentially harmful BRCA mutation in the family. From January 2020 to December 2021, we screened 28 patients (25 females and 3 males, media age 43 years). Patients were referred by family doctors (40%) and by Breast Screening Center in Strambino (60%). Median wait time for the first counseling was 30 days and from the visit to BRCA test was 10 days. During interview, operators collected demographic data evaluated family history of cancer to at least third degree of kinship and provided information and support about genetic testing for BRCA mutations.

Results: During this pilot year 23 of 28 screened patients (78,5%) met the criteria for BRCA test. In 22 cases, blood sample were obtained for genetic test in our Oncology Day Hospital in Ivrea (1/23 patients rejected the procedure). All patients signed informed consent. Detection of germline mutations BRCA1 and BRCA2 genes was performed by Genetic Laboratory of Molinette Hospital in Turin. Among 22 tested patients, 10 had a pathogenic mutation in BRCA1 and BRCA2 genes. All positive patients were referred to post-test Specialist Genetic Counseling, to psychological evaluation and to clinical management and surveillance program.

Conclusions: the need for Genetic Counseling in BRCA related cancer continues to grow. Our working group is a model to improve access to genetics services even in peripheral communities. Education of non-genetics health care providers and collaboration with genetics providers can reduces inappropriate testing and can increase the process of patient identification, informed consent and testing for BRCA mutations.

C44

AN INVASIVE DISEASE EVENT FREE SURVIVAL ANALYSIS FOR INVESTIGATING THE ROLE OF KI67 IN BREAST CANCER PATIENTS OF DIFFERENT AGES

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Breast cancer has always been the most common malignant disease among women, and its molecular heterogeneity has made it difficult to design targeted treatments for each tumor type. Over the past 10-15 years, however, therapy concept has evolved, and modern-day treatments have been driven by this molecular heterogeneity allowing clinicians to classify breast cancer into subtypes, and, consequently, to design personalized treatments for improving patients' prognosis and increasing survival probability. In clinical practice, breast cancer classification into subtypes is performed estimating the expression of main IHC prognostic markers, including the cellular marker for proliferation ki67.

In this study, we investigated the role of different threshold values of ki67 in estimating breast cancer-related invasive disease event-free survival (IDEFS), which includes local recurrence, the appearance of distant visceral and soft tissue metastases, contralateral invasive breast cancer or a second primary tumor, according to breast cancer patients' age. Firstly, we determined two sub-samples partitioning the starting dataset, comprising 900 female patients with a first invasive breast cancer diagnosis, according to an age threshold value equals to 50 years. Afterwards, we adopted a Kaplan-Meier approach for determining the IDEFS curves of patients belonging to the two sub-samples, with respect to the three above mentioned threshold values of ki67. Finally, we focused on patients with a Luminal-like tumor, in order to overcome the heterogeneity sample bias.

The analysis on under 50 years old patients resulted in a p-value<0.001, highlighting how the behaviors of patients characterized by a ki67 ranging from 10% to 20% and greater than 20% were significantly similar. Conversely, over 50 years old patients characterized by a ki67 ranging from 10% to 20% showed an IDE-free survival probability significantly greater than patients with a ki67 greater than 20%, with a p-value of 0.01.

As a result, our work suggests the adoption of two different ki67 threshold values, i.e., 10% and 20%, might be discriminant in designing targeted treatments for under 50 years old and over 50 years old patients, respectively, especially in doubtful or borderline cases, such as Luminal-like patients.

C45

ASTRID STUDY-BREAST TRIPLE NEGATIVE CANCER IN ADVANCED SETTING: THE THERAPEUTIC ALGORITHM IN MARCHE REGION

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Background: New therapeutic agents for metastatic triple negative breast cancer (mTNBC) are growing but chemotherapy remains the main treatment option. Several chemotherapies are available, but a therapeutic algorithm has not been established. The aim of this study is to identify the most used chemotherapy regimens in different treatment lines and their related prognostic impact in a real-world setting.

Patients and Methods: We retrospectively analyzed data of consecutive mTNBC patients treated from August 2007 to June 2021 in 8 Oncology Departments of Marche Region (Ancona, Urbino, San Benedetto del Tronto, Fabriano, Ascoli Piceno, Marche Nord, Macerata, Senigallia). We estimated Progression free survival (PFS) and overall survival (OS) using Kaplan-Meier method and we adopted univariate and multivariate Cox proportional hazard models.

Results: We selected 87 patients from a database of 120 patients, excluding those who were not eligible for first-line therapy. Median OS (mOS) was 19,4 months. The most used chemotherapy regimens in first-, second- and third-line were paclitaxel + bevacizumab (27,6%), platinum-based regimens (22,2%) and eribulin (28,6%) respectively. The use of different chemotherapeutic agents in the first 2 lines did not show a statistically significant difference in term of survival, while taxanes were associated with better PFS in third-line (median PFS=6,7 months, p=0.0018). Patients treated with monochemotherapy regimens in third-line showed worse median PFS than those treated with polychemotherapy (2,4 vs 6,6 months, p=0.017, HR 2,99). Comparing the most frequent therapeutic sequences used in the first two lines, taxanes followed by capecitabine (mOS=24,2 months) and capecitabine + vinorelbine followed by taxanes (mOS=23,9 months) were associated with better OS (p=0.04). The sequence consisting of taxanes followed by alkylating agents was associated with worst mOS when compared to another group inclusive of all other possible sequences (15,4 vs 24,2 months, p=0.03, HR 3,27). These results were not confirmed at multivariate analysis.

Conclusions: Our real-world data show that taxanes are preferred for first-line therapy but seem to suggest their use in subsequent lines. Capecitabine and its combination with vinorelbine are less used in early lines but are associated with remarkable OS. These results suggest the development of randomized studies focusing on treatment sequencing to define a reliable therapeutic algorithm for mTNBC.

D - Genitourinary and Gynaecological Tumours

D01*

IMMUNE TUMOR MICROENVIRONMENT (I-TME) ANALYSES IN METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS (PTS) TREATED WITH SECOND LINE NIVOLUMAB: RESULTS FROM THE MEET-URO 18 STUDY

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Background: To date, there are not well-established prognostic and predictive biomarkers able to predict response to immunotherapy for mRCC patients. Within the multicentric Meet-URO 18 study, we assessed the I-TME in mRCC pts treated with $=2^{nd}$ line nivolumab.

Methods: Immunohistochemistry (IHC) analyses were performed on the primary tumor or the metastases assessing histology, grading and T-lineage (CD3, CD4, CD8, CD8/CD4 ratio, peritumoral T cells), macrophages (CD68) and granulocytes (CD15). Phosphorylated mTOR (ph-mTOR), CD56 and PD-L1 (SP263) expression on tumor cells were also assessed. Receiver operating curves (ROC) based on responses were used to identify cut-off values of IHC parameters. Patients were dichotomized in *responders versus non responders* according to progression-free survival ($\geqslant$ 12 vs $\leqslant$ 3 months, respectively). Differences between the two pts groups were reported as odds ratios (OR) with the 95% CI and considered statistically significant with a p value of < 0.05.

Results: Overall, 116 tumoral tissues (59% primary tumors, 41% metastases) were evaluated with responders (N = 55) presenting lower expression of CD4 and higher levels of ph-mTOR and CD56. Responders tended to have higher CD3 expression ($\geqslant$40: 73% vs 56%, p=0.059) and CD8/CD4 ratio (median 1.74 vs 1.20, p=0.084). Non responders (N = 61) presented with clear cell histology (CCRCC) and higher grading. Significant results are summarized in Table 1.

Conclusions: In our study, responders to nivolumab were characterized by high expression of CD56, low levels of regulatory CD4 cells and other histologies than clear cell carcinoma. Phosphorylated mTOR could represent a new biomarker for immunotherapies to further investigate. Gene signature analyses are planned to integrate IHC analyses.

Parameter (cut-off)	Responder (%)	Non responder (%)	OR (95% CI), p value (p)
Histology			
CCRCC	62	85	3.57 (1.46-8.71); p=0.005
Other	38	15	ref
Grading			
1-2	49	20	ref
3	34	51	3.68 (1.30-10.40); p=0.014
4	17	29	4.25 (1.25-14.50); p=0.021
Ph-mTOR			
<15	29	49	ref
⩾15	71	51	0.42 (0.20-0.91); p=0.029
CD4			
<70	75	53	ref
⩾70	25	47	2.65 (1.21-5.83); p=0.015
CD56			
<40	73	88	ref
⩾40	27	12	0.35 (0.13-0.93); p=0.035

D02*

CLINICOPATHOLOGICAL FEATURES OF FGFR3 - MUTATED UPPER TRACT UROTHELIAL CARCINOMA: A GENOMIC DATABASE ANALYSIS

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Background: Upper tract urothelial carcinomas (UTUCs) arise in the renal pelvis or the ureter, accounting for approximately 5% of all urothelial carcinomas. Recent years have witnessed the publication of several studies aimed at assessing the molecular, biological, and clinical features of UTUC, reporting that FGFR3 mutations are the most observed genetic aberrations; however, several knowledge gaps persist in the understanding of the genomic landscape of this genitourinary malignancy with few treatment options.

Patients and Methods: In the current study, we aimed to comprehensively analyze clinicopathological features of FGFR3-mutated UTUCs patients in public datasets to increase the current knowledge on the molecular and biological profile of UTUC. Data regarding clinical outcomes, mutational profiles, and copy number alterations in patients affected by UTUC were downloaded from the cBioPortal for Cancer Genomics Database. UTUC data were available from four studies, for a total number of 358 patients; among these, 150 UTUC patients presented FGFR3 mutations.

Results: Survival analysis was performed on FGFR3-mutated and FGFR3 wild type patients for whom overall survival (OS) and disease-free survival (DFS) were available and which were previously treated with radical nephroureterectomy (RNU). As regards OS, survival data were available for 31 FGFR3-mutated and 40 FGFR3 wild type UTUC patients, respectively. According to this analysis, FGFR3 mutations were identified as a favorable prognostic factor; median OS in FGFR3-mutated patients was not reached, while it was 53.61 months (35.8 – Not Reached) in FGFR3 wild type UTUC patients receiving RNU (p=0.017). No statistically significant differences in DFS were observed between the two groups of patients receiving radical surgery, with median DFS of 7.2 months (4.4 – 31.5) and 9.1 (6.2 – 21.8) months in FGFR3-mutated and FGFR3 wild type UTUC patients, respectively (p=0.9). In addition, FGFR3 mutations were more frequent in low-grade UTUCs with early-stage disease (pT1, pT2, and pT3).

Conclusions: Despite the limitations affecting our study, this large-scale database analysis may support the design of appropriate prospective clinical trials and preclinical models to develop novel pharmacological approaches for UTUC patients. Genomic characterization of UTUC is destined to become increasingly important, and more efforts aimed at implementing UTUC genomics analysis are warranted.

D03*

THE ROLE OF MISMATCH REPAIR DEFICIENCY (DMMR) IN ENDOMETRIAL CARCINOMA (EC) AND LYNCH SYNDROME (LS)

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Background: dMMR is a frequent alteration in EC patients, with potential implications in terms of prognosis and prediction of treatment efficacy. dMMR testing is also part of the algorithm of Universal Screening (US) to identify patients with LS, an internationally recommended procedure that is not widely implemented yet. We aimed to evaluate the prevalence, association with clinicopathological variables, and role for LS diagnosis of dMMR testing in a vast cohort of EC patients.

Material and Methods: This is a monocentric retrospective study on 368 consecutive EC cases who underwent surgery and immunohistochemistry analysis for dMMR from 2013 to 2020. Clinicopathological variables including age, date of surgery, tumor histotype, grading, FIGO stage at diagnosis, lymphovascular invasion (LVSI) and survival status were collected in the whole study population. For patients in the dMMR cohort, data on genetic counselling (GC) and diagnosis of LS were also collected. Major survival outcomes were overall survival (OS) and relapse-free survival (RFS) in the whole study population and in the dMMR cohort. The study population was stratified based on PORTEC-3 Trial.

Results: 91/368 (25%) patients were dMMR. 84 had endometroid histotype, 7 other histotypes (92% vs 8%, p=0.01). Grading was G2 in 55%, G3 in 24% and G1 in 21% of cases (p=0.005). As compared to proficient MMR cases, an unfavorable trend in OS and RFS was observed for patients with dMMR (4-year OS 82% vs 74%, p=0.115; 4-year RFS 70% vs 54%, p=0.153). In the evaluable high-risk population (N=123), there was no difference in OS (p=0.894), whereas in the low/intermediate-risk subgroup (N=236) a statistically significant worse OS in dMMR patients was observed (HR=2.52, p=0.024). In a multivariate analysis, age ($p<0.001$), histotype ($p<0.001$), grade ($p<0.001$), stage (p=0.003) and LVSI (p=0.010) were associated to OS, while dMMR showed only a trend towards worse OS (p=0.10). Among dMMR patients, only 5 underwent GC (6.6%): LS was diagnosed in 1 patient (20%) with loss of MSH2/MSH6 expression.

Conclusions: This is the largest Italian cohort of US for LS in EC patients. dMMR prevalence was 25%, consistent with the literature. dMMR status showed a trend towards worse survival, especially in the low/intermediate risk subgroup. Further studies are needed to better define the prognostic role of dMMR in EC. Unfortunately, oncologists' compliance to international guidelines for genetic counselling referral for LS is very poor (6.6%).

D04*

PRACTICE PATTERNS AND TREATMENT-RELATED MORBIDITY IN EARLY-STAGE CERVICAL CANCER

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Background: To evaluate the impact of the Laparoscopic Approach to Cervical Cancer (LACC) Trial on patterns of care and surgery-related morbidity in early-stage cervical cancer.

Methods: This is a large Italian retrospective, a multi-institutional study evaluating outcomes of patients undergoing treatment for early-stage cervical cancer before (period I: 01/01/2016-06/01/2018) and after (period II: 01/01/2019-06/01/2021) the publication of the results of the LACC trial.

Results: Charts of 1,327 patients were retrieved. The study population included 199 (34.2%), 211 (36.3%), and 171 (29.4%) patients with stage IA, stage IB1, and stage IB2 treated in the period I and 293 (41.1%), 219 (30.6%), and 202 (28.3%) patients with stage IA, stage IB1, and stage IB2 treated in the period II (p=0.028; p-for trend <0.001). The proportion of patients receiving conservative treatments increase over the study period (13.6% vs. 20.6%;

p-for trend <0.001); while the proportion of patients receiving radiotherapy (with or without chemotherapy) remained stable in the two periods (5.8% vs. 7.3%; p=0.303). After the publication of the LACC trial, the number of patients treated with minimally-invasive radical hysterectomy decreased from 64.9% (304 out of 468 radical hysterectomies) to 30.4% (157 out of 515 radical hysterectomies) (p<0.001). The decrease of minimally-invasive radical hysterectomy rates was observed for patients with stage IA (81.8% vs. 58.2% (-23.6%); p<0.001), stage IB1 (68.8% vs. 20.3% (-48.5%); p<0.001), and stage IB2 (45.3% vs. 14.5% (-30.8%); p<0.001). Intraoperative complication rates were similar between period I and period II (2.4% vs. 1.4%; p=0.215). Overall, 90-day complications occurred in 110 (18.9%) and 119 (16.6%) patients in the period I and period II, respectively (p=0.795). Similarly, the number of severe (grade 3 or worse) complications were not influenced by the publication of the LACC trial (38 (6.5%) vs. 37 (5.1%); p=0.297). Overall and severe 90-day complications were consistent between periods even evaluating stage IA, IB1, and IB2, separately (p>0.20). Considering available data on length of hospital stay (n=341), mean (SD) postoperative recovery time was 2 (1.1) and 4 (2.4) days after minimally-invasive and open radical hysterectomy (p<0.001).

Conclusions: The present investigation highlighted that in referral centers the shift from minimally invasive to open radical hysterectomy does not influence 90-day surgery-related morbidity.

D05*

ALPELISIB IN PRE-TREATED PIK3CA-MUTATED, RECURRENT/ADVANCED CERVICAL CANCER

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Background: Immunotherapy has the opportunity to establish new standards of care in the treatment of cervical cancer. However, advanced/recurrent cervical cancer has limited therapeutic options, with a median progression-free survival after the failure of systemic treatments ranging between 3.5 and 4.5 months (with conventinal chemotherapy). Here, we reported our preliminary experience in the use of alpelisib in advanced/recurrent cervical cancer after failure of at least 2 lines of treatment.

Patients and Methods: From April 2020 to September 2020, 17 consecutive patients with recurrent cervical cancer had Next Generation Sequencing (NGS). Of these, six patients harboring the PIK3CA mutation were included in the study. All patients had been treated with at least 2 previous lines of systemic treatment: 3 patients received >2 prior lines of treatment in the recurrent or metastatic setting; 60% had received prior bevacizumab in combination with chemotherapy. All patients started alpelisib at the daily dosage of 300 mg.

Results: Overall, prospective data six patients were evaluated. Investigator-assessed confirmed objective response rate (ORR) was 33%. The disease control rate (DCR) was 100%. According to RECIST 1.1, two patients had a partial response (PR), and four patients had stable disease (SD). No complete response was observed. The mean duration of response (DOR) was 11.5 (SD 3.75) months; five patients had PR lasting for >9 months. One patient stopped the treatment at 0.82 months due to the onset of grade 2 adverse event (AE) (skin rash). Grade 3 treatment-related AEs included: lymphoedema (n = 1, 17%) and rash (n = 1, 17%). No treatment-related grade 4-5 AEs occurred.

Conclusions: Our preliminary data highlighted a high level of efficacy in this setting of patients. Further trials are needed to assess the safety and effectiveness of alpelisib in PIK3CA-mutated recurrent/advanced cervical cancer.

D06

OLAPARIB FIRST-LINE (1L) MAINTENANCE THERAPY IN BRCA1/BRCA2-MUTATED (BRCAM) ADVANCED OVARIAN CANCER (OC) PATIENTS (PTS): REAL-WORLD SAFETY PROFILE OF FIRST YEAR TREATMENT IN ITALY (PART OF THE OVAL-I STUDY)

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Background: Following the demonstration of olaparib efficacy in advanced stage BRCAm OC pts treated in 1L maintenance setting (SOLO-1 trial, Moore et al NEJM 2018). Olaparib is approved in this setting; however no Italian data are available regarding the use out of the registration trials. Here is presented a first year safety profile preliminary description related to the first 125 pts treated in Italy.

Material and methods: OVAL-1(NCT04532645) is a pan-European observational multicenter retrospective study. Italy included 19 sites that enrolled 125 pts diagnosed with BRCAm advanced (FIGO stage III-IV) OC followed-up for 12 months after their 1st olaparib dose taken between March 2019 and June 2020.

Results: All pts underwent BRCA testing before olaparib initiation: type of test was 52.8% blood sample and 47.2% tumor sample; 62.4% were BRCA1m and 37.6% were BRCA2m. Median age at diagnosis was 60.3 ($\pm$10.8) years; 34.4% of those were $\geqslant$65 years. 61.6% pts had upfront debulking surgery, 74.0% of those without residual disease; 33.6% had an interval debulking surgery, 78.6% of those without residual disease and only 4.8% pts did not receive a debulking surgery. Baseline characteristics are in accordance with the criteria of eligibility to maintenance with olaparib, except for a 4.3% enrolled after a stable disease response to platinum. Safety related treatment management lead to interruption and dose reduction in 35.2% and 36.0% pts respectively while $<$1% lead to permanent discontinuation. Adverse events (AE) that lead to treatment interruption, dose change or treatment discontinuation reported in the first year of treatment are showed in *Table 1*.

Conclusions: These preliminary descriptive analyses provide insights into the real-world management in Italy. Olaparib safety profile in this cohort is consistent with previous reports and only 0.8% of AEs lead to permanent discontinuation. Future extractions will focus on progression-free survival, overall survival and healthcare resource use.

Table 1. n (%) of AEs leading to treatment interruption, dose change or treatment discontinuation (over 125 pts).

Events	n (%)
Anemia	33 (26.5%)
Neutropenia	7 (5.6%)
Nausea	6 (4.8%)
Thrombocytopenia	5 (4.0%)
Fatigue	4 (3.2%)

D07

U-CHANGE PROJECT: APPROACHING THE NEW UROTHELIAL CANCER SCENARIO AMONG CLINICIANS, PATIENTS AND CAREGIVERS. A MULTIDIMENSIONAL CONSENSUS DOCUMENT

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Background: Advanced Urothelial Carcinoma (AUC) remains aggressive and hard to cure, while the new treatments will challenge clinicians and payors of the HC organizations.

Materials and methods: The U-CHANGE Project, had the objective to redesign the model of care of AUC, in order to identify limitations (AS IS Scenario) and recommend future actions (TO BE Scenario). 21 experts analized different scenarios in a Consensus, divided into three different tables: clinicians (epidemiologists, oncologists and urologists), patients (patients' associations, nurses, journalists, fisioterapists), institutions (pharmacists, economists, administrators). Each table developed statements for each domain (awareness, diagnosis, treatment, patient support, integrated care pathway, TMD, economic model) and a simplified Delphi methodology was used to establish consensus among all the experts.

Results: For the AS IS Scenario, 15 out of 16 statements, were approved; for the TO BE Scenario, all the 19 statements submitted, successfully overpassed the prespecified 75% cut-off point.All the contents, audio-video recorded, have been circulated among the partecipants, reporting all the relevant comments and proposed solutions for each dimension.Examples of recommended actions have been: increase awareness in the population, develop educational programs for HC professionals, strategies in the biomarkers area, support for dedicated PDTA in each Region, activation of TMD and patient/caregiver support programs with new services in the social, labour and psychological areas.

Conclusions: The U-CHANGE Project set up the ambitious objective to put on the same level, for the first time, different key stakeholders involved in the standard care of the patient with AUC. The new innovative targeted agents, may have the potential to change the clinical approach to the treatment of this very aggressive disease however, the U-CHANGE Project experience, shows that, to do so, it will be necessary to redesign the entire model of care in terms of: sustainability, possibility to anticipate the benefits of future treatments and the ability to target the right patient with the right agent, at the different stage of the disease.

The U-CHANGE Project received the patronage of Italian Association of Medical Oncology (AIOM), Italian Society of Uro-Oncologists (SIUrO), Italian Association of Hospital Pharmacists (SIFO), PaLiNUro Association of Patients, Italian Federation of Voluntary Association in Oncology (FAVO).

D08

IMPACT OF CIRCULATING PD-L1, PD-1, BTN3A1, PAN-BTN3AS, BTN2A1 AND BTLA LEVELS ON PROGNOSIS OF WOMEN WITH ADVANCED HIGH-GRADE SEROUS OVARIAN CANCER

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Background: High-grade serous ovarian cancer (HGSOC) has been shown to be is the most frequent subtype of epithelial ovarian cancer (OC) having the greater immunogenic potential due to the abundance of tumor-infiltrating immune cells which modulate the anticancer immune response. Cancer cells may evade immune surveillance, by activating immunomodulatory proteins such as programmed death protein (PD-1) and its ligand PD-L1, butyrophilin sub-family 3A/CD277 receptors (BTN3A), butyrophilin sub-family 2 member A1 (BTN2A1), and the B and T lymphocyte attenuator (BTLA). Since several evidences suggested an association between high PD-1/PD-L1 expression and poor prognosis in OC, our study aimed to assess whether circulating levels of different immunoregulatory proteins could be helpful for predicting survival of advanced HGSOC patients.

Patients and Methods: The plasma PD-L1, PD-1, BTN3A1, pan-BTN3As, BTN2A1 and BTLA concentrations were analyzed in 100 advanced HGSOC women prior surgery and starting therapy, using specific ELISA tests not yet commercially available. This investigation allowed, for each tested circulating biomarker, to discriminate advanced HGSOC patients based on long ($\geqslant$30 months) *versus* short PFS ($<$30 months).

Results: Through specific *cut-offs* obtained by ROC analysis, we showed that high baseline concentrations of PD-L1 ($>$0.42 ng/mL), PD-1 ($>$2.48 ng/mL), BTN3A1 ($>$4.75 ng/mL), pan-BTN3As ($>$13.06 ng/mL), BTN2A1 ($>$5.59 ng/mL) and BTLA ($>$2.78 ng/mL) were associated with unfavorable prognosis and median progression-free survival (PFS) from 6 to 16 months shorter. Additionally, age at diagnosis $>$60 years, BMI$>$25 or peritoneal carcinomatosis were correlated with a lower PFS ($<$30 months). Finally, a multivariate analysis highlighted that plasma levels of PD-L1$\leqslant$0.42 ng/mL (HR: 2.23; 95% CI: 1.34 to 3.73; p=0.002), age at diagnosis $\leqslant$60 years (HR: 1.70; 95% CI: 1.07 to 2.70; p=0.024) and absence of peritoneal carcinomatosis (HR: 1.87; 95% CI: 1.23 to 2.85; p=0.003) were significant prognostic factors for a longer PFS in advanced HGSOC women.

Conclusions: In conclusion, assessing circulating PD-L1, PD-1, BTN3A1, pan-sBTN3As, BTN2A1 and BTLA levels could facilitate the identification of high-risk patients with unfavorable disease outcomes, suggesting their potential use as prognostic biomarkers which could be helpful to improve patient clinical management.

D09

PBRM1 AND PD-L1 AS BIOMARKERS OF ANGIOGENESIS IN RENAL CELL CARCINOMA PATIENTS AT INTERMEDIATE PROGNOSIS

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Background: Immune checkpoint inhibitors (ICIs)-based combinations (both a VEGFR-TKI plus an ICI and dual-ICIs) are first-line recommended treatment options for metastatic renal cell carcinoma (mRCC) patients (pts) at

intermediate IMDC risk. No head-to-head studies comparing these strategies are available. To date, no biomarkers (BM) with a predictive value for selecting the most effective regimen have been identified so far. We investigated the prognostic role of PBRM1 and PD-L1 tumor immunohistochemistry (IHC) expression in a subgroup of mRCC pts at intermediate IMDC prognosis.

Materials and methods: Histological samples of mRCC pts treated with a VEGFR-TKI monotherapy or an ICI-based combination were collected and IHC for PD-L1 and PBRM1 was performed. PD-L1 positivity was defined as CPS⩾10, while PBRM1 positivity score was based on the percentage of positive cells and the intensity of nuclear expression (score 4-9 indicating positivity). PFS and OS were analyzed by Kaplan-Meier curves and a multivariate regression model was used to assess independent predictors of outcomes.

Results: A total of 76 pts were included in the final analysis. First-line therapy was a VEGFR-TKI in 80.3% of cases, nivolumab+ipilimumab in 11.8% and pembrolizumab+axitinib in 7.9%. PD-L1 was positively expressed by 17.1% of tumors, while 56.6% of tumors stained negatively for PBRM1. Loss of PBRM1 expression significantly correlates with PFS (p=0.013) and OS (mOS 39.3 vs. 24.9 months, p=0.005). No significant differences in clinical outcomes were observed based on the IHC status of PD-L1. When the two BM were considered together, tumors with loss of PBRM1 and PD-L1 negative expression (positively associated with the angiogenesis) had a significantly longer PFS (mPFS 23.8 vs. 11.9 months, p=0.007) and OS (mOS 52.2 vs. 24.9 months) compared to the others.

Conclusions: PBRM1 and PD-L1 negative expression was associated with improved clinical outcomes of mRCC pts at intermediate prognosis, mainly treated with a VEGFR-TKI. This study recognized PBRM1 and PD-L1 as BM able to identify the angiogenesis as a fundamental signature of some kidney tumors. Future analyses are warranted to prospectively validate the role of these BM as predictive factors of response to VEGFR-TKI+ICI combinations.

D10

A POOLED ANALYSIS FROM PHASE III CLINICAL TRIALS TO INVESTIGATE THE INCIDENCE OF BREAST CANCER (BC) IN BRCA-RELATED ADVANCED OVARIAN CANCER (AOC) DURING OLAPARIB-BASED MAINTENANCE THERAPY

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Background: After the introduction of poly ADP-ribose polymerase inhibitors- (PARPi) for germline BRCA mutated AOC, patients' prognosis is constantly improving as concern about the risk of second primary tumors, especially breast (BC). Actually, data on the incidence of BC in this setting are lacking and the need of screening strategy or risk reducing procedures is unclear.

Material (patients) and methods: Publications of recent phase III trials enrolling germline BRCA-mutated AOC were reviewed and analyzed. Only studies reporting at least one second primary solid tumor were included. Cases of second primary BC cancers were pooled to calculate cumulative incidence according to the median follow-up period for each trial. 95% confidence interval (CI) was considered.

Results: Four trials (SOLO1, SOLO2, SOLO3, PAOLA1), including 1186 germline BRCA mutated AOC patients were reviewed (BRCA-1 n = 816, BRCA-2 n = 360, both BRCA-1 and BRCA-2 n = 4, missing n = 6). Patients in the sperimental arms were treated with olaparib +/- bevacizumab (n= 788), while patients in the control arms had received placebo or standard therapies (n = 398). Age at diagnosis ranged from 29 to 87 years, with a median of 56. Women were followed along a period lasting from 3.9 to 5 years; during the follow up,10 new cases of BC in PARPi-based arms and 6 in control arms were found, resulting in a total of 16 new diagnosis of BC. Only two patients had a previous history of BC. The total cumulative incidence of BC was 1.37% (95% CI, 0.77-2.18), while cumulative incidences were 1.26% (95% CI, 0.61-2.31) and 1.51% (95% CI, 0.55-3.25) in PARPi-based arms and control arms, respectively. In a sensitivity analysis excluding the SOLO3 trial with the shortest follow-up, the total cumulative incidence was 1.63% (95% CI, 0.92-2.67). Other 20 cases of second primary solid tumors were registered, including 4 cases of non-small cell lung cancer.

Conclusions: In clinical trials of PARPi in BRCA-related AOC, the incidence of second primary BC was low suggesting that intensive screening should be avoided at least in early treatment phase. Population-based data are needed to better define BC risk and surveillance strategy.

D11

SAFETY AND TOLERABILITY OF PARP INHIBITORS AFTER FIRST LINE THERAPY IN OVARIAN CANCER: AN EXCELLENT CHOICE FOR ELDERLY PATIENTS

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Background: Olaparib and Niraparib are PARP inhibitors (PARPi) approved for clinical practice in January and December 2021 respectively as maintenance therapy (tp) for patients (pts) with high-grade, FIGO stage III-IV, serous or endometrioid ovarian cancer after first-line platinum-based tp, Olaparib for BRCA mutated pts, Niraparib independently of mutational status.

Material and methods: In this retrospective observational study we analysed data from all pts treated at Modena Cancer Centre between 2019 and 2022 who received Olaparib or Niraparib as maintenance after first-line platinum-based tp. We observed the tolerability and the toxicities of tp with attention to elderly pts (in particular, 14 = 75 years (y) and among them 7 = 80 y). Median age at the start of PARPi is 68 y (range 45-84), BRCA mutated 27 pts. All toxicities are calculated with CTC AE v5.0 scale.

Results: 27 pts received Olaparib and 15 Niraparib. 13 pts had dose reduction due to toxicity. Only one patient, 49 y, discontinued treatment for toxicity (after 4 months for Grade (G)4 increase liver enzymes). Toxicity were fairly common, but in most cases low G and manageable: anaemia (71.4% of which 2,4% G3-G4), asthenia (69%), nausea (40.5%), hypertension (38.1%), thrombocytopenia (26.2% of which 9.5% G3-G4), constipation (21.4%), leukopenia (11.9% of which 2.4% G3-G4), diarrhea, insomnia, renal and hepatic toxicity, stomatitis and arthralgia (less than 10%). No other toxicities were reported. 7 pts were concomitantly taking new oral anticoagulants and no increase in toxicities was noted. We found no statistically significant differences in none of toxicities between pts $\geqslant$ 75 and $<$ 75 (Fisher exact test) and likewise between pts $\geqslant$ 80 and $<$ 80. There was no significant difference on the number of toxicities per pts and age over or under 75 y or 80 y (Mann-Whitney test). Our median follow up time is 20.3 months (range 9.4-40). Median PFS and OS are not reached. 9 pts went to disease progression (3 BRCA mutated). 23 pts maintained the complete response obtained with chemotherapy and surgery, including 9 pts with reduced-dose tp.

Conclusions: The toxicities reported by our pts are substantially superimposable to those described in literature, both in terms of frequency and degree of toxicity. In particular, the rarity of G3-G4 adverse events should be noted. Despite the small number of pts analysed, PARPi are confirmed safe and well tolerated also by elderly patients, even those older than 80 y.

D12

CHARACTERIZATION OF EXTRACELLULAR VESICLES IN ASCITES AND SERUM OF OVARIAN CANCER PATIENTS

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Background: Ovarian cancer (OC) is a lethal cancer with a high rate of metastasis and relapse despite initial responses to surgery and chemotherapy. A large proportion of OC patients (pts) present ascitic fluid at the time of diagnosis. Ascitic fluid acts as a reservoir of a complex mixture of soluble factors, detached tumor cells and extracellular vesicles (EVs).

Methods: The aim of this study was to evaluate EVs and miRNAs in released in serum and ascites in OC. We analyzed a total of 40 paired samples (ascitic fluid and blood serum) from 20 OCs in terms of EVs number, size, superficial epitopes and miRNA cargo. We also compared unresectable and resectable disease to assess if the tumor burden can affect the above mentioned components. EVs were analyzed through NTA and cytofluorimetric assays, while miRNAs by array profiling.

Results: Ascitic fluid showed a lower number of EVs per ml ($p=0.01$); moreover, ascites contained larger EVs compared with serum ($p<0.01$). In ascitic fluid, distinct subpopulations of EVs were also observed, based on the size-profile results by the NTA. Cytofluorimetric analyses of epitopes expressed on EVs revealed significant differences between ascites and serum; indeed, 24 out of 39 epitopes investigated were significantly diverse ($p<0.05$) and the majority were reported in literature to be involved in promoting inflammation. In ascitic fluid, 48 and 11 miRNAs were significantly upregulated and downregulated, respectively, compared with serum. When we compared ascites from unresectable and resectable patients we did not observe any significant difference in EV number and size, as well as in epitopes expressed on circulating EVs. 46 miRNAs were upregulated in resectable patients and were mainly involved in pathways regulating cell cycle. miRNA levels were also analyzed with respect to recurrence and platinum response (complete vs partial/no response). 5 and 16 miRNAs in serum and ascites respectively were down-regulated in recurrent pts. With regard to response to platinum based chemotherapy, 2 and 19 miRNAs in serum and ascites, respectively, were upregulated in pts with partial or no response. On the contrary 14 and 1 miRNAs in serum and ascites, respectively, were downregulated in pts with partial or no response.

Conclusions: This study showed that ascitic EVs are different from the serum EV and are involved in sustaining inflammation process through expression of specific epitopes rather than through conveying specific miRNA cargo.

D13

A HYPOTHESIS GENERATING ANALYSIS ON THE ROLE OF TERT PROMOTER MUTATION IN ADVANCED UROTHELIAL CARCINOMA TREATED WITH IMMUNOTHERAPY

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Background: Immune checkpoint inhibitors (ICI) are approved in different settings for advanced urothelial carcinoma (aUC). However, only 20-25% patients (pts) responds to ICI and there is a lack of reliable predictors of response. Genomic profiling through next-generation sequencing (NGS) may help to identify predictive or prognostic markers able to guide therapeutic choices. TERT promoter (TERTp) mutation has been identified as a promising marker in several tumor types (e.g. melanoma, glioblastoma). A study on aUC treated with ICI showed an improved progression-free survival (PFS) for TERTp mutated pts.

We analyzed tissue samples of patients with aUC treated with ICI to assess the status of TERTp and the value of its mutation with regard to survival outcomes.

Patients and Methods: We performed a single-center retrospective analysis on 18 pts with aUC treated with an ICI to assess the status of TERTp, type of mutation/co-mutations, and evaluate its prognostic value. Tumor DNA was extracted from formalin-fixed paraffin-embedded (FFPE) specimens and then analyzed using a laboratory-developed NGS multi-gene panel. The panel allows to analyze a total of 343 amplicons in 27 oncogene/oncosuppressor markers (human reference sequence hg19/GRCh37, 21.77kb), including TP53, BRAF, RAS, and TERT genes among others.

Results: We evaluated FFPE tumor samples from 18 pts with aUC treated with an ICI from January 2020 to April 2022. A total of 11 of the 18 (61.1%) pts had samples adequate for NGS. One of these 11 was not evaluable for survival outcomes because ICI was not started. The most frequently altered genes were TP53 (63.6%) and TERT (36.3%). The only type of TERTp mutation was the c.124C>T (100%). In 50% of the cases, we found a concomitant mutation of TP53.

In our exploratory analysis pts with TERTp mutation had a lower median PFS compared with TERTp wild-type (wt) pts (3.8 vs 9.4 months - mo, respectively). Median overall survival (OS) in TERT mutated pts was 19.7 vs 26.8 mo in wt pts.

Conclusions: TERTp mutation is frequent in aUC and seems to be a potential prognostic and predictive factor. Our small pts sample supports this hypothesis and the need to further evaluate TERTp alterations in a wider cohort. Our results show a negative prognostic role of TERTp mutations, in contrast to other previous studies. Moreover, co-mutations value and PD-L1 expression should also be explored.

D14

CARDIOVASCULAR EFFECTS OF ABIRATERONE AND PARP-INHIBITOR COMBINATIONS IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER: A META-ANALYSIS

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Background: Combinations of an androgen receptor signaling inhibitor (ARSi, i.e. abiraterone acetate) and a poly-adenosine-diphosphate-ribose-polymerase inhibitor (PARPi, i.e. olaparib, niraparib) have recently proved their efficacy in metastatic castration–resistant prostate cancer (mCRPC) when compared to ARSi monotherapy. However, these drug classes both carry potential risk of cardiovascular toxicity (CVT) and hypertension. In this study, we analyzed the incidence and relative risk of developing CVT and hypertension in mCRPC patients treated with abiraterone and PARPi combination in order to establish the safety profile of this treatment strategy.

Methods: Prospective studies were identified by searching the MEDLINE/PubMed, Cochrane Library and ASCO Meeting abstracts. Data extraction was conducted according to the PRISMA statement. Combined relative risks (RRs) and 95% confidence intervals (CIs) were calculated using fixed- or random-effects methods, depending on studies heterogeneity. The statistical analyses were performed with RevMan software for meta-analysis (v.5.2.3).

Results: Three articles were selected for this meta-analysis, including a total of 1361 patients who were used to evaluate CVT. The incidence of treatment-related CVT of any- and high-grade was 12.7% and 7.4%, respectively. The combination of abiraterone and a PARPi was associated with a significant increased risk of any grade CVT (fixed-effects, RR = 1.57, 95% CI 1.14–2.17; p=0.005) but not with high-grade CVT (random-effect, RR=3.39, 95% CI 0.25–46.78; p=0.36) compared to abiraterone monotherapy. As concern hypertension, the incidence of events of any grade and high grade was 17.6% (compared to 17.1% in the control arms) and 7.0% (6.3% in the control arms), respectively. The combination of abiraterone and a PARPi did not significantly increase the risk of hypertension of any grade (RR=1.01; p=0.97) and high-grade (RR=1.11; p=0.60) compared to control.

Conclusions: Combinations of abiraterone and a PARPi have a reasonable cardiovascular safety profile. Despite a significant increase in any-grade CVT events, no difference was found in high-grade CVT compared to controls. Likewise, both the incidence and relative risk of any-grade

or high-grade hypertension were not significantly higher in the experimental arm compared to controls.

D15

PROGNOSTIC RELEVANCE OF HIGH PRE-TREATMENT LEVELS OF CIRCULATING IMMUNE CHECKPOINTS AND SERUM CA125 IN ADVANCED HIGH-GRADE SEROUS OVARIAN CANCER PATIENTS

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Background: Although high-grade serous ovarian carcinoma (HGSOC) is a potentially immunogenic tumor, clinical studies assessing the effectiveness of inhibitors of programmed death protein and its ligand (PD-1/PD-L1) in OC patients so far showed only response rates $<15\%$. However, recent studies revealed an interesting prognostic role of plasma PD-1/PD-L1 and other circulating immunoregulatory molecules, such as the B and T lymphocyte attenuator (BTLA), butyrophilin sub-family 3A/CD277 receptors (BTN3A), and butyrophilin sub-family 2 member A1 (BTN2A1) in several solid tumors. Since evidence showed the prognostic relevance of pretreatment serum CA125 levels in OC, the aim of our study was to investigate if soluble forms of inhibitory immune checkpoints can enhance prognostic power of CA125 in advanced HGSOC women.

Patients and Methods: Using specific ELISA tests, we examined the circulating PD-1, PD-L1, pan-BTN3As, BTN3A1, BTN2A1 and BTLA levels in eighty-five pretreated advanced HGSOC patients, correlating them with baseline CA125, age at diagnosis, Body Mass Index (BMI) and peritoneal carcinomatosis. Univariate and multivariate Cox proportional hazard regression models were built to identify significant prognostic factors for Progression-free Survival (PFS).

Results: High baseline levels (above specific concentration thresholds) of PD-1, PD-L1, pan-BTN3As, BTN3A1, BTN2A1 and BTLA were correlated with poor prognosis and shorter median PFS. Instead, CA125$\leqslant$401 U/mL, BMI$\leqslant$25, age at diagnosis $\leqslant$60 years or absence of peritoneal carcinomatosis were associated with longer PFS ($\geqslant$30 months). A multivariate analysis revealed that plasma BTN3A1$\leqslant$4.75 ng/mL (HR: 1.94; 95% CI: 1.23 to 3.07; p=0.004), age at diagnosis $\leqslant$60 years (HR: 1.65; 95% CI: 1.05 to 2.59; p=0.03) and absence of peritoneal carcinomatosis (HR: 2.65; 95% CI: 1.66 to 4.22; $p<0.0001$) were independent prognostic factors for a longer PFS ($\geqslant$30 months) in advanced HGSOC women. However, further analyses showed that each circulating immune checkpoint (PD-1$>$2.48 ng/mL, PD-L1$>$0.42 ng/mL, pan-BTN3As$>$13.06 ng/mL, BTN3A1$>$4.75 ng/mL, BTN2A1$>$5.59 ng/mL, BTLA$>$2.78 ng/mL) individually correlated in a statistically significant way with serum CA125$>$401 U/mL levels, suggesting shorter PFS ($<$30 months) and poor prognosis.

Conclusions: Therefore, plasma PD-L1, PD-1, BTN3A1, pan-sBTN3As, BTN2A1 or BTLA levels could be helpful biomarkers able to increase prognostic value of CA125.

D16

CAN GERMLINE BRCA1/2 ALTERATIONS BE ASSOCIATED WITH PERITONEAL CARCINOMATOSIS, BODY MASS INDEX AND CIRCULATING BTN3A1 LEVELS FOR PREDICTING SURVIVAL OF ADVANCED OVARIAN CANCER PATIENTS?

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Background: Ovarian cancer (OC) is the seventh most commonly diagnosed cancer and the eighth leading cause of cancer death in women worldwide. Although the most OC cases are sporadic, 10-15% of them shows a hereditary nature caused by germline alterations in two high-penetrance susceptibility genes called *BRCA1* and *BRCA2*. Since some studies highlighted a correlation between *BRCA1/2* mutational status, immunogenicity and survival in OC, our study aimed at assessing the potential impact of

germline *BRCA1/2* alterations in association with other factors on prognosis of advanced OC women.

Methods: One hundred advanced OC women, prospectively enrolled from May 2018 to July 2021 at the University Hospital Policlinico "P. Giaccone" of Palermo (Italy), were genetically tested for germline *BRCA1/2* pathogenic/likely pathogenic variants (PVs/LPVs) by Next-Generation Sequencing analysis. Pretreatment plasma butyrophilin sub-family 3 member A1 (BTN3A1) receptor levels were analyzed by a specific ELISA test and correlated with age at diagnosis, Body Mass Index (BMI), CA125, peritoneal carcinomatosis, and *BRCA* status.

Results: The mutational screening revealed that 31 out of 100 patients were carriers of germline *BRCA* PVs/LPVs (19 *BRCA1* and 12 *BRCA2*) and exhibited a median PFS which was 20 months longer than patients without *BRCA* mutation. Survival analysis showed that OC women harbouring *BRCA1/2* PVs/LPVs (HR: 0.33; 95% CI: 0,20 to 0.57; $p<0.0001$) with baseline BMI$\leqslant$25 (HR: 1.54; 95% CI: 1.02 to 2.34; p=0.04), absence of peritoneal carcinomatosis (HR: 3.27; 95% CI: 2.05 to 5.22; $p<0.0001$) and plasma BTN3A1 levels $\leqslant$4.75 ng/mL (HR: 1.71; 95% CI: 1.08 to 2.70; p=0.023) exhibited a longer PFS ($\geqslant$30 months) and better clinical outcomes than *BRCA-wild-type* patients.

Conclusions: These findings suggest a link between *BRCA1/2* mutational status, BMI, peritoneal carcinomatosis and plasma BTN3A1 expression, suggesting that germline *BRCA1/2* mutations may be a protective factor underlying a better prognosis in OC women compared to *BRCA-wild-type* patients.

D17

COMBINING CHEMOTHERAPY WITH RADIOTHERAPY IN RESECTED ENDOMETRIAL CARCINOMA: A REAL ADDED VALUE? A META-ANALYSIS

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Introduction: Although endometrial carcinoma (EC) has a favorable prognosis in the localized stages, recurrence can occur either locally or in distant sites. Aiming to reduce the relapse risk of EC, pelvic radiotherapy (RT) or systemic chemotherapy (CT) is usually administered, and recently the combination of these two options has been investigated. With our meta-analysis, we ought to address the real benefit of CTRT in delaying the relapse risk and prolonging survival.

Methods: We systematically searched the PubMed, EMBASE, and Cochrane databases for randomized clinical trials (RCTs) concerning the combination of chemotherapeutic regimens and radiotherapy (CTRT) compared with RT alone. We extracted hazard ratios (HRs) for relapse-free survival (RFS) and overall survival (OS).

Results: 4 phase III RCTs were selected. 1,951 patients received CTRT (n=981) or RT alone (n=970). Compared to RT, the CTRT combination significantly improved RFS in older patients (HR=0.72; 95% CI: 0.61-0.86; P=0.0002). However, OS was not clearly prolonged (HR=0.80; 95% CI: 0.64-1.00; P=0.05).

Conclusions: Our meta-analysis demonstrates that the addition of chemotherapy to radiotherapy significantly delays relapse in patients with endometrial carcinoma in the post-operative setting. However, the advantage of overall survival is not clear. A more accurate stratification for risk factors will help an appropriate patients selection. More studies are warranted.

D18

CLINICAL OUTCOME OF PATIENTS WITH NON-CLEAR METASTATIC RENAL CELL CARCINOMA TREATED WITH PEMBROLIZUMAB-AXITINIB COMBINATION. NEMESIA (NON CLEAR METASTATIC RENAL CELL CARCINOMA PEMBROLIZUMAB AXITINIB) STUDY, A SUBGROUP ANALYSIS OF I-RARE OBSERVATIONAL STUDY (MEET-URO 23A)

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Table 1. Characteristics of patients. IMDC (International Metastatic RCC Database Consortium); ECOG PS (Eastern Cooperative Oncology Group Performance Status); yrs (years); met (metastasis).

	N (%)
Median Age	68 yrs
IMDC score	
Good	4/25 (16)
intermediate	15/25(60)
Poor	6/25(24)
Previous Nephrectomy	15/25 (60)
ECOG PS	
0	18/25 (72)
1	5/25(20)
2	2/25 (8)
Synchronous metastatic disease	10/25 (40)
Bone met	3/25 (12)
Liver met	7/25 (25)
Lung	8/25 (32)
Nodes	20/25 (80)

Background: Non-clear cell renal cell carcinoma (nccRCC) represents a heterogeneous histological group which amount 20-25% of RCC. nccRCC have limited therapeutic options due to their exclusion from phase III randomized trials. Therefore, the aim of this study was to investigate the efficacy of pembrolizumab- axitinib in chromophobe and papillary metastatic RCC patients enrolled in the I-RARE observational ongoing study (Meet-URO 23).

Methods: Baseline characteristics, outcome data including progression-free survival (PFS) and toxicities were retrospectively collected from nccRCC pts treated in 12 Italian referral centers adhering to the Meet-Uro group, from December 2020 to April 2022. Only patients with cromophobe and papillary histology were considered eligible.

Results: 25 eligible patients received pembrolizumab-axitinib as first-line treatment. 11/25 (44%) patients had cromophobe histology whereas 14/25 (56%) were classified as papillary RCC. Characteristic of patients are reported in table 1. The disease control rate was 86.3% (10/25 patients achieved stable disease and 9/25 patients obtained partial response: 5/9 papillary, 4/9 chromophobe). 2/25 (8%) patients were primary refractory. Median PFS was 10.8 months (95%CI 1.7-11.5). 7/25 (28%) patients interrupted the full treatment due to immune-related adverse events (irAEs) (G3 hepatitis (n=4), G3 hypophisitis (n=1), G2 pneumonia (n=1), G3 pancreatitis (n=1), whereas 2/25 (8%) patients interrupted axitinib only due to persistent G2 hand-foot syndrome or G2 hypertension.

Conclusions: Pembrolizumab- axitinib could be an active option in papillary and cromophobe RCC.

D19

TRENDS IN INCIDENCE AND MORTALITY IN KIDNEY CANCER PATIENTS OVER THE LAST 25 YEARS IN A PROVINCE OF THE NORTH ITALY

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Background: In the last years, the incidence of kidney cancer has rapidly increased in Western countries. Starting from the first decade of this century new treatments have markedly improved the clinical outcomes. In these patients (pts) the increase in survival has allowed to observe the emergence of other illness including cardiovascular disease (CVD). The aim of our study is to examine the trend in incidence and mortality for tumors and for CVD in renal cell carcinoma (RCC) pts of Reggio Emilia Province using data update to 2020.

Material and Methods: The study included patients with kidney cancer registered in the Reggio Emilia Cancer Registry in the period 1996-2020 and reports incidence of cardiovascular and cancer mortality in relation to sex, age, year of diagnosis, and the standardized mortality ratio (SMR), adjusted for sex and age.

Results: 2,331 pts with RCC were identified, mainly males (1,504 cases) and aged 60-79 years (1,240 cases). There were 1,257 deaths, with no differences by sex but with a significant gradient according to age (12.1% among young people and 80.4% among over 80 years). The standardized incidence rate showed an increase in males between 1996 and 2011 (APC= 2.3) and then decreased. In females the trend appeared stable. Mortality dropped significantly among those who received diagnosis in the recent years (79.4% in 1996-2000 vs 25.2% in 2016-2020). The standardized mortality rate decreased both in males (APC= -3.3%) and in females (APC= -4.5%). Comparing the same periods, kidney cancer specific mortality decreased from 81.8% to 43.7% ($p<0.01$). The opposite occurred for CVD mortality with an increasing not-statistically significant trend. Moreover the risk of CVD mortality increased as we move away from the diagnosis (from 6.2% to 27.5%, $p<0.01$). The same trend was observed for other causes of death (from 12.6% to 32.1%, $p<0.01$).

Conclusions: Overall, the percentage of mortality from RCC has decreased over the years, while that from CVD

has slightly increased starting from 2009. Outcomes after CVD in cancer survivors seem to be poor, emphasizing the need for additional study to define how the cancer specif treatment could impact on long-term CVD risk.

D20

EFFICACY AND SAFETY OF PEMBROLIZUMAB/AXITINIB COMBINATION IN METASTATIC RENAL CELL CARCINOMA (MRCC): A MULTICENTRIC PROSPECTIVE ANALYSIS (PROPAXI STUDY)

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Background: Pembrolizumab/Axitinib (PAXI) combination is approved as first-line therapy in mRCC. The aim of this study is to evaluate outcomes of PAXI combo in the real-world in Italy.

Methods: This is a prospective study including patients (pts) diagnosed with mRCC who received PAXI as first-line therapy in recruiting Italian Centers. Data about patient characteristics, safety and outcome were collected.

Results: 96 pts have been treated from January 2021 to April 2022. The majority had clear-cell histology (81%). Sarcomatoid features was present in 22.9% (48 pts unknown). Grade 3-4 histology was the most represented accounting for 72%. About one half of pts (44%) had synchronous metastasis. In 68% of cases nephrectomy was performed. The most common metastatic sites were: lung (61%), lymph nodes (47%), bone (39%). Liver and brain were involved in 20% and 9% of cases respectively. IMDC was assessed in 87 pts: 19% were good-risk, 60% intermediate-risk, 21% poor-risk. At time of analysis, treatment was ongoing in 70% of pts, both pembrolizumab and axitinib were still ongoing in 65% of cases. Progression occurred in 25% of pts. Landmark 6-mos and 12-mos progression-free survival were 77% (95%CI 66-84) and 60% (95%CI 46-72) respectively. With a median follow-up of 8 mos and 16% of deaths, landmark 6-mos and 12-mos overall survival were 90% (95%CI 81-95) and 74% (95%CI 59-84) respectively. Among 76 evaluable pts, 79% reached disease control rate, with 4% complete response, 49% partial response and 26% stable disease. About half of pts (57%) presented clinically significant adverse event (AE), defined as AE requiring corticosteroids (29%), hormone replacement (11%), drug delay (71%), discontinuation (16%) or dose reduction (36%). The most frequent AE were hepatic (18%), endocrine (14%) and gastro-intestinal (16%). Grade =3 was reported in 28% of cases. In 19 pts (21%) a second clinically significant AE also occurred. Among the 29 pts that discontinued treatment, 59% received a subsequent line of therapy.

Conclusions: Our findings support the effectiveness and safety of first-line PAXI combination in mRCC pts also in routine clinical practice

D21

AN ITALIAN, MULTICENTER, REAL-LIFE, RETROSPECTIVE ANALYSIS OF PROGNOSTIC FACTORS AND EFFICACY OF THERAPEUTIC STRATEGIES IN BRAIN METASTATIC RENAL CELL CARCINOMA: THE BMRCC STUDY

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Background: Renal cell carcinoma (RCC) metastatic to the brain remains an aggressive subset despite novel therapeutic strategies significantly improved life expectancy. Data from prospective studies of combination treatments for patients with brain metastatic RCC (BMRCC) are limited. Thus, our multicentre, retrospective and observational study investigates the prognostic impact of clinical-pathological features and the efficacy of multimodal therapeutic strategies in a real-life cohort of patients with BMRCC.

Patients and methods: A total of 228 patients with histological diagnosis of RCC and radiological evidence of brain metastases (BMs) were included from 22 Italian centers. All patients received treatments according to physician practice: 31 were directed to immunotherapy (IT) and 80 to targeted therapy (TT) as the first treatment after BMs diagnosis and 159 underwent encephalic radiation therapy (eRT). Both univariate and multivariate models were performed to investigate the impact of clinical features and multimodal treatments on both overall survival (OS) from BMs onset and intracranial Progression-Free Survival (iPFS). The chi-squared test evaluated the suitability of several features to predict death occurrence.

Results: Seventy-four percent of patients had metachronous BMs. The prevalent (66%) brain metastatic site was the supratentorial region. Forty-four percent experienced neurological symptoms that did not represent a negative prognostic factor (p=0.988), as evidenced in other tumor types. The median OS from the diagnosis of BMs was 18.8 months. The multivariate analysis revealed as independent favorable prognostic factors a Karnofsky Performance Status =70%, a stable extracranial metastatic disease, the number of BMs (1 vs = 2), and the number of systemic therapeutic lines received. Subgroup analyses did not show any difference in terms of iPFS by the type of the first line (IT or TT, p= 0,6543) or eRT (p= 0.78) performed as stereotactic radiosurgery in 47% of patients or Whole Brain eRT in 24% of them. Subgroup analysis showed that eRT significantly prolonged iPFS only if combined with immunotherapy (p= 0.0321).

Conclusions: Based on our results, eRT showed benefits in terms of iPFS only if associated with IT, suggesting a potential additive effect. Furthermore, BMRCC multitreated patients experienced a survival improvement, overcoming previous dogma that excluded them from randomized clinical trials due to their expected dismal prognosis.

D22

ONCOLOGY WORKLOAD GENERATED BY IMMUNOTHERAPY IN ADVANCED UROTHELIAL (MUT) AND RENAL-CELL CARCINOMA (MRCC) CANCER PATIENTS

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Background: The introduction of immune checkpoint inhibitors (ICI) changed the paradigm of genitourinary cancer care. To our best knowledge no data are available on the impact of ICI on oncology workload. Our study aims to compare the shift in 1-year-workload generated in a cohort of patients (pts) treated in the pre- and post ICI's era at the Oncology Department of the University Hospital of Udine.

Materials and methods: We analyzed from our electronic accountability system all cases of mUT and mRCC cancer between 01.01.15 and 31.12.17 (pre-ICI cohort, i.e. target therapy and chemotherapy) and between 01.01.18 and 31.12.20 (ICI cohort) leading to at least one treatment session during the following year. Data on number of cycle, treatment sessions, unplanned presentations, hospitalizations, re-evaluations, follow-up visit and inpatient oncology advices were collected. Statistical comparison was performed using a negative binomial regression model.

Results: 108 pts were included, 50 (46%) in the pre-ICI cohort, 58 (54%) in the ICI-cohort. In the ICI group we observed a greater mean number of treatment sessions (8.7 vs 6.3 p=0.016) and a lower mean number of follow up visit (0.50 vs 0.93 p=0.031) however no statistically significant difference in terms of hospitalization, re-evaluations, inpatient oncology advices and unplanned presentations has been found. In detail data are reported in Table1.

Conclusions: ICI are widespreadly used in UTm and RCm, leading to improved survival with manageable side effects. As a consequence, in the ICI cohort we observed a

Table 1. Number of clinical episodes in the first year of treatment (ICI vs pre-ICI cohort). Workload is represented by mean value and standard deviation (SD) statistical significance as $p<0.05$. Total number of episodes is shown (N).

Cancer treatments	Treatment sessions	Follow-up visits	Hospitalizations	Inpatient oncology advices	Re-evaluations	Unplanned presentations
Immunotherapy	8.7 (SD 7.71) N=435	0.50 (SD 0.89) N=25	0.58 (SD 0.81) N=29	0.26 (SD 0.90) N=13	1.14 (SD 1.44) N=57	1.92 (SD 1.85) N=96
Other Treatments	6.3 (SD 6.48) N=366	0.93 (SD 1.31) N=54	0.38 (SD 0.75) N=623	0.36 (SD 0.74) N=21	1.62 (SD 1.64) N=94	1.64 (SD 1.72) N=95
P-value	0.016	0.031	0.18	0.49	0.11	0.44

greater oncology workload in terms of treatment sessions, but a lower load of follow up visits. Overall workload resulted comparable in the two cohorts.The qualitative estimate of ICI-generated workload in a larger population is crucial for developing effective models of care and workforce supply.

D23

NEUROLOGICAL DISORDERS AND RISK OF FALLING IN OLDER PATIENTS (PTS) WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (M-CRPC) UNDERGOING CHEMOTHERAPY

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Background: Chemotherapy may also be a choice in older pts with mCRPC. Although an important benefit has been demonstrated with the use of Taxanes and other chemotherapies (Vinorelbine, Mitoxantrone and Platinum derivatives), neurological toxicity represents a quite common side effect. Furthermore, falls are a very frequent occurrence in the older patients.

Methods: We conducted a retrospective, observational Real-Life study of 39 older pts, aged $>$ 70 years, affected by m-CRPC, treated with chemotherapy in our center in the different lines of treatment from January 2014 to January 2022. The incidence of neurological disorders was investigated, specifically peripheral neuropathy and cognitive disorders. The correlation of these neurological events with the risk of falling was also evaluated.

Results: The retrospective cohort included 39 older pts (mean age 75.6, 23% older than 80 years) with mCRPC. The chemotherapy treatments carried out were the following: 100% had performed Docetaxel and 5% (2 pts) Carboplatin-Vepesid in 1L; 58,9% (23 pts) performed Cabazitaxel, 15.3% (6 pts) Vinorelbine, 2.5% (1 pts) Mitoxantrone and 2,5% (1 pts) Cyclophosphamide-Adriamycin-Vincristine (CAV) in the following lines. 34% had an ECOG PS $\geqslant$ 2. Neurological comorbidities (mainly cerebral vasculopathies) were present in 2.5% of pts, 23% had also poorly compensated diabetes mellitus. Neurological disorders (90% peripheral neuropathy of any degree and 10% cognitive disorders) treatment related were seen in 28.2% (11 pts), all had undergone treatment with Docetaxel, 3 of them had been treated also with Cabazitaxel (13% of 23 pts treated), 2 with Vinorelbine (34% of 6 pts), 1 with Mitoxantrone (100% of 1 pts) and 1 with Carboplatin-Vepesid (50% of 2 pts). The fall event was seen in 34% (13 pts), all treated with Docetaxel, 46% (6 pts) also with Cabazitaxel, 23% (3 pts) with Vinorelbine and 1 with Mitoxantrone; 69% of those who had experienced a fall also had peripheral neuropathy. A significant correlation was found between the fall event and the neurological toxicity ($p<0.001$; Cramer's V index: 0.645).

Conclusions: Older patients with mCRPC treated with chemotherapy may have an elevated risk of developing neurological disorders and this toxicity may be related to a higher incidence of falls. Broader prospective studies would be needed to substantiate this thesis.

D24

SAFETY OF RUCAPARIB AS MAINTENANCE THERAPY AFTER PLATINUM-BASED CHEMOTHERAPY IN PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER: THE REAL-LIFE EXPERIENCE IN PUGLIA

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Background: Rucaparib, a poly (ADP-ribose) polymerase inhibitor, significantly improved progression-free survival versus placebo after response to platinum-based chemotherapy in patients with high-grade, recurrent, platinum-sensitive ovarian cancer, as demonstrated by the ARIEL 3 trial. However, in the same therapy setting, also regardless of the mutational status, there is the availability of other effective PARP inhibitors, characterized by mainly haematological toxicity. The unmet need is selection criteria for the best therapy choice. In order to bridge this gap, we collected real world data of the first patients in Puglia treated with Rucaparib in the last 2 years.

Methods: In this multicentre observational study clinical data of 30 patients were collected in an excel spreadsheet; a statistical descriptive analysis, with frequency and corresponding percentages calculation and chi-square test were performed.

Results: At diagnosis, frequently in advanced stages (87% IIIC-IV), median patients age was 57 years, the ovarian cancer histology was serous (87%) or endometrioid (13%), BRCA status was mostly wild-type (77% wt vs 23% mut). 80% of patients on Rucaparib maintenance therapy had received only 2 prior lines of platinum-based chemotherapy, reporting mostly haematological toxicity in 80% of cases (87% G1/G2 vs 13% G3/G4). Best radiologic response to Rucaparib was assessed in 20/30 patients with an overall response rate of 56.6% (CR 23% + PR 23% + SD 10%). 10/30 patients discontinued Rucaparib, only 2/10 patients for toxicity, the others for disease progression or other causes. The most frequent toxicity with Rucaparib was gastrointestinal (52%). Haematological toxicity, mainly G1/G2 grade, occurred in 33% of cases. In some patients who had previously experienced any degree of haematological toxicity to platinum-based chemotherapy (24/30), haematological toxicity was confirmed during maintenance therapy with Rucaparib (16/30), even if with downgrading in 50% of cases. The difference of haematological toxicity between the two treatments (platinum chemotherapy and rucaparib) performed was statistically significative with $p < 0.05$.

Conclusions: Maintenance treatment with Rucaparib, although in a small group of real world patients, is confirmed to be effective but above all safe, even in the case of previous haematological toxicity to platinum-based chemotherapy. These and further observations could provide tools to prescribe the best PARP-I for each patient.

D25

IO-IO VS IO-TKI COMBINATION AS FIRST LINE TREATMENT OF MRCC PATIENTS: A MONOCENTRIC EXPERIENCE

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Background: In the last few years, the therapeutic chances of patients (pts) with metastatic renal cell carcinoma (mRCC) have been radically increased. Combination therapies including immunotherapy (IO-IO) or immunotherapy and anti-VEGF (IO-TKI) have improved the survival outcomes of mRCC pts and have changed our clinical practice.

Material (patients) and methods: A retrospective analysis of all patients with diagnosis of mRCC between 2014 to 2021 treated with IO-IO or IO-TKI combination as first line therapy at Modena Cancer Center was performed. Pts treated as part of a clinical trial were included.

Results: A total of 40 mRCC pts (32 male and 8 female) received a fist line combination therapy: 11 ipilimumab-nivolumab, 17 pembrolizumab-axitinib, 7 atezolizumab-bevacizumab, 3 lenvatinib-pembrolizumab, 2 avelumab-axitinib. The median age at the diagnosis was 63 years old. The histologies detected were clear cell (86%), papillary (6%), chromophobe (2%) and unclassified (6%). 29 pts were intermediate risk, 4 pts good risk and 7 pts poor risk according to IMDC risk group. Clinical and pathological characteristics of the two groups were well balanced. At the time of the analysis 25 pts had discontinued first line treatment: 16 pts due to a progression disease while 3 pts due to a high grade gastrointestinal toxicity. 18 pts started second line therapy (12 with cabozantinib, 4 with sunitinib, 1 with sorafenib and 1 with axitinib) and 15 pts had died. Only one pts had a complete radiological response with atezolizumab-bevacizumab. There was no difference in terms of PFS (p=0.4) between two treatments with a median PFS of 11 months in pts treated with IO-TKI and not yet reached in pts treated with IO-IO and in terms of median OS (p=0.8) (mOS of 38 months for IO-TKI and not yet reached for IO-IO). Interestingly, the mOS was better in pts aged $>$ 65 years with a median OS not reached (versus 25 months in pts $<$ 65 years old (p=0.049). The analysis of a custom NGS panel of 87

genes on the tumour tissue including the most common alterations in mRCC is ongoing.

Conclusions: Our study represents a real-world evidence of first line therapy combinations and we hope that the ongoing analysis of a custom NGS panel could generate data to inform clinicians and helping therapeutic decision making process. Finding predictive biomarkers for choosing the most suitable treatment for every pts and overcoming therapy resistance remains an unmet need in mRCC.

D26

PARP-INHIBITORS AS FIRST-LINE THERAPY FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER AFTER DOCETAXEL IN THE CASTRATION-SENSITIVE DISEASE

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Background: The lack of prospective data aboutfirst-line therapy of metastatic castration-resistant prostate cancer (mCRPC) after progression to intensified regimens in the castration-sensitive disease leads to the necessity of defining the best therapeutic algorithm in this setting. We performed a meta-analysis with the aim of assessing the efficacy of first-line therapy with a PARPi for mCRPC patientsaccording to prior docetaxel treatment in the castration-sensitive phase of the disease.

Methods: Prospective studies were identified by searching the MEDLINE/PubMed, Cochrane Library and ASCO Meeting abstracts. Data extraction was conducted according to the PRISMA statement. Combined relative risks (RRs) and 95% confidence intervals (CIs) were calculated using fixed- or random-effects methods, depending on studies heterogeneity. The statistical analyses were performed with RevMan software for meta-analysis (v.5.2.3).

Results: Two articles were selected for this meta-analysis, including a total of 1219 patients. Both studies compared the combination of abiraterone plus a PARPi (niraparib and olaparib, respectively). Treatment with a PARPi plus abiraterone significantly improved radiographic PFS (rPFS) compared to control (fixed-effect, HR=0.68; 95% CI 0.48–0.97; p=0.03) in the subgroup of patients treated with prior docetaxel at mCSPC stage, with the caveat that patients' numbers are limited in this analysis (only 264 patients). Similarly, in the subgroup of patients that did not receive early docetaxel for mCSPC, rPFS was significantly improved with the PARPi compared to the control (fixed-effect, HR=0.71; 95% CI 0.59–0.85; p<0.0002).

Conclusions: First-line treatment with a PAPRi significantly prolongs rPFS of mCRPC patients, even in those with more aggressive tumors who have previously received docetaxel in the castration-sensitive phase of the disease. Final OS data and prospective studies focused on the efficacy of PARPi in the specific subgroups of patients progressed after an "intensified" approach (a triplet of ADT plus docetaxel plus an ARTA) for *de-novo*metastatic castration sensitive prostate cancer are highly expected.

D27

POTENTIAL PROGNOSTIC FACTORS IN METASTATIC RENAL CELL CARCINOMA PATIENTS TREATED WITH IMMUNE-CHECKPOINT INHIBITORS

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Background: Recently, metastatic renal cell carcinoma (mRCC) has seen a considerable development of therapeutic strategies focused on Immune-checkpoint inhibitors (ICIs) alone or in combination with target therapies, which have now become the standard of treatment. Due to the increase in treatment options, several studies were looking for prognostic and predictive factors. Currently, there are no validated biomarkers. Therefore, the aim of this study was to identify prognostic and/or predictive factors in a group of mRCC patients treated with ICIs.

Material and methods: Data were retrospectively collected from 45 pts belonging to Medical Oncology Unit of Cagliari University Hospital from 2010 to 2022. All pts had histologically confirmed metastatic clear cell renal cell carcinoma and they received an ICI in first or further line. Statistical analysis was performed with MedCalc package. Survival distribution was assessed by Kaplan-Meier curves. Finally, multivariate analysis was performed, taking into consideration the following factors: IMDC group, N/E ratio, N/L ratio, Mediastinal Lymph nodes (MLN).

Results: Median age was 67 y.o. (range 47-80 y.o.), 12 were female and 33 were male, 27 had an ECOG PS 0 and 18 had an ECOG PS 1. Among the parameters evaluated, MLN involvement, IMDC group, N/E ratio and N/L ratio were statistically significantly related to overall survival (OS) at univariate analysis. Specifically, a worse IMDC group, a N/E ratio >30, a N/L ratio >3.8 and the presence of metastatic MLN were related to a statistically significant worse OS. Subsequently, we performed multivariate analysis including all previously evaluated parameters, in

which MLN involvement and IMDC group were identified as independent factors.

Conclusions: The results of this study, albeit with limitations related to the retrospective nature and the small group of cases, might indicate a correlation between N/E ratio, N/L ratio, presence of MLN metastasis and a different prognosis to ICIs. These findings might be a useful tool to identify a subgroup of pts with reduced benefit from ICIs, that could be investigated in a larger population.

D28

ADVANCED NON-CLEAR CELL RENAL CELL CARCINOMA: A SINGLE REFERRAL CENTRE EXPERIENCE AND REVISION OF THE LITERATURE

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Background: Non-clear cell renal cell carcinoma (nccRCC) represents a highly heterogenous group of kidney cancer entities according to most recent classification. As most clinical trials predominantly include patients with clear cell RCC (ccRCC), nccRCC treatment guidelines are mainly extrapolated from recommendations in ccRCC and lack of strong evidence. Here, we review the historic series of nccRCC treated in our Institution and review current data on the treatment of nccRCC.

Patients and methods: To evaluate the real-world setting management of advanced nccRCC, we reviewed data of our patients from January 2010 to December 2021. We also briefly reviewed the literature on this topic.

Results: Out of 640 metastatic or locally advanced RCC patients, 66 had a diagnosis of nccRCC (cromophobe RCC 14 (21.2%); collector duct RCC: 6 (9%); papillary RCC 40 (60.6%); other histologies 6 (9%)). Most of them (75.8%) had and ECOG PS 0 to 1 and were at intermediate risk per IMDC classification (54 pts evaluable; good vs intermediate vs poor risk: 29.6% vs 38.9% vs 31.5%). Fifty-eight patients received first line active treatment. ORR vas 14%. Median OS and PFS of the cohort were 13.0 and 6.0 months. Papillary RCC (pRCC) had a trend towards a better prognosis and a significantly better PFS when treated in first line setting. Besides, patients treated with IO-combos in the more recent years had a better chance of survival compared to the use of single TKI agent (OS NA vs 12.0 mos, p=0.07; PFS 27.0 vs 3.5 mos, p=0.03). We applied the Meet-URO score to all the cohort of treated patients and it retained its prognostic value ($p<0.0004$).

Conclusions: Although nccRCCs are relatively uncommon, they account for a subgroup of up to 20-25% of all RCC. Advances in histopathology and molecular genetics, along with clinical evidence, have improved understanding and treatment of these tumours in recent years. Some selective trials for nccRCC with novel therapies including IO and new targeted agents are ongoing and their results are urgently needed to further improve patients' outcome.

D29

EFFECTIVENESS AND TIMING OF PSA NADIR OF CHEMOHORMONAL TREATMENT FOR DE NOVO METASTATIC HORMONE-SENSITIVE PROSTATE CANCER: A SINGLE CENTER EXPERIENCE

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Background: Despite advances in systemic treatments, *de novo* metastatic hormone-sensitive prostate cancer (mHSPC) remains a highly aggressive disease. Addition of Docetaxel (DOC) to androgen deprivation therapy (ADT) represents a standard of care in these patients (pts), resulting in a significant advantage in terms of OS. This study aims to report our experience in *de novo* mHSPC patients treated with 3-weekly DOC plus ADT in routine clinical practice.

Materials (patients) and methods: We retrospectively identified 38 pts treated with ADT plus DOC 75 mg/m^2 every 3 weeks for 6 cycles for *de novo* mHSPC between February 2016 and February 2022. Time to castration-resistant prostate cancer (CRPC) and OS were calculated with the use of Kaplan-Meier estimates; time to Prostatic Specific Antigen nadir (TTN) and its relationship with clinical outcome were also evaluated.

Results: Pts baseline characteristics are summarized in Table 1; all pts met the CHAARTED definition for high volume disease. After a median follow-up of 27.8 months (mos), 50% of the patients experienced disease progression to CRPC; median time to CRPC was 25.2 mos (95% confidence interval [CI] 14.9-32.2) and median OS was 44.4 mos (95% CI of 41.9-45.9). Using median TTN (9.7 mos) as cut off value, we found that median time to CRPC was significantly longer among pts who have developed the PSA nadir more slowly (30 vs 14.9 mos, HR 0.32 [95% CI 0.12-0.84] p=0.0047). Median OS was also slightly higher in pts with a slower PSA nadir, but such difference

AGE - years	
range	45-75
median	64
Visceral Metastases - no.(%)	2 (5%)
GRADE GROUP - no. (%)	
2	2 (5%)
3	2 (5%)
4	26 (68%)
5	8 (18%)
PSA level at start of ADT - ng/ml	
range	3.19 - 6275
median	103.8
Time from start of ADT to Docetaxel - mos	
range	0-4
median	1
Homologous Recombination Repair (HRR) status - no (%)	
BRCA mutated	3 (8%)
wild type	15 (39%)
unknown	20 (53%)

was not statistically significant (46 vs 36.8 mos, HR 0.35 [95% CI 0.08-1.44] p=0.0866).

Conclusions: With the limitations of the small sample and the retrospective nature, this study confirms effectiveness of DOC plus ADT in mHSPC. Furthermore, according to the literature, our analysis shows that slower PSA nadir achievement seems to provide a better long term clinical outcome.

D30

OPTIMIZING CANCER CARE OF GYNAECOLOGICAL CANCER PATIENTS IN THE MULTIDISCIPLINARY TEAM

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In many health care systems globally, cancer care is driven by multidisciplinary cancer teams (MDTs). Especially for gynaecological cancers an integrated system of treatments is required and should be garanteed in a short time in the MDTs. Case Manager is a central figure in every MDTs, a professional specifically trained to manage clinical cases on the basis of predefined paths. In our institution, gynaecological MDT is active from December 2020.

From December 2020 to march 2022, 35 patients with gynaecological cancer were included in the case management project of the Gynaecological MDT (GynMDT): most patients were affected by endometrial cancer (74%); followed by ovarian cancer (14%), vulvar cancer (9%) and cervical cancer (3%). Median age was 62 years (18-84). Study endpoint were: timing between patient entry in the GynMDT and staging (CT scan, MRI), staging and cancer treatment (surgery, radiotherapy, chemotherapy) and patient reported outcomes (PROs). Most patients received surgery alone (80%), 11% underwent surgery followed by chemo-radiotherapy; 6% surgery and post-operative radiotherapy, only 3% received chemotherapy alone after surgery. Median time from GynMDT entry to disease staging was 30 days (1-120 gg); median time from disease staging to surgery was 13 days (4-47); median time from disease staging to first treatment (surgery, chemotherapy, radiotherapy or chemo-radiotherapy) and adiuvant chemotherapy or radiotherapy was 13 days (4-47) Many patients are still receiving anti-cancer treatments, so definitive PROs are not yet available. Even if data are still to be improved, this ongoing study demonstrates the central role of case manager to allow inter-professional collaboration in MDTs in order to ensure time-limited pathways for cancer diagnosis and therapy.

D31

NON-CLEAR RENAL CELL CARCINOMA (NCCRCC): A MONOCENTRIC RETROSPECTIVE COHORT

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Background: nccRCC accounts for 20-25% of all RCC cases. Recently, the better understanding of histology-specific pathophysiological mechanisms and molecular drivers, together with recent results from single-arm focused phase II clinical trials, has led to an overall improvement in the management of patients with metastatic nccRCC.

Patients and methods: This is a retrospective analysis of 24 metastatic nccRCCs, that came to our attention over the last 12 months.

Results: Histologically, tumors were classified as papillary (40%, 50% type I and 50% type II), chromophobe (20%), unclassified (32%), MiT translocation (4%) and collecting duct (4%). Sarcomatoid features were observed in 33% of patients. Distant and/or nodal metastases were present at diagnosis in 75% of patients. Only 4% of patients developed brain metastases. All the patients received systemic therapy, with an average interval between the diagnosis and the start of the treatment of 1.7±4 years.

Therapeutic lines received by each patient ranged from 1 to 4, with a median overall survival (OS) of 13.9 months from the start of the systemic therapy. The most common first-line treatments were Tyrosin Kinase Inhibitors (TKI) alone (50%) or in combination with Immune Checkpoint Inhibitors (ICI) (42%), while 8% of patients received single ICI or a two-ICIs combination. Dose limiting toxicities were observed in 8% of the patients. Objective responses rate (ORR) was 25% of the patients, while disease control rate (DCR) was 62.5%. The median progression-free survival (PFS) for the first therapeutic line was 8.9 months. In second line, the use of TKI alone was less represented (20%), in favor of ICI monotherapy (70%). The PFS for the second line therapy was 3 months, with an ORR of 10% and a DCR of 30%.

Conclusions: In our nccRCC cohort, the neoplasm is commonly diagnosed in a metastatic stage. The most common histologic subtypes are papillary and unclassified. Consistent with recent literature data, in our case series, first-line systemic treatment based on TKI monotherapy or TKI/ICI combination resulted in a relevant disease control rate in the heterogeneous nccRCC class.

D32

RENAL CELL CARCINOMA IN YOUNG ADULTS: A MONOCENTRIC RETROSPECTIVE COHORT AND A COMPARISON WITH ELDER PATIENTS

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Background: Renal cell carcinoma (RCC) is commonly a pathology of older adults. RCCs in young adults has its own features.

Patients and methods: This is a retrospective analysis of 25 metastatic RCCs diagnosed in patients <50 years that came to our attention over the last 12 months and compared with patients >50 year (n = 77) in the same period.

Results: Histologically, tumors were classified as clear cell (66% in under-50 vs 76% in over-50), papillary (12% vs 12%), chromophobe (4% vs 5%), unclassified (16% vs 6%). Sarcomatoid features were observed in 20% (vs 36%). Distant or nodal metastases were present at the diagnosis only in 32% of patients (vs 50%). Notably, 28% of patients developed brain metastases (vs 7.5%, p=0.01). In younger patients, tumor size and Fuhrman's grade showed statistical correlation (Spearman's rho = 0.4408, p=0.04). According to the IMDC scoring system, 32% (vs 0%) of patients were classified as good risk, 52% (vs 96%) were intermediate risk, 16% (vs 4%) were poor risk. All the patients received systemic therapy, with a mean average interval between the diagnosis and the start of the treatment of 3.6±5.4 years (vs 1.5±3.2, p=0.01). Therapeutic lines received by each patient ranged from 1 to 8 (vs 1 to 4 for elder patients), with a median overall survival (mOS) of 18.4 months from the start of the systemic therapy (vs 12.3 months, ns). The most common first-line treatments were TKI alone (64% vs 49%) or in combination with ICI (32% vs 41%).

Dose limiting toxicities were observed in 12% (vs 18%). Objective responses were observed in 28% (vs 26%), while disease control was reported in 72% (vs 68%). The median progression-free survival (PFS) for the first therapeutic line was 7.3 months (vs 7.6 months). The 1 year-PFS was 32% (vs 36%). In second line, the use of TKI alone was less represented (23% vs 39%), in favor of ICI monotherapy (69% vs 57%). The PFS for the second line therapy was 11.4 months (vs 5.1 in the elderly), with an ORR of 31% (vs 21%) and a DCR of 53% (vs 50%).

Conclusions: In our case series of young patients RCCs were most often localized at the time of diagnosis. One third of mRCCs was included in the favorable risk prognostic category according to IMDC score. One third of the patients developed brain metastases. A first line systemic treatment based on TKI (±ICI) has resulted in a relevant disease control rate. When compared with the elderly population, young RCC patients had a longer OS from the start of systemic treatment.

D33

PRELIMINARY RESULTS FROM SIESTA, A PILOT OBSERVATIONAL STUDY INVESTIGATING SLEEP QUALITY IN PROSTATE CANCER PATIENTS

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Background: Sleep disorders have been reported to be associated with prostate cancer (PC) treatments, mainly with androgen deprivation therapy (ADT). Trials in this field are scarce, mostly lacking objective measurements. The main aim of this study is to verify the effect of ADT on sleep quality compared to other treatments.

Methods: SIESTA is a pilot, observational cohort study, planned to enrol thirty patients with localised, or metastatic PC divided into 3 groups: ADT plus novel hormonal therapy (NHT), ADT plus radiotherapy (RT) or RT alone. Sleep quality measurements consist of home polysomnography (PSG) and salivary melatonin dosage, actigraphy, validated sleep and quality of life questionnaires, blood and urine samples. Preliminary results of 16 patients are presented.

Results: An important rate of screen failures (19%) due to severe sleep apnoea syndrome (SAS) was recorded. Subjective sleep quality at baseline was impaired in 56.3% of patients. PSG and actigraphic parameters did not differ from baseline at the planned time points. One patient developed a transient restless legs syndrome (RLS) between 3 and 12 months of ADT plus RT, another patient a worsening and persistence of RLS symptoms after 6 months of ADT and Enzalutamide. The mean dim-light melatonin onset (DLMO) shift (n=7) was 67.6 ± 57.2 minutes. In all patients DLMO was anticipated, importantly in patients receiving RT alone or plus ADT ($p = 0.02$).

Conclusions: Preliminary data of SIESTA show a high percentage of pre-existing severe SAS in PCa patients. ADT seems not to affect significantly sleep quality. However, a possible effect of ADT in inducing or worsening RLS needs to be better explored. An anticipation of the DLMO in patients under radiotherapy was found.

Trial registration: ClinicalTrials.gov NCT04543799

D34

PRIMARY NEUROENDOCRINE NEOPLASM OF THE URINARY BLADDER: A CASE-SERIES OF 24 PATIENTS TREATED AT THE MODENA ONCOLOGY CENTRE

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Background: Primary neuroendocrine (NE) neoplasm of the urinary bladder is an extremely rare disease that accounts for less than 1% of all urothelial neoplasms. The NE differentiation confers a worse prognosis, and it is often associated with earlier distant metastasis than typical urothelial carcinoma. Small-cell carcinoma (SCCB) is the most common variant of the NE neoplasms of the urinary bladder (incidence 0.3-1.35% of all urothelial neoplasm). Haematuria is present in 95% of cases. The median overall survival (OS) of all stages is 19.6 months, with 8.1% of global survival at 5 years.

Material (patients) and methods: We studied 24 cases of NE neoplasm of the urinary bladder (22 SCCB, 1 large cell NE carcinoma and 1 with both components), 22 men and 2 women treated in our centre in the last 20 years. Median age at diagnosis was 71 years (range 46-87).

Results: In the 50% cases NE neoplasms presented as a pure form. Of the whole group, only 8 had metastases at the onset and the most affected sites were lymph-nodes and bones. Due to the delicate clinical conditions, only 4 patients received first line platinum-based chemotherapy and 2 of them had to stop treatment due to complications. Of the 16 non-metastatic patients, 12 underwent cystectomy. 10 of them had a $T \geqslant 2$ and 5 had local lymph-node involvement. Only 4 with locally advanced stage underwent adjuvant chemotherapy that was platinum-based in 3 of 4 cases. 10 patients had a relapse. In the 90% of cases were observed distant metastases (mainly lymph-nodes and peritoneum). Also in this case, platinum-based chemotherapy was administered as the first line. Of the patient cohort considered, only 7 patients are currently still alive. 17 died mainly from disease-related causes. Median OS was 21 months (95% CI 7,3-34,7). In patients with localized disease and metastatic disease at onset median OS was 34 months (95% CI 6,26-61,74) and 2 months (95% CI 0-4,77), respectively.

Conclusions: As a rare disease the treatment for primary neuroendocrine (NE) neoplasms of the urinary bladder is still uncertain. However, in the era of platinum-based treatment, the prognosis of these patients remains poor. According to our knowledge, our case series represents one of the most numerous real-life studies published in the literature even if its limit is the retrospective nature.

D35

IMMUNE CHECKPOINT INHIBITORS (ICI) AND TYROSIN-KINASE INHIBITORS (TKI) COMBINATIONS IN RENAL CELL CARCINOMA (RCC): LESSONS FROM A REAL-LIFE RETROSPECTIVE MONOCENTRIC COHORT

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Background: Recently, the combinations of Immune Checkpoint Inhibitors (ICI) and Tyrosin-Kinase Inhibitors (TKI) were established as a standard first-line therapy for metastatic clear cell RCC (ccRCC) and non-clear RCC (nccRCC). From December 2020 to January 2022 the combination of Pembrolizumab plus Axitinib was the only ICI-TKI combination authorized in Italy for initial treatment of metastatic RCC.

Patients and methods: This is a retrospective analysis of 24 metastatic RCCs who received Pembrolizumab plus Axitinib as a first-line systemic therapy in our department, over the last 12 months.

Results: The mean age of the population was 61±12 years. Twenty (84%) patients were diagnosed with ccRCC, and 16% with nccRCC including 2 (8%) papillary, 1 (4%) chromophobe and 1 (4%) with MiT translocation RCC. Sarcomatoid features were present in 9 patients (37%). In 14 cases (58%), the disease presented nodal and/or visceral/bone metastases from the diagnosis, while 10 patients (62%) had an initially metastatic disease. The median time between the diagnosis and the start of the systemic therapy was 3.83 months. Both the median Progression-Free Survival (mPFS) the median Overall Survival (mOS) were both unreached. The 1-year PFS is 25% at the current time. An Objective Response Rate (ORR) of 21% and a Disease Control Rate (DCR) of 71% were reported, with a median Duration of Response of 6.4 months.

Among the factors that could predict the outcome of the disease, the number of metastatic sites at the diagnosis was the most accurate. Patients with less than 3 metastatic sites had a better DCR (90.1% vs 46.1%, p= 0.034), ORR (27.2% vs 15.3%, p= 0.629), median PFS (unreached vs 5 months, p = 0.156) and median OS (both unreached, p = 0.138) than those with more than 3 metastatic sites.

Interestingly, also the BMI of the patients correlated with the response to Pembrolizumab plus Axitinib. Overweight patients (BMI over 25) had a better DCR (66.5% vs 41.7%, p= 0.413), median PFS (unreached vs 4.7 months, p = 0.132) and median OS (both unreached, p = 0.11) than those with a normal weight (BMI under 25).

Conclusions: In this real-life cohort, Pembrolizumab plus Axitinib showed a good clinical performance in terms of efficacy and in untreated metastatic ccRCC and nccRCC. Patients with less than 3 metastatic sites have shown better and more durable clinical responses. The better clinical performance of patients with BMI over 25 is coherent with many recent retrospective reports.

D36

FIRST-LINE COMBINATION THERAPIES FOR ADVANCED RENAL CELL CARCINOMA (ARCC): AN ITALIAN SINGLE-CENTRE REAL-WORLD CLINICAL EXPERIENCE

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Background: Pembrolizumab plus Axitinib (PA) was approved by the Italian Medicines Agency (AIFA) on December 2020 as a 1st-line treatment for aRCC. After one year Nivolumab plus Ipilimumab (NI) was approved in the same setting, only for intermediate/poor risk patients (pts). Both combinations have shown an improvement in OS and PFS compared to Sunitinib. As observed in pivotal phase III clinical trials, careful attention must be given to overlapping toxicities. This study aims to evaluate the real world experience of an italian single-centre with both combinations.

Methods: We retrospectively evaluated 32 aRCC pts, treated with 1st-line NI and PA between 2019 and 2022 at our Institute. Pts were identified by computerized records.

Results: 16 pts received NI and 16 pts received PA. 3 NI-pts and 9 PA-pts are still on treatment. Pts baseline characteristics are shown in the table below:

	NI	PA
Median age, yr	63	57
Sex, no. (%)		
Male	12 (75)	11 (69)
Female	4 (25)	5 (31)
ECOG PS, no. (%)		
0	5 (31)	4 (25)
1	11 (69)	12 (75)
Histologycal Type, no. (%)		
Clear Cell	11 (69)	11 (69)
Papillary	1 (6)	0 (0)
Chromophobe	0 (0)	1 (6)
NOS	4 (25)	4 (25)
Sarcomatoid component, no. (%)	1 (6)	2 (13)
Heng Risk Group, no. (%)		
Favorable	0 (0)	0 (0)
Intermediate	12 (75)	16 (100)
Poor	4 (25)	0 (0)
Liver metastases, no. (%)	5 (31)	6 (38)

In the NI group, 1 patient obtained Complete Response (CR), 4 pts Partial Response (PR) and 5 Progression

Disease (PD) as best response. In the PA group, 8 pts obtained PR and 4 PD as best response. With a median follow up of 30,8 mos in the NI group and 9,4 mos in PA group, mPFS was 7,0 and 5,9 mos respectively. mOs was 16,3 mos for NI pts. mOS was not reached in PA group and 87,5% of pts is still alive. 100% of pts experienced a toxicity of any grade in both groups, 25% of NI pts and 37,5% of PA had G3-4 Adverse Events (AEs). 6 (38%) PA pts had an AE leading to Axitinib dose reduction. Most frequent NI G3-4 AEs included: anemia (12,5%), pneumonia (6,2%) and fatigue (6,5%). Instead, most frequent PA G3-4 AEs included: hypertransaminasemia (18,8%), HFS (6,3%), oral mucositis (6,3%) and arthralgia (6,3%).

Conclusions: With the limitations of the retrospective nature and the small number of pts involved, our analysis shows safety profile and the effectiveness in routine clinical practice of two first line combination treatments for aRCC.

D37

SUPER-HIGH-RISK (SHR) SUBGROUP AMONG PATIENTS (PTS) WITH METASTATIC RENAL CELL CARCINOMA (MRCC) TREATED WITH ICIS-BASED TREATMENT AS FIRST-LINE THERAPY AT MODENA CANCER CENTER

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Background: Immune checkpoints inhibitors (ICIs) have changed the therapeutic landscape of mRCC. However, there is still a subset of refractory pts and mechanisms driving resistance are poorly understood. The aim of our retrospective analysis is identifying clinical and pathological characteristics of mRCC pts treated with first-line ICIs-based combinations (IO+IO or IO+TKIs) and with PFS ⩽ 6 months.

Patients and methods: We performed a single-center retrospective analysis of 8 (20%) out of 40 mRCC pts treated with first-line ICIs-based combinations from July 2016 to December 2021 and with PFS ⩽ 6 months: 5 (62,2%) and 3 (37,5%) of those received Nivolumab plus Ipilimumab (IO+IO) and Pembrolizumab plus axitinib (IO+TKI), respectively.

Results: SHR pts were 7 males (87,5%) and 1 female (12,5%). Median age at diagnosis was 53 years (range: 47-80). All pts had a performance status sec.ECOG 0-1. All histotypes were classified as clear cell (ccRCC), of which 3 (37,5%) with sarcomatoid differentiation; 1 (12,5%) with rhabdoid differentiation; 1 (12,5%) with sarcomatoid plus rhabdoid differentiation. Seven (87,5%) pts had a metastatic disease at onset. Four (50%) pts underwent to nefrectomy. Median number of sites of metastases was 4 (3-7). Five (62,5%) pts had T ⩾ 10 cm (median T diameter was 11,7 cm). Seven (87,5%) pts had neoplastic thrombosis (6 at diagnosis, 1 during the course of treatment). At diagnosis 5 (62,5%) and 3 (37,5%) pts had an intermediate and poor risk according to the International Metastatic Database Consortium (IMDC) risk model, respectively. Median Neutrophil-to Lymphocyte ratio (NLR) at baseline was 4; an increase in the NLR respect to baseline occured in 5 pts (25%) at the time of disease progression (PD). The best response to ICIs was: PD in 7 pts (87,5%), 4 in IO+IO group and 3 in IO+TKI group; PR in only 1 patient (12,5%). Seven patients (87,5%) received ⩽ 3 cycles of ICIs. Median PFS and OS was 1 and 4 months, respectively. Four (50%) pts (1 in IO+TKI cohort and 3 in IO+IO cohort) received a second-line therapy with TKIs and 2 pts (both in IO+IO cohort) a third-line therapy (TKIs and mTORIs).

Conclusions: Therefore, this subgroup of mRCC pts with metastatic disease at diagnosis or recurrence within 3 months from diagnosis, sarcomatoid and/or rhabdoid differentiation, T⩾ 10 cm, neoplastic thrombosis, may be defined "super-high-risk" pts, characterized by a very poor prognosis despite having received the best treatment available today.

D38

CARBOPLATIN FOLLOWED BY OLAPARIB VERSUS BEVACIZUMAB IN MANTEINANCE THERAPY IN ELDERLY PATIETS WHIT ADVANCED OVARIAN CANCER

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Background: Poly(ADP-ribose) polymerase inhibitor olaparib has shown antitumour activity in patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer with or without BRCA1 or BRCA2 mutations. The aim of our study was to assess the efficacy and tolerability of Carboplatin in single agent therapy, followed by olaparib maintenance monotherapy, versus manteinance therapy bevacizumab in elderly patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer according to BRCA status.

Methods: In our retrospective study, old patients (median age 80) with platinum-sensitive, recurrent, high-grade serous ovarian cancer received carboplatin (area under the curve [AUC] 4 mg/mL per min, according to the Calvert formula, administered intravenously on day 1)followed by olaparib monotherapy (400 mg capsules twice daily, given continuously) or Bevacizumab 15 mg/kv ev on day 1 every 21 days until progression The primary endpoint was progression-free survival.

Findings: Between Feb 17 and July 30, 2021, 17 patients were eligible and were assigned to the two treatment groups (5 to the olaparib group and 12 to the bevacizumab group). BRCA mutation status was known for all patients (either at baseline or determined retrospectively): 5 of 17 had a BRCA mutation Progression-free survival was significantly longer in the olaparib group (median 24.2 months [95% CI 9.7-15.0]) than in the bevacizumab group (median 9.6 months [95% CI 9.1-9.7) (HR 0.51 [95% CI 0.34-0.77]; p=0.0012), especially in patients with BRCA mutations (HR 0.21 [0.08-0.55]; p=0.0015). Adverse events more commonly reported in the olaparib group than in the placebo group (by more than 10% of patients) were nausea (68% vs. 35%), fatigue (49% vs. 38%), vomiting (32% vs. 14%), and anemia (17% vs. 5%); the majority of adverse events were grade 1 or 2.

Interpretation: Carboplatin in monotherapy followed by olaparib in manteinance therapy significantly improved progression-free survival versus bevacizumabl plus carboplatin alone, with the greatest clinical benefit in BRCA-mutated patients, and had an acceptable and manageable toxicity profile.

D39

AN OBSERVATIONAL, MONOCENTRIC, RETROSPECTIVE ANALYSIS OF MEN WITH NEW DIAGNOSIS OF HIGH-RISK METASTATIC CASTRATION NAÏVE PROSTATE CANCER FOLLOWING ABIRATERONE ACETATE PLUS PREDNISONE AND ANDROGEN DEPRIVATION THERAPY

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Background: The milestone of treatment of metastatic castration naïve prostate cancer (mCNPC) is androgen deprivation therapy (ADT). The phase III trials LATITUDE evaluated abiraterone acetate plus prednisone (AAP) and ADT in high risk mCNPC pts showing a longer OS than placebo plus ADT. Our research aims to analyze clinical features and outcomes of men with newly diagnosed mCNPC treated with AAP plus ADT based on results from LATITUDE trial.

Material (patients) and methods: We conducted a monocentric, retrospective collection of data of men with high risk mCNPC that received AAP and ADT at AOU Policlinico of Modena between January 2018 and August 2021 after a special request to NOP (Nucleo Operativo Provinciale) of Emilia Romagna region.

Results: Ten men with high risk mCNPC were included in our analysis. The median age at diagnosis was 71 years (rang 57-75 years). At baseline ECOG performance status was 0 in 7 pts (70%), 2 men (20%) had ECOG PS of 1 and one pts had ECOG PS 2 (10%). PSA level at diagnosis was between 9.76 to 1420 ng/ml. Only one man received radical prostatectomy. Four pts (40%) had a Gleason score (GS) of 8, 5 pts (50%) showed a GS of 9, one man (10%) had a GS of 10. Metastatic localizations were identified with a CT scan of chest and abdomen and a total body bone scan. Two men (20%) showed visceral metastasis (mts), 3 pts (30%) had bone mts alone, 6 pts (60%) had bone and lymph nodes mts. Five pts (50%) had a number of bone mts >= 10. Seven pts (30%) had comorbidities. Seven pts (70%) had hypertension, 2 pts (20%) had hypercholesterolemia, 3 pts (30%) had diabetes. The median observational period was of 13 moths (range 5 - 48 moths). Three pts (30%) accused bone pain with necessity of opioid treatment during AAP. During AAP treatment 7 pts (70%) showed > 50% PSA decline after 4 weeks of treatment ("early PSA responder"). At nadir time PSA level was between 0.01 and 2.77 ng/ml with a median PSA level of 1.39 ng/ml. Pts with visceral mts were included in "early PSA responder". Three pts (30%) discontinued the treatment with AAP and ADT for radiographic progression disease, 7 men (70%) are still receiving AAP with good tolerance. Adverse events occurred in 3 pts (30%). Two pts showed hyperglycemia grading 1 (G1), 1 pt had diarrhea (G1), 1 pt had hypertension (G2) and 1 pt had hypokalemia (G1).

Conclusions: Our analysis suggested that AAP and ADT in mCNPC men was efficacy and safe in real word also in pts with visceral mts and comorbidites.

D40

FIRST LINE TREATMENT WITH CABOZANTINIB FOR PATIENTS WITH INTERMEDIATE OR POOR RISK METASTATIC RENAL CELL CARCINOMA: A MONOCENTRIC RETROSPECTIVE ANALYSIS

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Characteristics (n=12)	Mean or frequency	Range or%
Age, median	71.5	45-79
Histotype		
Clear cell	8	66.6%
Chromophobe	2	16.6%
Mixed clear cell histology	1	8.4%
NAS	1	8.4%
Sarcomatoid features		
Yes	0	0%
No	12	100%
Sex		
Male	10	83.3%
Female	2	16.7%
ECOG PS		
0	5	41.6%
1	7	58.4%
IMDC risk group		
Intermediate	9	75%
Poor	3	25%
Bone metastases		
Yes	3	25%
No	9	75%
Liver metastases		
Yes	4	33.3%
No	8	67.7%
Prior nephrectomy		
Yes	6	50%
No	6	50%

Background: Metastatic renal cell carcinoma (mRCC) is an insidious and incurable disease. Patients with IMDC intermediate and poor risk have an unfavorable prognosis.

In the last few years first line treatment of mRCC has achieved several advances, with the approval of combination therapies with immunocheckpoint inhibitors (ICIs) or ICIs and target-therapies.

However, monotherapy with Cabozantinib (CABO) could still represent a valid treatment option in this setting.

Patients and methods: A retrospective study was performed in patients with mRCC who underwent a first line treatment with CABO at starting dose of 60 mg/die between November 2019 and November 2021 at our Institute. Pts were identified by computerized records and retrospectively analyzed. We evaluated efficacy and safety of this treatment.

Results: We identified 12 pts with mRCC treated with CABO, with a median follow-up of 8.5 months. Pts' baseline characteristics are summarized in Table 1.

Objective response rate (ORR) was 58.3%: 0 pts achieved a complete response, 7/12 (58.3%) a partial response, 4/12 (33.3%) a stable disease, 1 patient (8.4%) progressive disease. Median PFS was 8 months and 6 pts are still on treatment. The median OS was not reached.

The incidence of any grade treatment related adverse event (trAE) was 100%. Grade 3 trAEs were observed in 3/12 pts (25%): asthenia, anorexia and hypertension. No grade 4 trAE or treatment discontinuation because of trAE were observed.

CABO dose reductions (to 40 or 20 mg/die) or schedule modifications (5 days on and 2 days off treatment) occurred in 10/12 pts (83.3%).

Conclusions: In our real-word picture, despite the small size of the sample and the retrospective nature of the study, literature data are confirmed in terms of safety and efficacy and CABO proves to be a useful therapeutic option in this setting, particularly in pts with contraindications to combination therapies.

D41

PEMBROLIZUMAB AS SECOND LINE TREATMENT IN METASTATIC UROTHELIAL CANCER: A MULTICENTER REAL LIFE STUDY

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Background: Checkpoint inhibitors have been approved for the treatment of advanced metastatic urothelial cancer in the second line setting in patient progressed on platinum compounds based chemotherapy. Among Food and Drug Administration (FDA) approved checkpoint inhibitors on urothelial carcinoma (Pembrolizumab Atezolizumab, Nivolumab, Durvalumab, Avelumab) phase III trials suggested better results in favor of Pembrolizumab. On Keynote 045 study Pembrolizumab increased overall survival and was associated with better toxicity profile compared with chemotherapy: the Median overall survival in the total population was 10.3 months (95% confidence interval [CI] 8.0 to 11.8) in Pembrolizumab group compared with 7.4 months (95% CI 6.1to 8.3) in chemotherapy group (HR for death 0.73; 95% CI 0.59 to 0.91; P=0.002). Additional analyses suggested that patients treated with pembrolizumab had a stable or improved global health status/quality of life whereas those treated with investigator's

choice chemotherapy experienced declines in global health status/quality. However it is known that several cancer patients are excluded from randomized clinical trials, above all older patients with ECOG PS>1 or because of comorbidities. The scientific community urgently recommends to verify trials results by mean of real life studies. In addition, high costs of immunotherapy necessitates an assessment of its value by considering both efficacy and costs. The aim of this multicenter retrospective observational study is to evaluate the results in terms of overall survival, disease control rate, progression free survival and toxicity in a real life context.

Methods: In our multicenter retrospective observational study, patients with metastatic urothelial cancer received Pembrolizumab every 21 days until progressive disease or unacceptable toxicity. The primary endpoints were overall survival, disease control rate, progression free survival and toxicity in a real life context.

Findings: At the time of this writing 26 patients were eligible and were enrolled in the study.

Interpretation: Update efficacy and toxicity data with a larger group of enrolled patients and mature data will be available for the AOIM congress.

E - Precision Oncology

E01*

THE ROME TRIAL: UPDATE ANALYSIS OF THE ACTIVITY OF MOLECULAR TUMOR BOARD

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Background: The Rome Trial (MAR-BAS-18-005) is a prospective, randomized, multicenter, Phase II trial (NCT04591431). The aim is to evaluate the efficacy of 2 different strategies: Tailored Therapy (TT) vs Standard of Care (SoC) in patients (pts) with solid tumors. Pts with a molecular alteration potentially targeted by a specific therapy or immunotherapy were discussed in a Molecular Tumor Board (MTB) and possibly randomized to TT vs Soc.

Patients and Methods: Pts with refractory solid tumor were enrolled. Tumor tissue and liquid biopsy specimens were centrally analized with NGS. MTB weekly discussed each case with an actionable genomic alteration. The 3 main outcomes were: A) assignment of a TT and randomization B) screening failure (SF) for inconsistency of targetable alterations C) SF for the trial but with relevant information from the genomic test. Pts with outcome C were divided into 3 groups: 1) indication to receive a personalized standard treatment different from the planned one 2) identification to access to another clinical trial/compassionate use/EAP 3) indication to perform a germline test (GT).

Results: From Oct 2020 to Apr 2022, 794 pts were enrolled from 40 Italian sites and 720 have completed the screening phase. Of them 409 (57%) had relevant genomic alterations and were discussed to the MTB. Tissue and liquid molecular profiling was avalilable in 356 out of 409 (87.0%) pts, while 12 (3.0%) and 41 (10.0%) pts had only tissue or liquid evaluation, respectively. After the MTB discussion (68 weekly meeting) about clinical/molecular exclusion criteria and multiple actionable or resistance mutations: 201 pts (50%) were randomized, 110 pts (26.9%) were considered SF, and 91 (22.3%) were set as SF but with an additional indication. In this group, 17 pts (18.7%) changed standard treatment (group 1) and 46 (50.5%) had indication to receive TT outside the trial (group 2). MTB suggested a GT to 73/409 pts (17.8%, group 3). To date, 10/14 GT performed confirmed a germline mutation. Finally, 292 pts, 72.6% of those discussed to MTB and 40% of the entire population, were randomized or received at least one specific indication following the extended molecular assessment with NGS.

Conclusions: We demonstrate, in the context of a large trial, that a controlled pathway of molecular profiling, discussion in MTB, network of sharing among oncologists, access to clinical studies can substantially modify the treatment strategy in 40% of patients with advanced solid tumors.

E02*

NEXT-GENERATION SEQUENCING (NGS) FOR IDENTIFYING ACTIONABLE MOLECULAR ALTERATIONS IN NEWLY DIAGNOSED AND RECURRENT IDHWT-GLIOBLASTOMA (GBM) PATIENTS: A LARGE MONO INSTITUTIONAL EXPERIENCE

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Background: NGS panels allow the identification of alterations within hundreds of cancer-related genes and can guide a personalized strategy in glioma treatment.

Material (Patients) and Methods: From Nov 2019 to Jan 2022 at Veneto Institute of Oncology, Padova, Italy, a large cohort of IDHwt-GBM tissues was analyzed by NGS (FoundationOne®CDx). We identified all potential actionable molecular alterations at diagnosis and/or at recurrence. High tumor mutational burden (TMB) was defined as =10 mutations/megabase.

Results: We analyzed 429 IDHwt-GBM samples: NGS profile was available for 419 samples (97.7%); sample failures in 10 cases (2.3%). 351 (84%) and 68 (16%) GBM samples derived from surgery at diagnosis and recurrence, respectively. All patients received radiotherapy and/or temozolomide as first line therapy. Among all the analyzed samples, the most frequent actionable molecular alterations were: CDKN2A (57%), CDKN2B (53%), EGFR amplification (39%), EGFR mutation (24%), PTEN loss (27%), RB1 (23%), NF1 (18%), PIK3CA (18%), CDK4 (15%), MDM2 (10%), PDGFRA (8%), BRCA1-2 (7%), FGFR1-3 (7%), Myc (6%), JAK (6%), ROS1 (5%), METmut (2%), METampl (2%), BRAF V600E (2%). No NTRK1/2/3 druggable alterations were observed. High TMB was found in 18 samples.

The incidence of alteration of EGFR (ampl/mut), RB1, PIK3CA was statistically different between the two subgroups of newly diagnosed and relapsed GBM samples (Fisher test).

To date, 10% of patients received a personalized treatment as compassionate use, off-label use or in clinical trials (9 Dabrafenib/Trametinib, 8 Alpelisib, 3 Erdafitinib, 2 Ipatasertib, 1 Alectinib, 1 Capmatinib, 1 Palbociclib, 1 Entrectinib, 1 Pamiparib). Activity analysis is still ongoing.

Conclusions: NGS is feasible in GBM samples. Potentially, a high rate of patients could receive a personalized treatment. The activity analysis is ongoing. However, the incidence of actionable molecular alterations may differ between diagnosis and recurrent GBM samples.

E03*

MOLECULAR CHARACTERIZATION OF EXTRA-PULMONARY, ADVANCED NEUROENDOCRINE CARCINOMAS AND MIXED ADENO-NEUROENDOCRINE CARCINOMAS: THE NIRVANA STUDY

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Background: Extra-pulmonary (EP) poorly differentiated neuroendocrine carcinomas (NECs) and mixed adeno-neuroendocrine carcinomas (MANECs) are rare and aggressive neoplasms with a very poor prognosis. We aim to realize a retrospective - prospective observational database with clinical, pathological, and biomolecular data of patients with advanced EP-NECs and MANECs in order to identify prognostic and predictive factors which could potentially correlate with clinical outcomes.

Methods: We reviewed clinical and pathological data of advanced EP-NECs/MANECs managed at our Institute between 2015 and 2021 with available surgical/biopsy specimens. All the tumor tissues were tested for 26 genes by next-generation sequencing (NGS) using a targeted multigenes NGS panel. Descriptive analyses will be performed. Primary and secondary endpoints are descriptive in nature, therefore no formal statistical hypotheses were pre-specified. The study is approved by IEO Ethical Committee.

Results: Among 55 EP-NECs and MANECs cases, 26 EP-NEC and 7 MANECs resulted eligible. Right colon and rectum were the most frequent primary sites, respectively. Almost all cases showed at least one somatic mutation in > 5% of the tissue. The most frequently mutated genes were TP53 (48%) e KRAS (36%). Other genes, including BRAF, AKT, RB1 and CTNNB1 were mutated in 6% of the cohort, PTEN and PI3K in only 3%. All but one MANECs (86%) showed TP53 mutation in the NEC component and 4 out 7 (57%) MANECs had KRAS mutation on both neuroendocrine and non-neuroendocrine component. The most frequent mutations were observed in the right colon (91% NEC, 9% MANEC), and rectum (33% NEC and 33% MANEC). More than three quarter of the population (76%) received at least one line therapy of chemotherapy, mostly represented by cis/carbo-platinum-based regimens. Among them, (N = 18) 72% received a second-line therapy, mainly

irinotecan-containing. Only one tenth (12%, N = 3) of patients received more 2-line therapy.

Conclusions: Although these data are preliminary, they seem to suggest that the EP-NECs and MANECs carcinogenesis relies on its morphological differentiation, site of origin, and lastly, molecular profile. Specific targetable alterations indicate a high potential for personalized treatments. The study is ongoing and actively recruiting.

E04*

SEQUENTIAL MOLECULAR PROFILING OF ADVANCED THYROID CANCERS FOR PRECISION ONCOLOGY: FLOWCHART FROM AN ITALIAN REFERRAL CENTER

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Background: Standard therapies for patients (pts) with advanced thyroid carcinomas (TC) are limited. In Italy, radio-iodine refractory differentiated papillary (PTC), follicular (FTC) and poorly differentiated TC (PDTC) pts are treated in 1st line with lenvatinib and 2nd line with cabozantinib (L.648/1996). TC harboring BRAF mutation can be tackled by BRAF/MEK inhibitors in managed access program (MAP) or basket clinical trials. Chemotherapy is standard for BRAF wild-type anaplastic TC (ATC). Actionable molecular targets (AMT) may expand the therapeutic options for pts who progress to standard therapy or are not amenable to start it. Several tests are available, with different timings and costs. Considering the most common alterations of TC histotypes, and in light of our preliminary experience, we developed and propose a flowchart to rationalize the sequence of analyses.

Material and methods: Pts with ATC/PTC/PDTC and ECOG PS 0-2, candidate to receive systemic therapy, were tested upfront for BRAF mutation by single-gene analysis (results in 2-3 days); if BRAF was wild-type, a DNA Next Generation Sequencing (NGS) to detect gene mutations was performed (results in 10-14 days); if DNA NGS was negative for AMT, an RNA NGS to detect gene fusions was performed. FTC were tested upfront with DNA NGS.

Results: From January 2020 to April 2022, 91 pts with TC received at least one molecular test: n.60 (65.9%) before 1st line therapy and n.31 (34%) after 1st line. The most frequent alterations were mutations of BRAF (44% - absent in FTC) and NRAS (9.9%), fusions of RET (21.6%) and NTRK (7.3%). Tumor mutational burden (TMB) was assessed in 5 cases and 2 had TMB > 10 Mut/Mb. Overall, 69.2% of this cohort had at least one AMT allowing access to new therapies, ranging from 33.3% (PDTC) to 92.7% (PTC).

Conclusions: Patients with good PS and no access to standard treatments should have the opportunity of being offered molecular analysis to expand their therapeutic options. The choice of the most appropriate tests and sequence is crucial to assure cost-effectiveness and rapid results.

TC	N. P ts offered molecular test	Type of analysis performed		n. Pts with AMT		N. cases that could access to innovative therapies (clinical trials or MAP)
		Mutations (%)	Fusions (%)	Mutations (%)	Fusions (%)	
PTC	41	41 (100)	20 (48.8)	29 (70.7)	10 (50)	38 (92.7)
FTC	14	14 (100)	7 (50)	8 (57.1)	0	7 (50)
PDTC	15	15 (100)	11 (73.3)	5 (33.3)	1 (9)	5 (33.3)
ATC	21	21 (100)	4 (19)	12 (57.1)	0	13 (61.9)
Total	**91**	**91 (100)**	**42 (46.1)**	**54 (59.3)**	**11 (26.1)**	**63 (69.2)**

F - Simultaneous Care

F01*

AN ESTIMATION OF CLINICAL EFFICACY AND SAFETY OF MELANOMA ADJUVANT (ADJ) THERAPIES BY MEANS OF NUMBER NEEDED TO TREAT (NNT) AND NUMBER NEEDED TO HARM (NNH)

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Background: New immunotherapy and targeted therapy options have recently shown significant recurrence-free survival (RFS) improvements when offered to patients (pts) with Stage (St) II-III melanoma in the Adj setting. Our study aims to evaluate anti-PD-1 antibodies and BRAF-MEK inhibitors efficacy and safety in terms of NNT and NNH calculated from respective phase III trials.

Material (patients) and methods: We extracted data from publications of clinical trials evaluating Adj therapies in melanoma versus placebo (KEYNOTE-716 [KN-716], KEYNOTE-054 [KN-054] and COMBI-AD [C-AD]). NNT for RFS was calculated as the reciprocal of the absolute risk reduction, rounded up to the nearest whole number. NNH for grade $\geqslant$ 3 (AEG$\geqslant$3) and grade 5 adverse events (AEG5) was also calculated as the reciprocal of the absolute risk increase, rounded down to the nearest whole number. Estimations were performed in all comers and according to principal clinical subgroups (SG), when feasible.

Results: In KN-716, we obtained a NNT of 12 in the overall population, with lower values in the T3b and T4a SG (respectively 8 and 10, versus 27 [no RFS benefit demonstrated at SG analysis] in T4b); conversely, in KN-054 a NNT of 7 was observed in the overall population, which tended to slightly lower as the St worsened (9 [no RFS benefit demonstrated at SG analysis] in St IIIA, 7 in St IIIB and 6 in St IIIC). A similar trend was noted in C-AD, with NNTs spanning from 7 in St IIIA to 5 in St IIIB and IIIC. In KN-054, NNT kept substantially unchanged according to *BRAF* status (7 for wild-type, 6 for mutated). In C-AD, *BRAF*-mutated pts were only considered, and we calculated a NNT of 6. After SG analysis, NNTs were lower in pts presenting both ulceration and macroscopic lymph node invasion (LNi) (4 in C-AD, 5 in KN-054) as compared to pts with microscopic LNi and no ulceration (7 in C-AD, 9 [no RFS benefit demonstrated at SG analysis] in KN-054). NNH for AEG=3 and AEG5, respectively, was found to be 3 and 435 for C-AD, 7 and 509 (calculated as treatment-related adverse events) for KN-054, 11 and -162 for KN-716.

Conclusions: We provided a simple, but clinically useful insight into efficacy and safety of anti-PD-1 antibodies and BRAF-MEK inhibitors, which generally proved effective and well-tolerated in the Adj setting. Despite study limitations, our results suggest that in some clinical SG the risk-to-benefit ratio may be a little more favorable. These data could aid in the clinical decision-making process.

F02*

SARS-COV-2 OMICRON (B.1.1.529) VARIANT INFECTION LEADS TO HIGH MORBIDITY AND MORTALITY IN UNVACCINATED PATIENTS WITH CANCER

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Background: The Omicron (B.1.1.529) SARS-CoV-2 variant is highly transmissible and escapes vaccinal immunity. Evidence is lacking as to the impact of Omicron in oncological patients.

Methods: Capitalizing on OnCovid study data (NCT04393974), we analysed COVID-19 morbidity and case fatality rate at 28 days (CFR_{28}) of unvaccinated patients across 3 phases defined following the evolution of the pandemic in Europe, according to date of COVID-19 diagnosis: "Pre-vaccination" phase (27/02/2020-30/11/2020), "Alpha-Delta variant" phase (01/12/2020-14/12/2021), "Omicron variant" phase (15/12/2021-31/01/2022).

Findings: By the data lock of 04/02/2022, 3820 patients from 37 institutions across 6 countries were entered. Out of 3473 eligible patients, 2033 (58.6%), 1075 (30.9%) and 365 (10.5%) were diagnosed during the Pre-vaccination,

	Omicron vs Pre-vaccination OR (95%CI)	Omicron vs Alpha-Delta OR (95%CI)
CFR_{28}	0.43 (0.19-0.94)	0.56 (0.25-1.24
Hospitalization	0.30 (0.12-0.72)	1.07 (0.46-2.51)
Oxygen therapy	0.39 (0.18-0.84)	0.77 (0.35-1.66)
COVID-19 complications	0.47 (0.22-1.01)	0.84 (0.39-1.79)

Alpha-Delta and Omicron phases. In total 659 (61.3%) and 42 (11.5%) were unvaccinated in the Alpha-Delta and Omicron. Unvaccinated patients across the Omicron, Alpha-Delta and Pre-vaccination phases experienced similar CFR_{28} (27.5%, 28%, 29%, respectively). Following propensity score matching, 42 unvaccinated Omicron patients were matched with 122 and 121 patients from the Pre-vaccination and Alpha-Delta phases respectively, based on country of origin, sex, age, comorbidity burden, primary tumour, cancer stage and status, and the receipt of systemic anticancer therapy at COVID-19. Unvaccinated Omicron patients experienced improved COVID-19 outcomes in comparison to patients diagnosed during the Pre-vaccination phase. Morbidity and mortality were comparable to those of unvaccinated patients diagnosed during the Alpha-Delta phase.

Interpretation: Despite time-dependent improvements in outcomes reported in the Omicron phase, patients with cancer remain highly vulnerable to SARS-CoV-2 in absence of vaccinal protection. This study provides unequivocal evidence in support of universal vaccination of patients with cancer as a protective measure against morbidity and mortality from COVID-19.

F03*

SIX-MONTH HUMORAL AND CELLULAR IMMUNE RESPONSE TO THE BNT162B2 MRNA COVID-19 VACCINE BOOSTER IN THE PATIENTS WITH SOLID TUMORS ON ACTIVE TREATMENT: FOCUS ON VARIANTS OF CONCERN (VOCS)

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Background: The role and the durability of immunogenicity of the 3rd dose of vaccine against COVID-19 variants of concern (VOCs) in cancer patients remains to be elucidated. The aim of this study is to evaluate the immunogenicity of the 3rd dose of the SARS-CoV-2 BNT162b2 mRNA vaccine in triggering both the humoral and the cell-mediated immune response in the patients with solid tumors undergoing active treatment 6 months after booster

Methods: We have prospectively evaluated kinetics of humoral and cellular immune response elicited by booster BNT162b2 anti-SARS-CoV-2 vaccine dose up to 6 months. Samples were collected at the enrollment (T0), 21 days after the booster (T1) and 6 months after (T2). Sera were tested for Spike trimeric IgG (cut off 33.8 BAU/mL) and SARS-CoV-2 neutralizing antibodies (NT Abs; cut off 1:10), T-cell response against Spike protein was detected by IFNγ release assay (IGRA from Euroimmun).

Results: One-hundred patients (36F/50M; median age 65, range 26-89) were included in the study. In 9 subjects, a COVID-19 infection was reported before the administration of the 1st dose of vaccine. Preliminary analyses were performed in a cohort of 79 previously unexposed subjects. The 3rd dose was administered at median 176 days (range 91-281) after the 1st dose. At T0 anti-S IgG response was median 170 (IQR 67.8-421.4) BAU/mL and it increased to median 2080 (IQR 2080-2080) BAU/mL at T1; a decrease of response was observed at T2 (median 1605 IQR 822-2080 BAU/mL). Overall, 11/79 (13.9%) patients were negative at baseline and 10/11 reached positive level of response at T1. Only 2 subjects were negative for serological response at T2. A similar trend was observed for SARS-CoV-2 NTAbs. In 65 patients we compared NT Abs levels reached against wild type (WT) strain, Delta and Omicron variants at T2. Median response against WT strain was 1:320 (IQR 1:40-1:640) while it decreased to 1:80 (IQR 1:20-1:320) and 1:10 (IQR <1:10-1:40) against Delta and Omicron variants (p value 0.08 and <0.001, respectively). Overall, 4/65 (6.2%) patients were negative for WT SARS-CoV-2 NT Abs while 6/65 (9.2%) and 17/65 (26.2%) were negative for Delta and Omicron SARS-CoV-2 NT Abs, respectively.

Conclusions: Preliminary data suggest an enhanced immunogenicity elicited by booster in cancer patients, also against variant strains, even if a decrease NT Abs level was observed against Omicron. T-cellular response and multivariable analysis on demographic/clinical data will be presented at the meeting.

F04*

SIMULTANEOUS CARE OUTPATIENT CLINIC OF ISTITUTO ONCOLOGICO VENETO (IOV) ESMO-DC: A 7-YEAR EXPERIENCE OF EARLY INTEGRATION BETWEEN ONCOLOGIC TREATMENT AND PALLIATIVE CARE

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Background: Early palliative care has been shown to improve symptoms and quality of life for patients with advanced cancer.

Yet, no optimal and shared model for delivery of early palliative care has been defined. At Istituto Oncologico Veneto (IOV) IRCCS a simultaneous care outpatient clinic (SCOC) has been activated since 2014, in which patients with advanced-stage disease are evaluated by an oncologist together with palliative care team. Patients are referred to the SCOC through a referral form which is scored to prioritize patients' access. We prospectively assessed SCOC patients'characteristics and SCOC outcomes through the internal procedure indicators.

Patients and methods: Patients referred to SCOC by IOV, Oncology Unit 1, after referral form adoption were eligible. Data were retrieved from the SCOC prospectively maintained database.

Results: Eligible patients were 753. Median age was 68 years; 73.6% patients had gastrointestinal cancer, 13.7% had urological cancer and 12.7% had other types of cancer. 90.9% had metastatic disease at the time of the SCOC evaluation. The predominant symptoms were appetite loss (67.5%), psychological disorders (69.4%) and pain (65.9%). Median survival from the SCOC first visit was 7.3 months. The proportion of referred patients with survival <6 months has increased during the years from 40.3% in 2018, to 65.9% in 2021 ($p<0.0001$). Survival estimates by the oncologist at the time the referral form was filled was significantly different from the actual survival. Full awareness of cancer diagnosis was detected in 95.3% of patients, of whom 58.5% had also a full awareness of the prognosis. Psychological intervention was deemed required and undertaken in 34.6% of patients and nutritional support in 37.9% of patients. On the basis of the needs detected by ESAS score, activation of palliative care services was undertaken for 77.7% of patients. After the SCOC visit, 22.6% of patients had unplanned emergency room admissions. Out of 357 patients whose place of death is known, 69.2% died in a proper location (home, hospice and residential care). With regard to indicators' assessment, the threshold was reached for 9 out of 11 parameters requested by procedure.

Conclusions: This study confirms the importance of close collaboration between oncologists and palliative care team to respond to all cancer patients needs. The introduction of a procedure with indicators allowed us to evaluate the performance of the team so as to improve it.

F05*

FINANCIAL DISTRESS AND OUT OF POCKET COSTS FOR CANCER-DIRECTED AND SUPPORTIVE CARE MEDICATIONS AMONG CANCER PATIENTS FROM ITALY: PRELIMINARY DATA FROM A PILOT OBSERVATIONAL STUDY

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Background: Out-of-pocket spending (OOPS) in our country has always represented approximately 20% of the total health expenditure. In the last ten years it has increased to reach 23.7% of the total health expenditure in 2017, alongside the sharing in the expenditure foreseen for many health services, specialist visits and drugs. Due the economic crisis, the share of patient payments in healthcare spending increased from 21% in 2009 to 23.5% in 2017, due to growing cost-sharing obligations for many health services and medicines in different regions.

In Italy, the percentage is clearly above the EU average, equal to 16%, reaching a ceiling of 30% as regards the expenditure for outpatient pharmaceutical products (for drugs not fully covered by the NHS, in the event that tickets are imposed at the level of regional, and in the case of expenses due to the existence of a price difference between the pharmaceutical product purchased and the price of an equivalent cheaper alternative product).

This data is of particular importance for patients who need drugs for the management of symptoms related to burden of disease or indirectly to treatments-related toxicities.

Patients and methods: This is a multicentric observational pilot study among cancer patients to assess the burden of OOPS among cancer patients who require non-cancer drugs to manage disease- or treatments-related symptoms. The COST questionnaire was used to identify financial toxicity and PERSONS score was used to patients' symptom assessment. Financial burden of drugs prescribed for cancer-associated symptoms was also evaluated by specific query.

Study was approved by Central Ethics Committee of Sapienza University of Rome, prot. 79 SA/2022.

Results: At today 87 patients were enrolled in the study. At the time of enrollment 38/87 (44%) were off therapy. 26/87 (30%) declared financial distress > **7** evaluated by NRS scale. 76/87 (**87%**) declared they directly purchases the medications for managing cancer-related symptoms. Mainly purchased drugs were for cancer pain (24%), constipation (17%), nausea and vomiting (15%), fatigue (9%), anorexia/cachexia syndrome (7%). Not all data can be available until the end of the study.

Conclusions: This study highlights the costs of many drugs for symptom control and the total patient burden of purchasing them. This represents a fundamental aspect in the management of financial toxicity and must be regulated by government bodies, scientific societies, and patient advocacies.

F06*

EXTENDED INTERVAL DOSING IN PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITORS: SAFETY ANALYSIS FROM THE MULTICENTRIC INTERNATIONAL EDICI STUDY

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Background: Alternative immune check-point inhibitors (ICIs) regimen schedules, able to offer longer dose intervals, have been catching on in clinical practice due to issues related to healthcare costs and frequency of patients (pts) access to oncology departments. The extended interval dosing (ED) of nivolumab and pembrolizumab was approved based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. We aimed to investigate real-life immune-related adverse events (irAEs) incidence in pts treated with ED-ICIs.

Methods: Clinicopathological and therapeutic characteristics of solid cancer pts treated with ICIs (pembrolizumab, nivolumab) monotherapy who received at least one cycle of the ED (pembrolizumab 400 every 6 weeks or nivolumab 480 mg every 4 weeks) were collected from 37 European Oncological Department.

Results: Among 756 pts enrolled, 733 pts (229 treated with pembrolizumab, 504 with nivolumab) were included in the final safety analysis (median follow up time: 24.7 months). 501 (68%) of the enrolled pts started ICIs with canonical interval dosing (CD, median number of cycles administered: 13) and then switched to ED after a median time interval of 210 days. 197 pts (39%) developed irAEs of any grade and 14 patients (3%) G3/G4 events during CD-ICI; after switching to ED-ICI treatment, which was administered for a median of 7 cycles and 336 days, irAEs of any grade and G3/G4 events were experienced by 155 (36%) and 20 (5%) pts, respectively; 73 (47%) cases of any grade-toxicity and 12 (60%) of G3/G4-toxicity were de novo. 33 (7%) pts switched back to CD, in 45% of the cases due to toxicity. Pts who started upfront with ED (n=232, 32%) were exposed to the drug for a median of 7 cycles; 56 of them (25%) developed irAEs of any grade and 9 (6%) G3/G4 irAEs. Skin (12% of pts), endocrine (11%), rheumatic (10%) and gastrointestinal (9%) were the most common irAEs during ED; 42% were "multiple-site" irAEs, showing no difference with CD ($p = 0.21$). Lower creatinine values before switch to ED (adjusted odds ratio [aOR], 1.24; 95%CI, 1.03-1.48; $P = 0.02$) and previous toxicity during CD (aOR, 1.20; 95%CI, 1.08-1.33; $P < 0.01$) were independent risk factors for development of irAEs during ED.

Conclusions: ED treatment showed similar safety profile compared to CD, confirming ED-ICI as a safe option in clinical practice. Future studies are needed to investigate the efficacy and economic impact of this treatment strategy.

F07

PREDICTORS OF HEALTHCARE NEEDS FOR END-OF-LIFE BREAST CANCER PATIENTS

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Background: Palliative care is considered a mainstay of end-of-life cancer patients and many trials demonstrated its positive impact in terms of quality of life. The present study aims at evaluating healthcare needs and predictors of healthcare need among end-of-life breast cancer patients

Patients and methods: In this mono-institutional study, we reviewed hospital charts of end-of-life breast cancer patients during the last 6 months of life. Breast cancer patients treated at IRCSS Policlinico San Martino and died between 2017 and 2021 were eligible. Objectives of the analysis were to describe care healthcare of breast cancer patients and define predictors of healthcare needs.

Results: We included 121 breast cancer patients. The majority received active treatment in the last six months of life: 75.2% (N=91) received chemotherapy or 45.4% (N=55) hormonal therapy. At least one oncological counselling was undergone by 101 patients (83.5%). On the contrary antalgic, nutritional and psychological evaluations were extremely uncommon (14.0%, 7.4%, 8.3% respectively). Regarding radiological assessments, 81.5% of patients underwent at least one CT scan during the last 6 months of life with a median interval from last CT scan to death of 46 day (range 1-182 days). More than half (52.9%) of the included patients had at least one hospital admission during the last six months of life. The majority of these admissions were at the Oncology Unit. Comorbidities, use of concomitant medications and brain metastases are the factors that influence the majority of healthcare needs. Most of the patients died at home (66.1%) but only 27.3% received palliative home care. Only 10.7% of patients died in Hospice and 18.2% died in hospital.

Conclusions: Our analysis demonstrate that healthcare needs are related not only with the spread of the disease but also with patients' individual characteristics such as comorbidities and medications taken. In our analysis palliative care evaluations seems to be suboptimal in end-of-life breast cancer patients. Moreover, the number of patients that died without the support of home care is considerable and this is confirmed by the number of inappropriate hospital admissions in the last months of life.

F08

PHYSICAL SYMPTOMS AND PSYCHOLOGICAL DISTRESS IN ONCOLOGICAL PATIENTS AND THEIR CAREGIVERS IN EARLY PALLIATIVE CARE

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Background: Oncologic disease is one of the leading causes of death worldwide, with 181,330 deaths per year in Italy. It can negatively affects patients' health on a somatopsychic level: previous studies on oncological patients underlined both somatic symptoms and psychological distress that often compromise their compliance. The NCCN Guidelines define distress as "multifactorial unpleasant experience of a psychological, social, spiritual, and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment". Moreover, the diagnosis can have a great psychological impact also on their family caregivers (FCs), who take charge of the burden of care. The term "burden" defines the degree of impairment that the FC perceives in terms of various domains such as physical and emotional health, social life, and financial status. Literature seems to suggest that early palliative care is one of the best treatments options for cancer patients with a short life expectancy, uncontrollable symptoms, and concerns about the progress of the disease. Thus, the present study aims at evaluating physical symptoms and psychological distress in oncological patients, as well as their FCs' burden.

Material (patients) and methods: From January 2021 to March 2022, 41 oncological patients and 27 FCs were recruited at the Ambulatory of Continuity of Care at the San Giovanni Bosco Hospital in Turin. During the first visit, patients were administered the Integrated Palliative Care Outcome scale (IPOS) whether their FCs were administered the Caregiver Burden Inventory (CBI). Moreover, outpatient nurses administer patients the Distress Thermometer (DT) during their phone weekly follow up.

Results: Oncological patients were mostly males (56.1%), with an average age of 80.3 years (range: 43-93). Lung cancer was the most frequent diagnosis (26.8%). IPOS showed in particular pain (25.2%) and psychological symptoms (21.8%), while the DT underlined a mild level of distress (M = 5.1). For what concerns the caregivers, CBI showed that caregivers needed to be supported in the

experience of care (M = 23.8, DS =± 16.0), and that the 22% of them were at high risk of burnout.

Conclusions: Results are consistent with previous literature, underlining the need for an integrated oncological and psychological care for both patients and their caregivers. The future goal is to conduct further research to develop a model that can be expanded.

F09

SIMULTANEOUS EARLY PALLIATIVE CARE (SC) IN PATIENTS (PTS) TREATED WITH TYROSINE KINASE INHIBITORS (TKI) FOR RENAL CELL CARCINOMA (MRCC)

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Background: SC are activated for non-terminal PTS, in active antiblastic treatment, who also need palliative care to improve the quality of life. SC could help manage the toxicities of oral antiblastic drugs that require home intake.

Material (patients) and methods: We considered PTS treated in first line with TKI for MRCC, to assess whether SC can help to manage the toxicity, to prevent treatment dose reductions or definitive interruption, and to evaluate the reasons for activation of SC in these PTS.

Results: From January 2020 to April 2022, 53 PTS were treated for MRCC, whith TKI on first line.

We activated SC for 13 PTS at first line of treatment (PSC): in 12 for physical reasons (10 tumor related, 2 only age-related frailty) and in 1 patient for psychological reasons.

PSC were predominantly poor risk, non PSC (NPSC) were predominantly intermediate risk:

PSC: 8% good, 38% intermediate, 54% poor;

NPSC: 10% good, 38% intermediate, 54% poor.

TKI treatment was reduced in 29/53 = 54%:

PSC 7/13 = 53%;

NPSC 22/40 = 55%.

First-line treatment was permanently discontinued due to toxicity in 9/53 PTS (17%):

PSC 2/13 = 15%;

NPSC 7/40 = 17%.

Hospitalization due toxicity occurred in 7 patients:

PSC 3/13 = 23% (1 PTS was hospitalized in an emergency room and 2 PTS in non-emergency);

NPSC 4/40 = 10% (all PTS were hospitalized in emergency room).

Conclusions: In our experience for PTS with metastatic renal cell carcinoma we have activated the SC more frequently for patients with poor risk. Activation of the SC does not seem to have influenced the reductions or interruptions of treatment, but in the PSC we had fewer emergency hospitalizations due to toxicity.

F10

EVALUATION OF THE PALLIATIVE PROGNOSTIC INDEX IN CANCER PATIENTS

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Background: The Prediction of survival in patients with locally advanced or metastatic cancer, during palliative treatment or palliative care, is mandatory. The aim of our study was to evaluate the Palliative Prognostic Index (PPI) in the assessment of overall survival (OS) of patients with locally advanced or metastatic cancer.

Methods: This is a retrospective study including patients diagnosed and treated for locally advanced or metastatic cancer at the department of medical oncology in Sfax in 2020. These patients should have a performance status (PS) ⩾2 and poor prognosis (central nervous system cancers (CNS), lung cancer, hepatocarcinoma, oesophageal cancer, pancreatic cancer and gastric cancer).

Results: Thirty patients were included. The median age was 57. Tumour locations were as follows: lung in 40%, CNS in 30%, stomach in 17%, pancreas 7%, oesophagus in 3% and hepatocarcinoma in 3%. The tumour stage was metastatic in 63% of cases. 33% of patients had ⩾3 metastases. Metastatic brain localization was present in 32%. Current treatment was based on palliative chemotherapy in 47% of cases, palliative radiotherapy in 13% of cases and palliative care in 40%. PS 2 represented 83% of cases. The OS estimations using PPI were equal to 90 days 17%, 61 days in 27% and 12 days in 57%. Median real OS was equal to 274 days. The difference was significant comparing the survival estimation using PPI and the real OS (p=0.0001). Subgroup analysis showed a significant difference of the PPI in case of PS⩾3 and metastatic disease.

Conclusions: In contrast to the data of the literature that validated the role of PPI score in the estimation of survival in locally advanced and metastatic cancers, in our study this score seems to underestimate survival in these patients. It may be more suitable to apply it for patients with a PS⩾3 and metastatic stage.

F11

EARLY PALLIATIVE MULTIDISCIPLINARY APPROACH IN HOME CANCER PATIENTS TO IMPROVE THE QUALITY OF LIFE

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Background: The early multidisciplinary approach to the cancer patient at home allows to improve the quality of life by slowing down the anorexic cachexia syndrome and improving cancer pain.

Materials and Methods: We followed the cancer patients of the ROC - oncological network of Campania - through palliative, nutritional, nursing and oncological visits at home. We measured cachexia with MNA, pain with the NRS scale, fatigue with the Vas and Karnofsky PS scale.

The cachectic patients presented an accentuation of neoplastic pain. In advanced cancer patients, immunological function is severely impaired: a deficiency of cell-mediated immunity associated with chronic inflammation coexists with elevated levels of pro-inflammatory cytokines and acute phase inflammatory proteins (fibrinogen and C-reactive protein). These patients received megestrol acetate in 160 mg tablets at high doses (3 per day). At subsequent checks, we found an improvement in appetite and a decrease in fatigue, with an improvement in Karnofsky ps. We also evaluated bowel function in all patients, who used opioids longer than one month, treating OIC(opioid-induced constipation)with a blocker of intestinal opioid μ receptors(PAMORA).

Results: Pain remains a milestone in all stages of cancer, regardless of age or type of cancer, so we treated opioid drugs for ATC (around the clock) and ROO (rapid onset opioid) for BTCP, oral morphine titrated slow-release. Pain assessment and management are particularly essential in palliative care. The anorexia cachexia syndrome causes the discontinuation of antineoplastic therapies. However, we supported with ONS (Oral Nutrition Support) and parenteral nutrition with the Picc nursing team for the home implantation.

Conclusions: The early multidisciplinary approach is optimal for patients included in the territorial home care of the ASL NA1 Center through ROC. It uses of Oncologist, Palliatist, Nutritionist, Nurse, Social Assistant who collaborate to improve QOL.

The Campania Oncology Network (ROC) allowed admission of hospitalized patients directly to discharge in continuity between hospital and territory.

The monitoring of this setting of patients selected for ps Karnofsky min-equal 60 evaluated an improvement in Qol through scales for Nutrition-Sleep Quality-Fatigue and the resumption of active therapies in 60% of cases.

G - Head and Neck Tumours

G01

BIOLOGICAL CHARACTERIZATION BY GENE EXPRESSION (GE) ANALYSIS OF YOUNG PATIENTS (PTS) WITH LOCO-REGIONALLY ADVANCED ORAL CAVITY SQUAMOUS CELL CARCINOMA (OCSCC)

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Background: Loco-regionally advanced OCSCC is a malignant tumor treated with surgery and post-operative (chemo)radiation, mostly occurring in the 5th-6th decades of life. A fraction of OCSCC is diagnosed at younger age, and it is debated whether these pts have different outcomes. The aim of this work is to explore the biological features of young OCSCC pts.

Patients and methods: This is a retrospective analysis of clinical and GE data of stage III-IVa/b (TNM 8th edition) OCSCC pts enrolled in the BD2Decide, an observational study funded by the EU Horizon2020 program [PMID 33107152]. Pts were divided in 2 groups: under 40 ($\leqslant$40 years) vs. over 40 ($\geqslant$41 years). We described their clinical characteristics, survival and 3 GE prognostic signatures (sig) selected through a metagene analysis: immunosuppressive [PMID 34422810]; metabolism-related [PMID 34195087]; 172–gene sig [PMID 24827125].

Results: Out of the 429 OCSCC pts included in the study, 293 were enrolled in 2 Italian centers, and informative GE was available in 246 cases. Clinical characteristics are reported in the table:

	Under 40 (19 pts)	Over 40 (227 pts)	p
Gender			0.34
M	8 (42%)	126 (56%)	
F	11 (58%)	101 (44%)	
PS ECOG			0.69
0	16 (84%)	73 (76%)	
1	3 (16%)	51 (23%)	
2-3	-	3 (1%)	
Smoking			0.23
Current/former	8 (42%)	134 (59%)	
Never	11 (58%)	93 (41%)	
TNM			0.08
III	7 (37%)	44 (19%)	
IVa/b	12 (63%)	183 (81%)	
Treatment modalities			**0.0008**
1	1 (5%)	54 (24%)	
2	5 (26%)	111 (49%)	
3	13 (69%)	62 (27%)	
Survival			**0.03**
2-year OS	82%	66%	0.05
2-year DFS	74%	57%	
Immunosuppressive sig			**0.02**
Low	14 (74%)	28 (12%)	
High	5 (26%)	129 (88%)	
Metabolism-related sig			0.75
Low	17 (89%)	189 (83%)	
High	2 (11%)	38 (17%)	
172-gene sig			0.79
Low	4 (21%)	59 (26%)	
High	15 (79%)	168 (74%)	

At multivariate analysis (OS) including stage, GE sig, gender and age, the first 2 covariates had an independent significance: HR 2.27 (95% CI 1.27-4.08) for stage IV vs III (p=0.006), HR 1.73 (95% CI 1.15-2.6) for high vs low immunosuppressive sig (p=0.008).

Conclusions: Young OCSCC pts received more intensive treatments than elder ones. Their survival was longer, possibly due to lower stage and lower immunosuppressive sig. Despite the low number of cases, our findings suggest an age-related immune suppression profile. Further biological and bioinformatic analyses are ongoing to deeply dissect these differences, that may have a potential therapeutic reflection in the immunotherapy era.

G02

A SINGLE-INSTITUTION PROPOSAL OF MOLECULAR PROFILING IN ADVANCED SALIVARY GLAND CANCERS: WHY, HOW AND WHEN

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Background: Salivary Gland Cancers (SGCs) include more than 20 histotypes classifiable in two macro-categories: adenoid cystic carcinoma (ACC) and non-ACC. Both groups represent two sides of the same coin: an orphan-drug disease. Therefore, the role and the perspectives of molecular profiling (MP) need to be assessed. Here, we report our Institutional proposal and experience of MP in SGCs.

Methods: SGC patients (pts) eligible for MP are those with: ECOG PS 0-2 and life expectancy =/>3 months; metastatic or recurrent disease not amenable to curative loco-regional treatment; histology internally reviewed; no further feasible and/or available therapies. The Institutional proposal of MP in SGCs is dichotomized per ACC and non-ACC. In ACC, cases are upfront tested by FISH MYB/NFIB, MYB and NFIB. In case of any MYB rearrangement, no further step is recommended (ASCO Guidelines, 2021). In case of lack of MYB alterations, each case is discussed at Institutional Molecular Tumor Board to decide whether or not undergoing to MP. In non-ACC, high-grade (HG) tumors are first tested for immunohistochemistry (IHC) of androgen receptors (AR) and HER2; if these IHC tests are negative, a DNA Next Generation Sequencing (NGS) is performed; if DNA NGS is negative, a RNA NGS to detect gene fusions is advised; The low-grade (LG) non-ACC are primarily tested for IHC NTRK 1-2-3. Only if this target is negative, cases undergo to DNA NGS and RNA NGS (the latter only in case of negative DNA NGS). Since Jan 2022, tumor mutational burden (TMB) was added to DNA NGS in HG non-ACC.

Results: From May 2021 to Apr 2022, 28 SGCs pts were considered (9 ACC, 19 non-ACC: 16 HG and 3 LG). Out of 3 ACC without MYB fusions, none of them had a positive MP. Out of 3 LG non-ACC, 2 had undruggable DNA mutations (PTEN, JAK3). In HG non-ACC, the majority (12/16, 75%) had at least one DNA mutation, of which four druggable (4/12 mutated=33.3%; 4/16 profiled=25%) with tipifarnib, ipatasertib and dabrafenib (D) + trametinib (T) for HRAS (2 cases), AKT and BRAF mutations, respectively. Of them, 3 pts started therapy with 2 partial responses (1 on tipifarnib and 1 on D+T) and 1 still ongoing (ipatasertib). In LG non-ACC, IHC NTRK was positive in 1 case without NGS confirmation. In HG non-ACC, no RNA NGS fusions were detected and TMB was high (=/>10 Mut/Mb) in 1 out of 3 cases.

Conclusions: MP of advanced SGCs is suggested, overall in HG tumors of non-ACC cohort, in order to discover further therapeutics opportunities.

G03

VALIDATION OF A PROGNOSTIC NOMOGRAM TO PREDICT PFS IN METASTATIC ADENOID CYSTIC CARCINOMA PATIENTS TREATED WITH LENVATINIB

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Background: Adenoid cystic carcinoma (ACC) is a salivary gland tumor with frequent distant metastases, and slowly growing behavior. Management of metastatic ACC patients (pts) ranges from systemic active treatments that may include lenvatinib or a wait-and-see approach. In this scenario, survival predictors would be extremely useful to guide a better informed choice. To predict metastatic ACC pts overall survival (OS), we developed and externally validated a prognostic nomogram with easily retrievable clinical data [*Cavalieri S et al. EJC 2020*]: gender, disease-free interval, presence of lung, liver and bone metastases. However, we lack data on the applicability of this nomogram in prediction outcome in presence of systemic treatments.

Patients and methods: According to our clinical prognostic nomogram, 3-year OS (measured from the onset of metastatic disease) is >75% in pts with score<80 (low risk, LR) vs. <75% in those with score⩾80 (high risk, HR). To predict PFS of metastatic ACC pts treated with lenvatinib we retrospectively applied our nomogram in pts enrolled in a phase 2 study conducted at our Institution, and previously published [*Locati LD et al. Cancer 2020*].

Results: Out of the 28 pts included in the trial, 26 had metastatic disease: 10 LR, 16 HR (median age 57 vs. 55 years, respectively; p=0.711). Median PFS was 9.1 months, as already reported in the study paper. Six-month PFS was 61.5% in the whole study population: 50% in HR vs. 80% in LR (p=0.056). Median OS was not reached. Further details are reported in the following table (p = 0.056, log-rank test):

Group	Median PFS (95% CI)	6-month PFS
LR	14.34 (3.85-35.95)	80%
HR	6.83 (4.44-10.13)	50%

Conclusions: This post-hoc analysis data showed a trend towards better survival for LR vs. HR pts. The worse PFS of HR pts (50%) vs. the one observed in the unselected cohort (61.5%) confirms the predictive ability of our nomogram suggesting that HR ACC pts need to be promptly treated. On the other hand, we cannot make general conclusions on the LR population since it is possible that the 6m-PFS observed in 80% of the LR group could be owed to the good prognosis of their disease independently of the drug antitumor effect. In this scenario we may argue that LR pts may safely undergo a wait and see approach without undermining outcomes. In conclusion, these results show that the clinical prognostic nomogram may help clinicians to guide their everyday decision making in the management of metastatic ACC pts.

G04

THE EFFECT OF PREBIOTIC INULIN ON PATIENTS (PTS) AFFECTED BY RECURRENT METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA (R/M HNSCC) TREATED WITH IMMUNE CHECKPOINT INHIBITORS (ICIS): THE PRINCESS STUDY

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Background: Several studies demonstrated that gut microbiome (GM) confers either resistance or sensitivity to ICIs. In recent years ICIs (nivolumab and pembrolizumab +/- chemotherapy) showed a positive clinical effect in R/M HNSCC, even if with a marginal impact on response rate and overall survival. Modulation of GM might improve activity of ICIs. Inulin, a mixture of polymers and oligomers prebiotic composed of fructosyl units, may modulate GM.

Materials and Methods: PRINCESS is a non-pharmacological, open-label prospective observational trial designed

to characterize inulin effects on GM, circulating cytokines and immune cells in pts affected by R/M HNSCC treated with ICIs +/- chemotherapy. The study is designed to analyze the longitudinal changes of circulating cytokines and GM during treatment. Data from Nivactor study will be used as comparator (ECHNO/ICHNO 2021 Abstr P89). Eligible pts are older than 18 years, have ECOG 0-1, and no previous or current exposure to ICIs. Enrolled pts receive oral inulin (5-10 g daily) and ICIs (i.e. nivolumab 240 q14 or pembrolizumab 200 q21 +/- chemotherapy) according to approved indications. Stools and blood samples are collected at scheduled time points: baseline (T0); every two months up to 4 times maximum (T1,T2,T3,T4); progression (TPD). Responses are assessed according to RECIST Criteria (version 1.1). A panel of 17 cytokines (ccl2, ccl4, ccl22, cxcl10, IL-2, IL12, IL-15, IFN-y, TNF-a, IL-4, IL-5, IL-6, IL8, IL-10, IL-13, VEGF, TGF beta) will be analyzed at each time point. No "a priori" sample size and statistical power calculation is performed due to the exploratory nature of the study.

Results: Between November 2021 and April 2022 10 pts have been enrolled and 8 completed the first re-evaluation. Among them, reduction of clinically evaluable disease was observed in all pts and was radiologically confirmed in 3 pts. All the pts reported improvement of well-being. No unexpected side effects have been recorded. The study will be updated at the meeting, including cytokine analysis presently in progress.

Conclusions: With the limits of a preliminary report, inulin did not induce unexpected side effects in pts treated with ICIs +/- chemotherapy. A self-reported improvement of well-being was recorded in all pts at the first re-evaluation (two months). Clinical up-date and preliminary analysis of circulating cytokines will be presented at the meeting.

G05

SAFETY AND EFFICACY OUTCOMES IN HEAD AND NECK CANCER (HNC) PATIENTS (PTS) TREATED WITH FIRST-LINE (1L) PEMBROLIZUMAB (P), ALONE OR WITH CHEMOTHERAPY (CT)

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Background: P±CT has become the standard of care for 1L treatment in pts with PD-L1 positive HNC, according to Keynote 048 (KN048) trial results. Only few data are available about predictive/prognostic factors and real-life outcomes.

Material and methods: We retrospectively analysed a series of HNC pts in 1L treatment with P±CT in 3 Italian Oncology Units. We performed a Kaplan-Meier analysis for median progression-free survival (mPFS), analysed the incidence of adverse events (AEs) and evaluated the correlation of baseline inflammatory (IS) markers and body-mass index (BMI) with best response (BR) achieved and safety.

Results: We evaluated 36 pts with at least 3 months of follow-up: tumor primary sites were oral cavity (22%), oropharynx (42%), larynx (28%) and hypopharynx (8%). 44% had PD-L1 CPS=20 and 56% had CPS<20; 11 pts received P alone, 25 received P+CT. In global population (GP) mPFS was 3.3 months (m), with no substantial differences in the subgroup analysis (CPS≥20 vs <20 = 3.3m vs 3.8m; P vs P+CT = 3.8m vs 3.3m). ORR in GP was 33.3% (P vs P+CT = 33.3% vs 36.4%). Incidence of AEs of any grade in GP was 86.1%, with AEs≥G3 of 38.9%. P pts experienced less AEs≥G3 in comparison with P+CT pts (27.3% vs 44%). Younger age was associated with AEs≥G3 in both the P pts and P+CT pts. Neither baseline BMI nor principal IS biomarkers (neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, white blood-cells count, platelets and eosinophils count) were correlated with best response to treatments.

Conclusions: In this real-world series, we identified PD-L1 CPS distribution like that of the KN048 trial. With the limitation of low numbers, we were not able to detect differences in mPFS and ORR between P and P+CT. Younger pts experienced more treatment-related AEs. Prospective collection of larger sound clinical data from real-world series are eagerly awaited.

G06

PEMBROLIZUMAB ALONE OR WITH CHEMOTHERAPY FOR RECURRENT OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (R/M HNSCC): A SINGLE INSTITUTIONAL RETROSPECTIVE REPORT

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Background: First-line (1L) immunotherapy (IO) has improved outcomes in patients (pts) with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) in clinical trial and is now routinely used alone

or combined with chemotherapy. Although efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy have been established in the phase III KEYNOTE-048 trial, little is known about their performance in real-world setting.

Material and methods: We aimed to characterize real-world outcomes for pts with R/M HNSCC treated with 1L pembrolizumab monotherapy and pembrolizumab plus chemotherapy from December 2020 at University Hospital of Modena. Index data was defined as date of 1L treatment initiation; data cut-off date was April 30, 2022.

Results: The overall cohort include 15 pts. The median age was 64 years, all pts were male and the majority of them had a smoking history (11, 73%). Most of pts had a primary cancer in oral cavity (5, 33%) or oropharynx (6, 40%). The majority of pts had the disease recurrence within two years from the primary treatment and 5 pts (33%) were pretreated with platinum in curative or adjuvant setting. Most of pts (11, 73%) had metastatic disease, while 4 pts (27%) had only recurrent disease. Regardless PD-L1 expression,10 pts (67%) had PD-L1 CPS 1-19 and 5 pts (33%) PD-L1 CPS =20. Only 2 pts (13%) received pembrolizumab monotherapy, while most of pts (13, 87%) was treated with pembrolizumab plus chemotherapy. Median follow-up was 13 months (1-22); overall survival (OS) rate at 6 and 12 months were 26% and 7%, respectively. The overall response rate (ORR) was 12.5%, while the disease control rate (DCR) at 8 weeks was 50%. Best overall response (BOR) was partial response in 2 pts (13%), stable disease in 6 (40%) and progression disease in 7 pts (47%). No complete response has been observed in this court of pts. Among pts with PD-L1 CPS $\geqslant$20 DCR at 8 weeks was 80%. The most common adverse events were chemotherapy-related, such as anaemia (9, 60%), neutropenia (5, 35%) and mucosal inflammation (5, 35%), while only 2 pts (13%) experienced immune-related toxicities.

Conclusions: Survival estimates were generally lower than those reported in pivotal clinical trial. These findings indicate that there remains room for improvement of real-world survival outcomes in pts with R/M HNSCC who receive pembrolizumab and pembrolizumab plus chemotherapy and for identification of subgroups of pts not benefitting from IO-based regimens.

G07

HEAD AND NECK MULTIPLE PRIMARY CARCINOMAS AND BIOMARKER PROFILING: SEARCHING TUMOR IDENTITY CARD

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Background: Head and Neck cancers are a very particular family of tumors. Despite many strong treatment options, about 50% will recur within 2 years or, in a smaller percentage in less than 6 months. In approximately 30% of patients these tumors present with synchronous or metachronous multiples, so called multiple primary tumors (MPT). Aim of the project is to study the molecular and genetic characteristics that best identify prognostic or predictive profiles of response to systemic treatments.

Patients and methods: All patients treated from our oncology unit from 2019 with relapsed, locally advanced or metastatic HNSCC is being enrolling. Each patient undergoes blood sampling for liquid biopsy for NGS analysis before starting first line treatment. Data are studied by analyzing correlations with patient's histological and clinical aspect

Results: Nowadays we have studied 11 patients with MPT. All of them had different mutations in potentially target genes. We found a total of 27 variants in 19 different genes. The most frequently mutated genes were TP53 (6 patients), MET, APC, Her-2 (2 patients).

Conclusions: These results indicate that in patients with MPT, liquid biopsy represents an opportunity to identify potential therapeutic targets. Performing it at diagnosis gives you time to evaluate these possibilities and in the future it probably could replace endoscopy and radiological exams, identifying a new tumor in advance and in less-invasive way. Performing it at diagnosis of whatever HNSCC can potentially signal patients who are most at risk of presenting MPT.

H - Melanoma and Skin Cancers

H01

METABOLOMIC PROFILE OF PATIENTS WITH METASTATIC MELANOMA (MM) TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background: Checkpoint inhibitors immunotherapy (CII) has significantly improved the treatment landscape for MM with a significant proportion of them obtaining long-lasting and deep responses. Despite these results, over half of patients present primary or acquired resistance to treatment. Among the currently unmet needs, there is a lack of predictive biomarkers able to identify non-responders or patients at high risk of recurrence. Recently metabolomics analysis has demonstrated important applications in the medical field for diagnostic and prognostic purposes. Our first aim was to develop a metabolomic-based model able to predict clinical outcomes in CII-treated MMs.

Patients and methods: We analysed 71 serum samples from MM patients treated with anti-PD1 (43 as first-line) from 2017 to 2021. Samples were cryopreserved at the Institutional Biobank of IRCCS-Istituto Tumori in Bari and then analysed by 1HNMR at CERM – University of Florence. The metabolomic fingerprint and profile of patients was then related to clinical outcomes. Main characteristics included: cutaneous melanoma 80%, LDH<ULN 55%, M1c stage 32.4%, median age: 61 years (31-92), median ECOG: 0 (0-2). State-of-the-art Random Forest (RF) analyses were performed to classify patients accordingly to their survival outcomes. In detail, patients have been stratified by median overall survival (OS) and progression free survival (PFS).

Results: The best overall response rate (BORR) including complete/partial response and stable disease lasting more than 6 months, was 33.8%. The median PFS was 3 (95%CI: 3-5)) months, and the median OS was 14 (95%CI:7-37) months. RF analyses applied to serum metabolomic fingerprints from whole NMR spectra showed good performances, with accuracies reaching 72.6%, both for discriminating patients stratified for median OS and PFS. A preliminary analysis in the sub-group treated with ICI as first line (median PFS: 4 months, 95%CI: 3-10) has been also performed. The accuracy of RF model reached 66.7%, a very promising result considering the small sample size.

Conclusions: The preliminary results confirmed the hypothesis that there is a metabolic fingerprint associated to the outcome in patients treated with CII. Further, the metabolomic profile could be useful to identify biomarkers able to predict the survival outcome. However, in the next step we will focus on the best predictors to gain an easy-to-use tool to be routinely available in the clinical practice.

H02

PATTERNS OF RESPONSE TO/PROGRESSION AFTER FIRST-LINE (1L) TREATMENT WITH DABRAFENIB (D) AND TRAMETINIB (T) IN PATIENTS (PTS) WITH UNRESECTABLE/METASTATIC BRAF V600-MUTANT MELANOMA: FINAL ANALYSIS FROM THE T-WIN STUDY

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Background: D+T combination therapy is one of the recommended options in 1L treatment for pts with *BRAF* V600-mutant metastatic melanoma. However, limited data are available on the patterns of

disease progression and the impact of the D+T combination on the clinical outcomes of subsequent treatment lines in a real-world setting.

Methods: This multicenter, prospective, non-interventional study was conducted in pts with BRAF V600-mutant unresectable/metastatic melanoma with either limited (cohort A: lactate dehydrogenase [LDH] = upper limit of normal [ULN]) or bulky (cohort B: LDH >ULN) disease burden treated with D+T in routine clinical practice. Patterns of response/progression based on the number of metastatic sites, time to develop new metastases, ECOG PS, and the potential clinical biomarkers associated with tumor response or progression, following 1L and 2L treatment, were evaluated.

Results: At the data cut-off (August 31, 2021), of the 205 pts enrolled, 201 (cohort A, n=104; cohort B, n=97; median age, 63 y) were evaluable. At baseline visit, 14 (13.5%) pts in cohort A and 37 (38.1%) pts in cohort B had metastatic brain lesions; 99 (95.2%) and 82 (84.5%) pts had ECOG PS =1 in cohorts A and B, respectively. The median time to develop subsequent new metastases was 19 mo (95% CI, 12.5-38.5) and 13 mo (9.9-23.3) in cohorts A and B, respectively. The median progression-free survival with 1L D+T was 12.4 mo (10.9-17.0) and 8.1 mo (6.3-9.4), and the median overall survival was 32.4 mo (20.1-NE) and 10.5 mo (8.3-14.4) in cohorts A and B, respectively. The objective response rate was 70.2% in cohort A and 49.5% in cohort B. Any-grade adverse events (AEs) were observed in 93 (89.4%) and 78 (80.4%) pts in cohorts A and B, respectively. Pyrexia was the most common AE in both cohorts (A: 58 [55.8%]; B: 42 [43.3%]), but typically low grade. Treatment-related AEs were observed in 70 (67.3%) and 60 (57.7%) pts in cohorts A and B, respectively. No new safety signals were observed.

Conclusions: These data are concordant with the efficacy and safety of D+T observed in the pivotal phase 3 clinical trials and extend them to a real-world heterogeneous patient population. Of note, this patient population had high tumor burden, including those with brain metastases and ECOG PS >1, who are commonly associated with poor prognosis and excluded from phase 3 trials, supporting the use of this combination in routine clinical practice for patients with BRAF-mutant metastatic melanoma.

H03

LATE TOXICITIES AND LONG TERM BENEFIT OF CEMIPLIMAB IN ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA: UPDATE OF A REAL-WORLD STUDY

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Background: In 2018 Cemiplimab was approved for patients with advanced cutaneous squamous cell carcinoma (cSCC). Our group has already reported results from a real-world experience of 18 Italian centers, that showed acute toxicity profile and overall responses similar to clinical trials.

Materials and methods: We analysed the long-term follow up of the 134 patients previously included in the multicenter retrospective, observational study REAL CEMI. We have collected data concerning late toxicities rate, considering treatment-related adverse events (trAEs) that occurred after at least 6 months since cemiplimab start, the updated objective response rate (ORR) and disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). We analysed correlations between clinical outcomes and baseline clinical-pathological characteristics, and we described patients who obtained a complete response (CR).

Results: At the data cut-off (31 January 2022) median follow up was 14 months (range 1-32), and cemiplimab was ongoing in 29 patients (21,6%). Median duration of treatment was 7 months (1-29+). 11,2% of patients had a late trAEs, of grade (G) 1/2 in 73,3% of cases. Median time to trAEs' onset was 12 months. Two patients stopped cemiplimab due to a late adverse event (G3 maculopapular rash pemphigoid-like and G3 nausea and vomiting). Updated ORR was 58,9% and DCR was 72,4%. Median PFS was 9 (95% confidence interval (CI) 2.45-15.55) months and median OS was 21 (95% CI 9.41-32.59) months. In the multivariate analysis, the best response obtained, and Performance Status were found to be significantly related to both PFS and OS, while chronic intake of steroids was only related to PFS. Twenty-six (19,4%) patients obtained a CR. Median time to CR was 4 months (1-23) and median duration of treatment after obtaining CR was 8 months (0-35+); at the data cut-off, 19 (73,1%) patients had stopped treatment with cemiplimab, and all these patients had ongoing complete response.

Conclusions: Real-world data at a longer follow up confirm the activity of cemiplimab. We showed a relatively

low late toxicities rate; however, some trAEs may occur even after several months from the start of cemiplimab treatment. Patients who obtained a complete response often maintain it for long time despite cemiplimab discontinuation.

H04

AGE AND PHARMACOTHERAPY AS PREDICTOR OF OUTCOME IN METASTATIC MELANOMA TREATED WITH FIRST LINE TARGET THERAPY

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Background: Elderly patients represent a peculiar setting for cancer therapy, with specific characteristics mostly in terms of comorbidities and concomitant therapies. Therefore, the optimal therapeutic strategy for elderly patients represents an intriguing clinical challenge. In pivotal clinical trials older patients are underrepresented but real-world data showed that outcomes are similar to that of the younger ones. A relationship between concomitant therapies and BRAF+MEK inhibitors was never evaluated as well as the attrition rate toward subsequent lines in this setting.

Material and methods: We evaluated retrospectively in a cohort of metastatic melanoma patients treated at our center with approved first line BRAF+MEK inhibitor combinations how age and concomitant medications might influence clinical outcomes and subsequent melanoma specific treatments. We performed a Kernel distribution to confirm the distribution of age in our sample. Kaplan Maier function was used to describe overall survival (OS) and progression free survival (PFS). Cox regression was used to evaluate difference in OS and PFS based on age groups ($<$ or $>$ of 70 years old) and pharmacotherapy (proton pump inhibitors, steroids, beta-blockers). X-square test was used to compare attrition rate (defined as the proportion of patients that didn't receive a second line therapy, if indicated) by the age group.

Results: We analyzed data from 76 consecutive patients. Median age at start of therapy was 61.5 years with a right skew deviation in the age distribution. 24 (31.5%) of patients were older than 70 years and 6(7.8%) older than 80 years old. Global median PFS and OS were 20.9 months (range 0.4-98.2) and 30.6 months (range 0.4-98.2) respectively. There wasn't difference in PFS and OS between age groups (p=0.23 and p=0.24). Use of steroids in combination with PPI was associated with a worse OS (p=0.085) but use of steroids or PPI alone doesn't impact outcome. Attrition rate in the global population was 43%, but it was sharply different between age groups (27% vs 56%, p = 0,08).

Conclusions: In the analyzed cohort age nor concomitant therapies did not influence clinical outcomes. In regard of subsequent melanoma specific therapies older patients seemed to have a higher attrition rate compared to younger population. This data confirm that target therapy is a safe and effective strategy also in older patients prompting future studies to identify the tailored first line in this frailer population.

H05

MICROSATELLITE INSTABILITY (MSI) IN METASTATIC MELANOMA: AN OBSERVATIONAL AND RETROSPECTIVE STUDY

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Background: Mismatch repair deficit (dMMR) and microsatellite instability (MSI) have been reported in skin melanoma and are thought to be a progression dependent phenomenon seen in thicker primary lesions and metastases. Few studies on frequency, predictive and prognostic value of MSI in melanoma are available, in particular using the pentaplex panel of markers approved for colon cancer. The primary aim of this study was to provide a descriptive analysis on the presence of MSI in distant melanoma metastases, regardless of BRAF status and type of first-line treatment.

Matherial and methods: We retrospectively reviewed a consecutive series of patients with stage IV melanoma, treated from January 2011 to December 2018 at the Academic Hospital of Udine, Italy, and for which archival tumor tissue of the metastases was available. MSI was

evaluated with the pentaplex panel of mononucleotides markers (NR-27, NR-21, NR-24, BAT-25, and BAT-26), choosing the sample temporally closest to the beginning of first-line treatment. The study protocol was approved by the Friuli-Venezia Giulia Region Ethical Committee (protocol number 0025936), and written informed consent for analysis on the archival tissue was obtained from all living patients.

Results: A total of 90 patients were enrolled. They were mostly males (63.3%) and 82 out of 90 (91.1%) had metastatic tissue suitable for microsatellite analysis. Of note, 18 patients had *de novo* metastatic disease and the remaining developed metastases during the study period. In particular, 18.9%, 15.6%, 41.1% and 24.4% were stage M1a, M1b, M1c and M1d, respectively. Median age at the beginning of first-line treatment was 68 (range 30-87). BRAF V600 mutation was seen in 40 out of 90 cases and LDH value was above the upper normal limit in 28.9%. The most frequent sites of metastases were: skin and subcutaneous tissue (30.0%), lymph nodes (28.9%), lung (17.8%), liver (6.7%), central nervous system (5.6%), other sites (11.0%). Microsatellite Stable (MSS) status was detected in 81 out of 82 (98.8%) samples.

Conclusions: This retrospective and observational study shows a very low frequency of MSI (1.2%) in metastatic melanoma samples. Nonetheless, further research is needed in order to identify the possible predictive and prognostic role of MSI in metastatic melanoma.

H06

RETROSPECTIVE-PROSPECTIVE OBSERVATIONAL STUDY OF ITALIAN PATIENTS TREATED IN MELANOMA ADJUVANT COHORT MAP TO EVALUATE RELAPSE FREE SURVIVAL AND OVERALL SURVIVAL – MADAM (MAXIMING ADJUVANT MAP) STUDY

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Background: Adjuvant therapy has shown improvement in the outcome of patients with resected stage III melanoma, reducing the risk of recurrence by elimination of residual disease after surgery. Since receiving approval from European Medicines Agency (EMA) in 2018, dabrafenib + trametinib (D+T) has been the only targeted therapy available for adjuvant systemic treatment in patients affected by BRAF V600 mutant melanoma. However, the benefit of adjuvant systemic therapy against its potential toxicity is still a point of debate, particularly in patients with stage IIIA disease and lymph node maximum diameter of the largest lesion (MDLL) $<$ 1mm. These patients are often excluded from phase 3 clinical trials and, up to date, real-world data that might support the use of targeted therapies in this setting of diseases are lacking.

Methods: This multicenter, retrospective-prospective, non-interventional study aims to include the patients treated with at least one dose of D+T within the melanoma adjuvant managed access program (MAP CDRB436F2001CM) running in Italy from June 2018 to December 2019. Data from patients providing informed consent and meeting eligibility criteria will be collected according to clinical practice for 5 years starting from the time of completion/discontinuation of adjuvant D+T treatment for any reason. The primary endpoint of the study is to evaluate Relapse Free Survival (RFS) and Overall Survival (OS) of the patients that received the treatment with D+T while the secondary endpoint is to describe the pattern of disease relapse and the treatment received at disease relapse or discontinuation of previous treatment line.

Results: The study is currently enrolling, with an estimated target of 460 patients to be included in the study by the end of December 2022.

Conclusions: The MADAM study will investigate the characteristics and outcomes of patients that received the adjuvant treatment in the MAP cohort. Moreover, it will provide an overview of the current clinical practice in the management of stage III melanoma patients harboring BRAF V600 mutation as well as the treatment strategy adopted in first line metastatic patients who experiment progression of disease after receiving adjuvant treatment. This real-world evidence will support the clinical practice and further consolidate the data already available from phase 3 clinical trials in order to define the best therapeutic algorithm for BRAF mutated melanoma patients.

H07

CEMIPLIMAB IN CUTANEOUS SQUAMOUS CELL CARCINOMA (CSCC)

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Squamous cell carcinoma (cSCC) is the second most common non-melanoma skin cancer. It originates from epidermal keratinocytes or adnexal structures (such as eccrine glands or pilosebaceus units). Most cSCC are successfully treated by surgery, but local and distant metastasis develop in approximately 5% of cases; this proportion is higher in certain forms of cSCC with high risk factors: poor differentiation, tumor size $>$ 2 cm, depth $>$ 2 mm, Clark level

>=IV, immunosuppression, perineural or lynphovascular invasions, inadequate tumor resection, UV radiation, cronic viral carriage and high risk anatomic location (labial mucosa, pinna of the ear). Furthermore multiple studies confirm that even well-differentiated and small tumor (< 2 cm) may metastasize.

Treatment includes surgical excision, radiotherapy and systemic therapy. No systemic chemotherapy have been approved for the treatment of advanced cutaneous squamous cell carcinoma. This cancer may be responsive to immune therapy, because the mutation burden of the tumor is high and the disease risk is strongly associated with immunosuppression.

Cemiplimab belongs to a class of drugs that binds to the programmed death receptor-1 (PD-1), blocking the PD-1/PD-L1 pathway.

We report our experience with Cemiplimab in patients with locally advanced or metastatic cutaneous squamous cell carcinoma. Cemiplimab induced a response rate in approximately half the patients (47%) and was associated with adverse events that usually occur with immune checkpoint inhibitors (anemia, diarrhea and fatigue). No life threatening event occurred. No grade 3-4 toxicities were observed.

Cemiplimab is effective and well tolerated, and may prolog survival with a relatively good quality of life in patients with SCC of the skin.

M - Brain Tumours

M01

THE GENETIC PROFILE OF PRIMARY AND RECURRENT GLIOMAS: A MONO INSTITUTIONAL EXPERIENCE USING NEXT-GENERATION SEQUENCING

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Background: The use of next-generation sequencing (NGS) tests is currently increasing in neuro-oncology, to identify alterations of cancer-related genes and establish a better personalized glioma treatment. However, the genetic profile may change during glioma progression. Here we analyzed the difference between matched primary and recurrent gliomas by extensive NGS.

Methods: From Nov 2019 to Jan 2022, at Veneto Institute of Oncology in Padua, we collected glioma FFPE blocks at initial surgery and at recurrence. NGS was performed using FoundationOne®CDx assay.

Results: We identified a dataset of 46 tumor samples from 23 pts who underwent surgery at diagnosis and at first-recurrence surgery [16 M, 7 F, median age: 54 y (34-71)]. According to WHO 2021 classification, samples were classified into: 1) IDH-wildtype glioblastoma (GBM) (n=36); 2) IDH-mutant astrocytoma (n=2 Grade 2, n=5 G3 and n=1 G4); 3) IDH-mutant and 1p/19q co-deleted oligodendroglioma (n=1 G2, n=1 G3). In 3 pts an evolution to higher histological grade was detected at recurrent. All pts received temozolomide with or without radiotherapy after the first surgery. Median OS was 24.4 months (10.5-181). NGS was successfully performed in 44/46 gliomas, while data were not reported due to sample failure in 2 cases, both among first resections.

Recurrent gliomas exhibited de novo mutations in 7 pts: TP53 (4/23; 17.4%), PTEN loss (4/23; 17.4%) and NF1 alterations (6/23; 26%). Alterations such as TERT promoter mutation (18/21), CDKN2A (14/21) CDKN2B (12/21) loss, MTAP loss (6/21), BRCA2 mutation (4/21) and PIK3CA mutation (2/21) were early events observed in initial samples, maintained at recurrence; 2 and 4 pts have lost CDKN2A loss and EGFR mutation/amplification/fusion, respectively, during progression.

In one GBM, a BRCA2 germline mutation (Q2354*) was recognized; another GBM pt had a conserved BRAF V600E somatic mutation; both pts benefited from target therapy as a consequence of NGS. Median tumor mutational burden (TMB) was 1.68 (0-6.30) and 14.9 (0-129.8) mutations/megabase in initial and subsequent resection, respectively.

Conclusions: By extensive NGS, we observed 3 "de novo" gene alterations in 7 (30.4%) recurrent tumor patients; 6 (26%) patients showed lost of genetic alterations during progression. High TMB in second samples is consistent with reports of treatment-induced hypermutagenesis. We showed that NGS should be performed both at diagnosis and at relapse.

M02

PROGNOSTIC ROLE OF IMMUNE INFILTRATE MARKERS IN GLIOBLASTOMA PATIENTS UNDERGOING CONCOMITANT RADIO-CHEMOTHERAPY (STUPP)

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Background: Glioblastoma (GBM) is the most aggressive brain tumor with a median overall survival (OS) of less than 15 months. GBM is characterized by a strong immunosuppressive tumor microenvironment (TME), mainly consisting of tumor associated macrophages (TAMs), and of a variable degree of tumor infiltrating lymphocytes (TILs), whose prognostic role is not yet fully clarified. We previously reported a better outcome in GBM patients, treated with Stupp regimen, who had a systemic inflammatory index (SII) <480 (2019_TMJA_Supplemento AIOMXXI). In this study, we aimed to investigate the prognostic role of selected TME infiltrating immune cells and their correlation with SII in a retrospective cohort of GBM patients.

Material and methods: In 16 GBM patients treated with Stupp regimen, selected TME immune markers were assessed at baseline by immunohistochemistry using the VENTANA BenchMark Ultra. The following markers were investigated by monoclonal antibodies (Ab): CD3, CD4, CD8, CD20, CD45, CD68, CD163, CD66b and PDL-1 on formalin fixed paraffin embedded patient's tissues. Expression values were classified according to special Score from 0 to 4. The tissue distribution and intensity was recorded to evaluate biomarker positivity in two tumoral area: Vascular (V) and diffuse in tumor parenchyma (D).

Results: Regarding overall survival analyses, we considered each immune-component in V and D area to understand its possible relation and we reported in Table 1 the most significant. Considering a ratio CD8/CD163: pts with SII>480 had a higher presence of M2-tissues infiltrate (CD163) and pts with SII<480 higher level of TIL (CD8) but had not statistical significant impact on outcome.

Conclusions: Our results suggest a potential prognostic role of CD3D, CD68V-D in GBM patients. Despite the limited series, a trend in relation between SII and different TME infiltrating immune cells was found. Further studies are needed in large series to explore the prognostic role of selected TME immune molecules in GBM patients.

Table 1. Overall surivival in immuno markers.

Variables	N° PT	N. Death	Median OS (95%CI)	p- value (log-rank test)
All pts	16	16	14.4 (10.7-18.1)	-
CD3 V				
Score 0-1	9	9	14.7 (5.8-21.7)	0.458
Score 2-4	7	7	14.1 (8.9-17.4)	
CD3 D				
Score 0-1	9	9	18.1 (5.8-22.1)	0.007
Score 2-4	7	7	12.7 (8.9-14.7)	
CD68 V				
Score 0-2	9	9	18.1 (9.8-22.1)	0.009
Score 3-4	7	7	12.7 (5.8-14.7)	
CD68 D				
Score 0-2	8	8	17.4 (14.1-22.1)	0.025
Score 3-4	8	8	10.7 (5.8-15.5)	

M03

CORRELATION BETWEEN THYROID FUNCTION AND REGORAFENIB ACTIVITY IN RECURRENT IDH WILD-TYPE(IDHWT) GLIOBLASTOMA(GBM) PATIENTS: A LARGE MONOCENTRIC STUDY

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Introduction: GBM is the most frequent CNS malignant tumor, with high aggressiveness and poor prognosis. Regorafenib demonstrated promising activity in terms of survival in recurrent glioblastoma patients. The impact of thyroid function on regorafenib activity has alreasy described in other tumors types. This study aimed to investigate the relationship between baseline thyroid variables (TSH, fT3, fT4, fT3/fT4 ratio) and survival in IDHwt GBM patients treated with regorafenib.

Methods: We retrospectively evaluated all consecutive recurrent IDHwt GBM patients treated with regorafenib at the Veneto Institute of Oncology in Padua for which

baseline thyroid function assessment was available prior to starting regorafenib. Major inclusion criteria were: histological diagnosis of IDHwt glioblastoma, regorafenib as second-line treatment, basel thyroid values available. The relationships between baseline thyroid variables and outcomes (PFS, OS) were investigated with Cox regression models, where thyroid variables were modeled with first order polynomial or restricted cubic splines.

Results: We enrolled 108 recurrent IDHwt glioblastoma patients treated with regorafenib at our center From November2015 to January2022:70% were male and median age was 50yo. All patients received post-surgical treatment with concomitant radiochemotherapy as first-line therapy. From starting regorafenib the median follow-up was 7.3 months(IQR4.0-12.7). MedianPFS was 2.2months(95%CI2.0to3.4), and PFS rate was 43-13-4% at 3-6-12ms, respectively. MedianOS was 10.4 months(95%CI7.5to14.5), and OS rate was 92-70-46% at 3-6-12ms, respectively. Disease Control Rate was 42.7%. Univariate analysis suggested that the relationship between PFS and baseline fT4 may be modelled with first order polynomial(linear term p=0.06/non-linear term p=0.61) and also suggested a non-linear relationship between PFS and baseline fT3/fT4(linear term p=0.06/non-linear term p=0.04).When adjusting for major clinical confounding factors(age, ECOG PS, second surgery, MGMT) multivariate analysis identified that baseline fT4(as a continuous variable) is an independent risk factor for PFS(HR1.09,95%CI1.02to1.17;p=0.02). We did not find any statistically significant associations between all baseline thyroid variables with OS and response.

Conclusions: Our study demonstrated fT4 value to be a predictive biomarker of PFS in recurrent glioblastoma patients treated with regorafenib. No correlation was showed between baseline thyroid function and survival.

M04

DIFFERENT DOSAGE OF BEVACIZUMAB TREATMENT IN RECURRENT IDHWT GLIOBLASTOMA/IDHMUT GRADE 4 ASTROCYTOMA AND ITS IMPACT ON OUTCOME

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Background: Angiogenesis is one of the most distinctive hallmarks of glioblastoma (GBM).Although bevacizumab did not show to improve OS in phase-3 trials, it was approved by FDA and is often prescribed as off-label therapy in the recurrent clinical setting.The aim of this study is to evaluate the difference in terms of survival and safety between the 5mg/m2 and 10mg/m2 schedule in recurrent GBM.

Methods: All pts treated at Veneto Institute of Oncology from May 2013 to March 2022 were retrospectively reviewed. Major inclusion criteria were:histologically confirmed diagnosis of IDHwt GBM/IDHmut grade4 astrocytoma,relapse after first or subsequent line of therapy,treatment with bevacizumab at 5mg/m2 or/and 10mg/m2 at physician's discretion every 2 weeks.

Results: 81 pts were enrolled. mFollow-up was 10.9ms [95% CI 9.8-14.0] and mAge was 53ys (range 18-81).33pts (41%) received the 5mg/m2 schedule.Among them,2 (6%) were IDHmut grade4, 8 (24%) had =65ys and ECOG-PS was 0-1 in 16 (48%) and =2 in 17 (51%) respectively. MGMT was methylated in 15 of 30 (50%) evaluable pts. mNumber of prior lines of treatment was 2 (range 1-4) and 30% of pts received bevacizumab at first recurrence. 28pts (84%) were evaluable for response:7 (21%) and 5 (15%) showed PR and SD. 48pts received the 10mg/m2 schedule: 5 (10%) were IDHmut grade4;29 (60%) had an ECOG-PS of 0 or 1 and 4 (8%) had >=65ys, MGMT was methylated in 20 of 44 (45%) evaluable pts. 36pts (75%) received bevacizumab beyond the second line of therapy. 46pts (96%) were evaluable for response: 6 (12%) had PR, 19 (39%) SD. mOS from the bevacizumab start was 7.3ms (95% CI 4.3-6.4), mPFS was 4.4ms [95% CI 3.7–6.4]. At univariate analysis, pts who received the 5mg/m2 or the 10mg/m2 schedule had a mOS of 5.4 and 7.7ms (p=0.08); mOS for pts with ECOG-PS < or =2 was 9.0 and 5.4ms (p=0.04) while mOS for pts with <2 or =2 lines of therapy was 4.7 and 7.7ms (p=0.056). Age and type of tumor were not significant. At multivariate analysis, MGMTmet status was the only factor associated with OS (HR=0.48,95% CI,p=0.002) and PFS (HR=0.33,95% CI,p=0.001),while a number of prior lines of therapy ⩾2 (HR=2.07,95% CI,p=0.02) was associated only with PFS. Grade 3-4 most common adverse events were hypertension (18%) in pts treated with 5mg/m2 and hypertension (16%) and proteinuria (2%) in pts treated with 10mg/m2.

Conclusions: Bevacizumab at 5mg/m2 and 10mg/m2 seems to give comparable outcome in terms of survival in recurrent GBM. No difference was demonstrated for safety.

M05

BEVACIZUMAB IN ATYPICAL AND ANAPLASTIC MENINGIOMAS: A MONO-CENTRIC EXPERIENCE

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Background: meningiomas are the most frequent primary brain tumours. Despite the high rate of relapse after surgical resection and radiotherapy no systemic treatment is indicated. Few data are available regarding the effectiveness of bevacizumab (BEV) in this setting. We performed a retrospective analysis investigating the efficacy and safety of BEV in meningioma patients relapsed after receiving surgery and radiotherapy. Gene mutations were also collected

Material and methods: we analyzed pts treated with off-label BEV from Jul 2019 to Feb 2022. Inclusion criteria were diagnosis of grade 2-3 meningioma, previous treatment with surgery and radiotherapy, no indication to further surgery or reirradiation, absence of contraindications to the use of BEV. Data were estrapolated from clinical records. BEV was administered until progressive disease, death, unacceptable toxicity. Kaplan-Meier curves were used to estimate the survival rate; CTCAE v 5.0 was used to estimate toxicities; RANO criteria were used for radiological assessment; Foundation One panel was used for molecular data

Results: median follow up was 13 months (3-30 range). 26 pts were enrolled. Median age was 68 ys (29-84); male pts were 16 (61%);61% (16 pts) with atypical meningioma, 38.5% (10 pts) with anaplastic meningioma; 27% (7 pts) underwent 2 or more surgeries; 58% had 2 or more RT treatments; 96.1% (25 pts) received <2 previous lines of systemic treatment. 77% (20 pts) and 23% (6) received BEV 10 and 5mg/Kg q2w, respectively. For 61% of patients (16 pts), NGS analyses were available; 62% (10 pts) had NF2 mutations (1 pt had a confirmed diagnosis of neurofibromatosis type 2), 23% (6 pts) CDKN2A/2B deletion, 11% (3 pts) PTEN mutation, 8% (2 pts) FGFR mutation, 8% (2 pts) JAK alteration. OS rate was 82% and 62% at 6 and 12 months respectively; 6 months PFS rate was 83%. 4 pts showed PR, 11 SD, 6 PD, no pt had CR; 5 pts were not evaluable for response. The DCR was 71% and the ORR was 19%. Median PFS and OS were not reached. 19% (5 pts) experienced CTCAE grade 1 or 2 toxicity, mainly hypertension (4 pts).

Conclusions: BEV showed promising activity in recurrent meningioma. The treatment was well tolerated. BEV should be considered an optimal therapeutic option in this setting. The NGS results might be useful in identifying targetable mutations in case of further recurrence

M06

THE ROLE OF MOLECULAR BIOMARKERS OF BRAIN TUMORS IN SYMPTOMATIC TUMOR-RELATED EPILEPSY. A PRELIMINARY STUDY ON 151 CASES

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Background: The annual incidence of malignant brain tumors is 7.08 per 100,000 inhabitants in Italy and epilepsy is one of the most common presenting symptoms. Patients with brain tumor-related epilepsy (BTRE) suffer from two challenging pathologies simultaneously: glioma and epilepsy. The pathogenesis of brain tumor-related epilepsy (BTRE) is not fully described. The integration of molecular data and histology changed the diagnostic approach and prognostic characterization for patients with brain tumors. Further studies are needed to demonstrate a possible correlation between molecular patterns and epilepsy. The aim of this study is to explore the associations between histo-molecular data and epilepsy features, in a group of patients suffering from brain tumors.

Methods: A retrospective cohort of 151 consecutive glioma patients (males 93, mean age: 57 ± 8,48) was evaluated at our hospital, with 66 (43.7%) suffering from BTRE. The association between tumor features (tumor location, histopathological subtype, synaptophysin and GFAP expression, ATRX, p53 and IDH status, ki67 index, MGMT gene promoter methylation and 19/19q status) and epilepsy features (seizures' type and clinical characteristics) were examined by Pearson's chi-squared test. Survival data were analyzed by applying Kaplan-Meier curves and Cox proportional hazards models. All the statistical analyses were performed by R-3.4.1 software.

Results: Negative synaptophysin was significantly associated with the presence of epilepsy ($p<0.05$). There was no significant association between MGMT methylation, ATRX and1p/19q deletion and the presence of epilepsy. Progression-free survival (PFS) and overall survival (OS) were significantly associated with well-known prognostic and diagnostic molecular markers, such as IDH, 1p/19q and MGMT as expected from literature data. Moreover, it

was found that patients with no epilepsy had worse OS (HR 1.86; p=0.052).

Conclusions: In the present study we identified no statistically significant relationship between epilepsy and the main brain tumor molecular markes. Our results suggest that the lack of expression of synaptophysin, may be implicated in epileptogenesis. Moreover, in our sample the presence of epilepsy tended to be associated with a better prognosis. More studies will be needed in the future to confirm the role of molecular markers in BTRE.

N - Neuroendocrine Tumours

N01

DEVELOPMENT OF ANTI-SOMATOSTATIN RECEPTORS CAR T CELLS FOR TREATMENT OF NEUROENDOCRINE TUMORS

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Background: Neuroendocrine tumors (NETs) overexpress somatostatin receptors (SSTRs).

Methods: We developed and patented a second-generation, ligand-based, anti-SSTR chimeric antigen receptor (CAR) incorporating the somatostatin analog octreotide in its extracellular moiety.

Results: Anti-SSTR CAR T cells exerted antitumor activity against SSTR+ NET cell lines in vitro. The killing activity was highly specific, as demonstrated by the lack of CAR T cell reactivity against NET cells engineered to express mutated variants of SSTR2/5 by CRISPR/Cas9. When adoptively transferred in NSG mice, anti-SSTR CAR T cells induced significant antitumor activity against human NET xenografts. Although anti-SSTR CAR T cells could recognize the murine SSTRs as shown by their killing ability against murine NET cells, no obvious deleterious effects on SSTR-expressing organs such as the brain or the pancreas were observed in mice.

Conclusions: Taken together, our results establish anti-SSTR CAR T cells as a potential candidate for early phase clinical investigations in patients with NETs. More broadly, the demonstration that a known peptide drug can direct CAR T cell targeting may streamline the potential utility of multiple peptide motifs and provide a blueprint for therapeutic applications in a variety of cancers.

N02

VENOUS AND ARTERIAL THROMBOEMBOLISM IN PATIENTS WITH PANCREATIC NEUROENDOCRINE NEOPLASMS

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Background: venous thromboembolism (VTE), including deep-vein thrombosis (DVT), pulmonary embolism (PE) and visceral vein thrombosis (VVT) and arterial thromboembolism (AT) are leading causes of morbidity and death in cancer. The incidence of VTE is increased in several cancers as well as during cytotoxic chemotherapy or targeted agents. Pancreatic ductal adenocarcinoma is highly associated with VTE, however limited evidence is present about the thrombotic risk for pancreatic neuroendocrine neoplasms (pan-NENs). Neuroendocrine neoplasms are divided into well-differentiated neuroendocrine tumors (NETs), further classified in low (G1), intermediate (G2) and high-grade (G3) and poorly differentiated neuroendocrine carcinomas (NECs). The main aim of our study was to identify the rate of VTE and AT in the specific context of pancreatic neuroendocrine neoplasm and the differences, if any, between NETs and NECs.

Methods: we conducted a retrospective study on histologically confirmed pancreatic neuroendocrine neoplasm (any grade, any stage) evaluated and managed at our Institution from 2018 to 2021. We collected demographical information, medical history, tumor characteristics and VTE or AT events experienced after cancer diagnosis (within 1 months before the diagnosis).

Results: we included 250 patients (52.5% male) with a median age of 52 years (23 - 87). The overwhelming majority (90.4%) were NETs, but than 20% of the cases were high-grade tumors (NEC and NET G3). Nearly 75% of the total were stage IV. Somatostatin analogues and chemotherapy were the most common treatments, even though one quarter of patients were not receiving any systemic treatment. Totally, 35 patients experienced VTE (14.0%), with 17 DVT, 8 PE and 10 VVT. Twenty-nine events were detected in low grade tumors (16.2% of the total), while 6 in high grade ones. At the time of VTE, 14 patients were on chemotherapy (40%), 11 on TKIs (31.5%) and 5 without any active treatment (14.3%). Thirteen patients had a medical history of arterial thromboembolism (5.2%), but only 2 events occurred after cancer diagnosis.

Conclusions: VTE occurred in around one sixth of patient with pan-NENs, a rate similar to other high-risk malignancies.

The rate was greater in low grade NETs compared to NEC, even though this population was much more represented. Further studies are warranted to highlight high-risk subgroups of NEN, in order to identify patients potentially deserving routinely assessment and thromboprophylaxis.

N03

ANALYSIS OF CTDNA IN PATIENTS WITH PANCREATIC NEUROENDOCRINE TUMORS

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Background: Circulating tumor DNA (ctDNA) constitutes a promising, minimally invasive biomarker with many potential applications in patients' diagnosis, prognosis and follow-up. It is currently unknown whether ctDNA can be useful in the diagnosis, prognosis and follow-up of pancreatic neuroendocrine tumors (panNETs). Here, we aimed at 1) evaluating the presence of ctDNA in patients with panNETs; 2) assessing the degree of concordance in terms of mutational signature between FFPE material and ctDNA in patients with panNETs; 3) evaluating the impact of ctDNA on the prognosis of panNET patients.

Material and Methods: Consecutive patients with any stage well-differentiated panNETs have been included in this study. After extraction from FFPE surgical specimens or biopsies (>80% of tumor cells), the tumor DNA has been subjected to targeted sequencing using a panel comprising 19 genes frequently altered during panNET tumorigenesis (MEN1, DAXX, ATRX, PTEN, PIK3CA, TSC2, TP53, CDC42BPB, DST, DEPDC5, KLF7, BCOR, PRRC2A, URGCP, ARID1A, ZNF292, DIS3L2, MLL3, and SETD2). CtDNA was extracted from blood using standard procedures and was then analyzed by ddPCR. Primers and probes were designed according to the mutated sequences detected by NGS analysis in FFPE samples.

Results: We enrolled 29 patients with a median age of 64 years (M:F ratio: 1.4; G1/G2: 80%; stage IV: 52%; surgical sample: 59%; bioptic sample: 41%). Gene mutations were detected in 19/29 FFPE samples. The corresponding mutation was found in ctDNA in 16/19 cases. A very high concordance between the allele frequency detected by NGS on FFPE material and the fractional abundance detected by ddPCR on the ctDNA (r=0.89; p=0.0003, 95% CI, 0.62-0.97) was observed, suggesting that ctDNA could be used as a surrogate of tissue for molecular characterization. A trend towards worse prognosis could be seen in patients from whom ctDNA was isolated as compared with those with unmeasurable ctDNA (p=0.1).

Conclusions: CtDNA can be detected in patients with panNETs and can be used as a surrogate of tissue for tumor molecular characterization. Longitudinal monitoring of ctDNA may improve our ability to stratify responses to treatment and tailor therapeutic interventions.

P - Sarcomas

P01

ROLE OF GERIATRIC ASSESSMENT AND ONCOLOGICAL MULTIDIMENSIONAL PROGNOSTIC INDEX (ONCO-MPI) IN OLDER PATIENTS (AGE >=70 YEARS) WITH ADVANCED SOFT TISSUE SARCOMA IN A REAL-WORLD SETTING

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Background: Incidence of soft tissue sarcomas (STS) increases with age. Yet, older patients (pts) are underrepresented in STS clinical trials and evidence-based guidelines for chemotherapy are lacking. International oncological societies suggest using geriatric tools to evaluate older pts with cancer to optimize treatment. Comprehensive Geriatric Assessment (CGA) is a multidimensional assessment of older subjects, based on which pts can be classified as fit, vulnerable or frail. OncoMPI is a CGA-based score which also considers tumour characteristics, classifying pts in high-risk, intermediate-risk, low-risk group.

Material and methods: Consecutive pts with metastatic STS (mSTS) aged ⩾70 years treated at Istituto Oncologico Veneto from January 2009 to June 2020 were retrieved from a prospectively maintained database. Pts' demographics, CGA and tumor characteristics were analysed. Overall survival (OS) was calculated from diagnosis of metastatic disease to death for any cause. Kaplan-Meier curves and a Cox proportional hazards model were used to perform survival analyses. Statistical analysis was performed with R version 3.4.3.

Results: Out of 101 pts, median age 77 years, 76 received chemotherapy (75.3%), which was anthracycline-based for 46 pts (60.5%). Anthracyclines were used in a significantly higher proportion in fit pts (58.9% fit Vs 45.1%

vulnerable Vs 12.5% frail pts). Frail pts and pts in OncoMPI high-risk group experienced higher rate of chemotherapy-related toxicities. Median OS was 13.8 months (95% CI 11.3-17.7 months). According to CGA, mOS was 19.53 months (95% CI 15.23-36-8) for fit pts, 12.83 months (95% CI 9.7-17.5) for vulnerable and 7.75 months (95% CI 2.73-30) for frail pts (p=0.005). OncoMPI confirmed a predictive value for 1-year survival with intermediate risk pts not reaching mOS at 1 year, and high-risk pts having median-1 year OS of 11.5 months (95%CI 9.7-NA), p=0.02. In multivariate analysis, oncoMPI and CGA were associated with survival (high risk oncoMPI: HR 5.5, 95%CI 1.25-24.7 p=0.02; fitness at CGA HR 0,552 95% 0,314-0,973; p=0.040) as well as chemotherapy use (HR 0.24, 95% CI 0.11-0.51, p<0.005).

Conclusions: Both CGA and oncoMPI retain prognostic value for survival in mSTS. Our data show OS survival figures for fit pts comparable to younger adults. Pts frail/vulnerable at CGA and pts within the oncoMPI high risk category should be offered an oncogeriatric management approach in order to optimize survival and reduce toxicity.

P02

UPDATE OF CLINICAL OUTCOMES OF SUNITINIB (SU) FOR PATIENTS (PTS) WITH DESMOID TUMORS (DT)

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Background: The incidence of DT is steadily increasing in pts affected by familial adenomatous polyposis (FAP) and represents the first cause of death for pts who underwent preventive proctocolectomy. Currently, there is no standard therapy for DT and Tamoxifen (20 mg once daily) + Meloxicam (15 mg once daily) (TM) is the most commonly used regimen in clinical routine. We sought to evaluate the efficacy of Su, the most active PDGFR TKI, as 1st line therapy for pts with DT.

Methods: In this phase II IRB approved prospective study, pts with progressive, symptomatic, or recurrent DT were randomized to receive either Su (52 mg once daily) or TM. The primary end point was progression-free survival, defined as time from treatment start to clinical or radiological progression, whichever came first, at 2 years (2yr-PFS). Secondary endpoints were rates of objective response (OR), evaluated per RECIST criteria version 1.1, time to OR (ttOR), and toxicity. Adverse events (AE) were assessed per NCI-CTCAE version 4.02.

Results: Of the 42 pts enrolled, 22 received Su and 20 TM. In both groups, median age at diagnosis was 43.5 years No OR was observed in the TM group. In the Su group, 7 pts had a partial response and 5 stable disease and the ORR was 75% (95% CI, 50 to 100). At a median follow-up of 27 months, the 2yr-PFS was 81% (95% CI, 69-96) and 36% (95% CI, 22-57) in the Su cohort and TM cohort, respectively (HR = 0.13; 95% CI, 0.05- 0.31; P<0.001). The median ttOR among pts who had an OR was 24 months. In the TM group, no toxicity was observed. The most frequently reported AE in the Su group were grade 1 or 2 hypothyroidism (73%), fatigue (67%), hypertension (55%), and diarrhea (51%). (HR: 0.260; p = 0.0035). All AE responded to dose reduction (37.5 mg).

Conclusions: In a cohort of pts with progressive, recurrent, or symptomatic DT, Su seems to be well tolerated and improve 2yr-PFS and OR rate compared with TM therapy. Further prospective studies with larger samples are needed to verify these results.

P03

GIANT CELL TUMORS OF THE BONE: FROM BENIGN TO MALIGNANT. ARE WE STILL IN TIME?

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Background: Giant cell tumor of bone (GCTB) is benign, locally aggressive primary bone neoplasm (5% of all bone tumours). Uncommonly, GCTB undergoes sarcomatous transformation into a malignant tumor (4% of all GCTB).

Material (patients) and methods: Retrospective analysis was carried out on patients (pts) with GCTB diagnosed and treated at Regina Elena National Cancer Institute in Rome, from February 2005 to December 2021. Clinical data and treatment outcomes were extracted from clinical records.

Results: A total of 101 pts with central confirmed diagnosis of GCTB were analyzed (female/male 56%/44%; median age: 36 years (yrs), range: 11-88 yrs). 3 out of 101 patients (3%) went through histologically confirmed malignant transformation: pt 1 female, 20 yrs, site of disease (SoD): femoral head; pt 2 female, 29 yrs, SoD: distal femur; pt 3 male, 48 yrs, SoD: proximal tibia. All 3 patients underwent surgical curettage after primary diagnosis of GCTB. In pt 2 and 3, a recurrence was documented and a treatment with denosumab was administered for about 4 months. Suspicion of malignant transformation emerged from radiological presence of specific findings in CT and MRI exams, highlighted by the presence of cortical permeation associated with soft-tissue mass that reflect aggressive behavior of disease. Appearance of suspicious lesions was evaluated by biopsy or resection. In all 3 cases, histological examination showed different morphological features from the primary neoplasm, with proliferation of atypical cells and no evidence of giant cells, deposing for malignant transformation of GCTB in osteosarcoma. Time from GCTB diagnosis to malignant transformation was 9 months for both pt 1 and 2, 50 months for pt 3. First 2 patients died 5 and 43 months after malignant transformation, respectively, despite aggressive chemotherapy. Quickly understanding of radiological changes in pt 3 and histological confirmation of malignant transformation allowed us to treat him surgically and with adjuvant chemotherapy. At the last follow-up, he was still negative for local relapse or metastases.

Conclusions: In conclusion, history of GCTB malignant transformation is unclear and unpredictable. Nevertheless, an accurate imaging could highlight suspicious lesions with aggressive findings that could justify a needle core biopsy to detect early malignant transformation. For this reason, even the rarity of this event, a strict follow up is recommended.

R - Covid-19

R01

THE IMPACT OF COVID-19 ON DELAYING DIAGNOSTIC-THERAPEUTIC PATHWAYS OF ENDOMETRIAL CANCER PATIENTS: THE ITALIAN REAL-WORLD SCENARIO

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Background: Coronavirus disease 2019 (COVID-19) outbreak has correlated with the disruption of screening activities and diagnostic assessments. Endometrial cancer (EC) is one of the most common gynecological malignancies and it is often detected at an early stage, because it frequently produces symptoms. Here, we aim to investigate the impact of COVID-19 outbreak on patterns of presentation and treatment of EC patients.

Materials and Methods: This is a retrospective study involving 54 centers in Italy. We evaluated patterns of presentation and treatment of EC patients before (period 1: March 1, 2019 to February 29, 2020) and during (period 2: April 1, 2020 to March 31, 2021) the COVID-19 outbreak.

Results: Charts of 5,164 EC patients were retrieved. Overall, 2,718 and 2,446 women with EC received treatment in period 1 and 2, respectively. The prevalence of patients aged $>$ 65 years was similar between the 2 study periods (1,400 [51.5%] in period 1 vs. 1,248 [51.0%]; p=0.726). Considering data on the histological characterization, the prevalence of endometrioid FIGO grade 1, 2, and 3 was consistent over the study period (p=0.855). However, the prevalence of non-endometrioid EC was lower in period 1 than in period 2 (15.6% vs. 17.9%; p=0.032). Surgery was the mainstay of treatment before and during the COVID-19 pandemic. Overall, 2,539 and 2,286 women received surgery in period 1 and 2, respectively (93.4% vs. 93.5%; p=0.948). Primary conservative attempts (i.e., progesterone-based therapy) was performed in 72 (2.7%) and 56 (2.3%) patients in period 1 and 2, respectively (p=0.406). The adoption of minimally invasive surgery was consistent in the two study periods (p=0.976). Overall, 1,280 (50.4%) and 1,021 (44.7%) patients had no adjuvant therapy in period 1 and 2, respectively ($p<0.001$). The adoption of vaginal brachytherapy as adjuvant treatment remained stable in the study periods (11.9% vs. 11.1%; p=0.325). Adjuvant therapies indication has increased during the COVID-19 pandemic ($p<0.001$). In particular, the use of adjuvant radiotherapy (26.8% vs. 30.7%; p=0.001) and chemotherapy (25.1% vs. 30.1%; $p<0.001$) alone or in combination increased from period 1 to 2.

Conclusions: Our data suggest that the COVID-19 pandemic had a significant impact on the characteristics and patterns of care of EC patients. These findings highlight the need to implement healthcare services during the pandemic.

R02

THE INCIDENCE OF CANCER AT THE TIME OF COVID IN NORTHERN ITALY

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Background: Recent studies have assessed the impact of the COVID-19 pandemic and related control measures on the number of new cancer diagnoses. The aim of this work was to evaluate the real impact of the lockdown on new cancer diagnoses in 2020.

Material and methods: To compare the incidence of tumors in 2020 with that in 2019, we used data collected by the Reggio Emilia Cancer Registry. We reported the variations (number of cases and% values) of all tumors and of the main sites by sex and period of lockdown. We calculated the standardized incidence and mortality rate of the last twenty years (2001-2020) for all tumor sites and the main sites (breast, colorectal, lung and prostate) by sex.

Results: In 2020, 4,031 cases of cancer were recorded, 669 fewer than in 2019 (-14.2%). The sites that recorded the largest decline compared to 2019 were: skin (non-melanoma) (-281 cases), prostate (-110 cases), melanoma and bladder (-53 cases) and colorectal (-38 cases). The incidence trend in males decreased from 491.74 cases per 100,000 p/y in 2001 to 471.58 in 2019 and dropped to 386.59 in 2020. Mortality also decreased over the years from 250.8 cases per 100,000 p/y in 2001 to 164.4 cases in 2019 and 161.9 in 2020. In women, the incidence remained almost constant over the years, whereas there was a decline in mortality. The decrease in cancers recorded, especially during the lockdown, has been widely reported in the literature, but the data usually only cover the months leading up to September 2020.

Conclusions: The COVID-19 pandemic has caused delays in the diagnosis of new cancers. However, it is necessary to document with data the real impact the pandemic has had on new diagnoses, taking into account the tumor site, gender, the presence of cancer screening, and in general the organization of healthcare of the territory in question.

R03

THE IMPACT OF COVID-19 ON BREAST CANCER NEWLY DIAGNOSES AND SURVIVAL: REAL WORLD DATA FROM 12912 CASES

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Background: Studies evaluating COVID-19 in cancer patients beyond the effects of the infection itself are generally from single institutions, voluntary surveillance registries, or

Table. Number of cases by main cancer sites and year of diagnosis 2019-2020.

Site	Year		Difference 2020 vs 2019	
	2019	2020		
	n.	n.	n.	%
Stomach	124	102	–22	–17.7
Colorectal	325	287	–38	–11.7
Liver	77	77	0	0.0
Pancreas	152	143	–9	–5.9
Lung and other thoracic organs	397	370	–27	–6.8
Skin, melanoma	212	159	–53	–25.0
Skin, non–melanoma	1133	852	–281	–24.8
Breast	509	524	15	2.9
Cervix uteri	12	18	6	50.0
Corpus uteri	100	69	–31	–31.0
Ovary	49	53	4	8.2
Prostate	387	277	–110	–28.4
Testicle and other genitals	22	19	–3	–13.6
Bladder (malignant and non–malignant)	248	195	–53	–21.4
Kidney and urinary duct	117	107	–10	–8.5
Brain (malignant and non–malignant)	132	111	–21	–15.9
Thyroid	110	97	–13	–11.8
Non–Hodgkin Lymphoma	146	120	–26	–17.8

surveys. To extend the limited evidence available, we analyzed both the incidence and one-year mortality of breast cancer (BC) female patients at a population level in Lombardy, the first Italian region affected by the pandemic and the most populous one.

Methods: The regional COVID-19 database, including all SARS-CoV2 cases based on a positive swab result, was integrated with the Regional Health Information System, collecting data from 10 million habitants on primary medical care; hospitalization; pharmaceuticals; and survival status. From the database, we extracted data of newly-diagnosed not previously treated BC patients, including patient characteristics and comorbidities (respiratory insufficiency, diabetes, chronic kidney disease, cerebral vasculopathy, hypertension and cardiovascular disease), BC stage, and treatment.

Results: The study population consisted of 12912 newly-diagnosed/not previously treated BC patients, 7349 in 2019 and 5563 in 2020. There were two drops of newly diagnosed cases, one in the first wave (March-May 2020; -37.2%), the other in the second wave (October-December 2020; -15.8%). No major differences were found between characteristics of cases occurring in 2019 and 2020; with the exception of a reduced use of both chemotherapy (86.2% *vs* 53.4%) and radiotherapy (65.7% *vs* 42.1%) in 2020. One-year overall survival was 97.6% in 2020 *vs* 98.3% in 2019, Hazard Ratio [HR] (95% Confidence Interval [95%CI]): 1.51 (1.18-1.93); p=0.0010 at univariate analysis; HR 0.91 (0.71-1.17), p= 0.47, after adjusting for age, stage, BC treatment and comorbidities at multivariable analysis. COVID-19 occurred in 250 of 5563 (4.5%) newly-diagnosed BC cases in 2020. Notably, the time-dependent COVID-19 effect was significantly associated with mortality (multivariable Cox analysis HR 2.25 (1.35-3.74); p=0.0018) even after adjusting for age, stage, treatment and comorbidities.

Conclusions: Breast cancer incidence and survival were both reduced in 2020, and COVID-19 was an independent predictor of death in BC patients. While follow-up is ongoing to assess long sequelae of COVID-19, these results encourage prevention of infection regardless of BC stage; and at the same time warn against suboptimal treatment and overlooking new diagnoses to ensure a favourable prognostic outcome.

R04

IMMUNOGENICITY AND CLINICAL EFFICACY OF TWO DOSES OF MRNA-BASED COVID-19 VACCINES FOR PATIENTS WITH SOLID TUMORS ON ACTIVE ANTI-CANCER TREATMENT

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Background: Real world studies on the immunogenicity of BNT162b2 and mRNA-1273 in patients (pts) with cancer showed a reduced seroconversion. The aim of the study is to evaluate the immunogenicity and clinical efficacy of two doses of mRNA vaccines in cancer pts, during or after active treatment.

Patients and Methods: This is a single institution, prospective, observational study, conducted at Luigi Sacco Hospital in Milan, IT. Seric antibody levels were measured in solid cancer pts and in healthy controls before the 1st dose (T0) and 30 days after the 2nd one (T1) by a fluorescence bead-based assay. Seroconversion (SR) was defined as anti-S and anti-RBD > 700 MFI (Median Fluorescence Intensity). Previous exposure was defined as anti-N >700 MFI (E-group: exposed; nonE-group: non exposed). Clinical efficacy was defined as the percentage of subjects who did not develop COVID-19 six months after the second dose.

Results: 195 cancer pts: median age 64.1 y (Q1-Q3 53.8-72.0); female 138 (70.8%); E-group (12.6%); active therapy 144 (86.7%); advanced stage of disease 131 (67.2%); breast cancer 100 (51.3%); chemotherapy 65 (33.3%), targeted therapy 69 (35.4%); multiple comorbidities 44 (22.6%); prophylaxis with G-CSF 15 (7.7%). 20 healthy subjects were enrolled as controls: median age 28.5 y

(Q1-Q3 25.0-42.0), female 11 (55.0%). SR in nonE-group was lower than in healthy controls (66.7% vs 95.0%, p=0.0085). Conversely, SR in E-group was comparable to healthy controls (93.3%, p=0.0020). In cancer pts, multiple comorbidities (p=0.0274) and the use of G-CSF (p=0.0151) negatively correlated with SR; mRNA-1273 induced a higher SR (p<0.0001). Clinical efficacy in pts was 97.4%. 7 pts were diagnosed for SARS-CoV-2 infection and confirmed by a RNA test. 5 pts developed COVID-19: 3 of them did not seroconvert at T1. COVID-19 disease was mild and managed at home. Only 1 hospitalization was recorded, but no ventilation or no intensive care admission was required.

Conclusions: In our study, cancer pts with a previous SARS-CoV-2 infection showed a higher SR, similar to the one observed in healthy people. Besides, the presence of comorbidities and the use of G-CSF negatively affected the SR, while mRNA-1273 induced a higher SR. Interestingly, no COVID-19 serious complication or

death were observed in all subgroups. Finally, as the third dose is the actual standard, identification of persistent non-responder pts is critical in order to select who could benefit of new treatments as monoclonal antibodies.

R05

EFFECTS OF DIFFERENT ONCOLOGICAL TREATMENTS ON THE ANTIBODY RESPONSE TO COVID19 MRNA VACCINE

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Background: A satisfying development of antibody title after vaccine finds out his protagonist in immune system. In oncological patient immune system can be influenced by type of active treatment as Immunotherapy, Target therapy, Chemo therapy and its premedication with anti inflammatory steroids. This study aim to determine whether cancer medical treatment influenced antibody title response to Covid 19 mRNA vaccine.

Material and Methods: We retrospectively analyzed 256 vaccinated patients with two doses of Covid19 mRNA vaccine, undergoing treatment with immuno chekpoint inhibitors, target therapy, chemo therapy, in our institution between february and july 2021. Total IgG and antiSpike protein anti SARS Covid 19 antibody title, a complete blood cell count and blood dosage of vitamine D have been determined at four weeks from the end of vaccination cycle.

Differences in antiCovid19 antibody title has been evaluated and compared with t-student, test Wilcoxon Mann Whitney, Kilmogorov Smirnov among each subgroup of patients according to different types of treatment.

Bivariate analysis has been performed in order to asses correlation between continous variables: blood dosage of vitamine D, Neutrophils-lymphocyte-ratio (NLR) and antiSpike protein antibody title.

Results: No statistically significant difference has been observed in total and antispike protein antibody title between subgroups according to type of oncological treatment. Bivariate analysis revealed a correlation between blood levels of vitamine D, NLR and antiSpike protein title reached.

Conclusions: Different types of Oncological treatment as Immunotherapy, Target therapy and Chemotherapy do not influence the development of antibody title response to Covid19 mRNA vaccine; Vitamin D seems to have an important role to promote humoral immunity as well as NLR.

R06

DIFFERENCES IN MRNA-1273 (MODERNA) AND BNT162B2 (PFIZER-BIONTECH) SARS-COV-2 VACCINE ANTIBODY RESPONSES IN CANCER PATIENTS

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Background: Severe acute respiratory syndrome coronovirus-2 (SARS-CoV-2) is the cause of the coronavirus disease 2019 (COVID-19) pandemic. Vaccination is considered the core approach to containing the pandemic, but differences in immunogenicity between mRNA SARS-CoV-2 vaccines have not been reported in patients with cancer.

Material (patients) and methods: We conducted a retrospective monocentric study on oncological patients, treated at the Piacenza hospital, who received the BNT162b2 or mRNA-1273 SARS-CoV-2 vaccines. The aim was to investigate the humoral response determining IgG antibody levels against the SARS-CoV-2 receptor-binding domain developed according to the type of vaccine. To reduce the possibility of selection bias and make the baseline characteristics of the two groups more comparable we conducted propensity score matching (1:1 nearest-neighbor without replacement). Serum samples were evaluated for SARS-COV-2 antibodies prior vaccinations and 2-6 weeks after the administration of the second vaccine dose, data about age, gender, anticancer treatment, type and stage of cancer were collected.

Results: Between 20 March 2021 and 12 June 2021, 293 consecutive patients with solid tumor underwent a program of COVID-19 vaccinations and 257 were evaluable; after propensity score matching 76 were included in each group. The IgG antibody levels were different among the two groups: median 319.5 AU/ml [IQR 76.15-401] mRNA-1273 vs 53.55 AU/ml [IQR 5.83-152] BNT162b2, $p<0.001$.

Conclusions: We found greater antibody response with the mRNA-1273 vaccine than the BNT162b2 vaccine in patients with cancer and the other factor that has the greatest impact on the intensity of the vaccine response, regardless of its type, was the active anticancer treatment. These two factors should be taken into consideration when choosing the type of vaccine and the timing of administration based on the oncologic-hematologic treatment.

R07

EFFECTS OF COVID19 PANDEMIC ON THORACIC MALIGNANCIES: DELAY OF DIAGNOSES, INCREASE OF ADVANCED STAGES, AND WORSE OVERALL SURVIVAL

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Background: COVID19 pandemic has been an important clinical issue in patients (pts) with lung cancer, who, if affected by this infection, had a higher mortality rate. COVID19, however, has also brought several

indirect consequences in pts with thoracic malignancies: several experiences have highlighted its possible negative role on the clinical history of these pts.

Material and Methods: We evaluated all pts with thoracic malignancies affering to our Centre from March 2019 to February 2020 (pre-COVID group) and compared them to all pts affering from March 2020 to February 2021 (post-COVID group). We evaluated: the total number of accesses, the mean time from symptom onset and the first imaging evaluation (in symptomatic pts), the mean time from first symptoms or

first imaging evaluation (whichever came first) and the histological diagnosis, the stage at diagnosis, the prescribed therapies, and the pts'overall survival (OS, from diagnosis to death).

Results: 208 pts accessed our centre in the pre-COVID era, whereas only 152 accessed in the first year of the post-COVID era, with a reduction of 26.9%. The mean time from symptom onset to first imaging was 36.18 ± 48.38 days in the pre-COVID group and 48.42 ± 52.73 days in the post-COVID group, but this difference was not statistically significant ($p = 0.07$). However, we observed a statistically significant longer mean time from first symptoms or first imaging evaluation (whichever came first) and the histological diagnosis in the post-COVID group (99.52 ± 72.58 vs 83.38 ± 65.35 days, $p = 0.04$). In the post-COVID group we had more stage-IV cancer (74.8% vs 63%, $p = 0.03$) and fewer stage I-II cancer (7.1% vs 15%, $p = 0.03$). The median OS has not been reached yet (only 27 events have been censored), but the estimated mean OS was 38.73 months (95CI% 35.85-41.63) in the pre-COVID group versus 17.55 months (95%CI 15.97-19.12) in the post-COVID group (log-rank $p = 0.029$).

Conclusions: In our experience, the COVID19 pandemic determined a reduction in the number of accesses of pts to our Oncology Centre. We observed a statistically significant delay in achieving a histological diagnosis in pts with cancer. We also experienced a relevant increase in the percentage of pts presenting with advanced disease at diagnosis. Finally, we observed a worse mean OS in the post-COVID era.

R08

BEHIND THE MASK: EMOTIONS IN HEALTHCARE OPERATORS IN THE ONCOLOGICAL AREA DURING COVID-19 EMERGENCY

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Background: Healthcare operators, with several roles and mansions, had to face an emergency without precedents, facing everyday an insidious and invisible danger which solicited SSN to the highest degree, increasing the charges of work and the psychic and physical tension. In a similar context the increase of environmental stressors exposes to a tangible burn-out risk with consequences also in the cognitive, behavioral, physical and emotional field. Therefore, considering the current healthcare emergency it was considered useful to lead a cognitive survey in order to evaluate the operating in oncological area healthcare operators' psychological status, with final purpose to plan preventive, care and welfare interventions in the psychological field.

Material (patients) and methods: The pattern consists of 168 selected operators belonging to UU.OO. who joined this study. The listed questionnaires were administered: a specific test in order to evaluate the emotional unease connected to the emergency situation caused by the pandemic COVID-19, the Anxiety Stress Scale-21 (DASS–21 and the Maslach Burnout Inventory tests).There were practiced also descriptive and inferential analyses (correlation between indexes and multivariant Anova).

Results: The specific test definitely and positively correlates ($p < 0,01$) with the Depression Anxiety Stress Scale-21 (DASS–21) DASS-2, with the Maslach Burnout Inventory (MBI) test, in the subscales Emotional Exhaustion (EE) and depersonalization (DP) and correlates negatively in the the subscale personal Realization (RP). Moreover differences statistically significative are in these following variables: sex, years of work and professional role at the indexes of the administered tests.

Conclusions: The results confirm the negative impact of the pandemic Covid-19 on the wellness of the healthcare operators with differences statistically significative among

the following variables: sex, years of work and professional role. Considering the results it was fundamental to activate psychological interventions for operators of the oncological area. In this study will be presented data and the activated psychological interventions as a multidisciplinary work, in oncological area.

R09

SEROLOGICAL RESPONSE TO THIRD DOSE OF SARS-COV-2 MRNA VACCINE IN PATIENTS AFFECTED BY THYMIC EPITHELIAL TUMORS WHO DID NOT ACHIEVE SEROCONVERSION AFTER THE SECOND DOSE

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Background: Thymic epithelial tumors (TETs) are rare malignancies associated with dysregulation of the immune system with humoral and cell mediated immunity abnormalities. Anti-syndrome coronavirus type 2 (SARS-CoV-2) vaccine is effective at preventing COVID-19 morbidity and mortality. No published data are available regarding the post-vaccine immunization in TET patients (pts). The aim of our study was to evaluate the immunization in TET pts, who received the third mRNA vaccine dose and who did not achieve seroconversion after the previous two doses.

Methods: Starting from November 2021 to March 2022, 23 consecutive TET patients (pts) found to be serologically negative after two doses of SARS-Cov-2 mRNA vaccine (BNT162b2 by Pfizer-BioNTech) were enrolled at the Rare Tumors Coordinating Center of Campania Region (CRCTR - Naples, Italy). SARS-CoV-2 spike-binding IgG antibody serological levels were centrally analyzed by chemiluminescent immunoassay (CLIA) at two different time-points: T0 (before the third dose) and T1 (one month after the third dose). Cut-off for Ab titers positivity was >25 AU/mL.

Results: Among the 23 enrolled pts, 10 (43,5%) were female and 13 (56,5%) males; 17 pts had thymoma and 6 thymic carcinoma. Autoimmune disorders were detected in 20 TET pts (87%), of whom 3 (15%) suffered from Myasthenia Gravis, 8 (40%) from Good's Syndrome, 7 (35%) from both diseases, and 2 (10%) from other autoimmune disorders. By the time of third vaccine dose 2 pts had died, 2 pts were lost to follow up, 5 pts had suffered from SARS-CoV-2 infection. Of the remaining 14 pts, 7 achieved seroconversion whereas 7 maintained negative serological antibody titers. Two of these 7 pts had SARS-CoV-2 infection after the third dose. Interestingly, among these 7 pts who did not develop positive antibody titers, 6 had active cancer disease and only one was disease-free. Moreover, 6 out of these 7 pts suffered from Good's Syndrome. On the other hand, among the 7 pts who developed positive antibody titers, only 3 had active disease.

Conclusions: Our preliminary results showed that TET pts who did not achieve seroconversion even after the third SARS-Cov-2 vaccine dose in most cases had active cancer disease. If confirmed on larger cohorts of patients, these data may have important clinical implications and may help to better identify fragile pts who could benefit the most from prophylactic therapy with monoclonal antibodies.

R10

CANCER AND COVID-19: A PRELIMINARY STUDY ON THE TRAUMA ASPECTS OF CORONAVIRUS IN CANCER PATIENTS

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Background: Cancer patients turned out to be more susceptible to Covid19 infection than healthy population. Due to the Covid-19 pandemic, many important changes have occurred in several hospitals: delay in treatments, modification of chemotherapy regimens, and prolongation of intervals between treatment cycles. These changes, coupled with loneliness and imposed social isolation, have become additional sources of stress for cancer patients, with the risk of developing PTSD (DSM-V). The purpose of this study was the evaluation of the impact of Covid19 in terms of Post-Traumatic Stress Disorder and Depression and the potential association with coping strategies.

Materials and methods: This study was conducted in the Oncology Department of Fondazione Poliambulanza, Brescia, Italy, between November 2020 and April 2021. We conducted an exploratory study with 106 patients undergoing treatment, using following questionnaires: Screening Questionnaire for Disaster Mental Health (SQD) and Mini-Mental Adjustment to Cancer (Mini-MAC).

Results: The majority of the patients were women (60,4%), the mean age was 58.24 years (range 31–80), 70.8% of patients were married and 44.1% were retired with a high school education (48.5%). The majority of patients had a metastatic disease (51,4%). The primary site of the disease in our sample were digestive tract (45.7%) and breast (32.4%). Only 25.5% of our sample showed symptoms of PTSD and 6.6% revealed a probable presence of depression. In addition, it came up a significant correlation between SQD_P and the coping styles "Hopelessness" ($r = 0.41$ $p < .001$) and "Anxious Preoccupation" ($r = 0.45$, $p < .001$). A strong correlation also emerged between non-Covid 19 patients and PTSD.

Conclusions: Our preliminary data did not reveal a prevalence of PTSD, but the persistence of the health emergency requires to focus future research on protective and risk factors related to PTSD and psychological distress in cancer patients, in order to reduce the mental health burden of Covid-19.

R11

OUTCOME OF COVID-19 IN CANCER PATIENT: DATA FROM AN ONCOLOGY WARD IN EMILIA-ROMAGNA

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Background: Emilia Romagna recordered a very high percentage of hospitalized COVID-19 patients out of the total number of COVID-19 affected people. Data reveal cancer to be a major risk factor for adverse outcomes and death for patients with Sars CoV2 infection. This increased susceptibility could be due to the chronic immunosuppression, exerted by the cancer itself and exacerbated by cytotoxic therapies.

Materials and Methods: We retrospectively evaluated 93 oncological patients, followed for cancer at the Sant' Anna University Hospital in Ferrara, and diagnosed with COVID-19 infection in 3 different pandemic periods (February 2020- September 2020; October 2020-August 2021; September 2021- March 2022). We analyzed demographic and clinical features of the population: age at diagnosis, gender, tobacco consumption, comorbidities (according to the Charlson Comorbidity Index), cancer subtype and stage, therapy ongoing and ECOG PS before and after COVID-19 infection. We also described the severity of the infection through the symptoms developed and need for eventual hospitalization.

Results: The gender distribution of the cohort was broadly equivalent (Female/Male, 49/44), with a median age at COVID-19 diagnosis of 71 years (35-99). Current or previous smoking was reported by 28% and 14% of patients, respectively. The most common comorbidity was hypertension (79%) VS pulmonary disease (14%); the median CCI was 6. A symptomatic infection was observed in 38% of patients. A worse clinical outcome was associated to higher ECOG PS (2-3) (p 0,013) and to the first pandemic period ($p<0,0001$). A mortality rate of 36% has been observed among hospitalized patients due to severity of infection ($p<0,0001$). Increased age at cancer diagnosis (median age 66 years) was a significant risk factor for severe COVID-19 disease. Eighty-six percent of the study population had an active disease that correlated with high proportion (21%) of death ($p<0,003$). The most prevalent malignancies were breast (19,4%) and lung (15%), and the diagnosis of lung cancer was associated with a worse outcome; in contrast, cancer stage, ongoing anticancer therapies and treatment toxicities had no effect on clinical outcome.

Conclusions: This study highlights a high mortality rate related to COVID-19 infection among cancer patients. Worse outcomes are driven by features such as pandemic period, cancer status and subtype, ECOG PS and median age at cancer diagnosis.

R12

EFFECTS OF COVID19 PANDEMIC ON QUALITY OF LIFE IN PATIENTS WITH NEWLY DIAGNOSED SARCOMA IN A REFERRAL CENTRE IN ITALY: RESULTS FROM THE SARCORD STUDY (COMETA PROJECT)

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Background: Sarcomas are extremely rare and disabling tumours causing physical impairments as well as psychological issues. The Health-related quality of life (HRQoL) in these patients (pts) is impaired as a consequence of their illness and its treatments. It is widely demonstrated the harmful impact of covid19 pandemic and its effects on the HRQoL of the general population and especially on cancer pts. We investigated this important aspect in sarcoma pts.

Material (patients) and Methods: We performed a retrospective observational study including pts with diagnosis of soft tissue (STS) and bone sarcoma (BS) referred to

Regina Elena National Cancer Institute in Rome and with histological diagnosis obtained during the year preceding (Control group - Ctg) or following (Covid group - Covg) the start of covid19 lockdown in Italy (March 9th 2020). Patients were evaluated with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), with scores analysed as continuous scales, and with the Distress Thermometer (DT), where the pts were accounted for as having low/absent (score 0-4) or high distress (5-10).

Results: We enrolled a total of 115 pts, 76 in the Ctg and 39 in the Covg; 43 women and 72 men. Median age was 55 years (range 94-21). In the Ctg and in the Covg respectively, the most common diagnosis was STS (N=52 vs 27) followed by BS (N=24 vs 12). Most pts had a localized disease at diagnosis (N=64 vs 34) and only 17 (N=12 vs 5) had distant metastasis. The first treatment received was surgery in 75 pts (N=52 vs 23), chemotherapy in 30 pts (N=18 vs 12), concomitant chemo-radiotherapy in 4 pts (N=3 vs 1), and 6 pts (N=3 vs 3) had a follow-up strategy. In the Covg, compared with the Ctg, we found a decline in Social functioning (average score (μ)=81,64; SD=30,54 vs 91,38; SD=16,24 respectively; p=0,027) as well as an increase in financial difficulties (μ=11,95; SD=22,31 vs 3,93; SD=13,29; p=0,017) and increased nausea (μ=5,13; SD=13,31 vs 1,12; SD=4,24; p=0,018). We also found a higher rate of patients with emotional distress in the Covg (50% vs 71,8% p=0,025). Worsening, although not statistically significant, was observed in almost all questionnaire domains.

Conclusions: Our study suggests that the covid19 pandemic had a detrimental effect on HRQoL in sarcoma patients. This study makes an effort on the strong need of improvement psychological support for both emotional and physical effects in our pts.

R13

SEX DIFFERENCES IN SAFETY AND TOLERABILITY OF A M-RNA-1237 MODERNA COVID-19 VACCINE BOOSTER DOSE (FOURTH DOSE) IN CANCER PATIENTS: OUR EXPERIENCE

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Background: *COVID-19 is a disease due to a new form of coronavirus called SARS-CoV2 which causes an acute infection with respiratory symptoms. This new virus is different from those that cause SARS (severe acute respiratory syndrome) or MERS (respiratory syndrome of Middle East).* Clinical manifestations can range from asymptomatic infection to life-threatening disease.

By November 2021, more than 250 million people have had confirmed covid-19 and more than four million have died worldwide.

Literature data show increased mortality from COVID-19 in cancer patients (pts). *Moreover, cancer pts* often fail to respond adequately to the initial vaccination.

The aim of our study was to evaluate, sex differences in safety and tolerability of m-RNA-1237 Moderna COVID-19 vaccine booster dose (fourth dose) in oncology pts, *focusing on the first week after vaccination.*

Material and methods: We have retrospectively analyzed sex differences on safety and tolerability of m-RNA-1237 Moderna COVID-19 vaccine booster dose (fourth dose) in 37 cancer patients (pts).

All pts were vaccinated in March 2022 while undergoing active cancer therapy.

There were 21 men (56.7%), 16 women (43.2%)

Mean age 70 years (range 48-82)

We analyzed the following adverse events (AE): *fever, joint pain, injection site pain, lymphadenopathies, chills, nausea and vomiting, headache, diarrhea.*

AE were analyzed and stratified in grades from G1 to G4 according to CTCAE scale.

Results: Of 37 pts analyzed, 9 (24.3%) developed AE and all within one week of vaccination.

All pts with AE were female

All AE were G1 and G2.No pts presented G3-G4 AE.

The AE found in the 9 pts were fever (100%) and *injection site pain (100%)*

No pts had joint pain, lymphadenopathy, chills, nausea and vomiting, headache and diarrhea.

Using the Fischer test we found that the difference in the two sexes between the development of adverse events related to vaccination was statistically significant (p 0.0001)

Conclusions: Our results demonstrate that m-RNA-1237 Moderna COVID-19 vaccine second booster dose (fourth dose) is usually well tolerated among cancer pts: all AE were G1 and G2.

No pts presented G3-G4 AE.

In addition, despite the limited number of pts, we found a statistically significant difference between male and female pts in the development of adverse events related to vaccination.

S – Miscellanea

S01

RANDOMIZED TRIAL OF SUCROSOMIAL IRON SUPPLEMENTATION IN PATIENTS WITH CHEMOTHERAPY-RELATED ANEMIA TREATED WITH ESA

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Background: Iron supplementation improves the erythropoiesis-stimulating agents (ESAs) response in chemotherapy-related anemia. The primary aim of our study is to assess the efficacy of sucrosomial iron, a new oral iron formulation, in cancer patients with chemotherapy-induced anemia treated with ESA. The secondary objectives included the efficacy into two subgroups of patients (iron replete and functional iron deficiency) between the two study arms, safety and the effect on transfusion need.

Methods: In this randomized, multicentre, open-label, phase III clinical trial, 60 cancer patients were enrolled. Each patient was randomly assigned (1:1) to receive 12 weeks of oral sucrosomial iron at the dose of 30 mg daily in combination with ESA or no supplementation to ESA treatment. The endpoint considered for efficacy was the proportion of patients achieving complete haematological response at 12 weeks (increase in Hb $>$ 2 g/dL from baseline, without RBC transfusions in the previous 28 days or achieving Hb $\geqslant$ 12 g/dL).

Results: There was a statistically significant association between oral sucrosomial iron supplementation in combination with ESAs and the achievement of a complete haematological response. This response was achieved within 12 weeks by 31% of patients in the control group and by 52% of patients supplemented with oral sucrosomial iron. A trend of greater response in sucrosomial iron arm was found in both subgroups. No difference was observed about safety and transfusion need.

Conclusions: Sucrosomial iron is well tolerated and its combination with ESAs improves the hematological response in cancer patients with chemotherapy-related anemia.

S02

CARDIOVASCULAR TOXICITY IN PATIENTS TREATED WITH A PARP INHIBITOR FOR SOLID TUMORS: A META-ANALYSIS

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Background: Poly (ADP-ribose) polymerase inhibitors (PARPi) have changed the treatment landscape of several types of solid tumors in the last years, but little is known about their cardiovascular safety profile. This meta-analysis aimed at assessing the incidence and relative risk (RR) of PARPi-related cardiovascular toxicity (CVT) and hypertension (HTN).

Material and Methods: Prospective studies were identified by searching the MEDLINE/PubMed, Cochrane Library and ASCO Meeting abstracts. CVT events included acute myocardial infarction, cardiac failure, ischaemic stroke, thromboembolic events, arrhythmia, and cardiac arrest. Data extraction was conducted according to the PRISMA statement. Combined RRs and 95% confidence intervals (CIs) were calculated using fixed- or random-effects methods, depending on studies heterogeneity. RevMan software for meta-analysis (v.5.2.3) was used to perform statistical analyses.

Results: Twenty-two studies were selected for the analysis of CVT, with a total of 7078 patients. The incidence of any grade and high-grade CVT was 6.5% and 2.4% with PARPi, respectively, compared to 3.9% and 1.6% in the controls. Treatment with a PARPi significantly increased the risk of any grade CVT (fixed-effects, RR=1.80, 95% CI 1.42–2.27; $p<0.00001$) and of high-grade CVT (fixed-effects, RR=1.62, 95% CI 1.15–2.28; p=0.006) compared to controls. Similarly, when considering only those studies testing a PARPi monotherapy in the experimental arms, the risk of CVT of any grade (RR=4.49, p=0.008) and high-grade (RR=3.16, p=0.006) was significantly higher compared to controls. As concern HTN, twenty-one studies were selected, with a total of 8365 patients. The incidence of HTN of any grade and high-grade was 19.2% and 4.7% with PARPi therapies, respectively, compared to 13.7% and 3.3% in the controls. Treatment with a PARPi significantly increased the risk of HTN of any grade compared to controls (random-effects, RR=1.77, 95% CI 1.07–2.92; p=0.03), but not of high-grade (RR=1.61, 95% CI 0.89–2.89; p=0.11). However, PARP-inhibitors monotherapy was associated with a higher risk of HTN of

high-grade (RR=2.33; p =0.0005), but not of any grade (RR 4.30, p =0.07).

Conclusions: Patients receiving PARPi have a significant increased risk of developing CVT and HTN. Therefore, clinicians should take into account patient's cardiovascular comorbidities and accurately monitor, early recognize and manage treatment-related cardiovascular complications.

S03

CARDIOVASCULAR TOXICITY OF IMMUNE CHECKPOINT INHIBITORS PLUS TYROSINE-KINASE INHIBITORS FOR SOLID TUMORS: A META-ANALYSIS

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Background: Combinations of an immune checkpoint inhibitor (ICI) and a tyrosine-kinase inhibitor (TKI) are current therapies for certain cancer types, however little is known about their toxicity profile. Here, we analyzed phase II and III randomized studies to comprehensively evaluate the incidence and relative risk (RR) of cardiovascular toxicity (CVT) and hypertension in patients treated with ICI+TKI combinations for solid tumors.

Material and Methods: Prospective studies were identified by searching the MEDLINE/PubMed, Cochrane Library and ASCO Meeting abstracts. CVT events considered were acute myocardial infarction, cardiac arrest, and myocarditis. Data were extracted according to the PRISMA statement. Combined RRs and 95% confidence intervals (CIs) were calculated using fixed- or random-effects methods, depending on studies heterogeneity. RevMan software for meta-analysis (v.5.2.3) was used to perform statistical analyses.

Results: Seven studies were selected for the analysis of CVT, with a total of 4029 patients. The incidence of any grade and high-grade CVT was 0.7% and 0.6% with ICI+TKI combinations, respectively, compared to 0.2% in the control arms. Treatment with ICI+TKI combinations significantly increased the risk of any grade CVT compared to controls (fixed-effects, RR=2.67, 95% CI, 1.09–6.54; p=0.03). Conversely, treatment with IO+TKI combinations did not increase the risk of high-grade CVT (fixed-effect, R =2.21,95% CI, 0.88–5.56; p=0.09). Twelve studies were selected for the analysis of hypertension, with a total of 5899 patients. The incidence of hypertension of any grade and high-grade was 37.4% and 18.8% with ICI+TKI combinations, respectively, compared to 25.8% and 12.1% in the control arms. ICI+TKI combinations significantly increased the risk of hypertension any grade compared to controls (random-effects, RR=1.57, 95% CI, 1.02–2.40; p=0.04), but not of hypertension of high-grade (RR=1.41, 95% CI 0.86–2.34; p=0.18).

Conclusions: Our analysis shows that combinations of ICI+TKI are associated with a low incidence of CVT, but with a consistent rate of hypertension. These combinations significantly increased the risk of CVT and hypertension of any grade but not of high-grade compared to controls. These results suggest the need for an accurate monitoring of patients during ICI+TKI cancer therapy.

S04

THE ROLE OF BLOOD CHOLESTEROL QUALITY IN PATIENTS WITH ADVANCED CANCER RECEIVING IMMUNE CHECKPOINT INHIBITORS

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Introduction: Immune checkpoint inhibitors (ICIs) have reshaped the treatment landscape of several solid tumors. However, a limited fraction of patients (pts) achieves a long-term benefit. Cholesterol, both at plasmatic and intracellular level, emerged as promising biomarker. Cholesterol efflux capacity (CEC) mediated by ABCA1 and ABCG1 and cholesterol passive diffusion (CPD) are critically implicated in modulating immune function through T cells activation. The aim of the present study was to investigate the CEC mediated by serum transporters (ABCA1- and ABCG1) and CPDwith the clinical outcome of advanced non-small cell lung cancer (NSCLC) and metastatic renal cell carcinoma (mRCC) pts treated with ICIs.

Material and methods: We retrospectively enrolled advanced NSCLC and mRCC consecutively treated with ICIs at our center between October 2013 and October 2018, in order to correlate CEC and CPD with the overall survival (OS, primary endpoint). The secondary endpoints were the correlation between CEC and CPD with progression-free-survival (PFS) and clinical benefit (CB, complete/partial response or stable disease).

Univariable and multivariable semi-parametric Cox regression models were implemented to assess associations between cholesterol parameters and survival; the logistic regression model was used to assess the association with the CB. Stepwise backword selection approach was performed to identify the most parsimonious model through Akaike information criterion (AIC).

Results: Among 70 pts enrolled, a serum sample suitable for CEC and CPD determination was available for 68 pts. 94.2% of pts was affected by NSCLC. Median OS and median PFS was 5.2 and 2.4 months, respectively. Thirty-two pts (45.7%) obtained a CB as best response to ICIs. At the univariate analysis blood cholesterol, and serum ABCA1, ABCG1, CPD and CLC were associated with outcomes (OS, PFS, CB). At the multivariate analysis, only CPD was confirmed as protection factor for both OS and PFS as well as for CB [HR 0.77 (95%CI 0.67-0.89), $p < 0.001$; HR 0.81 (95%CI 0.74-0.90), $p < 0.001$; HR 1.26 (1.10-1.48) 95%CI, $p < 0.003$].

Conclusions: CEC and CPD, the major cholesterol diffusion modalities, may be considered as indirect measure of quality of total cholesterolemia. The positive association of CPD with both PFS and OS might reflect the presence of more immature HDL particles and more inflamed context that can explain the better response to ICI. Further prospective studies are needed.

S05

NUTRITIONAL STATUS, INFLAMMATORY PARAMETERS AND CANCER

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Background: Chronic inflammation and cytokine storm play a role in the development of many complex diseases including cancer. Interactions between tumour and its microenvironment through the immune system are critical for tumour development and progression. The tumour cell releases pro-inflammatory molecules IL-6, IL-1, TNF α, that reduce the desire for food and favouring the onset of anorexia.

Patients and Method: We evaluated 78 patients attending for follow up, adjuvant treatment or treatment for metastatic disease, administering MNA (Mini Nutritional Assessment) questionnaire. The serum of these patients were analyzed for different inflammatory parameters, including IL-6, CRP, ferritin, transferrin and β 2 microglobulin.

Results: 35% of patients evaluated had no clinical evidence of disease of which only 19% were at risk of malnutrition and none were malnourished; 65% of patients were metastatic and among them 48% were at risk of malnutrition, 26% frankly malnourished. Patients at risk of malnutrition and the patients with malnutrition were evaluated for nutrition therapy.

Comparing the results of inflammatory parameters, such as IL-6, CRP, ferritin, transferrin and β 2 microglobulin, according to the MNA score, between patients without clinical evidence of disease and metastatic patients, there is a significant difference of the mean values for IL-6 (p 0.001), CRP (p 0.01), ferritin (p 0.004), transferrin (p 0.01) and β 2 microglobulin (p 0.001). If we consider the metastatic patients, the patients with malnutrition, the patients at risk of malnutrition and the patients with normal nutritional status according to the MNA score, show a difference between the mean values of IL-6, CRP, β 2 microglobulin, ferritin and transferrin. This difference is statistically significant for IL-6 (p 0.02), CRP (p 0.004), β 2 microglobulin (p 0.05) and ferritin (p 0.01) when considering the patients at risk of malnutrition and normal nutritional status group and for IL-6 (p 0.01), CRP (p 0.03), β 2 microglobulin (p 0.01), ferritin (p 0.01), trasferrin (p 0.02) when considering the patients with malnutrition and the patients with normal nutritional status.

Conclusions: The results confirm a correlation between inflammation, cancer disease and the state of malnutrition. IL-6, CRP, Ferritin, β 2 microglobulin can be used as early biomarkers to supplement the MNA evaluation to identify patients who are at risk of malnutrition that need nutritional support.

S06

TIME TRENDS (2012-2016 VS 2017-2021) IN THE INCLUSION OF HEALTH-RELATED QUALITY OF LIFE (QOL) AMONG STUDY ENDPOINTS AND PRESENCE OF QOL RESULTS IN PUBLICATIONS: A SYSTEMATIC REVIEW OF ONCOLOGY RANDOMIZED PHASE III TRIALS

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Background: In our previous systematic review (Marandino et al, Ann Oncol 2018) of phase III trials in solid tumors published between 2012 and 2016, in many publications QoL was not included among endpoints or QoL results were not reported in the primary publication. To assess time trends in QoL inclusion among endpoints and in reporting of QoL results in publications, we reviewed phase III oncology trials published in major journals between 2017 and 2021, compared to the previous 5 years.

Methods: All issues published between 2017 and 2021 by 11 major journals were hand-searched for primary publications of phase III trials in adult patients with solid tumors. Information about endpoints was derived from paper, study protocol and ClinicalTrials.gov, when available. Secondary QoL publications were searched in PubMed. Results were compared with trials published in 2012-2016 included in the previous analysis.

Results: 388 publications between 2017 and 2021 were eligible and compared with 446 publications between 2012 and 2016. QoL was included among endpoints in 68.0% of the trials published in 2017-2021 vs 52.9% in 2012-2016 ($p<0.001$). Considering the advanced/metastatic setting, QoL was included in 75.8% of trials in 2017-2021 vs. 59.9% in 2012-2016 ($p<0.001$). QoL was included in 82.3% of profit trials, vs 48.1% of non-profit trials ($p<0.001$). Out of 264 primary publications of trials published in 2017-2021 with QoL among endpoints, QoL results were available in 51.9%, vs 62.3% in 2012-2016 ($p=0.02$). Overall, QoL was included among endpoints and presented in primary publications in 35.3% of trials in 2017-2021 vs 33.0% in 2012-2016 ($p=0.83$). In the advanced/metastatic setting, QoL was included and presented in 39.4% of publications in 2017-2021 vs. 37.9% in 2012-2016 ($p=0.77$). QoL was included and presented in 39.8% and 29.0% of publications of profit and non-profit trials, respectively ($p=0.03$). For trials without QoL results in the primary publication, probability of secondary publication was 10.8%, 29.0% and 42.4% at 1, 2 and 3 years respectively.

Conclusions: The proportion of oncology trials including QoL among endpoints significantly increased in the last 5 years compared to 2012-2016, although the inclusion of QoL remained worse in non-profit trials. However, when QoL was included, a significantly lower proportion of recent trials reported QoL results in primary publications. QoL is still subject to relevant underreporting and delay in publication.

S07

IMMUNE-RELATED ADVERSE EVENTS AS POTENTIAL SURROGATES OF IMMUNE CHECKPOINT INHIBITORS' EFFICACY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED STUDIES

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Background: Immune-related adverse events (irAEs) are frequently reported during immune checkpoint inhibitor (ICI) therapy and are associated with long-term outcomes. It is unknown if the irAE occurrence is a valid surrogate of ICIs' efficacy.

Methods: We identified articles reporting the results of randomized trials of experimental ICI therapy in solid tumors with a systematic search. The control arms could be placebo, cytotoxic/targeted therapy, or ICI therapy. We extracted the hazard ratios for overall survival (OS) with the number of OS events per arm and the number and percentages of overall and specific irAEs of grade 1-2 and grade 3-4 per arm. We estimated the treatment effect on the potential surrogate outcome with the odds ratio (OR) of the irAE rate between the experimental and the control arm. The primary analysis was planned in specific tumor types for which a significant number of randomized trials were available (i.e., NSCLC, melanoma, renal cell carcinoma, upper GI cancers). The statistical analysis consisted of weighted linear regression on a logarithmic scale between treatment effects on irAE rate and treatment effects on OS. The coefficient of determination (R^2) was used to quantify the surrogacy level.

Results: Sixty-two randomized trials were included for a total of 79 contrasts and 42,247 patients. The median follow-up of the included studies ranged from 6.5 to 51 months, with a median of 19.0 months (IQR, 11.8-27.5 months). The analyses found no significant association between the treatment effects on irAEs and OS for overall grade 1-2 or grade 3-4 irAE rates or specific (skin, gastrointestinal, endocrine) irAE rates. In NSCLC trial subset, we observed a negative association between treatment

effects on overall grade 1-2 irAE rate and treatment effects on OS in studies enrolling patients selected for PD-L1 (R^2 = 0.55; 95% confidence interval [CI], 0.20 - 0.95; R = -0.69). In melanoma trial subset, a negative association was shown between treatment effects on gastrointestinal grade 3-4 irAEs and treatment effects on OS in trials without an ICI-based control arm (R^2 = 0.77; 95% CI, 0.24 - 0.99; R = -0.89).

Conclusions: We found low-strength correlations between the ICI treatment effects on overall or specific irAE rates and the treatment effects on OS in several cancer types. Hence, irAEs did not seem to capture the whole effect of the ICI therapy on OS.

S08

EFFICACY AND SAFETY OF IMMUNOTHERAPY IN ELDERLY PATIENTS: A RESTROSPECTIVE MONOCENTRIC ANALYSIS

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Background: In the last decade immunotherapy (IT) has become one of the main treatments for many cancer types, still, there is limited evidence on its benefits in pts with ⩾70 years of age, since they are usually excluded from all the randomized clinical trials. The aim of this study is to investigate the efficacy and safety of immune checkpoint inhibitors (ICI) in the elderly.

Methods/patients: We retrospectively included pts ⩾70 years of age, treated with IT in our Institution. The objective response rate (ORR) and toxicity in terms of immune-related adverse events (irAEs) were the principal endpoints that we considered.

Results: 111 pts aged between 70 and 87 years old were evaluated, with a median age of 75 (70-87). 82 pts were male and 29 were female. Clinical conditions were generally good (ECOG PS was 0 in 23 pts, 1 in 83 and 2 in 5) and most pts (91) were taking >1 concomitant medication. Lung cancer, GU cancers and melanoma were the most represented (55, 19 and 21, respectively) and all pts except 5 were in stage III-IV. Pembrolizumab and nivolumab were the most used drugs and pts received a median of 13 cycles (1-93). Best response was stable disease (SD) in 59 (53.1%) pts, partial or complete reponse (PR/CR) in 38 (34.2%) and progression disease (PD) in 14 (12.6%). Overall, treatment was discontinued in 17 pts due to toxicity and poor compliance. 41 pts reported all grade irAEs: the most frequent (13.5%) were pruritus and skin erythema (1 pt ⩾grade 3), colitis (5.4%, 1 pt ⩾grade 3), thyroiditis (13.5%, hyperthyroidism/ipothyroidism in 8/7 pts, respectively), pancreatitis (4.5%, 1 pt ⩾grade 3), and arthralgia (8.1%). One patient experimented immune-related grade 3 pneumonia. No treatment-related deaths were documented. Most patients (59.5%) are currently alive and treatment is ongoing.

Conclusions: Despite its retrospective nature, our analysis demonstrated the efficacy and the good tolerability profile of IT also in the elderly, that seem to be similar to those reported in younger pts. Prospective studies including this specific population are needed.

S09

CHEMO OR CHEMO-FREE REGIMENS IN HEAVILY PRETREATED MULTIPLE MYELOMA? ROLE OF BENDAMUSTINE-BORTEZOMIB-DEXAMETHASONE (BVD) IN NOVEL AGENTS' ERA

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Bendamustine is an old bi-functional alkylating agent which has proved to be effective in relapsed, refractory and in new diagnosed Multiple Myeloma (MM). Thus, aiming to provide further insights in this field, also in novel agents'era, we present here a retrospective, real-life analysis of patients with relapsed/refractory MM (rrMM), who had received salvage therapy with bendamustine in combination with bortezomib and dexamethasone (BVD).

81 patients (44 M/37 F), with rrMM, median age at diagnosis 59.4 years (r. 36-82), median age at start of treatment 63.6 years (r.37-86) treated with several lines of treatments (median 6, r. 2-11), every refractory to all the drugs previously received (also Bortezomib), received BVD (B 90 mg/sqm days 1,2; V 1.3 mg/sqm days 1,4,8,11, D 20 mg days 1,2,4,5,8,9,11,12, Pegfilgrastim day +4) every 28 days, until progression.

All patients had previously received bortezomib-based and IMIDs-based treatments, and 32% (26/81) had also received radiotherapy. 69% (56/81) had undergone single or double autologous and three (2%) allogeneic stem cell transplant. All patients were relapsed and refractory to last therapies received before BVD.

Bendamustine was well tolerated, with grade 3-4 transfusion-dependent anemia in 56% (46/81) of patients, and 43% (35/81) grade 3-4 neutropenia (no ospedalization was required, no septic shocks were observed). No severe extrahematologic toxicity was observed, only grade 1 gastrointestinal side effect (nausea), treated by common antiemetic drugs.

According to IMWG, ORR was 63% (51/81: 7 CR, 18 VGPR, 15 PR, 11 MR) with 11 PD and 19 patients in SD, which can be considered as an impressive result in this subset of rrMM patients. In particular, for 11 patients, BVD was, after having achieved at least a PR, a bridge to second auSCT, and for two patients a bridge to alloSCT. Eight patients have surprisingly achieved a notable PR after failure of novel agents (i.e. Carfilzomib, Daratumumab and Pomalidomide).

Median time to response was 1.3 months (r.1-3), median OS from diagnosis was 67.3 months (r.6-151), median OS from start of Bendamustine was 9.6 months (r.2-36).

The triplet Bendamustine-Bortezomib-Dexamethasone has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic resources, and, in particular cases, it could be considered as a bridge to a second autologous or allogenic SCT, also after failure of novel agents.

S10

TUMOUR-AGNOSTIC INDICATIONS: ARE WE MOVING TOWARDS A MUTATION-DRIVEN APPROACH IN PRECISION ONCOLOGY?

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Background: Oncology landscape is rapidly evolving to fulfill clinical unmet needs. One of the most recent and investigated fields is molecular characterization of disease to detect molecular alterations that can be selectively targeted, irrespective of histological features. Various clinical trials are investigating this tissue-agnostic approach, such as NCI-MATCH (NCT02465060) and ROAR (NCT02034110) trials. Especially the ROAR trial showed a robust clinical activity of dabrafenib/trametinib (DT) in patients (pts) with a variety of solid tumors harboring BRAF V600E mutation.

Methods: Two managed access programs (MAPs) were designed to offer access to targeted treatment, either with DT or PI3K inhibitor & degrader alpelisib (A), based on agnostic-tumor indication, in accordance with italian DM 7/09/2017. Eligible pts had (1) solid tumors harboring either BRAF V600E or PIK3CA mutations; (2) contraindications to standard therapy and/or (3) no further treatment options and (4) no contraindication to DT or A treatment.

Results: As of March 1st, 2022, 68 pts were treated with DT and 48 with A. Median age was 57 years [range 4-87] for D/T and 60 [25-81] for alpelisib. Pts were prevalently males (56%) for DT, female (60%) for A.

Conclusions: These results suggest that MAPs based on an agnostic approach may offer a viable therapeutic opportunity for pts affected by tumors harboring actionable mutations and lacking therapeutic alternatives. Despite further data are needed to confirm the effectiveness of this approach, MAPs have a crucial role both in patient's care

Table 1. Reports the most frequent histologies treated in both MAPs.

	Dabrafenib/trametinib	Alpelisib
	n (%)	n (%)
Thyroid cancer		
Papillary	21 (31)	1 (2)
Anaplastic	11 (16)	0
Glioma		
High Grade	15 (22)	7 (15)
Low Grade	4 (6)	0
Colon-rectal carcinoma	0	13 (27)
Endometrial carcinoma	0	10 (21)
Other histology	11 (16)	6 (13)
Biliary tract	4 (6)	1 (2)
Head and neck cancer	0	3 (6)
Lung Cancer	0	2(4)
GU squamous cell carcinoma	0	2(4)
Gastro-duodenal carcinoma	0	2(4)
Pediatric melanoma	2 (3)	0
Primary unknown cancer	0	1 (2)

Table 2. Shows the treatments received by this heavily pretreated pts before entering the MAPs.

	Dabrafenib/trametinib	Alpelisib
	N (%)	N (%)
Previous surgery	52 (76,5)	42 (88)
Previous radiotherapy	37 (54,4)	31 (65)
Previous systemic treatment	50 (73,5)	48 (100)
0*	18 (26,5)	0
1 line	34 (50)	4 (8,3)
2 lines	7 (10,3)	16 (33,3)
⩾ 3 lines	8 (11,8)	28 (58,3)
Missing	1 (1,5)	0

*Pts with contraindications to start standard therapy.

and generation of real-world data that might support clinical practice and future areas of investigation.

S11

3D-INFORMED TARGETING OF THE CLEAVED-ACTIVATED FORM OF TROP-2 DRIVES SELECTIVE CANCER VULNERABILITY

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Background: The sacituzumab govitecan-hziy (TRODELVY) anti-Trop-2 antibody-drug conjugate (ADC), was granted FDA accelerated approval for metastatic triple-negative breast cancer and urothelial tumors (1). Next-generation, high-effectiveness anti-Trop-2 monoclonal antibodies (mAb) suffer from dose-limiting toxicities as on-target/off-cancer effects, related to the expression of Trop-2 in normal tissues. Trop-2 is a transmembrane signal transducer (2), that is cleaved and activated by ADAM10 to drive cancer growth and metastatic diffusion (3, 4). This cleavage exposes hidden, activation-specific epitopes. We seeked mAbs capable to recognize these cancer-exposed sites.

Material and methods: Existing Trop-2-targeted mAbs recognize a single immunodominant epitope. Such mAbs have limited therapeutic index. 3D-structure analysis informed the deletion mutagenesis removal of such epitope and target site recognition, through immunization with multi-phyla end-glycosylation recombinant proteins. Screening for cancer-specific mAbs was performed on mutagenized Trop-2 by cell-based ELISA assays, biolayer interferometry, flow cytometry, fluorescence microscopy.

Results: The 2G10 mAb was obtained that efficiently bound Trop-2 expressing cancer cells (Kd=10-12 M), and was able to inhibit cell growth in vitro. The humanized Hu2G10 mAb retained an extremely high affinity for cancer-specific, cleaved Trop-2, and showed 10,000-fold lower binding to wtTrop-2 in normal tissues. In vivo the naked Hu2G10 antibody was effective at inhibiting the growth of breast, colon, ovary and prostate cancers. In the ADC setting Hu2G10 drove high anticancer specificity and effectiveness.

Conclusions: Hu2G10 shows unprecedented specificity and efficacy, for best-in-class anti-Trop-2 anticancer therapy and testing in upcoming clinical trials.

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S12

PREVALENCE OF DRUG INTERACTIONS AND POTENTIALLY INAPPROPRIATE MEDICATIONS IN CANCER PATIENTS

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Background: Biomedical literature evidences a correlation between polytherapy in advanced age and the onset of adverse reactions (AR) due to drug interactions. In oncology, the use of multiple medications for supportive therapy in addition to cancer and comorbidities treatments increases the risk of drug toxicities and AR. This study aims to estimate the prevalence of patients exposed to potentially severe drug interactions and to assess the risk of developing AR.

Patients and Methods: Data collection started in January 2020 and ended in February 2021. We enrolled 385 oncological patients and examined age, sex, alcohol drinking, smoke exposure, intake of grapefruit juice, caffeine nutritional supplements, phytotherapeutics, and homeopathic agents, comorbidities, home therapy, cancer drugs. Data Analysis Software evaluated drug interactions, the prevalence of potentially inappropriate medications (PIMs), and the risk of developing ARs (GerontoNET ADR Risk Score Algorithm).

Results: Preliminary results relating to 200 patients show a prevalence of 33% in patients exposed to potentially severe drug interactions. Cardiovascular medications (diuretics, beta-blockers, antiarrhythmics), analgesic medications, antidepressant drugs, and proton pump inhibitors are most frequently involved in pharmacological interactions with antiblastic drugs, especially Capecitabine, and hormone therapy (tamoxifen and Letrozole). The most common and severe AR is QT-prolongation. Furthermore, the risk of developing an AR is 25% for an *ADR Risk score* higher than 4 (high-risk patients) on a scale of 0-10.

Conclusions: Preliminary data from this study demonstrate the necessity of careful treatment evaluation to prevent poor clinical outcomes due to drug interactions and to avoid the prescription of potentially inappropriate drugs in elderly cancer patients, suffering from concomitant diseases. A drug interaction checker tool could improve clinical decision-making and patient safety.

S13

FROM HOSPITAL TO TERRITORY: HOW TO RESPOND TO THE CANCER PATIENTS' NEEDS

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Background: The cancer prevalence in Italian people is about 5,7% which includes both patients in active treatment and follow-up. Care networks are important to respond to these patients' needs and the goal of these networks is the facilitation and the organization of diagnosis, treatment and home care. The socio-sanitary needs are often not supported by an effective integration between hospital and territory. The world of voluntary organizations can satisfy many of these crucial needs, but its activity is not homogeneous and most importantly it is not always recognized and structured in the diagnostic and treatment pathways. In our experience we conceptualized a design of cancer care with a strong level of integration between hospital and territory with the collaboration of the association LILT.

Methods: In 2019, a collaboration was started with local associations of LILT and the Oncology in San Benedetto (AP) and Termoli (CB), thanks to a research project that allowed access and integration of specialists such as dieticians, psychologists, social assistants and voluntaries. A computerized database of patient records has been set up to create a virtual network of shared information for integrated homecare. We administered tests such as PDI (Psychological Distress Inventory) to assess distress and MNA, phase angle and BMI for nutritional assessment.

Results: From June 2019 to June 2021, 384 patients (pts) (32% M, 68% F, average age: 62.5 years) affected by solid or hematological cancer benefited from our integrated services. Of these patients: 18% were in follow-up, 56% in active treatment, 12.5% in adjuvant therapy. The analysis showed an increase in distress levels (29% of 298 pts with PDI>35). Most patients with PDI > 35 were in an active phase of treatment (chemotherapy). For nutritional assessment: 47% of 216 pts were at risk of malnutrition and 12% had poor nutritional status. Moreover, 181 pts required assistance for social service and 60 pts were transported to treatment centers. The 90% of pts expressed a high level of fulfillment in the satisfaction questionnaire for the professional figures they choose, which means that the LILT staff were able to respond to relevant needs in patients' path.

Conclusions: The project, through a path of rehabilitation with a bio-psycho-social approach, has provided useful tools to integrate multidisciplinary aspects in the treatment and care of the cancer patient.

S14

IMMUNE-CHECKPOINT INHIBITORS-RELATED NEUROMUSCULAR AND CARDIAC ADVERSE EVENTS: A RETROSPECTIVE, MULTICENTRIC ANALYSIS AND SYSTEMATIC REVIEW OF CASE REPORTS AND SERIES

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized clinical practice in oncology, with significant benefits in terms of efficacy, quality of life and safety in several tumors. In most cases, the immune-related adverse events (irAEs) are clinically easy to manage and paucisymptomatic. However, in rare cases irAEs may be life-threatening, especially those affecting the neuromuscular and cardiac system. The management of these irAEs is not clear due to the lack of consistent data. Therefore, we collected cases from selected Italian centers and carried

out a systematic literature search to collect case reports and case series on this topic to improve our understanding of these irAEs.

Methods: We collected retrospective data from patients treated in 6 Italian centers with ICIs (PD-1 or PD-L1 and/or CTLA-4 inhibitor) for any solid tumor who experienced neuromuscular and/or cardiovascular toxicity. Then, to increase the caseload, we performed a search of case reports and series of neuromuscular/cardiac irAEs from ICIs with any solid tumor.

Results: The muscular/cardiac irAEs outcome analysis has been conducted including both cases from our institutions (n=18) and the case reports identified in our systematic literature search (n=112), for a total of 130 patients. Among these patients, 44 had complete resolution of their neuromuscular/cardiac irAEs, in 21 there was a clinical improvement with mild sequelae, and 52 patients died as a result of the irAEs. Factors statistically significantly associated with worse outcomes were the earlier irAE onset, within the first 2 cycles of ICI (Fisher P$<$ 0.0001), clinical manifestation of both myositis and myocarditis if compared to patients who developed only myositis or myocarditis (Chi-square P= 0.0051), and the development of arrythmia (Fisher P= 0.0051).

Conclusions: To our knowledge, this is the widest collection of individual cases of immune-related myocarditis/myositis. Early irAE onset, concurrent development of both myositis and myocarditis and occurrence of arrythmias are associated with worse outcomes and should encourage an aggressive immunomodulatory treatment.

S15

THE IMPORTANCE OF THE MALNUTRITION UNIVERSAL SCREENING TOOL (MUST) IN NEWLY DIAGNOSED NEOPLASMS: THE MODENA CANCER CENTER EXPERIENCE

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MUST is a five-step calculator aimed to detect nutritional risk of adult patients (pts); it identifies the risk of malnutrition based on 3 variables: Body Mass Index (BMI), weight loss and food intake. A score between 0 to 2 reveals the risk of malnutrition. The early and appropriate management of any nutritional deficiency can improve outcomes and quality of life.

We performed MUST in a pool of newly diagnosed cancer pts at the University Hospital of Modena between January to December 2021 at the time of first visit. We reported the main differences in terms of gender, age, primary tumor location (PTL), and disease setting between the three risk classes.

We recorded MUST score in 365 pts: 214 males (59%) and 151 females (41%), median age of 71 years old (y), range: 34-94 y. PTL were gastro-entero-pancreatic (GEP) tract (198 pts, 54%) and intrathoracic district (37 pts, 10%), mainly in metastatic setting (175 pts) as they represent pts with highest nutritional risk. The purpose was to early identify pts with the need for a nutritional evaluation and the development of a personalized care plan. 199 pts (55%) were classified as MUST-0, 74 pts (20%) as MUST-1, and 92 pts (25%) as MUST-2 with an incidence of undernutrition/malnutrition of 45%. No gender gap was reported (44% of males with MUST-1/2 vs 48% of females). We found an increased risk of malnutrition in elderly ($>$75y) vs adult pts (54% vs 42%) without any improvement in pts younger than 50y. Pts with GEP tumors had a significant risk of malnutrition: 62% of GEP pts showed MUST 1-2 compared to 28% of non-GEP pts. We found an unexpectedly large percentage of malnourished pts in colorectal cancers (almost a half of new diagnoses), also in 37% of pts with localized disease. Only 55% of pts with MUST-1/2 were diagnosed in metastatic setting (60% of pts with MUST-2 and 50% of pts with MUST-1), stressing that there is a large percentage of non-metastatic pts at high nutritional risk (45%).

MUST is an easy-to-use tool and should be implemented in the initial clinical workup of oncological pts. Excluding head and neck cancer pts that are routinely evaluated from the diagnosis by the Nutritional Team, GEP-tumors are associated with the highest nutritional risk with minor differences in terms of gender, age, and, more unexpected, setting. With these assumptions, we aim to perform MUST in all new diagnoses of GEP pts and evaluate the possibility to expand this opportunity to all pts with a new cancer diagnosis.

S16

CLINICAL FEATURES ASSOCIATED WITH MALNUTRITION IN ELDERLY CANCER PATIENTS

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Table.

Variables	Category	Malnourished	At risk	Not malnourished
Number pts	All	82 (46%)	67 (37%)	31 (17%)
Functional Status	Median scoreADL (0-6)/IADL (0-8)	2	5	5
	Pts not evaluated	0	0	0
Cognitive Status	Pts with MMSE <= 19	19 (35%)	9 (14%)	4 (14%)
	Pts not evaluated*	28 (34%)	3 (4%)	3 (9%)
Depression	YES	38 (68%)	23 (35%)	9 (32%)
	NO	18 (32%)	42 (65%)	19 (68%)
	Pts not evaluated*	26 (32%)	2 (3%)	3 (9%)
Geriatric Syndromes	Median number of Geriatric Syndromes	2	1	1

*Pts not evaluated for poor general medical condition.
IADL/ADL: Instrumental/Activities Daily Living.
MMSE: Mini Mental State Examination.
GDS-5Items: Geriatric Depression Scale 5 Items.

Background: Malnutrition is common in elderly cancer patients (pts) and it is associated with an increased risk of morbidity, disability and mortality. Early identification of characteristics associated with this condition could implement nutritional support strategies.

Material (patients) and methods: Cancer pts hospitalized aged ⩾ 70 years were screened by G8 questionnaire to define if necessary Comprehensive Geriatric Assessment (CGA). CGA identified, through the Mini-Nutritional Assessment (MNA), malnourished patients, patients at risk of malnutrition and patients not at risk.

Results: From Febraury 2019 to April 2021, we screened 190 pts by G8: 5% were not at risk and 95% were at risk. We evaluated, by CGA, 180 pts at risk (60% male, 40% female; median age: 78, range 70-94 years). 162 (90%) pts had a metastatic cancer, 64 from digestive tract (36%) and pts with other cancers were 116 (64%), 64 lung cancers, 16 genito-urinary, 12 breast, 7 prostate and 17 others.

Through the MNA we identified: malnourished pts, pts at risk of malnutrition and pts not malnourished. See Table.

Among malnourished pts 63 died with a median survival of 55 days, among pts at risk 44 died with a median survival of 85 days.

Conclusions: Malnourished patients are characterized by a depressive state associated with a worse functional and cognitive decline than at risk or non-malnourished patients. Early identification of patients at risk, could allow the implementation of preventive nutritional support strategies.

S17

EFFICACY OF ANTIEMETIC REGIMENS FOR HIGHLY EMETOGENIC CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING: A NETWORK META-ANALYSIS

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Background: Several regimens have been introduced in clinical practice in the last years to treat chemotherapy-induced nausea and vomiting (CINV). Direct comparative data remain insufficient. Here, we indirectly compared the efficacy and safety of all combinations used for HEC-induced nausea and vomiting.

Methods: We retrieved randomized controlled trials (RCTs) published in Pubmed, Embase, and Cochrane Library until October 01, 2021. We included II-III RCTs, including adults with any cancer receiving HEC, and compared different antiemetic regimes to prevent CINV. The primary outcome was overall complete response (defined as the absence of CINV from 0 to 120 hrs since chemotherapy); secondary outcomes were acute (absence

of CINV 0-48 hrs after chemotherapy) and delayed (48-120hrs) response and adverse events (AEs).

Results: A total of 41 RCTs enrolling 15575 patients were included. We classified the different antiemetic regimes into 18 different groups. Overall, 4-drug regimens containing a combination of dexamethasone, second-generation 5HT3 antagonists, NK antagonists, and olanzapine proved to be the most effective regimen in terms of complete response (p-score 0.95, 0.88 respectively, for the 5 mg and 10 mg olanzapine dosage). On the contrary, regimens containing a combination of dexamethasone and 5-HT3 antagonist confirm the poor efficacy in preventing episodes of nausea.

Conclusions: In our network meta-analysis, 4-drug regimens displayed the highest probability of efficacy in terms of complete response.

S18

CREATION OF AN ITALIAN INTER-HOSPITAL MULTIDISCIPLINARY TEAM FOR THE MANAGEMENT OF IMMUNE-RELATED TOXICITIES

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Introduction: Immunotherapy (IT) acts by enhancing the immune system response against tumor. Immune-checkpoint blockade can cause inflammatory side-effects that most commonly involve the gastrointestinal tract, endocrine glands, skin, lung and liver (Champiat S, Ann Oncol 2016; Postow M, New Engl J Med 2018). Although international guidelines on the management of immune-related toxicities (IRTs) are available, clinical interventions are still heterogeneous among centers and sometimes mistaken due to lack of expertise. Our project aims at creating an Italian inter-hospital multidisciplinary team (MDT) for the correct management of IRTs.

Materials and methods: In 2021, the Medical Oncology Team at Ospedale Maggiore Policlinico (Policlinico) in Milan identified a group of physicians each of whom gave a recorded talk and wrote a chapter on the specific management of IRTs. During the Oncology Management Fast Track course held by Bocconi University School of Management (2020-2022), two oncologists at Policlinico in Milan and ASST of Bergamo Est in Seriate conceived a model of teleconsultation involving an MDT composed by oncologists and other dedicated specialists. A checklist with patients (pts) specific signs and symptoms was created to help physicians in identifying IRTs while Microsoft Teams™ was used as meeting platform.

Table 1. IRT spectrum.

Total IRTs	73 (%)
Pneumonia	19 (26)
Hypothyroidism	16 (22)
Colitis	10 (14)
Hepatitis	9 (13)
Nephritis	8 (11)
Cutaneous	7 (10)
Hyphophysitis	2 (2)
Miocarditis	1 (1)
Neurological	1 (1)

Results: Both centers revised retrospectively the cohorts of pts treated with IT in 2020. A total of 248 cases were evaluated with 55 pts (22.2%) suffering from one IRT and 19 (7.7%) having more than one IRTs (Table 1). Treatment was stopped definitely in 23 cases (31.1% of all IRTs), 9 pts were admitted (12.2%) and 3 died (4.1%). IRTs were managed by more than one physician in 20 cases only (27%). Since January 2022, five cases have been managed with MDT so far. In two cases steroids administration was necessary while in the remaining three simple treatment delay was required. All five cases continued treatment eventually.

Conclusions: With this innovative model of telematic MDT, we aim at improving healthcare assistance and clinical outcomes of pts treated with IT. Positive long-term effects may be the reduction of emergency room accesses and hospital admissions due to IRT. The next future challenge is the MDT expansion to other centers.

S19

ITALIAN MULTICENTER SURVEY TO EVALUATE LUNG CANCER PATIENTS' AWARENESS ABOUT CLINICAL TRIALS

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Background: One of WALCE's aims is to increase the awareness of people with lung cancer and provide them educational initiatives. It has been recently investigated patients' knowledge and attitudes towards clinical trials in order to gain better insights from their experience.

Material and methods: from January to April 2022, an anonymous questionnaire with 22 multiple-choice and 4 open-ended questions was carried out by WALCE.

Results: 109 patients from 7 Italian cancer centers have filled out the questionnaire. 58% were women and the average age was 62 years. 86% have heard about clinical trials and 90% said to be interested in knowing more about them, but only 46% acknowledged to have looked for information, using different top sources. The majority of patients prioritized their oncologists (44% of cases), over consulting websites (31%), magazines (11%), family and friends (9%) and social media (8%), they've got it during the news about COVID (7%), or by other medical specialists (6%) and patient associations (5%) and more than half of patients (83%) confirmed to have found the information they were looking for (even if 39% only "sometimes"). However, 66% believe their level of knowledge about it is still poor (i.e. 84% are not aware of the different trail phases). At the same time, 72%said to be more inclined to participate in a clinical trial after the COVID Vaccine and 88% were interested to know more about them. According to 97% of patients, clinical trials generate data about safety (47%), efficacy (40%) and prognosis (27%), only 6% answered that the objective is to evaluate the costs of clinical procedures. Only 26% participated in a trial, but 50% would have liked to and "hope" was the reason for half of them, while the remaining 50% preferred not to participate because of fear and lack of information (16% of cases). The collaboration between researchers and patients is considered beneficial by 73% of the respondents, mainly to bring out the needs of patients (41% of the cases). Finally, 85% are willing to receive more information about clinical trials by newsletters (54%) or through the oncologists (18%).

Conclusions: the survey has highlighted the need of lung cancer patients to receive more comprehensive information about clinical trials and to cooperate with researchers to include the voice of patients.

S20

RELIABILITY OF TOXICITIY-RELATED PROS DURING ADJUVANT CHEMOTHERAPY

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Background: It is remarkable how toxicity-related PROs are taken for granted by the oncologic community and regulatory agencies in the light of the demonstrated lack of concordance between patients' real-time and retrospective evaluations of painful experiences. This work explores the reliability of cancer patients in reporting toxicities of adjuvant chemotherapy.

Patients and Methods: Questionnaires on 7 chemo-related toxicities on a 5-grade scale (asthenia, diarrhea, nausea, hand-foot syndrome, paresthesia, dysgeusia and general health status) were self-administered on days 2, 5, 8, 11, 14 and 17 of each cycle. These questionnaires were sealed in envelopes to avoid the influence of the previous experienced evaluations on the next rating by the patients. These results were compared with the same questionnaires administered by the oncologist at the end of each cycle.

The Lins's Concordance Correlation Coefficient (CCC) and the mean difference were used to analyse the concordance between real-time and retrospective evaluations. An acceptable concordance level was set at $\geqslant 0.5$ (range from -1 to 1). The potential systematic tendency to overestimate or underestimate symptoms by patients was also evaluated.

Results: A total of 7182 assessments from 1096 questionnaires were collected from 30 patients with colorectal, ovarian, endometrial, or pancreatic cancer. We observed an acceptable concordance between the retrospective evaluations and the toxicity assessments at early, peak, and late timepoints. In addition, the mean of all the real-time evaluations for each cycle correlated with the retrospective evaluations (CCC for mean ranging from 0.52 to 0.77).

No systematic discrepancy was found between real-time and retrospective evaluations, except for the peak, which was systematically underestimated as expected. Lower

and upper boundaries of the limit of agreement were close to a mean difference of +/-1, which is not clinically relevant considering that is related to a 5-grade scale.

Conclusions: Contrary to what has been demonstrated for painful experiences outside the oncology context, this is the first study to demonstrate that the patients' reported toxicities at the end of the chemo cycles reflect what they have actually experienced without any significant distortion.

S21

EFFECTS OF NUTRITIONAL INTERVENTIONS IN CANCER PATIENTS

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Background: Malnutrition is a frequent critical problem for cancer patients (pts) following diagnosis, which impairs Quality of Life, clinical outcomes and requires appropriate and well-timed multidisciplinary management by professionals with specific skills and training. Early nutrition evaluation, assessment, and support should be instituted in the appropriate clinical setting and nutritional therapy being prescribed and monitored by clinical nutrition specialists, or professionals with specific skills in clinical nutrition.

Material and methods: In Our centre of Oncology in Termoli (Molise) a collaboration with a clinical nutrition specialist of LILT association of Campobasso allows us to have for cancer pts: nutritional screening and assessment, indications for nutritional support, nutritional counseling and evaluation for enteral and parenteral nutrition. Nutritional support is request directly by the healthcare professionals working in the oncology unit. We collected data of pts: Mini Nutritional Assessment (MNA), Body Mass Index (BMI), Phase Angle (PA) both at diagnosis and at regular time points during the course of disease according to tumor type, stage and treatment.

Results: From Dec 2018 to Dec 2021 we investigated 234 pts (93 M/141 F) with solid or hematological cancer for nutritional status. In detail: colon (48 pts), breast (61 pts), high digestive system (37 pts), lung (16 pts), hematological (5 pts) and head and neck (5 pts), other cancer (62 pts). At first evaluation, 57 pts (of 84 pts that completed MNA) have risk of malnutrition or malnourished. A very low BMI (<21) was reported in 41 pts with gastric, oesophageal, pancreas, head and neck cancer at first evaluation. A low PA (age and sex adjusted) was reported in 73 pts. Seven pts need for artificial nutritional support (pts suffering from neoplasm in the neck head district treated with chemo-radiotherapy and patients with gastric neoplasm). Nutritional status was decisive or crucial for 40 pts in assessing wether anticancer treatment was practicable or would be tolerated. A personalized nutritional program and nutritional assessment was required for 204 pts.

Conclusions: In our experience the nutritional support for pts with tumor has an important part of multidisciplinary treatment, so collaboration between oncologists and clinical nutritionists is necessary. A creation of regional recommendation/protocols could improve the nutrional care practices in cancer pts.

S22

MANAGING RESOURCES IN ONCOLOGICAL DAY HOSPITAL: THE IMPACT OF PATIENTS PHONE CALLS IN THE NORMAL DAILY PRACTICE

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Background: Outpatient and Day Hospital activities represent the main commitment for a Medical Oncology. Part of the relationship with outpatients is necessarily maintained by telephone. We wanted to quantify the commitment represented by managing patient calls in our daily practice.

Material and Methods: From 1/1/21 to 30/6/21 we recorded the telephone movement that took place at our Oncological Day Hospital (DH). The DH activity involves 9 doctors and in 2021. 946 patients were followed for chemotherapy (CT) and 7298 courses of CT were administered. Phone calls received from 8:00 to 16:00 were recorded by the administrative staff in a specially built database and then were routed to each doctor who proceeded to recall the patient within 24 hours.

Results: We recorded 2901 phone calls divided according to the following arguments: 757 (26.1%) concerned treatment toxicity, 622 (21.4%) symptoms related to disease, 520 (17.9%) concerned organizational issues, 466 (16.1%) were asked for explanations about prescribed therapies, 327 (11.3%) were asked for evaluation of new exams, 209 (7.2%) concerned Covid vaccines. We then analyzed the database by quantifying the number of telephone accesses for each individual patient and we noticed that, 55 patients made more than 10 phone calls, 39 patients made between 8 and 10 phone calls, 119 patients between 5 and 7 phone calls. This group of 213 patients (22.5% of the total) was responsible for 1762 phone calls (60.1%). According to the Literature, the average duration of a telephone call varies from 9 to 12 minutes, therefore the weight of the

Medical activity carried out by telephone is approximately 4.4-5.8 hours daily. Furthermore, each phone call (about 29 a day), as an interruption of scheduled activities, is a potential source of distraction and therefore of error for every professionist. These data, however important, are certainly underestimated because they don't take into account the telephone calls received directly to the Physicians (mobile, instant messaging, e-mail) that were not recorded.

Conclusions: In our Oncology Day Hospital, taking care of patient calls takes up to 4.4-5.8 hours daily and is a significant source of interruption of scheduled activities. According to our data a small group of patients is responsible for a large part of phone calls. To reduce the effort required by patient phone calls, it is necessary to early identify this subgroup and make it subject of a monitoring active program.

S23

THYROID DISFUCTION INDUCED BY IMMUNE CHECKPOINT INHIBITORS IN ADVANCED SOLID CANCERS

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Background: Immune checkpoint inhibitors (ICIs) revolutionized the treatment of various advanced cancers, but their employment is often associated with immune-related adverse events (irAEs). IrAEs involve different organs and tissues above all thyroid. We aimed to assess the incidence and management of ir-thyroid disfunction in advanced cancer patients (pts) treated with anti-PD1/PD-L1 monoclonal antibodies (mAbs).

Material and methods: We retrospectively evaluated pts with metastatic cancers, including NSCLC, Merkel cell carcinoma, melanoma, squamous cell carcinoma of the skin (SCC), head and neck cancer, renal cell (RCC) and urothelial carcinoma. From January 2017 to April 2022, 179 pts were treated with anti-PD1/PD-L1 mAbs at Unit of Medical Oncology of Crotone. We monitored TSH, FT3, FT4 and thyroid Abs (TPOAb, TgAb and TRAb) on blood at baseline. Thyroid function blood tests were repeated every two treatment cycles, while thyroid Abs were re-tested in case of TSH alteration. Pts with thyroid disease at baseline were excluded. Response to immunotherapy was assessed according to iRECIST criteria.

Results: We included 179 pts: male/female (77%/23%), median age 59 years (range, 31-87), ECOG 0/1 (53%/47%), affected by NSCLC (n=105), SCLC (n=3), Merkel cell carcinoma (n=2), melanoma (n=21), SCC (n=7), head and neck cancer (n=22), RCC (n=11) and urothelial carcinoma (n=8). The pts were treated with anti-PD1/PD-L1 mAbs: nivolumab (N=100), pembrolizumab (N=62), cemiplimab (N=7), atezolizumab (N=8) ed avelumab (N=2). Immunotherapy was administered as first- (33%), second- (65%) or third-line (2%) treatment. During the study period, 53 pts (29.6%) developed hypothyroidism, among whom 44 pts had transient thyrotoxicosis followed by hypothyroidism. Symptoms were usually nonspecific and mild, and management strategy was thyroid hormone replacement with levothyroxine. Only one patient had symptoms of hypothyroidism (fatigue, increased sensitivity to cold and muscle weakness) so, we also tested morning cortisol and ACTH test identifying a concurrent hypophysitis and secondary adrenal insufficiency. No one developed autoimmune hyperthyroidism with TRAb increased. No correlation was observed between the onset of thyroid side effects and response to ICIs.

Conclusions: Thyroid dysfunction is a common irAEs in pts receiving anti-PD1/anti PD-L1 mAbs. Its early recognition, correct management and monitoring allow continuing ICIs therapy to improved clinical outcomes.

S24

PAN-CANCER ANALYSIS OF EXPRESSION ACROSS SOLID TUMORS AND NORMAL TISSUES OF ANTIBODY-DRUG CONJUGATE (ADC) TARGETS UNDER CLINICAL DEVELOPMENT

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Background: ADCs represent one of the most promising and fastest-growing class of compounds in oncology. In solid tumors, four ADCs (T-DM1, T-DXd, Sacituzumab Govitecan and Enfortumab Vedotin) are already approved. This work aimed to evaluate the expression of ADC molecular targets across tumor types and normal tissues.

Methods: On ClinicalTrials.gov, ADCs under clinical development in solid tumors were identified (by 07 March, 2022), and the list of the corresponding molecular targets was defined. mRNA expression of ADC targets was evaluated across pan-cancer and normal tissue by using two publicly available resources: The Cancer Genome Atlas (TCGA) program (including gene expression of >9.000 human tumors across 31 different cancer types) and the Genotype-Tissue Expression (GTEx) project (including samples collected from 31 non-diseased tissue sites across nearly 19.000 individuals).

Results: The ADCs under clinical development in solid tumors recognize forty-five molecular targets. The two targets with the largest number of ADCs under development were HER2 (13 ADCs) and Trop 2 (5 ADCs). Some of the molecular targets have an established role in cancerogenesis (e.g. ERBB2, MET, EGFR, ERBB3, FGFR2, FGFR3, IGF1R), but many others do not have relevant or known biological functions. Expression of these 45 targets across normal tissues displayed significant individual and tissue-type heterogeneity. For instance, salivary gland and lung showed a frequently high expression of more molecular targets, whereas other organs (e.g. stomach, bladder, adrenal gland, pancreas) had only one target significantly expressed. Expression profiles of the 45 targets across tumor types were extremely heterogeneous, with several tumor types having more than 75% of the samples with expression of the target above the 90th percentile of the pan-cancer dataset. Interestingly, the ratio of expression of some molecular targets between normal tissue and tumor was low.

Conclusions: This pan-cancer analysis provides a unique resource describing the heterogeneous expression of 45 ADC targets under clinical development in solid tumors and normal tissue, indicating tumor types in which the development of some specific ADCs should be prioritized and providing clue on interpreting off-tumor side effects. Notably, the ratio of expression of some targets between normal tissue and tumors is low, suggesting that other mechanism are implicated in tumor-specificity of these compounds.

S25

HEALTH PROMOTION: PRELIMINARY ONLINE EVENTS FOR PATIENTS WITH HEREDITARY OR FAMILIAL CANCER RISK

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Background: The hereditary cancer risk has important personal, social and health consequences. The cancer predisposition is multifactorial in origin, caused by a complex interplay between genetic factor and a multitude of non-genetic exposures such as environmental influences, reproductive and life style factors. Increasing rates of obesity, lack of physical activity, sedentary behavior, and frequent alcohol consumption are major lifestyle-related risk factor for cancer. Data indicate that even simple behavior modifications could have a considerable impact on cancer prevention. So, the information about risks factors, prevention and virtuous life style is very important to reduce oncological diagnosis or increase early diagnosis and change the disease history. The recent collaboration between the CGO (Oncology Genetic Counseling) and Department of Fragility of Mantova start with the aim to inform ad motivate patients with genetic or familiar increased cancer risk.

Patients and results: Currently, 950 patients, with genetic or familiar increased cancer risk, are followed for prevention by CGO. With the aim of inform and motivate the patients with hereditary cancer risk, we have been organized the online events with the collaboration of oncologist and biologists of CGO, psychologist of health promotion department, nutritionists and physiotherapist of clinical nutrition department. Three online events were organized and we talked about: 1.genetic basis of hereditary cancer, oncology genetic counseling and oncogenetic risk calculation, surveillance and risk reduction strategies 2.life style related risk factors for cancer, secondary prevention: nutrition and physical activity 3. psychological aspects and perception of risk. Each event were divided into oral presentation of specific topic and discussion between professional and participant. The press and communication office created a poster to advertise the online events in web site of hospital. We invited 100 patients, carriers of pathogenetic mutation, and about 30/40 took part in each event very interested and asking many questions.

Conclusion and future prospettive: Considering the interest of patients, we have decided to convert the oral presentations to a brochure downloadable from the hospital web site. In collaboration with press and communication office, we sent a questionnaire to participants to get feedback on the event and to ask them about topics of interest for future events.

S26

DIGNITY AND TIME PERSPECTIVE: A PILOT EXPLORATIVE STUDY IN CANCER PATIENTS

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Background: The disease and cancer treatments often affect the sense of dignity and meaning and profoundly alter the concept of temporality, leading cancer patients to redefine their temporal perspective. For this reason, the aim of our study was to investigate the possible correlation between dignity-related emotional distress and dysfunctional temporal orientations in the context of cancer. We referred to two theoretical models: Zimbardo and Boyd's "Time Perspective" model and Chocinov's dignity model.

Materials and methods: This study was conducted in the Oncology Department of Fondazione Poliambulanza, Brescia, Italy, between December 2019 and August 2020. We conducted an exploratory study referring to a sample of 107 patients in active treatment for solid tumors, using following questionnaires: Patient Dignity inventory (PDI-IT) and Zimbardo Time Perspective Inventory Scale (ZTPI).

Results: From the PDI-IT emerged that our sample reported high levels of physical and psychological distress. Furthermore, we founded higher distress in patients under 55 years ($p = 0.04$) and lower distress in retired patients ($p = 0.01$). The ZTPI showed in our patients prevailing orientations to the past-positive (39.3%) and the future (37.4%). We noticed a gender difference: men were mainly oriented to the future while women to the past-positive. Moreover, married subjects reported a prevalent orientation to past-positive and the future. Finally, data analysis found moderate positive correlation between the "Negative Past" dimension of ZTPI and high levels of physical ($r = .203$, $p = 0.03$) and psychological distress ($r = 236$, $p = 0.01$).

Conclusions: In our experience in oncology, dignity and time perspective play a central role as indicators of the quality of care. Our study showed the importance of a treatment path that integrates the constructs of Dignity and Time Perspective to favor a better psychological adaptation.

S27

MANAGEMENT OF CHEMOTHERAPY - INDUCED PERIPHERAL NEUROPATHY (CIPN): ACUPUNCTURE APPROACH. FEASIBILITY AND EFFECTIVENESS IN PATIENTS REFRACTORY TO DRUGS

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CIPN affects many cancer survivors and impacts on QoL in medium and long term. Currently there are no pharmacological drugs of documented efficacy for CIPN. In common practice pregabalin and other antiepileptic drugs or antidepressants or integrators are used but patients often stop treatment for side effects. Studies support oncological acupuncture in treatment of nausea and vomiting, hot flashes, xerostomia, pain and fatigue. In this preliminary experience we investigate feasibility and effectiveness of acupuncture in a territorial Hospital. This procedure is recognized by National Healthcare system insides activities of a Pain Hospital Service but standard of care is still lacking. METHODS since march 2022 we are enrolling cancer survivors with CIPN. Recruitment and analysis are ongoing. We exclude patients with underlying diseases with potential neuropathic symptoms: diabetes or neurologic injury. Every patient must have tried at least 3 months of standard care with no result. The protocol consists of traditional acupuncture points: BL17, LI4, LR3, ST36, GB34 bilaterally, CV12, CV6, CV4, GV24, bafeng and baxie. These last two categories of points can be used together or not, depending on whether the hands and feet are involved at the same time or not. The patients were treated once a week for 12 weeks. Needles are left for 30 minutes and an infrared lamp placed on the abdomen was used. At each appointment pain is assessed with the NRS. Patients receive SF 36 questionnaire for QoL at the beginning and at the end of the acupuncture cycle. RESULTS At the moment we have on treatment 10 patients (9 females and 1 male). Age varies from 41 to 80 years. Average age: 63.5 years, median age 65 years. Drugs involved: platin and derivate: n.4 pts, taxanes: n.4 pts, vinca alkaloid n.2 pts. Average time from the end of chemotherapy: 2.3 years, median time: 1 year. 3 out of the first 10 patients are finishing the course of acupuncture treatment. Acupuncture determined a decrease of pain in NRS from three to five points, improvement in QoL and mood, reduction of limitations to normal daily activities. Similar results are referred even by other patients after only 6 treatments. The only side effect was a small hematoma at the needle insertion site. CONCLUSION in this initial experience acupuncture is feasible and contributes to recovering from CIPN. Costs analysis will be performed: patients could stop every symptomatic drug with a better quality of life.

S28

THE IMPACT OF UNPLANNED ACCESSES IN THE DAILY PRACTICE OF ONCOLOGICAL DAY HOSPITAL

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Background: The normal activity of Oncology Day Hospital (DH) provides the possibility of having unscheduled access for patients who have urgent needs dictated by uncontrolled symptoms related to the disease or to the treatment in progress. This type of service allows immediate specialist assessment avoiding emergency care access analyzed the effects of unscheduled service in the three DH that constitutes the Medical Oncology of the ASL Città di Torino in a typical month.

Materials and Methods: From 1/1/2022 to 31/01/2022, all unscheduled accesses were recorded at the Oncology DH of the San Giovanni Bosco (SGB), Maria Vittoria (OMV) and Martini (MRT) Hospitals. Unplanned visits were stratified by reason, outcome and type of referral (spontaneous or suggested by another physician).

Results: In the period in question, out of a total of 1214 DH accesses, 156 unscheduled accesses were found (12.8% of the total) distributed as follows by center: SGB 81 (12% of the total), OMV 28 (14%), MRT 47 (14%). The causes of unscheduled access were summarized as follows: chemotherapy toxicity: 71 (45.5%), uncontrolled symptoms: 39 (25%), problems with central venous catheters or other devices: 25 (16%) and non-deferrable organizational issues: 21 (13.5%). Patients presented themselves of their own free will in 91% of cases while in 9% they were referred by another Physician or other Health Services. In 48% of cases the patient was sent home without any type of additional service, in 9% of cases a hospitalization was necessary and in 43% of cases the patients needed additional therapies. In particular, of these 67 patients 13 (8.3%) underwent blood transfusion and 54 (34.7%) underwent intravenous symptom support therapies.

Conclusions: Unscheduled accesses are an indispensable resource for the management of the cancer patient as they allow for the assessment and management of out-of-control symptoms as well as for the early assessment and management of treatments related toxicities. However, it increases physicians' workload and may have a negative impact on the quality of care. Proactive telemonitoring interventions are being studied to reduce unplanned access with the aim of making the Oncological DH more efficient.

S29

SEARCHING FOR PREDICTORS OF RESPONSE TO ZOLEDRONATE IN PATIENTS WITH BONE METASTASES

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Background: Bone metastases (BM) are common complications of cancer and potentially lead to skeletal-related events (SRE). Several studies evaluated the role of bone turnover markers (BTM) in assessing BM onset and progression, or as prognostic biomarkers. In addition, sporadic reports in the literature describe that routine bone densitometry (DXA) can reveal the presence of BM. However, no clinical studies have been performed so far to combine these techniques during BM follow-up, for prognostic/predictive purposes.

Patients and methods: 47 patients with BM from solid tumors were enrolled at the Medical Oncology Unit of the University Hospital "Policlinico" of Bari. Eligibility criteria included age$\geqslant$18 years, ECOG-PS 0-2, adequate renal function and life expectancy$\geqslant$6 months. No prior anti-resorptive treatment was allowed. Clinicopathological data were recorded in anonymized form. All patients received anti-cancer therapy and 4 mg iv zoledronate every 4 weeks, plus calcium and vitamin D. Full-body CT and bone scan were performed before the initiation of zoledronate (T0) and 6 months later (T1). Bone tumor response was assessed according to the MD Anderson criteria. At T0 and T1, blood samples were collected to measure serum (s) levels of five BTM (BALP, CTX, NTX, osteocalcin, OPG) and patients underwent DXA evaluation. Bone mineral density (BMD) and T-score were assessed at lumbar spine and femur neck. From each patient, a target bone lesion was also selected for DXA evaluation, after manual determination of the region of interest. Statistical analysis was conducted by MedCalc statistical software 12.7.

Results: High tumor burden in bone correlated with increased sCTX ($p=0.007$) and sNTX ($p=0.005$) levels at T0. As for SRE risk, it was found to correlate with low baseline lumbar T-score and femur BMD ($p<0.001$), as well as with lower BMD at T1 in the target lesion ($p=0.01$). Moreover, reduced concentrations of osteocalcin and OPG at T0 were associated with the onset of at least one SRE, while their improvement at T1 correlated with reduced risk of such complications ($p<0.05$). sOPG$<$5.2 pmol/l at T0 predicted disease progression in bone, whereas sNTX normalization at T1 significantly correlated with improved survival, calculated from BM diagnosis (42.9 vs 11.9 months, $p=0.002$).

Conclusions: Combining BTM and DXA evaluation may provide additional prognostic and predictive information in patients with BM receiving zoledronate. Prospective clinical studies are warranted.

S30

BUILDING THE PATHWAYS FOR PRECISION ONCOLOGY: A BOTTOM-UP APPROACH TO PURSUE PROFESSIONAL CONSENSUS

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Background: Precision oncology (PO) pathways must be quickly introduced to bring innovation of cancer genomics to patient's bed. The adoption of precision medicine to clinical oncology workflows is a complex process, involving different professionals, with very few organizational guidelines. Up to date, in Italy some Regions have faced this topic implementing Molecular Tumor Boards (MTBs) in a top-down approach, experiencing some challenges in the integration of these centralized groups within the current care pathways. Our research project aims to identify through a bottom-up approach the main issues of PO implementation in clinical practice and discussing critical aspects with the main stakeholders in order to achieve consensus on potential solutions.

Method: A project Steering Committee has been established. A panel of experts including pathologists, oncologists, and medical directors, has been invited representing 6 Italian Academic or Hub Hospitals and 2 IRCCS in 4 different Regions. After a comprehensive literature research, direct observation of our MTB's one year's activities and a nationwide horizon-scanning, following a non-RAND modified Delphi method, we identified a set of critical issues regarding PO integration in clinical practice. A series of statements have been consequently formulated and submitted to the panel of experts. Two more consensus rounds are planned.

Results: The identified questions, arose from MTB's activity and shared with the expert panel, were related to the use of Next-generation sequencing (NGS), laboratory activities, informed consent for genomic analysis, NGS report, MTB's role and activities, referral of patients. Consensus has been achieved in several topic after the first rounds, when areas of disagreement have been recognized. The more controversial issues were the appropriateness of panel extension, the applicability of informed consent and the integration of MTB activities into current histology-based care pathways. The statements are being evaluated on a Likert scale to define the final consensus of the panel: the results will be presented.

Conclusions: We applied an experimental bottom-up approach to point out organizational issues related to PO implementation into different contexts. We are pursuing a structured professional consensus on solutions that could be effectively implemented into current pathways to meet clinical needs.

S31

A NATIONAL SURVEY ON PRECISION ONCOLOGY IMPLEMENTATION: THE STATE OF THE ART IN ITALY

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Background: Extended genome sequencing technologies and Molecular Tumor Boards are fundamental tools for precision oncology implementation but their application in clinical practice has shown differences within regional healthcare systems. CIPOMO (Italian association of oncology Departments directors), within an ASUFC (Friuli Centrale Healthcare authority)-SDA Bocconi research project, has promoted a survey to evaluate the state of the art of precision oncology in Italy in view of the National Recovery and Resilience Plan. The results are here reported.

Material and methods: On February 10th 2022, 20 queries were sent via Survey Monkey platform to 169 heads of medical oncology departments. The answers were collected until February 28th 2022. The investigated topics included the diffusion and application of Next-generation sequencing (NGS) technologies, types of patients' informed consent for molecular analyses, the contents of NGS report, MTBs' diffusion and their activity.

Results: 129 directors of oncology Departments from 19 out of 21 Italian Regions replied and 113 sets of answers were analyzed. The 47.8% of Centers base molecular diagnostic on single gene analysis techniques, while 52.2% use NGS technologies more or less extensively. Different opinions emerged on what should be included in the genomic report: for 58.2% of participants all the tested

biomarkers must be listed in the report, for the 18.2% it should include only the ones suggested by guidelines, and 23.6% support the use of different reports for clinicians and patients. Consent policy too varies among units: 53.5% always submit it for molecular diagnostic, 36.6% never provide it for routine clinical practice, and 9.9% use a consent only for NGS. MTBs are present in 13 out of 19 Regions but overall 33.6% of Italian oncology units declare not to have access to one. 7 regional and 38 intra-regional MTBs have been set up, in some cases co-existing. Among units who have access to a MTB, 23.9% routinely refer cases for consultation, 43.7% haven't done it yet, and 32.4% report that the actual organization does not fit their needs.

Conclusions: The implementation of precision oncology, NGS technologies and MTBs into clinical oncology workflows is widely heterogeneous in Italy, suggesting the need of outlining professional and managerial best practices and achieving consensus between clinicians and healthcare authorities for a more standardized deployment of these activities in our Country.

S32

ITALIAN MULTICENTRE SURVEY ON CANCER DIAGNOSIS COMMUNICATION

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Background: Effective cancer communication can improve patients' awareness about health status, build trusting relationship and handle emotional distress. We aimed to describe the perspectives of doctors, patients and caregivers on cancer diagnosis communication and on its implications.

Methods: In April 2022, a survey about cancer diagnosis communication was conducted across three institutions in Piedmont, Italy. Three different questionnaires with similar items were administered to patients, caregivers and oncologists. We included patients affected by solid tumours without restriction for histology and stage. We performed a descriptive analysis as pivotal evaluation for designing an observational multicentre study.

Results: 52 subjects were recruited: 9 patients, 6 caregivers, 37 oncologists; median age 37 yrs old; 29 (56%) females. Oncologists' communicative skills were rated as adequate and completely satisfying by 33 (89%) and 2 (5%) physicians, respectively. Communication experience with doctors was described as adequate and completely satisfying by 6 (40%) and 9 (60%) by the group of patients-caregivers, respectively. End of life and progression disease communication were the most stressful topics according to 18 (49%) and 7 (19%) oncologists. In 94% of cases, doctors and patients-caregivers agreed that the setting, time available and language used were adequate for the dialogue. Interruptions during visits were considered relevant by 31 (84%) doctors and 1 caregiver. More than 90% of interviewed reported that doctors verified the patient's level of awareness about disease before starting communication. 25 (68%) oncologists inquired what clinical details patients would like to receive. According to physicians, 81% of patients and 92% of caregivers understood the severity of the disease. The health status was defined as "worrying" by 46% of patients with advanced disease and their caregivers. Oncologists provided a potential proper time to discuss with patients about their concerns according to 13 (87%) patients-caregivers and 33 (81%) doctors. 16 (43%) oncologists followed training courses on communication and 8 (22%) provided cancer diagnosis with psycho-oncologists (up to 4 times per year).

Conclusions: Oncologists, patients and caregivers reported a discrete satisfaction regarding cancer communication experience, although this data requires further validation on a larger observational study.

S33

EXPLORING THE ROLE OF THE CLINICAL RESEARCH COORDINATOR IN CLINICAL TRIALS

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Background: After many years, the role of clinical research coordinator (CRC) in Italy remains a research Achilles heel. The lack of institutional recognition and an official job description have created a lot of heterogeneity of activities and, very often, an overlap with other professional figures. The purpose of this project was to determine the standard tasks performed by these professionals.

Methods: 136 CRCs were anonymously surveyed, using a self-administered questionnaire focused on demographics,

qualifications and professional experience. The questions on responsibilities consisted of an ad-hoc 51 items, organized in 8 macro areas, where respondents had to rate the frequency of involvement in the listed activities using a 3-point scale. We defined as "standard" a task rated as "in all/nearly all trials" by at least half of the participants.

Results: Most of the respondents (79.4%, n=108) work in oncology and onco-hematology, mostly for University Hospitals (33.8%, n=46). A large portion (90.5%, n=123) works for clinical centers that promote academic studies. None of the activities is considered standard for CRC by all respondents; the most frequently (standard for the 91.2%, n=124) is the collection of staff documents, followed by the participation in monitoring visits (83.1%, n=113) and data entry/queries resolution (81.6%, n=111). The investigational drug (IMP) related activities is quite frequent, with the IMP management and storage considered standard for the 39.7% (n=54) of CRC and the IMP accounting for 56.6% (n=77). Furthermore, a considerable number of CRCs are involved as a standard activity in the management of periodic communications with the ethics committee (74.2%, n=101) and in supporting the compilation of feasibility questionnaires (63.2%, n=86). None of the typical activities of academic trials (eg: support to protocol/documents set up or to Competent Authority submission, data monitoring) can be considered standard, not even restricting the analysis to only participants who work in institutes promoting trials.

Conclusions: The activity of CRCs in Italy is profoundly varied and dependent on the workplace organization, just as the active involvement of this professional figure in the creation and organization of research projects is still very limited.

S34

CLINICAL RESEARCH - THE GREAT ABSENTEE OF ITALIAN UNIVERSITY TRAINING PROGRAMS

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Background: In an era characterized by a great complexity of clinical trials and by high standards imposed by regulatory authorities, the education of clinical research professionals became crucial. Education and training is also one of the ICH-GCP guiding principles, thus it should be ensured and included in the undergraduate and post-graduate training programs.

Methods: The Italian Group of Data Managers (GIDMcrc) has spread among the professionals involved in clinical research an online survey aimed to investigate the quality and characteristic of clinical research training provided during undergraduate and post-graduate Italian programs.

Results: The survey was completed by 280 professionals: 178 study coordinators, 29 CRAs, 20 project managers, 7 study nurses and 44 others. The largest part of responders were 25-45 years old (86.4%), works at experimental sites (75.4%) and 90.0% have at least a master's degree (mainly in biology/biotechnology 64% and pharmacy 19.1%). The clinical research education carried out during the degree course was considered poor by 73.7%, medium by 24.6%, and excellent by 1.8%. The knowledge about the clinical research professional world at the time of graduation resulted poor for 71.7% of responders, like the knowledge about career opportunity in this field (71.1% poor, 27.9% medium, 1.1% excellent). For 85.0% of professionals it was necessary additional post-graduate trainings to fill this lack of knowledge on clinical research (55.0% university master courses and 55.4% courses provided by private institutions). Post-graduate trainings were considered very useful by 71,4%.

Conclusions: This survey highlights the lack of undergraduate programs on clinical research education that do not provide the basic information about clinical research field and about possible professional careers. As consequence, most of professionals have to fill this lack of knowledge with specific additional post-graduate course on clinical research (provided both by university or other institutions). This data underline the necessity to improve clinical research education in undergraduate training programs for a better orientation and knowledge of future clinical research professionals.

S35

ANALYSIS OF BURNOUT AND ITS RELATIONSHIP WITH SCIENTIFIC ACTIVITY IN A SAMPLE OF PROFESSIONALS CARING FOR ONCOLOGICAL PATIENTS AT THE ASST VALLE OLONA

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Background: The bornout syndrome is an uncomfortable situation, resulting from psychophysically exhausting

work. Iit often affect healthcare professionals who manage cancer patients and could be increased by the stress related to the SARS-CoV-2 pandemic.

We conducted a survey targeting public health professionals caring for cancer patients after two years pandemic, assuming that there might be an association between scientific activity and lower risk of emotional exhaustion and depersonalization.

Materials (patients) and Methods: In March 2022, a survey was proposed to physicians and psychologists of our company involved in the cancer patient's care pathway, and collected the results anonymously.

Participants were tested with the Maslach Burnout Inventory (MBI) providing three subscales: (A) emotional exhaustion (EE), depersonalization (DP), and personal accomplishment (PA). A profile analysis was performed.

From the literature, cut-off scores for these three scales had been identified that categorize subjects into three ranges: low, medium, and high emotional exhaustion, depersonalization, and personal accomplishment.

A chi-square analysis was performed to observe whether there was a statistically significant association between burnout dimensions and the number of publications made in the past 10 years (0, <5, $\geqslant 5$).

Results: Data from 58 anonymous questionnaires were collected and analyzed. The responders had different specialties: surgery (33.9%), medical (39%), or other (27.1%).

A statistical significant multivariate effect was found: Wilk's $\Lambda = 0.83$, $p = 0.035$. Professionals with higher scientific production (a number of $\geqslant 5$) reported statistically significant lower levels of EE ($p = 0.027$), lower levels of DP ($p = .016$), and more scientific publications appear to be associated with higher PA ($p = 0.035$) than colleagues with limited or no scientific production, regardless of the type of medical specialty.

Conclusions: Increased scientific activity appears to protect health care workers from burnout risk.

These results highlight the importance of involving professionals in different activities that allow them not to focus only on strictly patient-related activities – providing protective factors against the burn-out syndrome.

S36

INTEGRATIVE ONCOLOGY AMONG CANCER PATIENTS: A COMMUNICATION ISSUE?

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Background: Although the use of complementary and alternative medicine (CAM) is spreading among cancer patients (pts), in the lack of a pts-centered communication this remains largely underestimated with potential negative effects on care pathways and clinical outcomes. Integrative Oncology aims to coordinate the delivery of evidence-based CAM with conventional cancer care. The aim of our survey was to investigate the use of dietary supplements, as well as diet and lifestyle modifications, in pts undergoing active cancer treatment.

Material (patients) and methods: We conducted a survey by anonymous written questionnaires, including 17 multiple choice questions, among all consecutive cancer pts referred to our Institution for active oncological treatment. Data were collected from 16 June to 30 June 2021. Statistical analysis was performed using Fisher's exact test or chi-square test as appropriate.

Results: A total of 250 pts completed the survey. Among the respondents, more than one third (37.2%) admitted the consumption of dietary supplements during cancer treatment, under oncologists' prescription in only 13% of cases. The majority of these pts referred the use of multivitamins complexes (41.6%) without an ascertained deficiency condition in 46.2% of cases. A significant subgroup of pts (8.4%, p=0.0005) declared to practice periodic fasting or fasting-mimicking diets, generally during oncological therapy (57.1%) and oncologists were informed in 55.2% of cases. These pts also reported a moderate to high benefit (85%) from fasting, particularly in terms of emesis reduction (50%) and overall well-being (22.2%). A modification in the everyday dietary pattern (p=0.01) and the engage in meditation/mindfulness practices since cancer diagnosis (p=0.002) were seen to be significantly associated with fasting. Among the survey participants, only a small portion (14%) was informed about Integrative Oncology. Similarly, this was also associated (p=0.018) with the decision of fasting during cancer treatment.

Conclusions: Our survey reveals new insights into the use of CAM among cancer treating pts. These findings suggest that more effort should be made in putting Integrative Oncology into practice. Future nationwide investigations on this matter will furtherly contribute to safely and effectively improve pts quality of life and outcomes.

S37

CLINICAL TRIAL INCLUSION IN LUNG AND GENITO-URINARY CANCER PATIENTS: A REAL-WORLD EXPERIENCE

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Background: One major area of need for clinical trials is to include patients truly representative of the real world population. Critical barriers to the enrollment of cancer patients are heterogeneous and related to study design, patients' comorbidities and caregiver difficulties.

Patients and methods: We prospectively collected data of lung and genito-urinary cancer patients receiving new treatment indication at San Luigi Gonzaga University Hospital from April to October 2021, in order to evaluate trial participation rates and factors limiting trials enrollment.

Results: Overall, 346 patients were included in the analysis: 155 (44.8%) with lung cancer, 131 (37.8%) with prostate cancer, 40 (11.6%) with urothelial cancer and 20 (5.8%) with kidney cancer. 280 patients (81%) presented with metastatic disease. ECOG performance status (PS) $\geqslant$ 2 patients were 16% (56) of the included population and 288 (83%) presented with at least one major comorbidity. 310 patients (90%) were candidate to active anticancer therapy. Among them, 253 (82%) patients received treatment as per clinical practice, 16 (5%) targeted treatments in expanded access programs and 41 (13%) were included in experimental clinical trials. The majority of the studies were phase III (23, 56%) and II (16, 39%), mainly sponsored by pharma company (39, 95%), with a superiority (30, 73%) open-label (25, 62%) design, not requiring re-biopsy (29, 71%), nor placebo-containing (24, 59%). Targeted therapy $\pm$ other drugs (14, 34%), antibody-drug conjugate therapy (13, 32%) and immunotherapy $\pm$ other drugs (10, 24%) were the most common experimental treatments. The main barriers to clinical trial enrollment were: disease/molecular characteristics not satisfying inclusion criteria (63, 25%), the unavailability of studies at home/near institutions (57, 23%), poor PS (34, 13%), presence of relevant comorbidities or non-permissive medical history (19, 8%), patient's refusal (18, 7%) mainly related to blinded (50%), and placebo-containing (50%) studies or to trials requiring re-biopsy (17%). No main differences were detected between lung and genito-urinary subgroups.

Conclusions: Patient enrollment in clinical trials remains crucial, especially in a period of great therapeutic innovations, but the process is, unfortunately, still unsatisfactory. Continued focus on this topic is critical in order to overcome barriers and ensure the best treatment option to all patients.

S38

CONTRAST-ENHANCED ULTRASOUND (CEUS) FOR DIAGNOSING HEPATOCELLULAR CARCINOMA: OUR EXPERIENCE WITH FRAGILE PATIENTS

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Introduction: Differentiating benign from malignant liver lesions affects the patient's prognosis and the subsequent diagnostic and therapeutic process. Conventional ultrasound is insufficient to address the diagnosis of a liver lesion properly. CEUS (Contrast Liver Ultrasound) is a technique that allows overcoming some limits of B-mode ultrasound. It is highly controversial and not univocally accepted by national and international guidelines, whether CEUS can have a role as a first-line test for typing a lesion detected during a CT/MRI examination. In our hospital in Termoli (CB) we started a collaboration with our center's radiologists aimed at using CEUS to evaluate and characterize liver lesions undefined on basic ultrasound imaging in fragile patients (pts).

Materials and methods: Pts with undetermined liver lesions, referred by the oncology clinic, were evaluated. Two radiologists evaluated the reported pts with CEUS. The test was conducted in double-blind mode: the LI-RADS classification was used. In case of questionable tests the patient was referred for abdominal MRI.

Results: From January 2021 to January 2022, 24 pts were investigated. Of the 24 pts, one had no focal structural changes, so he was excluded from the study. Twenty-three pts (6 F/17 M) with a median age of 68.6Sy were evaluated. Of the 23 cystic or solid-cystic lesions, CEUS allowed a correct classification according to the "Liver Imaging Reporting And Data System" (LI-RADS) In the diagnosis. Of these: 11 lesions were classified as LI-RADS1, 1 lesion as LIRADS 2 and 1 lesion as LIRADS 3. In Doppler ultrasound, 9 of the 23 inhomogeneous nodal lesions showed a predominantly peripheral vascularization. After IV contrast medium infusion, these neoformations showed an intense and inhomogeneous enhancement with a predominantly peripheral globular and/or ring-shaped pattern with associated irregular central septations and central hypoechogenicity in all phases, compatible with LIRADS 4 and 5. One focal lesion was compatible with a metastatic lesion.

Conclusions: CEUS is an easy-resolution, repeatable method with a very high safety profile. Although using

CEUS as a 1st level test does not seem to be the best strategy in terms of cost- effectiveness, in our experience with fragile pts it has proven to be a sensitive and safe method. Therefore, close collaboration between radiologists and oncologists for case-by-case evaluation is necessary to avoid more invasive tests in fragile pts.

S39

RESCUE THERAPY IN MALIGNANT PERITONEAL MESOTHELIOMA (MPM)

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Background: Mesothelioma is a very rare malignancy of serosal menbranes, including the pleura, pericardium, peritoneum and the tunica vaginalis testes. It is most commonly encountered in the visceral pleura with the second most common location in the peritoneum. Malignant peritoneal mesothelioma (MPM) commonly presents with diffuse, extensive spread throughout the addomen with rare metastatic spread beyond the abdominal cavity. Though the first-line treatment for MPM is cytoreductive surgery (CRS) plus heated intra-peritoneal chemotherapy (HIPEC), not all patients are appropriate candidates for surgical intervention. Systemic chemotherapy is the alternative treatment for those that are ineligible or wish to pursue non surgical management. Peri-operative chemotherapy has also been used in patients who are high-risk or extensive disease, though the efficacy of peri-operative chemotherapy is still being investigated. Most studies of chemotherapeutic agents have been done for pleural mesothelioma, often excluding MPM. In 2003 Vogelzang and associates published the results of a phase III randomized trial that showed a media survival of 12.1 months with Pemetrexed plus Cisplatin, compared 9.3 months in the Cisplatin only group. Currently, the data supports Pemetrexed with Cisplatin/ Carboplatin as the first line chemotherapy regimen with other drug combinations reserved for second-line therapy.

Methods: From March 2019 to July 2021 3 patients (3 males with a median age of 56 years, range 50-63) with MPM were eligible for analysis. Carboplatin- Pemetrexed doublet was administered in all patients in first-line. Patients with histologically confirmed measurable or evaluable MPM, ECOG PS 0-2 received Docetaxel 75 mg/m2 day 8 and Gemcitabine 900 mg/m2 day 1 and 8 every 21 days.

Results: In all patients partial response was achieved. No life threatening event occurred. No grade 3-4 toxicities were observed. Hypertransaminemia grade 1 in 2 pts, neutropenia grade 2 in 2 pts, anemia grade 1 in 3 pts, asthenia grade 1 in 2 pts, nausea grade 1 in 3 pts, constipation grade 1 in 2 pts and alopecia grade 2 in 3 pts.

Conclusions: preliminary data suggest that this schedule is well tolerated and may abrogate disease progression in patients with MPM refractory to Carboplatin-Pemetrexed schedule.

S40

THE CANCER AND RESEARCH CENTER OF MARCHE REGION (CORM): A NEW INSTRUMENT TO OFFER OPPORTUNITIES FOR DIAGNOSIS AND TREATMENT TO CANCER PATIENTS

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Following the new health needs emerged during the covid pandemic, in June 2021, the Cancer and Research Center of Marches Region, CORM (www.corm-marche.it) was instituted at the Department of Oncology of the Academic Hospital Ospedali Riuniti, Ancona (IT) with the Italian Ministry of Health patronage.

The CORM includes:

- The digital platform for telemedicine to offer the ability to admit de novo diagnosis of solid tumors, as well as provide second opinions and to promote continutiy of care between hospital and territory
- The Molecular Tumor Board, a multidisciplinary board including clinicians, pathologists and biologists to recommend personalized therapy in the "Precision Medicine" era. High throughput genomic profiling tests may be indicated by MTB team: foundation one cdx/liquid biopsy/ heme, 16 genes DNA panel and other panels that are relevant in different types of tumors, NTRK evaluation and PDL1 test. The molecular profiles are useful to indicate new treatment strategies, but also to understand the mechanism of resistance otherwise not justificable with a standard approach.
- The Clinical Trial Unit which performs about 40 interventional trials/year and includes a phase 1 unit, certified by AIFA. Every year, 100 patients are enrolled in clinical trials, about 10/year in phase 1 trials.
- The Regional Center of High Specialization in Oncological Genetics. In December 2004, the Regional Center of High Specialization in Oncological Genetics was instituted and

we developed an increasing expertise in genetic counseling and tests for hereditary syndrome (hereditary breast and ovarian cancer syndrome and Lynch syndrome). Last year, we conducted 3166 genetic counseling, consisting of collecting genetic information and drawing pedigree, making or validating diagnosis, communicating clinical and genetic information and supporting the family to reach a decision and take appropriate actions. From January 2022, we activate the telemedicine platform also for genetic counseling to select patients who deserve genetic testing and come from distant territories.

We aim to create a technological network between the oncology departments and general practitioners, patient associations and all the other specialists to guarantee the continuity of care and to overcome the disparities in oncological health services, simplifying cancer clinical management.

S41

PROMOTING PATIENT CENTERED-APPROACH IN CLINICAL RESEARCH: THE EVOLVING ROLE OF CLINICAL TRIAL CENTER

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Background: In the last years, the implementation of Clinical Trial Centers (CTCs) has presented numerous advantages for patients: new diagnostic and therapeutic opportunities, a dedicated multidisciplinary team, new challenges in the adoption of innovative technologies and tools. Their role in clinical research is changing contributing to clinical decisions-making.

CTC of Papardo Hospital of Messina, certified ISO 9001:2015 since 2017, promotes a patient centered approach to improve research quality and a more active patients' participation. The aim of this study was to investigate the involvement of patients in the activities of our CTC and assess their knowledge and perceptions regarding clinical research.

Material and methods: From December 2021 to April 2022, we launched an on line questionnaire consisted of multiple choice and Likert-score questions for cancer patients enrolled in observational and clinical studies. The survey included three parts: demographic information, therapeutic treatments and patients' perception of CTC activities. Participation was voluntary and anonymous. Data was analysed using standard research procedures.

Results: A total of 90 cancer patients completed the survey. Participants were primarily female (75%) with a mean median age of 55.4 years. Regarding level of education, 45% of the patients have a high school diploma and 35% a degree. The most common tumour site was breast (45.5%), followed by lung cancer (35%), gastroenteric cancers (9.5%). The highest proportion of patients was in active cancer treatment (73%). Focusing on research activities, most of patients (74.3%) were aware of the CTC role in the management of clinical studies and the direct implications for research quality improvement and patients' support.

They had received information on the specific activities mainly by the research team (86%) and 14% from informative materials. In addition, a significant number of patients (85,7%) consider the participation in clinical studies an important therapeutic opportunity.

Conclusions: Integrating a patient-centered approach represents an important process for CTCs to improve overall quality of services and care. Further communication strategies will be implemented, including social media for a better patients' involvement and awareness on the evolving research scenario and the development of new therapeutic opportunities.

S42

PATIENTS WITH BLOOD TUMOURS HAVE LESS ACCESS TO PALLIATIVE CARE THAN THOSE WITH SOLID CANCERS: WHY?

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Background: Patients with haematological malignancies have less access to Palliative Care (PC) and delayed referrals than patients with solid tumours, although both have complex situations and need support throughout the course of the disease. Which is the reason?

The aim of this survey was to analyse the perceptions of health professionals involved in haematological

patients'care on PC, to identify which are the barriers preventing access to PC and if facilitators exist that could help the trust.

Material and methods: A questionnaire was created for this study, containing specific questions regarding the presence of a hospital PC team, transfusions, multidisciplinary collaboration, education in PC and referral timing of the patients to the PC services. The questionnaire was then submitted to medical and nursing staff of 6 Haematological Units. Finally, data collected were analysed using quantitative and qualitative methods.

Results: Of the 320 questionnaires sent, 142 were completed: 96 by nurses and 46 by physicians. Analysing specifically the answers: only 72 participants have a PC team in their hospital; 77 professionals have never attended a PC course, 42 did it on their own initiative outside their hospital, while 23 within their hospital; the majority of operators (113) agreed that cooperation between the 2 disciplines benefits both patients and caregivers, but only 100 knew the PC team role; on a Likert scale, 70 professionals thought it could be appropriate to refer patients to PC at the beginning of their care pathway, while 75 when the prognosis is less than 3 months and 75 when the symptoms are incoercible; most professionals (24/46 doctors and 53/96 nurses) agreed with transfusions even in the last stages of the disease.

Concerning the facilitators: for 93 professionals the presence of a PC team within the hospital is fundamental as for 67 the presence of a dedicated case manager; 117 health professionals believe the training courses on PC are important.

Conclusions: The attitude of respondents tends to be favourable to the proposed integration of the 2 disciplines. However, they believe that there are few referrals to the PC team because of clinical, cultural, educational, organisational and resource issues. Nevertheless, the interest in the subject is undeniable, as confirmed by the 44,4% response rate, which is satisfactory when compared with that of similar studies conducted abroad.

S43

OFF-LABEL USE IN ITALY: IS THERE SPACE FOR HARMONIZATION?

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Background: In Italy with Law no. 96 "Legge di Bella" (1995) and subsequent updates, the use of authorized medicinal products is allowed outside of the summary of product characteristics (SmPC) indications under the direct responsibility of the prescriber and in patients who cannot be treated satisfactorily with authorized standard treatments, provided that at least favorable clinical trial data from phase III or phase II trials are available for this use. With LAW 296/2006 "Legge Finanziaria anno 2007" prescribing centers were asked to identify by February 28, 2007 the person responsible for the application procedures for off label use according to Law 648/96, and temporarily attributed this responsibility to the Health Director for each prescribing center. Considering that to date no guidelines on request and authorization procedures for off-label use have been established at a national, or at least regional level, an anonymous survey was conceived to outline the current Italian framework on this topic.

Materials and methods: The survey was structured with 10 multiple choice answers and checkboxes, and one comments section. All questions were mandatory. The link to access the electronic questionnaire was sent by email firstly to selected Italian physicians to test the tool. Corrections were made in line with observations and suggestions and it was then shared between the 6th and the 13th of April with a wider audience through the "Gruppo Italiano Data Manager" (GIDM) mailing list.

Results: The total number of completed surveys collected was 29. In Italy the off-label use requests are performed in most cases by the prescribing physicians alone (58.6%, n=15) or with the help of a study coordinator (41.4%, n=11). Moreover, most sites (62.1%, n=18) have a Pharmaceutical commission evaluating the off-label use requests, and in almost half (48.3%, n=14) the Health director is responsible for the final authorization. The latter is granted in less than a week in 41.4% (n=12). 75.9% (n=22) of respondents confirmed in urgent cases the evaluation can be expedited.

Conclusions: From the completed surveys so far, it is clear that despite a common approach in the majority of cases, there is still a notable variability in the request and authorization processes for off-label use among prescribing sites in Italy. It is clear that there is an urgent need for an update in legislation on this topic to standardize the process throughout the Country.

S44

THE CANCER PATIENT BETWEEN COMPLICATION AND COMPLEXITY: THE EXTERNAL INDIVIDUAL WORLD IN CANCER TREATMENT

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Background: Complication and complexity are two aspects that the cancer patient carries with him during the time he spends in cancer treatment. The tumor is to be considered a disease that is part of the biological complications that affect one or more organs of our body, which refer to a very specific treatment, to surgical interventions of a certain type, to any pain therapy, etc. Complexity, on the other hand, represents a term that refers to the description of the ensemble that make up the individuality of the cancer patient. Therefore, within the treatment, various elements that are part of the patient's world and that can represent a strength in the oncological path must be taken into consideration.

Material and methods: 80 patients from the oncology ward participated in the research, recruited in 2019 (n = 40) and in 2020-2021 (N = 40). The semi-structured clinical psychological interview, lasting one hour, was used as a data collection tool, which examined the evaluation of the patient's depression, anxiety and altered emotional states regarding the presence or fewer family affections during hospitalization, visits from friends, knowledge of one's status as a cancer patient.

Results: From the analysis of the data it emerges that the oncological patients who suffered from depression, anxiety or elements attributable to altered emotional states in 2019 are 32.50% of the sample examined while in 2020 and 2021 the recorded incidence includes about 90.00% of the sample. This higher incidence derives mainly from the consequence of the closure to visits by family members in the medical oncology ward for the sars-cov-2 pandemic, rather than from the other factors taken into consideration, leading, in the most serious cases, to requests for early discharge by of the patient himself.

Conclusions: Understanding the worlds within the cancer patient should not be seen as an obstacle to treatment but as a resource to be used to improve patient compliance. Placing the complexity of the individual at the center of the analysis determines a decrease in anxiety, depression and altered emotional states with an increase in the doctor-patient relationship, effectiveness of treatments, circulation of information and trust in care.

T - Oncology Nursing

T01*

PROPOLIS FOR ORAL MUCOSITIS IN PATIENTS WITH ADVANCED CANCER IN PALLIATIVE CARE: A PHASE II STUDY

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Background: Oral mucositis (OM) with dry mouth, dysphagia, dysgeusia, dysphonia and pain significantly impacts nutrition, social interaction and QoL of cancer patients. There are no effective interventions for OM of patients with advanced cancer in palliative care. Propolis has anti-oxidant, antimicrobial and anti-inflammatory properties for oral mucosa. It reduced oral ulcers in patients with stomatitis and oral mucositis in patients undergoing chemotherapy.

Methods: Prospective monocentric Phase II study aimed at evaluating safety, tolerability and activity of a propolis-based product (Faringel Plus) in addition to oral hygiene protocol for prevention and treatment of oral mucositis in patients with cancer in palliative care (hospice or home care). The sample (n=77), was defined by Simon's Optimal approach in 2 steps: step1_26 cases, step2_51 cases with P0: 0.45; P1: 0.60; Alpha: 5%; Power: 80%. If in >41/77 cases OM does not arise or improves, the hypothesis under study will be accepted and further studies justified. Patients with life expectancy <7 days, inability to swallow, head/neck cancer or tracheostomy were excluded.

OM is evaluated with the Oral Assessment Guide (OAG). The intervention lasts 2 weeks. FaringelPlus is administered twice/day to patients with no mucositis, and increases with severity of mucositis to 3 or 4 times/day. Eating comfort, meal completion, treatment adherence and oral pain are also assessed. Quality of life is measured with the European Quality of Life Utility Scale and Oral Mucositis Daily Questionnaire.

Results: Step1 was satisfactorily completed and step2 is ongoing. Most of 35 patients who completed the study (n=20 male, 57%; mean age 73.4 [DS 10.8] range: 45-91) were diagnosed with lung (n=8), colorectal (n=6), or pancreas, breast or haematological (n=4 each) cancer. In all patients OM was either absent at accrual and did not arise (n=5), either improved (n=30, from day 1 OAG=12.7 (SD 3.25, range 8-21) to day 15 OAG = 9 (SD 1.77, range 8-15). Eating comfort rose from 6.4 to 7.7 (NRS 1-10) and meal completion rose from 68% to 86%. Adherence was 100% in 52,8% cases and mean adherence 87,6%.

Conclusions: The encouraging results are close to determining safety, acceptability and activity of Faringel Plus in protecting oral mucosae. A multicentre triple-blind randomized trial controlled with placebo will be planned to evaluate its effectiveness in prevention and treatment of OM in patients with advanced cancer in palliative care.

T02*

THE IMPACT OF DISTRESS AND DEPRESSION ON THE IMMUNE RESPONSE TO SARS-COV-2 MRNA BNT162B2 VACCINE IN CANCER PATIENTS

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Background: The prevalence of moderate or severe emotional distress in cancer patients ranges from 30 to 45%. There is evidence that distress and depression can impair the immune system's response to vaccines, and this effect may be greatest in vulnerable groups such as cancer patients. We have previously shown that chemotherapy, targeted therapy, hormone therapy, lymphocyte count $< 1\times109$/L and increasing age predicted poor antibody response at 6 weeks (Buttiron Webber T. et al, Eur J Cancer. 2021). Here we assessed the effect of psychological distress on the antibody response at 6 months after two doses of vaccine.

Material (patients) and methods: Before the first dose of vaccine, after 42 days and at six months the clinical research nurse administered the Distress Thermometer questionnaire to the participants. The main outcome measure was the antibody response at 6 months. Multivariable logistic and linear mixed-effects models for repeated-measures analysis were applied adjusting for possible confounding variables.

Results: Between March and July 2021, 320 subjects were recruited, and 290 were assessable both for distress and antibody response at 6 months. Main patient characteristics were the following: median age 68.2, female 59%, stage IV 59%, no treatment 22%, chemo 39%, hormone 24%, target or immuno 15%. At baseline, high distress (5+) was present in 26% of subjects, with a higher rate in women vs men (34.4% vs 23.8%, p=0.08). Women with the highest educational level (degree) were significantly more distressed during time (p=0.04). Younger age predicted a higher risk of elevated distress in terms of personal relationships (p=0.004) and practical problems (p=0.01). The percentage of non-responders at 6 months was 10.1% in patients with low distress vs 20.6% in those with high distress (Odds Ratio [OR]=2.5; 95% Confidence Interval [CI] 1.1-5.8, p=0.04). Also advanced stage and increasing age significantly predicted a poor seroconversion. High distress at baseline was also associated with lower CRP response, a marker of vaccine response (p=0.003). Depression was also associated with lower antibody response at 6 months (p=0.003).

Conclusions: Distress and depression are important predictor of poor seroconversion to SARS-CoV-2 vaccine. These findings indicate the need for a multidisciplinary approach with the contribution of a psycho-oncologist to manage psychological disorders in cancer patients and further studies by the clinical research nurse.

T03*

WORKPLACE VIOLENCE AGAINST CANCER NURSES: A DESCRIPTIVE ANALYSIS

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Background: Workplace violence (WPV) impacts negatively both healthcare workers and healthcare organizations. Nurses are the most exposed healthcare workers to vertical WPV. This study aimed to describe the WPV against nurses in medical cancer inpatient units in Italy.

Material and Methods: This is a secondary analysis conducted in medical cancer inpatient units from a larger national study between January and April 2021. Data were collected through the Practice Environment Scale of the Nursing Work Index (PES-NWI); and the adapted version of the Violence in Emergency Nursing and Triage (VENT) Questionnaire. Descriptive analyses were conducted.

Results: The analysis was conducted on 201 cancer nurses (84.6% female, mean age 41.2 years, SD 10.8). Seventy-two nurses (35.8%) reported WPV in the last year and/or the last week and 38 (18.9%) only in the last week. In most cases, the perpetrator was male (49%) and was between 56 and 65 years old (32.1%). The major cause of WPV was the perpetrator's anxiety and agitation (29.2%, n=21), followed by the perpetrator's fear (12.5%, n=9). WPV violence was perpetrated especially while nurses were communicating with the patient and/or caregivers (19.5%, n=14) and managing the long waiting times (15.3%, n=14). The WPV episodes were reported by 20.8% (15/72) of nurses, in most cases (53.3%) they reported orally to the head nurse. Seventy-two cancer nurses (35.8%) thought that WPV is an inevitable part of the work and 129 (64.2%) that WPV is increasing. Specific training programme (STP) was identified as a WPV prevention measure by

68.2% (n=137) of nurses. STPs were attended by 24.6% (n=49) of the sample of whom 47.9% (n=23) of them completed it.

Conclusions: Public healthcare services should reduce WPV by investing in improving the nurse work environment. Integrated and multimodal programs for the prevention and management of WPV are useful to address it.

T04

THE CARRY OUT PROJECT OF THE PRIMARY NURSING MODEL (PN) AT THE ONCOLOGICAL DAY HOSPITAL OF THE MARIA VITTORIA HOSPITAL IN TURIN

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Background: Primary nursing is a care system in which all nursing care for a patient is managed by nurse.

The nurse is responsible for the planning, implementation, evaluation, and coordination of the nursing care until the patient's discharge Most the experience of PN are referred to Internal of Medicine Ward, but few experiences are described in oncological patient care and in DayHospital setting. The present report include the first eight months experience of PN.

Material (patients) and methods: The experience and the related PN method has been planned and developed since September 2021 and included 43 patients in adiuvant or palliative settings for different types of tumors.

Six nurses were involved in the PN project after a theorical and practical training on PN. Patients involved in the study were identified after a multidisciplinary discussion involving nurses team, medical oncologist, psychologist, social worker.

The identified patient is contacted by nurse who explain the method, the development and the aim of the study.

Informed written consent is required by the Ethical Committee.

The plain of care is decided in a multidisciplinary approach, but the care plan is decided by the primary care nurse.

All data are stored in a specific electronic medical record.

Results: The first report is relative to 40 patients, but the study is well accepted and more than 70 patients will be included before the end of the year.

All the patients were assigned to nurse team of primary care at the Maria Vittoria Hospital Oncological DH, who planned the care pathway from the beginning to the end of the oncological care.

Conclusions: The PN method is apply in Oncological DH and is very useful to a personalize of the care plan and introduce a patient centered care approaches. The whole data about this experimental approach will be be presented at the AIOM National Congress.

The limitation of this study are: A lock of randomization study between PN system and an usual care pathway.

The risk of inequality between patients introduced into Pn method and the patients following according to common model of assistance. The extreme personalization of the nurse-patient relationship. The goals are: a higher level of care, strict cooperation between nurse end patient, better adherence to the therapy plan, increase of humanisation of the care's pathways, improved collaboration between nurse-patient-caregiver and family.

The study is in progress.

T05

CARE GIVER EDUCATIVE PROGRAM FOR MANAGEMENT OF THE CENTRAL VENOUS CATHETER (CVC) IN CANCER PATIENT AND CREATION OF A CARE BOOK AS A SUPPORTING INSTRUMENT OF THE TRAINING PATHWAY

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Background: Most of the modern medical treatment of cancer diseases request the implant of a central venous catheter (CVC) which can remain "in situ" for a long time, moreover its management could became very significant at the patient's home. The goal to achieve is to decrease the unnecessary access at the place of care considering the frailty of the oncological patient. On the other side, the same line of central venous catheter can be used for parenteral nutrition, pain treatment, continuous and supportive care. As a consequence, an educative program for the informal caregivers must be organized in order to avoid distress to cancer patients.A specific educative program for the management of the central venous catheter was implemented at the Oncological Day Hospital (DH) of Maria Vittoria Hospital in Torino with practical examples and achieving of the electronic booklet.

Material and Methods: Both the caregiver training and the booklet were composed by the following sections:

Introduction of the different kinds of CVC. The best choice for the single patient needs.

The second step is to achieve the informed consent from the caregiver on the educative program of the CVC management.

Training on hands hygiene, on the antiseptic technique, inspection of the insertion site of the catheter in order to recognize early of any possible sign or symptoms of infection.

Cleaning of the CVC, its maintenance and dressing.

How to employ the demonstration videos accessible by QR code.

Reference phone contacts.

Steps of the study.

Theoretical phase developed on the booklet with training certification for the acquired skills according to the best practice guidelines.

Practical phase with a training course for Caregivers.

Results: Phase 1 concluded: booklet with an informative-training-certification value which, unlike those already produced by other companies, also presents the training course carried out by the user, with relative "certification"by the nurse of the skills acquired according to best practices.

Phase 2: Creation of a training/certification course addressed to a caregiver of a person with an oncological disease and whose is carrier of CVC.

Conclusions: Our target is to lead the caregivers to achieve the autonomy in management of the device, through an educative program, practical approaches in the front of the nurse team, using the care-book as an informative / educative / certification instrument about the caregiver's autonomy and skills improved during this program.

T06

HOME VENOUS ACCESS DEVICE INSERTION DURING COVID-19 PANDEMIC, FROM AN EMERGENCY RESPONSE TO A DAILY WORK PRACTICE

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Background: Reliable venous access device(VAD) is essential in providing effective care for many cancer patients. VAD are placed by a specialized team using ultrasound guidance in a dedicated room of the hospital, however, during the pandemic COVID-19, many not autonomous or bedridden cancer patients were unable to reach the hospital for VAD insertion, due to unavailability of ambulance for the transport. For this reason the specialized team organized a modality of positioning VAD at patients' homes.

Material (patients) and methods: In January 2012, a VADs-team was established by the health authority in the oncology-hematology department at the hospital of Piacenza, it initially served the care of cancer patients in the oncology and hematology department of the Piacenza hospital; subsequently, during the COVID-19 pandemic, the team was able to reach patients at home to positioning VAD for people unable to go to the hospital. The positioning of the VAD was performed under ultrasound guidance, according to the same modalities used in the hospital. In the present study we retrospectively analyzed data of patient who positioned a VAD.

Results: Between March 2020 to December 2020 and January 2021 to December 2021, VADs were positioned in 28 and 31 cancer patients respectively, in both groups there were patients with advanced cancer. The VAD utilized was the Midline for each patients. The mean age of the patients was 88 years, the majority were female (>60%). VADs allowed the planned treatment in 94% of the patients. The complications were low: VAD dislocation (<1%), thrombosis (<2%). No infections were registered.

Conclusions: During COVID-19 pandemic the VAD-team demonstrated the feasibility of VADs home positioning, in for cancer patients, subsequently, the VAD-team served also non-cancer patients who need home Vad positioning. The results of our study allowed this procedure to become routine practice for not autonomous or bedridden cancer patients with a need for VADs who are unable to reach the hospital for the insertion.

T07

NARRATIVE MEDICINE IN ONCOLOGY DEPARTMENT OF PIACENZA: TELL THE CHANGE OF HELPING RELATIONSHIP WITH THE USE OF PERSONAL PROTECTIVE EQUIPMENT (PPE)

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Background: After Covid-19 emergency, operators always had to work with approved and safe Personal Protective Equipment (PPE) for patients and professionals, but which limited communication, the approach to assistance and the helping relationship. Those who practice professional health care practices as they are exposed to the suffering of others should be aware of the need for

themselves to equip themselves adequately to face difficult situations through suitable narrative practices of self-care. This study has a dual purpose: to investigate the experience of the health care personnel of the Piacenza's Oncology Department through narrative medicine following the use of PPE and to help operators become aware of it through creative writing.

Material and methods: We conducted a qualitative study, the data collection tool is creative writing, consisting of write unconditionally by first reading a preface consisting of sequential questions. The sample selection has been voluntary based subject to prior informed consent signature. 14 texts writed by nurses and oss were collected. The data analysis took place with analysis of the thematic content. Qualitative analysis involves the fragmentation of data into simpler units and the subsequent recomposition in new ways.

Results: The results of creative writing were divided into four macrocodes: PPE Data Changes, Strategies, PPE Negative Side, PPE Positive Side, in turn divided into several microcodes. Emerge the difficulties of the health care personnel in using PPE in the care approach and the strategies that were introduced in the face of these difficulties.

Conclusions: From the analysis emerged all the changes that the PPE have involved: the impossibility of approaching, seeing and touching each other, in particular not being able to show the face and to be recognized and to smile. Through examples of everyday life, the disadvantages of the use of PPE have been highlighted but at the same time it is evident that the use of protective devices has made it possible to re-elaborate the approach to the patient, reminding professionals of the need for empathy and listening, devising creative ways to deal with these difficulties such as the use of video calls, gazes. They noticed a greater humanization thanks to the use of PPE: less abrupt and frenetic ways have been introduced during the satisfaction of needs and a greater willingness to stay "here and now" in the care relationship to limit the shortcomings.

T08

THE NURSING CARE OF THE PATIENT WITH COLORECTAL CANCER: EXPERIENCE AT THE PERCORSI CLINIC OF THE A.USL OF PIACENZA

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Background: In Emilia Romagna in 2004 the incidence was about 32/100,000 women and 37.2 / 100,000 men and represents the second most common cause of death from neoplastic causes in males and the third in females.

Case management of colorectal cancer should be discussed by a multidisciplinary working group.

Material and methods: Since 2018 the outpatient clinic that deals with the overall care of the patient who has to face the colon rectal oncological disease has been active in Piacenza e 223 patients were treated in 2021 all patients were evaluated with brass iadl conley painand.

A booklet with telephone numbers is also left to ensure continuity of care. The nutritional need has been identified with the compilation of the must and sending to the nutrition team if necessary. Blood management is guaranteed by sending to the hematology team for hemoglobin value of less than 12% for women and 13% for men the exams of the diagnostic work up are scheduled and a direct access service is available with the psychologist if the patient himself expresses the need everyone is expected to have a meaningful interview with the clinical referent after the multidisciplinary discussion if the value of the brass scale is higher than 11, a report is made to the acute post office for management at the time of discharge.

Conclusions: The role of the nurse in taking global load of the person affected by colorectal cancer allows the realization of the attention to the person as such and the satisfaction expressed with the customer satisfaction administered is very high for 77 percent.

Late Breaking Abstract

LBA01* - Plenary Session

OPTIMAL MAINTENANCE TREATMENT STRATEGY FOLLOWING AN ANTI-EGFR-BASED INDUCTION THERAPY IN PATIENTS WITH RAS WILD TYPE METASTATIC COLORECTAL CANCER (MCRC): AN INDIVIDUAL PATIENT DATA POOLED ANALYSIS OF RANDOMIZED CONTROLLED TRIALS (RCTS)

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Background: In mCRC, fluoropyrimidine plus bevacizumab is the recommended maintenance after first-line bevacizumab-based doublet/triplet chemotherapy. Anti-EGFR agents and doublet chemotherapy is a guideline-endorsed upfront option for RAS/BRAF wild-type (wt) mCRC patients, with no clear definition of the optimal post-induction strategy and maintenance schedule. Several phase II RCTs investigated the optimal deintensification strategy following a 3-4 month induction among the following: 5-fluorouracil/leucovorin (5-FU/LV) plus anti-EGFR, monotherapy with anti-EGFR or 5-FU/LV, treatment break.

Methods: We performed an individual patient data meta-analysis of Valentino, Panama, MACRO-2 and COIN-B trials including RAS wt mCRC patients who received first-line FOLFOX/panitumumab or cetuximab followed by a maintenance strategy or treatment break. Only patients who received treatment as per-protocol (those who started the post-induction phase according to the assigned study arm) were included. Data on baseline characteristics and treatment received were pooled. Patients were categorized according to the type of post-induction strategy and PFS and OS were calculated for each treatment group from the start of maintenance/observation; toxicity was evaluated by NCI CTCAE during maintenance.

Results: A total of 591 patients were included in the pooled analysis. Overall, 123, 185, 210 and 50 patients received maintenance with 5-FU/LV, anti-EGFR, 5-FU/LV+anti-EGFR and treatment break, respectively, thus 308 patients received monotherapy maintenance (5-FU/LV or anti-EGFR) and 210 combination (5-FU/LV+anti-EGFR). Median PFS was 9.0, 5.6, 6.2 and 4.3 months (P=0.003) and OS was 28.0, 25.7, 24.0 and 17.2 months (P=0.01) in 5-FU/LV+anti-EGFR, 5-FU/LV, anti-EGFR and observation arms, respectively. PFS and OS were significantly superior in combination versus monotherapy (median PFS: 9.0 vs 5.9 months; HR 0.80, 95% CI 0.66-0.97; P=0.02; median OS: 28.0 vs 24.1 months; HR 0.80, 95% CI 0.64-0.99; P=0.04).

Conclusions: This pooled analysis including four randomized phase II trials showed that a combination maintenance schedule with 5-FU/LV and anti-EGFR in RAS wt mCRC is superior in PFS and OS as compared to single-agent maintenance while full treatment break conferred the worst outcomes. The results mirror the available evidence on the guideline-recommended maintenance strategy after bevacizumab-based first-line therapy.

CLBA02*

LHRHA INDUCED MENOPAUSE IN BREAST CANCER PATIENTS: A PROSPECTIVE RANDOMIZED CLINICAL TRIAL TESTING THE EFFICACY OF EARLY ACUPUNCTURE TREATMENT FOR VASOMOTOR SYMPTOMS AND SLEEP DISORDERS (ACUHOTFLASH STUDY)

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Background: Debilitating symptoms such as hot flashes and sleep deficiency, due to luteinizing hormone-releasing hormone analogues (LHRHa) induced ovarian suppression in premenopausal Breast Cancer (BC) patients, affect quality of life and adherence to endocrine therapies (ET).

Pharmacological options available to improve these conditions are limited and often burdened by significant side effects.

Acupuncture can be considered for vasomotor symptoms management according to several clinical trials and guidelines, including The National Comprehensive Cancer Network (NCCN) and ESMO Advanced Breast Cancer (ABC) symptom control Guidelines.

The aim of this study is to evaluate the impact of acupuncture in preventing worsening of hot flashes and sleep disorders, in terms of frequency/severity, in premenopausal BC patients undergoing LHRHa plus ET (tamoxifen or aromatase inhibitors).

Trial Design: This is a prospective RCT of superiority of acupuncture–compared to usual care for prevention/early treatment of vasomotor symptoms and sleep impairment in LHRHa induced amenorrhea.

The primary endpoint will be a reduction in frequency and intensity of hot flashes between the intervention arm compared to standard care, measured by the Hot Flash Composite Score (HFCS) at 6 months following the protocol.

Among the secondary outcomes, sleep quality will be measured by the Pittsburgh Sleep Quality Index (PSQI) and quality of life by the Menopause-specific Quality of Life Questionnaire (MenQOL) and EORTC Quality of Life Questionnaire (EORTC QLQ-C30).

A total of 90 premenopausal BC (stage I-III) patients undergoing LHRHa plus ET after surgery will be randomized 1:1 in two arms:

- Arm A: 10 acupuncture sessions twice per week for 4 weeks followed by 2 more sessions once per week
- Arm B: usual care

After our local Commitee approval (ID 4523 Fondazione Policlinico Gemelli-IRCCS) recruitment has begun on January 2022.

To date, 21 patients have been enrolled,11 randomized in Arm A,10 in Arm B (some clinical features are listed in TAB1).

	Arm A	Arm B
Type of surgery	4	5
Quadrantectomy	4	4
Mastectomy	3	1
Bilateral surgery		
pT	8	6
1	1	3
2	2	1
3		
pN	6	6
0	5	4
1		

Tab1

Unfortunately, the clinical outcomes to date are insufficient due to high patient dropouts (10/21) and short follow-up.

A significant reduction in the outbreak of hot flashes and insomnia in the intervention arm would consolidate an evidence-based integration of acupuncture in the management of BC patients undergoing ET, leading to an improved quality of life.

RLBA03

IMMUNOGENICITY AFTER THE THIRD DOSE OF MRNA-BASED COVID-19 VACCINES IN PATIENTS WITH SOLID TUMORS

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Background: Despite of the administration of multiple doses of vaccines (vax), cancer patients (pts) are a group at high risk of COVID-19 complications. The aim of this study is to evaluate the factors associated with the humoral response to the 3rd dose (D) of mRNA-based vax in cancer pts during or after active treatment.

Patients and Methods: Single institution, prospective study conducted at the L. Sacco Hospital, Milan, between 5/2021-4/2022. 30 days after the 2nd and 30 days after the 3rdD of BNT162b2 or mRNA-1273 (selected based on local pharmacy availability), seric levels of 3 antibodies (Ab) were measured in solid tumors pts during or after the active treatment, by a fluorescence bead-based assay. Anti-S and anti-RBD IgG to determine the humoral response to vax, anti-N IgG to identify a previous exposure to SARS-Cov-2. Primary objective: to assess the seroconversion (SC) rate and the Ab titres after 3rdD. Secondary objectives: to detect any relation between the 3rdD response and pre-defined pts variables; to evaluate the humoral response to 3rdD in pts not responding to the 2ndD.

Results: 99 of 110 pts were evaluated: 67.7% female, median age 63 ys, 49.5% breast cancer, 67.7% advanced stage. Active treatment: 40.4% biologic agent, 23% chemotherapy (alone or combination), 11.1% hormone. 3rdD vax type: 74.8% BNT162b2, 25.2% mRNA-1273. SC after 3rdD was obtained in 99% of pts. The use of GCSF was associated with a lower amount of anti-RBD IgG (p=0.03). A 6 vs 5 months interval between 2nd and 3rdD was correlated with higher anti-S IgG level (p<0.001). The heterologous vax regimen was associated with higher rate of anti-S IgG (p=0.04), especially the sequence mRNA-1273 x 2 –> BNT162b2 (p=0.001). No significant correlation at the multivariate analyses was found between Ab levels and the other variables tested (age, BMI, cancer type, tumor stage, use of steroids, previous exposure to SARS-CoV-2, anti-cancer therapy, neutropenic potential of the therapy). 21/22 pts not responding to the 2ndD obtained SC after 3rdD.

Conclusions: 3rdD of anti-COVID-19 vax is effective in cancer pts with solid tumors undergoing or after recent treatment. In this group the 3rdD oversteps all the negative influence of the factors related to the 2ndD vax failure, achieving the same response of the healthy population and demonstrating efficacy in not previously responders, too. The better performance of the heterologous vax regimen could be due to an exposition to a wider range of epitopes.

CLBA04

OVER NINETY OLD WOMEN(ONOW) WITH ADVANCED BREAST CANCER(ABC): COULD AN EFFICIENT BUT SAFE TREATMENT BE POSSIBLE FOR THESE KIND OF PATIENTS?

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Aim: The purpose of this study is to preliminarly evaluated the overall treatments toxicity by specifics tests to be adopted in frail patients such as OnoW to get the most efficacy but safe treatment according to "precision oncology medicine"

Methods: 24 patients Age: between 90th to 00th with ABC-were enrolled in the study criteria: acquired written consensus; confirmed diagnosis of ABC, measurable lesions, bone or visceral, no brain secondarisms, Charlson's Score Comorbidity Scale max 1-3 score points; CGA Evaluation Score(CGA-ES) permissive for treatment-All patients were tested with: CARG -TS(**C**ancer and **A**ging **R**esearch **G**roup-Test Score) and CRASH-TS(**C**hemotherapy **R**isk **A**ssessment **S**cale for Very Old Patients(VOP) **T**est S) are rated for predictive assessment of the risk of severe chemo-tox in VOP with cancer.

Results: CARG-Test predicts severe overall tox; CRASH-Test additionally predicts hematologic and nonhematologic tox. Using a combination of CGA-ES + CARG-TS +CRASH-TS, we were able to obtain three categories of tox risks: **Low risk** (score 0-5): **Medium risk** (score 5-10): **High risk** (score over 10) .**The High and Medium risk** people(14 pts) were placed in the endocrine therapy-only group (if ER-PGR+) if negative radiation treatment only with Dose Fractionement Criteria (DFC) The Low -risk group experienced schedule with eribulin alone (Treatment plan: E 0.96-1.1 mg/sqm IV on d1 every 21 -dosage according with Creatinine clearance evaluation (Kintzel-Dorr's), Schedule continued until intolerable tox). Further Evaluations Tools: Clinical Benefit (CB) as stable disease + objective response rates (ORR) according to ESMO CB scale v.2a; Tox Profile using CTCAE v3.0 Criteria; quality of life (QoL) score EORTC QLQ-C30 questionnaire.

Conclusions: No groups discontinued the treatment for intolerable tox. Hematologic Tox grade 4 only in 3 out of 10.in Low Risk group(chemo). Non Hematologic tox (grade 3) only in rad-treat sub-group people controlled by opportune therapy. QoL was generally acceptable, especially in those with good nutrition status in patients in post therapy (6 months re-evaluation), onset signs of cachexia and fatigue (Eortc Cax24 / Fa12 modules) and signs of worsening (Eld14) of the aging parameters were evaluated. No worsening in the low risk group (10 patients). Slight worsening of Fa12 in the high / medium risk group. These outcomes encouraging further recruitment to validate these preliminary results as more efficient&safe treatment-strategy in oNOW ABC

SLBA05

TELEONCOLOGY FOR SYMPTOMS MANAGEMENT, LIFESTYLE MODIFICATIONS AND PATIENT EMPOWERMENT IN CANCER SURVIVORS (ONCONAUTI): A DIGITAL-ENHANCED PROGRAM OF INTEGRATIVE REHABILITATION OF "ONCONAUTI" ASSOCIATION

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Background: Healthy lifestyle promotion is one of the most relevant strategies to improve quality of life (QoL) and long-term outcomes of therapies in cancer survivors.

Digital health tools (DHT) allow to provide nutritional support, yoga webinars and exercise training during and after cancer treatments by delivering personalized and flexible interventions under close supervision.

Furthermore, digital technology allows healthcare providers to monitor the course of treatment-related chronic symptoms such as pain and fatigue, in order to optimize care programs.

The aim of this report is to evaluate the impact of the smartphone-based digital health platform *Pinktrainer®* on health promotion within the Onconauti Association program of rehabilitation for cancer survivors (so called Onconauti).

Material and methods: A total of 27 cancer survivors were asked to use the DHT *Pinktrainer®,* in order to investigate different domains of QoL and to deliver personalized body-mind and physical activity (PA) programs.

At the beginning of the rehabilitation program, three questionnaires were submitted to patients using the smartphone application to assess *pain* (Brief Pain Inventory – BPI) *fatigue* (Multidimensional Fatigue Inventory, MFI-20) and *lifestyle habits* (Onconauti Lifestyle questionnaire, OLq).

Customized PA programs and body-mind practice tutorials were delivered via video directly available on the app and assigned to each patient.

Informative contents (videos and articles) about healthy lifestyle were also assigned to patients according to their needs and preferences.

Results: To date, 12 of the 27 patients enrolled have completed the rehabilitation program.

Preliminary results show an improvement in each of the three domains of QoL investigated (Tab1), of which general (p=0,016)* and physical fatigue (p=0,010) ** scores reached a statistical significance.

Lifestyle	Pre (N=11)	Post (N=11)
Balanced Diet	81,82%	100%
Daily Physical Activity	40,70%	57,14%
Sedentary Behavior	45,45%	27,27%
Mfi	**Pre (N=12)**	**Post (N=12)**
General Fatigue	Moderate (Mean 11,95)*	Mild (Mean 7,92) *
Physical Fatigue	Moderate (Mean 11,92) **	Moderate (Mean 8,58)**
Bpi	**Pre (N=11)**	**Post (N=11)**
Pain Severity	Mild (Mean 2,72)	Mild (Mean 2,02)
Pain Interference	Mild (Mean 3,14)	Mild (Mean 2,55)

Tab. 1

Conclusions: Initial data provided by the digital-enhanced program of Integrative Rehabilitation of "Onconauti" Association are very promising and confirm the role of DHT in promoting healthy lifestyles in cancer survivors.

SLBA06

EMPOWERMENT AND ENGAGEMENT OF CANCER PATIENTS: IT'S TIME TO MOVE!

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Background: During last years, there has been an increase of patient's empowerment. It is process of patient's awareness of the possibility to become active in their treatment process. It has been proved that engagement of patients could help to improve sustainability, efficiency and humanization in health systems. As observers of this revolution we have decide to give it a voice and to concretize it in our Oncology Department ASST Rhodense in Rho, Milan. We have activated the pilot project: "Article 17 – Patients have the right to be active". Some selected patients have joined the healthcare staff during the day-hospital activities.

Material (patients) and methods: During last seven months three cancer survivor volunteers of "La Lampada di Aladino Onlus" have observed, listened and supported the patients and the staff, noting their comments. We've defined them SMART patients. They are cancer patients that have already concluded their treatment and are cured and in addition they have acquired specific knowledge and training before start the study.

Results: In this first step of the project, SMART patients have followed day-hospital activities of doctors and nurses. Then they observed patient's experiences at time of the visits, in waiting rooms and during their interaction with all oncological staff. We've collected about 120 reports from which interesting food for thought emerged. Role of caregiver in the different moments of diagnostic process, time dedicated to visits and interaction between doctors and nurses are some of the main observations emphasized by SMART patients. We would subsequently define if their presence could apport an improvement in these steps for patients and all medical staff. At the same time we are outlining some features of the SMART patient.

Conclusions: To increase empowerment and engagement of patients is the future of our health systems. We would like to create a model of concrete actions for prepared patients in cure and treatment process. We are also working to define which characteristics and training the SMART patient should have. In the same time by collaboration with Nurse Culture Centre and Research in ASST Rhodense in collaboration with University of Study of Milan we would fill the gap of literature and evidence about the formed patients, or SMART patients. https://www.lampada-aladino.it/indagini-gruppi-di-studio/progetto-articolo17

CLBA07

PERSONALITY FACTORS, FAMILY DYNAMICS AND RISK OF PSYCHOLOGICAL DISTRESS IN BRCA 1-2 GENETIC CANCER COUNSELING

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Genetic Oncological Counseling (CGC, NSGC, Resta et al., 2006), in Italy since 2013 defined CGO (Oncological Genetic Counseling, AIOM, SIGU, 2013), identifies genetic mutations for hereditary neoplastic disease. To date, the literature is poor regarding the psychosocial factors that characterize patients who follow this path. A more in-depth understanding would assume clinical relevance in order to identify patients at risk of negative effects following (or preceding) the test and implement counseling protocols that

minimize these effects by also providing tailored psychological support interventions (Lerman, 2008). In this context, the present observational study is inserted with the aim of describing a psychological profile that distinguishes the patient with breast and / or ovarian cancer with a previous individual and / or family history of disease that accesses the CGO.

Sample: In the CGO clinic of the A.O.P.V.E. of Catania 68 SS were recruited (mean age = 49.6; range 22-64;) with a diagnosis of mammary K (N = 53) and / or ovary (N = 15). This study was conducted during the first preliminary interview of the CGO path.

Material and method: Each patient underwent a preliminary interview followed by a semi-structured interview during the pre-test consultation and subsequently, in the form of a self-report, completed the SCL-90-R (Derogatis, 1994); the BFQ (Caprara et al. 1993), the FACES IV (Olson, 2007).

Results: Research is still ongoing. Preliminary data show a tendency to psychosocial vulnerability correlated with the factors of age, family cohesion, cognitive flexibility, experiences of anxiety and depression.

Conclusions: From the comparison with the general population (T-Test for homogeneity), a greater tendency emerges to develop a condition of distress that could interfere with the entire process of CGO, especially in the process of understanding information; in sharing the outcome with the family context; in the choice between clinical surveillance vs surgical prophylaxis. Personalized and integrated psychological paths could therefore represent a protective factor for the well-being of patients who access the CGO.

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See you at the

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