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Abstract Book

Guest Editor: Giordano Beretta

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Abstract Book of the 23rd National Congress of Italian Association of Medical Oncology (AIOM)

22-23-24 October 2021 – Virtual Meeting

Guest Editor

Giordano Beretta
Director of Medical Oncology Humanitas Gavazzeni, Bergamo; President, Italian Association of Medical Oncology (AIOM)


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23rd National Congress of Italian Association of Medical Oncology (AIOM) 22-23-24 October 2021 – Virtual Meeting

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

Giordano Beretta
Director of Medical Oncology Humanitas Gavazzeni, Bergamo
Italy

Dear Colleagues,

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

The abstracts are published in a supplement of *Tumori Journal*. The number of submitted abstracts has continuously increased over years suggesting, once again, the presence of a widespread research activity in spite of the shortage of public funds and lack of interest of public authorities. Many and many young oncologists are coauthors of the abstracts and several of them are first authors. This should be an encouragement for all of us: there is a present and also a future for AIOM.

In this Covid Era the Scientific Committee introduce a special oral session about Cancer and Covid19.

As you can realize by reading this issue, the abstracts cover all topics of medical oncology, including prevention, screening, diagnosis, treatment, follow-up, simultaneous care, patients and media communication always with a multidisciplinary approach. These topics will be debated in several educational and scientific sessions co-organized with other scientific societies and also National and regional health agencies. We would like to highlight as the innovations in the field of immunotherapy and targeted therapy and all the results of Italian research are a relevant part of the program of the meeting. As clinicians involved in the care of the patients, we have to keep in mind that research activity improves the care of cancer patients.

The ability to conjugate these two aspects is the only way to improve the chance of cure for our patients.

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

Enjoy the virtual meeting!

The Board of Directors for the years 2019-2021 includes:

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This abstract book will be available on-line and will also be freely available to subscribers to the following website congresso.aiom.it from October 25, 2021

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Plenary Session

01*

EXTENDED THERAPY WITH LETROZOLE AS ADJUVANT TREATMENT OF POSTMENOPAUSAL PATIENTS WITH EARLY-STAGE BREAST CANCER: A RANDOMISED, PHASE 3 TRIAL OF THE GRUPPO ITALIANO MAMMELLA

Del Mastro L.[1], Mansutti M.[2], Bisagni G.[3], Ponzone R.[4], Durando A.[5], Amaducci L.[6], Cognetti F.[7], Frassoldati A.[8], Michelotti A.[9], Mura S.[10], Urracci Y.[11], Sanna G.[12], Gori S.[13], De Placido S.[14], Garrone O.[15], Barone C.[16], Bighin C.[17], Poggio F.[17], Lambertini M.[1], Bruzzi P.[17]

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Background: The benefit of extended adjuvant therapy with aromatase inhibitors (AIs) in postmenopausal hormone-receptor positive breast cancer patients treated with tamoxifen for 2-3 years followed by an AI for 2-3 years is still controversial. We aimed to determine whether, after 2-3 years of tamoxifen, 5 years of letrozole is more effective than the standard duration of 2-3 years.
Methods: This is a prospective, open-label, phase 3 trial conducted in 64 Italian hospitals within the Gruppo Italiano Mammella (GIM). Stage I-III breast cancer patients, free of recurrence after 2-3 years of tamoxifen, were randomly allocated (1:1) with a centralized, interactive online system to receive 2-3 years (control arm) or 5 years (extended arm) of letrozole. Primary endpoint was disease-free survival (DFS) in the intention-to-treat population. Overall survival (OS) and safety were secondary endpoints. The trial is registered with EudraCT, 2005-001212-44 and ClinicalTrials.gov, NCT01064635.
Results: Between August 1, 2005, and October 24, 2010, we recruited 2056 patients. After a median follow-up of 11.7 years (IQR 9.5-13.1), 262 (25%) of 1030 patients in the control arm and 212 (21%) of 1026 patients in the extended arm experienced a DFS event. The 12-year DFS was 62% (95% CI 57-66) in the control arm and 67% (62-71) in the extended arm (Hazard Ratio [HR] 0.78, 0.65-0.93; p=0.006); 12-year OS was 84% (82-87) in the control arm and 88% (86-90) in the extended arm (HR 0.77, 0.60-0.98; p=0.036). Arthralgia (31% vs 38%), myalgia (8% vs 12%), hypertension (1% vs 2%) and osteoporosis (5% vs 8%) were significantly more frequent in the experimental arm.
Conclusion: In post-menopausal breast cancer patients treated with 2-3 years of tamoxifen, extended treatment with 5 years of letrozole resulted in a significant and clinically meaningful improvement in both DFS and OS compared to the duration of 2-3 years of letrozole.

LBA01*

FOLFOXIRI PLUS BEVACIZUMAB (BEV) PLUS ATEZOLIZUMAB (ATEZO) VERSUS FOLFOXIRI PLUS BEV AS FIRST-LINE TREATMENT OF UNRESECTABLE METASTATIC COLORECTAL CANCER (MCRC) PATIENTS: RESULTS OF THE PHASE II RANDOMIZED ATEZOTRIBE STUDY BY GONO

Rossini D.[1], Antoniotti C.[1], Morano F.[2], Murgioni S.[3], Salvatore L.[4], Moretto R.[5], Marmorino F.[1], Borelli B.[1], Ambrosini M.[2], De Grandis M.C.[6], Di Stefano B.[4], Masi G.[1], Boccaccino A.[1], Tamberi S.[7], Tamburini E.[8], Frassineti G.L.[9], Cappetta A.[10], Fontanini G.[11], Boni L.[12], Falcone A.[1], Cremolini C.[1]

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Background: FOLFOXIRI/bev is an upfront therapeutic option for selected mCRC pts. Immune checkpoint inhibitors (ICIs) reported remarkable achievements in dMMR but not in pMMR mCRC. The association of cytotoxics and bev

may promote the sensitivity to ICIs increasing the exposure of neoantigens, inducing immunogenic cell death, and increasing the immune infiltration in tumor microenvironment while reducing the activity of Tregs.
Methods: AtezoTRIBE was a prospective, open label, phase II, comparative trial in which initially unresectable mCRC patients, irrespective of MMR status, were randomized 1:2 to receive up to 8 cycles of FOLFOXIRI/bev (arm A) or FOLFOXIRI/bev/atezo (arm B), followed by maintenance with 5-FU/bev or 5FU/bev/atezo until disease progression. The primary endpoint was PFS. Assuming a median PFS of 12 months in arm A, 201 patients and 129 events were required to detect a HR of 0.66 in favour of arm B with 1-sided α and β errors of 0.10 and 0.15. Trial info: NCT03721653.
Results: From November 2018 to February 2020, 218 pts were enrolled (arm A/B: 73/145) in 22 Italian sites. Main pts' characteristics were (arm A/B): right-sided 44%/44%, synchronous metastases 89%/86%, liver-only 22%/22%, RAS mutant 71%/73%, BRAF mutant 14%/8%, dMMR 7%/6%. At a median follow up of 19.9 mos, 159 (arm A/B: 60/99) PFS events were collected. A significant advantage by the addition of atezo was observed in PFS (13.1 vs 11.5 mos, HR 0.69, 80%CI 0.56-0.85, p=0.012), but not in ORR (59% vs 64%, p=0.412). No safety issues were evident. Significant interaction effect between MMR status and treatment arm was found (p=0.010). In the pMMR subgroup (N=199, arm A/B: 67/132), 147 (arm A/B: 54/93) PFS events were collected. Significantly longer PFS was reported in arm B (12.9 vs 11.4 mos, HR 0.78, 80%CI 0.62-0.97, p=0.071).
Conclusions: The primary endpoint was met: the addition of atezo to FOLFOXIRI/bev prolongs PFS of mCRC patients. While the magnitude of benefit is significantly higher in dMMR tumors, signals of efficacy are reported also in the pMMR subgroup. Translational analyses to identify predictive biomarkers are ongoing.

02*

PHASE II STUDY OF PREOPERATIVE (PREOP) CHEMORADIOTHERAPY (CTRT) PLUS AVELUMAB (AVE) IN PATIENTS (PTS) WITH LOCALLY ADVANCED RECTAL CANCER (LARC): THE AVANA STUDY

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Background: Preop CTRT is considered the standard of care in the management of LARC. RT can revert the tolerance to a low neoantigen-burden by the induction of antigen release from the tumour and activation of dendritic cells leading to a CD8+ T lymphocyte-mediated anticancer immune response. In LARC patients, neoadjuvant CTRT increases PD-L1 expression in tumor cells, strongly suggesting a neoadjuvant combinatory strategy with RT and PD-1/PD-L1 pathway blockade. Based on such considerations, we have designed the AVANA study to investigate the role of Ave in combination with preop CTRT in LARC.
Methods: This is an Italian multi-center, phase II study. Pts with resectable LARC received standard preop CTRT (capecitabine 825 mg/sqm/bid 5 days/week+ 50.4 Gy in 28 fractions over 5.5 weeks) plus 6 cycles of Ave 10 mg/Kg every 2 weeks. Surgery with total mesorectal excision was performed at 8-10 weeks after the end of CTRT. The primary end-point was the pCR rate (ypT0N0). Secondary end-points were R0 resection rate, tumor downstaging, local recurrence, sphincter preservation rate, PFS, OS, safety profile, and the evaluation of exploratory predictive and/or prognostic biomarkers. Assuming as null hypothesis p0 a pCR rate of 15%, a significance level of 5% (one-side), and a power of 80%, a sample size of 101 pts was needed to detect an absolute increment of 10% in pCR rate (from 15% to 25%). The experimental regimen is considered for further studies if, in at least 22 pts, we observe a pCR.
Results: From April 2019 to November 2020, a total of 101 resectable LARC pts were enrolled in 10 Italian Centers. The median age was 63 years (23-82), 62 (61.4%) pts were male, 93 (92%) had ECOG PS 0. At baseline, 95 (94%) and 16 (16%) pts had cN+ and cT4 LARC, respectively. All pts completed the induction phase. Out of 100 pts evaluable for pathological response, 23 pts achieved a pCR and 60 pts a major pathological response. At this time, microsatellite status is available only in 39 pts of which only one was instable. The rate of grade 3-4 non-immune and immune-related adverse events was 8% and 4%, respectively. Avelumab was early interrupted in 9 pts out 101, mainly due to toxicity.
Conclusions: The combination of preop CTRT plus Ave showed a promising activity and a feasible safety profile. According to our statistical considerations, the experimental regimen will be considered for further studies. Sponsored by GONO and partially supported by Merck. EUDRACT 2017-003582-10; ClinicalTrials.gov ID: NCT0385479

03*

MAYA TRIAL: TEMOZOLOMIDE (TMZ) PRIMING FOLLOWED BY COMBINATION WITH LOW-DOSE IPILIMUMAB AND NIVOLUMAB IN PATIENTS WITH MICROSATELLITE STABLE (MSS), MGMT SILENCED METASTATIC COLORECTAL CANCER (MCRC)

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Background: The activity of TMZ in patients with mCRC is modest, but it increases in those with MSS status and MGMT silencing (negative IHC + *MGMT* methylation). In this hyperselected population, acquired resistance to TMZ is linked to emergence of mutations in mismatch repair genes and hypermutation. Thus, TMZ may be used as priming agent for immune-sensitization of MSS CRCs.
Methods: MAYA was a multicenter, single-arm phase II trial enrolling patients with pretreated MSS mCRC and MGMT silencing as centrally assessed by IHC + pyrosequencing (NCT03832621). The trial was designed to evaluate the safety and efficacy of 2 priming cycles of TMZ 150 mg/sqm d1-5q4w followed, in absence of disease progression, by its combination with ipilimumab 1 mg/kg q8w and nivolumab 480 mg q4w. Primary endpoint was 8-month progression-free survival rate (8m PFS). Secondary endpoints were overall survival (OS), overall response rate (ORR), safety, patient-reported outcomes. According to a single-stage design, 27 patients were required to increase 8m PFS from 5% to 20% with a- and ß-error of 5% and 20%.
Results: Among 703 patients prescreened from March 2019 to November 2020, 204 (29%) were molecularly eligible and 135 started the priming phase, of whom 33 (24%) reached the second treatment phase. For these, median age: 58 years, M/F 52/48%, *RAS* mutated/wild-type 76/24% (no BRAF mutated); 1/2/3 or more previous lines 6/45/49%. Overall, 10 were alive and progression free after 8 months, 21 had PFS <8 months (2 too early). The primary endpoint was met: 8m PFS was 32%; median PFS and OS: 7.1 and 18.5 months; ORR 39%, with delayed/gradual responses consistent with efficacy of immunotherapy. The rate of any grade/grade 3 or higher immune-related adverse events was 48/6%, all easily manageable according to protocol guidelines. On/post-therapy re-biopsies were analyzed in 9 cases with emergence of either tumor mutational burden (TMB)>10 mut/mb or MGMT expression, which predicted 8m PFS status. Data on plasma TMB will be presented.
Conclusions: MAYA study proved the immune-sensitizing role of TMZ in MSS/MGMT silenced mCRC. The safety and efficacy of TMZ priming followed by ipilimumab/nivolumab combo strategy is worthy of further development and extensive biomarker analyses are ongoing.

04*

BEVERLY: A MULTICENTER, RANDOMIZED, PHASE III TRIAL OF BEVACIZUMAB + ERLOTINIB VS ERLOTINIB ALONE AS FIRST-LINE TREATMENT OF PTS WITH EGFR-MUTATED, NON-SQUAMOUS, ADVANCED NSCLC

Piccirillo M.C.[1], Bonanno L.[2], Garassino M.C.[3], Dazzi C.[4], Cavanna L.[5], Esposito G.[6], Burgio M.A.[7], Rosetti F.[8], Rizzato S.[9], Arenare L.[1], Gargiulo P.[1], Di Liello R.[1], De Marinis F.[10], Crinò L.[11], Morgillo F.[12], Ciardiello F.[12], Normanno N.[13], Gallo C.[14], Gridelli C.[15], Perrone F.[1], Morabito A.[16]

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Background: Adding bevacizumab to erlotinib prolonged PFS in the Japanese NEJ026 and the Chinese CTONG 1509 trials, but limited data are available in non-Asian patients (pts). BEVERLY is an Italian no-profit, randomized, open-label, multicenter phase III trial of bevacizumab (BEV) plus erlotinib (E) vs E alone as first line treatment for EGFR-mutated advanced NSCLC.
Methods: Eligible pts were randomized 1:1 to E (150mg daily) alone or combined with BEV (15mg/kg iv q3w) until disease progression or unacceptable toxicity. Center, ECOG PS and type of mutation (ex19 deletion vs ex21L858R vs others) were stratification variables. Co-primary endpoints were investigator-assessed PFS (IA-PFS) and blinded-independent centrally-reviewed PFS (BICR-PFS). Secondary endpoints were OS, quality of life (QoL), IA- and BICR-objective response rate (ORR) and safety. 126 events out of 160 randomized pts were required to detect a PFS prolongation with BEV from 10 to 16.7 mos (HR 0.60), with 2-sided α=0.05, 80% power.
Results: From Apr 11, 2016 to Feb 27, 2019, 160 pts were randomized to BEV+E (80) or E alone (80). Pts were mainly female (63.8%) and never smokers (51.9%), ECOG PS 0-1 (98.1%), median age 66 (IQR 59-73); 55% of pts had ex19Del and 41% L858R mutation. At a median follow-up of 31 mos, 130/160 (81.3%) pts had a PFS event (progression or death) and 84/160 (52.5%) died. BEV+E significantly prolonged IA-PFS over E alone with a median of 15.4 vs 9.7 mos (HR 0.60; 95%CI 0.42-0.85, log-rank P=0.0039). Median OS was 28.4 vs 23.0 mos in BEV+E and E arms, respectively (HR 0.70; 95% CI 0.46-1.10, log-rank P=0.12).

Data for IA-ORR evaluation were available for 149 patients. IA-ORR was 73% (95% CI 62%-83%) vs 54% (95% CI 42%-66%) in BEV+E and E arms, respectively (P=0.014). One toxic death was reported, due to intracranial hemorrhage with BEV+E. Hypertension (any grade: 49% vs 18%; grade⩾3: 24% vs 5%), skin rash (grade⩾3: 31% vs 14%), thromboembolic events (any grade: 11% vs 4%), and proteinuria (any grade: 23% vs 6%) were more frequent with the experimental combination treatment.

Conclusions: The addition of BEV to E significantly prolonged IA-PFS compared with E alone as first line treatment in Italian EGFR-mutated NSCLC patients, with no unexpected safety issues. Blinded radiologic revision of PFS and ORR is ongoing and will be presented at the meeting. Clinicaltrial.gov NCT02633189. EudraCT 2015-002235-17. Roche provided partial funding and experimental drugs.

A – Breast Cancer

A01*

OVERALL SURVIVAL IN METASTATIC BREAST CANCER PATIENTS ACCORDING TO DIFFERENT FOLLOW UP STRATEGIES FOR EARLY BREAST CANCER

Blondeaux E.[1], Boni L.[2], Ruelle T.[3], Di Lauro V.[4], Molinelli C.[5], Piezzo M.[4], Fratini B.[6], Poggio F.[5], Pugliese P.[7], Ferzi A.[8], Buzzatti G.[5], Russo S.[9], Garrone O.[10], Gasparro S.[11], D'Alonzo A.[5], De Laurentiis M.[4], Fabi A.[11], Arpino G.[12], Bighin C.[5], Del Mastro L.[5]

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Background: Few studies, conducted in the late 1980s, failed to demonstrate increased overall survival (OS) for early breast cancer patients receiving intensive follow up (IFU). We evaluated, in a modern cohort of patients, survival outcomes of metastatic breast cancer patients (mBC pts) according to the type of diagnosis of metastatic disease.

Material and methods: The GIM14/BIO-META (NCT02284581) is an ongoing italian retrospective/prospective observational multicenter study enrolling consecutive mBC pts. For the present analysis, mBC pts relapsed after treatment for primary tumor were divided in two groups according to the type of diagnosis of metastatic disease: standard follow up (SFU; suspicious signs or symptoms of metastatic disease at routine follow up visits) or IFU (increased tumor markers or metastatic lesion detected with routine radiological exams). Primary objective was to compare OS between SFU and IFU groups.

Results: From January 2000 to December 2019, 2752 mBC pts were enrolled of whom 1433 were included in the present analysis: 597 in the SFU group and 836 in the IFU group. Patients in the IFU group had a shorter median disease-free interval (60.6 and 52.9 months for SFU and IFU respectively, p=0.01). No differences in OS were observed with a median OS of 62.53 (95%CI 54.44-70.89) and 59.38 (95%CI 53.36-63.88) months for SFU and IFU groups respectively (HR 1.04, 95%CI 0.89-1.21, p=0.64). In the subgroup analysis, no differences in OS were observed according to nodal involvement of primary tumor and among HER2-positive and luminal-like breast cancer patients. A worse outcome was demonstrated for triple negative breast cancer patients diagnosed through IFU (HR 1.98, 95%CI 1.30-3.04). Among the 157 HER2-positive mBC pts diagnosed after 2015, no differences in OS were demonstrated for patients diagnosed through SFU or IFU (HR 0.86 95%CI 0.44-1.67).

Conclusions: IFU seem to anticipate diagnosis of metastatic disease without increasing survival. Further randomized trials are needed to evaluate the role of different IFU strategies considering the current advances in imaging and anticancer treatments available nowadays.

A02*

THE PROGNOSTIC PERFORMANCE OF PREDICT+ IN PATIENTS (PTS) WITH HER2-POSITIVE (HER2+) EARLY-STAGE BREAST CANCER (EBC)

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Background: PREDICT+ is a widely used, online tool based on traditional clinico-pathological features, including HER2, developed to predict individual mortality of EBC pts and to aid clinical decision making for adjuvant therapy. However, its prognostic role in HER2+ EBC pts treated with chemotherapy (CT) and anti-HER2 therapies remains unclear. We aimed to investigate the prognostic performance of PREDICT+ in HER2+ EBC pts enrolled in the ALTTO trial.

Methods: ALTTO is a phase III study evaluating adjuvant lapatinib (L) +/- trastuzumab (T) vs. T alone in pts with HER2+ EBC. Pts enrolled in ALTTO and receiving T-based therapy started concurrently with CT were eligible for this analysis. We calculated PREDICT+ estimates using variables extracted from the ALTTO database, blinded to pts outcomes. The prognostic performance of PREDICT+ was evaluated by assessing its calibration and discriminatory accuracy. For calibration, median predicted 5-year (5-yr) overall survival (OS) was compared to

observed 5-yr OS. For discriminatory accuracy, the area under the receiver-operator characteristic (AUC under the ROC) curve and corresponding 95% confidence intervals (CI) for predicted 5-yr OS were calculated. Subgroup analyses were performed according to type of anti-HER2 therapy, type of CT, age, hormone receptor (HR) status, nodal status and tumor size.

Results: This analysis included 2,794 pts. After a median follow-up of 6.0 years (IQR, 5.8-6.7), 182 deaths were observed. Overall, PREDICT+ underestimated 5-yr OS by 6.7% (95% CI, 5.8-7.6): observed 5-year OS was 94.7% vs. predicted 88.0%. The underestimation was consistent across all subgroups (Table 1). For discriminatory accuracy, AUC under the ROC curve was 73.7% (95%CI 69.7-77.8) in the overall population, ranging between 61.7% and 77.7% across the analysed subgroups.

Conclusions: In HER2+ EBC pts enrolled in the ALTTO trial, the PREDICT+ score highly underestimated OS. The low performance of this prognostic tool was consistent across all subgroups. PREDICT+ should be used with caution to give prognostic estimation in HER2+ EBC pts treated in the modern era with effective CT and anti-HER2 targeted therapies.

		(Predicted – Observed) 5-yr OS (%) (95% CI)
Anti-HER2 Therapy	L + T	–7.0 (–8,5 –5,5)
	T alone	–6,3 (–7,8 –4,7)
	T → L	–6,8 (–8,3 –5,4)
CT	Non anthracycline-based	–8,1 (–10,3 –5,9)
	Anthracycline-based	–6,6 (–7,5 –5,6)
Age	⩽40	–5,2 (–7,1 –3,4)
	41-64	–6,7 (–7,7 –5,7)
	⩾65	–9,7 (–12,9 –6,6)
HR status	Negative	–13.0 (–14,4 –11,5)
	Positive	–2,7 (–3,7 –1,7)
Number of N+	0	–6,1 (–7,4 –4,9)
	1-3	–9.0 (–10,2 –7,8)
	>3	–15,8 (–18,3 –13,3)
Tumor size (mm)	⩽20	–6,2 (–7,1 –5,3)
	21-50	–7,3 (–8,7 –6.0)
	>50	–15,3 (–20,4 –10,2)

A03*

EFFICACY AND SAFETY OF FIRST-LINE RIBOCICLIB (RIB) COMBINED WITH LETROZOLE (LET) IN POSTMENOPAUSAL PATIENTS WITH HORMONE RECEPTOR–POSITIVE (HR+), HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2–NEGATIVE (HER2–) ADVANCED BREAST CANCER (ABC): RESULTS FROM PHASE IIIB BIOITALEE STUDY

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Background: In MONALEESA studies, the combination of RIB and endocrine therapy showed an improvement in efficacy outcomes and OS (MONALEESA -3 and -7) with manageable tolerability in patients with HR+, HER2– ABC. BioItaLEE (NCT03439046) is an Italian study investigating a large panel of biomarkers in the same patient setting of MONALEESA-2 trial. Here, we present efficacy and safety data, which were secondary endpoints.

Methods: Postmenopausal women with recurrent endocrine sensitive or de novo HR+, HER2– ABC received RIB 600 mg/day (3 weeks on/1 week off) and LET (2.5 mg/day) as first-line therapy for metastatic disease. Secondary study endpoints included progression-free survival (PFS), overall response rate (ORR), clinical benefit rate (CBR) and safety.

Results: A total of 287 patients were evaluated with a median follow-up of 26.9 months. The median age was 65 years (range, 47-86) with 34.2% (n=98) of patients aged =70 years. Luminal B disease and de novo disease were seen in 64.5% (n=185) and 39.7% (n=114) of patients, respectively. Bone only and visceral metastases were observed in 22.3% (n=64) and 44.3% (n=127) of patients, respectively. Median PFS was 23.39 months (20.8, NE). Median duration of response was not reached (27.89, NE). ORR and CBR in patients with measurable disease were achieved in 52.5% (n=84) and 70.6% (n=113) of patients, respectively. Most of the patients (98.6%, n=283) experienced =1 Adverse Event (AE); 79.8% (n=229) experienced grade =3 AEs. The most common all-grade AEs were neutropenia (67.3%), nausea (31%), leukopenia (30%) and asthenia (30%). Grade =3 Adverse Events of Special Interest (AESI) included neutropenia (60.3%, n=173), QTcF increase (1.7%, n=5), increased ALT (9.8%, n=28), increased AST (5.6%, n=16), and liver toxicity

(0.4%, n=1). Fatal cases due to AESIs were not reported. Serious AEs (SAE) occurred in 18.8% (n=54) of patients, of which, 6.3% (n=18) were suspected by the investigators to be related to RIB treatment. Of 10 fatal SAEs occurred, ABC was identified as the cause of death in 4 cases, and in the remaining 6 cases, 3 (1.0%) were related to RIB (due to respiratory failure [n=1], pneumonia [n=1], undetermined death [n=1]) and 3 were not.

Conclusion: Results from BioItaLEE confirm the safety and efficacy profile of RIB+LET as a first-line treatment in postmenopausal women with HR+, HER2– ABC.

A04*

PREGNANCY AFTER BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Many patients and physicians remain concerned about the potential detrimental effects of pregnancy after breast cancer (BC) in terms of reproductive outcomes and maternal safety. This systematic review and meta-analysis aimed at providing updated evidence on these topics.

Material and methods: A systematic literature review was conducted to identify studies including patients with a pregnancy after BC (PROSPERO number CRD42020158324). Likelihood of pregnancy after BC, their reproductive outcomes and maternal safety were assessed. Pooled relative risks (RRs), odds ratios (ORs), and hazard ratios (HRs) with 95% confidence intervals (CI) were calculated using random effects models.

Results: Of 6,462 identified records, 39 were included involving 8,093,401 women from the general population and 114,573 BC patients of whom 7,505 had a pregnancy after diagnosis.

BC survivors were significantly less likely to have a subsequent pregnancy compared to the general population (RR=0.40, 95%CI 0.32-0.49).

Risks of caesarean section (OR=1.14, 95%CI 1.04-1.25), low birth weight (OR=1.50, 95%CI 1.31-1.73), preterm birth (OR=1.45, 95%CI 1.11-1.88), and small for gestational age (OR=1.16, 95%CI 1.01-1.33) were significantly higher in BC survivors, particularly in those with prior chemotherapy exposure, compared to the general population. No significant increased risk of congenital abnormalities or other reproductive complications (spontaneous or induced abortion, gestosis, antepartum or postpartum hemorrhage) was observed.

Pregnancy after BC was not associated with a negative impact on patients' outcomes: compared to BC patients without subsequent pregnancy, those with a pregnancy had better disease-free survival (HR=0.66, 95%CI 0.49-0.89) and overall survival (HR=0.56, 95%CI 0.45-0.68). Similar results were observed after correcting for potential confounders and irrespective of patient, tumor, and treatment characteristics, pregnancy outcome and timing of pregnancy.

Conclusions: These results provide reassuring evidence on the safety of conceiving in BC survivors. Patients' pregnancy desire should be considered a crucial component of their survivorship care plan.

A05

PATIENTS' QUALITY OF LIFE AND SIDE EFFECT PERCEPTIONS IN MONARCHE, A STUDY OF ABEMACICLIB PLUS ENDOCRINE THERAPY IN ADJUVANT TREATMENT OF HR+, HER2-, NODE-POSITIVE, HIGH-RISK, EARLY BREAST CANCER

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Background: We report patient (pt)-reported outcomes (PROs) from monarchE, phase 3 study of endocrine therapy (ET) with/without abemaciclib for adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (EBC).

Material (patients) and methods: Pt-reported health-related quality-of-life (HRQoL), ET symptoms, fatigue and side-effect burden were assessed at baseline (BL), 12/24 months on treatment and follow-up (FU) in safety population (n=5591). A mixed effects repeated measures (MMRM) model compared mean subscale and item scores by treatment arm, excluding 24-month/FU data. Exploratory analyses were conducted on items reflecting common adverse events (AEs; diarrhea, fatigue, arthralgia, hot flushes), and the frequency of scores for "I have diarrhea" and "I am bothered by side effects of treatment" were assessed.

Results: Compliance was high (>90% of expected pts/visit). MMRM mean summary/items scores (fatigue, arthralgia, hot flushes) were numerically similar between trial arms at BL and post-BL assessments. MMRM mean scores for diarrhea were ⩽1.37 (abemaciclib) and ⩽0.21 (ET only). Most pts experiencing diarrhea in abemaciclib arm reported having "a little bit" or "somewhat". Diarrhea decreased after discontinuation of abemaciclib (Table 1). Most pts in both arms reported being bothered "a little" or "not at all" by side effects of treatment (Table 2).

Conclusions: Similar HRQoL between the treatment arms suggests a tolerable profile for abemaciclib in EBC pts.

Table 1. FACT-ES-C5 "I have diarrhea" item scores.

FACT-ES C5				
Item score	BL	Month 12	Month 24	FU
0; not at all	2354(86.77)	974(42.61)	317(48.92)	559(79.63)
1; a little bit	251(9.25)	526(23.01)	118(18.21)	94(13.39)
2; somewhat	76(2.80)	434(18.99)	101(15.59)	35(4.99)
3; quite a bit	26(0.96)	242(10.59)	72(11.11)	7(1.00)
4; very much	6(0.22)	110(4.81)	40(6.17)	7(1.00)

Table 2. FACT-B-GP5: "I am bothered by side effects of treatment", in Arm A (abemaciclib+ET) & B (ET only).

FACT-B GP5				
Item score	BL	Month 12	Month 24	FU
0; not at all; Arm A/B	1256(46.73)/1181(44.00)	826 (36.18) 1046 (45.14)	229(35.18)/330(49.25)	290(41.02)/276(41.44)
1; a little bit; Arm A/B	816(30.36)/849(31.63)	809(35.44)/728(31.42)	219(33.64)/194(28.96)	226(31.97)/227(34.08)
2; somewhat; Arm A/B	432(16.07)/430(16.02)	442(19.36)/355(15.32)	151(23.20)/98(14.63)	138(19.52)/90(13.51)
3; quite a bit; Arm A/B	142(5.28)/176(6.56)	167(7.31)/144(6.21)	44(6.76)/34(5.07)	35(4.95)/50(7.51)
4; very much; Arm A/B	42(1.56)/48(1.79)	39(1.71)/44(1.90)	8(1.23)/14(2.09)	18(2.55)/23(3.45)

A06

CHARACTERIZATION OF VENOUS THROMBOEMBOLIC EVENTS (VTE), ELEVATED AMINOTRANSFERASES (EAT) AND INTERSTITIAL LUNG DISEASE (ILD) IN MONARCHE

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Background: VTE/EAT/ILD are adverse events (AEs) for abemaciclib. In monarchE, patients (pts) receiving abemaciclib+endocrine therapy (ET) as adjuvant treatment (txt) of HR+, HER2- high-risk early breast cancer (EBC) reported these AEs more frequently vs ET Alone pts.

Material (patients) and methods: Safety population (pop) comprised 5591 treated (tx) pts (median duration of abemaciclib=17 months). Protocol included management guidance for AEs. Risk factors for VTE (Khorana risk score) and adjuvant radiotherapy (95.4% pts) were balanced across arms.

Results: *In abemaciclib tx pts:*

Most VTEs were G⩾3 (1.3%), primarily pulmonary embolism (0.9%) (Table 1). Of pts experiencing VTE, 94% received anti-coagulants/19.4% discontinued abemaciclib or all txt due to VTE. VTEs were increased with tamoxifen txt; G⩾3 VTEs were higher in pts with body mass index (BMI)>25 (1.8%) vs BMI<25 (0.6%).

85% of G⩾3 EAT were single occurrences; incidence was highest early on txt (~3 months). Of pts experiencing G⩾3 EAT, 71% had dose hold/reduction and 16% discontinued due to EAT. No pts had drug-induced liver injury (no Hy's law cases).

Most ILD events were G1 (1.4%). Of pts experiencing ILD, 52% were tx with steroids/antibiotics and 23% discontinued abemaciclib or all txt due to ILD. ILD was higher in Asians (6.6%; G1: 4.9%; G⩾3: 0.3%; 13% of Asian pts with ILD discontinued (0.9% of pop)).

Conclusions: VTE, EAT and ILD were manageable with dose adjustments and comedications in pts with EBC; results were consistent with the known safety profile of abemaciclib. Although ILD was higher in Asian pop, G⩾3 AEs and discontinuations were similar. Most pts experiencing these AEs could continue abemaciclib.

Table 1. Characteristics of VTEs, EAT and ILD.

	Abemaciclib+ET			ET		
	N=2791			N=2800		
	VTE	EAT[b]	ILD[d]	VTE	EAT[b]	ILD[d]
Pts with ⩾1 TEAE; n (%)						
Any grade	67 (2.4)[a]	356 (12.8)	82 (2.9)	16 (0.5)	181 (6.5)	34 (1.2)
G⩾3	37 (1.3)	87 (3.1)[c]	11 (0.4)	7 (0.3)	24 (0.9)	1 (0.1)
Serious AEs	33 (1.2)	11 (0.4)	14 (0.5)	8 (0.3)	2 (0.1)	1 (0.0)
Deaths	0 (0.0)	0 (0.0)	1 (0.0)[e]	1 (0.0)	0 (0.0)	0 (0.0)
Discontinuations	13 (0.5)	22 (0.8)	19 (0.7)	2 (0.1)	0 (0.0)	0 (0.0)
Time to onset of first AE; median, days	182	113	190	188	140	158

[a]1st ET tamoxifen 4.1%; AIs 1.7%.
[b]9 preferred terms, incl ALT and aspartate aminotransferases (AST).
[c]safety pop v Asians: ALT: 2.4% v 4.2%; AST: 1.8% v 3.1%.
[d]ILD incl pneumonitis, radiation pneumonitis.
[e]possibly related to txt.

A07

THE PREGNANCY AND FERTILITY (PREFER) STUDY INVESTIGATING THE NEED FOR OVARIAN FUNCTION AND/OR FERTILITY PRESERVATION STRATEGIES IN PREMENOPAUSAL WOMEN WITH EARLY BREAST CANCER

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Background: Offering ovarian function and/or fertility preservation strategies in premenopausal women with newly diagnosed breast cancer candidates to undergo chemotherapy is standard of care. However, few data are available on uptake and main reasons for refusing these options.

Methods: The PREFER study (NCT02895165) is an observational, prospective study enrolling premenopausal women with early breast cancer, aged between 18 and 45 years, candidates to receive (neo)adjuvant chemotherapy. Primary objective is to collect information on acceptance rates and reasons for refusal of the proposed strategies for ovarian function and/or fertility preservation available in Italy.

Results: At the study coordinating center, 223 patients were recruited between November 2012 and December 2020. Median age was 38 years (range 24 – 45 years) with 159 patients (71.3%) diagnosed at ⩽40 years. Temporary ovarian suppression with gonadotropin-releasing hormone agonists (GnRHa) was accepted by 58 out of 64 (90.6%) patients aged 41-45 years and by 151 out of 159 (95.0%) of those aged ⩽40 years. Among patients aged ⩽40 years, 57 (35.8%) accepted to access the fertility unit to receive a complete oncofertility counseling and 29 (18.2%) accepted to undergo a cryopreservation technique. Main reasons for refusal were fear of delaying the initiation of antineoplastic treatments and contraindications to the procedure or lack of interest in future childbearing. Patients with hormone-receptor positive breast cancer had higher acceptance rates of ovarian function and/or fertility preservation strategies than those with hormone-receptor negative disease.

Conclusions: More than 90% of premenopausal women with early breast cancer, and particularly those with hormone receptor-positive disease, were concerned about the potential risk of chemotherapy-induced premature ovarian insufficiency and/or infertility and accepted GnRHa administration. Less than 1 out of 5 women aged ⩽40 years accepted to undergo cryopreservation strategies.

A08

BREAST, OVARIAN AND PANCREATIC CANCERS: AN APPROACH WITH MULTI-GENE PANEL TESTING

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Background: Hereditary breast (BC), ovarian (OC) and pancreatic (PC) cancers are the main *BRCA*-associated tumours. However, some patients with *BRCA1/2*-non informative results show a strong cancer personal and/or family history. These patients need a deeper investigation through a multi-gene panel testing containing other high- and moderate-risk susceptibility genes. Recently, Next-Generation Sequencing (NGS) allowed to study multiple genes at the same time, reducing analysis costs, leading to an increase in genetics data, and offering more significant information to patients.

Patients and Methods: Our work was aimed to assess if some BC, OC and PC patients should be offered multi-gene panel testing based on well-defined criteria. These criteria regarding the cancer personal and/or family history were: early onset of cancer, occurrence of multiple tumours, and presence of two or more affected first-degree relatives. For this reason, 205 *BRCA1/2* non-informative BC, OC and PC patients with significant cancer personal and/or family history were genetically tested for germline pathogenic or likely pathogenic variants (PVs/LPVs) in several high- and moderate-risk susceptibility genes.

Results: Our study showed that 15.1% of 205 patients harboured germline PVs/LPVs in several genes, such as *PALB2, CHEK2, ATM, MUTYH, MSH2, RAD51C*. Specifically, we found that 11 out of 24 (45.8%) BC patients with PVs/LPVs in no-*BRCA* genes showed a bilateral BC. Interestingly, in the absence of multi-gene panel testing, a considerable fraction (15.1%) of PVs/LPVs would have been lost in patients affected by BC, OC and PC with *BRCA*-non informative result.

Conclusions: Offering a multi-gene panel testing to BC, OC and PC patients with *BRCA1/2*-non informative result and with a strong cancer personal and/or family history could significantly increase the detection rates of germline PVs/LPVs in high- and moderate-risk susceptibility genes beyond *BRCA1/2*. The use of a multi-gene panel testing could improve the inherited cancer risk estimation and clinical management of patients and unaffected family members.

A09

ADDING WEEKLY CARBOPLATIN TO SEQUENTIAL ANTHRACYCLINE AND PACLITAXEL-BASED CHEMOTHERAPY AS NEOADJUVANT TREATMENT FOR TRIPLE NEGATIVE BREAST CANCER (TNBC) PATIENTS: A PROPENSITY SCORE-MATCHED STUDY

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Background: The addition of carboplatin (Cb) to neoadjuvant anthracycline and taxane -based chemotherapy for TNBC increases pathological complete response (pCR) rate at the cost of worse hematologic toxicity. However, treatment schedules and doses adopted in randomized trials were not always consistent with current clinical practice. We evaluated the role of adding weekly Cb (wCb) to neoadjuvant sequential anthracycline and paclitaxel.

Methods: Clinicopathological data of TNBC (ER & PgR$<$10%) patients treated at three Institutions (Istituto Oncologico Veneto IOV-IRCCS – Padova, Policlinico Gemelli – Roma, AOUI – Modena) were retrieved. Patients should have received sequential treatment with anthracycline-based chemotherapy and weekly paclitaxel (A/wP) with or without wCb. Propensity score was used to control selection bias. Variables considered for matching were: age (continuous), cT (cT1 vs cT2 vs cT3-4), cN (pos vs neg), histologic grade (2 vs 3), BRCA status (mutated vs non informative or unknown). A caliper width of 0.2 was applied for matching. Binary logistic regression was used to test the association of Cb treatment with pCR (ypT0/is ypN0). Cox regression was used for survival analyses.

Results: 247 patients were included: 60% treated with A/wP+wCb, 40% with A/wP. Main characteristics: median age 51 yrs, ductal histology 95%, histologic grade 3 95%, cT1 18%, cT2 66%, cT3-4 16%, cN+ 51%, BRCA mutated 13%. After propensity score matching, pCR rate was significantly higher for A/wP+wCb vs A/wP in logistic regression analysis corrected for matching variables: 47% vs 33% (OR 2.14 95%CI 1.08-4.23, p=0.029). Grade$\geqslant$3 neutropenia was more frequent with wCb (35% vs 47%). The achievement of pCR was significantly

associated with improved disease-free survival (HR 0.26, 95%CI 0.11-0.63, p=0.003). No difference in disease-free survival was observed comparing A/wP+wCb vs A/wP: HR 1.50, 95%CI 0.79-2.85, p=0.220.
Conclusions: The relative and absolute positive effect on pCR of adding wCb to sequential A/wP in a clinical practice setting is in line with data from randomized trials adopting different treatment schedules. Inclusion of wCb increases the risk of hematologic toxicity. Additional data are needed to clarify the impact on long-term survival. These results support the conditional positive GRADE recommendation for Cb inclusion in neoadjuvant chemotherapy for TNBC provided by the AIOM Guidelines on Breast Cancer.

A10

HER2-LOW EXPRESSION IN PATIENTS WITH METASTATIC BREAST CANCER (MBC) RECEIVING FIRST LINE (1L) TREATMENT WITH ENDOCRINE THERAPY (ET) +/- CDK 4/6 INHIBITOR (CDKI)

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Background: HER2-low expression, defined as HER2 immunohistochemistry score of 1+ or 2+ with negative in situ hybridization assay, characterizes nearly 50% of BC. Despite antibody-drug conjugate in late development showed meaningful activity, no anti-HER2 agents are currently approved in Europe for this subgroup. This retrospective study aimed to investigate the clinical relevance of HER2 low status as an independent prognostic factor in 1L setting of luminal-like mBC.
Material and methods: Data of 322 consecutive luminal-like (i.e. hormone receptor positive, HER2-negative) mBC patients (pts) were analyzed. The whole cohort received 1L treatment with ET or ET in combination with a CDKi (ET+CDKi) at the Oncology Departments of Udine and Aviano (Italy) from 2008 to 2019. Association analyses were investigated through Fisher-exact test. The prognostic impact of HER2-low was analyzed through Cox regression, and differences in progression free survival (PFS) and overall survival (OS) were explored by log-rank test.
Results: Overall, 63.8% of pts were older than 65, 88.1% were post-menopausal, 34.3% had metastatic disease at diagnosis, 23% of pts had ⩾3 sites of involvement, 37.7% had visceral disease. As 1L, 238 pts (73.9%) received ET while 84 pts (26.1%) were treated with ET+CDKi. In the total series, HER2 score 0 BC were 212 (65.8%) while HER2-low cases were 110 (34.2%). No significant association was detected between HER2-low status and visceral disease, number of sites of disease, and menopausal status ($p>0.05$). By univariate analysis, HER2-low status was not associated with prognosis neither in terms of PFS (HR 0.98, P=0.91, 95% CI 0.76-1.26) nor OS (HR 1.01, P=0.932, 95% CI 0.76-1.34). Similarly, no prognostic effect was observed according to the type of 1L treatment (ET+CDKi, HR for PFS 0.98, P=0.96, 95% CI 0.55-1.76, and HR for OS 0.89, P=0.79, 95% CI 0.38-2.10; ET, HR for PFS 0.98, P=0.94, 95% CI 0.74-1.31, and HR for OS 1.04, P=0.79, 95% CI 0.76-1.41).
Conclusion: In pts with luminal-like mBC treated with 1L ET or ET+CDK4/6i, no prognostic role has been demonstrated for HER2-low status. Prospective studies are needed to further investigate the different levels of HER2 expression.

A11

HEREDITARY BILATERAL BREAST CANCER: LOOKING BEYOND THE BRCA1/2 GENES

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Background: Bilateral breast cancer (BBC) is generally uncommon (1-2.6% of all patients with breast cancer), but its incidence increases particularly by up to 3% in *BRCA1* or *BRCA2* pathogenic variant (PV) carriers. The aim of our study was to evaluate whether all BBC patients should be offered multi-gene panel testing, regardless the criteria concerning personal and family history of cancer and age at diagnosis established by the current guidelines.
Patients and Methods: We retrospectively collected and analyzed all clinical information of 150 BBC patients

enrolled from October 2015 to April 2021, at the Sicilian Regional Center for the Prevention Diagnosis and Treatment of Rare and Heredo-Familial Tumors" of the Section of Medical Oncology of University Hospital Policlinico "P. Giaccone" of Palermo. Recruited patients have been genetically tested for germline PVs in other gene beyond *BRCA1* and *BRCA2* by NGS-based multi-gene panel testing.

Results: In our investigation 58 (38.6%) out of 150 BBC patients harbored germline PVs in high and intermediate-penetrance breast cancer (BC) susceptibility genes, including *BRCA1, BRCA2, PTEN, PALB2, CHEK2, ATM, RAD51C*. Twenty-two out of 58 positively tested patients harbored a PV in a known BC susceptibility gene (no-*BRCA*). Interestingly, a noteworthy correlation between PVs in *PALB2* or *CHEK2* and BBCs was observed. In addition, our study showed that *CHEK2* PVs are correlated with a luminal A/B phenotype and *ATM* PVs with a luminal B subtype. Most of BBC-related *BRCA1/2* PVs were frameshift variants primarily located inside the exon 11 for *BRCA1*, and near the PALB2 binding site (at the N-terminus) and the DNA binding helical domain (at the C-terminus) for *BRCA2*. In conclusion, we found that, in the absence of an analysis performed via multi-gene panel, a significant proportion (14.7%) of PVs in genes different from *BRCA1/2* would have been lost.

Conclusions: Our investigation led us to hypothesize that a deeper genetic analysis, through NGS-based multi-gene panel testing, could increase the detection rates of germline alterations in BBC patients. Particularly, in the near future, the evaluation of PVs could help to identify family members with a greater risk of developing BC (or other tumors) and consequently implement prevention and surveillance programs for these subjects. However, larger study cohorts are needed in order to define more accurate rates of PVs in BBC patients with previously negative *BRCA* genetic testing.

A12

SAFETY OF ASSISTED REPRODUCTIVE TECHNOLOGIES BEFORE AND AFTER ANTICANCER TREATMENTS IN YOUNG WOMEN WITH BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Controlled ovarian stimulation (COS) for oocyte/embryo cryopreservation before starting chemotherapy is standard of care for young women with breast cancer wishing to preserve fertility. However, some oncologists remain concerned on the safety of COS, particularly in patients with hormone-sensitive tumors. Moreover, limited evidence exists on the safety of assisted reproductive technologies (ART) in breast cancer survivors after completion of anticancer treatments.

Material and methods: A systematic literature review with no date restriction up to March 31, 2021 was conducted to identify studies reporting results of oncological outcomes in breast cancer patients and survivors who underwent COS or other ART compared to patients and survivors who did not access these techniques. From each included study, recurrence ratio, event-free survival (EFS) and mortality ratio were extracted. Pooled relative risks (RRs) and hazard ratios (HRs) with 95% confidence intervals (CI) were calculated using the random effects models.

Results: Out of 14 included studies (n=4,371), 10 reported outcomes of patients who underwent COS for fertility preservation before starting chemotherapy, and 4 of survivors who underwent ART following anticancer treatment completion. Compared to women who did not receive fertility preservation at diagnosis (n=2,237), those who underwent COS (n=1,471) had reduced risk of recurrence (RR 0.56, 95% CI 0.44-0.71) or mortality (RR 0.50, 95% CI 0.34-0.73). No detrimental effect of COS on EFS was observed (HR 0.78, 95% CI 0.53-1.15). A similar trend of better outcomes (in terms of EFS) was observed in women with hormone-receptor positive disease who underwent COS (HR 0.36, 95% CI 0.20-0.65). Compared to women not exposed to ART following completion of anticancer treatments (n=540), those exposed to ART (n=123) showed a tendency for better outcomes in terms of recurrence ratio (RR 0.34, 95% CI 0.17-0.70) and EFS (HR 0.43, 95% CI 0.17-1.11).

Conclusions: Despite including mostly retrospective studies, this meta-analysis provides clear evidence that accessing COS at diagnosis or ART following treatment completion is not associated with detrimental prognostic effect in young women with breast cancer. These results are important to reassure patients and oncologists on the safety of these procedures in order to increase the chances of future conception.

A13

PRIMARY OUTCOME ANALYSIS OF INVASIVE DISEASE-FREE SURVIVAL FOR MONARCHE: ABEMACICLIB PLUS ADJUVANT ENDOCRINE THERAPY FOR HIGH-RISK EARLY BREAST CANCER

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Background: monarchE (phase 3, open-label) evaluated abemaciclib+endocrine therapy (ET) vs ET-alone in node-positive, HR+, HER2-, high-risk early breast cancer that resulted in a statistically significant improvement in invasive disease-free survival (IDFS) at a pre-planned interim analysis.

Material (patients) and methods: Following the positive interim analysis, patients continued to be followed for IDFS, distant recurrence and overall survival. 5,637 patients were randomized (1:1) to standard-of-care adjuvant ET with/without abemaciclib (150mg BD for 2 years). Patients with ⩾4 positive nodes, or 1-3 nodes and either grade3 disease, tumor size⩾5 cm, or central Ki-67⩾20% were eligible. We present results of the primary outcome IDFS analysis which was planned after ~390 IDFS events.

Results: At the primary outcome analysis, median follow-up of ~19 months (mo) in both arms. With 395 IDFS events observed, abemaciclib+ET continued to demonstrate superior IDFS vs ET-alone (p=.0009; HR=0.713). Two-year IDFS rates were 92.3% (abemaciclib+ET) and 89.3% (ET-alone). With 324 distant relapse-free survival (DRFS) events observed, abemaciclib+ET improved DRFS vs ET-alone (p=.0009; HR=.687). Two-year DRFS rates were 93.8% (abemaciclib+ET) and 90.8% (ET-alone).

A key secondary endpoint was efficacy in patients with centrally assessed high Ki-67 (⩾20%) (Ki-67H, n=2498). Abemaciclib+ET demonstrated superior IDFS vs ET-alone (p=.0111; HR=.691) and 2-year IDFS rates of 91.6% and 87.1%, respectively.

Conclusions: Abemaciclib+ET demonstrated a clinically meaningful improvement in IDFS in the study population with a statistically significant improvement in IDFS in patients with central Ki-67⩾20%.

A14

DRUG-DRUG INTERACTIONS BETWEEN PALBOCICLIB AND PROTON PUMP INHIBITORS MAY SIGNIFICANTLY AFFECTCLINICAL OUTCOME OF METASTATIC BREAST CANCER PATIENTS

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Background: Proton pump inhibitors (PPIs) are widely used in cancer patients to mitigate adversegastroesophageal events polypharmacy-associated. However, drug-drug interactions (DDIs) atabsorption level should be considered as it may affect clinical outcome. Palbociclib is a weak basewith pH-dependent solubility that rapidly decreases as pH increases above 4.5 (Clin Pharmacol DrugDev 2017;6:614-6).

The current study was aimed at investigating the effect of concomitant PPIs on palbociclibprogression free survival (PFS) in metastatic breast cancer (mBC) patients.

Materials and methods: ER+, HER-2- mBC patients candidate to palbociclib as first line treatment were enrolled in thisretrospective observational study. Patients were defined as "no concomitant PPIs" if no PPI wereadministered during palbociclib, and as "concomitant PPIs" if the administration of PPIs covered theentire or not less than 2/3 of treatment with palbociclib. All clinical interventions were madeaccording to clinical practice.

Results: A total of 112 patients were enrolled; 56 belonged to "no concomitant PPIs" during palbociclibtreatment and 55 to the "concomitant PPIs" group. Seventy-one patients were endocrine sensitive(ES) and were administered palbociclib + letrozole and 43 were endocrine resistant (ER) and weretreated with palbociclib + fulvestrant. The most prescribed PPI was lansoprazol. Patients werestratified according to PFS, showing that patients taking PPIs had a shorter PFS compared to patientsassuming palbociclib + hormone-therapy alone (14 vs 38 months, $p<0.0001$). Multivariate analysisconfirmed the use of concomitant PPIs as the only independent predictive factor for shorter PFS(p=0.0002). PFS was significantly longer in ES mBC with no concomitant PPIs compared to patientstaking PPIs or ER patients with and without PPIs ($p<0.0001$). No correlation with adverse events wasfound considering G>2 hematological toxicities.

Conclusions: The present study demonstrates that concomitant use of PPIs in mBC patients treated withpalbociclib

has a detrimental effect on PFS. Therefore, it is recommended to prescribe PPI withcaution in these patients, or administering H2-antagonists or PPI for very short periods.

A15

BASELINE TUMOR BURDEN ASSESSMENT IN PATIENTS WITH HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE METASTATIC BREAST CANCER: THE ROLE OF LIQUID BIOPSY

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Background: Liquid biopsy-based biomarkers, including circulating tumor DNA (ctDNA), are gaining prominence in the characterization of metastatic breast cancer (MBC). Currently, CA15.3 is broadly used as a serum marker for monitoring the burden of disease. To date, no liquid biopsy-based biomarkers have been proposed for this scope in clinical practice.

Methods: The CRO-2018-56 multicenter study prospectively enrolled 83 patients (pts) with luminal-like MBC treated with first line endocrine therapy (ET), alone or in combination with CDK4/6 inhibitors. All pts were characterized for ctDNA through droplet digital PCR (ddPCR) from 2018 to 2021. Clinicopathological and laboratory characteristics at baseline were tested for associations with tumor markers, *ACTB* fragments lengths, methylation status of *ESR1* main promoters (expressed as promA and promB ratio, i.e., met_ratio) and *ESR1/PIK3CA* mutational status through Kruskal-Wallis test and Chi-square test.

Results: At baseline, 26 (31%) pts presented with *de novo* metastatic disease and 20% showed a primary endocrine resistance. 17 (20%) pts had at least 3 metastatic sites and 41 (49%) pts had < 5 metastatic lesions. Concerning the metastatic site, 53 (64%) pts had bone involvement while liver and lung metastases were found in 21 (25%) and 30 (36%) pts. According to ctDNA analysis, an *ESR1* mutation was detected in 15% pts and a *PIK3CA* wild type status was found in 34% pts. Met_ratio was > 1.5 in 35 (42%) of pts. Median CA15.3 was 48.2 U/mL and median CEA was 3.8 U/mL. Pts with *ESR1* mutation showed a higher number of both liver metastasis and metastatic sites (respectively, $P = 0.0055$ and $P = 0.0208$). CA15.3 and ctDNA yield were significantly higher in pts with $\geqslant 3$ metastatic sites (respectively, $P = 0.0164$ and $P = 0.0239$). A *PIK3CA* mutation was significantly associated with the presence of bone metastases ($P = 0.040$), while the presence of at least 3 metastatic sites was significantly associated with *ESR1* mutation ($P = 0.022$). Different *ACTB* DNA fragments and CEA levels showed no association with tumor burden. Met_ratio > 1.5 was significantly associated with a lower number of metastatic lesions ($P = 0.031$).

Conclusions: In pts with luminal-like MBC, some liquid biopsy-based biomarkers (i.e., ctDNA-detected *ESR1* and *PIK3CA* mutations, ctDNA yield) were significantly associated with the burden of disease. The potential clinical validity and utility of these results need to be tested in an expansion cohort.

A16

HIGH-RISK BREAST CANCER PATIENTS WITH RAD51-LOW TUMORS ARE CHARACTERIZED BY GOOD PROGNOSIS

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Background: Triple Negative Breast Cancer (TNBC) that do not achieve pathological complete response (pCR) have unfavorable prognosis. The RAD51 score is a functional assay able to identify Homologous Recombination Repair (HRR)-deficient tumors. In this setting, it may add prognostic value and guide post-neoadjuvant treatments.

Methods: We quantified RAD51 and BRCA1 foci by immunofluorescence, content of tumor-infiltrating lymphocytes (TIL) and expression of immune markers on diagnostic tumor biopsies of 26 high-risk breast cancer (BC) patients (pts), namely TNBC or early onset BC ($\leqslant 35$ yo) or gBRCA1/2-mutated BC admitted at the University Hospital of Parma between 01/2011 and 03/2020. All pts received neoadjuvant chemotherapy (neoCT) based on epirubicin, taxanes and cyclophosphamide. Functional HRR deficiency (HRD) was predefined as a RAD51 score $\leqslant 10\%$ (RAD51-low).

Results: RAD51 was successfully scored in 26/29 (90%) samples. 16/26 (62%) tumors were RAD51-low (HRD). 14 pts presented HRR alterations: 4 gBRCA1, 2 gBRCA2 and 2 gPALB2 mutations and 6 BRCA1-low foci, surrogate of lack of BRCA1 function likely due to promoter hypermethylation. Median RAD51 score was 3.4 in HRR-mutated tumors and 19.2 in HRR-WT tumors (p=.01). Disease-Free Survival (DFS) at 4 years was 100% for pts who achieved pCR vs 67.5% for non-pCR tumors (p=.12). The addition of RAD51 status to pCR information improved the model capacity to predict DFS (ANOVA test, p=.05). Pts with HRD tumors by RAD51 showed a trend towards better DFS (HR=0.28, 95% CI 0.05–1.54, p=.14). 4 out of 5 TIL-high tumors in this cohort were RAD51-low, suggesting a crosstalk between HRD and an active antitumor immune response. In support, RAD51-low/ TIL-high tumors had higher CD20+ TIL (p=.01), lower CD3+ TIL (p=.02), higher PD-L1 Combined Positive Score (p=.03), and a trend towards higher PD1+ TIL (p=.05); no statistically significant differences were found in FOXP3+ TIL. Moreover, only 1 out of 4 RAD51-low/TIL-high tumors achieved pCR but none of them relapsed.

Conclusion: The RAD51 test is able to identify HRR-altered tumors, beyond gBRCA1/2 mutations, and to select a cohort of RAD51-low pts with better prognosis in a platinum-free neoCT setting. Biomarker analyses on treated paired tumors and on a larger cohort of pts are ongoing. Results will be available for the congress.

A17

CONCOMITANT RADIOTHERAPY AND CYCLIN-DEPENDENT KINASE INHIBITORS (CDKI) IN THE TREATMENT OF METASTIC BREAST CANCER (MBC): ADVANTAGES AND RISKS IN CLINICAL PRACTICE REVIEW OF THE LITERATURE

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Background: Targeting cell cycle has become the gold standard for metastatic breast cancer (MBC), being cyclin-dependent kinase inhibitors (CDKIs) cornerstones of its treatment, alongside radiotherapy (RT). To date, no definite evidence regarding safety and efficacy of the combination of CDKIs plus radiotherapy (RT) is currently available. Purpose of this review is to collect data in favour or against the feasibility of the association of CDKIs + RT, describing its potential adverse events. Our review shows how CDKI + RT allows an overall satisfying disease control, proving to be effective and causing a grade of toxicity mainly influenced by the site of irradiation, leaning to favourable outcomes for sites as liver, spine or brain and to poorer outcomes for thoracic lesions or sites close to viscera; controversial evidence is instead for bone treatment. Toxicity also varies from patient to patient. To sum up, our contribution enriches and enlightens a still indefinite field regarding the feasibility of CDKIs + RT, giving cues for innovative clinical management of hormone-responsive MBC.

Material and Methods: This review is based on clinical records collected across several cancer centres with scope of assessing possible advantages or disadvantages of CDKI + RT combination therapy. To select the relevant papers for the analysis, we performed a literature search on PubMed, updated until year 2020, with the following keywords: "RT + Palbociclib + metastatic breast cancer"; "RT + CDKI + metastatic breast cancer". Overall, 2 letters to the editor, 1 review, 5 retrospective analyses and 3 case reports were selected and reviewed.

Results: According to collected data, it can be concluded that the combination of CDKI + RT allows an overall satisfying disease control, proving to be effective and causing a grade of toxicity influenced by some factors as the site of irradiation, leaning to favourable outcomes for sites as liver, spine or brain and to poorer outcomes for thoracic lesions or sites close to viscera; controversial evidence is instead for bone treatment. Toxicity also varies from patient to patient: in this context, the acknowledgment of toxicity and comorbidities history becomes of crucial importance.

Conclusions: according to our analysis we believe that the association of CDKI + RT might be effective and safe, and it is surely deserving more deepening through further analyses.

A18

MONITORING TUMOR BURDEN WITH LIQUID BIOPSY IN PATIENTS WITH HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE METASTATIC BREAST CANCER (MBC): A PROOF OF PRINCIPLE STUDY

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Background: Liquid biopsy-based biomarkers, including circulating tumor DNA (ctDNA), are increasingly important for disease characterization in MBC. To date, CA15.3 is the most commonly used serum marker for monitoring

disease burden, while no liquid biopsy-based biomarkers have been proposed for this aim in clinical practice.
Material and methods: In the MAGNETIC.1 multicenter study, 83 patients (pts) with luminal-like MBC treated with first line endocrine therapy and CDK4/6 inhibitors were enrolled and characterized for ctDNA through droplet digital PCR at baseline (BL) and after three months, at the first radiological evaluation (E1). Associations between clinicopathological characteristics, ctDNA and serum biomarkers were tested through Kruskal-Wallis test. Variations between BL and E1 were tested through Wilcoxon sign-rank test.
Results: At BL, 31% pts had = 3 metastatic sites (vs 25% at E1). Bone metastases (mts) were detected in 72% of pts (vs 68%), liver mts in 29% of pts (vs 28%), lung mts in 22% of pts (vs 22%), node mts in 54% of pts (vs 43%). ctDNA-detected *ESR1* mutations (muts) and *PIK3CA* muts were found in 11% and in 28% of pts, respectively. *ESR1* muts were associated with liver metastases (mts) ($P < 0.0001$) and a higher number of metastatic sites (met_sites) ($P = 0.0304$). ACTB short fragments (*ACTB*_s) were significantly higher in pts with node mts ($P = 0.0428$). At E1, liver mts, serosal mts and higher met_sites were associated with *ESR1* muts (respectively, $P < 0.0001$, $P = 0.038$ and $P = 0.0135$). Liver mts were also associated with higher methylation of *ESR1* promoter B (promB) ($P = 0.046$). CEA was significantly higher in pts with bone lesions ($P = 0.0483$), while CA15.3 higher than the median value was significantly associated with liver lesions ($P = 0.009$).
In pts without disease progression at E1, *ACTB*_s and met_sites significantly decreased at E1 vs BL (respectively, $P < 0.0001$ and $P = 0.0005$). A significant increase was observed for promA ($P = 0.00139$) and promB ($P = 0.0084$), while no significant variations were observed for CEA, CA15.3 and total ctDNA yield.
Conclusions: Liquid biopsy-based biomarkers were significantly associated with disease burden in luminal-like MBC. Changes in biomarkers were consistently observed at different timepoints, further supporting ctDNA as a key tool for disease monitoring. An expansion cohort is needed to test the potential clinical validity and utility of these results.

A19

DOES THE INTRODUCTION OF NEW AGENTS INCREASE MEDICAL ONCOLOGY WORKLOAD? THE CASE OF CDK4/6 INHIBITORS (CDKI)

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Background: Over the last few years, the introduction of new systemic therapies (e.g. CDKi) significantly changed the treatment paradigm of patients (pts) with luminal-like MBC. The purpose of this work is to evaluate the impact of CDKi adoption in clinical practice on medical oncology workload.
Material and methods: We examined a consecutive series of 492 pts who received therapy for MBC at the Academic Hospital of Udine during two historical cohorts A (2016-2017) and B (2018-2019), respectively before and after the first CDKi approval in Italy. In order to avoid confounding effect of SARS-CoV-2 pandemic, 2020 data were not collected. The aim of the study was to evaluate differences in terms of number and type of outpatient oncological visits (i.e. planned visits, unplanned presentations and i.v. treatment sessions) between the two cohorts.
Results: We analyzed a total number of 5,001 oncology activities deriving from 86 pts (A) and 85 pts (B) who started first line treatment for luminal-like MBC. In the cohort A, HER2, triple negative and luminal-like subtypes were respectively 19%, 19% and 63%. Pts enrolled in clinical trials were 19. In the cohort B, HER2 triple negative and luminal-like subtypes were respectively 20%, 10% and 66%. Notably, 29 pts with luminal-like disease received CDKi. 7 pts were treated in clinical trials. During the period of observation (two years), mean number of planned visits for each patient was 16.5 (A) vs 15.5 (B), mean number of unplanned presentations was 2 (A) vs 2.1 (B) and mean number of treatment i.v. sessions was 11 (A) vs 11.1 (B). Excluding pts with no luminal MBC or enrolled in clinical trials, for each patient the mean number of planned visits was 15.3 (A) vs 15.7 (B), the mean number of unplanned presentations was 1.9 (A) vs 2 (B) and the mean number of treatment i.v. sessions was 9.9 (A) vs 8.7 (B).
Conclusions: No differences in terms of medical oncology workload were observed between two historical cohorts of pts with luminal-like MBC. These findings support the handy use of CDKi into clinical practice. Further analyses are ongoing to evaluate the impact in terms of instrumental and blood chemistry tests.

A20

MODULATION OF THE IMMUNE SYSTEM BY MODERATE PHYSICAL ACTIVITY (MPA) IN BREAST CANCER PATIENTS DURING NEOADJUVANT CHEMOTHERAPY. THE NEO-RUNNER STUDY

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Background: MPA positively affects immune functions. It is possible that MPA favors response to anticancer therapy through the modulation of the immune system. We investigated the immune effect of moderate MPA, nordic or fit walking, during neoadjuvant chemotherapy (NACT) in pts with breast cancer.

Matherial and methods: Pts received sequential epirubicin and cyclophosphamide for 4 cycles followed by paclitaxel for 12 weeks.

Blood samples from pts underwent MPA (TR) were collected before starting chemotherapy (CT) (T0), before starting MPA at day 1 of week 6 of paclitaxel (T1), before surgery (S) (T2) and after S (T3). Samples were also collected in 17 pts who declined MPA (UN) and in 15 healthy volunteers (HV). MPA consisting of 3 workouts per week, 1 hour each, in the 9-10 weeks before S.

18 cytokines (cy) (IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, IL-21, CCL-2, CCL-4, CXCL-10, CCL-22, IFN-γ, TGF-β, TNF-α, VEGF) were measured at each time-point.

Differences among the median values were analysed using non parametric Mann-Whitney U test. Principal component analysis (PCA) and Hierarchical Clustering on Principal Components (HCPC) were computed to compare and cluster pts based on the best discriminating cy, identified by ROC analysis, at T1, T2, T3 and in HV. Pts having similar cy values were plotted in the near position in the PCA.

Results: Thirty-five out of 46 pts (18 TR, 17 UN) have been analysed. At T0 UN pts had IL-10 value higher than TR. The longitudinal analysis between T0 and T1 showed IL-4, IL-6, IL-8*(* = statistically significant), CXCL-10 increase in UN compared to TR pts. IL-21 increased in TR pts.

Between T1 and T2 IL-6*, IL-8* and CCL-2* value was higher in UN compared to TR pts, while IL-21*, CXCL-10*, CCL-22* value was higher in TR compared to UN pts.

At T2 VEGF* was higher in UN than in TR pts.

Normalized values of 7 cy identified by ROC (IL-4, IL-6, IL-8, IL-21, CCL-2, VEGF, TNF-a) were used in PCA and in HCPC at each time-point. At T1 and T3, TR and UN pts were mixed; at T2 the majority of TR pts was clustered together.

Conclusions: NACT contributes to upregulation of some inflammatory cy. TR pts showed downregulation of IL-6, Il-13 and CCL-2 and upregulation of IL-21, CXCL-10 and CCL-22 compared to UN during MPA. These data suggest that MPA might damp the inflammatory response to NACT. Most important, PCA showed that, after MPA, TR pts reach an immune profile similar to HV, suggesting a positive modulation of immune system by MPA.

A21

INSIGHT INTO CLINICOPATHOLOGICAL FEATURES AND SURVIVAL OUTCOMES OF HEREDITARY AND SPORADIC MALE BREAST CANCER PATIENTS IN MARCHE REGION

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Background: Male breast cancer (MBC) is a rare disease and limited knowledge is available about clinical-pathological features, prognostic factors and survival rates. Germline pathogenic variants (gPV) in BRCA1/2 genes are associated with hereditary predisposition to female breast/ovarian cancers and also to MBC. Our study aimed at evaluating clinical-pathological characteristics and prognostic factors of BRCA-wild type (sporadic) and BRCA-related (hereditary) MBC in Marche Region.

Patients and Methods: From October 1998 to November 2020 MBC patients (pts) were selected to undergo genetic counselling and BRCA testing: direct sequencing of DNA and MLPA or Next generation sequencing technique were used to examine the entire BRCA1/2 coding sequence. Enrolled pts were classified as mutation-positive or -negative according to the genetic testing result. Detection rate (DR), defined as the probability to detect a gVP in BRCA genes, was calculated for pts with and without positive family history.

Results: 108 MBC pts were included; among them 27 (25%) carried a gPV in BRCA genes, while 12 (11.1%) had a Variant of Uncertain Significance (VUS). Median age at diagnosis was 65 years (range 37-89) without significant differences between sporadic *vs* hereditary MBC pts.

Positive family history for BRCA-related tumors was reported in 49 (46.7%) pts, while 56 (53.3%) had no family history. In the first group 20 pts had a gVP, while in the second group only 7 pts carried a gPV. DR was significantly higher (40.8%) in MBC pts with a positive family history *vs* pts without familiarity (12.5%) (p = 0.0005).

Concerning pathological features, ductal carcinoma was the most frequent histotype (91.3%) and hereditary MBC *vs* sporadic MBC showed significant lower median expression of ER (85% *vs* 90%, p=0.03) and PgR (55% *vs* 80%,

p=0.02) and higher median expression of Ki67 (35% *vs* 25%) (p=0.01).
Regarding prognostic factors (tumor grade, Her2 expression, luminal A or triple negative subtypes, BRCA status and nodal involvement), at multivariant analysis only the presence of a BRCA gVP significantly affected overall survival (OS) (p=0.03). A trend toward a worst OS was also observed among pts who received as adjuvant endocrine therapy the association of aromatase's inhibitors and LHRHa compared to those who received tamoxifen.
Conclusions: Our results provide further knowledge regarding clinical and pathological features, prognostic factors and outcomes of sporadic and hereditary MBC.

A22

CELL-FREE DNA (CFDNA) WORKFLOW FOR THE RISK ASSESSMENT OF NEUTROPENIA IN PATIENTS TREATED WITH FIRST-LINE ENDOCRINE THERAPY (ET) AND CYCLIN-DEPENDENT KINASE 4/6 INHIBITORS (CDK4/6I) FOR METASTATIC BREAST CANCER (MBC)

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Background: Neutropenia is the main dose limiting toxicity related to the use of ET in combination with CDK4/6i, which currently represent the standard of care for hormone receptor (HR)-positive/HER2-negative MBC. The present study aimed to evaluate the feasibility of a cfDNA-based workflow as a new tool to assess the risk of treatment induced neutropenia in patients (pts) treated for luminal MBC.
Methods: A prospective cohort of 83 luminal MBC pts treated with first line ET and CDK4/6i in the MAGNETIC multicenter study was analyzed. cfDNA was characterized through droplet digital PCR (ddPCR) based on different ACTB DNA fragments lengths: short (s), medium (m) and long (l). Blood samples were collected before treatment start (BL) and at the first clinical evaluation after 3 months (E1). Associations between clinical characteristics, neutropenia and cfDNA were explored through Kruskal Wallis, while time to G3 neutropenia (NG3) (TTN) was analyzed through log-rank and Cox regression.
Results: out of 83 pts, G4 neutropenia was observed in 2 (2%), whereas NG3 in 44 (53%). 60% of NG3 occurred within 3.7 months and median TTN was 1.8 months. Pts who experienced NG3 had significantly lower BL neutrophils count (Neu) and WBC (p=0.0013 and p=0.0020 respectively). Overall, 10 pts (12%) reduced CDK4/6i dose after NG3, while 74 (89%) resolved toxicity within 7 days. De novo metastatic pts had numerically higher Neu, but only a numerically lower risk of NG3 was observed (HR 0.53 p=0.064). Bone involvement was not associated with a higher risk of developing NG3 however, the total number of metastatic lesions was associated with a higher risk of NG3 (p=0.0016). In particular, >5 metastatic lesions were associated with higher NG3 risk (p=0.013). Pts that experienced NG3 had significantly lower E1 ACTB_m than BL (median 100% vs 16%, p=0.0136 in NG3 no vs yes). 4 TTN risk groups were described after dichotomization and combination of BL Neu and ACTB_m (p=0.0006). Notably, pts with low BL Neu and low E1 ACTB_m had a median TTN of 0.9 months, while pts with high BL Neu and high E1 ACTB_m have not experienced NG3 after a median follow-up of 16.1 months.
Conclusions: The present study suggested that cfDNA can be used not only as a tumor-related biomarker in MBC, but also as a tool to assess the risk of drug-related adverse events, such as CDK4/6i-induced neutropenia. Based on these results, a prospective study focused on a multiparametric neutropenia risk assessment will be started.

A23

TARGETED RNA-SEQ SIGNATURE OF BREAST CANCER (BC) CIRCULATING TUMOR CELLS (CTCS) CORRELATES WITH THE ONSET OF BONE-ONLY METASTASES

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Background: Bone is the most common site of BC metastases, but no biomarkers are currently available to predict skeletal dissemination in this disease.
Methods: CTCs were isolated from 40 stage IV BC patients through immunomagnetic enrichment with autoMACS® and DEPArray® sorting. A panel of 134 genes involved in the bone metastasis (BM) cascade was standardized by targeted RNAseq on subclones of the MDA-MB231 BC cell line with different organotropism (P0: bone & viscera; P7: bone; LM: viscera) and then applied to patients' CTCs, grouped according to the sites

of radiologically-confirmed metastases, namely BM, extra-skeletal (ES) or both.

Results: The transcriptome heatmap of unsupervised hierarchical clustering of BC cell lines, based on normalized read counts, successfully separated the cell populations according to their organotropism. Once the targeted RNAseq was performed on CTCs, by applying an absolute fold change (FC)≥2 and a false discovery rate (FDR) threshold of 0.25, 31 DEGs were identified in BM vs ES CTCs (Table 1), including MAF, CAPG, GIPC1 and IL1B, playing key prognostic roles in BC. According to Gene Ontology and KEGG pathway analyses, most DEGs were enriched in biological processes correlated with skeleton rearrangement. The potential prognostic role of the top-10 (4≤FC≤-4) most deregulated genes was explored within METABRIC dataset, where a significantly longer survival emerged in the group of early-stage patients harboring the gene deregulations, compared to controls (199 vs 112 months, P=0.014).

Conclusions: CTCs are suitable biological sources for osteotropism investigation through targeted RNAseq and deserve further investigation in wide scale prospective studies.

Table 1. DEGs emerged from the comparison of "BM vs ES" CTCs.

Gene	P-value	FDR step up	FC
CAPG	1.73^{-02}	2.02^{-01}	30.79
HRAS	1.34^{-02}	2.02^{-01}	11.67
IL1B	2.46^{-02}	2.02^{-01}	5.37
FGFR4	1.99^{-02}	2.02^{-01}	5.28
MAF	2.38^{-02}	2.02^{-01}	4.39
SERPINB2	2.79^{-02}	2.02^{-01}	4.38
CTSK	1.91^{-02}	2.02^{-01}	4.06
MAFA	2.77^{-02}	2.02^{-01}	3.92
COL3A1	8.53^{-03}	2.02^{-01}	3.75
TTYH1	1.37^{-03}	2.02^{-01}	3.62
AURKB	3.38^{-02}	2.08^{-01}	3.48
HMMR	1.66^{-02}	2.02^{-01}	2.97
NAP1L3	2.59^{-02}	2.02^{-01}	2.88
EPHB3	3.04^{-02}	2.02^{-01}	2.82
SYNM	5.47^{-02}	2.64^{-01}	2.74
GIPC1	3.06^{-02}	2.02^{-01}	2.43
RERGL	3.03^{-02}	2.02^{-01}	2.38
ITGB4	3.38^{-02}	2.08^{-01}	2.34
PRDX1	2.23^{-02}	2.02^{-01}	2.25
ST3GAL1	8.12^{-03}	2.02^{-01}	2.2
MEF2C	3.79^{-02}	2.24^{-01}	2.19
DKK1	5.46^{-02}	2.64^{-01}	2.18
MAPK1	4.30^{-02}	2.32^{-01}	2.17
FGF5	3.01^{-02}	2.02^{-01}	2.15
SOX9	4.92^{-02}	2.57^{-01}	2.04
FGFR3	1.30^{-02}	2.02^{-01}	–2.75
HPRT1	1.24^{-02}	2.02^{-01}	–2.79
SMAD2	2.62^{-02}	2.02^{-01}	–2.86
HMGA2	2.33^{-03}	2.02^{-01}	–4.11
MCM2	3.91^{-02}	2.24^{-01}	–4.56
ANLN	9.02^{-03}	2.02^{-01}	–12.02

A24

RECURRING NEUTROPENIA AND NEUTROPENIA-INDUCED DOSE REDUCTION IN PATIENTS TREATED WITH FIRST-LINE ENDOCRINE THERAPY (ET) AND CYCLIN-DEPENDENT KINASE 4/6 INHIBITORS (CDK4/6I) FOR METASTATIC BREAST CANCER (MBC) THROUGH A CELL-FREE DNA WORKFLOW (CFDNA)

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Background: The standard of care for hormone receptor (HR)-positive/HER2-negative MBC is the combination of ET with CDK4/6i with neutropenia (NP) as the main dose limiting toxicity. This study aimed to evaluate the feasibility of a cfDNA-based workflow as a new tool to assess the risk of treatment induced recurrent-neutropenia (rec-NP) and NP-induced dose reduction (DR) in patients (pts) treated for luminal MBC.

Material and methods: A prospective cohort of 83 luminal MBC pts treated with first line ET and CDK4/6i in the MAGNETIC.1 multicenter study was analyzed. cfDNA was characterized through droplet digital PCR (ddPCR) based on different ACTB DNA fragments lengths: short (s), medium (m) and long (l). Blood samples were collected before treatment start (BL) and at the first clinical evaluation after 3 months (E1). Associations between clinical characteristics, cfDNA, rec-NP (=3 NP events) and DR were explored through Kruskal Wallis.

Results: Among 83 pts, 46 (55%) had NP higher than G2. Overall, 29 pts (35%) developed rec-NP and 12 pts (26%) reduced CDK4/6i dose after NG3-G4. Notably, BL neutrophils count (Neu), WBC and lactate dehydrogenase (LDH) were significantly lower in pts that developed rec-NP (respectively P=0.0009, P=0.0008 and P=0.0375), while no significant associations with DR were observed. De novo metastatic pts had a lower risk of DR (P=0.0304), while pattern of metastasis was not associated with significant DR. BL ACTB_m was higher in pts that experienced DR (P=0.0096), while no associations emerged between ACTB_m and rec-NP. BL neu and ACTB_m were then combined to describe 4 distinct risk subgroups after dichotomization at the median value. Although pts with high ACTB_m and high Neu did not experience any DRs, no significant differences were observed among subgroups (P=0.577).

Conclusions: The present study suggested that cfDNA can be used not only as a tumor-related biomarker in MBC, but also as a tool to assess the risk of drug-related adverse events, such as CDK4/6i-induced dose-limiting neutropenia. Additional investigations are planned to further refine the concept.

A25

BREAST CONSERVING SURGERY IN BRCA-MUTATION CARRIERS. A SINGLE INSTITUTION EXPERIENCE

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Background: BRCA-mutation carriers have a lifetime risk of breast cancer (BC) that ranges from 36 to 70%. For patients (pts) without mutation, breast conserving surgery (BCS) (followed by radiation therapy) is the treatment of choice since it offers similar survival to that of unilateral mastectomy. However, the optimal local management in BRCA-mutation carriers remains a matter of debate and the role of bilateral salpingo-oophorectomy (BSO) in reducing BC risk might be influenced by age and medical BC treatments (such as GnRH analogues).
Patients and methods: We retrieved clinical pathologic characteristics of 124 BRCA-mutated BC pts, consecutively tested at our Institution from 2008 to 2018. Primary end-point was recurrence-free survival (RFS) evaluation in terms of disease-free survival (DFS), distant DFS (DDFS) and overall survival (OS). Secondary end-point was identification of independent predictive factors for BCS. Clinical pathologic characteristics were evaluated and compared using univariate and multivariate analysis. Kaplan-Mayer curves were used to describe DFS, DDFS and OS.
Results: Median age at BC surgery was 41 years (range 24-74), most of the pts (79%) were pre-menopausal and presented with ductal invasive carcinoma (91.9%). As per biological subtype, 63 (50.8%) pts had luminal-like BC, 52 (41.9%) triple negative (TN) BC and 9 (7.3%) HER2 enriched-like BC. More than half pts (62.9%) presented with G3 tumors and median Ki-67 was 40% (range 5-95). 17 (13.7%) and 80 (64.5%) pts underwent neo-adjuvant and adjuvant chemotherapy, respectively; 64 (51.6%) pts received adjuvant endocrine therapy, 39 (31.5%) with the addition of GnRH analogue. When comparing BCS to mastectomy, regardless of BSO, we could not observe any statistically significant difference in all the RFS endpoints. 10-year DFS rate was 56.4% and 79.5%, respectively (p=0.187); 10-year DDFS rate was 83.7% and 82.3%, respectively (p=0.689); 10-year OS rate was 87.7% and 85.1%, respectively (p=0.947). At a multivariate analysis, age ⩽41 years (p=0.008; OR 0.309; 95% CI 0.190-0.513) and primary tumor dimension ⩽21 mm (p=0.008; OR 0.320; 95% CI 0.114-0.426), were the only predictors of breast surgery type (BCS compared to any other surgical treatment).
Conclusions: Our data suggest that young pre-menopausal BRCA-mutated pts with small tumors may not need upfront mastectomy and BSO might be postponed, when ovarian cancer risk epidemiologically risesand potential reproductive desire is fulfilled.

A26

HEALTH EQUITY AUDIT: INIQUITIES' BREAST CANCER MULTIDISCIPLINARY TEAM OF FERRARA- A SINGLE CENTER ANALYSIS

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Background: The breast multidisciplinary team is important in the management of BC from the diagnosis to metastatic/FU status. The Healt Equity Audit is used to plan health service to fight disequity in the distribution of health resources. Is this indicator useful in the integrated evaluation of an equity iter planification in the BC multidisciplinary team?
Material (patients) and methods: The primaty end point of this single center study was building a HEA to analize and to avoid disequity in BC diagnostic and therapeutic iter.
The building process of HEA in this study is composed by 4 steps: priority, production of equity profile, identification of iniquities, elements to fight iniquities. We analized data of 387 pts (median age 66.41) with a new diagnosis of BC discussed in BMT from March 2018 to February 2019. We selected 7 indicator related to diagnostic surgery and therapeutic areas.
Results: The most significant indicators are:

- Indicator 1 (time from first diagnostic imaging to comunication of diagnosis): the patient with partners (68%) showed a best compliance to clinical control (p=0.012).

- Indicator 2 (time from comunication of diagnosis to surgery): the most significant (p=0.016) factor was a diagnosis from screening test (56%) rather than diagnosis from other way (44%).
- Indicator 5 (time from surgery to adiuvant therapy): a distance from home to Sant'Anna Hospital < 15 km was significant (p=0.024).

Conclusions: To build HAE we have to take into consideration not only clinical but also socio-democratic and logistic setting. The best management of each patient is always an integrated evaluation of disease, social, working, family and topographic item to granted an equity of care distribution resources.

A27

DO NOT FORGET BREAST CANCER RISK ASSOCIATED WITH RAD51C, RAD51D AND RAD50 PATHOGENIC VARIANTS

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Background: *RAD51C, RAD51D* and *RAD50* encode for proteins involved in DNA repair by homologous recombination. Previous research has shown a strong association between *RAD51C/D* pathogenic variants (PVs) and increased risk for ovarian cancer (OC), while breast cancer (BC) screening is not recommended yet. In case of *RAD50* PVs an evident association with BC and OC lacks, so cancer risk management is based mainly on family history. The aim of our study was to explore the characteristics of BC in carriers of *RAD51C/D* and *RAD50* PVs identified in the Modena Family Cancer Clinic (MFCC).
Materials and methods: The Genomics Laboratory of the MFCC has provided multigene panel testing to patients with a personal and/or family history of BC and/or OC according to regional criteria since 2018. When a PV was detected in the index case, all relatives interested (starting from the first degree) underwent targeted genetic testing to search for the PV found in the family.
Results: We retrospectively identified 18 women with a *RAD51C/D* PV in 8 families and 7 women with a *RAD50* PV in 5 families. In *RAD51C/D* PV carriers, 7 BC patients (of which 2 with bilateral BC), one BC and OC patient and 3 OC patients were reported. In *RAD50* PV carriers, 5 BC patients (of which 2 with bilateral BC) were observed. Median age at first BC diagnosis was 52.4 years in *RAD51C/D* and 39.6 years in *RAD50* patients. BC was diagnosed at an early stage (0-II) in all *RAD51C/D* and *RAD50* patients except one *RAD51C* carrier who presented locally advanced triple negative BC. Interestingly, five out of 10 *RAD51C/D*-related BCs were triple negative, while *RAD50*-related BCs were all hormone receptor positive. Eight out of 17 (47.1%) BCs were treated by mastectomy and the same number by breast conserving surgery. One patient underwent only axillary node dissection for CUP syndrome. Two out of 15 (13.3%) invasive BC patients received neoadjuvant and 4 (26.6%) adjuvant chemotherapy. After a median follow up of 10 years, two local recurrences were observed.
Conclusions: In our cohort RAD51C/D-related BCs were mainly triple negative, while RAD50-related BCs were all hormone receptor positive. In both subgroups, the prognosis of BC was good, with only two local recurrences observed and no distant relapse. The definition of biological and clinical features of RAD51C/D and RAD50-related BCs may improve diagnosis and treatment in this setting. Bilateral prophylactic mastectomy should be considered as in case of *BRCA* mutation carriers.

A28

HYPERGLYCEMIA INCREASES IPILIMUMAB INDUCED CARDIOTOXICITY AND BREAST CANCER RESISTANCE THROUGH GROWTH FACTORS, CYTOKINES AND NLRP3 INFLAMMASOME

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Background: Type 2 diabetes, obesity and metabolic syndrome are negative prognostic factors in breast cancer patients. Immune checkpoint inhibitors (ICIs) that target cytotoxic T lymphocyte antigen 4, programmed cell death-1, and PD-ligand 1 have revolutionized cancer treatment, achieving unprecedented efficacy in multiple malignancies. However ICIs are characterized by a broad spectrum of toxicity reactions, termed immune-related adverse events (irAEs) like cardiotoxicity and induction of diabetes. We aimed to study if hyperglycemia could enhance ipilimumab-induced cardiotoxicity in cardiomyocytes and immune-resistance in human breast cancer cells. We evaluated if the treatment with an SGLT-2 inhibitor (empagliflozin) or shifting from high glucose to low glucose may reduce carditoxicity.
Methods: Human cardiomyocytes (HL-1 cells) and PD-1+ ER?+, PR+, HER2- breast cancer cells (MCF-7 cell line) were exposed to ipilimumab (100 nM) at high glucose (25 mM) low glucose (5.5 and 2.5 mM) for 72 h. After the incubation period, we performed the following tests: determination of cell viability, through analysis of mitochondrial dehydrogenase activity; NLRP3, p65/NF-kB and leukotrienes expression through ELISA method.

Results: Ipilimumab-induced cardiotoxicity was enhanced by 2,3-fold during exposure to 25 mM glucose (High Glucose; HG) compared to 5.5 mM glucose (Low Glucose; LG) in human adult cardiomyocytes. Moreover, IC50 value of nivolumab against MCF7-cells increased significantly under HG vs LG ($P<0.001$). Moreover, during high glucose condition, cardiomyocytes and human breast cancer cells exposed to ipilimumab, increases the expression of NLRP3, p65/NF-kB, leukotrienes and cytokines. Notably, hyperglycemia increases significantly the intracellular calcium (iCa2+) content in cardiomyocytes exposed to ipilimumab. Shifting from HG to LG, as well as the administration of 50nM empagliflozin (anti SGLT2 drug with hypoglycemic properties) reduced the magnitude of cardiotoxic effects, indicating cardioprotective and immuno-enhancing properties.

Conclusions: Hyperglycemia exacerbates Ipilimumab-induced cardiotoxicity and immunoresistace and set the stage to preclinical and clinical trials aimed to decrease glucose through dietary or lifestyle changes or through new hypoglycemic drugs (gliflozins).

A29

TDM-1 EFFICACY IN TRASTUZUMAB-PERTUZUMAB PRE-TREATED HER2 POSITIVE METASTATIC BREAST CANCER PATIENTS: A META-ANALYSIS

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Background: Based on the results reported in Emilia trial population, current guidelines consider TDM-1 the standard 2nd line therapy for HER2 positive metastatic breast cancer (MBC) patients. Despite that, there are no prospective studies supporting the efficacy of TDM-1 following trastuzumab (T) + pertuzumab (P) and taxane 1st line treatment. Currently, only real-world data have investigated this sequence with controversial results.

Methods: We performed a meta-analysis of the available real world data to determine the efficacy of T-DM1 after 1st line TP in HER2 positive MBC patients. We used a random-effect model to find differences in the rate of 1-year progression free survival (PFS) between TP pre-treated population and the phase III Emilia trial (T pre-treated population).

Results: Seven studies were eligible, in three of them data were from sub-group population analysis. The meta-analysis showed a combined 1-years PFS risk difference for TDM-1 efficacy after TP in 2nd or more lines of -0.122, with lower and upper limits of -0.253 and 0.010, respectively (p=0.07), with low heterogeneity among studies ($I^2 < 0.0001$, p =0.836). Considering the four studies on TDM-1 in 2nd line setting, 1-years PFS risk was -0.034 (95% CI -0.207 – 0,139; p=0.701) ($I^2 < 0.0001$, p =0.91).

Conclusions: Results from the meta-analysis show that the efficacy of TDM-1 after TP double-block seems to be similar to the previously reported in Emilia trial. In the second line setting, available data are not mature enough to confirm TDM-1 efficacy in TP pre-treated population. Currently, TP pretreated patients should receive T-DM1 as indicated in the guidelines.

A30

FOCUS ON THE ROLE OF PCR AS A SURROGATE END-POINT FOR PREDICTION OF SURVIVAL IN PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY: THE MAUGERI CLINICAL INSTITUTE EXPERIENCE

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Background: Apart from the advantage of reducing the risk of distant recurrences and of mortality, neoadjuvant systemic therapy also has different additional benefits, among which the possibility to obtain information about the response to chemotherapy, which has shown to be a strong predictor factor; moreover, the presence or absence of residual tumor after neoadjuvant chemotherapy represents a relevant prognostic factor. Notably, pathological complete response (pCR) has been proposed as a surrogate endpoint for prediction of long-term clinical benefit.

The aim of our study is to determine the prognostic efficacy of pCR among patients treated with neoadjuvant chemotherapy at the Maugeri Clinical Institute in Pavia in the last 10 years, establishing its association with event-free survival (EFS) and overall survival (OS).

Patients and methods: Between 2010 and 2017, more than 200 cases of breast cancer were treated with different regimens of neoadjuvant chemotherapy at the Maugeri Clinical Institute. Clinical stage at diagnosis (AJCC system) was I in ~1%, II in ~59.4%, and III in ~36.6% of patients. A retrospective study was performed, analyzing pCR – ypT0/is ypN0 – for its association with EFS and OS, trying to assess whether pCR could be used as a surrogate endpoint for EFS and OS.

Results: The 5-year actuarial EFS rate of the entire pool of patients was 72%, with an estimated mean survival time of 83 months, while the 5-year actuarial OS rate was 79%, with an estimated mean survival time was 115,4 months. The achievement of pCR proved to be statistically significant for

both 5-year EFS and 5-year OS rates (P = 0.029), with rates of 5-year EFS equal to 85% (P = 0.029) in those who achieved it and of 66% in those who did not, and rates of 5-year OS equal to 90% (P = 0.045) in those who achieved it and of 75% in those who did not. On a multivariate analysis, however, pCR did not prove to be statistically significant for the long-term outcomes.

Conclusions: Even though pCR could not be validated as a surrogate end-point for long-term outcomes, the strong association between the achievement of pCR and the substantially improved outcomes in individual patients is promising for further investigations of pCR in defined subsets, and it can already be used for single patients counseling.

A31

QUALITY OF LIFE OF THERAPIES FOR HORMONE RECEPTOR POSITIVE ADVANCED/METASTATIC BREAST CANCER (HR+/HER2- MBC): REGULATORY ASPECTS AND CLINICAL IMPACT IN EUROPE

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Background: In recent years the number of trials that incorporated health related quality of life (HRQoL) data has increased. The impact of HRQoL on the regulatory decision making in the European regulatory context and on clinical practice is not well established. We conduct an analysis of the role of QoL data extracted from the pivotal trials of the drugs approved for HR+/HER2- mBC, to discuss their impact on the regulatory decision making in the European regulatory context and the possible impact on clinical practice.

Methods: We identified all products approved for mBC by the European Medicines Agency (EMA) based on the European public assessment reports (EPARs) that are publicly available on the agency's website.The following substances has been evaluated: letrozole, anastrozole, exemestane, fulvestrant, ribociclib, palbociclib, abemaciclib, alpelisib. The results of the HRQoL analysis form the pivotal trials have been collected and a metanalysis has been performed to evaluate the impact of experimental drugs if compared to the standard treatments. All the EPARs available from the EMA website have been checked to verify the presence of the HRQoL in the discussion and in the benefit risk assessment. The related summary of medicine products characteristics (SmPCs) have been verified to evaluate the presence of the HRQoL data in the section 5.1

Results: 7 out of the 9 active substances taken in account in the current analysis incorporated the HRQoL data in the description of the result of the pivotal trials. Seventeen trial has been identified, in fourteen the QoL was included as a secondary endpoint. A global improvement in the global QoL, considering the Time To deterioration >10, was observed, pointing out the consistency of the efficacy of the new substances if compared to the standard treatment. As regards the approval process from the analysis of the EMA documents, the HRQoL were reported quite shortly and contained and discussed in the EPARs of eleven trials in the approval process and cited in three cases in the EPARs and summary of medicine products characteristics (SmPC).

Conclusions: An effort should be done from all the stakeholders to increase the visibility of the HRQoL results in order to allow an increasing consideration in the approval process to make QoL data more easily and visibly available for the clinician and the patients. The evaluation should be reflected in the SmPC in order to increase the amount of information provided to the physician.

A32

THE ROLE OF HMGB1 IN EARLY AND METASTATIC BREAST CANCER

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Background: High mobility group box 1 (HMGB1) is an ubiquitous and highly conserved nuclear protein. When released, it is recognized as a damage-associated molecular pattern contributing to the inflammatory response. In cancer, HMGB1 is crucial in inducing immunogenic cell death (ICD) as well as in mediating immune evasion by promoting myeloid-driven suppressor cells and regulatory T cells, but its role in cancer patients remains unclear. Here, we investigated the levels of circulating HMGB1 in both early and metastatic breast cancer (BC) patients undergoing different therapies to assess its possible role as an immune biomarker of off-target effects of treatments.

Methods: 60 patients were enrolled in the study: 29 early BC patients (TNBC or luminal B like or HER2+) treated

with standard sequential neoadjuvant chemotherapy +/- trastuzumab and 31 HR+/HER2- metastatic BC patients treated with cyclin-dependent-kinase 4/6 inhibitors (CDK4/6i) plus endocrine therapy. Patients sera were isolated from blood at baseline (T0) and during therapy (T>0). Patients who achieve a partial or complete response were considered as responders (RP). HMGB1 levels were assessed by an enzyme-linked immunosorbent assay (ELISA) kit.

Results: HMGB1 appears to be differently modulated in the two cohorts. In patients treated with neoadjuvant chemotherapy, HMGB1 levels increased significantly from baseline during the treatment (p=0,01). Baseline HMGB1 is lower in responders (RPs) than in non-responders (NRPs) patients (p=0,05). Otherwise, HMGB1 levels are significantly reduced during CDK4/6i therapy (p=0,001), in particular in the responder patients (p=0,05). RPs to CDK4/6i show higher HMGB1 baseline levels than NRPs (p=0,05).

Discussion: During chemotherapy, the observed HMBG1 increase could be associated with the induction of ICD. In the metastatic setting, the HMGB1 down-modulation of the inflammatory response may be the result of a CDK4/6i effect on the inflammatory tumor microenvironment. The different HMGB1 kinetics in the neoadjuvant and CDK 4/6i cohorts, in particular in RPs, may be related to the different mechanism of damage on cancer cells and off-target effects on tumor microenvironment exerted by the two treatments.

A33

PREDICTIVE FACTORS FOR RELAPSE IN TRIPLE-NEGATIVE BREAST CANCER (TNBC) PATIENTS WITHOUT PATHOLOGIC COMPLETE RESPONSE (PCR)

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Background: Triple-negative breast cancer (TNBC) patients who do not obtain pathologic complete response (pCR) after neoadjuvant chemotherapy (NACT) present higher rate of relapse and worse overall survival. Risk factors for relapse in this subset of patients are poorly characterized. This study aimed to identify predictive factors for relapse in TNBC patients without pCR after NACT.

Methods: TNBC patients treated with NACT from January 2008 to December 2018 at the Modena Cancer Center were included in the analysis. Local or distant relapse was compared between patients with and without pCR using the Kaplan-Meier method. In patients without pCR, univariate and multivariable Cox analyses were used to determine factors predictive of relapse.

Results: 124 patients with median follow-up of 57 months (range, 7.6-143.8 months) were identified. After NACT, 82 had residual disease (pCR, 33.9%). Five-year relapse free survival (RFS) was 95% and 71% in patients with and without pCR, respectively. Factors independently predicting RFS in patients without pCR were the presence of bilateral disease (HR 6.06; 95% CI, 1.6–22; P=0.007), multifocal/multicentric disease (HR 4.7; 95% CI, 1.8–12; P=0.001), pathologic residual tumor (HR 1; 95% CI, 1-1.005; P=0.04), pathologic nodal positivity (HR 2.68; 95% CI, 1.36–5.3; P=0.004) and lymphovascular space invasion (HR 2.36; 95% CI, 1.25–5.36; P=0.004). Age at diagnosis, germline predisposing gene mutations, BMI, breast MRI, histologic subtype, grading, ki-67, clinical T or N stage, type of breast or axillary surgery, time from NACT end and surgery and time from surgery to radiation therapy were not predictive of relapse.

Conclusions: Lack of pCR after NACT resulted in worse outcome. In patients with residual disease after NACT, presence of bilateral or multifocal/multicentric disease, pathologic residual tumor, pathologic nodal positivity and lymphovascular space invasion predicted worse RFS. These data can be used to stratify patients and potentially guide treatment decision-making identifying appropriate candidates for treatment intensification.

A34

SURVIVAL OUTCOMES OF TRIPLE NEGATIVE BREAST CANCER (TNBC) PATIENTS IN THE PRE-IMMUNOTHERAPY AGE. AN ANALYSIS OF GRUPPO ITALIANO MAMMELLA (GIM) 14 BIOMETA STUDY WITH A FOCUS ON BIOLOGICAL SUBTYPES

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Background: Metastatic(me)TNBC is a subtype of Breast Cancer (BC) associated with an overall survival (OS) of around 19 months (ms). ER low disease is characterised by low ER and PgR staining (both <10%) and negative Her2. It is considered as having a survival and a biological behavior similar to that of TNBC. Germline BRCA mutations were the only predictive biomarker available in the past years for TNBC.

Materials and methods: Patients (pts) were identified in the GIM-14 study, an ambispective multicenter Italian study including pts with mBC diagnosed from 2000 to 2020. TNBC and ER low pts were eligible to this analysis. Pts characteristics and treatments were obtained for each pts. OS and Time to Treatment Failure (TTF) were calculated.

Results: Overall,195 pts were eligible (158 TNBC and 37 ER low). BRCA mutation was tested in 35 pts (18%), of whom 16 were pos and 19 neg. Pts' characteristics are summarized in table. Median (m)OS was 22.6 ms (95%CI:18.6-26.8); 84% and 57% of pts were alive at 1 and 2 years respectively. M 1st line TTF was 4.4 ms (95% CI: 3.8-5.1). MOS of TNBC pts was 20.2 ms (95% CI:17-25) while for ER low pts was 26.8 ms (17-73 ms) p 0.07. First line mTTF was 4.3 ms (95% CI 4-5) for TNBC and 5.5 ms (95% CI 4-9) for ER low pts, p 0.1. mOS in BRCA pos pts was 35 ms (20-NR) while for BRCA neg 16.3 was ms (95 CI%: 9-32), p 0.03.

Discussion: In this analysis OS of TNBC pts was similar to that reported in literature. BRCApos pts showed a better OS when compared to BRCAneg pts. A trend towards a better OS in ER low pts was found. Further investigation in these pts is warranted.

Variable	Pts=195
Age (mean)	58
Menopause	
No	47 (24%)
Yes	131 (67%)
NA	17 (9%)
DIsease Subtype	
TNBC	158(61%)
ER low	37(39%)
BRCA status	
BRCA positive	16(8%)
BRCA negative	19(10%)
Unknown	160(82%)
De novo me	
Yes	43(16%)
No	121(62%)
NA	21(22%)
Me Sites	
Non visceral	53(27%)
Bone	31(16%)
Visceral	105(54%)
NA	6(3%)
Number of me sites	
1	94(48%)
2	48(25%)
3	48(25%)
NA	5(2%)
Number of chemotherapy lines	
1	61(31%)
2	42(22%)
3	34(17%)
4	31(16%)
⩾5	22(11%)
NA	5(3%)
1st line CT	
Anthracyclines (single agent or combo)	22(11%)
Taxanes (single agent or combo w/o bevacizumab)	26(13%)
Taxanes + Bevacizumab	37(19%)
Platinum salt (single agent or combo)	21(11%)
Capecitabine	16(8%)
CMF	6(3%)
Nabpaclitaxel	6(3%)
Vinorelbine	3(1.5%)
Other (clinical trial included)	29(15%)
Missing	29(15%)
Stage localized disease	N=121
I	23(19%)
II	55(46%)
II	33(27%)
NA	10(8%)
Localized disease surgery	
Yes	117(97%)
No	4(3%)
Adjuvant CT	
Yes	110(91%)
No	7(6%)
NA	4(3%)

Table. (Continued)

A35

CANCER AND FEMININITY: ASSESSMENT OF QUALITY OF LIFE, BODY IMAGE, DISTRESS, DEPRESSION AND ANXIETY IN A SAMPLE OF YOUNG WOMEN WITH BREAST CANCER

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Worldwide, breast cancer is the most frequently diagnosed cancer in female and is also the leading cause of death in over 100 countries. Among young females, the incidence rate for breast cancer is about 5-7%, but the figure is increasing. The young patients present a different epidemiology, presenting successive phases and more aggressive

phenotypes. Clinical Psychology and Health Service, in collaboration with the Oncology Operative Unit, in particular Linea Arianna of San Raffaele Hospital in Milan, have launched this research study to evaluate how this specific oncological pathology may affect the quality of life of patients and may be associated with states of anxiety, depression and distress. Has been used test battery consisting of: anagraphic card, Sf-36 (36-Item Short Form Health Survey Instrument); BUT (Body Uneasiness Test); PDI (Psychological Distress Inventory); and HADS (Hospital Anxiety and Depression Scale). Those questionnaires are administered to 32 female patients aged 18 to 45 years, diagnosed with breast cancer. The sample examined obtained average deficiency scores in different sub-scales of the SF-36 which, in general, specify a compromised state of physical and mental health (ISF: Average = 44.44; DS = 9.11; ISM: Average = 39.69; DS = 11.77). Regarding specifically breast cancer in young women, it was observed that younger patients experienced greater limitations of the physical role ($r = 0.504$; $p = 0.003$). Furthermore, positive correlations were found between the level of distress and the levels of anxiety ($r = 0.670$; $p = 0.0001$) and depression ($r = 0.634$; $p = 0.001$). Multiple negative correlations have also been found that highlight how, with the increasing level of distress experienced by women, there are lower scores for Index of Physical Health (ISF) ($r = -0.364$; $p = 0.041$) and Index of Mental Health (ISM) ($r = -0.751$; $p = 0.0001$). High scores of the ISM correlate negatively with the levels of Anxiety ($r = -0.585$; $p = 0.0001$) and Depression ($r = -0.571$; $p = 0.001$) tested by the patients. The same relationship exists between ISF scores and Depression levels ($r = -0.396$; $p = 0.025$). Finally, the study highlights an increase in Distress levels in women who report having no children ($M = 34.63$; $DS = 7.11$; $t(30) = 2.684$; $p = 0.012$). The present study shows how breast cancer in young women has an important impact on quality of life and distress experienced by young women.

A36

THE BEST THERAPEUTIC SEQUENCE FOR HR POSITIVE HER2 NEGATIVE METASTATIC BREAST CANCER AFTER CDK4/6 INHIBITORS ADVENT IS STILL AN OPEN QUESTION? A SINGLE INSTITUTION EXPERIENCE

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Background: CDK4/6 inhibitors (CDK4/6i) have changed therapeutic management of hormone receptor (HR+) HER2- metastatic breast cancer (MBC). The earlier use of CDK4/6i + endocrine therapy (ET) has improved progression free survival (PFS) and overall survival (OS), even though there is not a standardized therapeutic sequence.

Patients and methods: In our retrospective study, we analysed female patients (pts) affected by HR+ HER2- MBC, referred to our Institution from 2017 to 2020 and treated with CDK 4/6i + ET as 1-2-3 lines settings.

Results:156 pts were included; median age was 56 years (range 32-80). As first line, 57.7% received CDK4/6i+ET, 26.9% ET and 15.4% chemotherapy (cht). mPFS was 11.2 months (m) (range 0.5-11.3), with 1.5% of complete response (RC), 41.5% of partial response (PR) and 40.8% of stability disease (SD). 16.2% had disease progression (PD), 64.8% in visceral sites. At univariate analysis, mPFS was statistically correlated to poor Performance Status (12.5m for ECOG1 vs 1.67m for ECOG2) (p=0.0489), to hormone sensibility (14.2m vs 8.1m) (p=0.0056) and to therapy (17.2m for ET vs 13.2m for CDK4/6+ET vs 7.2m for cht) (p=0.0234). These associations were not confirmed at multivariate analysis. About sequence, ET followed by CDK4/6i+ET followed by cht showed longer mPFS (19.95m) (p=0.0003), confirmed at multivariate analysis (p=0.0015). As 2nd line, 44.9% received cht, 39.3% CDK4/6i+ET and 15.8% ET, depending on previous scheme ($p<0.0001$) and hormone resistance (primary vs secondary) (p=0.0231). mPFS was 6.7m, with 16% of RP, 38.7% of SD and 42.7% of PD, 79.5% visceral. At univariate analysis, mPFS was statistically correlated to hormone resistance (3.23m for primary vs 10.7m for secondary) (p=0.0001), also at multivariate analysis (p=0.0045). As third line, 66.1% received cht, 17.7% CDK4/6i+ET and 16.1% ET, according to previous scheme (p=0,0174). mPFS was 5.1m (range 0.2-28.3), with 36% of SD and 56% of PD, 90.9% visceral. At multivariate analysis, mPFS was correlated to visceral PD (4.53m vs 11.8m) (p=0.0025) and to hormone resistance (3.78m for primary vs 17.68m for secondary) (p=0.0039). Only visceral PD was confirmed at multivariate analysis (p=0.0210).

Conclusions: Our study confirms the benefit of CDK4/6i+ET in earlier lines to improve PFS in HR+ HER- MBC, according to literature, relegating chemotherapy subsequently, based on increased hormone resistance and major visceral involvement. Nevertheless, further prospective trials will be indispensable.

A37

NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER. EXPERIENCE OF THE MOLISE BREAST UNIT

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Background: In 2020, in Italy, an estimated 54,976 new diagnoses of breast cancer were made. The State-Regions Agreement has issued the "*Guidelines on the organizational and welfare methods of the network on breast unit*", for diagnostic-therapeutic paths in senology.
Methods: In the 2018 the Molise Region established a Breast Unit (B.U.); the personalized approach, especially in breast cancer, is more effective by integrating the progress of breast surgery, with staging methods such as MRI, treatment methods, such as neoadjuvant therapy (NACT), able to improve survival and quality of life especially in positive HER2 tumors and typically more aggressive "*triple negative*" diseases.
Every week, in the COVID era on an online platform, the GOM meets to discuss cases; preoperative cases are discussed for which the methods of diagnosis and staging are proposed and the therapeutic hypothesis is discussed.
All patients eligible for conservative treatments are stadiated with imaging techniques, in particular MRI, the most accurate tool for the basic evaluation of disease extent, and a biopsy for the evaluation of biological variables.
Patological complete response (pCR), defined as the absence of invasive disease in the breast and lymphnodes, should be use to measure response to guide decision making.
Results: There were 125 patients diagnosed in 2019, in 2020 there were 157, in 2021 there were 50 (until 18 May). In the year 2019, the B.U. gradually structured. In 2020 the median age was 52 a. (32-72 BC). Of the 157 patients evaluated, 8 or 5.1%, performed neoadjuvant chemotherapy (7 T2 cases, 1 T1c case; 5 G3 cases, 3 G2 cases; 7 cases with positive RE of which 1 HER-2 score 3+, 1 triple negative). All have undergone quadrantectomy. In 2021 the median age of the 50 patients was 64.5 a. (35-81 BC) and 14 cases, or 28%, performed neoadjuvant chemotherapy (9 T2 cases, 5 T4 cases; 13 G3 cases, 1 Case G2; 6 HER-2 score 3+ cases; 3 triple negative cases and 11 cases with positive RE (all patients are still being treated).
Conclusions: In Italy NACT is proposeed to about 20% of women with breast cancer, the European average is about 30% with peaks of 50-60% in Germany and the United Kingdom. The activity data of the B.U. Molise and the systemic treatment with NACT indicate an approach in line with Italian data and with the tendency to improve them since closer to European standards denoting a more modern method and perhaps a real cultural change.

A38

ADJUVANT EXEMESTANE OR TAMOXIFEN PLUS OVARIAN SUPPRESSION IN PREMENOPAUSAL WOMEN: SINGLE INSTITUTION ANALYSIS

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Background: The combined analysis of data from TEXT and SOFT trials shows that among premenopausal women with hormone receptor-positive (HR+) breast cancer (BC), adjuvant endocrine therapy (AET) with exemestane (EXE) plus ovarian function suppression (OFS) improved disease-free survival compared to tamoxifen (TAM) plus OFS. We conducted a single institution analysis to compare the activity and safety of both treatment strategies.
Patients And Methods: The data on tumor and patient's characteristics of premenopausal women treated with AET from January 2014 to December 2018 in our institution were retrospectively collected. Treatment toxicities were graded according to CTCAE v5. Survival data were analyzed by Kaplan Meier curves and log rank test.
Results: 237 patients were included in the study: 120 on TAM / OFS and 117 on EXE/OFS. Notably, 43 patients (18%) started AET in 2014 (before TEXT/SOFT data): 93% of these were treated with TAM/OFS versus only 7% with EXE/OFS. Women on EXE/OFS had more high-risk early BC compared to those on TAM/OFS (STAGE III 23,9% vs 6,6%; luminal B-like 34,2% vs 21,6%; T> 2 cm 68,4% vs 32,5%; nodal status positive 66,6% vs 36,6% - all p value <0,01). According with risk of relapse, the number of patients pre-treated with chemotherapy was higher in EXE/OFS group (79,5% versus 37,5%, p value <0,001) than TAM/OFS one. Extended therapy was accepted by 50% of patients in the TAM/OFS group and 47% in the EXE/OFS group. Any grade adverse events (AE) were observed in 77 (64%) and 101 (86%) patients in TAM/OFS and EXE/OFS group, respectively. In particular, the incidence of G3 AEs was significantly higher in the EXE/OFS group and mainly represented by muscoloskeletal symptoms, osteoporosis and hypertension. Eighteen (15,4%) women discontinued EXE and switched to an alternate ET (TAM or NSAI) due to treatment toxicity. No statistically significant difference in terms of relapse free-survival was observed between the two groups.

Conclusions: In our analysis, the choice of the AET is driven mainly from the risk of relapse. EXE/OFS represents the main choice in the high-risk patients as per SOFT/TEXT trials results. TAM/OFS represent the main chose antecedent to the SOFT/TEXT results (2014/2015).The frequency and the grade of AEs were higher in EXE group than TAM one. The AET should be proposed based on both, risk of relapse and treatment toxicity profile. An update analysis will be presented at the meeting.

A39

NEXT GENERATION SEQUENCING (NGS): A POSSIBLE GAME CHANGER IN METASTATIC BREAST CANCER

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Background: NGS has been introduced into the clinics with the aim of sequencing long and complex genes for tumor sample, in order to identify driver and/or targetable alterations. Several companies and academic centers have implemented NGS assays to guide treatment decisions, even though there are no clear recommendations from scientific societies about their use in daily clinical practice.
Patients and methods: Since 2019 NGS analysis was performed in 32 MBC patients' tissues at Modena Cancer Center, as for clinical judgement during the course of MBC. Oncomine™ was mainly used for the assay. The aim was to define the PI3K mutational status, since Alpelisib - an a-subunit selective PI3K inhibitor - had shown to improve PFS in PI3K mutated HR+/HER2- MBC patients in SOLAR-1 and BYLIEVE trials.
Results: Twenty (62%) NGS analysis were performed on MBC samples, the other (13) on primary breast cancer. Table1 summarize the clinical-pathological characteristics of patients. At least 1 mutation was found in 25 (78%) samples. A PI3K mutation was detected in 14 (44%) cases, with E542K as the most frequent. In 10 out of 14 cases, PI3K mutation was associated with other gene mutations. FGFR3, FGFR4 mutations and FGFR2 amplification were described in 4, 2 and one patients respectively. Two patients showed AKT1 mutation, in one case was associated with PTEN mutation. Two of the patients with PI3K mutation were treated with Alpelisib + Fulvestrant. The patient with FGFR1 amplification was eligible for a phase II clinical trial.
Conclusions: NGS performed in this cohort of MBC patients allowed therapeutic decisions in about 10% of cases. Although PI3K mutational status for eligibility to Alpelisib can be cheaply studied by RT-PCR, NGS assay can provide wider information about other gene mutations, useful for patients' selection for clinical trials. In the era of precision medicine, knowing the mutational status of MBC early in patient history can change the therapeutic algorithm.

	N=32(%)
Median age	50 (29-76)
DeNovo MBC	8 (25)
Recurrent MBC	24 (75)
Hstotype:	
Ductal	26 (81)
Lobular	4 (13)
Other	2 (6)
Grading:	
1-2	15 (47)
3	17 (53)
Phenotype:	
luminalA-like	22 (69)
luminalB-like	6 (19)
HER2+	3 (9)
Triple negative	1 (3)
Neo-/adjuvant chemotherapy	31 (97)
Previous endocrine therapies	30 (94)
Bone only disease	4 (12)
Visceral disease	12 (38)
Both	16 (50)

A40

ASTRID STUDY-BREAST TRIPLE NEGATIVE CANCER IN ADVANCED SETTING: PRELIMINARY RESULTS OF THE MARCHE EXPERIENCE

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Background: Triple-negative breast cancer (TNBC) is an aggressive disease, associated with a worse prognosis and with high risk of recurrence even when diagnosed in early stage. Although chemotherapy is still the backbone of advanced setting treatment, recently Immunotherapy and PARPi became part of the therapeutic paradigm. The identification of prognostic factors and markers that allow us to

select patients based on the risk of disease is an important objective in this setting, that can lead Clinicians to choose the best therapeutic treatment. In this retrospective analysis, conducted in aTNBC female patients treated in six Oncology Institutions of Marche Region, we analysed clinical outcome (PFS) and we tried to highlight the role of some clinical and anatomo-pathological characteristics as prognostic factors.

Patients and Methods: TNBC patients referred to 6 Oncology Institutions in Marche Region (Ancona, Ascoli Piceno, Fabriano, Marche Nord/Pesaro, San Benedetto del Tronto and Urbino) from February 2011 until January 2021 and treated for at least 1 line settings for advanced disease were included.

Results: 71 patients were included; median age at diagnosis of metastatic disease was 63 years. The median PFS (mPFS) gradually decreases from first to following therapeutic lines: 4.5 months for 1st line, 3.1 months in 2nd line, 3 months in 3rd, finally 2.5 months in 4th line. Median OS (mOS) was 2.9 years from diagnosis of metastatic disease. In our retrospective study optimal ECOG PS (Performance Status) was associated with better mPFS (5.3 vs 4.5 months for ECOG 0 and 1.5 for ECOG 3, p=0.0002), as well as age >65 years (3vs 6.1 months, p=0.0270), a ki-67<14% (19.8 vs 4.6 months for high proliferation index, p=0.0400) and a partial response (PR) to 1st line chemotherapy (6.9 vs 5.8 months in patients with complete response, p=0.0421). Moreover, ECOG PS 0 at the end of 2nd line was associated with a better prognosis (10.27 vs 1.13 ECOG 2 PS, p=0.0116). Finally our retrospective study showed that ECOG=1 at the end of 1st line chemotherapy was a prognostic factor (5 vs 1.68 years of OS for ECOG=1, p=0.0002), together with a complete response or PR to 1st line chemotherapy (p=0.0020).

Conclusions: Our preliminary data confirm that an optimal ECOG PS in mTNBC is associated with a better PFS and OS and can be considered as a prognostic factor.

A41

COMPUTED TOMOGRAPHY-BASED ANALYSES OF BODY MASS COMPOSITION IN HER2-POSITIVE METASTATIC BREAST CANCER PATIENTS UNDERGOING FIRST LINE TREATMENT WITH PERTUZUMAB AND TRASTUZUMAB

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Introduction: In early breast cancer (BC) setting, several data indicate that a body mass index BMI⩾25 is associated with shorter survival. Instead,in metastatic BC patients,the evidence is conflicting,especially when the molecular subtypes are considered.BMI alone may not be the most suitable method to assess body composition. Computed Tomography (CT)-based regional analysis of muscle and fat tissue in the area of the third lumbar vertebra is tied to whole-body fat and muscle mass,represents a convenient method to study body composition in cancer patients;however, its prognostic value in patients with HER2-positive metastatic BC receiving first line treatment with pertuzumab/trastuzumab is unknown.We suspect that anti-HER2 drugs may be less active in obese patients,reducing their response to these agents due to a modification in their body composition paramters(BCp), (decrease in lean mass and increase in fat mass).

Material (patients) and methods: We retrospectively analyzed CT-based BCp from 43 patients with HER2-positive metastatic BC in first line dual HER2 blockade treatment between May 2009 and March 2020.To assess body mass composition, a single CT slice at the level of the third lumbar vertebral body was processed using a specific DICOM-viewer software (OsiriX© v.11.0.0). The impact of baseline CT-based BCp on progression-free survival (PFS) was tested using Kaplan-Meier estimates and univariate and multivariate Cox regression models.

Results: We found a significantly worse PFS for patients with high baseline subcutaneous fat index (median 7.9 vs 16.1 months, p=0.047, HR=2.04, 95%CI 1-4.17) and for those with high total abdominal fat index (8.1 vs 18.8 months, p=0.030, HR=2.17, 95%CI 1.06-4.46). Patients with baseline sarcopenia did not show shorter PFS compared to those without sarcopenia (10.4 vs 9.2 months, p=0.960, HR=0.98, 95%CI 0.47-2.03). Likewise, patients with BMI ⩾ 25 did not demonstrate a reduced PFS compared to normal body weight patients (9.2 vs 9.7 months, p=0.815, HR=0.92, 95%CI 0.45-1.86).

Conclusions: Total abdominal fat index remained a significant predictor of PFS at multivariate analysis. Our findings suggest that a high quantity of total abdominal fat tissue is a poor prognostic factor in patients receiving dual HER2 blockade first-line treatment for HER2-positive metastatic BC.Given that body fat and muscle mass represent modifiable elements, programs that aim to promote exercise and nutritional assessment before therapy should be offered to BC patients.

A42

TRIPLE NEGATIVE BREAST CANCER IN ADVANCED SETTING: A POSTCARD WITH PRELIMINARY RESULTS FROM MARCHE REGION

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Background: Metastatic triple negative breast cancers (mTNBC) are an aggressive subtype of breast cancers with poor prognosys. TNBC accounts for 15-20% of newly breast cancer diagnoses. It is renowned for poor overall survival (OS), especially in metastatic disease, and high possibility of relapse, the greater risk remaining in the first two years after diagnosis. The aim of our restrospective observational study was to identifying clinical and pathological characterstics in a cohort of triple negative breast cancer patients, undergoing at least one line chemotherapy.

Matherials and Methods: In this retrospective study, we enrolled 71 patients with locally advanced/metastatic TNBC treated at least with a first line chemotherapy, referred to six Oncologic Departements of the Marche Region from February 2011 to January 2021: Ancona, Ascoli Piceno, Fabriano, Marche Nord/Pesaro, San Benedetto del Tronto and Urbino.

Results: We enrolled 71 female patients with mTNBC, generally with high grade disease (90.3%). The median age at diagnosis of metastatic disease was 63 years old and 73.2% were postmenopausal; only 5 patients (7%) was ⩽35 years old.Median progression free survival (mPFS) to 1st and 2nd chemotherapy lines were 4.5 and 3.1 months respectively,while mOS was 2.9 years and mOS from recurrence is 1.3 year. The majority of patients enrolled (77.4%) underwent adjuvant chemotherapy and almost one third (26.8%) was treated with neoadjuvant chemotherapy. 25.4% of patients underwent 1st line chemotherapy with paclitaxel and Bevacizumab, only 2 (2.8%) were treated with paclitaxel + atezolizumab. 20% received capecitabine and vinorelbine as 2nd line and 6% was recruited in clinical trials. In 12 patients was found metastatic disease at diagnosis. Only in 18 patients the BRCA1/2 mutation test was performed and in 3 of them a BRCA1 mutation was found. The majority of patients (84.5%) had a disease relapse after adjuvant chemotherapy; in 53.3% of patients, a biopsy of a metastatic target lesion was performed. When metastatic disease was diagnosed, a half of patients had a BMI ⩽ 25; only 17% of patients was obese, showing a BMI ⩾ 30.

Conclusions: Preliminary data of our study confirm that mTNBC is an aggressive disease with poor prognosis. Patients in our Region are diagnosed in the sixth decade and chemotherapy still remains the first choise for Clinicians; this old paradigm may will soon change, implementing the PD-L1 analisys and combining immunotherapy to the chemo-backbone.

A43

EFFECT OF SCALP COOLING DEVICE IN PATIENTS UNDERGOING NEO (ADJUVANT) CHEMOTHERAPY FOR BREAST CANCER: EXPERIENCE OF 18 MONTHS

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Background: Chemotherapy-induced alopecia (CIA) is one of the most impactant toxicity for oncological patients (pts) and it cause treatment refuse in up to 8% of pts. Furthermore distress on body image, psychosocial uneasiness, and depression are directly related to CIA. In breast cancer cares high alopecizing regimes are used primarily in adjiuvant and neoadjuvant settings. Several studies showed that scalp cooling significantly reduces CIA also in pts treated with antracycline and taxanes with a good compliance. We conduced a descriptive observational study on breast cancer pts undergoing adjiuvant or neoadjuvant chemotherapy with alopecia prevention by scalp cooling (Paxman). Scalp cooling consists in 30 minutes of precooling prior to drug infusion, during administration of chemotherapy, and up to 90 minutes afterwards. Evaluation of alopecia was perfomed according to modified Dean scale. Results: Globally 63 breast cancer pts were included in our analysis from September 2019 to Mars 2021. 44 pts (70%) recived antracyclines and taxanes sequential chemoterapy, 13 pts (20%) recived taxanes monochemoterapy and 6 (10%) revided taxanes and cyclofosfamide chemoterapy. 59 pts (93,6%) completed scalp cooling treatment and each of them recived 15 cycles on average. We observed grade 3 alopecia in 33 pts (52,3%), grade 2 alopecia in 10 pts (15,9%), grade 1 alopecia in 17 pts (27%) and grade 0 alopecia in 3 pts (4,8%). Our data suggests that it's possible to obtain alopecia prevention in 25% of anthracyclines treated patients and in 59% of taxanes treated pts. Headache, nausea, chills, dizziness, scalp pain, dry skin, sinusitis,

paraesthesia, itching was most frequents side effects but none of these was higter than grade 2.
Conclusions: Our results confirm that scalp cooling device (Paxman) is effective and safe in chemotherapy-induced alopecia prevention with consequent reduction of psychological distress in breast cancer pts undergoing chemotherapy. Furthermore all our pts who completed therapy recommend the cold cap system to others pts receiving chemotherapy. Further evaluations in order of Quality of life are ongoing in our Service in this setting of pts.

A44

ARE CDK4/6 INHIBITORS PLUS ENDOCRINE THERAPY EQUALLY EFFECTIVE IN EVERY PATIENT AFFECTED BY HR POSITIVE HER2 NEGATIVE METASTATIC BREAST CANCER? A SINGLE CENTRE EXPERIENCE

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Background: CDK4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) have improved progression free survival (PFS) and overall survival (OS) for hormone receptor positive (HR+) HER2 negative (HER2-) metastatic breast cancer (MBC) patients (pts). In this retrospective analysis, we evaluated efficacy of CDK4/6i+ET, according to patients' characteristics and safety profile.
Patients and Methods: HR+ HER2- MBC pts referred to our Institution from April 2017 to December 2020 treated with CDK4/6i+ET as first line setting were included.
Results: 156 pts were included. Median age was 64 years. 60.9% were in post-menopausal state. 38.9% were metastatic at diagnosis. 64.4% had visceral metastasis, 71.1% bony and 61.1% lymph nodal. 90 pts (57.7%) received CDK4/6i + ET as first line: 55.6% palbociclib, 36.6% ribociclib and 7.8% abemaciclib. 74.4% received CDK4/6i plus aromatase inhibitors, while 25.6% plus fulvestrant. 78.8% of pts was in good performance status (PS) (ECOG0), 15.6% in ECOG1 and 5.6% in ECOG2. mPFS was 12.5 months (m) (range 0.5-38.1). 48% obtained partial response (RP), 40% disease stability (SD) and 12% disease progression (PD), 36.3% in visceral sites. At time of analysis, 60% are treatment ongoing, while 20% died. Regarding adverse events, 78.8% had neutropenia, 54.4% of grade 3, 53.3% anaemia, mainly of grade 1 (78.7%) and 31.3% thrombocytopenia, 85.7% of grade 1. Hematologic toxicity determined 24.4% of dose reduction and 5.6% of treatment interruption. 56.2% had diarrhoea of grade 1 and 37.5% vomit, even though only 3 pts have reduced or paused treatments. 12.6% had liver toxicity, 10.1% skin and 0% cardiac. At univariate analysis, mPFS was statistically correlated with hormone sensibility (14.9m vs 8.1m) (p=0.0412), visceral disease (8.2m vs 16.1m) (p=0.0442) and PS (26.5m for ECOG1 vs 1.42m for ECOG2) (p=0.0001). Moreover, mPFS was correlated to neutropenia (14.2m if present vs 4.2m if absent) (p=0.0064), skin toxicity (35.5m vs 11.1m) (p=0.0044) and treatment interruption due to hematologic toxicity (2.97m if interrupted vs 14.2m if not) (p=0.0058). Only the latter association was confirmed at multivariate analysis (p=0.0335).
Conclusions: According to literature, our study shows first line PFS improvement using CDK4/6i + ET in HR+ HER2- MBC, stressing poor PS and visceral disease as negative prognostic factors. Moreover, treatment interruption due to hematologic toxicity seem to be negatively correlated with PFS, as reported in preclinical trials.

A45

ARE PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AT RISK FOR INFECTION WHEN USING DENOSUMAB IN METASTATIC BREAST CANCER?

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Introduction: Denosumab, an inhibitor of the receptor activator of nuclear factor-ligand (RANKL), is indicated in bone metastatic breast cancer (MBC) to reduce skeletal-related events. RANKL has known immunomodulatory effect. Data from rheumatology demonstrated an increased incidence of infection. We aimed to further evaluate the risk of infection in denosumab-treated MBC patients with Chronic Obstructive Pulmonary Disease (COPD).
Patients and Methods: We retrospectively reviewed data of 209 MBC patients treated with denosumab at Humanitas Cancer Center from 2015 till 2021. We identified patients with a diagnosis of COPD by using clinical data in electronical medical records. We excluded patients with a long-standing history of smoking without a clear diagnosis.
Results: We found 9 patients with an ascertained COPD. Median age was 64 (range, 54-76). Smoking habit was present in 6/9 patients. Out of these 9 patients, 7 developed

infections during the period of treatment with denosumab with a total number of 17 episodes (11 pulmonary, 3 gastrointestinal, 1 urinary, 2 sepsis). The median number of denosumab administration in patients with infections was 9 while it was 8.5 in patients without infections.
In about half of these infective episodes, hospitalization was required. The median number of infective episodes for patient was 2 (range, 0-7). Median time between starting of denosumab and the first infection was 9 months (range, 1-14).
Conclusions: Although it was not previously reported, MBC patients with COPD seem to be at high risk of developing infections during denosumab treatment, as already reported for rheumatologic patients. The small number and the retrospective nature of this study are the major limitations of this result. Larger observational prospective study seems worthwhile.

A46

CDK4-6 INHIBITORS AND METASTATIC ER+/ HER2 - BC: FINDING OUT CLINICAL-PATOLOGICAL PREDICTOR FACTORS OF FAST PROGRESSOR PATIENTS

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Background: The association beetween CDK4-6 inhibitors and endocrine theraphy is the new standard of first line therapy for ER+/HER2-. The studies of registration of palbociclib, ribociclib and abemaciclib show an improvement in therms of PFS and OS versus endocrine therapy alone. Otherwise some patients (10-15%) have a primary resistance to these new treatments whit a progression beetween 6 month from the beginning of the therapy. Are there clinical/patological features to find out fast progressor patients?
Patients and methods: we analized 68 patients with metastatic BC ER+/HER2- treated whit CDK4-6 INHIBITOR in first line or more in Sant'Anna Hospital of Ferrara from January 2017 to January 2020. The primary EP was to find out clinical-patological features to predict fast progressor patients by the analisis of PFS using Kaplan -Mayer methods.
Results: The median PFS was 23 months (IC 95% 13,4-32,6). This study didn't show a correlation beetween clinical-patological features and primary resistence to CDK4-6 i + ET in metastatic breast cancer Er+/HER2-. We find that shorter PFS is related (not in a statistical significant way) to:

- ECOG PS >2 (3 months vs 25 months for PS=0)
- LOW Er Level (<30%)
- Luminal B + DFI from a previous adjuvant treatments <12 months(6 months)

Conclusions: These results are linked to small number of patients of this real word study. The fast progressor patients were 20% (higher than registration study). The need to a combined analyses not only of clinical and pathological features but also with a complete molecular profile will help to identify best sequence of treatment for ER+/Her2- breast cancer patients.

A47

EFFICACY AND SAFETY OF NEOADJUVANT DOCETAXEL, TRASTUZUMAB AND PERTUZUMAB IN HER2-POSITIVE EARLY BREAST CANCER: EXPERIENCE OF THE MEDICAL ONCOLOGY OF THE ST. SALVATORE HOSPITAL, L'AQUILA

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Background: Whether anthracyclines-free chemotherapy in combination with pertuzumab in neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (EBC) might be a feasible option in clinical practice, still has to be determined.
Patients and methods: A prospective observational study enrolling consecutive HER2-positive EBC patients was conducted at the Medical Oncology of the St. Salvatore Hospital, L'Aquila, since January 2017. Patients received six neoadjuvant cycles of docetaxel (75 mg/mq every 3 weeks) plus trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) plus pertuzumab (840 mg loading dose, followed by 420 mg every 3 weeks) (THP regimen).
The primary endpoint was to the evaluation of pathological complete response (pCR: ypT0/is ypN0).
The secondary endpoints were the evaluation of safety and the correlation between the phosphatidylinositol-3-kinase (PI3K) mutation status and pCR.
Results: Twenty-seven patients were enrolled, of which 21 (78%) evaluable for the primary endpoint in April 2021.
The median age of 27 patients was 48 years (range 37-79). All patients had ECOG PS 0-1 (100%). Cumulative Illness Rating Scales (CIRS) was: primary, 23 (85%); intermediate, 4 (15%). Clinical stage was: IIA, 4 (15%); IIB, 10 (37%); IIIA, 8 (30%); IIIB, 5 (18%). Hormone receptors

were: negative, 12 (44%); positive, 15 (56%). Median Ki67 was: 25% (range 5-80%).
Among 21 patients evaluable for pathological response, 15 patients achieved pCR (71%).
Adverse events related to THP were: G3 diarrhea, 2 (7%); G2 diarrhea, 6 (22%); G2 anemia, 5 (18%); G2 asthenia, 7 (26%). No cardiac toxicity, such as reduction in left ventricular ejection franction or alteration of brain natriuretic peptide and troponin I, was reported.
The determination of the phosphatidylinositol-3-kinase (PI3K) mutations on tumor tissue is ongoing.
Conclusions: This single-center study offers a real-life experience of using a neoadjuvant treatment without antracycline for HER2-positive EBC.

A48

SCALP COOLING DEVICE FOR CHEMOTHERAPY-INDUCED HAIR LOSS PREVENTION IN BREAST CANCER PATIENTS: OUR EXPERIENCE

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Background: Alopecia is a common side effect of chemotherapy treatments, associated with a significant psychological burden, exerting a strong change in self-perception and self - image, with variable degrees of distress, so that about 8% of women affected by breast cancer choose alternative medications in order to avoid hair loss. SC has been investigated to prevent or reduce hair loss during chemotherapy since the 1970s. The rate of hair preservation with scalp cooling (SC) may vary from 10 to 100%, depending on several factors (type and duration of treatment). Various mechanisms of action have been proposed for alopecia inhibition by SC: cooling induces vessels constrictions, reducing blood flow to follicle cells; SC slows metabolic activity of follicle cells, thus reducing cytotoxicity of chemotherapy agents.
Materials and methods: In our experience, 50 females (about 80% treated in adjuvant setting, whereas 20% in metastatic setting) have been enrolled to be treated with SC, from September 2020 so far. Chemotherapy regimens were based on anthracycline-taxane schedules.
Results: No patients developed serious adverse events with SC. Most frequent adverse events referred were: headache (70%), discomfort induced by chill (70%). Two patients withheld SC procedure. Alopecia was assessed during chemotherapy and at the end of treatment, according to CTCAE v4.0; no patients experienced G2 alopecia; 30 patients(60%) developed Grade1 alopecia (no wig needed, hair loss$<$50%).
Conclusions: Recent studies demonstrates that SC is successful in about 30-80% of patients. Our experience, among the first of South Italy, confirms these results, showing no Grade 2 alopecia in enrolled patients. For us, allowing a patient, a woman, to preserve the image of herself is an important step in order to increasingly humanize treatments. Threfore, SC safely prevents alopecia in cancer patients undergoing chemotherapy, reducing the psychological impact of one of the most feared side effect of this treatment, producing positive effects on quality of life of patient and improving compliance to oncological treatments.

A49

THE ITALIAN MANAGEMENT OF HER2-ENRICHED BREAST CANCER (BC): A MAZE FOR OPPORTUNITIES AND CHALLENGES

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Background: In HER2-enriched early stage BC, the addition of Trastuzumab to chemotherapy represents the standard of care in the adjuvant setting. Moreover, neoadjuvant treatment with anti-HER2 agents was introduced in clinical practice for inoperable, locally advanced or inflammatory BC in order to obtain both clinical and pathological downstaging. Recently, in Italy, anti-HER2 double block Pertuzumab and Trastuzumab has been made available for HER2 positive high risk BC patients in adjuvant setting. Based on these data, we tried to identify which HER2-positive BC pts are eligible to neoadjuvant or adjuvant treatment, since these strategies of therapy seem to be mutually exclusive. We reviewed both alternatives to establish the most suitable, considering anti-HER2 drugs available in Italy.
Material and methods: We conducted a literature revision of available data concerning the use of anti-HER2 agents in neoadjuvant versus adjuvant setting.
Results: Randomized clinical trials demonstrated the same survival benefit when chemotherapy was administered as neoadjuvant therapy as well as adjuvant therapy. A meta-analysis including 11,955 patients treated with neoadjuvant therapy demonstrated an improvement in EFS (ypT0 ypN0: HR 0.44, ypT0/is ypN0: 0.48) and OS (HR 0.36). In adjuvant setting, the APHINITY trial asserted the superiority of the combination Pertuzumab-Trastuzumab versus Trastuzumab-placebo in previously untreated pts. Analysis of IDFS, based on 508 events (intent-to-treat population) showed a HR of 0.76 and a 6-year IDFS of 91% and 88% respectively in the Pertuzumab arm and placebo arm. The node-positive subgroup continued to show a significant benefit in IDFS

from the addition of pertuzumab (HR 0.72; 6-year IDFS: 88% vs 83%). To date, a greater benefit has been highlighted in the subset of patients with positive lymph nodes, treated in adjuvant setting.

Conclusions: Our analysis underlines the unmet need of a therapeutic decision-making algorithm in order to support clinicians in identifying patients suitable to neoadjuvant or adjuvant therapy. Based on these data, we propose to consider eligible to Trastuzumab-chemotherapy in neoadjuvant setting the HER2+ early BC patients (stage I-IIa), while reserving adjuvant Trastuzumab-Pertuzumab for advanced HER2+ BC (stage IIb-III). Further prospective clinical trials should be performed in collaboration with other Italian Breast Cancer Centres for establishing the best strategy reserved to HER2+ BC.

A50

NEW POTENTIAL STRATEGIES TO SELECT EARLY HR-POSITIVE BREAST CANCER PATIENTS FOR NEOADJUVANT TREATMENT

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Background: Neoadjuvant treatment is administered in locally advanced, inoperable breast cancer (BC). It can also be used in operable BC with positive lymph nodes or to obtain a conservative surgery. While the benefit achieved through neoadjuvant chemotherapy (NAC) in HER2 positive or triple negative BC has already been established, its role in HR-positive/Her2 negative BC is still controversial. It is mandatory to stratify HR-positive BC patients (pts) in order to identify those who will gain a higher benefit from NAC in regard to pathological response and clinical outcome.

Material and methods: 35 BC patients enrolled in our center since 2018, were considered eligible to NAC. 43% of all pts were luminal B at stage IIB-IIIa. We selected only pts with ductal histotype. Histological characteristics analyzed on core biopsy were: hormonal receptor and HER 2 expression, grading and ki67 value. The preferred neoadjuvant therapy regimen was antracycline and taxane-based. We evaluated clinical and pathological response rate, disease free survival and its relation with Ki67 value variation pre and post NAC.

Results: All triple-negative and Her2 positive BC achieved a partial or complete pathological response, as expected. Our attention was focused on results derived from Luminal B patients. In particular, we correlated major pathological response with the higher rate of decrease in Ki67 value before and after surgery. A strong correlation was highlighted among pts with higher Ki67 index, hinting that these pts may obtain a better outcome. These data seems not be correlated with other clinical and pathological findings as grading and level of hormone-receptor expression. Collecting data on relapse free survival and overall survival require still an extended period of time. To date, all of pts did not experienced progression disease. Statistical analysis have not been performed due to the small size number.

Conclusions: The variation in Ki67 value between pre- and post- treatment could be used as an independent predictive response factor, aiding clinicians in choosing the best strategy in HR-positive BC. We could speculate that HR-positive, high Ki67, ductal breast cancer should be eligible to neoadjuvant chemotherapy independently from lymph node involvement. Moreover, a predictive score including PDL1, TIL, BRCA status, grading, ER and PgR percentage expression may be implemented in order to optimize therapeutic strategy in early HR positive pts.

A51

CAPECITABINE AS ADJUVANT TREATMENT IN TNBC PATIENTS NON ACHIEVING PATHOLOGICAL COMPLETE RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY: A SINGLE INSTITUTION REAL-LIFE EXPERIENCE

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Background: Neoadjuvant chemotherapy is considered the preferred treatment strategy for many early-stage TNBC. It allows to select patients, not achieving a pCR, for adjuvant treatments. The role of capecitabine in this setting is recognized by several guidelines, however real-life data are lacking.

Materials and methods: We retrospectively identified all pts with residual pathological disease after anthracycline/taxanes-based NAC and treated with adjuvant capecitabine at our institution between 2019 and 2020,. We collected pts demographics, tumor characteristics, pre/post-operative stage, capecitabine exposure, toxicity and efficacy (DFS and proportion of patients not progressing at 1 year).

Results: We identified 18 pts treated with adjuvant capecitabine administered at the dose of 1000 mg/mq bd on days 1 to 14 every 21 days. Median age was 51 years (34-67 years). 9 pts (50 %) were premenopausal and 3 pts (16%)

showed a BRCA 1-2 mut. 10 pts (56%) were diagnosed with clinical stage II whereas 8 pts (44%) had clinical stage III. After NAC 6 pts (33%) achieved a post surgery stage I, 5 pts (28%) stage II and 7 pts (39%) didn't reach a significant response. 16 pts (89%) received anthracycline followed by CBDCA+taxane NAC.
During adjuvant capecitabine main adverse events were: grade 2 nausea and diarrhea (1 pt,5%); grade 3 HFS (1 pt, 5%) grade 3 neutropenia and anemia (1 pt, 5%). Toxicity led to dose reduction in 1 pt (5%). 67% of pts completed the 6 cycles of capecitabine. Major reasons for discontinuations were: PD (3 pts,17%), toxicities (3 pts,17%). Overall, 7 pts (39%) experienced PD. Median DFS was 5.5 mos (1-10 mos); the proportion of pts free of PD at 1 year was 61%
Conclusions: Despite the retrospective nature of the study and the preliminary data, we observed a lower than expected efficacy of adjuvant capecitabine in TNBC pts (DFS at 1 year of 61% versus more than 80% in the CreateX trial) probably due to the lower dose of capecitabine. No particular safety issue was observed.
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A52

CENTENARIANS (C) AND EXTREMELY OLD WOMEN (EOW) WITH ADVANCED NON OPERABLE BREAST CANCER (NOBC): ROLE OF SPECIFIC TOXICITY PREDICTIVE TESTS (CARG+CRASH) TO PREVENT SERIOUS/IRREVERSIBLE ADVERSE REACTIONS (SIAR) OR FATAL EVENTS (FAE) IN THESE FRAIL PATIENTS

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Background: Due to current lengthening of average lifespan and progressive increase of malignant tumors in mankind, advanced NOBC is not uncommon disease also in C and EOW sub-group of patients but the extremely frailty of this sub-group,need constantly of new strategies to ensure much more efficient predictive tools to ensure more safety treatment for this kind of subjects. AIM:Purpose of the study is preliminary detection of the overall toxicity (OTox) through the use of specifics tests able to predict the toxicity of the therapies chosen for this type of patients.
Material and methods: 18 extremely old women (EOW) with advanced NOBC (aging between 92 to 100 y/o) with acquired written consensus and instrumental confirmed diagnosis of NOBC with one or two measurable lesions(bone or visceral) have been considered for this study from jan 2018 and dec 2020.No brain secondarisms;Charlson's Comorbidity Scale 1-3 score points;CGA Evaluation permissive for treatment.G8 score > 14 points.CARG-TS (Cancer and Aging Research Group-Test Score) calculator and CRASH-TS (Chemotherapy Risk Assessment Scale for High-Age Patients Test S) were rated for predictive assessment of the risk of severe OTox in all patients.Further Evaluations Tools: Clinical Benefit according to ESMO CB scale v.2a; Tox Profile CTCAE v3.0 Criteria;QoL by EORTC QLQ-C30.
Results: CARG-TS calculator predicts severe OTox; CRASH-TS predicts hematologic and nonhematologic toxicity. Using CGA-ES+CARG-TS+CRASH-TS, we could divide patients into three groups: G1 "Low risk" (LR-score 0-5); G2 "Medium risk"(MR score5-10);G3 "High risk" (score >10). Based on these results G1 people was directed to receive a reduced schedule of eribulin (0.90 mg/sqm d1,d 28 until P-progression or INT-intolerable toxicity (reduction of the dose based on evaluation of creatinine clearance according to A. Hurria et al), G2 experienced endocrine therapy or fractioned RT alone (it depend if ER/PGR positive or not). Finally the G3 received Palliative Care particularly directed to pain control.
Conclusions: The chance of knowing in advance the "expected tox" of various treatmens in EOW and C subjects allowed to choose the less toxic treatment with lowest risk of SIAR for all these patients.Furthermore,the use of "tailored"treatments seems to allows significative savings on general management costs of therapeutics strategies. Nevertheless, in order to confirm these first results, all data are till now under statistical evaluation.

B – Gynaecological Tumours

B01*

CHARACTERISTICS AND PATTERNS OF CARE OF ENDOMETRIAL CANCER BEFORE AND DURING COVID-19 PANDEMIC

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Background: COVID-19 outbreak has correlated with the disruption of screening activities, regular follow up visits, and diagnostic assessments. The risk of misdiagnosis and delayed diagnosis has consequently increased during the pandemic. Endometrial cancer is one of the most common gynecological malignancies and it is often detected at an early stage, because it frequently produces symptoms (e.g. abnormal vaginal bleeding). Here, we aim to investigate the impact of COVID-19 outbreak on patterns of presentation and treatment of endometrial cancer patients.

Material and methods: This is a retrospective study involving 53 centers in Italy. We evaluated patterns of presentation and treatment of endometrial cancer patients before (i.e. period 1: from 03/01/2019 to 02/29/2020) and during (i.e. period 2: from 01/04/2020 to 3/31/2021) the COVID-19 outbreak.

Results: Medical records of 5,117 endometrial cancer patients have been retrieved: 2,688 and 2,429 women treated in period 1 and period 2, respectively. The prevalence of endometrioid International Federation of Obstetrics and Gynecologists (FIGO) grade 1, 2, and 3 was consistent over the study period (p=0.769). However, the prevalence of non-endometrioid endometrial cancer was lower in period 1 than in period 2 (15.7% vs. 17.9%; p=0.015). The characteristics and pattern of different surgical approaches were consistent in the two study periods (p=0.664). Before COVID-19 pandemic, 1,838 (73.2%), 647 (25.7%), and 25 (0.9%) patients had minimally invasive, open and vaginal surgery, respectively. During the COVID-19 pandemic, 1,661 (73.2%), 567 (24.9%), and 41 (1.8%) patients had minimally invasive, open, and vaginal surgery, respectively. Nodal assessment was omitted in 684 (27.3%) and 478 (21%) patients treated in period 1 and 2, respectively ($p<0.001$). While, the prevalence of patients undergoing sentinel node mapping (with or without backup lymphadenectomy) has increased during the COVID-19 pandemic (46.8% in period 1 vs. 53.1% in period 2; $p<0.001$). Adjuvant therapy was omitted in 1,269 (50.5%) and 1,019 (44.9%) patients receiving treatment in period 1 and 2, respectively ($p<0.001$). Adjuvant therapy use has increased during the COVID-19 pandemic ($p<0.001$).

Conclusions: Our data suggest that the COVID-19 pandemic had a significant impact on the characteristics and patterns of care of endometrial cancer patients. These findings highlight the need to implement healthcare services during the pandemic.

B02*

EFFICACY OF PARP INHIBITORS MAINTENANCE IN OLDER PATIENTS WITH NEWLY DIAGNOSED OVARIAN CANCER: A META-ANALYSIS

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Background: In recent years, PARP inhibitors have shown to be effective as maintenance treatment in patients with newly diagnosed ovarian cancer responding to platinum-based chemotherapy. However, as most ovarian carcinomas develop before 65, older patients are underrepresented in clinical trials. We performed a meta-analysis to assess the efficacy of PARP inhibitors as maintenance after first-line therapy in older patients with ovarian cancer.

Methods: We systematically searched the PubMed, EMBASE, and Cochrane databases for randomized clinical trials (RCTs) concerning maintenance with PARP inhibitors in patients with newly diagnosed, advanced, ovarian cancer. We extracted trials including hazard ratios (HRs) for progression-free survival (PFS) stratified by patients' age (cut-off: 65 years).

Results: 5 phase III RCTs were selected. Olaparib, Niraparib, Rucaparib and Veliparib were administered. Among the 3251 treated patients, 1141 (35.1%) were over 65 (722 receiving PARP inhibitors maintenance and 419 receiving placebo in the control arm). Compared to placebo, maintenance with PARP inhibitors improved PFS in older patients (HR=0.59; 95% CI: 0.48-0.71; $P<0.00001$). No differences for PFS emerged compared to the young population (HR=0.52; P=0.31)

Conclusions: Our meta-analysis demonstrates that maintenance with PARP inhibitors prolongs PFS compared to PBO after first-line therapy in older patients with ovarian cancer. No OS data are disposable yet. Longer follow-up and data from further studies will increase the power of our analysis.

B03

EFFICACY OF NIRAPARIB BY TIMING OF SURGERY AND RESIDUAL DISEASE: A POST HOC ANALYSIS OF PATIENTS IN THE PRIMA/ENGOT-OV26/GOG-3012 STUDY

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Niraparib is a poly (ADP-ribose) polymerase (PARP) inhibitor approved as maintenance treatment for patients (pts) with newly diagnosed advanced or recurrent ovarian cancer following response to platinum-based chemotherapy (CT) doublet. The PRIMA/ENGOT-OV26/GOG-3012 (NCT02655016) study showed niraparib following first-line (1L) treatment improved progression-free survival (PFS) in the overall intention-to-treat (ITT) population (hazard ratio [HR], 0.62; 95% CI, 0.50–0.76).

This double-blind, placebo (PBO)-controlled, phase 3 trial evaluated niraparib in pts with newly diagnosed, advanced, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer with a complete or partial response to 1L CT. Pts were considered at a high risk for disease progression based on clinical characteristics. This post hoc analysis presents the efficacy of niraparib, measured by PFS, based on time of surgery and residual disease status.

Data cutoff was May 2019, with 733 pts randomized in the PRIMA study. Efficacy outcomes by surgical timing, either primary debulking surgery (PDS) or interval debulking surgery (IDS), and postoperative residual disease status, either visible residual disease (VRD) or no VRD (NVRD), are shown (**Table**). Pts who underwent PDS or IDS had similar efficacy with niraparib maintenance treatment versus PBO in the ITT population (PFS HRs were 0.67 and 0.57, respectively). Niraparib treatment reduced risk of progression by 42% in pts who received PDS and had VRD, 35% in pts with IDS and NVRD, and 59% in pts with IDS and VRD.

In this post hoc analysis, the impact of residual disease after PDS or IDS on niraparib efficacy was comparable across subgroups. Pts with IDS and VRD had the highest reduction in risk of progression.

Table. Efficacy results by time of surgery and visible residual disease status.

		ITT	NVRD (R0)	VRD (R1/R2)
All pts	N	733[a]		
	HR (95% CI)	0.62 (0.5–0.76)		
	P	<0.0001		
	mPFS (nir vs PBO), mo	13.8 vs 8.2		
	ΔmPFS, mo	5.6		
PDS	N	236[b]	37	183
	HR (95% CI)	0.67 (0.468–0.964)	NE	0.58 (0.391–0.864)
	mPFS (nir vs PBO), mo	13.7 vs 8.2	NE	11.8 vs 7.8
	ΔmPFS, mo	5.5	NE	4
IDS/ NACT	N	481[c]	304	149
	HR (95% CI)	0.57 (0.441–0.731)	0.65 (0.461–0.91)	0.41 (0.269–0.620)
	mPFS (nir vs PBO), mo	14.2 vs 8.2	18.2 vs 10.9	11.1 vs 5.6
	ΔmPFS, mo	6	7.3	5.5

[a]16 pts had no debulking surgery.
[b]16 pts had unknown residual disease status.
[c]28 pts had unknown residual disease status.
mPFS, median PFS; NACT, neoadjuvant CT; NE, not evaluable; nir, niraparib.

Clinical trial registration: NCT02655016

B04

INTERIM ANALYSIS OF THE IMMUNE-RELATED ENDPOINTS OF THE MISMATCH REPAIR DEFICIENT (DMMR) AND PROFICIENT (MMRP) ENDOMETRIAL CANCER COHORTS FROM THE GARNET STUDY

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Background: Dostarlimab is a humanized programmed death (PD)-1 receptor monoclonal antibody that blocks interaction with the PD-1 ligands. GARNET (NCT027 15284) is a phase 1 study assessing antitumor activity and safety of dostarlimab monotherapy in patients (pts) with solid tumors. Here, we report efficacy endpoints by irRECIST based on investigator assessment (IA) for the endometrial cancer (EC) cohorts.

Patients and methods: This is a multicenter, open-label, single-arm, dose-escalation and cohort-expansion study. Here, we report on 2 independent expansion cohorts of pts with recurrent or advanced EC (dMMR EC and MMRp EC, determined by immunohistochemistry [IHC]) that progressed on or after a platinum-based chemotherapy regimen. Pts received 500 mg dostarlimab IV Q3W for 4 cycles, then 1000 mg Q6W until disease progression, discontinuation, or withdrawal. The primary endpoints of objective response rate (ORR) and duration of response (DOR) by blinded independent central review (BICR) using RECIST v1.1, and safety have been reported previously (Oaknin *Ann Oncol* 2020). Immune-related endpoints (irORR and irDOR by irRECIST) are based on IA, and are prespecified secondary endpoints.

Results: In total, 126 dMMR and 145 MMRp pts identified by IHC were enrolled and dosed. Of these, 103 dMMR and 142 MMRp pts had measurable disease at baseline by BICR, and sufficient follow-up time (6 mo) for the primary efficacy analyses. After median (range) follow-up of 16.3 (0.03-30.6) and 11.5 (0.03-33.1) months for dMMR and MMRp pts, respectively, efficacy by RECIST v1.1 included ORRs of 44.7% and 13.4%; disease control rates (DCRs) of 57.3% and 35.2%; and DOR of not reached (NR) and NR.

For efficacy analysis of irORR and irDOR, 110 dMMR and 144 MMRp pts had measurable disease at baseline by IA and sufficient follow-up time (6 mo) and were included; some additional pts were considered to have measurable disease at baseline by IA. After median (range) follow-up of 16.5 (0.03-30.6) and 13.7 (0.03-33.1) months for dMMR and MMRp pts, respectively, efficacy by irRECIST included irORRs of 45.5% and 13.9%; irDCRs of 63.6% and 42.4%; and irDOR of NR and 12.2%.

Conclusions: Efficacy endpoints reported by RECIST v1.1 and irRECIST show similar results. irDCR was particularly of interest in the MMRp cohort, a group with a poorer prognosis. The potential benefit seen in this single-arm trial awaits confirmation in ongoing randomized controlled studies.

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B05

IDENTIFICATION OF HSA-MIR-499A AS A POTENTIAL NOVEL BIOMARKER IN ENDOMETRIAL CANCER

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Introduction: The Cancer Genome Atlas (TGCA) project identified four distinct prognostic groups of endometrial carcinoma (EC) based on molecular alterations among which two are correlated with an intermediate prognosis: the MisMatch Repair deficient (MMRd) and the No Specific Molecular Profile (NSMP) groups. NSMP represents a heterogenous subset of patients frequently harboring CTNNB1 alterations and presenting distinctive clinicopathologic features comparing with the CTNNB1 non mutant ones.

miRNAs are oncological key players that have not been integrated with the TCGA EC classification.

The study aimed to evaluate the miRNA expression profile in EC to identify potential novel biomarkers of diagnosis and prognosis.

Methods: We analyzed miRNA expression in 72 ECs specimens previously classified as MMRd (n=31) and NSMP (n=41), including 15 with CTNNB1 mutations. In the discovery step, miRNA expression profile was evaluated in 30 cases through TaqMan Advanced miRNA arrays. Subsequently, in the validation step, four miRNAs were analyzed in the total cohort of ECs by specific miRNA Assays.

Results: Comparison of CTNNB1 mutant versus non-mutant ECs (irrespective of MMRd/NSMP status) in the discovery cohort showed 39 differentially expressed miRNAs. The top deregulated 4 miRNAs (hsa-miR-187, hsa-miR-325, hsa-miR-499a-3p and 5p) were further validated in 72 ECs. hsa-miR-499a-3p and hsa-miR-499a-5p maintained the statistical significance showing higher expression in CTNNB1 mutant ECs ($p<0.0001$, for both). Furthermore, miR-499a expression was able to identify EC subgroups with longer recurrence free survival.
Conclusions: hsa-miR-499a may be a useful biomarker and could be integrated in the current TGCA classification scheme to better stratify EC patients.

B06

SAFETY AND EFFICACY OF PLATINUM DESENSITIZATION TREATMENT IN PATIENTS WITH OVARIAN CANCER AND PLATINUM HYPERSENSITIVITY

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Carboplatin (CBDCA)-Paclitaxel based chemotherapy is the standard first-line treatment for advanced ovarian cancer. More than 70-80% of patients (pts) develop a relapse on an average of 10-20 months later. Pts with potentially platinum (Pt)-responsive recurrent disease are usually treated with a Pt-based treatment. The repeated exposure to Pt agents can be associated with potentially life-threatening hypersensitivity reactions (HSR). Risk factors of HSR are prior Pt exposure, more than 6 cycles of Pt agents, BRCA 1/2 mutations, history of allergic reactions to Pt agents.
A retrospective study was performed in pts with ovarian cancer who underwent CBDCA or cisplatin (CDDP) with two different desensitization protocols (DP) between 2017 and 2021 at our Institute. CBDCA DP used a 4-step dilution process over 4 h; CDDP DP used a 16 steps protocol with different infusion rates. Demographics characteristic of pts, atopic status, chemotherapy histories, and DP safety and efficacy outcomes were analyzed.
20 pts with ovarian cancer treated with Pt DP were identified. Pts characteristics are summarized in Table 1. DP treatment included CBDCA based CT in 85% (17/20 pts) and CDDP based CT in 15% (3/20 pts). Of the 20 desensitization performed, 55% (11/20 pts) induced no reactions. Among pts who developed reactions during DP, symptoms and signs were mild (cutaneous rash and pruritus), with only 1 severe respiratory reaction requiring administration of epinephrine with complete resolution of symptoms. The overall disease control rate was 93% (14/15 pts), with 2/15 pts achieving a complete response, 1/15 patient partial response, 11/15 pts stable disease, 5 pts are not evaluable (4 pts are still on treatment).

Characteristics (n=20)	Mean or frequency	Range or %
Atopic status		
Yes	8	40
No	12	60
FIGO		
I-IIa	4	20
IIb-IV	16	80
Histotype		
High grade serous carcinoma	13	65
Other	7	35
BRCA		
Mutated	6	30
Wild-type	10	50
Unknown	4	20
Type of surgery		
Primary debulking surgery	14	70
Interval debulking surgery	6	30
First line CT		
CBDCA-Paclitaxel	14	70
CBDCA-Paclitaxel-Bevacizumab	6	30
Previous line with PARP-inhibitor		
Yes	6	30
No	14	70
Number of CT cycles before HSR	11	6-20
Pt retreatment interval - interval time between the last cycle of first-line chemotherapy and platinum retreatment (months)	29.7	11-93
Reason for using DP		
Positive in vivo skin test	6	30
Previous HSR	14	70

DP with Pt-based regimens are effective and safe. Disease control was achieved in the majority of patients, and no life-threatening hypersensitivity reactions occurred.

B07

TREATMENT RESPONSE TO NON-PLATINUM AGENTS IN PATIENTS WITH OVARIAN CANCER ACCORDING TO BRCA STATUS

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Background: Ovarian Cancer (OC) patients (pts) who are not candidates for platinum rechallenge, usually receive a single agent therapy with low chances of response and a poor prognosis. The predictive role of BRCA mutations (mut) in this setting has not been fully studied. Therefore, we described the single agent activity of non-platinum compounds in a large multicentric retrospective group of pts with OC and known BRCA status.

Patients and Methods: We evaluated OC pts with known BRCA status treated with pegylated liposomal doxorubicin (PLD), paclitaxel (ptx), gemcitabine (gem), topotecan, oral cyclophosphamide and etoposide as single agents in any line of therapy. Both overall response rate (ORR) and median progression free survival (mPFS) were analyzed.

Results: Our cohort included 432 OC pts from 5 centres, 98 (23%) with a BRCAmut (59% BRCA1 and 41% BRCA2) and 334 (77%) who were BRCA wild type (wt). Median overall survival (mOS) was 102.5 months (mo) and 141 mo for BRCAwt and BRCAmut pts respectively ($p < 0.005$). 53 pts received PLD (48 BRCAwt and 5 BRCAmut). ORR was 5.7% (3/53), 2.1% (1/48) and 40.0% (2/5) in the overall population, BRCAwt and BRCAmut subgroups (p=0.021); mPFS was16.1 weeks(w) vs 23.9w for BRCAwt and BRCAmut pts, respectively ($p > 0.05$). Gem was administered to 37 pts (30 BRCAwt and 7 BRCAmut) while ptx was administered to 36 pts (25 BRCAwt and 11 BRCAmut). There was a trend toward a higher ORR and PFS in BRCAmut subgroup compared to BRCAwt pts for both agents. On the other hand, data from the remaining drugs do not suggest a higher activity in the BRCAmut population (table1).

Conclusions: We confirm both that BRCAmut pts have a longer survival compared to BRCAwt ones and that benefit from single-agent treatment is little in this setting. Nevertheless, none of these compounds had a certain lack of activity in BRCAmut or BRCAwt subgroup in terms of both ORR and PFS.

Table 1. ORR and PFS according to treatment regimen.

Monotherapy	ORR in the whole population	ORR in BRCAwt pts	ORR in BRCAmut pts	p value (ORR)	PFS (w) in BRCAwt pts	PFS (w) in BRCAmut pts	p value (PFS)
PLD	3/53 (5.7%)	1/48 (2.1%)	2/5 (40.0%)	p=0.021	16.1	23.9	p=0.973
Paclitaxel	10/36 (27.8%)	6/25 (24.0%)	4/11 (36.4%)	p=0.35	20.9	23.9	p=0.825
Gemcitabine	7/37 (18.9%)	4/30 (13.3%)	3/7 (42.9%)	p=0.11	15.1	18.6	p=0.19
Topotecan	3/30 (10.0%)	3/24 (12.5%)	0/6 (0%)	p=0.50	21.0	15.4	P==0.25
Etoposide	4/27 (14.8%)	4/22 (18.2%)	0/5 (0%)	p=0.42	9.6	17.1	p=0.84
Cyclophosphamide	2/34 (5.9%)	2/30 (6.7%)	0/4 (0%)	p=0.78	15.0	12.4	p=0.69

B08

MELPHALAN: A PROMISING TREATMENT FOR BRCA-RELATED OVARIAN CARCINOMA

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Background: Melphalan, a bifunctional alkylating agent, has been described as effective in patients with BRCA-deficient epithelial ovarian cancer (EOC) only in few case reports. However, very little information is available regarding the clinical benefit of melphalan on platinum-resistant EOC patients and in particular on those with BRCA deficiency. We evaluated the efficacy of melphalan in patients with recurrent EOC after platinum-based therapy, in addition, we assessed the efficacy of this agent in patients harboring BRCA1/2 deficiency.

Methods: All consecutive patients with recurrent EOC treated with melphalan from February 2007 to July 2020 were enrolled in this retrospective study. Inclusion criteria were: histological confirmation of EOC, previous treatment with carboplatin plus paclitaxel, and disease recurrence during treatment or within 6 months of the end of the platinum-based chemotherapy.

Results: A total of 75 platinum-resistant EOC patients were included. Median age was 69 years (range 41-82). The median number of previous treatment lines before melphalan was 4 (range 1-7); median follow-up was 32 months (range 1-62). Overall, 1 complete response, 6 partial responses and 37 stable diseases were observed, with an overall clinical benefit rate of 58.7%. Median PFS and OS were 3.6 months (range 2.9-4.7) and 9.5 months (range 8.0-14.1) respectively. We observed longer PFS in BRCA1/2

mutant patients compared to BRCA1/2 wild type patients (6.2 versus 2.6 months; hazard ratio (HR) 0.25 [95% confidence interval (CI), 0.10-0.61]; P=0.002). OS was longer in BRCA1/2 mutant patients (25.9 versus 8.0 months; HR 0.38 [95% CI, 0.12-1.19]; P=0.097).

Conclusions: In this study, we describe the largest cohort of heavily-pretreated EOC patients receiving melphalan. According to our results, this study shows a considerable clinical benefit of melphalan on these difficult-to-treat patients. Improved outcomes and enhanced melphalan-sensitivity are more evident in BRCA1/2 mutated patients treated with this agent. These results need further confirmation with prospective studies.

B09

'SANDWICH' SEQUENTIAL CHEMORADIATION AS ADJUVANT TREATMENT IN HIGH-RISK ENDOMETRIAL CANCER: A REAL WORLD EXPERIENCE

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Background: The combination of chemotherapy (CT) and external beam radiotherapy (EBRT) is the current standard adjuvant treatment for patients (pts) with high-risk stage I-III endometrial cancer (EC). Despite this, the best schedule for chemoradiation (CR) has not been defined yet. We aimed at describing the clinical outcomes of pts with EC receiving platinum-based CT administered 2-3 cycles before and after radiotherapy (RT) as adjuvant treatment ('sandwich' chemoradiation, SCR).

Methods: We retrospectively analyzed a cohort of 83 consecutive pts with high-risk EC treated with adjuvant CR between January 2006 and December 2020 at the National Cancer Institute of Aviano, Italy. Pts had at least one of the following: high grade (G3), non endometrioid histology, lymphovascular invasion (LV1), positive lymph nodes (N1), positive peritoneal washing (PW). The association between clinico-pathological and treatment characteristics with outcomes (i.e. disease-free survival (DFS) and overall survival (OS)) was tested through Cox regression analysis.

Results: Median age at diagnosis was 65 [55;71] years. Pelvic lymphadenectomy was performed in 68 (82%) pts, lomboaortic lymphadenectomy in 23 (29%). Overall, 40 (48%) pts had a non endometrioid histology, 51 (62%) G3, 30 (40%) N1, 52 (74%) LV1, 5 (7%) PW. According to FIGO classification, stage was I for 26 (31%) pts, II for 13 (16%) pts and III for 44 (53%) pts. A total of 66 (80%) pts received SCR while the others received a different CR schedule. RT was administered as EBRT (84%), brachitherapy (5%) or both (11%); 81% of pts received concomitant CT. A platinum-based combination was used in 43 (52%) pts. Median follow-up was 43.5 months. At 36 months, 72% of pts were free from relapse and 82% were alive. SCR (HR 0.33, CI 0.14-0.79, p=0.013) and FIGO stage (HR 1.82, CI 1.07-3.08, p=0.026) retained their independent association with DFS after correction for patients' age, tumor histology and grading. Age was the only prognostic factor for OS (HR 1.07, CI 1.00-1.14, p=0.047). Only 7 (8%) pts suffered from grade 2 toxicities, 5 treated with SCR.

Conclusions: SCR is a feasible option as adjuvant treatment in pts with high-risk EC. Outcomes are comparable to those reported for other CR schedules, as well as the toxicity profile. Moreover, SCR allows a prompt beginning of therapy in comparison to upfront postoperative RT, that requires longer planning. Prospective studies are needed to confirm our retrospective data.

B10

MODENA EXPERIENCE OF FIRST YEAR OF DIAGNOSTIC AND THERAPEUTIC CARE PATHWAYS OF UTERO AND CERVIX CANCER

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Background: Gynecological cancers of the uterus and cervix are common malignancies in women. The correct management of these tumors involves many figures.

Material and methods: Therefore, to respond to these multidisciplinary needs in June 2019 in Azienda Ospedialiero-Universitaria of Modena was born a Diagnostic and Therapeutic Care Pathways (DTCP) with gynaecologists, radiotherapists, medical oncologists, radiologists, nuclear medical doctors, pathologists, anaesthesiologists, a nurse Case Manager and a patients' association representative. A molecular biologist, endocrinologists and nutritionists have already enriched the team after the

first year of activity. The group performs weekly collegial discussions of clinical cases and cohort visits, continued in the COVID era.
Results: The new diagnoses in the first year of activity were 53 endometrial cancers (EC) and 24 cervical ones (CC). The median age at diagnosis was 51 years between EC patients and 70 years in CC. 87% of EC were endometrioid subtypes, while 65% CC were squamous cell ones. 70% EC patients (pts) were stage (st) I (52% IA and 48% IB), 5,5% st II, 9,4% st III and 11,3% st IV. Immunohistochemical analysis for estrogen and progesterone receptor, p53 and mismatch repair (MMR) proteins were performed on 20 EC. All tumours tested are p53 negative. We found 3 pts who had MMR deficiency, none of them diagnosed with Lynch syndrome at the subsequent genetic counselling. After surgery, 66% pts in st I underwent observation and 34% made radiotherapy (RT). Among st II pts, 1 patient performed RT, one other platinum-based chemotherapy (pCT) and the third did not perform any adjuvant treatment for ECOG. All except one st III pts (67%) underwent pCT with RT. Among st IV one received surgery, pCT and palliative RT, the others (83%) made pCT. Most CC were diagnosed in early st. 9 pts underwent upfront surgery, followed in 2 cases with RT and in 3 with RT and pCT. One patient received neoadjuvant chemo-RT. Radical RT with weekly cisplatin was performed in 9 pts, other 4 pts made RT alone due to advanced age and/or ECOG. One patient started observation for age, ECOG and absence of symptoms.
Conclusions: In our experience, DTCP allows the optimization of the diagnostic and therapeutic strategy in EC and CC pts, especially in most complex cases.

B11

CARBOPLATIN PLUS ORAL CICLOPHOSFAMIDE (CTX) FOLLOWED BY ORAL CICLOPHOSFAMIDE (CTX) PLUS BEVACIZUMAB IN MANTEINANCE THERAPY IN ELDERLY PATIETS WHIT ADVANCED OVARIAN CANCER

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Background: The aim of our study was to assess the efficacy and tolerability of Carboplatin plus oral CTX, followed by CTX plus bevacizumab in manteinance therapy in elderly patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer. Patients arboring BRCA1 and BRCA2 mutation received Olaparib as manteinance therapy.
Methods: In this prospective observational study, elderly patients (median age 78) 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) and oral CTX 50 mg, days 1–14 followed by of oral CTX 50 mg, days 1–14 plus Bevacizumab 15 mg/kv ev on day 1 every 21 days until progression. The primary endpoint was progression-free survival. Secondary end point was Overall Survival.
Results: Between Feb 2018 and July 30, 2020, 17 patients were eligible and were enrolled to in the study. The median progression-free survival was 13.3 months, and the median overall survival was 33.2 month. Adverse events more commonly reported were nausea (35%), fatigue (38%), vomiting (14%), and anemia (5%); the majority of adverse events were grade 1 or 2.
Conclusions: Carboplatin and oral CTX followed by oral CTX 50 mg, days 1–14 plus Bevacizumab in manteinance therapy significantly improved progression-free survival and overal survival and had an acceptable and manageable tolerability profile in elderly patients with recurrent ovarian cancer.

C – Genitourinary Tumours

C01*

COMBINING PLASMA TUMOUR DNA AND FUNCTIONAL IMAGING: A PROGNOSTIC SCORE IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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Background: Plasma tumour DNA (ptDNA) and functional imaging with positron emission tomography with 18F-fluorocholine (FCH-PET/CT) have been recently considerated noteworthy biomarkers of response and treatment selection in patients with metastatic castration resistant prostate cancer (mCRPC). The aim of this study is to determine the efficacy of pre-treatment ptDNA in delineating the metabolic tumour burden in mCRPC patients integrating this data with functional imaging to obtain a better prognostic model.
Materials and Methods: PtDNA has been determined at baseline with targeted next-generation sequencing in 102 plasma samples from mCRPC patients treated with abiraterone (n=66) or enzalutamide (n=36) in pre- (n=27) or post-chemotherapy (n=75) setting. A basal FCH-PET/CT was used to evaluate maximum standardized uptake value

(SUVmax), total lesion activity (TLA), and metabolic tumour volume (MTV). The impact on overall survival (OS) of clinical, molecular and imaging features were combined adopting a Weibull multiple regression model obtaining a prognostic score. Each variable corresponds to a partial score. Every patients was assigned to a different risk group according to an 18-month OS probability: group I, >70%; group II, 30%-70%; and group III, <30%.

Results: A significant association between choline uptake as SUVmax, MTV, TLA and median ptDNA was observed into 2 groups of patients (low ptDNA ⩽0.188 versus high>0.188) (p<0.0001, p=0.0005, and p<0.0001, respectively). Patients were randomly divided into two sets: a training cohort (n=68) and a validation one (n=34). In the first cohort visceral metastasis, pre-treatment serum LDH, MTV and ptDNA were significantly associated with OS [HR 2.64, 95%CI 1.32-5.26, p=0.006; HR 3.69, 95% CI 1.98-6.87, p<0.0001; HR 1.91, 95%CI 1.13-3.21, p=0.015; and HR 2.64, 95%CI 1.32-5.26, p=0.003, respectively]. Furthermore median OS was significantly different among 3 risk groups (risk group I, 29.2 months [95% CI, 18.3-37.0 months]; risk group II, 15.9 months [95% CI, 10.6 to 24.0 months]; and risk group III, 8.7 months [95% CI, 6.3 to 15.4 months]; p<0.0001). Likewise was observed in the validation set groups (risk group I, 23.4 months [95% CI, 8.1 to 38.5 months]; risk group II, 13.3 months [95% CI, 3.7 to 18.0 months]; and risk group III, 7.3 months [95% CI, 2.6 to 11.8 months]; p=0.001).

Conclusions: PtDNA analysis combined to functional imaging may be useful to improve prognostic risk stratification and treatment selection in mCRPC patients.

C02*

NECTIN-4 AND DNA MISMATCH REPAIR PROTEINS EXPRESSION IN UPPER URINARY TRACT TUMORS: AN INNOVATIVE MODEL FOR TUMOR TARGETING APPROACHES? AN IMGO PILOT STUDY

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Background: Upper tract urothelial carcinoma (UTUC) accounts for about 5-10% of all urothelial cancers. UTUC has a poor prognosis, characterized by an aggressive and rapidly fatal behavior. However, detailed knowledges of its molecular profile are still lacking.

Materials and methods: We conducted an analysis of patients who underwent to a radical nephroureterectomy or diagnostic biopsy for UTUC between January 2015 and August 2020, treated at the Santa Maria Hospital of Terni, in Italy. The primary objective was to describe DNA mismatch repair (MMR) proteins and Nectin-4 immunohistochemical expression in UTUC, looking for a correlation between these molecular features. The secondary objective was to investigate the genomic instability in the cases of MMR proteins loss. Expression of proteins was assessed using immunohistochemistry and the evaluation of microsatellite instability (MSI) was performed by next generation sequencing. Nectin-4 expression was reported using an intensity scoring system (score, 0–3+), instead the expression of DNA MMR proteins was indicated as present (no loss) or not present (loss).

Results: A total of 27 tumor samples has been analyzed. Nectin-4 was found to be expressed in 44% of cases and 18.5% of patients showed defective-MMR phenotype. We found significant correlation between Nectin-4 expression and MSH2/MSH6 protein loss. Out of 7 patients with DNA MMR proteins loss or equivocal phenotype, 3 showed MSI.

Conclusions: This analysis provides a molecular description of UTUC and found a relationship between Nectin-4 and DNA MMR proteins expression. We identified also a clinically significant correlation between defective MMR phenotype and genomic instability.

C03

NIVOLUMAB PLUS CABOZANTINIB (N+C) VS SUNITINIB (S) FOR ADVANCED RENAL CELL CARCINOMA (ARCC): OUTCOMES BY BASELINE DISEASE CHARACTERISTICS IN THE PHASE 3 CHECKMATE 9ER TRIAL

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Introduction: First-line N+C significantly improved progression-free survival (PFS), overall survival (OS), and

objective response rate (ORR) vs S in aRCC patients (pts) in the phase 3 CheckMate 9ER trial, leading to FDA approval of N+C in this setting. Assessing outcomes of N+C vs S by baseline disease characteristics can help inform clinical decision making.

Methods: Pts with clear cell aRCC were randomized to N 240 mg IV Q2W + C 40 mg PO QD vs S 50 mg PO QD (4 weeks on/2 weeks off). In this post hoc exploratory analysis, PFS, OS, and ORR were assessed across pt subgroups: IMDC risk, number of organs with ⩾1 target/nontarget lesion (T/NT), sum of diameters of target lesions (sDTL), and site of metastasis (mets). PFS and ORR were evaluated per RECIST v1.1 by blinded independent central review.

Results: Median follow-up in ITT pts was 23.5 months. PFS, OS, and ORR outcomes are summarized in the **Table** across subgroups. PFS HR favored N+C vs S across all subgroups and median (m) PFS was longer with N+C. OS HR also favored N+C vs S across most subgroups. ORR ranged from 38%–66% (N+C) vs 10%–44% (S), and complete response benefits were seen with N+C in most subgroups.

Conclusions: Consistent with outcomes of the primary analysis, efficacy benefits with N+C vs S were maintained regardless of IMDC risk, site of mets, or extent of tumor burden at baseline, supporting N+C as a new first-line treatment option for pts with aRCC.

Subgroup (N+C v S, n)	PFS, HR (95%)	mPFS, mo	OS, HR (95%)	ORR per RECIST v1.1 (95% CI), %	Complete Response, %
IMDC favorable risk (74 v 72)	0.58 (0.36-0.93)	25 v 13	0.94 (0.46-1.92)	66 (54-77) v 44 (33-57)	9 v 10
IMDC intermediate risk (188 v 188)	0.58 (0.45-0.76)	17 v 9	0.74 (0.50-1.08)	56 (48-63) v 29 (22-36)	11 v 3
IMDC poor risk (61 v 68)	0.36 (0.23-0.56)	10 v 4	0.45 (0.27-0.76)	38 (26-51) v 10 (4-20)	5 v 1
1 organ site with T/NT (61 v 68)	0.53 (0.32-0.88)	25 v 13	0.79 (0.33-1.90)	62 (49-74) v 35 (24-48)	20 v 4
⩾2 organ sites with T/NT (261 v 258)	0.53 (0.43-0.67)	15 v 7	0.63 (0.47-0.84)	53 (47-59) v 27 (21-33)	7 v 4
sDTL <72.1 mm (160 v 167)	0.52 (0.39-0.71)	20 v 10	0.64 (0.38-1.06)	62 (54-69) v 36 (29-44)	16 v 8
sDTL ⩾72.1 mm (163 v 161)	0.53 (0.40-0.70)	11 v 6	0.64 (0.46-0.89)	48 (40-56) v 20 (15-28)	2 v 0
Pts w/ lung mets (240 v 251)	0.51 (0.40–0.64)	17 v 8	0.63 (0.46–0.86)	56 (49–62) v 29 (24–36)	8 v 4
Pts w/ bone mets (79 v 72)	0.38 (0.25-0.59)	18 v 4	0.64 (0.39-1.06	48 (37-60) v 11 (5-21)	6 v 0
Pts w/ liver mets (73 v 54)	0.51 (0.33-0.79)	11 v 6	0.47 (0.27-0.82)	49 (37-61) v 20 (11-34)	1 v 2

C04

VALIDATION OF THE MEET-URO SCORE IN METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS (PTS) TREATED WITH FIRST-LINE NIVOLUMAB PLUS IPILIMUMAB IN THE ITALIAN EXPANDED ACCESS PROGRAM (EAP)

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Background: The identification of biomarkers to select pts most likely to benefit from immunotherapy is a clinically unmet need and a critical issue of clinical research. However, no validated biomarker has reached everyday clinical practice yet. The combination of neutrophil-to-lymphocyte (NLR), IMDC score and bone metastases (Meet-URO score) has shown to better stratify mRCC pts treated with =2nd line nivolumab compared with the IMDC score identifying five prognostic groups [Ther Adv Med Oncol 2021, available at: http://bit.ly/Meet-URO15_ score]. The Meet-URO score is an easy tool for clinical practice at no additional costs and its validation on the new 1st line combination therapies is highly awaited.

Material and Method: The real-world series of IMDC intermediate- and poor-risk mRCC pts treated with 1st line

nivolumab plus ipilimumab in the Italian EAP was studied. Baseline NLR, IMDC score and the presence of bone metastases were evaluated. The primary endpoint was overall survival (OS). The Harrell's c-index was calculated to compare the prognostic accuracy of Meet-URO and IMDC scores.

Results: 306 mRCC pts were assessed with a median follow-up of 12.7 months (mo). The median OS was not reached, the OS at 1 year (1y-OS) was 66.8% and median progression-free survival (mPFS) was 8.4 mo. According to the IMDC score, intermediate- (67.3%) and poor-risk (32.7%) pts had an 1y-OS of 77.3% and 42.2% ($p < 0.001$) and a mPFS of 10.4 and 3.3 mo ($p < 0.001$), respectively. According to the Meet-URO score, two prognostic groups showed overlapping OS curves, probably for the absence of the favorable group, and the original five prognostic groups of the Meet-URO score were merged in four groups: group 1-2 (29.1%), group 3 (28.8%), group 4 (33.0%) and group 5 (9.1%). These four prognostic groups were characterised by distinctive 1y-OS: 91.6%, 71.8%, 50% and 21.2%, respectively ($p < 0.001$). These groups had also distinctive mPFS: 16.6, 7.5, 4.9 and 1.8 mo respectively ($p < 0.001$). Moreover, the Meet-URO score has shown to have a higher discriminative ability compared with the IMDC score alone (c-index of 0.72 vs 0.65) in terms of OS.

Conclusions: This analysis on the Italian EAP showed the prognostic role of the Meet-URO score also in mRCC pts treated with the 1st line immune-combination nivolumab plus ipilimumab. Moreover, the Meet-URO score has shown to have a higher accuracy in survival stratification compared with the standard IMDC score.

C05

A SIMPLIFIED CLINICAL AND GENOMIC DIAGNOSTIC MODEL TO IDENTIFY LETHAL CASES OF PROSTATE CANCER AT INITIAL BIOPSY: A PRELIMINARY IMGO PILOT STUDY

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Background: Prostate cancer, a "pluriform" neoplasm with glandular, cribriform, trabecular, solid and unicellular tumor patterns, is a paradigmatic tumor model for histological, clinical and molecular heterogeneity. The current knowledge of the disease biology suggests to integrate the main surrogates for disease prognostication with some genomic data. In patients with metastatic and castration-resistant prostate cancer (mCRPC) and especially de novo metastatic castration-sensitive prostate cancer (mCSPC), known to be tumors with a poor prognosis, some elements such as high Gleason Score (GS) and the presence of a cribriform pattern or intraductal carcinoma may become useful phenotypic markers of a potentially lethal prostate cancer.

Material and methods: This was an retrospective, conducted at three Oncology Centers in the Umbria region. Cases were divided into two groups: Group 1, 50 patients with high-risk, mCRCP; Group 2, 25 patients with mCSPC. A third group of cases, 50 patients with low risk disease and GS 6 (3 + 3) was added as a control. The primary objective of the study was to perform a centralized double blind histological review according to the new 2016 WHO classification and define the prevalence of the cribriform pattern and intraductal carcinoma, analyzed the treatment pattern and clinical course. Secondary endpoint was an explorative molecular analysis by NGS in patients with cribriform and intraductal carcinoma.

Results: Were identified 125 cases for histological review, a change in GS was documented in 33 patients (26%), with a 6% reduction in the prevalence of GS 6 (3 + 3) and a 9% increase in the prevalence of pattern 4 with GS. A cribriform pattern was reported in 45 patients (36%), 28 (56%) in Group 1 and 17 (68%) in Group 2; no cases were found in control group. The prevalence of the cribriform component is significantly higher in Group 2 (mCSPC) than in Group 1 (mCRPC)($p=0.001$). Results of the NGS analysis were available for 10 cases: mutations in the *TP53* gene were identified in all analyzed cases, a co-presence of TP53 and RB1 genes mutations were found in 4/10 patients and a mutation of the BRCA-2 gene was identified in 8 patients.

Conclusions: Our study confirm the high incidence of the cribriform pattern and the mutations in the TP53 and BRCA2 genes, especially in mCSPC. These elements support our idea to build a model of aggressiveness and a realistic phenotypic/biologic model available in daily clinical practice.

C06

CLINICAL, BIOLOGICAL AND METABOLIC FACTORS IN A COMPOSED SCORE TO PREDICT THE TIME TO TREATMENT FAILURE TO IMMUNOTHERAPY IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (MRCC)

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Background: The treatment efficacy of immunotherapy in renal cancer patients is widely variable, ranging from rapid disease progression to sustained complete remissions. Although biomarkers continue to evolve, to identify patients who will likely benefit from therapy is poorly predictable in daily clinical practice. Consortium (IMDC) risk score or Heng criteria remain the main criteria used in clinical practice, and also form the basis of risk stratification for clinical trials. However, IMDC risk groups were validated in a cohort of patients treted with targeted therapy, and their prognostic and predictive power may be lower in the new treatment landscape.

Methods: We integrated the IMDC with the following variables in a population of metastatic RCC patients treated with nivolumab: metastatic sites, number of metastasis, Body Mass Index (BMI), and basal plasma levels of soluble PD-1 (sPD-1), PD-L1 (sPD-L1), and BTN3A1 (sBTN3A1) measured using homemade ELISA assays not yet commercially available, designed according to investigator specifications. The primary outcome investigated was the Time to Treatment Failure (TTF). To identify independent prognostic factors for TTF, univariate and multivariate Cox proportional hazard regression models were built.

Results: From March 2017 to January 2019 fourty-one (41) patients were included in the study. All patients were clear cell renal cell carcinoma. The median TTF to nivolumab treatment was 22 months. Using thresholds by ROC analysis for soluble immune-checkpoints, and univariate/multivariate Cox proportional hazard regression models to statistical analysis, we found that the RCC patients with high baseline levels of sPD-1 ($>$2 ng/ml), and sBTN3A1 ($>$6.8 ng/ml), BMI$>$25, prognostic IMDC factor $>$ 1, no bone and/or brain metastases, metastatic sites $\leqslant$ 2, were associated to longer time to treatment failure. Data on overall survival (OS) are under-evaluation.

Conclusions: Although physicians are inundated from increased information related to the patients and tumor characteristics, to identify prognostic and predictive biomarkers remains an issue.

The use of a composed model including clinical, but also biological and metabolic factors specific for certain individuals, could provide important contributions to the development of most accurate prognostic and predictive score.

C07

A PHASE 2 PROSPECTIVE TRIAL OF CABOZANTINIB AS FIRST-LINE TREATMENT FOR METASTATIC COLLECTING DUCTS RENAL CELL CARCINOMA: THE BONSAI TRIAL (MEETURO 2) CLINICAL TRIAL INFORMATION: NCT03354884

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Background: Collecting duct carcinoma (CDC) is a rare variant of renal cell carcinoma characterized by aggressive course, lack of standard treatment and poor biological characterization. We recently described two molecular subtypes of CDC according to angiogenetic, metabolic and immune-related genes' expression profiles. Through its multi-kinase inhibitor activity, cabozantinib (cabo) could be active in metastatic (m) CDC.

Material and methods: In this prospective, single-institution, phase II trial, treatment-naïve mCDC patients (pts) received cabo 60 mg daily until disease progression or unacceptable toxicity. Primary endpoint was Overall Response Rate (ORR) according to RECIST1.1. A Simon's two-stage optimal design was applied. Secondary objectives were progression free survival (PFS), overall survival (OS) and safety. Exploratory objectives were to identify somatic mutations by targeted NGS-based sequencing, to define molecular subtypes, signatures and transcript fusions genes by RNA sequencing

Results: Between January 2018 and November 2020, 25 pts were enrolled and 23 pts started treatment. Median age was 66 years, 83% of pts were male. 39%, 34% and 26% of pts presented with 1, 2 or multiple metastatic sites, respectively, with lymph nodes (65%), bones (56%), lung (43%) and liver (17%) being the most common. At a median follow up of 18 months, PFS was 8 months. ORR was 35% (1 CR and 7 PR). Six (26%) pts had stable disease (SD). All pts reported at least one grade 1-2 (G1-2) adverse event (AE) and 39% of pts underwent dose reduction. The most frequently reported G1-2 AEs were fatigue (60%), anorexia (39%), hand-foot syndrome (30%), hypothyroidism (30%), mucositis (30%), diarrhea (22%) and hypertension (13%). Five G3 AEs were reported: 2 arterial hyperthension, 1 pulmonary thromboembolism, 1 bleeding, 1 fatigue. DNA sequencing in mCDC lead to

identification of 256 mutations, mostly missense, in 119 genes. Responsive pts (PFS > 6 months) showed high frequency of mutations affecting deubiquitination, cell-cell communication, and TGF-b signaling. Chromatin remodeling, transcriptional regulation and WNT pathways were frequently altered in non-responders.
Conclusions: The study met its primary endpoint showing promising efficacy of cabo in mCDC. Safety profile was acceptable. Correlation between treatment outcomes and genetic and molecular features were identified. Mature results according to mutational profile and gene signature are awaited.

C08

A PHASE 2 OPEN LABEL STUDY OF CABOZANTINIB IN PATIENTS WITH ADVANCED OR UNRESECTABLE RENAL CELL CARCINOMA AFTER A FIRST LINE WITH ANTI PD1 BASED IMMUNOTHERAPY: THE BREAKPOINT TRIAL (MEETURO TRIAL 03 - EUDRACT NUMBER 2018-000582-36)

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Background: Antiangiogenic therapy has been a milestone in the treatment of metastatic renal cell carcinoma (mRCC) for years. Recently, the positive results with immunotherapy are changing the frontline standard of care of these patients (pts). Prospective data are lacking to determine the efficacy of anti-VEGF therapy after IO-IO or IO-TKI. Cabozantinib (Cabo) showed to prolong survival in mRCC pts pre-treated with TKIs and to target kinases involved in immune- escape. So, it may represent an ideal agent to be used sequentially after ICIs.
Methods: This is the first open label, single arm, multicenter, phase II study evaluating efficacy and safety of Cabo in mRCC pts who received an anti-PD- 1/PD-L1-based adjuvant (adj) or 1st line tp. Cabo 60 mg/daily was administered until progressive disease (PD) or unacceptable toxicity.
The primary endpoint was progression free survival (PFS), secondary endpoints were overall survival (OS), objective response rate (ORR) and safety.
Results: In Jan 2021, due to the slow accrual rate, the trial was emended to include a retrospective cohort of pts. From July 2018, 49 pts were enrolled, 30 prospectively and 19 retrospectively. 48 pts were included in the analysis. Median age at baseline was 62.5 years (range: 30-78), 63% of pts were male. At baseline, 26% of pts had a good Heng risk score, 47% intermediate and 28% a poor risk, in 2% of pts the class of risk was undetermined. 74% of pts received an IO-IO combo as 1st line tp, 17% IO-TKI, 9% pts an adj IO monotherapy. Pts received a median of 13 cycles of Cabo (range 5-17 cycles). 23 pts (47.9%) are still on tp, 1 patient discontinued Cabo for AEs, 13 pts for radiological PD, 8 pts discontinued for clinical PD or death, while 2 pts for reasons other than AEs or PD. Among evaluable cases, 17 pts (43%) achieved a partial response and 16 pts (33%) stable disease. Complete responses were not observed. At a median (m) follow-up of 9.2 months (mo), 68.75% of pts were alive and mPFS was 9.3 mo (95% CI 7.1-29.0 mo). Grade (G) 3-4 adverse events (AEs) occurred in 34% of pts, including more frequently serum bilirubin increase, hypertension, hypocalcaemia, hyponatremia and oral mucositis. G1-2 were observed in 66% of pts, including in most of cases diarrhoea, nausea, oral mucositis, disgeusia, hand-foot syndrome, fatigue and hypothyroidism.
Conclusions: The BREAKPOINT trial showed that Cabo after IO-IO and IO-TKI was safe and active in mRCC, in both the cohorts of patients.

C09

A PHASE II PROSPECTIVE TRIAL EVALUATING ENZALUTAMIDE AND THE ROLE OF ARV7 IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER (MCRPC) PATIENTS (PTS) WITH VISCERAL DISEASE

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Background: The second-generation androgen receptor inhibitor Enzalutamide showed to prolong survival in different setting of prostate cancer. Due to poor prognosis,

men with visceral disease were often excluded in trials investigating hormone therapies especially in the pre-docetaxel setting. To date, there are no prospective studies ad hoc to test hormone therapies in this subgroup of pts.
Methods: In this phase II multicentre study mCRPC pts with visceral metastases received enzalutamide 160 mg as first or second line after docetaxel until progressive disease or unacceptable toxicity. Pts had to have measurable metastatic visceral disease (RECIST 1.1), including lesions in lung, liver or extraregional lymphnodes; PSA progression or radiographic progression (according to PCWG2). Primary endpoint was to determine the clinical benefit, as measured by 3-months (mo) disease control rate (DCR) defined as the proportion of pts with best overall response of complete (CR) or partial responses (PR) or stable disease as per RECIST 1.1 at mo 3. Secondary endpoints were safety, quality of life (assessed by EQ-5D-5L and FACT-P questionnaire), pain assessment (by BPI-SF questionnaire). Exploratory objectives were to assess the association between ARv7 splicing variants (in CTCs samples) and treatment response/resistance. For CTC and ARv7 detection, we used the Adna test Prostate Cancer Panel.
Results: From March 2017 to January 2021, 68 pts were enrolled. One pt never started treatment because of consent withdrawal. Median age was 70 years (IQR 65- 78). All pts presented with visceral disease at baseline: 27, 6, 55 pts presented with lung, liver and lymphnodes lesions. 15 pts received a previous treatment with docetaxel in the mCRPC phase. The median follow-up was 10 mo. The median time on treatment was 8 mo. At mo 3, 24 pts presented a stable disease, 1 pt achieved a confirmed CR and 20 pts a PR for a 3 mo-DCR of 67% (45/67). Discontinuations due to adverse-events, disease-related death, or disease progression occurred in 6%, 7%, and 40% of pts, respectively. Only 26 patients were evaluated for baseline CTC and ARv7. Interestingly, 75% of patients experiencing a progression at month 3 were classified as ARv7 positive at baseline.
Conclusion: The study met its primary endpoint showing efficacy of enzalutamide in men with mCRPC and visceral disease in both pre or post-docetaxel setting. CTCs status combined with ARv7 detection could be useful to personalize treatments.

C10

THE PROGNOSTIC STRATIFICATION OF THE MEET-URO SCORE COMPARED WITH THE IMDC SCORE IN PRETREATED METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS (PTS) RECEIVING CABOZANTINIB

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Background: The identification of prognostic and predictive biomarkers to select pts most likely to benefit from immunotherapy is a clinically unmet need and a critical issue of current clinical research. The combination of neutrophil to lymphocyte (NLR), IMDC score and bone metastases in the Meet-URO score has shown to better stratify pretreated mRCC pts treated with nivolumab compared with the IMDC score alone identifying five distinctive prognostic groups [Ther Adv Med Oncol 2021, http://bit.ly/Meet-URO15_score]. This score is an easy tool for clinical practice at no additional costs but the assessment of its predictivity was necessary.
Methods: A real-world series of mRCC pts treated with 2nd and 3rd line cabozantinib from a multicenter retrospective analysis was queried. Baseline NLR, IMDC score and the presence of bone metastases were analysed. The primary endpoint was overall survival (OS) and the Harrell's c-index was calculated to compare accuracy of survival prediction of Meet-URO and IMDC scores.
Results: 174 mRCC pts received cabozantinib as 2nd (52% of pts) and 3rd (48%) line and were assessed with a median follow up of 6.8 months (mo). Patients with high NLR ($\geqslant$ 3.2) (47%) and bone metastases (31%) were associated with a lower mOS compared to those who did not (11.1 versus - vs - 39.4 mo, $p = 0.022$ and 10.9 vs 15.5 mo, $p = 0.068$, respectively). According to the IMDC score, favorable- (25%), intermediate- (61%) and poor-risk (14%) pts were had a mOS of 15.5, 12.1 and 11.1 mo respectively ($p = 0.031$). Reclassifying the population according to the Meet-URO score, some prognostic groups showed overlapping survival curves so that the original five groups of the Meet-URO score were merged in three groups: group 1-2 (55%), group 3-4 (39%) and group 5 (6%) associated with distinctive mOS (39.4, 11.2 and 3.2 mo, respectively; $p < 0.001$). This merging of the survival curves could be explained by the low prognostic impact of bone metastases ($p = 0.068$) and/or the low numerosity of the patients included in the analysis. Moreover, the Meet-URO score has shown to have a higher discriminative ability compared with the IMDC score alone (c-index of 0.64 vs 0.60) in terms of OS.

Conclusions: This analysis showed the prognostic role of the Meet-URO score in mRCC pts treated with ⩾ 2nd line cabozantinib. It showed also that the addiction of NLR and the presence of bone metastases to the IMDC-score improve the prognostic ability of IMDC alone.

C11

EXPRESSION OF ANDROGEN RECEPTOR, SOMATOSTATIN RECEPTOR SUBTYPES, AURORA KINASE A AND INTERLEUKIN-6 IN PROSTATE CANCER BEFORE ANDROGEN ABLATION

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Background: Neuroendocrine differentiation (NED) in prostate cancer (PC) can be detected by immunohistochemistry as single cells in conventional adenocarcinoma. NEPC is a poor-recognized late presentation of hormone-refractory subtype of PC AR-negative. NEPC correlates with poor prognosis, tumor progression during androgen-deprivation therapy and frequent visceral metastases. Aurora kinase A (AURKA) and Interleukin-6 (IL-6) cooperate to induce NED. The aim of this study was to correlate the expression of somatostatin receptor (SSTR) 1- 2- 3- 4- 5 subtypes, AURKA and IL-6 in primary PC with NED pattern before androgen ablation and OS.

Patients and Methods: PC tissues were reviewed from 60 pts who had undergone biopsy or radical prostatectomy for previously untreated advanced or metastatic PC from 2010 to 2016. 10 samples expressed histologically chromogranin A (CgA), a marker of NED expression. Median age was 67 years (47-80), Gleason score = 7, median PSA was 60 ng/ml (1.3-1000), ECOG 0/1 and bone-visceral sites measurable in 90% of cases. For comparison purposes, 8 pathology specimens from pts with primary PC negative for CgA expression were used.

Results: SSTR1-2-4-5 were detected only in the nucleus of PC cells in 10/10 samples. AR was expressed in all 10 samples CgA positive. SSTR3 and AURKA were not expressed in all 10 samples. IL-6 was detected in 9/10 samples. All 10 pts developed early onset of CRPC, more aggressive clinical course with a rapid occurrence of visceral metastases and OS was <12 mos.

Conclusions: In metastatic prostate cancer, pretreatment NED pattern can be a predictor for progression and survival after hormonal and during standard chemotherapy. Most likely NEPC becomes AR negative during disease progression and in response to androgen deprivation therapy. We supposed, according to other data, that the novel potent AR-targeted drugs should be not used in this subset of patients. SSTRs and somatostatin analogs are not potential targets for prostate cancer.

C12

EVALUATION OF LONG-TERM TOXICITY IN A COHORT OF GERM CELL CANCER PATIENTS TREATED WITH BEP IN THE ADJUVANT OR METASTATIC SETTING

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Background: Testicular germ cell tumour (GCT) represents the most common solid tumor among young men. Cisplatin, etoposide and bleomycin (BEP) combination chemotherapy (CT) reaches cure rates of approximately 100% in localized stages and more than 80% in the case of disseminated disease. However, the BEP regimen is not devoid of long-term toxicity, notably secondary solid tumours or leukaemia, neuro/ototoxicity, nephrotoxicity, pulmonary toxicity, vascular disorders, and infertility.

Material and methods: We have collected data from a cohort of 60 patients (pts) with a previous diagnosis of GCT that had completed BEP for more than two years (time interval 2003-2018). All pts were treated at our Institution and received 1-2 BEP cycles in the adjuvant (ADJ) setting or 3-4 cycles in the metastatic (MTS) setting. In the two considered setting, we retrospectively investigated the prevalence of various long-term toxicities, including cardiovascular, neuro-otologic toxicity, secondary neoplasm, infertility, and others. Association between toxicities and the setting of disease were analyzed with the chi-square test.

Results: 19/60 pts received PEB in the ADJ setting, 41/60 in the MTS setting. 4/60 pts (6.7%) received 1 cycle, 15 (25%) 2 cycles, 27 (45%) 3 cycles, 14 (23.3%) 4 cycles. Overall, 28/60 pts (46.7%) showed long-term toxicity. In particular, 12/60 pts (20%) had infertility impairment, 6 (10%) ototoxicity, 4 (6.7%) cutaneous disorders (i.e. dermatitis and photosensitivity), 3 (5%) developed secondary solid tumours. Mucositis and cardiovascular toxicity were both reported with a prevalence lower than 5%. According to the number of cycles received, the prevalence of toxicity was 25 % with 1 cycle, 46.6% with 2 cycles, 44.4% with 3 cycles, and 57.1% with 4 cycles. No correlation was found between the setting of disease and the development of toxicity (p=0.63).

Conclusions: This analysis confirms that BEP-related long-term toxicity is relevant in GCT pts. The absence of

difference between toxicity in the ADJ and MTS setting may be explained by the similar prevalence of toxicity with 2 or 3 cycles of CT. Optimization of the number of BEP cycles is crucial to reduce the incidence of long-term toxicity in a highly curable neoplasm.

C13

REAL-WORLD EXPERIENCE OF ABIRATERONE ACETATE PLUS PREDNISONE IN CHEMOTHERAPY NAÏVE PATIENTS WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER: LONG-TERM RESULTS OF THE PROSPECTIVE ABITUDE STUDY

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Background: Limited real-world data exist on the effectiveness and safety of abiraterone acetate plus prednisone in the treatment of patients with metastatic castration resistant prostate cancer (mCRPC) naïve to chemotherapy. Most of the few available studies had a retrospective design and included a small number of patients. In the interim analysis of the prospective ABItude study, abiraterone showed good clinical effectiveness and safety profile in the chemotherapy naive setting over a median follow-up of 18 months.

Patients and Methods: We evaluated clinical and patients reported outcomes (PROs) of chemotherapy-naïve mCRPC patients treated with abiraterone acetate plus prednisone as for clinical practice in the Italian, observational, prospective, multicentric ABItude study. mCRPC patients were enrolled at abiraterone start (February 2016-June 2017) and followed for 3 years, clinical endpoints and PRO, including quality of life and perceived pain, were prospectively collected. OS and rPFS were evaluated using Kaplan-Meier curves. Quality of life were assessed by FACT-P, EQ-5D-3L and EQ VAS.

Results: Of the 481 patients enrolled, 454 were evaluable for final study analyses. At abiraterone acetate plus prednisone start, the median age was 77 years, with 58.6% elderly patients (⩾75 years) and 69% having at least one comorbidity (57.5% cardiovascular diseases). Visceral metastases were present in 8.4% of patients. Over a median follow-up of 24.8 months, median PFS (any progression reported by the investigators), time to abiraterone discontinuation and overall survival were, respectively, 17.3 months (95% CI, 14.1-19.4), 16.0 months (95% CI, 13.1-18.2), and 37.3 months (95% CI, 36.5-not estimable). Prostate-specific antigen reduction =50% was achieved by 64.2% of patients. Quality of life remained stable during treatment. Median time to pain progression according to Brief Pain Inventory data was 31.1 months (95% CI, 24.8 – not estimable). 62 patients (13.1%) had at least one adverse drug reaction (ADR) and 8 (1.7%) one serious ADR.

Conclusions: With longer follow up, abiraterone acetate plus prednisone therapy remains safe, well tolerated and active in a large unselected population.

C14

PROGNOSTIC ROLE OF TREATMENT DISCONTINUATION DUE TO ADVERSE EVENTS IN BONE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER PATIENTS TREATED WITH RADIUM-223. A RETROSPECTIVE MONOCENTRIC ANALYSIS

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Background: Radium 223 (Ra-223) was approved for the treatment of metastatic castration resistant prostate cancer (mCRPC) patients with bone-only disease, following demonstration of significant improvement in overall survival (OS). To date, there are no validated prognostic factors useful in predicting outcome of mCRPC patients treated with Ra-223 and the optimal place of Ra-223 in the sequence of currently available mCRPC treatments is not well established. Our retrospective study aims to evaluate the prognostic role of treatment discontinuation due to adverse events in mCRPC patients treated with Ra-223,

and to identify which factors correlate with the toxicity onset.

Materials and Methods: We performed a retrospective analysis of all consecutive mCRPC patients treated with Ra-223 from September 2013 to December 2019 at the San Luigi Hospital in Orbassano, Italy. Patients were divided in 2 groups according to the reason of Ra-223 therapy discontinuation: toxicity versus other causes. Outcome measures were progression-free survival (PFS) and OS.

Results: In the overall population (75 patients) median PFS and OS were 5.46 months and 11.15 months respectively. Patients who discontinued treatment due to toxicity had a lower median PFS (3.49 vs 5.89 months, HR: 1.88, 95% CI: 1.14-3.12, p=0.014) and OS (8.59 vs 14.7 months HR: 3.33, 95% CI: 1.85-6.01, p<0.001) than patients who discontinued therapy due to other causes. The risk of Ra-223 discontinuation due to toxicity correlates with the number of previous treatments (p=0.002), previous chemotherapy treatment (p=0.039), baseline LDH (p=0.012), Hb (p=0.021) and platelet-to-lymphocyte ratio (p=0.024).

Conclusions: Discontinuation due to toxicity is associated with worse outcomes in mCRPC patients treated with Ra-223. To reduce the risk of developing toxicities that may compromise treatment efficacy, Ra-223 should be used early in mCRPC patients.

C15

CLINICAL SAFETY AND ACTIVITY OF CABOZANTINIB (CABO) PLUS DURVALUMAB (DURVA) IN PATIENTS (PTS) WITH ADVANCED UROTHELIAL CARCINOMA (UC) AFTER PLATINUM CHEMOTHERAPY (ARCADIA): UPDATED RESULTS FROM A NON-RANDOMIZED, OPEN-LABEL, PHASE 2 TRIAL

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Background: The combination of anti-VEGFR drugs and checkpoint inhibitors exhibited synergic effect in UC pts. ARCADIA is a phase 2 trial evaluating the safety and efficacy of CABO, a multikinase inhibitor, plus the anti-PDL1 DURVA in pts with platinum-refractory advanced UC or variant histology (NCT03824691). Herein we report the preliminary updated results.

Methods: Pts were administered with CABO 40 mg daily, orally, in combination with DURVA 1500 mg, intravenously, every 28 days, until disease progression or unacceptable toxicity occurred. Key inclusion criteria were: ECOG-PS 0-1, UC or variant histology, failure of 1 or 2 platinum-based regimen for metastatic disease, non-measurable disease was permitted. Response was evaluated by RECIST criteria v.1.1 every 2 cycles by CT and ^{18}FDG PET/CT scans. The primary endpoint of the study was overall survival (OS). Other endpoints included safety, objective response-rate (ORR), duration of response, progression-free survival (PFS). PD-L1 expression was assessed by Ventana SP142 assay. Next-generation sequencing tests (FoundationOne) and immune profiling of PBMCs (by flow citometry assay) on pre-therapy tumor samples were performed.

Results: From September 2019 to May 2021, 35 pts were enrolled (median follow-up: 5 mo). Median age was 64 yrs, 63% were male, and 17% had ECOG PS 1. 8 pts presented variant histology, 5 pts had received 2 prior systemic anticancer therapies. In pts evaluable for efficacy analyses, 4 (11.4%) complete responses (CR) and 8 (22.9%) partial responses (PR) were observed. The ORR and DCR were 35.3% and 70.6% respectively. Treatment-related AEs (TRAEs) occurred in 21 pts (60%), including 2 grade 3 events within the first 2 cycles. 7 pts (20%) discontinued CABO due to toxicity; no interruption of DURVA was observed. The most common AEs by any grade were hypertransaminasemia (35.7%), asthenia (27%), diarrhea (27%), and hypertension (15%). Preliminary analysis of pre-therapy PBMCs samples (n=10; CR/PR: n=2; SD<6 months: n=6, PD: n=2) revealed a significantly higher frequency of CD19+ B cells, HLA-DR+ CD3+ CD56+ NKT cells, CD14HiCD16+ intermediate monocytes, and Lin- CD33+ HLA-DRLo CD14+ CD15- mMDSCs in patients with PD compared to patients with CR/PR or SD.

Conclusions: Combination of CABO and DURVA demonstrated promising preliminary activity and a manageable safety profile in pts with advanced UC and variant histology. More mature results according to response-related biomarkers and histology will be presented.

C16

REAL-WORLD STUDY OF CABOZANTINIB IN PTS WITH ADVANCED RENAL CELL CARCINOMA (ARCC) AFTER VEGF-TARGETED THERAPY (CASSIOPE): INTERIM DATA FOR PATIENTS WHO HAD RECEIVED PRIOR NIVOLUMAB

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Background: Cabozantinib is a TKI approved in EU for use in adults with aRCC who received prior VEGF-targeted therapy or are treatment naive with intermediate or poor risk. We report interim data on the real-world use of cabozantinib in patients (pts) with aRCC who received prior VEGF-targeted therapy and nivolumab.

Methods: CASSIOPE (NCT03419572) is an ongoing, non-interventional study of cabozantinib in pts with aRCC who received prior VEGF-targeted therapy; a pre-planned interim analysis was conducted when 50% of pts completed ⩾ 3 months of follow-up. This *post-hoc* analysis assessed pts characteristics, best overall response (BOR) based on RECIST 1.1, dose modifications and tolerability at 3 months in the pts subgroup who received prior nivolumab.

Results: CASSIOPE included 337 pts treated with cabozantinib following prior VEGF-therapy. Of all first-line therapies, sunitinib (56.7%) and pazopanib (32.3%) were most common; nivolumab was the most common second-line therapy. In total, 154 (45.7%) pts had received prior nivolumab in any line (median age, 67.5 years; 70.8% male, 87.7% clear-cell histology, 96.1% metastatic disease; 80.8% ECOG PS 0–1). Within this subgroup, 58.4% of pts initiated cabozantinib at 60 mg/day; median daily dose was 40 mg. Dose modifications and safety data are summarized in the Table. During the first 3 months, 58 pts in the prior nivolumab subgroup had an evaluable BOR: 39.7% had a PR, 44.8% SD and 12.1% PD (not evaluable for 3.4% of the pts).

Conclusions: This *post-hoc* analysis suggests that cabozantinib, used in routine care, is broadly tolerable and may offer tumour response in pts previously treated with VEGF-targeted therapy and nivolumab.

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Table. (Continued)

Dose modification, n (%)	Prior nivolumab subgroup (n = 154)	
	Any	Due to AEs
Any	121 (78.6)	103 (66.9)
Reduction	72 (46.8)	67 (43.5)
Interruption	84 (54.5)	72 (46.8)
Discontinuation	40 (26.0)	22 (14.3)
Most common TRAEs, any grade, n (%)		
Any	146 (94.8)	
Diarrhea	56 (36.4)	
Palmar-plantar erythrodysaesthesia syndrome	39 (25.3)	
Asthenia	35 (22.7)	
Nausea	34 (22.1)	
Fatigue	33 (21.4)	
Hypertension	32 (20.8)	
Decreased appetite	26 (16.9)	
Mucosal inflammation	25 (16.2)	
Stomatitis	23 (14.9)	
Deaths, n (%)		
All cause	17 (11.0)	

C17

MULTITARGET IMMUNOHISTOCHEMICAL (MIHC) ASSESSMENT OF THE IMMUNE TUMOR MICROENVIRONMENT (I-TME) IN RESPONDER VERSUS (VS) NON-RESPONDER METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS (PTS) TREATED WITH NIVOLUMAB (THE MEET-URO 18 STUDY)

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Background: The Meet-URO 18 is an ongoing multicenter study evaluating the prognostic role of the I-TME in mRCC pts treated with =2nd line nivolumab divided according to clinical benefit (median progression-free survival – mPFS): responder (mPFS ⩾ 12 months) vs non-responder (mPFS ⩽ 3 months) pts. Multitarget IHC analyses were conducted on the I-TME to identify differential I-TME patterns in the two clinical groups. Here we report the preliminary analyses.

Methods: Multitarget IHC analyses were conducted on the I-TME of the primary tumor and/or the metastases

assessing T-lineage (CD3, CD8), macrophage-lineage (CD68), CD56, CD15 and phosphorylated mTOR expression on tumor cells. Immunoreactive cells were counted and aligned to the x200 (0.933 mm2) microscopic field. Based on the clinical division of the patients (responder vs non responder), the mIHC results have been dichotomized as high/low density or expression. High density of CD3 and CD8 was set to >15 T-cells x high-power field (HFP). The cut-offs used for high neoplastic expression of CD15, CD68, CD56 and phmTOR were >20%, >50%, >10% and >10% of cells, respectively.

Results: Overall, 32 tumor tissue samples (primary tumors and/or metastases) were available: 15 pts had only primary tumor tissue, 5 pts had only metastasis tissue and 5 pts had both metastatic and primary tumor tissues. Responder pts have shown to have similar CD8 (65% vs 73%, D8%) and CD3 (82% vs 73%, D9%) density of the tumor-infiltrating lymphocytes compared with non-responder pts. Moreover, responder pts are associated with lower percentages of high expression of ph-mTOR (44% vs 60%, D16%), CD56 (12% vs 33%, D21%) and CD15 (59% vs 71%, D12%) and higher percentages of high CD68 (65% vs 47%, D18%) expression compared to non-responder pts. The p values of the analyses were not significant, probably due to the preliminary nature of the analyses.

Conclusions: As preliminary analyses of the Meet URO 18 study, we identified that the mIHC profiles show clinical differences between responder vs non-responders mRCC pts treated with immunotherapy, according to the stratification of the phmTOR, CD56, CD15 and CD68 simultaneous immuno-expressions. These mIHC parameters may be used on formalin and fixed tissue for prospective analysis in clinical trials.

C18

FROM PATHOLOGICAL EXAMINATION TO CLINICAL OUTCOMES IN RENAL CELL CARCINOMA WITH SARCOMATOID DEDIFFERENTIATION (SRCC): AN OBSERVATIONAL, MONOCENTRIC, RETROSPECTIVE ANALYSIS (SARCORA)

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Background: Sarcomatoid dedifferentiation is founding in 10% of any renal cell carcinoma (RCC) subtype and plays a negative prognostic rule. At diagnosis, most of patients (pts) had large tumoral mass and yet locally advanced or metastatic disease. The median overall survival (mOS) is 5-12 months (mo). Our research has the objective of analysing clinical features and outcomes of sRCC pts.

Material and methods: SARCORA is a monocentric analysis of pts with sRCC at AOU Policlinico of Modena between January 2007 and September 2020 after partial or radical nephrectomy.

Results: Thirty-two pts with sRCC were included in SARCORA. Of them at diagnosis 11 (34,4%) pts had localised disease and 21 (65,6%) pts had metastatic diffusion. An expert genitourinary pathologist performed a centralised revision of histological diagnosis. Rhabdoid components were found in 10 (31,25%) pts, 31 (96,9%) pts had tumor necrosis. Lymphatic invasion was evident in 26 (81,25%) pts, microvascular invasion was found in 19 (59,4%) pts, 28 (87,5%) pts presented large kidney tumor (T3a/T4), pN1 stage was in 14 (43,8%) pts. Lung was the most frequent (32,4%) site of metastatic localization. According IMDC score none pt had favourable prognostic risk, 8 (88.9%) pts had poor risk and only 1 (11.1%) pts had intermediate risk. Twelve (37,5%) pts did not receive first line treatment for ECOG PS 2-3. Only twenty (62.5%) pts received first line treatment: 15 (46,9%) pts underwent TKI treatment, one (3,1%) pt received mTOR inhibitors and 4 (12,5%) pts were treated with combinations of immunotherapy. Objective response rate (ORR) was achieved in 7 (35%) pts. Five (15,6%) pts underwent second line treatment. The median progression free survival was 10,08 mo (IC 95% 0,59-2,15) and mOS was 11,28 mo (IC 95% 0,59-1,40). Fuhrman nuclear grade G3/4 (p:0.4359), high rate of sarcomatoid components (⩾50%) (p:0.3745), rhabdoid components (p:0.0736), large tumoral mass (p:0.4868) and lymph node involvement (p:0.2303) were negatively correlated to OS although not statistically significant.

Conclusions: Data of SARCORA study confirm that sRCC pts have poor prognosis disease.

C19

CLINICAL OUTCOMES OF METASTATIC RENAL CELL CARCINOMA WITH RARE HISTOLOGIES: A MONOCENTRIC EXPERIENCE

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Background: The term nccRCC (non-clear cell renal cell carcinoma) includes a diverse set of RCC histologies with distinct clinical and biological features and therapeutic considerations. Although with a lower incidence than the

clear cell counterpart, nccRCC is still an incurable and fathal malignancy in the advantage stages. The therapies evaluated in clinical trials conducted in ccRCC are routinely used in non-clear RCC.
Methods: Clinical data of patients with diagnosis of metastatic nccRCC and sRCC (sarcomatoid renal cell carcinoma) from 2008 to 2019 at Modena Cancer Center were collected.
Results: A total of 60 patients (pts) were enrolled. Median age at first diagnosis was 66 years, 46 pts (77%) were male. 40 pts (77%) presented as nccRCC, while 20 pts (33%) as sRCC. 28 pts (47%) had metastatic sites at diagnosis. 50 pts underwent a first line treatment. In particular 40 pts (80%) received a Tyrosine kinase inhibitor (TKI), 4 pts (8%) an mTOR inhibitor, 5 pts (10%) an immune checkpoint inhibitor and 1 pts chemotherapy. According to IMDC risk classification 34 pts (60%) belonged to intermediate risk, 13 pts (23%) to poor risk and 10 pts (18%) to good risk. Median progression free survival (mPFS) was 3 months in both first (95% CI 2,1-3,9) and second line (95% CI 2,1-3,9) of therapy. All population had a Median Survival (mOS) of 10 months (95% CI 6,9-13,1): 16 months for papillary RCC (PRCC) (95% CI 10,8-21,2), 10 months for chromophobe RCC (CRCC) (95% CI 2,0-18,0), 8 months (95% CI 3,8-12,2) for sRCC and 8 months for unclassified RCC (URCC) (95% CI 1,0-15,0) (p=0.4).
Conclusions: Our experience confirms that nccRCC seems refractory to therapies typically used for ccRCC and are highly aggressive with consequently poor prognosis. For this reason, clinical trials when available should be the preferred management option for metastatic nccRCC. Creating specific subgroup analysis and focusing on specific molecular and genomic characteristics could be an interesting research perspective.

C20

CISPLATIN (CDDP)-BASED CHEMOTHERAPY FOR THE TREATMENT OF METASTATIC BELLINI'S DUCTS CARCINOMAS (MBDC): A RETROSPECTIVE ANALYSIS

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Background: mBDC are rare tumors originating from the collecting duct of the kidneys, endowed by a particularly poor prognosis, for which no standard treatment has been established so far. Since they resemble more urothelial cancers, as compared to classical parenchymal renal cell carcinomas, international guidelines suggest CDDP-based chemotherapy for their treatment.
Patients and methods: Here we report a retrospective analysis of mBDC patients treated with CDDP-based chemotherapy at two large institutions, one from Northern, and one from Southern, Italy.
Results: Data from 30 mBDC patients, treated from January 2013 to December 2020, were retrieved. Twenty-seven of them received a combination of CDDP and Gemcitabine, while 3 were treated with a triplet consisting of CDDP, Gemcitabine and Paclitaxel (as in Bellmunt J, et al. J Clin Oncol 2012;30:1107-13). As expected, there was a predominance of male patients (21/30, 70%), with a median age of 66 years (average: 65.1, range: 51-77); main metastatic sites were lung (20/30, 66,6%), liver (18/30, 60%), lymphnodes (28/30, 93,3%), and bones (16/30, 53,3%), more than 3 metastatic sites having been observed in all patients. Notably, only one patient was previously nephrectomized, having been initially misdiagnosed with a clear cell renal cell carcinoma. As a whole, 7/30 patients (23,3%) experienced a partial response (PR), while 6 (20%) had a disease stabilization (SD) as their best response to treatment. As a whole, disease control rate was 43,3%. Notably, none of the 3 patients treated with the triplet experienced any benefit (either PR or SD) from treatment. Median PFS was 6 months (average: 7; range: 3-15). Grade 3 or 4 treatment-related adverse events were observed in all patients treated with the triplet, and in 50% of those treated with CDDP and Gemcitabine. Grade 3 and 4 toxicities included thrombocytopenia, neutropenia (either febrile or not), anemia, kidney impairment, nausea, vomiting and paresthesias (observed only in patients treated with the triplet).
Conclusions: CDDP-based chemotherapy showed modest antitumor activity and efficacy in a real world setting with an acceptable safety profile. Our results are in line with those reported by Oudard et al. in their report of a prospective multicenter phase II study (J Urol 2007;177:1698-702). It is thus clear that novel, more active, treatments are badly needed in this setting.

C21

EFFICACY OF ANDROGEN RECEPTOR-TARGETED AGENTS (ARTAS) VS CABAZITAXEL (CAB) IN PROSTATE CANCER PATIENTS: REAL-WORLD DATA FROM A NON-CARD POPULATION

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Background: In the last decades, there have been many advances in the field of systemic therapy for prostate cancer patients (pts). The better sequence of treatments remains

a matter of debate. CARD trial demonstrated that cabazitaxel (CAB) significantly improve radiologic progression-free survival (rPFS) and overall survival (OS), as compared with ARTAs, in pts with metastatic castration-resistant prostate cancer (mCRPC) who were previously treated with docetaxel and progressed within 12 months (mos) while on treatment with the alternative ARTA. This study aims to evaluate which treatment option is more suitable for those pts who had disease progression (PD) after more than 12 mos of ARTA treatment.

Material and methods: We retrospectively evaluated 31 pts treated with ARTA (abiraterone or enzalutamide), for at least 12 mos, and docetaxel (before or after ARTA). Pts received CAB or the alternative ARTA as the next line of therapy. Biochemical PFS (bPFS), radiological PFS (rPFS), OS curves were generated with the use of Kaplan-Meier estimates. Association between biochemical response (reduction from baseline PSA level ⩾ 50%) and treatment were analyzed with Fisher's exact test.

Results: 15 of the 31 analyzed pts received CAB, while 16 pts received ARTA. Median bPFS was similar in the two groups of treatment (4.47 mos in the ARTAs group, 3.53 mos in the CAB group; p=0.14), such as rPFS (4.77 mos for ARTAs, 3.7 mos for CAB; p=0.11). Median OS was slightly higher in the ARTAs group as compared to CAB group (19.63 mos and 12.07 mos, respectively; HR 0.53 [CI95% 0.20-1.13]), but such difference was not statistically significant (p=0.09). PSA response was significantly higher in the ARTAs group [7/16 pts (43.8%)] than in the CAB group [1/15 pts (6.6%)] (p=0.037).

Conclusions: With the limit of a small sample and the retrospective nature of this study, where patients'clinical situation might have influenced the treatment choice at baseline, we identified no differences between the two groups of treatment in terms of bPFS and rPFS. Nevertheless, we found a clinical benefit in terms of OS for ARTAs (not statistically significant). On this basis, and in consideration of the known better safety profile of ARTAs, this treatment could be preferred in a non-CARD population.

C22

IMPACT OF PLATINUM-BASED COMBINATION CHEMOTHERAPY ON THE FERTILITY OF YOUNG MALE PATIENTS TREATED FOR GERM CELL TUMOURS

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Background: Testicular germ cell tumours (GCTs) represent the most common solid tumor associated with fertility disorders among young men. Many factors can negatively affect the fertility of these patients (pts): orchiectomy, retroperitoneal lymph node dissection, radiotherapy, and chemotherapy (CT). Cisplatin, etoposide and bleomycin (BEP) CT combination reaches high cure rates in the localized and metastatic setting, but it can induce infertility which is usually reversible within two years. This study aims to evaluate the incidence of fertility disorders after 2 years from the end of CT treatment.

Material and methods: We retrospectively evaluated 60 pts with a previous diagnosis of GCT that had completed BEP at our Institution between 2003 and 2018. Pts were treated with 1-2 BEP cycles in adjuvant (ADJ) setting or 3-4 cycles in metastatic (MTS) setting. We administered an anonymous survey to the pts to investigate their reproductive plans, their difficulties in procreating and the employment of medically-assisted procreation (MAP).

Results: In the study population median age at the tumour diagnosis was 34 [19-57 years].19/60 pts received BEP in the ADJ setting, 41/60 in the MTS setting. 36/60 (60%) underwent semen cryopreservation before CT. Overall, 19/60 pts (31.7%) attempted to procreate after CT; in this group of pts, 7/19 (36.8%) did not experience reproductive difficulties, while 12/19 (63.2%) failed to conceive within 12 months of regular unprotected sexual intercourse. 6 of these 12 pts achieved to meet their reproductive plans, with 3 of them resorting to MAP. Besides, we found that half of 12 pts with fertility impairment were treated in the ADJ setting and half in the MTS setting, but the percentage of pts with reproductive plans was higher in the ADJ group compared to the MTS group (42% vs 26.8%).

Conclusions: Our analysis confirms that CT-related fertility impairment is relevant in GCT pts. The lack of difference in the incidence of infertility between ADJ and MTS setting may be explained by the lower proportion of pts attempting to procreate in the MTS group. Considering the prevalence of infertility in BEP-treated pts, semen cryopreservation should be always available and offered.

C23

CHARACTERISATION OF TUMOR MICROENVIRONMENT IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA TREATED WITH FIRST-LINE IMMUNOTHERAPY COMBINATION: THE CENTRE-IT STUDY

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Background: Prognostic scoring systems are used to categorise patients (pts) with metastatic renal cell carcinoma

(mRCC) into risk groups by combining clinical independent prognostic factors for survival. Pathological and molecular biomarkers such as PBMR-1, BAP-1, CD8+ T cells, PD-L1, and CDKN2A, are being investigated as tools to improve pts' selection above IMDC, as the treatment landscape evolves with the approval of novel combinations. We evaluated whether these parameters could correlate with outcomes and predict response to immunotherapy (IO) in mRCC pts.
Patients and Methods: We analysed six pts who took part in the EAP for the Nivolumab – Ipilimumab combination in Modena Cancer Center, collecting demographic, clinical, laboratory, and pathological data. Specimens were scanned for sarcomatoid component. Immunohistochemistry (IHC) was used to evaluate PBMR-1, BAP-1, CD8+ T cells, PD-L1; FISH to analyse the CDKN2A locus, and RNAscope® to analyse PD-L1 specific RNA. We defined as "responders" pts who showed a sustained partial response (PR) and are still on IO, or who interrupted it due to immune-related adverse events (irAE), and as "non responders" the pts who experienced a disease progression (PD).
Results: We found heterogeneous characteristics among responders and non responders. Pts with PD-L1 expression >50%, as well as <1%, showed benefit from IO. RNAscope® was concordant with IHC PD-L1 evaluation. One BAP1 mutated patient had an excellent response to IO, which was held due to irAE, and still showing a sustained PR, off-treatment. The other two mutated pts showed an early and after 6 months PD. PBRM1 was mutated in two pts, both with sustained PR to IO. Loss of chromosome 9p encoding CDKN2A was found in two pts with opposite outcomes. We found a sarcomatoid dedifferentiation not known before in one patient.
Conclusion: A multiparametric molecular, histopathological and clinical analysis, combined in a cumulative score of single, double or multiple positivity, is feasible, reproducible, easily available and relatively cost-effective. Considering the small sample size and the retrospective nature of our series, further analyses in a larger and prospective one are warranted. This cumulative multiprofiling score could demonstrate a correlation with outcomes and help to predict response to IO.

C24

A PHASE 3, RANDOMIZED, OPEN-LABEL STUDY (CONTACT-02) OF CABOZANTINIB + ATEZOLIZUMAB VERSUS SECOND NOVEL HORMONAL THERAPY (NHT) IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

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Background: Cabozantinib inhibits multiple tyrosine kinases, including MET, VEGFR, RET, and TAM kinases (Tyro3, AXL, MER), which are involved in tumor pathogenesis and associated with the aggressiveness of prostate cancer. Cabozantinib also promotes an immune-permissive tumor microenvironment and may enhance response to immune checkpoint inhibitors. Cabozantinib in combination with the PD-L1 inhibitor, atezolizumab, has demonstrated clinical activity in mCRPC, (Agarwal ASCO 2020; Abstract 5564). We present the design of a phase 3 trial of cabozantinib + atezolizumab vs a second NHT in mCRPC.
Methods: This randomized, open-label phase 3 study (NCT04446117) evaluates the efficacy and safety of cabozantinib + atezolizumab versus a second NHT (abiraterone or enzalutamide) in patients with mCRPC who received a prior NHT for locally advanced or metastatic castration-sensitive prostate cancer (mCSPC), non-metastatic (M0) CRPC, or mCRPC. Other eligibility criteria include measurable visceral disease or extrapelvic adenopathy per RECIST v1.1, biochemical or radiological progression on first NHT and good ECOG score (⩽1). Exclusion criteria include previous non-hormonal therapy for mCRPC. Prior treatment with docetaxel for locally advanced or mCSPC is allowed. Patients (N = 580) will be randomized 1:1 to cabozantinib (40 mg PO QD) + atezolizumab (1200 mg IV Q3W) versus abiraterone (1000 mg PO QD) + prednisone (5 mg PO BID) or enzalutamide (160 mg PO QD). Designated and prior NHT must differ. Randomization is stratified by liver metastases, prior docetaxel treatment for locally advanced or metastatic CSPC, and disease state during first NHT. Treatment will continue until lack of clinical benefit, unacceptable toxicity, or withdrawal of consent. The primary endpoints are progression-free survival per RECIST v1.1 by blinded independent radiology committee (BIRC) and overall survival. Additional endpoints include objective response rate per RECIST v1.1 by BIRC, safety and quality of life. Enrollment is ongoing.
Clinical Trial Registry Number: NCT04446117

C25

INCIDENTALLY DIAGNOSED PROSTATE CANCER IN PATIENTS WITH MUSCLE-INVASIVE BLADDER CANCER: A RETROSPECTIVE ANALYSIS

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Background: Radical cystoprostatectomy (RCP) is the gold-standard treatment in patients with muscle-invasive bladder cancer (MIBC). The aim of this study was to verify the features of incidentally detected prostate cancer (PC) in RCP.
Material (patients): In this retrospective study we reviewed clinical and pathohystological data of 100 consecutive male patients who underwent radical RCP at University of Bari between 2018 and 2021.
Results: In this retrospective analysis, a total of 55 patients (55%) were diagnosed with concomitant PCa in RCP specimens. The median age was 73.4 years (54-89). In 70% of patients with diagnosed PC the Gleason score was 6, in the remaining 30% Gleason score was 7 (4+3) and 89% of the pathological T stage was pT2N0 and 11% was pT3N0. Only one patients out of 100 had biochemical recurrence and bone metastases after surgery from PC in RCP. Prostate apical involvement was reported in 11% of patients and in 70% involved peripheral zone. We are planning to search tumor biomarkers on histopathological samples and eventually require prostate sampling for histological detection.
Conclusions: This data indicate that the incidence of concomitant PC in RCP in this centre is 55%. Patients with MIBC should be tested with PSA level, undergo digital rectum examination (DRE) and eventually require prostate sampling for histological detection. Moreover imaging methods are also of importance to the multisciplinary management of patients with MIBC. The potential oncologic risk of prostate sparing RCP should be cosidered and resection of prostate must be complete.

C26

IS PSORIASIS A PROGNOSTIC FACTOR OF RESPONSE TO IMMUNOTHERAPY FOR METASTATIC RENAL CELL CARCINOMA (MRCC)?

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Background: Nivolumab has shown promising results in patients with advanced renal cell carcinoma. We have investigated the prognostic impact of immune-related side-effects (IrAEs) during Nivolumab therapy of previously treated mRCC patients, including exacerbation of pre-existing autoimmune diseases as Psoriasis.
Patients and Methods: We have retrospectivily reviewed our database of mRCC patients in Immunotherapy. Our aim was to investigate the incidence of sever cutaneous irAEs and in paticular exacerbation of pre-existing autoimmune diseases, describe patients characteristics, initial presenting symptoms, diagnostic and therapeutic modalities used, a casual link between the administration of Nivolumab and the Psoriasis exacerbation, and an eventual relationship between this irAEs and the prognosis of RCC patients
Results: The total number of RCC patients observed from 2004 to 2020 in our institution was of about 243 cases.16 patients received Nivolumab in second line and, out of these, only 1 patient (a 55-year-old) developed an exacerbation of a severe grade of Psoriasis during Nivolumab therapy. In our case, the sequence of events and a clearly observed flare-up of the lesions after each anti-PD-1 infusion suggest a causal link between the administration of nivolumab and the psoriasis exacerbation. Our patient was successfully treated with topical and systemic corticosteroids. Nivolumab should be discontinued for five months. When the rash improved to grade 1, the patient was subjected to a CT scan, that showed a partial response and so we reinitiated Nivolumab. The patient has been in a stable disease for more than three years.
Conclusions: Immunotherapy may induce a state of immune hyper-reactivity through the relaxion of negative control loops tightly regulating T-helper and T-cytotoxic cells, thereby causing IrAEs, including exacerbation of pre-existing autoimmune diseases. Psoriasis, having an autoimmune aspect, can be triggered during immunotherapy. Development of Psoriasis might also have a predictive value as some retrospective data suggested a better outcome for patients with cutaneous irAEs. Further studies are needed to confirm our findings, one above all in mRCC.

D – Thoracic Cancers

D01*

EFFICACY OF CENTRALIZED-MODEL FOR ROUTINE USE NEXT GENERATION SEQUENCING (NGS) IN ADVANCED NSCLC: PRELIMINARY RESULTS OF ACTIVATION EUROPEAN PROGRAM FOR ROUTINE TESTING OF PATIENTS WITH ADVANCED LUNG CANCER (EPROPA) IN A COMMUNITY HOSPITAL

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Background: In advanced non-squamous-non-small cell lung cancer (a-nsqNSCLC) identification of "druggable" oncogenes has provided new effective treatment targets with a progressive increase of survival rate. A targetable-driver alteration can be identified in 35-40% a-NSCLC and international guidelines recommend routine use of next-generation sequencing (NGS) for molecular screening in a-nsqNSCLC. At the present time in our clinical practice NGS is not reimbursed and molecular information for a-NSCLC can be achieved through single sequential gene test (SSGT) with a rapid "exhaustion" of biological material, a limited number of genes analyzed and a median turnaround time of 4 weeks. To fill our gap in molecular testing we participate in European Program for Routine testing of Patients with Advanced lung cancer (EPROPA) promoted to Women Against Lung Cancer in Europe (WALCE) Association. We report preliminary clinical EPROPA-effects.

Results: From January to April 2021 40 a-NSCLC patients (pts) required a molecular information to care-management. All pts agreed to participate in EPROPA. In 29 (72,5%) pts first molecular screening at diagnosis with SSGT (EGFR, ALK, ROS-1, BRAF,PD-L1) was locally performed and in 20 (70%) of these the residual tissue was not sufficient or not available at all to NGS-test. Then 19 pts were enrolled: 11(58%) with the request of first molecular screening and 8(42%) for a molecular re-characterization after disease progression to standard therapy. Seventeen samples (90%) were analyzed and 2 (10%) samples were not suitable for analysis for tissue exhaustion. Non-squamo\us NSCLC are prevalent histological type (95%) and 30% of pts are never-smokers. In 47% (8/17) pts a "druggable" oncogene was identified: in 75% (6/8) of these pts an effective targeted-therapy was prescribed in clinical practice (CP) or in Expanded Access Program and clinical trials (EAP/CTs). The median turnaround time was 2 weeks. Lorlatinib, Sotorasib and Pralsetinib EAPs were activated for 5 pts and two CTs have been proposed by EPROPA-team to allow the most effective treatment in molecular selected-pts.

Conclusions: Preliminary results of use EPROPA to profile a-NSCLC in our community hospital increased detection of common and rare oncogenic drivers and optimizing patients'access to most effective treatments both in CP and in EAPs or CTs. Identify actionable mutations simultaneously with NGS will reduce the number of pts with "exhaustion" tissue and the time for the molecular-screening.

D02*

MOLECULAR CHARACTERIZATION OF EPIDERMAL GROWTH FACTOR RECEPTOR-MUTATED (EGFR-M) NON-SMALL CELL LUNG CANCER (NSCLC) UNDERGOING HISTOLOGICAL TRANSFORMATION

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Background: Histological transformation of NSCLC is a rare mechanism of acquired resistance to *EGFR* tyrosine kinase inhibitors (TKIs). Information about molecular features and treatment outcomes in these patients (pts) is limited, regarding only small retrospective cohort studies or case reports.

Patients and methods: EGFR-m patients referring to four Italian Centers were retrospectively evaluated. Clinical data and biological samples of pts undergoing histological transformation over the last five years were collected. Centralized molecular characterization by Next Generation Sequencing (NGS) analysis was performed in tissue (Oncomine Comprehensive Assay v3, Thermofisher) at baseline and at time of progression, in plasma (Avenio cfDNA expanded panel, Roche) at baseline -when available- and at progression.

Results: Nineteen pts were identified (58% female, 53% never-smokers, 68% carrying EGFR exon 19 deletion). 13 (68%) presented histological transition into small cell lung cancer, 3 (16%) into squamous cell carcinoma and 3 (16%) into sarcomatoid/pleomorphic phenotype. Most of them (13, 68%) developed histological transformation during first line EGFR TKI treatment. The median time from diagnosis to histologic transition was 17.4 months (95% CI, 13.9 to 20.9) with a median overall survival of 32.2 months (95% CI, 24.6 to 39.8). At baseline, out of 9 tissue samples analyzed, TP53 mutation (mut) was found in 6 patients (67%), CBL mut in 2 patients (22%) as well as Rb1 mut (2, 22%) and EGFR amplification (2, 22%). At the time of histological transformation, tissue NGS analysis has been performed in 14 pts, the most common genetic

alterations were: TP53 mut (6, 42%), MYC amplification (4, 28%), CDKN2A mut (2, 14%), with the persistence of activating EGFR mut in all cases. Plasma NGS analyses, performed in 9 pts at the time of progression, confirmed the presence of EGFR sensitizing mut, with T790M mut (2, 22%), TP53 mut (3, 33%), MET amplification (3, 33%), RB1 mut (2, 22%). Mean cell-free DNA concentration was 228 ng/ml.

Conclusions: Histological and molecular evaluations are complementary in studying EGFR-TKI acquired resistance. NGS analyses in plasma might correlate with the risk of histological transformation and open new treatment perspectives.

D03*

SURVIVAL OUTCOMES IN ELDERLY PATIENTS WITH NON-SMALL CELL LUNG CANCER: WHAT CHANGES OVERTIME?

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Background: The advent of immune checkpoint inhibitors (ICIs) has revolutionized the non-small cell lung cancer (NSCLC) therapy algorithm, with the use of ICIs both in first and subsequent lines of treatment. Elderly patients are an under-represented category in clinical trials and therefore the benefit of immunotherapy in this special population is difficult to estimate. Aim of this study was to assess treatment patterns variation and survival outcomes in elderly patients with NSCLC treated in the immunotherapy era compared to a historical cohort.

Material and methods: A consecutive series of stage IIIB-IV non-oncogene addicted NSCLC ⩾75 years old patients diagnosed at the University Hospital of Udine, Italy, from January 2013 to December 2020, was reviewed. According to immunotherapy date approval in Italy for the treatment of NSCLC, patients were grouped into a historical (HC) and a contemporary cohort (CC), from 2013 to 2016 and from 2017 to 2020, respectively. Baseline variables, treatment patterns and overall survival (OS) of the two cohorts were compared.

Results: Overall, 180 patients were included with a median age of 80 years (range 75-93), predominantly males (78.3%). Of note, 25% had an ECOG PS ⩾2 and 24% had a Charlson Comorbidity Index ⩾3. The most represented histology was adenocarcinoma (63%) and 78% of patients had a stage IV disease, with bone as the most involved site (16.7%), followed by pleural (12.8%), adrenal (15%), SNC (8.9%), liver (8.3%) and soft tissue (6.7%) localizations. A greater proportion of patients in the CC received a first line (76% vs 62%, p=0.04) and a subsequent line therapy (47% vs 32%, p=0.09) compared to HC. Among treated patients in the CC, 27% received ICIs containing regimens as first line therapy. When considering both first and subsequent line treatments, ICIs were administered in 60% and 10% in CC and HC patients, respectively. Intriguingly, patients aged ⩾80 years at diagnosis were 63% in the CC compared to 43% in the HC. A significantly better OS was observed for the CC compared to the HC when considering the whole cohort (8.27 vs. 4.23 months, HR 0.65, p <0.01) or only actively treated patients (10.57 vs. 6.86 months, HR 0.61, p =0.01).

Conclusions: The introduction of ICIs for NSCLC treatment has resulted in an increased number of elderly patients treated in both first and subsequent therapy lines, with a significant impact on survival.

D04*

INTEGRATIVE MOLECULAR ANALYSIS OF COMBINED SMALL-CELL LUNG CANCER IDENTIFIES TWO MAJOR SUBGROUPS WITH DIFFERENT THERAPEUTICAL PERSPECTIVES

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Background: Combined small-cell lung cancer (C-SCLC) are composed of SCLC admixed with a non-small-cell cancer component. They currently receive the same treatment as SCLC. The recent evidence that SCLC may belong to either of 2 lineages, neuroendocrine or non-neuroendocrine, with different vulnerability to specific cell death pathways such as ferroptosis, opens new therapeutic opportunities also for C-SCLC.

Material (patients) and methods: 13 C-SCLCs, including 5 with adenocarcinoma (CoADC), 5 with large cell neuroendocrine carcinoma (CoLCNEC) and 3 with squamous cell carcinoma (CoSQC) components, were assessed for alterations in 409 genes and transcriptomic profiling of 20,815 genes.

Results: Frequent mutated genes included *TP53* in 12 cases, *RB1* in 7, *KRAS* in 4 and *PTEN* in 3. Potentially

targetable alterations included two *KRAS* G12C, two *PK3CA*, and one *EGFR* mutations. Comparison of C-SCLC transcriptomes with those of 57 pure histology lung cancers (17 ADC, 20 SQC, 11 LCNEC, 9 SCLC) showed that CoLCNEC and CoADC constituted a standalone group of neuroendocrine tumors, while CoSQC transcriptional setup was overlapping that of pure SQC. Using transcriptional signatures of neuroendocrine vs. non-neuroendocrine SCLC as classifier, CoLCNEC was clearly neuroendocrine while CoSQC was strongly non-neuroendocrine and CoADC exhibited a heterogeneous phenotype. Similarly, using ferroptosis sensitivity/resistance markers, CoSQC was classified as sensitive (as expected for non-neuroendocrine), CoLCNEC as resistant (as expected for neuroendocrine) and CoADC showed a heterogeneous pattern.

Conclusion: These data support the extension of routine *EGFR, KRAS* and *PIK3CA* mutational analysis to C-SCLC and their subclassification into neuroendocrine vs. non-neuroendocrine for inclusion in proper clinical trials.

D05

CEMIPLIMAB MONOTHERAPY AS FIRST-LINE (1L) TREATMENT OF PATIENTS (PTS) WITH BRAIN METASTASES (METS) FROM ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) WITH PROGRAMMED CELL DEATH-LIGAND 1 (PD-L1) >=50%; EMPOWER-LUNG 1 SUBGROUP ANALYSIS

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Background: In EMPOWER-Lung 1, a Phase 3 study, cemiplimab monotherapy provided significant survival benefit and an acceptable safety profile vs chemotherapy (chemo) in pts with advanced NSCLC and PD-L1 ⩾50%. EMPOWER-Lung 1 included pts with brain mets at baseline who are typically underrepresented in clinical trials. Other published exploratory analyses in single-cohort studies suggest benefit from immunotherapy in this patient population.

Patients and Methods: Pts were randomised 1:1 to cemiplimab 350 mg IV every 3 weeks or investigator's choice of chemo (NCT03088540). Pts with treated clinically stable brain mets (radiological stability not required) were eligible to enrol and are the focus of this post hoc subgroup analysis from the PD-L1 ⩾50% population (n=563) of EMPOWER-Lung 1. Data cut-off was 1 March 2020.

Results: A total of 68 of 563 (12.1%) cases had treated stable brain mets at randomisation. Pts were evenly distributed between cemiplimab (n=34) and chemo (n=34): median (range) age: 60.0 (45–76) vs 62.0 (48–77); male: 97.1% vs 85.3%; and non-squamous histology: 85.3% vs 76.5%; between cemiplimab vs chemo, respectively. Per independent review committee, median overall survival ([OS] 18.7 vs 11.7 months), median progression-free survival ([PFS] 10.4 vs 5.3 months), and objective response rate ([ORR] 41.2% vs 8.8%) were superior with cemiplimab vs chemo (Table). After baseline, central nervous system (CNS) disease progression occurred in 2 (5.9%) patients with cemiplimab vs 4 (11.8%) patients with chemo; extra-CNS disease progression occurred in 9 (26.5%) pts with cemiplimab vs 15 (44.1%) pts with chemo.

Conclusions: 1L cemiplimab monotherapy improved OS, PFS and ORR vs chemo, in pts with advanced NSCLC with PD-L1 ⩾50% and brain mets at baseline. Cemiplimab monotherapy represents a suitable option for this subgroup of pts.

Table. Clinical outcomes in pts with advanced NSCLC and brain mets.

	Cemiplimab (n=34)	Chemo (n=34)	HR (cemiplimab vs chemo)
Median duration of follow-up, months (IQR)	9.2 (3.7–16.3)	9.3 (6.1–13.3)	
OS, median, months (95% CI)	18.7 (17.3–NE)	11.7 (7.0–NE)	0.17 (0.04–0.76); *P*=0.0091
PFS, median, months (95% CI)	10.4 (4.2–NE)	5.3 (2.2–6.5)	0.45 (0.22–0.92); *P*=0.0231
ORR, % (95% CI)	41.2 (24.6–59.3)	8.8 (1.9–23.7)	

HR, hazard ratio; IQR, interquartile range; NE, not evaluable.

D06

INTRACRANIAL ACTIVITY OF SELPERCATINIB (LOXO-292) IN RET FUSION-POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS ON THE LIBRETTO-001 TRIAL

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Background: Patients with RET fusion-positive NSCLC have an ~50% lifetime prevalence of developing CNS metastases. Selpercatinib is a highly selective oral RET inhibitor that has demonstrated intracranial antitumor activity in a RET fusion-positive preclinical model.

Material (patients) and methods: The LIBRETTO-001 trial (89 sites, 16 countries; phase 1/2 NCT03157128) enrolled patients with advanced RET-altered solid tumors, including advanced NSCLC with baseline CNS metastases. Oral selpercatinib, 160mg twice daily, was given in 28-day cycles. CNS metastases were assessed by MRI/CT scan at baseline, every 8 weeks for 1 year, and every 12 weeks thereafter. Primary endpoint for this prespecified subgroup analysis was intracranial objective response rate (ORR, confirmed; RECIST v1.1) as assessed by independent review committee (IRC). Secondary endpoints included intracranial duration of response (DoR) by IRC. Only patients with follow-up ⩾6 months from first dose were included in efficacy analysis. Analyses were based on 17Jun2019 data cutoff date.

Results: A total 22 of 79 patients with RET fusion-positive NSCLC and baseline CNS metastases enrolled had measurable (⩾10 mm) CNS disease (per IRC); follow-up was adequate for analysis in 14 (median age 64 years [range 43-80]; ECOG PS 0/1=21%/79%; all had prior systemic therapy; 5 had prior intracranial radiotherapy [completed in all >2 months prior to selpercatinib]). Intracranial ORR was 93% (n=13; 95%CI=66.1-99.8), including 2 complete (14%) and 11 partial responses (79%). Median intracranial DoR was 10.1 months (95%CI=6.7-NE), with CNS progression events (n=5) or death (n=1) reported in 6/13 responders. The remaining responders (n=7) were ongoing. Presentation will include updated IRC data as of 16Dec2019.

Conclusions: Selpercatinib had marked intracranial antitumor activity in RET fusion-positive NSCLC patients with CNS metastases. Tumor responses were durable, independently confirmed, and observed in patients with prior systemic chemotherapy.

D07

EFFICACY AND SAFETY WITH SELPERCATINIB (LOXO-292) BY LAST PRIOR SYSTEMIC THERAPY RECEIVED IN PATIENTS WITH RET FUSION+ NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: We evaluated best responses to last prior therapy received before enrollment and to selpercatinib, a highly selective and potent RET kinase inhibitor, by last prior therapy subgroups.

Material (patients) and methods: Patients with *RET* fusion+ NSCLC enrolled in LIBRETTO-001, an ongoing global phase 1/2 trial, received recommended Phase 2 selpercatinib dose (160mg BID) after dose escalation. This analysis assessed outcomes by category of last systemic therapy received prior to enrollment. Efficacy was analyzed in first 105 consecutively enrolled patients pretreated with platinum chemotherapy (primary analysis set [PAS]). Adverse events (AE) were measured in all pretreated pts receiving selpercatinib by data cutoff date=16-Dec-2019.

Results: PAS patients (n=105) had median of 3 (range=1-15) prior systemic regimens, including chemotherapy only (30%), immune checkpoint inhibitor (ICI) only (13%), ICI and chemotherapy (10%), a multikinase

inhibitor (32%), and other combinations (15%). Objective response rates (ORR) with these regimens were 13%/7%/20%/18%/13% respectively. ORR with selpercatinib was 64% (95%CI=53.9-73.0) regardless of previous regimen type and 58%/64%/60%/68%/69% in each prior therapy subgroup above. In the pretreated safety population (n=269), most common treatment-related AEs reported in ⩾1 prior therapy groups in ⩾20% of patients were diarrhea, dry mouth, increased AST/ALT, rash, fatigue, thrombocytopenia, peripheral edema, increased blood creatinine or blood alkaline phosphate, and hypertension.

Conclusions: Patients enrolled in LIBRETTO-001 did not experience clinically meaningful ORRs to varied therapies administered prior to selpercatinib. By contrast, selpercatinib showed consistent, robust, and durable efficacy across these prior therapies in heavily pretreated patients with *RET* fusion+ NSCLC. There were no new safety signals.

D08

EPROPA: THE EUROPEAN PROGRAM FOR ROUTINE TESTING OF PATIENTS WITH ADVANCED LUNG CANCER

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Background: International guidelines recommend the routine use of next-generation sequencing (NGS) as a standard approach to profile advanced lung adenocarcinoma samples, with the aim of identifying targetable driver mutations that allow patients' access to effective targeted drugs either available in daily practice or in clinical trials. However, only a small proportion of these patients currently undergo a complete molecular testing, due to high cost, reimbursement issues and limited access to NGS-platforms in different countries. At the same time, inequalities in access to new drugs and clinical trials in Europe must be addressed and solved.

Methods: The Women Against Lung Cancer in Europe (WALCE) Association promotes the European Program for Routine testing of Patients with Advanced lung cancer (EPROPA) and provides a free molecular screening platform for NSCLC samples characterization with the aim of increasing the detection of common and rare oncogenic drivers and optimizing patients' access to matched biomarker-driven clinical trials. The centers participating in the program share anonymized clinical-pathological data and ship tissue samples to the laboratory of the Reference Center (University of Turin) in order to determine patients' eligibility for personalized therapies or clinical trials. All the patients over 18-years old, with histological/cytological diagnosis of NSCLC; stage IIIB/C-IV (8th TNM Staging System); formalin fixed paraffin embedded (FFPE) tissue sample availability for molecular analysis can benefit from EPROPA.

Results: Since January 2021, 14 cancer centers in 4 European countries (Italy, Greece, Slovenia and Romania) have participated to EPROPA and other countries will be onboard soon (Portugal, Poland, Serbia and Spain). To date overall 50 NSCLC patients have already received a tissue NGS-based molecular analysis as well as molecular tumour board (MTB) reports. For those patients candidated to clinical trials, WALCE provides adequate logistic support during the therapeutic process.

Conclusions: The preliminary results of the program confirms the need to implement NGS-based molecular characterization of NSCLC samples in highly specialized centers with the availability of a dedicated MTB in order to reduce the inequality in access to tests, drugs and clinical trials across Europe.

D09

THE PROGNOSTIC VALUE OF KRAS MUTATIONAL STATUS IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITOR (ICI) MONOTHERAPY

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Background: *KRAS* mutations occur in 20-30% of NSCLC. The prognostic value of *KRAS* mutational status and its subtypes remains unclear. Indeed, in *KRAS*-mutated subtypes high tumor mutational burden (TMB) and programmed

death-ligand 1 (PD-L1) expression have been observed, potentially implying response to ICIs. Aim of this study was to evaluate the prognostic impact of *KRAS* mutations in NSCLC patients (pts) treated with ICI monotherapy.

Material and methods: we retrospectively analyzed a consecutive cohort of 227 advanced NSCLC pts treated with ICI monotherapy at our institution from January 2016 to March 2021. Kaplan-Meier and Cox-regression methods were used to evaluate the prognostic impact of *KRAS* mutational status in terms of progression-free survival (PFS) and overall survival (OS).

Results: the analysis included 169 pts with known *KRAS* mutational status. Overall, 95% of pts had stage IV NSCLC and 83% were former or current smokers. Adenocarcinoma was the most frequent histotype (83%). Of note, 58% of pts had high PD-L1 expression (tumor proportional score =50%) whereas PD-L1 was negative in 25% of cases. *KRAS* mutations were detected in 30% of pts, mainly involving codon 12 (n=44; 25 pts with $KRAS^{G12C}$), codon 3 (n=4) and codon 61 (n=2). ICI monotherapy was prescribed as first-line or after at least two prior treatment lines in 38% and 15% of pts, respectively. *KRAS* mutations were associated with improved survival both in OS (26.94 vs. 12.02 months, HR 0.63, 95% CI 0.42-0.93, p=0.02) and PFS (6.76 vs. 3.84 months, HR 0.68, 95% CI 0.47-0.98, p=0.04). No significant difference in survival outcomes was observed in $KRAS^{G12C}$ vs. $KRAS^{non\text{-}G12C}$ -mutated NSCLC, neither in OS (HR 1.07, 95% CI 0.50-2.30, p=0.85) nor in PFS (HR1.29, 95% CI 0.64-2.62, p=0.47). The multivariate cox-regression analysis confirmed the independent prognostic impact of *KRAS* mutations on OS (HR 0.59, 95% IC 0.37-0.94, p=0.02) while no difference in PFS was observed (HR 1.39, 95% CI 0.93-2.08, p=0.10).

Conclusions: in this retrospective analysis, *KRAS* mutations were associated with improved survival in NSCLC pts treated with ICI monotherapy, with no differences according to mutation subtypes. Our results warrant further investigation in a prospective setting.

D10

PROGNOSTIC ROLE OF DRIVER GENETIC ALTERATIONS DETERMINED IN REAL-LIFE MOLECULAR TESTING ON 1,282 SARDINIAN PATIENTS WITH ADVANCED STAGE LUNG ADENOCARCINOMA

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Background: Lung cancer is one of the most lethal malignancies worldwide, especially when diagnosed in advanced stage. Novel therapeutic approaches, such as immunotherapy and gene targeted therapy, were developed in the last decade for the treatment of advanced stage pulmonary adenocarcinoma. Targeted therapies with tyrosine kinase inhibitors in patients with lung adenocarcinoma harboring epidermal growth factor receptor (EGFR) mutations have been approved for clinical use in 2015; since then, numerous further gene-specific targeted drugs have been developed making routine molecular testing necessary. The aim of this study was to evaluate the impact of driver genetic alterations on global survival in a real – life cohort of Sardinian patients with lung adenocarcinoma submitted to routine molecular testing.

Materials and methods: The demographic, clinical, and survival data of 1,282 consecutive Sardinian patients with lung adenocarcinoma who underwent genetic testing from January 2011 through July 2016 were collected. Genetic alterations in five genes (EGFR, ALK, KRAS, BRAF, and MET) relevant for the clinical management of the patients, were carried out. Molecular tests were based on the clinical needs of each single case (EGFR and ALK), and the availability of tissue (KRAS, BRAF, and MET). Testing was performed with pyrosequencing or fluorescence in situ hybridization, as appropriate.

Results. EGFR, KRAS, and BRAF mutations were detected in 13.7%, 21.3%, and 3% of tested cases, respectively, while ALK rearrangements and MET amplifications were found respectively in 4.7% and 2% of tested cases. The mean follow-up time of the patients was 46 months. Cases with EGFR mutations had a significantly longer survival in comparison to those without ($p<0,0001$), as opposed to KRAS mutations, which were associated with a significantly lower survival (p=0,0058). EGFR mutations provide a significant survival advantage in females and never smokers, as opposed to KRAS mutations which were shown to be negative prognostic factors in females and never smokers. Nevertheless, when corrected for other relevant prognostic factors in Cox regression analysis, only EGFR remain an independent prognostic predictor.

Conclusions. In our study EGFR mutations represented the only independent factor, which impacted significantly on global survival of Sardinian patients with advanced adenocarcinoma, regardless of the treatment received, or the age, sex and smoking status.

D11

DIAGNOSTIC CONCORDANCE BETWEEN PCR-BASED AND NEXT GENERATION SEQUENCING METHODS IN DETECTING EGFR T790M MUTATIONS IN LIQUID BIOPSIES OF PATIENTS WITH ADVANCED STAGE LUNG ADENOCARCINOMA PROGRESSED AFTER TYROSINE KINASE INHIBITOR THERAPY

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Background: Recent approval for clinical use of tyrosine kinase inhibitors (TKIs) in patients with advanced stage lung adenocarcinoma harbouring Epidermal Growth Factor Receptor (*EGFR*) mutations represents one of the most impacting innovations in oncology. *EGFR* T790M mutation is the commonest mechanism of acquired resistance to first- and second-generation anti-EGFR TKIs. Liquid biopsy of circulating tumor DNA is increasingly used to detect T790M mutations and make decisions on treatment strategies. In this study, we prospectively compared three different techniques for *EGFR* T790M detection in liquid biopsies of patients with advanced lung adenocarcinoma.

Methods: Fifty-four liquid biopsy samples from 48 consecutive patients with advanced adenocarcinoma treated with TKIs were tested for T790M and other relevant *EGFR* mutations with the Therascreen® EGFR Plasma RGQ PCR Kit on the Rotorgene Q platform (CE-IVD; Qiagen). Samples were subsequently tested with two different technologies: the real-time PCR based assay Idylla™ ctEGFR Mutation Assay (Biocartis), and a next generation sequencing (NGS) system with the Ion AmpliSeq Cancer Hotspot targeted Panel (Life Technologies), with the aim to compare the T790M detection rates. Differences in T790M detection rates between the techniques under investigation were evaluated by Fisher test or chi-squared test, as appropriate.

Results: The T790M concordance rate between Idylla™ and Therascreen® was 100%, while the NGS method identified only 37.5% of those detected with Therascreen® (Table 1). Concordance rates for other common druggable *EGFR* alterations were high between Idylla™ and Therascreen® (*EGFR* Del Ex19: 85.2%, p=0.562; *EGFR* L858R: 94.4%, p=1.000), and lower between Idylla™ and NGS (*EGFR* Del Ex19: 74.1%, p= 0.244; *EGFR* L858R: 94.4%, p=0.822) (Table 1).

Conclusions: Our results evidenced an equivalent ability in detecting *EGFR* T790M mutations between the PCR-based techniques (Therascreen® and Idylla™) investigated. The NGS assay allowed the detection of a wider range of *EGFR* and additional gene mutations, but showed a significantly poor ability to detect T790M.

Table 1. Therascreen®, Idylla™ and NGS in detecting clinically relevant EGFR genetic alterations.

Mutation	Therascreen	Idylla™	Agreement %	p
T790M	8/54	8/54	100	1.000
Del ex19	27/54	23/54	85.2	0.562
L858R ex 21	17/54	18/54	94.4	1.000
	Therascreen	NGS		
T790M	8/54	3/54	37.5	0.201
Del ex19	27/54	20/54	74.1	0.244
L858R ex 21	17/54	15/54	88.2	0.833

D12

HAS THE PROGNOSIS OF LUNG CARCINOSARCOMAS IMPROVED ALONGSIDE PROGRESS IN THE TREATMENT OF NSCLC? A CLINICAL TWENTY-YEAR' EXPERIENCE IN A HIGH VOLUME INSTITUTION

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Introduction: Primary sarcomatoid carcinoma of the lung is a rare subtype of non-small cell lung cancer, characterized by the presence of a sarcoma-like component. The reported prognosis is poor, as are response to chemo and radiation therapy, but literature is devoid of strong data on this peculiar histotype of lung cancer.

Material and methods: We retrospectively collected data on all patients diagnosed with lung carcinosarcoma who were treated at Humanitas Research Hospital between 2000 and 2020.

Results: From 2000 to 2020, fifty-nine patients with lung carcinosarcoma were treated in our Institution. Considering the whole population, median overall survival (mOS) was 8.6 months. Fourteen patients presented with localized (stage I-II) disease, twelve had locally advanced (stage III) disease, thirty-three patients had metastatic disease at diagnosis. Among patients affected by localized and disease, 93% patients underwent surgery, 21% of which received peri-operative chemotherapy. Eight out of 14

patients (57%) had disease recurrence, with a median disease free survival (mDFS) of 14.4 months and a mOS of 47.5 months. Considering the 12 patients diagnosed with stage III disease, 92% were treated with surgery and 58% received peri-operative chemotherapy. Six out of 12 (50%) patients had disease recurrence, with a mDFS of 7.9 months and a mOS of 10.9 months. Among patients with metastatic disease at diagnosis, 48% were not eligible for systemic treatment because of poor clinical conditions, while, among the 17 patients considered eligible for first-line systemic treatment, 15 (88%) received chemotherapy, one received immunotherapy, another one was treated with chemoimmunotherapy. Disease control rate (DCR) to first line treatment was 53% (9/17), of which 4/17 were partial responses (PR) and 5/17 were stable diseases (SD). Molecular analysis was performed in 9 out of 33 patients in this setting and only two of them presented molecular alterations of the tested genes. In patients affected by metastatic disease, mPFS and mOS were 3.0 and 5.6 months, respectively.

Conclusions: Lung carcinosarcoma is a peculiar clinical entity with unmet needs, still characterized by poor prognosis even when diagnosed in early stages. In the future, a deeper understanding of the biology of the tumor, along with the identification of potential new targets, could lead to a specific clinical approach towards these complex and rare entities.

D13

CLINICAL IMPLICATIONS OF ADIPOSE TISSUE DISTRIBUTION IN ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS (PTS) RECEIVING FIRST-LINE PEMBROLIZUMAB (PEMBRO)

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Background: Body composition (BC)-related phenotypes, including loss of muscle mass and distribution of fat tissue, have been suggested to potentially modulate immunotherapy outcomes in lung cancer pts. In this context, our study aimed to detect BC and its potential correlations with ECOG PS, comorbidities, and survival outcomes in NSCLC pts receiving first-line PEMBRO.

Material (patients) and methods: A retrospective analysis of consecutive advanced NSCLC pts treated with PEMBRO as first-line therapy at two academic medical institutions from August 2017 to August 2020 was performed. The area (cm^2) and density (Hounsfield Units [HU]) of skeletal muscle and adipose tissue (subcutaneous [SAT], visceral [VAT], and intermuscular [IMAT]) were measured on pre-treatment computed tomography scans at the level of the third lumbar vertebra. Data were correlated to progression-free/overall survival (PFS/OS) using a Cox and logistic regression model. Log-Rank analysis was used for Kaplan-Meier curves comparison.

Results: Data from 77 pts were gathered, with a median follow-up of 11 months (range 1-42). Forty (51.9%) pts were former smokers and 27 (35.1%) current smokers. ECOG PS was 0-1 in 56 (72.7%) pts and $\geqslant 2$ in 21 pts (27.3%). Comorbidities were reported in 49 (63.6%) pts. All BC parameters were significantly correlated with the presence of comorbidities and ECOG PS. Median PFS and OS were 3 (95% CI, 2-4) and 10 (95% CI, 8-13) months, respectively. At univariate analysis, high SAT negatively correlated with PFS. Pts with pre-treatment SAT$<$143 had significantly longer 6-month PFS (median 8 vs. 3 months, $p = 0.05$). Although BC parameters were not associated with OS, this was numerically shorter in those pts with higher SAT (median 12 vs. 18 months, $p = 0.11$).

Conclusions: These preliminary results support the hypothesis that BC, in particular SAT, may impact on survival of advanced NSCLC pts treated with PEMBRO, suggesting a potential interaction between the immune system, BC-related parameters and interventions (nutritional and physical activity support). Further analyses are ongoing in this pts' cohort in order to monitor BC changes during treatment, as well as to further explore the biological rationale supporting the emerging close relationship between immune system and BC.

D14

COMBINED DDPCR AND NGS ANALYSIS TO IMPROVE MRD DETECTION IN LUNG ADENOCARCINOMA RESECTED PATIENTS: PRELIMINARY RESULTS OF THE RESIDUAL STUDY

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Background: Blood circulating tumor DNA (ctDNA) is an effective tool to assess minimal residual disease (MRD) and could be used as a potential biomarker to predict the risk of recurrence in resected NSCLC patients (pts). The aim of this study was to detect MRD in post-operative plasma samples *via* a liquid biopsy NGS-based approach and correlate it with the post-operative outcome.
Material (patients) and methods: In this monocentric study, paired surgical tissue and plasma samples were collected from radically resected IB-III lung adenocarcinoma (ADK) pts. Blood withdraw were performed 7 days prior and periodically after resection. Surgical tissue and post-operative plasma samples (collected within 10 days) were analyzed with a tissue and liquid biopsy NGS-panel, respectively. Digital droplet PCR (ddPCR) assay was further employed to confirm NGS results, using available probes.
Results: A total of 47 pts were enrolled in the RESIDUAL study with median age 71 years (range 48-85), 29 (62%) were males. Nine pts met the inclusion criteria and were hence analyzed, while 38 were excluded [screening failure reasons were: stage IA (26.3%), sub-lobar lobectomy (18.4%), not ADK histology (26.3%) and other (29%)]. The stages were IB (5 pts), IIB (2 pts) and IIIA (2 pts). At the moment of this preliminary analysis 3 pts experienced a recurrence of disease.
In all surgical tissue samples, we found at least 1 pathogenic variant with KRAS (44%), TP53 (33%) and EGFR (22%) as the most frequently mutated genes, but no MRD (defined as the persistent presence of the pathogenic variant after resection) was found in the post-operative plasma samples. A ddPCR assay was set up for a more sensitive analysis in pts with EGFR or KRAS mutations (3/9). Of these, 1 patient plasma monitoring showed 0.05% of L858R allelic frequency (AF) in the pre-operative and 0.02% in post-operative sample, followed by negative samples up to 9 months after resection, at which time the AF started to rise again. The L858R AF was 65.2% at the time of relapse (13.9 months after surgery).
Conclusions: Although ctDNA is a powerful approach to detect MRD in NSCLC, early stages of the disease often consist of low levels of ctDNA that inevitably lead to the generation of false negative. In this preliminary analysis, the combinatory use of NGS platform and the ddPCR monitoring provided more reliable results to both identify pts with high risk of recurrence and pts who may benefit from an adjuvant treatment.

D15

IMPACT OF EARLY USE OF ANTIBIOTICS AND STEROIDS ON OUTCOME OF NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH CHEMO-IMMUNOTHERAPY

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Background: The alteration of gut microbiota induced by the early use of antibiotics may impair response to immunotherapy (IO) in non-small cell lung cancer (NSCLC). Moreover, the concomitant use of steroids during IO was associated with worse clinical outcomes. Recently, chemo-immunotherapy (CT-IO) has been approved as first line treatment in a large subset of metastatic NSCLC patients (pts). We investigated the impact of early use of antibiotics (ATB) and corticosteroids (CS) in mNSCLC pts treated with CT-IO.
Material and methods: Data from all consecutive pts treated with CT-IO at our Istitution between Sept 2016 and Mar 2021 were retrospectively collected. Use of ATB was considered significant when occurring between 30 days before and 3 months after the start of CT-IO. We defined the use of CS as administration of daily prednisone-equivalent dose $\geqslant$10 mg in the 30 days before the start of CT-IO. Survival was estimated by using the Kaplan-Meier method and log-rank test was used to compare the curves.
Results: Our population included 68 pts receiving CT-IO as first line treatment. 54 cases (79%) were adenocarcinoma, 11 (16%) NSCLC-not otherwise specified (NOS) and 3 (4%) squamous cell carcinoma. PD-L1 expression level was $>$50%, 1-49% and $<$1%/unknown in 4%, 45% and 41% respectively. 18 pts (26%) received ATB, generally for pulmonary infections, mostly fluoroquinolonics or penicillin derivative (19% had more than one antibiotic class). Median time of ATB treatment was 15 days. A subset of pts (19%) received CS for a median treatment time of 124,5 days. The median progression free survival (PFS) was 10.6 months (95% CI 7.3-NR), and the median overall survival (OS) was 10.9 months (95% CI 5.5-13.5). Based on ATB and CS use, no differences in OS (p=0.27 and p=0.67) and PFS were observed (p=0.80 and p=0.23, respectively). Also, the duration of the ATB treatment in relation with the duration of CT-IO did not affect the outcome.
Conclusions: To our knowledge, this is the first analysis investigating the effect of use of ATB and CS on outcome of pts treated with CT-IO. Subject to the limitations of this retrospective analysis and of the small series of pts, our data suggest that ATB or CS may not hamper response to CT-IO in mNSCLC patients. The combination of CT and IO, by acting on multiple variables and by modulating the activity of the immune system, may alter the detrimental outcome generally observed in pts receiving ATB or CS concomitant with IO alone.

D16

INFLUENCE OF PRIOR ANTIBIOTIC TREATMENT ON EFFECTIVENESS OF NIVOLUMAB THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Immune checkpoint inhibitors (ICIs), have revolutionized the treatment of lung cancer and it is of great interest to examine the factors potentially influencing the ICIs response.
Gut microbiota would play a role in shaping systemic immune responses: bacterial products can modulate systemic inflammation and antitumor immunity. Recent studies showed that use of antibiotics (AB), changing gut microbiota, may negatively influenced the efficacy of ICIs. The aim of our study was to examine the influence of prior AB treatment on effectiveness of Nivolumab therapy for NSCLC.
Patients and methods: We have retrospectively analyzed the influence of AB treatment and the effectiveness of immunotherapy in terms of progression free survival (PFS) and overall survival (OS) in 75 patients (pts) (48 men and 27 women) with advanced NSCLC treated with Nivolumab since April 2017 to April 2020. Mean age was 68 years (48-84). PFS is defined as the time from entry into the study to the first objective evidence of PD or death for any cause. OS is defined as the time from entering the study to the death of the patient or loss during follow-up. We defined pts treated with AB those who were subjected to AB therapy for 3 days within 30 days of Nivolumab therapy, regardless of the spectrums or the dosages of the AB, the administration routes or the purpose of AB use
Results: The median PFS achieved in the global population was 3.1 months (95% Confidence Interval (CI): 2.7-3.3), the OS 10.8 months (95% CI:10.2-11.8).
During the 30 days prior to Nivolumab therapy, 36/75 pts (48%) were treated with AB.
The median PFS time of pts treated with AB was 2.8 months and the median PFS time of pts not treated with AB was 3.5 months. (p value 0.47)
The median OS of patients treated and those not treated with AB was 6.5 months and 14.4 months respectively (p value 0.001).
Conclusions: Our results suggest that prior use of AB may negatively influence the survival of pts treated with Nivolumab for NSCLC. Future randomized studies with more pts are needed to investigate changes in the gut microbiome or types of microbiome that can predict responses to ICIS.

D17

THE ROLE OF NEUTROPHIL-TO-LYMPHOCYTE AND MONOCYTE-TO-LYMPHOCYTE RATIOS IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH CHEMO-IMMUNOTHERAPY

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Background: Chemo-immunotherapy has improved survival of patients with advanced Non-Small Cell Lung Cancer (aNSCLC). Different clinical variables and peripheral blood parameters have emerged as biomarkers in aNSCLC, but their role in aNSCLC patients receiving chemo-immunotherapy is still unexplored.
Material and methods: This was a monocentric retrospective study. We collected data of patients with aNSCLC treated with chemo-immunotherapy at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan between April 2019 and April 2021, to evaluate the impact of age (<=65 vs >65), ECOG performance status (PS) (0-1 vs 2), number of metastatic sites (1-3 vs >3), BMI (<=25 vs >25), neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) values on progression free survival (PFS) and overall survival (OS). The impact of these variables on PFS and OS was evaluated through Cox proportional hazard models.
Results: 73 NSCLC patients were included: 61 (84%) had adenocarcinoma, 7 (9%) had NSCLC-not otherwise specified (NOS), 5 (7%) had squamous cell carcinoma. Median follow up was 9.1 months. An association between higher NLR or MLR and lower PFS was found both at univariate and multivariable analysis (aHR 6.78, 95%CI 2.05-22.41, p= 0.002 and aHR 5.98, 95%CI 2.07-17.29, p<0.0001, respectively), while no other variable was associated with worse PFS. Moreover, an independent association between worse PS (aHR 4.73, 95%CI 1.50-14.93, p=0.008), higher number of metastatic sites (aHR 4.30, 95%CI 1.34-13.85, p=0.015), higher MLR (aHR 4.20, 95%CI 1.18-14.90, p=0.027) and worse OS was found, with a trend towards worse OS for higher NLR (aHR 2.90, 95%CI 0.72-11.68, p=0.135).
Conclusions: We found an association between higher NLR or MLR values and worse prognosis in patients with aNSCLC treated with chemo-immunotherapy. However, further prospective studies are warranted to validate these easy-to-measure biomarkers in patients with aNSCLC treated with chemo-immunotherapy.

D18

THE EXPRESSION OF THE KRAS MRNA ISOFORMS 4A AND 4B IN PLASMA: A COMPARISON BETWEEN LUNG ADENOCARCINOMA PATIENTS AND HEALTHY DONORS THROUGH LIQUID BIOPSY

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Background: Liquid biopsy represents an innovative tool in precision oncology to overcome current limitations associated with tissue biopsies. Circulating DNA, but also mRNA could be a useful source of cancer biomarkers.
The *KRAS* gene encodes two splice variants, 4A and 4B. Studies established that the two isoforms are both expressed, the ratio can be altered in tumors, and mutationally activated 4A and 4B both mediate lung carcinogenesis[1]. No data are available about their expression in plasma. We have recently started to collect plasma for a prospective analysis in metastatic lung adenocarcinoma (LA) patients (pts) that are candidate for immunotherapy and chemotherapy. We also started collecting plasma from healthy donors (HD). Herewith we present very preliminary results of a comparison of the *KRAS* mRNA isoforms (4A and 4B) expression levels between LA pts and HD.
Materials and methods: The *KRAS* isoforms mRNA (4A and 4B) expression levels in plasma were analyzed in 16 LA pts and 5 HD. The plasma from pts was collected at the beginning of the treatment and used to extract the RNA. The RNA was then transcribed in cDNA and 7ng were used to perform the quantitative real-time PCR (RT-qPCR) to detect the *KRAS* isoforms expression. The RT-qPCR Ct values (the higher value corresponds to a lower mRNA expression level) were converted in Cy0 by a tool for accurate and precise quantification of template and used to compare mRNA expression levels between pts and HD[2]. Data were analyzed with the Mann-Whitney test.
Results: The RNA concentration in LA pts and HD was significantly different (p=0.0318): the median concentration value in plasma was 32.3 ng/ml versus 23.5 ng/ml, respectively.
A significant difference was also found for the median values of the *KRAS* isoforms mRNA expression levels between LA pts and HD: Cy0=31.7 versus Cy0=34.6 (p=0.0034), respectively, for *KRAS* 4A; Cy0=31.5 versus Cy0=34.5 (p=0.0013), respectively, for *KRAS* 4B.
Conclusions: Although in a small size group, these data are very promising. They show a higher concentration of circulating RNA and a higher expression of both the *KRAS* isoforms in LA pts compared to HD. Patients enrollment is ongoing, and if the data here reported will be still confirmed, circulating *KRAS* mRNA could be a promising biomarker.

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D19

IMPACT OF NUTRITIONAL COUNSELLING ON THE QUALITY OF LIFE (QOL) OF ONCOGENE ADDICTED ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC) PATIENTS

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Background: Malnutrition is associated with poorer response to therapy and influences negatively QoL in advanced lung cancer patients (pts), including oncogene addicted subgroup. Nutritional counselling is a valid instrument to prevent malnutrition onset. In our study, we aimed to investigate the impact of nutritional counselling in oncogene addicted aNSCLC pts' QoL treated with tyrosine kinase inhibitors (TKIs). Here we present our preliminary data.
Material (patients) and methods: In oncogene addicted aNSCLC pts (EGFR mutated or *other*), nutritional counselling including evaluation of QoL was performed before starting TKIs therapy (T0). The Edmonton Symptom Assessment System (ESAS), a numeric rating scale (0-10) of 9 symptoms (pain, fatigue, nausea, depression, anxious, drowsiness, lack of appetite, illness, dyspnoea) and an optional 10th symptom (costipation or diarrhoea, mostly) was used. Enrolled patients underwent 3- (T3) and 6-months (T6) follow-up visits. The change in QoL was defined as the difference of the mean score for each symptom in T0 and T3 and in T3 and T6, the correlations were defined using *T- student test*.
Results: 49 pts were consecutively enrolled with median age (range) 67 *y* (35-84); male/ female 12/37; molecular alterations in EGFR/ *other* 32/17. At T3, a significant improvement in the perception of fatigue (+0.6904;

p=0.04); illness (+0.5952; p=0.03) and optional 10th symptom (+1.3095; p=0.03) was described. The positive effect on these symptoms was confirmed at T6 (p=0.05). Firstly, nutritional counselling did not affect the control of anxious and pain in T3 but improved these symptoms later in T6 (+0.5769; p=0.05 and +0.0.7692; p=0.01 respectively). A slightly detrimental role in the control of dyspnoea and drowsiness was disclosed in T3 and T6 (p>0.05). At this initial evaluation, the correlation between depression, lack of appetite and nutritional counselling remains unclear.

Conclusions: Our preliminary data suggests a possible positive role of the nutritional counselling in improving ESAS QoL and supports its use as a part of multimodality strategy in oncogene addicted aNSCLC pts.

D20

CORRELATION BETWEEN BODY MASS INDEX (BMI) AND IMMUNOTHERAPY EFFECTIVENESS IN NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH IMMUNE CHECKPOINT INHIBITORS (ICIS)

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Background: Obesity (OB) is estimated to be responsible for 20% of cancer cases and to be the second risk factor after smoking. BMI is a non-invasive surrogate for the measurement of body fat.

In OB a state of chronic inflammation occurs with an increase in anergic T cells due to the iperexpression of PD1 by the action of Leptin.

PD1 Iperexpression is related to an increase of the interaction PD1-PDL1 with impairment of the immune response: treatment with ICIs by inhibiting this interaction would allow CD8+ T cells to be more effective in killing cancer cells.

The aim of our study was to correlate BMI with treatment effectiveness, in NSCLC treated with ICIs.

Patients and methods: We have retrospectively analyzed the correlation between BMI with response rate (RR), progression free survival (PFS) and overall survival (OS) in 75 patients (pts), with metastatic NSCLC treated with Nivolumab after failure of first line chemotherapy since April 2017 to April 2020.

The BMI was calculated by dividing the weight expressed in kilograms by the square of the height, expressed in meters.

Pts were divided into two groups based on BMI (low <25 or high >25)

RR: complete response (RC), partial response (RP), stable disease (SD), progression disease (PD), disease control rate (DCR) (RC+RP+SD), overall response rate (ORR) (RP+RC).

PFS is defined as the time from entry into the study to the first objective evidence of PD or death for any cause.

OS is defined as the time from entering the study to the death of the patient or loss during follow-up

Results: 44/75 pts (58.6%) had low BMI while 33/75 (41.33%) had high BMI.

We did not find statistically significant differences in RR between low and high BMI.

(ORR 18.2% Vs 19.4% p 0.90; DCR 47.7% Vs 51.6% p 0.74)) while in PFS and OS appear to be significantly better in patients with higher BMI (PFS 3.6 months Vs 2.6 months p 0.036; OS: 12.1 months Vs 9.1 months p 0.02)

Conclusions: Our results suggest that pts with high BMI obtain more benefits from ICIs vs control compared with low BMI.

D21

IMPACT OF SARCOPENIA IN PATIENTS TREATED WITH CHEMO-IMMUNOTHERAPY FOR ADVANCED NSCLC

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Background: Sarcopenia, defined like wasting skeletal muscle mass, has been correlated to adverse outcome in lung cancer patients (pts). The aim of this work was to evaluate the impact of sarcopenia in metastatic NSCLC (mNSCLC) treated with chemotherapy+immunotherapy (CT+IT), the new standard of care in this setting.

Methods: We retrospectively collected clinical and radiological data of pts with non-squamous mNSCLC, treated with CT+IT at our Institution from January 2020 to May 2021. Sarcopenia was assessed using anthropometric parameters calculated on Computed Tomography (CT) images at the baseline. Total skeletal muscle area (SMA cm2) at D12 was considered for the analysis; sarcopenia was defined as SMA <92.3cm2 in male and <56.1cm2 in female pts (according to Martin criteria).

Results: Overall cohort included 26 pts, median age was 69.5 (51-81), 61.5% were males and 92.3% smokers. PD-L1 TPS was: <50% in 22 cases and >50% in 4. Median follow up time was 10.2 (mo). At data cut-off 10pts (38.5%) were still on treatment, 6 (60.0%) of these beyond progression disease (PD). Median overall survival (mOS) was 13,1months (mo) (CI 95%; 10,03 to 13,1); the median progression free survival (mPFS) was 9,3mo (CI 95%; 5.0 to 10.4); the median time to treatment failure (mTTF) was 11,8mo (CI 95%; 10,0 to 15,0). At diagnosis, according to Body Mass Index (BMI) 14 pts (53.8%) had normal weight and 12 (46.2%) were overweight; according to SMA analysis 8pts (30.8%) resulted sarcopenic

(SP), among these 5pts had normal BMI, 3pts were overweight. At univariate analysis a significant correlation between baseline SMA and OS was observed (p= 0,03). Kaplan-Meyer curve about TTF showed a better trend for pts did not presented sarcopenia (noSP) at diagnosis: the mTTF for noSP pts versus SP pts were 15mo and 10,45mo respectively, an important difference although not significant (p=0,12).

Conclusions: The statistically significant correlation between SMA and OS confirm the negative impact of sarcopenia in this setting. Moreover, the study underlines the limits of BMI like surrogate of sarcopenia, on the contrary this condition may be simply assessed using CT. Detection of body composition and identification of sarcopenia may be a predictive factor of response to CT+IT in mNSCLC.

D22

EVALUATION OF TUMOR MUTATIONAL BURDEN (TMB) ASSESSMENT ON ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) CYTOLOGICAL SAMPLES

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Background: Currently, the administration of immune-checkpoint inhibitors (ICIs) represents a valid option in non-oncogene addicted advanced non-small cell lung cancer (NSCLC) patients. Beyond the evaluation of the expression level of programmed death-ligand 1, other promising predictive biomarkers, including high tumor mutational burden (TMB-H), have been under investigation. However, no relevant evidence has been emerigng on the adoption of scant specimens, such as cell blocks (CBs), to evaluate TMB. We aimed to evaluate the feasibility of analyzing TMB on CBs in advanced stage NSCLC patients by comparing results with those obtained on corresponding histological specimens.

Material and methods: Run parametrics and detected number of non-synonymous mutations per megabases (Mbs) from eight pairs of histological and CB samples from advanced NSCLC patients were analyzed and compared by adopting the Oncomine Tumor Mutational Load Assay on Ion Torrent S5 GS next-generation sequencing (NGS) platform.

Results: Overall, molecular analysis, carried out by adopting the broad NGS panel approach, was successfully performed on almost all CBs (6/8, 75.0%). Interestingly, no relevant differences were observed between histological and CB samples considering median total reads (7207048.80 vs 7558817.80), median mapped reads (7075753.83 vs 7513822.00), median read lengths (115.50 vs. 113.00), the median percentage of reads on-target (97.49% vs. 98.45%), median average reads per amplicon (454.67 vs 476.14), and the median uniformity of amplicon coverage (83.52% vs 84.13%). Overall, the median number of non – synonymous mutations/Mbs was 28.52 and 26.2 for histological and CB samples, respectively.

Conclusions: In this pilot study, we highlighted the technical feasibility of assessing TMB on CB specimens by adopting a targeted NGS panel on matched paired histological and cytological samples.

D23

SURVIVAL AND PROGNOSTIC FACTORS FOR EXTENSIVE-STAGE SMALL CELL LUNG CANCER: A COMPREHENSIVE ANALYSIS OF 249 PATIENTS

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Background: Small Cell Lung Cancer (SCLC) accounts for approximately 15% to 17% of all diagnosed lung cancers. Most patients with SCLC have an extensive stage disease at the presentation, resulting in a poor prognosis. Standard care first-line treatment is double-platinum chemotherapy combined with etoposide. Despite a high response rate to this therapy, the overall survival (OS) is only about 10 months. Recently, the addition of immunotherapy to platinum based chemotherapy has improved the OS of these patients, although only about 2 months. Herein, we report our centre experience over the last decade.

Methods: A total of 249 patients from 2010 to 2020 with SCLC have been enrolled and divided in two groups: 71 SCLC patients from 2010 to 2015 (group A), 178 SCLC patients from 2015 to 2020 (group B). The Kaplan-Meier test has been performed for progression free survival (PFS) and OS. The prognostic factors have been examined by Mann-Whitney, Wilcoxon, and Kruskal-Wallis tests.

Results: The median PFS following first line chemotherapy is 9 months for group A and 7 months for group B without statistical significance. The OS is 18 months for group A and 10 months for group B (p=0.001). No differences in the use of cisplatin and carboplatin or age have been found between the two groups. Conversely, significant differences concern the presence of comorbidities (53,5% group A vs 72, 5% group B, p=0.004), liver metastasis (22,5% group A vs 34,8% group B, p=0.039), performance status (14,1% of patients with ECOG2 in the group A vs 27% in the group B) and mediastinal radiotherapy (51,1 % group A vs 41,4% group B, P<0.001).
Conclusions: Our analysis shows a better outcome for SCLC patients from 2010 to 2015 than SCLC patients from 2015 to 2020. This difference could be explained, at least in part, by the extension of active cancer treatments to more frail patients during the last decade. In agreement with this, a higher percentage of patients with comorbidities, ECOG 2, and liver metastasis have been described in group B. Moreover, a higher number of group A patients received mediastinal radiotherapy, suggesting a more disease extension in the group B. Nevertheless, the OS of the group A exceeds the value reported in literature, differently from the group B. At the same time, the possible occurrence of new resistance factors to chemotherapy cannot be excluded. As a consequence, appropriate translational studies are needed.

D24

A RETROSPECTIVE MULTICENTRE ANALYSIS OF RENAL EFFECT OF ALECTINIB IN ALK REARRANGED NON-SMALL CELL LUNG CANCER

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Background: Significative reduction of creatinine-based estimated glomerular filtration rate (eGFR) during crizotinib has been reported in several study. The reversibility after discontinuation, the scarce cumulative effect and the discrepancy between different methods of renal function estimation suggest a direct effect of crizotinib on creatinine tubular secretion. In clinical trials serum creatinine increased in 7.2% of patients with alectinib. We hypothesized a class effect of ALK inhibitors (ALK-I) on creatinine secretion.
Methods: We collected retrospectively data from 39 patients (pts) with ALK rearranged NSCLC treated with alectinib in three institutions from December 2013 to April 2021. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-based eGFR was assessed at baseline, 15 days, 30 days and 3, 6, 12 months after starting alectinib.
Results: Normal renal function (eGFR >90 mL/min/1.73 m2) was observed in 23 pts (59%) at baseline, while 36 pts (92%) had an eGFR grade <3a (eGFR>45).
Median serum creatinine increased from 0.85 mg/dL (baseline) to 0.95 and 0.98 mg/dL at days 15 and 30, and remained substantially stable in subsequent measurements (0.99, 1.00 and 0.99 at 3, 6 and 12 months respectively). 10 pts (26%) had an increase > 0.2 mg/dL of serum creatinine at day 30 compared to baseline.
Median eGFR decreased from 86.6 mL/min/1.73 m2(baseline) to 79.2 and 78.3 at days 15 and 30, and remained relatively stable at 3, 6 and 12 months (77.7, 75.7 and 76.8 mL/min/1.73 m2). 8 pts (21%) had a reduction > 20 mL/min/1.73 m2 in eGFR at day 30 compared to baseline.
During alectinib, worsening in chronic kidney disease (CKD) stage was found in 18 pts (46%) and 4 pts (10%) shifted in stage 3b-5 CKD at days 30 without significant cumulative effect at 12 months. Dose modifications for renal impairment were required in 3 pts (8%). No significant correlations were found between eGFR worsening and comorbidity, drugs, previous chemotherapy or crizotinib.
Conclusions: We reported a non-negligible incidence of renal impairment during alectinib; stabilization of renal function over time without cumulative effect support the hypothesis that the eGFR reduction may be related to a possible effect on tubular creatinine secretion rather than to a real nephrotoxicity. Renal function impairment may lead to treatment discontinuation or dose modification, thus in patients treated with ALK-I alternative methods for assessing renal function should be considered.

D25

CORRELATION BETWEEN IMMUNE-RELATED ADVERSE EVENTS (IRAES) AND EFFECTIVENESS OF NIVOLUMAB THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Immune checkpoint inhibitors (ICIs), have revolutionized the treatment of lung cancer: it is of great interest to examine the factors potentially influencing the ICIs response.
Treatment with ICIs, although generally better tolerated than conventional chemotherapy, presents as peculiar profile of toxicity due to their mechanism of action, the appearance of irAes that may potentially affect any organ or apparatus.

A clear knowledge of irAes is important for proper management and use in clinical practice.
The aim of our study was to analyzed correlation between irAEs and the effectiveness of immunotherapy.
Material and methods: We have retrospectively analyzed safety and tolerability of Nivolumab in 75 patients (pts) (48 men and 27 women) with advanced NSCLC since April 2017 to April 2020. Mean age was 68 years (48-84). IrAEs were analyzed and stratified in grades from G1 to G5.
We analyzed correlation between irAEs and the effectiveness of immunotherapy in terms of progression free survival (PFS) and overall survival (OS)
Results: Of 75 pts analyzed, 14/75 (18.66%) had not developed any irAes compared to 61 patients (81.33%).
The irAEs reported had a G1-G2.
irAes were respectively: Diarrhea/Colitis: 17 pts(22.6%); Endocrine toxicities:23 pts (30.66%); Pneumonitis: 12pts (16%); Hepatic toxicities: 15pts(20%); Hematological toxicity:14pts(18.6%); Dermatologic toxicities: 33pts(44%) Myalgia: 16pts (21.3%)
The median PFS achieved in the global population was 3.1 months (95% Confidence Interval (CI): 2.7-3.3), the OS 10.8 months (95% CI:10.2-11.8).
The median PFS time of pts who had not developed any irAEs was 2.1 months and the median PFS time of pts who had developed irAes was 6.3 months. (p value 0.004)
The median OS of patients without any irAes and those with IrAEs was 8.9 months and 14.2months respectively (p value 0.05)
Conclusions: Our results suggest that there is a correlation between the development of irAEs and the effectiveness of treatment with Nivolumab in terms of PFS and OS

D26

CORRELATION BETWEEN TOBACCO SMOKING AND IMMUNOTHERAPY EFFECTIVENESS IN NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH NIVOLUMAB

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Background: After breast and colon rectal, lung cancer is the third most common cancer in Italy.
Tobacco smoking is undoubtedly the most important risk factor: 85-90% lung cancers is attributable to smoking. The relative risk of smokers compared to non-smokers increases about 14 times, and increases further up to 20 times in heavy smokers (over 20 cigarettes per day).
Immunotherapy has revolutionized the treatment of lung cancer: studies have indicated that there is a better overall response rate among smokers than non smokers treated with immunotherapies.
This is due to a higher programmed death ligand 1 (PD-L1) tumour proportion score (TPS) among smokers.
The aim of our study was to correlate tobacco smoking with (response to Nivolumab therapy in NSCLC patient.) treatment effectiveness, in NSCLC treated with Nivolumab.
Patients and methods: We have retrospectively analyzed the correlation between tobacco smoking with response rate (RR), progression free survival (PFS) and overall survival (OS) in 75 patients (pts), with metastatic NSCLC treated with Nivolumab after failure of first line chemotherapy since April 2017 to April 2020
Pts were divided into groups based on tobacco smoking: smokers (S) and non smokers (NS): 54 pts were S (72%) and 21 NS (28%).
RR: complete response (RC), partial response (RP), stable disease (SD), progression disease (PD), disease control rate (DCR) (RC+RP+SD), overall response rate (ORR) (RP+RC).
PFS is defined as the time from entry into the study to the first objective evidence of PD or death for any cause.
OS is defined as the time from entering the study to the death of the patient or loss during follow-up
Results: We found a statistically significant difference in favor of smokers in DCR: 31 (57.4%) Vs 6 (28.6%) (p 0.02) and PFS: 4.1 months Vs 2.1 months (p 0.04) but substantially overlapping in terms of OS: 11.9 months Vs 10.1 months (p 0.4)
Conclusions: Our results suggest that in NSCLC treated with Nivolumab after failure of a previous chemotherapy there is a better overall response rate among S pts than NS while OS is not statistically different.

D27

CORRELATION BETWEEN PROGRAMMED DEATH LIGAND 1 (PD-L1) EXPRESSION AND IMMUNOTHERAPY EFFECTIVENESS IN NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH IMMUNE CHECKPOINT INHIBITORS (ICIS)

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Background: Immune checkpoint inhibitors (ICIs), have revolutionized treatment of lung cancer and it is of great interest to examine factors influencing the ICIs response.
PD1 is a glycoprotein expressed in different cell types: cell T, cell B NK, monocytes; pro-inflammatory cytokines

such as INF IL4 TNF can induce expression of PD1 which binds to PDL1 (B7-H1) PDL2 (B/-DC) which are expressed on dendritic cells,antigen presenting cells, endothelial cells.
At the moment the determination of expression of the PDL1 remains the only approved biomarkers to guide the choice of treatment with ICIs in clinical practice: it allows selection of the patient by predicting response to treatment.
The aim of our study was to correlate PD-L1 expression with treatment effectiveness, in NSCLC treated with ICIs.
Patients and methods: We have retrospectively analyzed the correlation between PD-L1 expression with response rate (RR), progression free survival (PFS) and overall survival (OS) in 75 patients (pts), with metastatic NSCLC treated with Nivolumab after failure of first line chemotherapy since April 2017 to April 2020.
The evaluation of the PD-L1 membrane expression was conducted on bioptic material using immunohistochemical staining with Ventana platform with SP263 Ventana clone (CE IVD).
Pts were divided into groups based on PD-L1 membrane expression (low $<1\%$ or high $>1\%$).
RR: complete response (RC), partial response (RP), stable disease (SD), progression disease (PD), disease control rate (DCR) (RC+RP+SD), overall response rate (ORR) (RP+RC).
PFS is defined as the time from entry into the study to the first objective evidence of PD or death for any cause.
OS is defined as the time from entering the study to the death of the patient or loss during follow-up
Results: 36/75 pts (48%) had PD-L1$<1\%$. 39/75 pts (52%) had PD-L1$>1\%$.
We did not find statistically significant differences in RR, PFS and OS between low and high PD-L1 expression.
(ORR:12%VS23% p0.11; DCR:44.5% VS 55.5% p 0.09; PFS: 2.7 months VS 3.8 months. P:0.81; OS: 9.6 months VS 12.9 p 0.08)
Conclusions: Our results suggest that there is no correlation between benefit of immunotherapy treatment and expression of PD-L1 in NSCLC treated with Nivolumab.

D28

SAFETY AND EFFICACY OF DIRECT ORAL ANTICOAGULANTS (DOAC) IN NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS (ICI): A SINGLE-CENTRE EXPERIENCE

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Background: DOAC are increasingly used for venous thromboembolism (VTE) treatment/prophylaxis and non-valvular atrial fibrillation (NVAF) stroke prevention in patients with solid tumors. NSCLC patients are at increased risk of VTE, especially when treated with chemotherapy. However, recent data suggest a possible pro-thrombotic role of ICI too. DOACs use in NSCLC patients treated with single-agent ICI has never been described.
Methods: We retrospectively reviewed clinical data of advanced NSCLC concomitantly treated with ICIs and DOACs from April 2017 to February 2021 in our Institution. DOACs safety was the primary end-point, while efficacy was a secondary end-point.
Results: We identified 10 patients, all affected by unresectable NSCLC and treated with single-agent anti programmed death 1 (PD-1) or its ligand 1(PD-L1) monoclonal antibodies (80%: 2nd line). All patients were at intermediate Khorana Score risk. Median overall survival (mOS) from ICI start was 23 months and overall response rate (ORR) was 50%. 6 patients experienced VTEs during ICI (4 during 1st line), thus starting edoxaban 60 mg daily dose.
Notably, one of them was already receiving full-dose fondaparinux. 4 patients received edoxaban 60 mg daily dose as secondary prophylaxis of pulmonary embolism (n:3) or as NVAF stroke prevention (n:1). Median duration of DOAC was 17 months. No major or minor bleeding occurred during DOAC and ICI. No VTEs occurred during DOAC treatment and no delays or changes in planned cancer treatment occurred.
Conclusions: Our small cohort suggests that DOACs could be safely use in NSCLC patients treated with ICIs. This population may be at high risk of developing VTEs. Further studies in this specific setting are warranted.

E – Covid-19

E01*

PREVALENCE AND IMPACT OF COVID-19 SEQUELAE ON TREATMENT PATHWAYS AND SURVIVAL OF CANCER PATIENTS WHO RECOVERED FROM SARS-COV-2 INFECTION

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Background: The long-term impact of COVID-19 in cancer patients (pts) is undefined.
Methods: Among 2795 consecutive pts with COVID-19 and cancer registered to OnCovid between 01/2020 and 02/2021, we examined clinical outcomes of pts reassessed post COVID-19 recovery.
Results: Among 1557 COVID-19 survivors, 234 (15%) reported sequelae including respiratory symptoms (49.6%), fatigue (41%) and cognitive/psychological dysfunction (4.3%).
Persisting COVID-19 sequelae were more likely found in males (p=0.0407) aged ⩾65 years (p=0.0489) with ⩾2 comorbidities (p=0.0006) and positive smoking history (p=0.0004). Sequelae were associated with history of prior hospitalisation (p<0.0001), complicated disease (p<0.0001) and COVID-19 therapy (p=0.0002).
With a median post-COVID-19 follow up of 128 days (95%CI 113-148), multivariable analysis of survival revealed COVID-19 sequelae to be associated with an increased risk of death (HR 1.76, 95%CI 1.16-2.66) after adjusting for sex, age, comorbidities, tumour characteristics, anticancer therapy and COVID-19 severity. Out of 473 patients who were on systemic anticancer therapy (SACT) at COVID-19 diagnosis; 62 (13.1%) permanently discontinued therapy and 75 (15.8%) received SACT adjustments, respectively. Discontinuations were due to worsening performance status (45.1%), disease progression (16.1%) and residual organ dysfunction (6.3%). SACT adjustments were pursued to avoid hospital attendance (40%), prevent immunosuppression (57.3%) or adverse events (20.3%). Multivariable analyses showed permanent discontinuation to be associated with an increased risk of death (HR 4.2, 95%CI: 1.62-10.7), whereas SACT adjustments did not adversely affect survival.
Conclusions: Sequelae post-COVID-19 affect up to 15% of patients with cancer and adversely influence survival and oncological outcomes after recovery. SACT adjustments can be safely pursued to preserve oncological outcomes in patients who remain eligible to treatment.

E02*

THE IMMUNOGENITY, EFFICACY AND SAFETY OF BNT162B2 ANTI-SARS-COV-2 VACCINE IN CANCER PATIENTS TREATED WITH PD-1/PD-L1 INHIBITORS: AN OBSERVATIONAL AMBISPECTIVE MULTICENTER STUDY

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Background and Aim: Cancer patients are underrepresented in ongoing phase 3 clinical trials of COVID-19 vaccines. The aim of this study is to evaluate the magnitude of the T- and B-cell response in these patients treated with Immune Checkpoint Inhibitors (ICIs) and receiving the BNT162b2 vaccine. A group of vaccinated healthy subjects has been used as a validation control
Methods: Consecutive cancer patients in ICIs were enrolled from the beginning of the vaccination campaign for frail patients. Samples were collected before vaccination (T0), at time of the 2nd dose (T1) and 21days after complete vaccination schedule (T2). Sera were tested for S1/S2 IgG (cut off 15 AU/mL) and SARS-CoV-2 neutralizing antibodies (NT Abs; cut off 1:10), while peripheral blood mononuclear cells (PBMC) were isolated and used for Spike specific ELISpot assay (cut off 10 net spots/million PBMC)
Results: Preliminary results on 65 patients (18 females and 47 males;median age 67) were obtained. At T0,8/65 (12.3%) were positive for S1/S2 IgG since they had experienced COVID-19 disease (median 61 IQR 27.5-133.5 AU/mL). All subjects developed a sustained humoral response at T1 in terms of both S1/S2 IgG (median 2735 IQR 2220-3768 AU/mL) and SARS-CoV-2 NT Abs. 35/57 patients (61.4%) were still seronegative at T1 since they showed a S1/S2 IgG level lower than 15 AU/mL. The level of humoral response at T1 was significantly reduced compared to the level observed in healthy subjects (p=0.0187). Spike-specific T-cell response was analyzed in 26 subjects at T0 (median 5 IQR 0-16.5 net spots/million PBMC). Response increased significantly from T1 to T2 (median 22.5 IQR 5-95 and 180 IQR 92.5-380 net spots/million PBMC). The most common side-effects were pain at the injection site (6%, 4/65) and fever (5%, 3/65). One patient presented 2 immune-related side-effects (hepatitis and colitis G3) 10 days after the 1st dose of vaccine: she received high-dose steroid therapy, with clinical remission
Conclusions: BNT162b2 mRNA vaccine elicited a humoral response after the 1st dose in about 40% of the patients. Differences with healthy subjects may depend on the older age and time gap between start of ICIs and vaccine administration. Additional data, including long term analysis (+6months), T-cellular response and multivariable analysis on demographic/clinical data, will be presented at the meeting. Overall, our preliminary data suggest a reassuring safety profile of vaccination in cancer patients undergoing ICIs

E03*

SARS-COV-2 INFECTION RISK AND COVID-19 PREVALENCE IN CANCER PATIENTS DURING THE FIRST WAVE OF COVID-19 PANDEMIC IN A NORTHERN ITALY'S VIRUS EPICENTER AREA

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Background: Patients with cancer are purported to be more vulnerable to coronavirus disease 2019 (COVID-19). However, cancer encompasses a spectrum of heterogeneous tumor subtypes. The aim of this study was to investigate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection risk and COVID-19 prevalence according to tumor subtype in the resident cancer patient population of the Province of Parma (Emilia Romagna Region, Northern Italy) during the first wave of COVID-19 pandemic in Italy.

Methods: We analyzed data from the Parma Province Cancer Registry, COVID-19 hospital medical records, and local surveillance system of all laboratory-confirmed cases tested positive for SARS-CoV-2 from the beginning of the outbreak (20th of February) to the 19th of July 2020. All the Parma resident population of cancer patients was classified as either "active" or "inactive" according to the evidence of any referral to health services, for any reason, during the observation period. Study analyses were adjusted for patient demographics, tumor subtype and period of cancer diagnosis.

Results: 40,148 cancer patients (mean age 68 years; 57.8% females; 45.1% active) were analyzed. The cumulative risk of SARS-CoV-2 infection was 11.2% for cancer patients vs. 7% for non-cancer subjects ($P < 0.0001$). The overall COVID-19 attack rate was 2.2% (95% CI, 2.0-2.4) and 2.6% (95% CI, 2.4-2.9) for inactive and active cancer patients, respectively. The cumulative incidence of COVID-19 was higher in active vs. inactive cancer subjects (HR 1.18, $P = 0.01$). In the active cancer group, the cumulative incidence of COVID-19 was higher in lung cancer patients vs. other tumor subtypes (HR 4.3). In the same group, HR for breast cancer patients was 0.86. Interestingly, the subgroup analysis of COVID-19 cumulative incidence showed a significant interaction between active patient status and hematological malignancies.

Conclusions: In our study, patients with cancer were more susceptible to SARS-CoV-2 infection. The cumulative incidence of COVID-19 was higher in active vs. inactive cancer subjects. However, cancer is a heterogeneous group of diseases and patients with different tumor types had differing susceptibility to COVID-19 phenotypes. COVID-19 fatality rates for subgroups will be reported at the meeting.

E04*

SAFETY OF COVID-19 VACCINE IN ONCOLOGICAL PATIENTS: THE ISTITUTO ONCOLOGICO VENETO EXPERIENCE

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Background: No data have been published on the safety of Covid-19 vaccines in cancer patients (pts).

Patients and methods: Pts undergoing anti-cancer treatment who were vaccinated with anti-SARS-CoV-2 Pfizer-BioNTech vaccine (Comirnaty©) at Istituto Oncologico Veneto – IOV, IRCCS, Padova, were instructed to report adverse drug reactions (ADRs) through the national pharmacovigilance platform (www.vigicovid.it) either directly or through the treating oncologist. ADRs were then retrieved from vigiCOVID.

Results: From March 6th to May 9th 2021, a total of 5297 pts treated at Istituto Oncologico Veneto - IOV for either solid (87%) or onco-hematologic malignancies (13%) have been vaccinated with two 30 μg doses of BNT162b2 Pfizer-BioNTech vaccine. Overall 10.820 doses of vaccine have been administered, with 226 pts (1.8%) who received the first dose not completing the planned second dose because of either worsening of general conditions, admission to other hospital wards, occurrence of COVID-19, or death. Globally 207 pts (3.9%) refused vaccination. About 80% of pts were actively receiving oncological treatment, and 20% had completed it in the past 6 months, with half of the pts receiving cytotoxic chemotherapy, and the other half either immunotherapy, targeted therapy or a combination of targeted therapy and endocrine therapy. No specific timing regarding chemotherapy schedule was required, except pts were not vaccinated on the same day of chemotherapy, and vaccine was preferentially administered before chemotherapy start. Eight ADRs were reported.

Seven were non-severe ADRs (fainting, hypertensive episode, hypotension; skeletal pain, muscle pain, fever, rhinitis; back pain, fatigue, fever; reddening at injection site, hot flashes; tongue pruritus; paresthesia, pruritus, skin rash; headache, myalgia, fever, rigidity), and resolved within 48 hours. The severe ADR was a central retinal artery thrombosis in a patient treated with gefitinib for EGFR-mutated non small cell lung cancer, causing blindness in the affected eye. Patient was treated with acetilsalicilic acid, with condition not resolved to date. Only 4 pts experienced hypersensitivity reactions, which were not serious and resolved in less than one hour.

Conclusions: Though it is likely that frequent, minor ADRs such as pain at the injection site may be underreported, our data confirm safety of the Pfizer-BioNTech vaccine in the largest cohort of cancer pts reported to date.

E05

NEUTRALIZING ANTIBODY RESPONSES AGAINST SARS-COV-2 IN CANCER PATIENTS AFTER THE FIRST MRNA-1273 VACCINE DOSE

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Background: Vaccination against SARS-CoV-2 could be an important preventive strategy against COVID-19 for cancer patients (pts), but its efficacy and safety in these pts is largely unknown. Herein, we report the development of neutralizing antibodies (NAbs) against SARS-CoV-2 in cancer pts after the 1st dose of the mRNA-1273 vaccine.

Patients and methods: A cohort of pts with solid tumors from IRCCS MultiMedica and San Giuseppe Hospital, Milan, were enrolled in the VITTORIA (VaccInazione anTi-COVID-19, moniTORaggio della rIsposta Anticorpale) project, a prospective observational cohort study, conducted by IRCCS MultiMedica, designed to investigate trend of immunoglobulin G (IgG) in serum samples of volunteers who undergo anti-COVID vaccination in Italy. Seroprevalence was assessed through TGS COVID-19 IgG chemiluminescent immunoassays. Cut-off for positivity was defined as >11.5 AU/ml. These pts are vaccinated with mRNA-1273 vaccine and undergo to a maximum of 4 IgG evaluations during time: at the 1st and 2nd vaccine administration and after 2 weeks from each administration. In this preliminary analysis, we evaluated median values (range interquartile (IQR)) of IgG during the first 3 time points and we assessed trend with non-parametric Sign test for dependent samples.

Results: 61 pts were enrolled in April 2021. 68.9% were females with a mean age of 63.7 ± 10.5 yrs. 28 have breast cancer, 7 lung, 15 gastrointestinal, 3 prostate, 2 kidney, 2 head and neck, 4 gynecological cancer. 44.3% were on chemotherapy (CT), while 55.7% on non-CT treatment (i.e target or immunotherapy). Median baseline IgG value was 0.0 AU/ml (IQR 0.0-0.0) and it statistically increased after 2 weeks (4.4 AU/ml, IQR 0.0-14.9, $p<0.0001$). At 2nd dose, IgG was available until today for 42 pts (68.9%) and the median value was 12.5 AU/ml (IQR 5.4-38.9, $p<0.0001$). 34.4% had positive IgG value 2 weeks after the 1st dose and 52.4% at 2nd dose. IgG value increases independently from treatment (CT vs non-CT), steroid use and tumor subtype, with a trend towards positivity for non-CT treatment ($p=0.067$). No serious adverse events vaccine-related were reported and no COVID-19 infection occurs after 1st dose.

Conclusions: Our preliminary data indicate that the first dose of mRNA-1273 vaccine leads to initial production of NAbs against SARS-CoV-2 in a cohort of cancer pts. Enrollment is still ongoing and future analysis will be performed to assess the increase and duration of NAbs in pts with solid tumors.

E06

SEROLOGICAL RESPONSE TO COVID-19 VACCINATION IN PATIENTS WITH CANCER OLDER THAN 80 YEARS

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Background: The randomized study of BNT162b2 mRNA vaccine enrolled 43,548 patients (pts) aged between 16 and 91 years, but excluded pts receiving immunosuppressive therapy and those diagnosed with an immunosuppressive condition. Considering the important need of real-life data related to COVID-19 vaccine in older pts with cancer, we decided to conduct a study to evaluate the seroprevalence of the SARS-CoV-2 IgG in cancer patients aged $\geqslant$ 80 years one month after administering the second dose of BNT162b2 vaccine.

Materials and Methods: This was a spontaneous, not-sponsored, mono-institutional, cross-sectional control study conducted at San Camillo-Forlanini Hospital in Rome. We screened 74 older patients with cancer, 45 of them accepted to receive the vaccination and we collected serum samples from 36 pts. A group of medical doctors and nurses of our Hospital was used as a control in a 1:2 ratio.

Results: Pts' data are summarized in Table 1. Median serum IgG were 2396,10 AU/ml (range 0-32763,00) in cancer pts and 8737,49 AU/ml (398,90-976280,00) in control group, $p<0.0001$. Additional subgroup analyses were performed comparing males and females, chemotherapy versus other therapies (immunotherapy, targeted therapy), solid tumors versus hematological malignancies, early (I-II) versus advanced (III-IV) stage of disease, continuative corticosteroid use or not. None of them reached statistical significance. None of the pts enrolled in this study experienced COVID-19 infection after vaccination, regardless of the level of IgG response.
Conclusions: Our study shows for the first time that cancer pts cancer aged =80 years can have a serological response to the BNT162b2 COVID-19 vaccine one month after vaccination. Additional serological tests will be performed after 6 and 12 months from vaccination in order to evaluate the duration of immunological response in our pts.

	Cancer Pts n 36 (%)
Median Age (range)	82 years (80-89)
Sex	
= Female	21 (58.4)
= Male	15 (41.6)
Tumor type	
= Haematologic tumors	10 (27.3)
= Solid Tumors	26 (72.2)
GU	9
GI	8
Breast	7
Others	2
Staging	
= I-II	6 (16.7)
= III-IV	23 (63.9)
= NA	7 (19.4)
Comorbidities	
= Cardiovascular	25 (69.4)
= Diabetes	8 (22.2)
= Other	15 (41.7)
Cancer Treatment	
= Active treatment during vaccination	31 (86.1)
- Chemotherapy+ mAb	11
- Chemotherapy	10
- Targeted Therapy	4
- Hormonal Therapy	2
- Immunotherapy	2
- Radiotherapy	2
= Out of treatment	5 (13.9)
Corticosteroid therapy	
= Yes	9 (25.0)
= No	26 (72.2)
= Unknown	1 (2.8)

E07

SHORT-TERM SAFETY OF MRNA COVID-19 VACCINES IN PATIENTS WITH CANCER

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Background: Healthcare authorities at National and Regional level have prioritized vaccinations for cancer patients. Patients with cancer are among the very high-risk groups for adverse outcomes including hospitalization and/or death from COVID-19. The Medical Oncology Unit in Florence encourage vaccination for all patients with cancer being actively treated, regardless of treatment type, performance status, or life expectancy. A COVID-19 vaccination campaign, with the support of the Health Departments, was launched on April 02. The Pfizer BNT162b2 mRNA or the Moderna mRNA-1273 vaccines, based on availability, were used. Data regarding the safety of the mRNA vaccines in patients with cancer were collected.
Material (patients) and methods: Between April 02 and May 07, vaccination was offered to patients actively undergoing cancer treatment. Side effects were monitored via detailed telephone questionnaires.
Results: 913 patients were offered the vaccine. 22 (2%) refused the vaccination, mostly due to fear of side-effects, 73 (8%) patients did not answer the call, while 181 (20%) patients were had already been vaccinated. 637 patients received the first vaccination dose, of whom 601 (94%) received the second dose. The second dose was omitted if the patient contracted SARS-CoV-2 infection between three and six months before the first dose. The most common side-effects after the first dose were local, with 126 (24%) of 523 evaluable patients reporting pain at the site of injection. Systemic side-effects included fatigue (34 [6%]), headache (18 [3%]), muscle pain (14 [2%]), fever (17 [3%] and chills (3 [1%]). Two of 523 patients were admitted to hospital for acute allergic reactions. Three patients died after the first dose due to disease progression and two patients refused the second dose. More systemic side-effects were observed after the second dose of vaccine. Pain at the injection site was reported in 18 [3%] of the 502 evaluable patient, whereas the most common systemic side effects were muscle pain (39 [34%]), fatigue (19 [34%]), headache (31 [16%]), fever (102 [10%]), chills (17 [10%]). None of the reported side-effects required

admission to hospital or any other special intervention. Two patients developed asymptomatic SARS-CoV-2 infection after the first and the second dose of vaccine, respectively.

Conclusions: The reassuring safety signal regarding the mRNA COVID-19 vaccines in patients with cancer support call for vaccination of cancer patients.

E08

COVID-19 IMPACT ON COLORECTAL CANCER CARE IN 2020: PRELIMINARY DATA FROM THE ITALIAN COVID-DELAY STUDY

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Background: Since March 2020, Coronavirus disease 2019 (COVID-19) has rapidly spread worldwide causing a massive Health Care crisis with Italy among the most affected countries. Oncology care has been widely derailed and cancer screening programs halted to effectively face the pandemic. Aim of our multicenter study is to assess how COVID-19 has impacted on the likelihood of receiving timely diagnosis, staging and treatment for colorectal cancer (CRC) patients (pts) during the 2020 compared to pre-pandemic period.

Material (patients) and methods: All consecutive medical records of newly diagnosed CRC pts referred to 4 Italian Oncology Departments between March and December 2020 were evaluated. Monthly access rate and temporal intervals between date of symptoms onset, radiological and cytohistological diagnosis, treatment start and first radiological evaluation were analyzed and compared with the same months of 2019. Differences between the two years were evaluated using Fisher's exact or chi-square test for categorical variables and unpaired Student t test, or the Mann-Whitney U test for continuous variables.

Results: A considerable drop (20%) in newly diagnosed CRC cases emerged compared to 2019 (214 vs 268). The lockdown period was more impacted by such decrease compared to the other months (percentage drop 40% vs 12%). New CRC diagnoses in 2020 were less likely to be diagnosed with early stage (stage I-II-III) CRC (67% vs 72%). Other clinical and tumor characteristics such as age, gender, sidedness and mutational status were similar regardless of the year. Looking at pts management, no differences were seen in terms of interval between symptom onset and radiological diagnosis (median 19 days in 2020 vs 28 days in 2019, p=0.88), symptom onset and cytohistological diagnosis (25 vs 36 days, p=0.27), symptom onset and treatment start (median 86 vs 100 days, p=0.79). However, less CRC were discussed in multidisciplinary tumor meetings during the 2020 (45% vs 54%, p=0.07).

Conclusions: While COVID-19 effects on cancer pts' outcome might unfold in the years to come, our preliminary data show a remarkable drop in early stage CRC diagnoses throughout 2020. The Italian Oncology Departments managed to optimally tackle the quality care issue ensuring prompt diagnosis and treatment despite the pandemic evolving scenario. Further investigation, including larger case series, are warranted to offer a more exhaustive picture of the impact of COVID-19 emergency on cancer care.

E09

FEWER EARLY STAGE BREAST CANCER DIAGNOSES AFTER COVID-19 OUTBREAK: PRELIMINARY REPORT FROM THE ITALIAN COVID-DELAY STUDY

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Background: The coronavirus disease (COVID-19) has imposed an unprecedented challenge on the Health Care System. With the reallocation of crucial health resources to effectively exit the crisis, the pandemic has profoundly affected cancer patients' (pts) management. Breast cancer (BC) diagnosis results, especially in the early stage, from screening programs temporarily paused during COVID-19 outbreak. The aim of our multicenter study is to investigate the impact of COVID-19 on the likelihood of receiving timely diagnosis, staging and treatment for BC pts compared to pre-pandemic period.

Material (patients) and methods: Medical records of all consecutive newly diagnosed BC pts referred to 4 Italian Oncology Departments between March and December 2020 were assessed. Monthly access rate and temporal intervals between date of symptoms onset, radiological, cytohistological diagnosis and treatment start were analyzed and compared with those of the same period in 2019. Differences between the two years were analyzed using Fisher's exact or chi-square test for categorical variables

and unpaired Student t test, or the Mann-Whitney U test for continuous variables.

Results: A significant reduction (23%) in newly diagnosed BC pts was seen when compared with 2019 (552 vs 719). Newly BC pts in 2020 were less likely to be diagnosed with early stage (stage I-II) BC (77% vs 84%, $p < 0.01$), had a worsened ECOG PS (19% had PS > 0 in 2020 vs 16% in 2019, $p = 0.15$) and were more symptomatic at diagnosis (43% vs 23%, $p < 0.01$). Other clinical and tumor characteristics (such as histotype [$p = 0.23$] and molecular subtype [$p = 0.71$]) were similar regardless of the year. Looking at pts management, time intervals between symptom onset and radiological diagnosis (median 17 days in 2020 vs 21 in 2019, $p = 0.04$), symptom onset and cytohistological diagnosis (26 vs 35 days, $p = 0.06$), cytohistological diagnosis and treatment start (median 62 vs 76 days, $p < 0.01$) were maintained or even improved. However, less BC cases were discussed in multidisciplinary tumor meetings during the 2020 (52% vs 69%, $p < 0.01$).

Conclusions: While the COVID-19 effects on cancer care will be likely felt for years to come, our data indicate a sharp decline in BC detection in 2020 with major impact on early stage diagnosis. Despite the upheaval generated by this global Health Care crisis, our study proves the effectiveness of the actions taken by Oncology Departments to guarantee diagnostic-therapeutic pathways.

E10

ACCESS TO EARLY PHASE CLINICAL TRIALS DURING THE COVID-19 PANDEMIC

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Background: The Covid-19 pandemic has radically changed healthcare organizations. Here, we describe the attitude among Italian physicians toward referring patients to early-phase clinical trials during the pandemic.

Methods: We analyzed the responses recorded in the first 72 hours from the beginning of the survey. A 20-question web survey was sent to all the associates of the Italian Association of Medical Oncology.

Results: Ninety-five physicians completed the survey; 87 (96%) were medical oncologists. Table 1 summarizes participants' characteristics.

Overall, 37% of the respondents work in an early clinical trial unit. The vast majority of interviewees (74%) already used to refer patients to early clinical trials in the pre-COVID era. Among these, about 30% sent fewer patients during the pandemic particularly due to logistical issues. Interestingly, 25 (26%) never referred patients because of ineffective networking among institutions.

It will take more than 12 months to return to pre-pandemic attitude according to half of the physicians. Most of the respondents affirm that one possible tool to facilitate the recovery is: fostering the clinical research network, favouring alliances between referral and satellite centers, and strengthening telemedicine.

More than 70% of participants believe that the COVID-19 pandemic will have an impact on the development of new molecules in the coming years both due to a decrease in the number of open studies and to a diversion of funds towards Covid-19 research.

Conclusions: In this analysis, we intended to offer an early snapshot of the Covid -19 effects on early phase trials in Italy. One-third of the participants had to decrease the number of referred patients due to the difficulties of a system exposed to unprecedented stress. Furthermore, the challenges of the last year will have repercussions on drug development in the coming years for the majority of interviewees.

Table 1. Participants' characteristics.

Characteristics	n (%)
Gender	
Female	52 (55%)
Male	43 (45%)
Age (years)	
⩽ 30 years old	8 (8%)
30-45 years old	56 (59%)
> 45 years old	31 (33%)
Working region	
Northern Italy	41 (43%)
Central Italy	37 (39%)
Southern Italy	17 (18%)
Work Setting	
University Hospital	32 (34%)
Cancer Centre/Research Centre	32 (34%)
General/Community Hospital	20 (21%)
Private Centre	6 (6%)
Other	5 (5%)
Area of interest/types of malignancy	
Lung	33 (35%)
Breast	26 (27%)
Gastrointestinal	27 (28%)
Genito-urinary	24 (25%)
Other	15 (16%)
Melanoma	14 (15%)
Gynecological	13 (14%)

E11

EVALUATION OF COVID-19 IMPACT ON DELAYING DIAGNOSTIC-THERAPEUTIC PATHWAYS OF LUNG CANCER PATIENTS IN ITALY: REAL-WORLD EVIDENCE FROM THE COVID-DELAY STUDY

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Background: The coronavirus disease 2019 (COVID-19) had an unprecedent impact on the global health care system since March 2020. Lung cancer (LC) patients (pts) represent a vulnerable population, and diagnostic/therapeutic delays might affect the years to come. Aim of the multicenter, real-world, Italian COVID-DELAY study was to evaluate how the 2020 COVID-19 pandemic impacted on LC pts' access to diagnosis and treatment compared to pre-pandemic time.

Patients and methods: All consecutive newly diagnosed LC pts referred to 25 Italian Oncology Departments between March and December 2020 were reviewed. Monthly access rate and temporal intervals between date of symptom onset, diagnosis and treatment start were analyzed and compared to the same period of 2019. Differences between the two years were analyzed using Fisher's exact test or chi-square test for categorical variables and unpaired Student t test, or the Mann-Whitney U test for continuous variables.

Results: Less LC cases (1523 vs 1637, -6.9%) were diagnosed during the 2020 pandemic compared to 2019. LC pts in 2020 were more likely to be diagnosed with stage IV disease ($p < 0.01$) and to be current smokers ($p < 0.01$). A major drop of new LC cases was seen during the lockdown period (percentage drop -13.2% vs -5.1%) compared to the other months included. Moreover, a geographic migration was observed with more LC patients referring to low/medium volume hospital in 2020 compared to 2019 ($p = 0.01$). Looking at pts management, no differences emerged in terms of interval between symptom onset and radiological diagnosis ($p = 0.94$), symptom onset and cytohistological diagnosis ($p = 0.92$), symptoms onset and treatment start ($p = 0.40$), treatment start and first radiological revaluation ($p = 0.36$). However, less LC patients were treated in the context of clinical trials during 2020 (5% vs 7%, $p = 0.07$).

Conclusions: Our study pointed out a decrease of new LC cases and a shift towards a higher stage at diagnosis in 2020. Despite this, the efforts put in place by the Italian Oncology Departments ensured the maintenance of the diagnostic-therapeutic pathways of LC patients.

E12

SHORT-TERM ADVERSE EVENTS AND PSYCHO-SOCIAL EFFECTS OF THE BNT162B2 MRNA COVID-19 VACCINE IN CANCER PATIENTS. A SINGLE-CENTRE EXPERIENCE

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Background: Soon after the Italian Medicine Agency (AIFA) authorized the first mRNA COVID-19 vaccine, BNT162b2 (Comirnaty®), the Italian Ministry of Health launched a national vaccination campaign. Giving the high risk of mortality from COVID-19, cancer patients were considered a priority group. However, data about BNT162b2 safety in this population are still lacking and the impact on patients' psychological state and social life was not studied. Herein we describe the adverse events (AE) related to the vaccine and the subjective experience of cancer patients treated and vaccinated at San Luigi Gonzaga University Hospital.

Materials and methods: All cancer patients who accepted to participate in our campaign were vaccinated with BNT162b2 and included in the descriptive analysis. Patients who tested positive for COVID-19 after January 1st, 2021 were not recruited. An anonymous questionnaire about AE and psycho-social impact of the vaccination was administered to the study population 21 days after the first dose. The short-term AE reported after the second dose were investigated via a telephone questionnaire.

Results: A total of 997 patients were included in the study, of whom 618 were affected by advanced cancer. At the time of the vaccination, 223 patients were receiving chemotherapy and/or immunotherapy. 49 patients have been infected and recovered from COVID-19. AE were reported in 37.3% cases after the first dose and in 48.5% cases after the second dose. The most common AE were muscle pain (26.7% and 27.4%, after the first and second dose respectively) and fatigue (10.4% and 16.8%). No severe AE had been reported. Before receiving the vaccine, 18% patients felt fearful and/or insecure about the vaccination, while 76.4% felt hopeful and/or enthusiast. After the first dose, 57.5% patients changed their feelings positively and 79.5% patients stated to feel much more confident in their social life. Patients' opinion about the vaccination was mainly influenced by the specialist/family doctor (38.7%) and by mass-media (25.8%), and the information they were given was considered adequate by 86% patients.
Conclusions: Our data support the short-term safety of BNT162b2 in cancer patients, regardless of the disease staging and the concurrent treatment. Before the vaccination, most of our patients consulted the specialist or the family doctor receiving adequate information and being reassured. Moreover, the vaccination showed a positive psychological and social impact.

E13

A YEAR OF PANDEMIC COVID-19: RESULTS FROM THREE CONSECUTIVE AIOM SURVEYS AMONG ONCOLOGY HEALTH WORKERS IN THE NORTH-WEST OF ITALY

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Background: SARS-CoV-2 pandemic changed oncology clinical practice. Health care workers (HCW) in oncology experienced double concerns as they had to guarantee patients global care while protecting them from the infection. We performed a longitudinal survey during this year to evaluate how daily practice and life of cancer HCW has changed.
Methods: Three online surveys were sent to Italian Association of Medical Oncology (AIOM) members of Piedmont and Valle d'Aosta during the first wave, just before the second wave and at the end of the second wave. The 5 main topics were: population characteristics, changes in working practice, SARS-CoV-2 swab management, the influence of the pandemic on diagnostic, and on therapeutic paths.
Results: 201, 186 and 136 HCW responded to the 3 surveys, respectively. 45% were oncologists, 28% nurses, 5% palliative doctors, and 9% interns. 75% did not received adequate training and 50% adequate personal protective equipment during the 1st wave. Screening by molecular swabs increased during time (from 6% in the 1st wave to 93.7% at the end of the 2nd wave). HCW main concerns were on beloved ones, lack of COVID-19 guidelines and practical skills (1st survey), the fear of a 2nd wave and its consequences (2nd survey), the persistence of emergency despite vaccines (3rd survey). Most HCW intended to be vaccinated (94%). Pandemic changed HCW-patient relationship due to the lack of physical contact and hampered non-verbal communication. A moderate to significant reduction of first oncological consultations occurred. Most follow-up visits were remotely conducted and palliative care activation was delayed in 40% of cases.
Conclusions: This survey explored how cancer HCW suffered and reacted in different phases of SARS-CoV-2 pandemic. To know the discomforts, fears and perplexities of HCW must indicate where to act to restart and continue to guarantee patients and their families the best therapies and paths.

E14

WHY DO PROSTATE CANCER CLINICAL TRIALS (CT) DISCONTINUE PREMATURELY IN THE ERA OF COVID-19? AN ANALYSIS OF 559 CT FROM CLINICALTRIAL.GOV

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Background: The COVID-19 pandemic (C19P) is producing several detrimental effects on cancer care globally. CT play a decisive role to provide high quality literature evidence and "poor accrual" is the most common reason for their early discontinuation (ED). At our best knowledge, no data are available on ED of prostate cancer CT after the beginning of C19P.
Material and methods: ClinicalTrial.gov was queried for terminated (T), withdrawn (W) and suspended (S) CT for the following terms: "cancer", "neoplasm" and "tumor".

CT not related on prostate cancer were excluded. The search was made for all the CT available from the inception to 26th February 2021, without any restrictions. The following characteristics were extracted: reason for ED, study type (interventional [In] vs observational), sponsor (yes vs not). ED rate was compared between CT discontinued for C19P or not ($\chi 2$); $p < 0.05$ was set as statistically significant. A multiple linear regression analysis was also conducted to identify independent factors of ED.

Results: 9990 CT were identified and 7901 CT were excluded because not related to prostate cancer. Thus, 559 CT were included: 67% was T, 27% was W and 5% was S. Among CT classified as T, W and S, the frequency of In CT were 90%, 82% and 81% respectively, while the frequency of sponsored CT was 48%, 27% and 19% respectively. The most common reasons for ED were: "poor accrual" (31%), "lack of funding" (7%) and "sponsor decision" (5%). No reason for ED was available for 13% of CT. Ten (2%) CT were discontinued for C19P (20% was T, 10% was W and 70% was S). Comparing CT discontinued due to C19P with those discontinued due to other causes, a lower rate of In-CT (88% vs 91%, $p<0.05$) was found in the C19P group. At the multiple linear regression analysis, it was found that C-19 was strongly positively correlated with ED (coefficient 0,62677, $p<0.0001$) whereas sponsored CT resulted negatively correlated with ED (coefficient -0,03717, p=0.0369).

Conclusions: "Poor accrual" continues to be the main reason for ED of cancer CT, whereas C19P represents a new additional cause of ED. Sponsored trials showed less risk for ED. Further research is needed to maximize the expected benefit of cancer CT, reducing the anticipated risks.

E15

COVID VACCINATION IN CANCER PATIENTS – EXPERIENCE OF MANTOVA ONCOLOGY UNIT

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Background: All the registrative trials of COVID-19 vaccine excluded patients with active malignancies, and thus data on the safety, tolerability and efficacy of the vaccines in patients with cancer are currently unknown. Considering the high morbidity and mortality from COVID-19 in patient with cancer, they are considered a high-priority subgruop for COVID -19 vaccination and preliminary recomandation supporting vaccination in all patients with cancer, including those receiving active therapy

Material and methods: Since 24th March to 11st May, at the Oncology Unit of Mantova Hospital vaccination was encouraged for all patients with actively treated cancer, regardless of disease stage, performace status or life expectancy. Only patients previously infected with COVID 19 or those with acute conditions were excluded.

The 2 m-RNA vaccines were administered at the standard recomended dose on days 1 and 21 (MODERNA) and on days 1 and 28 (PFIZER). Most patients received first administration of vaccine before the oncological treatment and all patient after evaluation of emocrome and after oncologist evaluation. Safety and side effects like muscle pain, fatigue, headache, fever, gastrointestinal were monitored directly by the nurse team on day +1 and with a detailed telephone questionnaires done on days + 2 and +3

Results: 709 cancer patients of which 564 in active cancer treatment, received at least one dose of m-rna vaccine. The day after therapy, the nursing team by phone, registered all the side effects of the patients.

Conclusions: All patients felt reassured that their own oncologists and nurses vaccinated them. The tolerance to therapy was not changed by the addition of the vaccine.

Regarding the efficacy of COVID-19 vaccine in our patients is too early, but we'll follow them over the next year. This vaccination time was a great opportunity to make the oncologists the nursing team closer and closer to the patients.

Table 1. Patients characteristics (n°709).

M/F	Median Age	Chemo	Biological	Target	Follow Up	Octher
319 / 390	66	284	239	41	115	30
45% - 55%	(23-91)	(40%)	(34%)	(6%)	(16%)	(4%)

Table 2. Tumors types.

Breast	218	31%
Colo-Rectal	54	8%
Lung	96	13,5%
Ginecological	31	4,5%
Genito-Urinary	83	12%
Pancreas	24	3%
Hematological	136	19%
Other	67	9%

Table 3. Side effects.

No Sympthoms	396
Injection Site Pain	201
Fatigue	36
Muscle/Bone Pain	21
Fever	27
Erythema	12
Headache	10
Other	71

E16

THE PSYCHOLOGICAL IMPACT OF THE SARS-COV-2 OUTBREACK AND ASSOCIATED FACTORS TO ADJUSTMENT TO THE CONTEXT OF LIFE AND OF CARE IN ITALIAN CANCER PATIENTS

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Introduction: The purpose of this study is to investigate the psychological impact of the SARS-CoV-2 and the effects on functional adaptation to the context of life and care in Italian cancer patients.
Methods: We adopted a cross-sectional survey design to assess the psychosocial impact in cancer patients during the COVID-19 outbreack. To assess the behavior of patients in this stressful situation, we developed the 31-item self-assessment questionnaire "ImpACT".
Results: 445 patients from 17 Italian regions participated in the study (79.8% women, average age 58 y). 85.9% received satisfactory responses from oncologists, 81.0% from nurses, 72.1% from psychologists, 66.3% from GPs and 58.3% in Emergency rooms; 59.8% reported feeling very safe in their oncology unit. 87.7% of pts reported perceiving changes in their lives compared to before the pandemic; 89.9% reported feeling worried, 97.1% said they pay attention to possible signs of physical discomfort attributable to the coronavirus, 97.6% say they strictly follow the rules provided by the government and doctors. Patients who reported being anxious were more likely to be afraid medical staff may get sick (OR = 3.01; 95% CI = 1.49-6.30), or not to sleep because of worries (OR = 2.42; 95% CI = 1.23-4.83), to use medicines to manage anxiety (OR = 4.04; 95% CI = 1.43-13.34) or to think that faith might help them (OR = 3.47; 95% CI = 1.62-7.69). Who reported being angry were more likely to feel lonely (OR = 3.58; 95% CI = 1.98-6.63), but less likely to report not thinking about the coronavirus (OR = 0.34; 95% CI = 0.13-0.82). The patients who reported to be calm, showed less fear for the future (OR = 0.20; 95% CI = 0.09-0.43), less insomnia due to worries (OR = 0.46; 95%) CI = 0.25-0.83), less risk of suicidal thoughts (OR = 0.10; 95% CI = 0.00-0.63) and were less likely to think that faith would help them (OR = 0.47; 95% CI = 0.24-0.91). Men were more likely to reported being calm than women (OR = 2.60; 95% CI = 1.27-5.43).
Conclusions: The results suggest that the majority of cancer patients have faced the situation related to the SARS-CoV-2 pandemic, with concern of being infected, and the consequences on their health and on the anticancer treatments. How healthcare professionals respond to patients' needs can facilitate understanding of information and emotionally support patients.

E17

CAREGIVING DURING COVID19 PANDEMIC: THE NEW CHALLENGE IN ONCOLOGY ASSISTANCE?

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Introduction: Coronavirus disease 2019 (COVID-19) outbreak has been declared a pandemic unprecedented. Italy has been one of the first and heavily affected countries. The hematologic toxicity due to chemotherapy is the main reason why cancer patients are considered fragile patients, due to the high risk of infection. This led to important restrictions and recommendations during first and even more during second peak of COVID-19 pandemic with the prohibition of caregivers admission. In the above scenario, our study has the aim of evaluating the impact of COVID19 pandemic in caregiving in oncology.
Materials and Methods: Between 02/09 and 04/02 2021 our team conducted a cross-sectional study by submitting a survey to caregivers of patients with solid cancer undergoing active treatments in Oncologic Departments of Marche region. An anonymous, paper questionnaire regarding perception of patient safety and continuity of care was submitted.
Results: A total of 112 caregivers responded to our survey. The majority of them were between 46 and 65 years old (46.4%), female (57%), declared to take care of the patient for 0-2 hours/day (36.6%) and declared to have increased assistance time during the pandemic (59.3%). Half of the participants declared there were no economic difficulties in assistance of their relatives and more than half (55.4 %, n=62) did not report major change in this setting. Almost all caregivers (99.1%) declared that the Oncology Departments has complied with the safety recommendations to limit virus spread. Although 86 (76.8%) of them confirmed that access has been restricted due to pandemic, only 10 caregivers (8.9%) perceived these precautions too restrictive, while 107 (95.5%) of the all sample defined them effective. Despite these constraints, approximately

all respondents declared that they had the chance to dialogue with health care providers and had the possibility to access the oncologic department if necessary (respectively 106 subjects, 94.6% and 101, 90.1%). Moreover, more than half of caregivers (n=57, 50.9%) perceived that the quality of care has not been affected by the pandemic.
Conclusions: Despite the COVID-19 pandemic has overwhelmed the Italian National Health System, maybe more than in other countries, Oncology Departments was considered worthy of the emergency care in terms of safety and care management by caregivers. Caregivers perceived and believed in an adequate quality of care for their relatives without economic implications.

E18

A VENETO INSTITUTE OF ONCOLOGY - IRCCS SURVEY ON THE MEASURES IMPLEMENTED TO CONTAIN THE SPREAD OF SARS-COV-2 AND ON THE ANTI-COVID VACCINATION DURING THE COVID-19 PANDEMIC: LESSON FROM CANCER PATIENTS

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Introduction: The SARS-CoV-2 spread has led to a revolution in the healthcare. Veneto Institute of Oncology has adopted contagion containment measures to guarantee a greater level of protection to cancer patients. The anti-COVID vaccination for cancer patients has been a priority for the national health system and the institute has implemented a vaccination campaign to ensure coverage for patients. A survey was developed to assess the impact of the COVID-19 pandemic on patients' perceptions about the measures taken to limit the risk of SARS-CoV-2 infections and their concern about their cancer care. A questionnaire on the degree of satisfaction with vaccination was administered after anti-COVID vaccination.
Methods: The Survey was distributed to all patients who entered in hospital during analysis period and it was divided into 3 items: characteristics of patients, concerns about the pandemic on their cancer path, perception of the measures adopted by the institute to limit the spread of the infection. The vaccination questionnaire was distributed to a cohort of vaccinated patients and explored the degree of satisfaction with the vaccination campaign.
Results: From May18th until June15th, 3238 questionnaires were completed. Most of the responders said they were concerned about SARS-CoV-2 pandemic while keeping the concern for oncological disease as a priority. All measures (triage for hospital access, restrictions for caregivers, use of personal protective equipment, sanitization of environments) have been appreciated by patients. Telemedicine was positively evaluated by the responders while, the absence of the caregiver during visit, does not seem to have determined discomfort in about two thirds of patients. From April26th until May14th 2021, 356 vaccination questionnaires were completed. 60% of responders were female; 90% were on active cancer treatment and 33% of the patients reported adverse events related to the anti-COVID vaccination. Patients expressed a high degree of satisfaction with the vaccination campaign (99% were satisfied/very satisfied)
Conclusions: This survey reported the point of view of cancer patients regarding the impact of the COVID-19 pandemic on the oncological activities of which they are protagonists and patients' perceptions of the anti-COVID vaccination campaign. We believe that the perspective of patients can be crucial to help the reorganization of the health system, especially in this period of medical emergency.

E19

IMPACT OF THE CANCER SCREENING (CS) AND TREATMENT DURING THE COVID-19 LOCKDOWN PERIOD ON BREAST CANCER (BC) DIAGNOSIS: A SINGLE CENTRE EXPERIENCE

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Background: The outbreak of the COVID-19 pandemic led to a rapid reorganization of health care system in Italy. Therefore, CS slowed down during the two lockdown periods including for BC primary prevention such as mammography and breast ultrasound. Hence, the aim of our retrospective analysis was to evaluate the impact of the discontinuation of CS and subsequent delay in surgical treatment during COVID-19 on BC diagnosis.
Patients and methods: All patients who underwent breast surgery after BC diagnosis from March 8, 2019 to March 8, 2021 were included in the study. Our population was then divided into two groups: group A, pre-Pandemic group, considered women who underwent surgical procedures from March 2019 to March 2020. Group B, Pandemic

group, included patients who underwent breast surgery from March 9, 2020 to March 8, 2021.

Results: A total of 524 newly diagnosed patients were evaluated; n=239 and n=285 in the pre-Pandemic and Pandemic, respectively. We observe an increase of patients with lymph-node involvement (35% vs 29% p= 0.14) and with a higher cancer stage (Stage III-IV 20% vs 15% p=0.13), but not statistically significative in the Pandemic Group compared to the pre-Pandemic group.

Conclusions: In our analysis, the slowdown of CS for BC did not have a significant impact on BC diagnosis even though our data reveal a slight increase of advanced BC stage in pandemic group. Hence, a potential explanation could be identified in our efforts to keep diagnosis and treating oncological patients. Nevertheless, new data about post covid BC diagnosis are not still available. Reasonable, our findings are most likely going to be re-debeated in few years to clarify if this trend could be confirmed.

E20

THE IMPACT OF COVID-19 OUTBREAK ON BREAST CANCER PATHOLOGICAL STAGE AT SURGERY: A RETROSPECTIVE MONOCENTRIC STUDY

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Background: In March 2020, due to the spread of Sars-Cov2 infection and the subsequent declaration of global pandemic by the World Health Organization, several services provided by the Italian Healthcare System were interrupted or heavily limited until May 2020, including breast cancer screening and surgery. We conducted a retrospective analysis to evaluate the impact of these 3-month-limitation on breast cancer stage at surgery in the Breast Unit of San Martino Hospital in Genoa.

Material and methods: In this retrospective study we compared the pathological stage of breast cancer patients who underwent surgery in our Breast Unit (San Martino Hospital, Genova) in 2020 with those treated in 2019, focusing on the period between March and May.

Results: We observed a remarkable reduction in breast cancer surgical interventions in 2020 compared to 2019 (671 vs 491, -26.8%). As expected, the most relevant reduction was observed during the lockdown period, accounting for 39% (70 out of 180) of the total reduction. Out of 671 surgical interventions performed in 2019, 96 were ductal carcinoma in situ (14.3%). Out of the 491 in 2020, 44 were ductal carcinoma in situ (9%), which represents a 5.3% reduction compared to 2019 (p-value 0.0061). Notably, there was no relevant increase in pT and nodal involvement between breast cancer patients treated in 2020 compared to 2019, irrrespective of biological subtype. Similar data were observed focusing on the period between March and May 2019 and 2020.

Conclusions: This single-centre analysis showed a decrease in the number of breast cancer surgeries in 2020 compared to 2019, particularly in the period between March and and May, with a significant reduction of in situ ductal carcinoma diagnoses in 2020 compared to 2019. We did not observe a statistically significant increase in breast cancer pathological stage in 2020 compared to 2019. These results were confirmed across different breast cancer subtypes and after restricting the analysis on the March-May period. Our data show that the 3-month-limitation on breast cancer screening and surgery did not turn into increased dimensions or nodal involvement of breast cancer patients treated in 2020 compared to 2019.

E21

AUTO-IMMUNE TOXICITY OF SARS-COV2 VACCINE IN PATIENTS WITH THYMIC EPITHELIAL TUMOURS: A PROSPECTIVE ANALYSIS FROM THE TYME NETWORK

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Background: There are many assumptions that raise fears of auto-immune toxicity of SARS-COV-2 vaccine in patients affected by Thymic epithelial tumours (TETs).

TETs are associated with paraneoplastic autoimmune disorders and vaccine autoimmune cross reactivity is associated with many syndromes such as Guillain-Barre, multiple sclerosis, demyelinating neuropathies. Moreover, a cross-reaction between SARS-Cov-2 anti protein spike antibodies and several tissue proteins has been reported.

Material and methods: We are prospectively collecting data on safety and new onset or recurrence of autoimmune disorders in patients with TETs who received SARS-COV-2 vaccine and are treated in referral centres of the TYME network.

Patients with both Thymoma [T] and Thymic carcinoma [TC], with and without pre-existing autoimmune disorders, treated with chemotherapy, immunotherapy, TKI or just in follow up are included in the analysis.

Association between epidemiological-clinical factors and risk of general Adverse Events (AEs), immune-related AEs and worsening of autoimmune disorders will be assessed.

Results: Preliminary data from the first 20 patients (14 TC and 4 T) suggest that the administration of SARS-COV-2 vaccines is well tolerated, with no safety signals nor reactivation or new onset of autoimmune diseases observed.

Prospective data collection of all TETs patients treated in referral centres of the TYME network is ongoing and will be presented at the time of AIOM congress.
Conclusions: Preliminary data suggest that the administration of SARS-COV-2 vaccines is safe and well tolerated in patients affected by TETs. A comprehensive characterization of general and immune-related safety profile of SARS-COV-2 vaccines in such rare oncological population, enriched for potential risk factors for AEs, is ongoing.

E22

COMPLIANCE, SIDE EFFECTS AND IMMUNIZATION IN CANCER PATIENTS RECEIVED ANTI SARS-COV2 VACCINE

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Background: Sars-Cov-2 is a novel Coronavirus, of animal origin, detected in China, that caused a serious interstitial pneumonia in humans and a fatal sistemic inflammatory syndrome (COVID 19). It caused the global pandemia in the last year, reaping milions of death in the world. No drugs resulted effective to cure it, so farmaceutical industries worked hard to make an efficient vaccine to prevent it and going out of pandemia. The vaccine was administered to all people and patients, also cancer patients. The aggression of Sars Cov 2, the unknow reactions to vaccine and lack of any previous experience make this event a medical act worthy of study and observation.
Patients and methods: From March to May 2021 we analyzed a sample of 100 (on a total of 400) patients that received the Anti-Sars-Cov2 vaccine in our Division of Medical Oncology. These 100 patients are all adults > 18 years old with a median age of 56. All patients are receiving an active antitumoral treatment for solid tumors with cytotoxic drugs, monoclonal antibodies, check-point inibithors or cdk 4/6 inhibitors. All patient received the dose of vaccine within 3-4 days before treatment, after complete blood count. Weekly treatment were delayed just one week for cytotoxic drugs.The second dose of vaccine sometimes was delayed up to 2 weeks for cdk 4/6I.
Results: About compliance, just few patients were scared and refused vaccination. In the sample we analyzed,just 16 patients had a previous immunization from infection or an asymptomatic contact with the virus, as showed by sierological AbAnti SarsCov2. 3 patients did not receive the second dose of vaccine. Less than half of patients reported pain in the injection-side.19/100 patient reported mild side effects such as: fuel, asthenia, myalgia. 3 patients had serious side effects such as: temperature >38,5 °C, nausea and vomiting, edema on injection side and linfoadenopathia in axilla. Every side effect is lasted at most 3 days and has regressed with FANS. All patients showed immunization after two dosed of vaccine and 7 patients that dosed the most specific AbAnti SPIKE after the first dose of vaccine resulted just immunized.
Conclusions: Cancer patients, considered frail patients, had a good compliance, a good tolerance profile and an early immune responce just after one dose of vaccine if studied for AbAnti Spike. This late aspect appears of some interest.

E23

THE IMPACT OF SARS-COV-2 ON DIGITAL IMPROVEMENT AMONG ONCOLOGY UNITS IN ITALY. TLX ASSESSMENT

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Background: The effects of Sars-CoV-2 were extensive and not only limited to diagnostics and therapeutic treatments. the organization of the oncology units had to change in order to face the emergency and guarantee the treatments despite the social distancing. During 2020 in most oncology units the approach to the patients changed, therefore we made a survey to evaluate these changes and the impact on the work overload.
Methods: 1700 Oncologists were administered a Survey subdivided in 3 parts: personal data, work changes and modified NASA-Task Load Index survey (0 = low, 20 = high). Only 55 surveys were completed.
Most of the participants in terms of digital define themselves as autonomous (78.2%) or advanced (18.2%), while only 3.6% as basic utent and no one as not capable of using digital devices (level zero).
The standard equipment was a non-personal computer (60%), personal computer (43.6%), webcam (18.2%), laptop (27.3%); open intranet (54.5%), free WiFi (16.4%). No upgrade was indicated after the pandemy. The access to social networks was limited to Youtube (54.3%), Facebook and Linkedin (34,8%), Twitter (23.9%), Instagram (26.1%), no extended access was indicated after the pandemy. No bigger changes were indicated in first access visit (82.7%), re-evaluation visits (84.3%) or under therapy visits (827%); while follow up visits was suspended (26,4%), incurred in telemedicine (13.2%), carried out by phone (34%), by email (32.1%), by skype or similar (11.3%).
No changes were found in the filling of ministerial forms (drug monitoring and ADR) but a reduction in the time dedicated to compilation was reported (9.6%-5.8%).
The nasa TLX analysis shows: Temporal Demand (M= 13.4; SD= 4.74), Mental Demand (M= 13.0; SD= 5.22), and Effort (M = 13.1; SD = 4.99) were the highest rated

workload subscales. Not to underestimate Frustration (M=12.3; SD=5.62), within the limits Physical Demand (M= 9,4; SD= 5,03) and Performance (M=9.9; SD= 5.17).
Conclusions: The Impact of procedures on the medical personnel are underestimated and often considered irrelevant. The low participation can be explained with a lack of hope; technical equipment and medical softwares are not up to date. Future efforts will focus on digitalizating the users, in order to optimize the workload and the performance for an improved medical care.

E24

ADHERENCE TO NUTRITIONAL AND LIFESTYLE RECOMMENDATIONS FOR CANCER PATIENTS IN COVID-ERA: OUR EXPÉRIENCE

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Background: Nutritional and lifestyle factors are thought to be associated with a higher risk for cancer and recurrence of disease. The literature confirms an important inverse association between adherence to a Mediterranean Diet (MedD) and cancer mortality (1,2). A recent survey reveales that improving physical activity advices in cancer care, in particular if given in a timely manner after diagnosis leads more patients (pts) to make exercise or start a rehabilitation with a specialist when indicated (3). The aim in this study was to analyze adherence to nutritional recommendation and physical activity in Covid-19 era. A secondary aim was to investigate the association between disease progression and specific aspects of diet and lifestyle.
Methods: Personnel of LILT administered all questionnaires. All participants answered questions related to the adherence to MedD (MEDI-LITE questionnaire) at baseline (T0) and after 6 months (T1). Adherence scores to MedD were classified as "very low" (score 0-5), "low" (score 6-9), "moderate" (score 10-15), and "high" (score 16-18). IPAQ (questionnaire for monitoring physical activity) was administered (score Met<700: "low", Met 700-2519: "moderate", Met>2520: "high" physical activity). Medical history and BMI were collected too.
Results: Seventy-nine pts (20 males/59 females) were recruited from March 2020 to February 2021. Cancer diagnoses were: breast (36), colon (14), gastric (12), gynaecological (4), lung (2) and other cancer (9). Sixty-two pts completed at baseline MEDI-LITE questionnaire and 77 the IPAQ questionnaire. All patients had a personalized dietary program, but for limitation due to pandemic Covid-19 era, only 29 pts had access to the control assessment. At T0 MEDI-LITE: 46 pts reports a score moderate, 13 pts score low and 3 pts has an score high. At T0 IPAQ questionnaire: 43 pts report score moderate physical activity, 29 pts score low, and 5 pts report score high. At T0 BMI: 27 pts results overweight, 22 pts are obese, 2 pts are underweight. At T1: 25 pts reported adequate nutrition. The correlations with the socio-anagraphic variables are in progress.
Conclusions: The results suggest that adherence to the recommendations on body weight and MedD were relatively high in Covid-19 era and dietary habits of the pts followed by the specialist have improved. Physical activity was poor/moderate for lockdown, so it is very important to promote physical activity in oncology departments.

E25

PITFALLS DURING COVID19 VACCINATION RECRUITMENT FOR ONCOLOGY PATIENTS

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Background: The purpose of this work is to analyse the pitfalls of recruitment during the COVID19 vaccine campaign for patients in active treatment for solid tumours in an Oncological Department. Every Oncology Department in Veneto developed a way to recruit patients in order to vaccinate them (and afterwards their caregivers). Here we report the Alta Padovana experience during the first month of COVID19 vaccination period.
Methods: Patients in active treatment (or previous 6 months), for solid tumours, with chemotherapy, immunotherapy or target therapy were identified. Every single patient were evaluated: exclusion criteria for vaccination were a recent (last 3 months) COVID19 infection, previous COVID19 vaccination, a very poor Performance Status (PS), previous serious anaphylactic reactions, concomitant use of G-CSF and severe neutropenic situation. Every single patient was contacted and was offered a mRNA-1273 Moderna Inc. COVID19 vaccination. Each patient signed an informed consent, filled in a questionnaire about medical history, a psychological questionnaire regarding the vaccine and their relative side effects (the emotional distress (HADS) thermometer and the emotional status check list).

Results: From 6/3/2021 and 13/3/2021 a total of 529 patients were evaluated: 349 (66%) patients received the first dose of vaccination by the oncologic units; 180 patients were not vaccinated due to different reasons. Some (8,6%) have been previously vaccinated (mainly because health professionals or 80 years older). Some (4,7%) patients were not vaccinated due to a recent (last 3 months) COVID-19 infection. Due to important comorbidities, severe previous anaphylactic reactions or very poor PS, 12% of patients were not vaccinated. Initially 44 patients (8,3%) refused the vaccine: for the fear of side effects, for the very little trust in the vaccination or other personal opinion. After a couple of weeks, to all sceptic patients were proposed again the vaccination and 16 accepted the vaccination; 8 "sceptic patients" had a COVID infection and two died due to it.
Conclusions: Due also to the "social terrorism" created by the "AstraZeneca vaccine Affaire", some patients initially refused; unfortunately some "sceptic patients" had infections and two of them, with advanced tumour disease, died due to COVID19. Oncology team should adequately educate cancer patients (and their care-givers) regarding COVID infection and the risk related to vaccine refuse.

E26

COMPARISON ABOUT STRESS, DEPRESSION, ANXIETY AND INSOMNIA OF HEALTH WORKERS IN MEDICAL ONCOLOGY DURING SARS-COV-2 A YEAR LATER

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Background: A year ago we conducted a survey using self-administered questionnaires that showed a relevant picture regarding insomnia and stress for most of the sample and depression for some categories more exposed to close contact, such as nurses and social health workers. It showed the symptoms of a sudden, destructuring and emergency emotional impact. We performed the same survey one year later, with the aim to reveal how the coping strategies inherent in human nature have worked in the emotional management of the SARS-CoV-2 pandemic.
Material and Methods: Dass-21 and the Insomnia Index questionnaires were administered. The interviewed heterogeneous sample (health personnel, nurses, social health workers, administrators), proved to be collaborative, open and available. The questionnaires were delivered, completed and returned independently to ensure privacy and the free expression of the real situation experienced. A code was assigned in order to guarantee anonymity. The list of names with the corresponding codes were archived separately from the questionnaires.
Results: Overall, in the subjects attending the Medical Oncology Unit of the University Hospital of Cagliari who were included in the research, the questionnaires showed improvement data on all four dimensions in a heterogeneous way: normal values were obtained from 64.29% about stress, 78.57% about anxiety, 78.57% about depression and 35.71% about insomnia. Those who achieved high anxiety, stress and insomnia scores in May 2020 reported normal levels of stress, anxiety and insomnia in 2021. Depression data also improved, with a reassessment of the issues and emotional burden that the SARS-CoV-2 pandemic has brought, allowing for a reassessment of priorities and what is actually important and what is not.
Conclusions: It is believed that the medical staff of our Medical Oncology Unit is basically trained to manage emergencies. It has excellent coping strategies and good global functioning, thanks also to an organization on shifts for both nurses, social health workers, doctors and trainees, and for the structuring of the procedures to be followed, a timely vaccination campaign and the possibility of dialoguing with psychologists present in the department. It would be interesting to administer it once in May 2022 to detect if and how the post-emergency situation of the pandemic will have changed.

E27

A ONE-YEAR SURVEY ON CANCER PATIENTS AFFECTED BY SARS-COV-2 INFECTION: CLINICAL CHARACTERISTICS AND DISEASE EVOLUTION IN A SINGLE INSTITUTION EXPERIENCE

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Background: Patients affected by cancer are considered particularly susceptible to SARS-CoV-2 infection complications. We aimed to study the effect of COVID on patients with solid tumors at our Oncology Unit at Policlinico San Matteo of Pavia.
Material and methods: Data of patients affected by solid tumors and COVID-19 were extracted from medical records between February 21, 2020 and May 15, 2021. COVID diagnosis was confirmed by RT-PCR on nasal swab. Associations between demographic, clinical characteristics and outcomes were measured with HR with 95%CI using Cox regression.

Results: Seventy-five patients affected by solid tumors with COVID diagnosis were included in the analysis. The incidence of SARS-CoV-2 infection in our cancer patients was similar to that observed in the global Italian population (5.8 vs 6.2%), but lower compared to the local population of Lombardia (8.2%) and Pavia (7.9%).
In 34 patients (45.9%) COVID diagnosis was obtained through screening, in 40 patients (54.1%) because of symptoms or radiologic findings. Median age was 64.4 years (25th-75th 56-75); the majority had an ECOG PS of 0-1 (89.2%), was affected by breast, lung or gastro-intestinal cancer (28.0, 26.7 and 21.3% respectively), had stage IV disease (72.2%) and was on therapy at the time of COVID (76.0%); 26 patients (36.1%) were hospitalized; 21 patients (28.0%) died, 13 of them (17.3%) for COVID complications. COVID determined a median delay of the oncologic treatment of 14.0 days (25th-75th 0-25). Mortality rate was higher in our cancer population than that observed in the global Italian population (3.0%), in local population of Lombardia (4.0%) and Pavia (5.9%).
In the univariable analysis, being older than 66 years (HR: 2.64, 95%CI 1.06-6.55, p=0.029), with ECOG PS $\geqslant$ 2 (HR: 5.81, 95%CI 2.18-15.49, p=0.002), >1 comorbidities (HR: 2.72, 95%CI 1.14-6.48, p=0.023), having dyspnea at the time of COVID diagnosis (HR: 6.10, 95%CI 2.37-15.68, p=0.0001), and being hospitalized (HR: 6.75, 95%CI 3.06-36.89, p<0.001) were associated with increased risk of death.
In multivariable analysis, ECOG PS $\geqslant$ 2, dyspnea, hospitalization and days of treatment delay were associated with increased risk of death.
Conclusions: The incidence of SARS-CoV-2 infection in our cancer patients was lower than that observed in the local population of Lombardia and Pavia, while mortality rate was higher. Predictive factors of death in cancer population correlate consistently with those alreay published about global population.

E28

COVID-19 VACCINATION IN CANCER PATIENTS - THE ROLE OF ANXIETY, DEPRESSION AND DISTRESS IN THE PERCEPTION OF VACCINE EFFICACY

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Background: Following the establishment of the vaccination plan to counter the spread of the SARS-CoV-2 virus, cancer patients were immediately included among the population groups most at risk. Despite the recommendations, many patients did not adhere to the vaccination plan, showing skepticism and low confidence in the vaccine. For this reason, this research was established, with the aim of investigating, from a multifactorial and multidimensional point of view, the variables that influenced the perception of trust in the anti-Covid-19 vaccine, in order to intervene on them and encourage vaccination membership.
Material (patients) and methods: A questionnaire was created, containing the Anxiety and Depression Scale (Zigmond & Snaith, 1983), the Distress Thermometer (Roth et al., 1998) and four questions investigating the perception of vaccination efficacy or ineffectiveness, which can be evaluated on a simplified scale 1-4. This questionnaire was administered to cancer patients immediately before the inoculation of the anti-COVID-19 vaccine. This questionnaire was administered both during the first (T0) and during the second dose (T1) of the vaccine, so as to be able to detect the differences between the variables considered.
Results: Preliminary data on a sample of 342 patients were analyzed: the average age was 66.22 and its composition was mostly female (57.9%). In both vaccine administrations, distress, anxiety and depression were found to be within normal and below threshold values, while the perceived efficacy of the vaccine was found to be slightly higher at T1 than at T0. Distress was found to affect all the variables considered; its reduction, therefore, involves the modification of the average values of anxiety, depression, efficacy and ineffectiveness of the anti-Covid-19 vaccine.
Conclusions: The reduction in perceived distress and the related increase in overall confidence in the anti-Covid-19 vaccine can be explained by historical and contextual factors, given the high sensitivity of the Distress Thermometer in detecting perceived distress within the 7 days prior to its compilation. Further data will be presented, given the ideas that this research poses for future studies.

First dose (T0)

	Distress	Anxiety	Depression	Vaccine efficacy	Vaccine ineffectiveness
M	3.03	5.0	5.0	3.3	1.9
DS	2.7	3.2	3.5	.66	.82

Second dose (T1)

	Distress	Anxiety	Depression	Vaccine efficacy	Vaccine ineffectiveness
M	2.3	4.1	4.7	3.4	1.6
DS	2.4	3.3	3.7	.7	.67

E29

ONCOLOGICAL PROCEDURES AND RISK ASSESSMENT OF COVID-19 IN THORACIC CANCER PATIENTS: A PICTURE FROM AN ITALIAN CANCER CENTER

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Background: Since Sars-Cov2 infection (COVID-19) has rapidly spread around the world, Italy has quickly become one of the most affected countries. Patients (pts) with thoracic malignancies had the highest frequency of severe complications. Healthcare systems introduced strict infection control measures to ensure optimal cancer care. This study aimed to investigate the efficacy of pre-procedure screening for COVID-19 and whether infection influenced the opportunity of patients to receive timely diagnosis and therapy.
Material (patients) and methods: We retrospectively collected data of oncological procedures of pts with confirmed or suspected thoracic malignancies, treated at Oncology Dept or coming from Emergency Dept of San Luigi Gonzaga Hospital between Jun 2020 and Mar 2021 (from the end of the 1st wave until the middle of the 3rd one). Outpatients were evaluated by a nasopharyngeal swab (NPS) performed 24/48 hours before procedures. Inpatients were tested by NPS before and after hospitalization according to a predetermined schedule.
125 pts were included in this analysis. Median age was 72 years; males were 64%. ECOG Performance Status was 0-1 in 90% of pts. Histological types were: NSCLC (86.4%), SCLC (7.2%), mesothelioma (5.6%), amartochondroma (0.8%). Stages IV were 80%. 135 procedures were performed: 102 were diagnostic (75 lung biopsies, 21 bronchoscopies, 1 lumbar puncture, 2 thoracoscopies, 1 thoracentesis, 1 gastroscopy and 1 thoracic surgery), 25 palliative and 8 therapeutic. 89 and 46 procedures were performed in outpatients and inpatients, respectively. Of the 132 NPS performed, 8 were found to be positive. Positive pts were infected during the 2nd wave (from Nov 2020 to Jan 2021). One patient was infected during hospitalization, the other ones in community. Most of pts were asymptomatic, only 2 had mild symptoms. 6 procedures (4.4%) were postponed (5 diagnostic, 1 palliative), an explorative bronchoscopy was canceled and a diagnostic biopsy was performed even though the patient tested positive. The median time to resolution of the infection was 17 days (range 11-36). The median delay of the procedures was 36 days (range 14-55). 4 patients started systemic treatment in a median time of 40.5 days (range 21-57).
Conclusions: Our analysis pointed out that Sars-Cov2 infection led to the postponement of a small but not negligible number of diagnostic and therapeutic procedures and that a structured screening for COVID19 is critical for the best management of scheduled procedures during pandemic.

E30

SURVEY ON THE EFFICACY OF TELEPHONE-BASED COMMUNICATION WITH RELATIVES OF HOSPITALIZED CANCER PATIENTS IN COVID-19 ERA IN ITALY

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Background: Physical distancing and no-visitor policies adopted to prevent COVID-19 spread in hospital wards have deeply impacted communication with patients and their relatives. Whereas in pre-COVID-19 era family-clinician meetings were held in person, during the SARS-CoV-2 pandemic interactions often take place over the phone. The frequently unilateral direction of the communication might cause feelings of uncertainty and distress to those who are at home. Until now little data about this topic have been collected, and most of them refer to COVID-19 patients. Literature about hospital communication with non-COVID-19 patients and their relatives during the pandemic is lacking.
Material and methods: After no-visitor policy was adopted in the Onco-Hematological Unit of Modena, inpatients' relatives were contacted daily for clinical updates. After discharge, a telephone satisfaction survey was administered to all relatives of patients consecutive admitted between December 2020 and January 2021 (n=97). Mean score of response and potential statistically significative differences depending on respondents' characteristics were assessed. Suggestions were collected.
Results: Most relatives were satisfied with the communication received, with a mean score over all items of 4.69 on a 5-point Likert scale (standard deviation: 0.60). Results showed high satisfaction rate with both the informative (mean±SD: 4.66±0.64) and emotional (mean±SD: 4.66±0.58) content, with no significant difference depending on respondents' demographic characteristics ($p>0.05$). Among suggestions, 13% found it useful to organize more video calls; 12% would have preferred to have always talked to the same clinician; 4% suggested the first meeting be held in person and 2% would have liked to have seen the patient before discharge, especially after a long hospital stay.

Conclusions: Our findings show that a structured telephone-based interaction might help overcome communication barriers imposed by pandemic-related restrictions. We believe that these findings could stimulate other clinicians to think about ways to involve relatives in continuous care of their loved ones when personal contact is impossible and might lead to other studies with a higher number of participants. In our view, anything that can help with the identification of relational and communication strategies that have worked during the pandemic will contribute to the creation of a precious know-how in view of future crises.

E31

SARS-COV-2 SCREENING THROUGH SERIAL NASOPHARYNGEAL (NP) SWABS AMONG CANCER PATIENTS IN AN ITALIAN HIGH PREVALENCE AREA

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Background: SARS-CoV-2 infection and the associated COVID-19 pneumonia have dramatically disrupted the management of cancer care worldwide. Indeed, this crisis has raised the urge of thoughtfully balancing the risk of delaying potentially curative treatments and the risk of developing a life-threatening respiratory infection. In this study, we report the experience of an Italian Reference Cancer Center, where close triage procedures had to be promptly adopted.

Patients and methods: We retrospectively analyzed a consecutive cohort of 787 cancer patients (pts) who accessed the Day Hospital (DH) of the Oncology Department of Udine from April 6th to June 19th 2020. Screening NP swabs and RT-PCR analysis were performed at every access in pts who, after passing the triage, were admitted to receive intravenous therapies. Clinicopathological data were collected from electronic health records and include sex, age, tumor type, disease stage, type of treatment, number of swabs received and RT-PCR results.

Results: In a population of 787 cancer pts receiving intravenous therapies, 2602 NP swabs were performed. Among all pts 55.7% were female and 44.3% male pts, respectively; 54.9% of pts aged ⩾65. Of note, 28.2% of pts had gastrointestinal tumors, 23% breast cancer, 19.8% lung cancer and 14.2% tumors of the genitourinary tract. Approximately 32% of pts had early-stage disease whereas 68% of pts received therapies for advanced disease. Treatments most frequently included chemotherapy (60%), immunotherapy (14.7%) and target therapies (9.8%) whereas 11.1% of swabs were performed in pts who entered to DH for supportive therapy. The median number of SARS-CoV-2 tests per patient was 3 and 26% of pts received ⩾5 swabs. In the whole population, only 10 SARS-CoV-2 tests (1.3%) resulted positive and the isolating procedures were promptly activated.

Conclusions: In the pandemic context, the adoption and gradual improvement of rigorous procedures aimed at minimizing COVID-19 spread among pts and healthcare professionals are mandatory to ensure continuity of care for cancer pts. In our experience systematic triage, sequential screening with NP swabs and the prompt identification of asymptomatic SARS-CoV-2 carriers limited COVID-19 spread among cancer pts accessing the Oncology DH.

E32

IRRATIONAL BELIEFS, DYSFUNCTIONAL EMOTIONS AND PSYCHOLOGICAL ILLNESS IN CANCER PATIENTS DURING THE PANDEMIC: THE COGNITIVE BEHAVIORAL APPROACH AND HUMOR

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Background: Since March 2020, Sars-Cov-2 lead to an immediate reprogramming of all aspects of private and professional life. The fear of contagion and the new rules to follow also imply in cancer patients the progressive birth of irrational beliefs, such as not being treated, dysfunctional emotions, namely anxiety, depression, anger, guilt and a marked psychological illness. At the same time, in the health workers of the Oncology Department this translates into stress, a heavy working climate, a slowdown in activities. We developed a project for the management of the emotions of the patients group and of healthcare professionals through the Cognitive Behavioral Approach (CBT).

Material and Methods: The intervention with patients was carried out by telephone, while two interviews of 15 minutes each in the working shift were carried out for health workers. Some CBT techniques postulate that individuals try to achieve their goals in a reference environment where they are subjected to activating events (including emotions, memories, reality perceptions) that tend to favor or not the achievement of the goals themselves. The emotional and behavioral consequences are the reactions to the contents of thought. In both groups we worked on rational or irrational thoughts (everything we think about the world and ourselves): for cancer patients

we used the logical and empirical questioning based on inductive reasoning, teaching, analogies, while for health professionals we used the logical and empirical discussion often integrated by the self-reinforcing humor.
Results: Globally, 25 cancer patients and 15 health workers at the Medical Oncology Unit of the University Hospital of Cagliari were included in our project. 90% of the patient group reported an improvement on psychological malaise, on the reduction of irrational thoughts and on the change of dysfunctional emotions towards more functional ones, reducing the sense of abandonment. The whole group of health workers obtained a significant improvement in stress and the perceived organizational climate resulting from the easing of tension and a review of the situations that occurred.
Conclusions: The new keys of interpretation and alternative analysis of one's thinking create a substantial improvement in one's internal perception and external perception of events and one's behavior by reflecting on relationships. Humor becomes an effective coping strategy for reducing emotional impact.

E33

SARS-COV-2 VACCINE IN CANCER PATIENT: REAL LIFE EXPERIENCE IN A NORTH WEST PIEDMONT SPOKE HOSPITAL

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Background: Cancer patients (Pts) present an increased risk of a severe form of SARS-cov-2 disease because of immunodepression status induced by treatments and cancer. National and international organizations recommend vaccination against SARS-cov-2 in this specific population. An efficient vaccination procedure in oncologic Pts is particularly relevant. ASLVC Oncology spoke (North West Piedmont, Italy) includes two hospitals: one in Vercelli and one in Borgosesia. We report here our real life experience about SARS-Cov-2 vaccination in cancer patients, in both hospitals.
Material and methods: Hospital Administration approved a local vaccination procedure for cancer pts on April 2021. Medical, nursing and administrative staff of Oncology Unit were trained for the vaccination of their Pts and worked out a specific disclosure. A member of a Voluntary Association welcomed and helped Pts. Each patient benefited from an individual medical examination with an oncologist before the first administration of the vaccine. Medical history, allergy and ongoing treatments were reviewed before administration. Blood tests were performed to every patient treated by chemotherapy. A consent form was signed. Information about Covid-19 status and vaccination were reported in the oncologic medical record.
Results: Vaccines used for vaccination were Pfizer-BioNTech according to current guidelines. Two doses were scheduled three to four weeks apart. Since April 26th to May 19th in Vercelli there were 9 injection sessions; 115 Pts.were vaccinated: 91 (79%) had first dose and 24 (21%) second; while in Borgosesia 45 Pts were vaccinated, 32 (73%) had first dose and 12 (27%) second. Nobody had acute reaction or serious adverse event, 20 (12.5%) Pts had late and mild adverse events. Most frequently reported adverse event were arm pain, arthralgia, muscle weakness, headache. Only one patient (0.6%) with a history of severe allergic reaction was vaccinated in intensive care.
Conclusions: Vaccination against Sars-Cov-2 in cancer Pts is safe and is still ongoing in our hospitals. An appropriate and specific procedure permitted to manage and efficient vaccination in cancer Pts even through chemotherapy.

E34

CLINICAL PRESENTATION OF PATIENTS WITH A NEW DIAGNOSIS OF GASTROINTESTINAL MALIGNANCIES IN AN UNIVERSITY HOSPITAL IN MILAN DURING THE FIRST YEAR OF SARSCOV2 PANDEMIC

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Background: on January 2020 in China was isolated a new aggressive Coronavirus rapidly spreading all over the world. On March 8th a national lockdown was imposed in Italy. During lockdown most of the planned procedures in the hospitals were delayed and the screening cancer programs stopped, leading to a reduction of the diagnosis of early cancer and precancerous lesion. Considering colorectal cancer screening, it is calculated that in Italy, during 2020, a total of 1200 diagnosis of adenocarcinoma and 6700 diagnosis of adenoma was missed. Moreover, during lockdown the population was recommended to avoid hospital access, leading to a delay between the onset of symptoms and diagnosis.
We analized the patients with a new diagnosis of gastrointestinal (GI) cancer during 2020 to verify the impact of screening suspension.
Matherial and methods: we selected the clinical records of patients visited in 2020 with a new diagnosis of GI cancer: colorectal, gastroesophageal, pancreatic and other cancers, and analyzed patients with colorectal cancer across the six quarters of the year.

Results: From 1st Jan 2020 to 31 Dec 2020 a total of 150 patients with a diagnosis of GI cancer came to our departement for a first visit. The number of patient was stable during the year: 35 new patients in Jan-Mar period, 36 new patients in Apr-Jun, 39 new patients in Jul-Sep and 40 in Oct-Dec. The site of primary cancer was colorectal in 74 patients. If we consider the stage, disease, we found 36 patients with an initial stage; 27 patients with a more advanced disease needing adjuvant treatment and 9 patients with metastatic disease.
In the first half of the year, 8 patients came from screening, while none was found in the second half. Symptomatic patients invastigated as outpatients were distribuited as follows: 10 patients in Jan-Mar, 9 patients in Apr-Jun, 10 patients in Jul-Sep and 11 patients in Oct-Dec. Patients diagnosed in Emergency Department due to severe anemia or bowel obtruction increased along the year: 3 patients in Jan-Mar, 5 patients in Apr-Jun, 7 in Jul-Sep and 11 patients in Oct-Dec.
Conclusions: our data show a mild reduction of activity during the first year of SarsCOV2 pandemic. We noted an unavoidable decrease through the year of patients coming from screening programs and an increase of those that needed an emergency surgery. The effect of screening delay will be seen probably in the subsequent years. A quick restart of screening regional program is warranted.

E35

REAL LIFE EXPERIENCE OF SARS-COV2 INFECTION AND VACCINE ADMINISTRATION: PRELIMINARY DATA

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Background: Oncology patients, with active, lung, metastatic (m) disease, 1st y after diagnosis, have higher risk of SARS-COV2 infection, 26% severity/mortality vs 2-3% overall. Individual risk depends from age, comorbidity, PS. Infection impaired diagnosis/surveillance. Population includes patients with active early (E) or m disease on treatment (OT), untreated m and long survivors. mRNA-based vaccines demonstrated >90% efficacy to prevent disease. Immunization level depends from tumors/sites, therapy, administration timing, immune dysfunction and fitness. Adverse events were local reaction, systemic reactivity, asthenia, headache and pyrexia.
Methods: We reported prevalence of infection/disease, ongoing vaccine administrations among patients followed at Oncology Territorial Care, S. Salvatore Hospital L'Aquila.
Results: 18 patients reported infection, 8 asymptomatic, 2 mild symptoms (pyrexia), 8 severe (bilateral pneumonia, fever, respiratory failure, 6 hospitalized): 9 OT, 2 m colorectal, 1 m pancreatic, 1 m ovarian, 1 m neuroendocrine, 1 m renal cell, 1 pancreatic with previous m colorectal, 2 E colorectal (3 chemotherapy/target agents, 1 chemotherapy, 2 biological agent, 2 surgery, 1 locoregional therapy); 8 survivor, 3 with history of m; 1 with active disease before treatment beginning. 5 thereafter received 1 vaccine dose. From 4thJan to 20thMay 2021, 194 patients (87 M, 107 F) underwent vaccine administration, 24 affected by E disease OT, 64 m OT, 1 m out of treatment, 105 survivors. Tumors: 18 lung (11 m, 2 E OT), 64 gastrointestinal (19 m, 6 E OT), 33 breast (9 m, 2 E OT), 20 genitourinary (8 m, 2 E OT), 5 cutaneous/melanoma (3 m OT), 20 gynecological (6 m, 2 E OT), 6 HN (3 m, 1 E OT), 5 CNS, 17 multiple (1 m, 6 E OT), 6 rare (3 m, 1 E OT). Administered vaccines: 106 Pfizer-BioNTech, 17 Moderna, 4 Astra Zeneca. All grade adverse events: pain at injection site, 37, fever 9, asthenia 8, myalgia/articolar pain 7, headache 3, diarrhea 1, erythema 1, vomiting 1, hypertension 1, conjunctival hemorrhage1, hemolitic syndrome, 1. Conclusion: Open questions are long-term efficacy, protection again mild/severe infection, immunity in aged, contagiousness of vaccinated patients, intervals between administrations. Vaccination in oncology population prevents frail patients from infection and severe disease, monitoring in clinical practice safety/effectiveness, not included in trials. Mature data will be presented.

F – Gastrointestinal (Colorectal) Cancers

F01*

A PHASE II STUDY OF CAPECITABINE PLUS CONCOMITANT RADIATION THERAPY FOLLOWED BY DURVALUMAB (MEDI4736) AS PREOPERATIVE TREATMENT IN RECTAL CANCER: PANDORA STUDY FIRST-STAGE (NCT04083365)

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Background: The combination of capecitabine plus long course radiotherapy (RT) is the standard preoperative therapy in cT3-4 cN+ rectal cancer. Pathologic Complete remission (pCR) can be considered as surrogate end point of efficacy of treatment in terms of disease free survival (DFS). Preclinical data points heavily toward a strong synergy between RT and immune treatments.
Methods: This is a prospective phase II, open label, single arm, multi-centre study, conducted with support from AstraZeneca, in patient with locally advanced rectal cancer who receive concomitant CT/RT therapy (825 mg/m2 twice daily capecitabine every day and 5040 cGy radiotherapy for 5 days per week for 5 weeks) followed by durvalumab (1500 mg Q4W for 3 administrations). Surgery is performed after 10-12 weeks from neoadjuvant therapy. The primary endpoint is pCR rate after at least 1 cycle of durvalumab. The sample size has been estimated by using the optimal Simon's two-stage design. If more than 4 complete responses are observed in the first 19 enrolled patients, 36 additional patients will be accrued for a total of 55 evaluable patients.
Results: Between November 2019 and July 2020, 20 patients were accrued and 19 were evaluable for study objectives, concluding the first stage of the trial. Baseline characteristics of the first 19 evaluable patients enrolled are listed in the table. All patients received 3 infusions of durvalumab; 18 patients underwent surgery after a median of 13 weeks from CHT/RT end. Five complete pathological responses (ypT0N0) were observed, allowing proceeding to the second stage. About toxicity, four patients had Grade 3-4 adverse events (AE); the most frequent G3-4 AE related to the neoadjuvant therapy were anemia (n=1), diarrhea (n=2) and neuthropenia (n=2). No grade 3 and 4 adverse events related to Durvalumab treatment were observed. Eight patients had G1-2 AE related to durvalumab, the most common being asthenia (n=2) and nausea (n=2).
Conclusions: At the end of study's first stage the preoperative treatment with radiotherapy plus capecitabine followed by durvalumab showed a safe toxicity profile and promising activity in terms of pCR rate. The second part of the trial is ongoing, and the accrual is under completion (44 patients enrolled as of 10 February 2021).

F02*

ENCORAFENIB PLUS CETUXIMAB WITH OR WITHOUT BINIMETINIB IN BRAFV600E MUTATED (MUT) METASTATIC COLORECTAL CANCER (MCRC) PATIENTS: AN ITALIAN MULTICENTER REAL-LIFE EXPERIENCE

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Background: The BEACON study recently demonstrated improved ORR, PFS and OS with encorafenib plus cetuximab with or without binimetinib compared to chemotherapy plus anti-EGFR in previously treated *BRAF*V600E mut mCRC patients (pts). Although no formal comparison was planned, the addition of binimetinib did not provide significant advantage. In the last year FDA and EMA approved encorafenib plus cetuximab for pre-treated BRAFV600E mut mCRC pts. In July 2019 a nominal use program was launched in Italy to offer the new target combination to *BRAF*V600Emut mCRC pts.
Patients and methods: This is a retrospective study designed to evaluate the activity, efficacy and safety of encorafenib plus cetuximab with or without binimetinib in the real-life setting. We collected data from pts treated at 18 Italian centers.
Results: Out of 105 pts included in this study, 35 (33%) and 70 (67%) received triplet and doublet, respectively. Most pts (86%) had ECOG PS 0-1 and 66% had synchronous disease. 71 (68%) pts had right-sided primary tumours and 20 (19%) cases were MSI-High. Globally, 101 (96%) pts were previously exposed to oxaliplatin, 88 (84%) to anti-VEGF and 9 (9%) to anti-EGFR. 70 (67%) and 35 patients (33%) had received 1 or >1 prior line of therapy, respectively. 97 (92%) pts (62/70 with doublet and 35/35 with triplet) were eligible for response analysis. Among pts evaluable for RECIST response, ORR was 25% (24/97) [21% (13/62) with the doublet and 31% (11/35) with the triplet (P=0.4)] and disease control rate

was 71% (69/97) [66% (41/62) with the doublet and 80% (28/35) with the triplet (P=0.2)]. Median PFS was 4.2 months [4.2 and 4.7 months with the doublet and the triplet, respectively (P=0.6)]. Main adverse events (AEs) are summarized in the table. G1-2 skin toxicity was reported in 1/35 (3%) and 18/70 (26%) pts receiving triplet and doublet, respectively.

Conclusions: Our real-life data are consistent with those reported in the BEACON trial. The safety profile appears feasible with no unexpected AEs. A lower incidence of AEs is reported with the doublet, except for G1-2 skin toxicity.

AEs

	Triplet (N=35)		Doublet (N=70)	
	Any Grade N (%)	Grade 3-4 N (%)	Any Grade N (%)	Grade 3-4 N (%)
Asthenia	22 (63)	3 (9)	42 (60)	5 (7)
Anti-EGFR related skin rash	23 (66)	1 (3)	30 (43)	0
Nausea	18 (51)	3 (9)	16 (23)	1 (1)
Diarrhea	13 (37)	1 (3)	12 (17)	1 (1)
Vomiting	10 (29)	1 (3)	9 (13)	1 (1)
Skin toxicity	1 (3)	0	18 (26)	0
Anemia	12 (34)	5 (14)	17 (24)	3 (4)

F03

MOLECULAR CORRELATES OF CLINICAL BENEFIT IN PREVIOUSLY TREATED PATIENTS (PTS) WITH BRAF V600E-MUTANT METASTATIC COLORECTAL CANCER (MCRC) FROM THE BEACON STUDY

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Background: Encorafenib + binimetinib + cetuximab (enco/bini/cetux; triplet) and enco + cetux (doublet) regimens improved overall survival and objective response rate vs standard of care in pts with previously treated BRAF V600E-mutant mCRC in the randomized phase 3 BEACON study. To identify molecular correlates of clinical outcome, we performed molecular profiling in tumors from pts in the study.

Methods: Baseline tumor samples were retrospectively analyzed by whole-exome sequencing (WES) and whole transcriptome sequencing (WTS) using ImmunoID NeXT (Personalis, Menlo Park, CA, USA). BRAF-mutant (BM) and consensus molecular subtypes (CMS) were determined using published classifiers. Pathway activities were evaluated with gene set variation analysis. Objective tumor response was evaluated according to each subtype. Additional association and interaction analyses between molecular features and clinical outcomes by treatments are ongoing and will be presented.

Results: Baseline tumor samples were analyzed by WES and/or WTS from 527 of 665 (79.2%) randomized pts. The biomarker analyses set is representative of the total pt population and had similar clinical outcomes. Of the 460 pts analyzed by WTS (165/224 [73.7%] in the triplet arm, 146/220 [66.4%] in the doublet arm, and 149/221 [67.4%] in the control arm), 84.6% were classified as either CMS1 (n=225) or CMS4 (n=164). The proportion of pts classified as BM1 was 32.2% (n=148) and the majority (84.5%) of these were CMS4, whereas many of those classified as BM2 (67.8%, n=312) were CMS1 (64.7%). In the BM1 and CMS4 tumors, expression of inflammatory response and epithelial mesenchymal transition genes were elevated, and expression of cell cycle genes was reduced. The response rate in pts with CMS4 and/or BM1 tumors was higher in the triplet arm (CMS4: 33.3% [95% CI: 21.7–46.7]; BM1: 33.3% [95% CI: 21.4–47.1]) compared with the doublet arm (CMS4: 19.2% [95% CI: 9.6–32.5]; BM1: 14.9% [95% CI: 6.2–28.3]).

Conclusions: Molecular characteristics and biological properties observed in BRAF V600E-mutant mCRC suggest that a subset of pts with specific molecular features may derive greater clinical benefit from triplet than doublet therapy. Additionally, these findings support the utility of gaining further understanding of the biological landscape in BRAF-mutant mCRC to enable potential hypotheses for pt selection to improve clinical outcome in future studies.

F04

NEOADJUVANT CHEMO-RADIOTHERAPY RESPONSE IN PATIENTS AFFECTED BY MISMATCH REPAIR DEFICIENT (DMMR) LOCALLY ADVANCED RECTAL CANCER

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Background: Only few data on microsatellite instability in rectal cancer are available in literature, and dMMR role in pre-operative chemoradiotherapy (CRT) response is under debate. The aim of our study was to evaluate the frequency and therapeutic implications of dMMR status in patients (pts) with locally advanced rectal cancer belonging to our Center.

Methods: Data were retrospectively collected from 201 pts belonging to the Oncology Unit of the University Hospital of Cagliari from 2014 to 2020. All pts were affected by locally advanced rectal adenocarcinoma (cT3-4 +/- N1-2). All pts included in the study underwent neoadjuvant CRT treatment with capecitabine and RT long course (total dose of Gy 50.4) and subsequently underwent total mesorectal excision (TME) followed by adjuvant chemotherapy. Mismatch repair (MMR) expression was evaluated through immunohistochemistry on surgical samples.

Results: Pts median age was 67 years (range 34-89). 130/201 were male and 71 were female. 62 (31%) had stage II disease and 139 (69%) had stage III disease. Considering MMR, 195/201 (97%) pts had proficient mismatch repair (pMMR), while 6/201 (3%) had dMMR. In dMMR pts defective proteins were: MSH2 in 3 pts, MLH1 and PMS2 combined in 2 pts and MSH6 in 1 pt. dMMR pts showed, unlike pMMR pts, poor or no response to CTR. Responses were assessed through TRG evaluation (Ryan and Dworak scoring systems) on the primary tumour. 4 pts presented a TRG-3 and 2 pts showed a TRG-4, according to Ryan score. All of them had a grade 1 regression, according to Dworak.

Conclusions: The results of our study, albeit with limitations related to the retrospective nature and the limited number of dMMR cases, might indicate a correlation between microsatellite instability and little or no response to preoperative CRT. It would be useful to analyze the data prospectively and further evaluate MMR as a predictor of response to combined chemo-radiotherapy.

Tab n. 1. Pts characteristics.

	pMMR	dMMR
N.	195	6
Stage II	60	2
Stage III	135	4
Ryan score*[1]		
TRG-1	85	
TRG-2	101	
TRG-3	9	4
TRG-4		2
TRG-5		
Dworak score*[2]		
Grade 0		
Grade 1	9	6
Grade 2	101	
Grade 3	64	
Grade 4	21	

*[1]TRG-1 no visible cancer cells; TRG2 single cells or small group of cancer cells; TRG3 residual cancer outgrown by fibrosis; TRG4 significant fibrosis outgrown by cancer; TRG5 no fibrosis with extensive residual cancer.

*[2]Grade 0, no response; Grade 1, minimal response; Grade 2, moderate response; Grade 3, near complete response; Grade 4, complete response.

F05

ANGIOPOIETIN-2 EARLY INCREASE PREDICTS BENEFIT FROM REGORAFENIB IN METASTATIC COLORECTAL CANCER (MCRC) PATIENTS: THE PROSPECTIVE REGOLAND STUDY

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Background: Regorafenib is a treatment option for refractory mCRC patients with no validated predictors of benefit. We previously showed that, among several circulating angiogenic factors, low baseline Ang-2 and Tie-2 plasma levels were associated with good prognosis and that the early increase of Ang-2 during the treatment could predict benefit from regorafenib *(Antoniotti et al, J Clin Oncol 36:675-675, 2018)*. To prospectively validate these retrospective findings, we conducted the REGOLAND study.

Methods: Ang-2 and Tie-2 were assessed by ELISA on plasma samples collected at baseline (d1) and after 15 days (d15) of treatment in a cohort of mCRC patients receiving regorafenib, as per indication. To detect a HR for PFS of 0.50 in favour of the early increase (Δd15-d1) of Ang-2 levels, setting two-sided α=0.05 and β=0.10, 87 events were

required according to Schoenfeld design. Comparisons among concentrations of each marker at d1 and d15 were performed by Wilcoxon test. Median values at baseline were used as cut-off to discriminate patients with low versus high plasma levels and their correlation with outcome was analysed.

Results: One hundred patients were included. Median PFS and OS were 2.5 and 6.7 months, respectively. The early increase of Ang-2 at d15 was reported in 42 patients and was associated with longer PFS (median 2.7 vs 2.4 months; HR for PFS: 0.72 [95%CI:0.48-1.08], *P*=0.095). As compared to d1, an overall decrease of Tie-2 levels at d15 was observed (*P*=0.007), but it was not associated with clinical outcome. Low levels of Ang-2 at baseline were associated with longer PFS (HR: 0.59 [95%CI:0.39-0.89], *P*=0.005) and OS (HR:0.62 [95%CI:0.41-0.94], *P*=0.017), while Tie-2 levels were not. In the multivariate model, the association of Ang-2 levels with PFS was confirmed (HR:0.48 [95%CI:0.31-0.76], *P*=0.001), but not in OS (HR: 0.80 [95%CI:0.49-1.28], *P*=0.351).

Conclusions: Ang-2 is a prognostic marker and its early modulation predicts clinical benefit among mCRC patients treated with regorafenib. We hypothesize that Ang-2 levels early increase as a consequence of the successful inhibition of Tie-2 by regorafenib that leads to a compensatory increase of the ligand and correlates with anti-tumour activity.

F06

POST-INDUCTION MANAGEMENT IN LEFT-SIDED RAS AND BRAF WILD-TYPE METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH FIRST-LINE ANTI-EGFR-BASED DOUBLET REGIMENS: A MULTICENTER, "REAL-LIFE" STUDY

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Background: Few data regarding post-induction management following first-line anti-EGFR-based doublet regimens in patients with left-sided RAS/BRAF wild-type metastatic colorectal cancer (mCRC) are available.

Methods: This multicentre, retrospective study aims at evaluating clinicians' attitude, safety and effectiveness of post-induction strategies in consecutive patients affected by left-sided RAS/BRAF wild-type mCRC treated with doublet chemotherapy plus anti-EGFR as first-line regimen, who did not experience disease progression within 6 months from induction initiation, at 22 European Institutions. The measured clinical outcomes were: PFS, OS, adverse events, and ORR.

Results: At the data cut-off, among 686 consecutive patients with left-sided RAS/BRAF wild-type mCRC treated with doublet plus anti-EGFR as first-line regimen from March 2012 to October 2020, 355 eligible patients have been included in the present analysis. Among these, 118 (33.2%), 66 (18.6%), and 11 (3.1%) received maintenance with 5-fluorouracil/leucovorin (5FU/LV)+anti-EGFR, anti-EGFR, and 5FU/LV, respectively, while 160 (45.1%) patients continued induction treatment (non-maintenance) until disease progression, unacceptable toxicity, patient decision or completion of planned treatment. The median period of follow-up for the overall population was 33.7 months (95%CI: 28.9-35.6). Median PFS of the 5FU/LV+anti-EGFR, anti-EGFR, 5FU/LV, and non-maintenance cohorts was 16.0 (95%CI: 14.3-17.7; 86 events), 13.0 (95%CI: 11.4-14.5; 56 events), 14.0 (95%CI: 8.1-20.0; 8 events), and 10.1 months (95%CI: 9.0-11.2; 136 events), respectively ($p<0.001$). Median OS was 39.6 (95%CI: 31.5-47.7; 43 events), 36.1 (95%CI: 31.6-40.7; 36 events), 39.5 (95%CI: 28.2-50.8; 4 events), and 25.1 months (95%CI: 22.6-27.6; 99 events), respectively ($p<0.001$).

Conclusions: Among treatment strategies following an anti-EGFR-based doublet first-line induction regimen in patients affected by left-sided RAS/BRAF wild-type mCRC treated in a "real-life" setting, 5FU/LV+anti-EGFR resulted the most adopted, effective and relatively safe regimen.

F07

CIRCULATING PRO-ANGIOGENIC FACTORS DYNAMIC CHANGES DURING TREATMENT WITH FOLFIRI-AFLIBERCEPT: INTERIM ANALYSIS OF DISTINCTIVE STUDY - A GISCAD TRIAL

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Background: To date, no biomarkers for second-line anti-angiogenic treatment in RAS wild type (wt) metastatic colorectal cancer (mCRC) patients (pts) progressing after first-line anti-epidermal growth factor receptor (EGFR) agents have been validated. Here, we present our findings on the dynamic changes of circulating pro-angiogenic factors levels during treatment with FOLFIRI-aflibercept from the pre-planned interim analysis of DISTINCTIVE trial (NCT04252456).

Material (patients) and methods: RAS wt mCRC pts with progression after first-line treatment containing oxaliplatin and an anti-EGFR monoclonal antibody are treated with second-line FOLFIRI-aflibercept. Pts are prospectively allocated to a favorable (>4 ng/ml) or unfavorable (⩽4 ng/ml) prognostic group, according to Elisa-assessed baseline VEGFR2 plasma levels. The changes of circulating pro-angiogenic factors between baseline (BL), first tumor assessment (TA1) and disease progression (PD) are evaluated. Primary endpoint is overall survival (OS) according to VEGFR2 levels. Secondary endpoints are OS, progression free survival (PFS), response rate, safety and pro-angiogenic factors levels. Statistical analysis is performed with MedCalc (survival distribution: Kaplan-Meier; survival comparison: log-rank test).

Results: Globally, 73 pts were enrolled from April 2018 to June 2020; 44 pts were eligible for the interim analysis. Median OS was 11.9 months (95% CI: 10-14.2). OS was significantly improved (not reached [NR] vs 11.2 months, 95% CI: 8.2-14.2) in pts with increase of interleukin-8 levels between BL and PD (HR 0.30, p=0.0226) and between TA1 and PD (HR 0.16, p=0.0092) and increase of neuropilin-1 between TA1 and PD (HR 0.18, p=0.0143). Median PFS was 8.3 months (95% CI: 4.2-24.2). PFS was longer in pts with decreased levels between BL and PD of endoglin (9.8 months [95% CI: 4.7-11.6] vs 4 months [95% CI: 2.2-24.2), HR 0.3, p=0.0128), C reactive protein (10.6 months [95% CI: 8.3-11.9] vs 5.3 months [95% CI: 3.7-24.2], HR 0.40, p=0.0158) and serum amyloid protein (10 months [95% CI: 5.8-14.2] vs 4.7 months [95% CI: 2.5-24.2], HR 0.39,p=0.0175).

Conclusions: Based on the results of our analysis, the change of pro-angiogenic factors levels during FOLFIRI-aflibercept might be a promising predictive factor for treatment efficacy.

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F08

ADJUVANT CHEMOTHERAPY FOR RECTAL CANCER PATIENTS RECEIVING PREOPERATIVE TREATMENT: A META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

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Background: There is no clear evidence on the role of adjuvant chemotherapy in patients with locally advanced rectal cancer (LARC) who have received preoperative treatment.

Materials and methods: A systematic review of MEDLINE, EMBASE and Cochrane Systematic reviews databases from January 1966 to February 2021 was performed independently by two Authors. All randomized phase III trials comparing, after preoperative treatment, post-operative chemotherapy with observation, or comparing monotherapy with intensified treatment or observation with polychemotherapy were considered eligible and included into the analysis. Primary end point was the Overall Survival (OS). Heterogeneity between the trials was assessed using the Mantel-Haenszel test. An alpha error<5% was assumed as index of statistical significance. All selected trials were analysed and pondered using theJadad score.

Results: Five randomized trials were included into the primary analysis, and 3 in the secondary one. No significant

differences in favor of adjuvant chemotherapy were observed in OS and DFS both in the primary (HR=0.95, IC95%: 0.83-1.09, p=0.48 and HR=0.91, IC95%: 0.80-1.03, p=0.14 respectively) and in the secondary analysis (HR=1.02, IC95%: 0.85-1.22, p=0.84 and HR=0.83, IC95%: 0.64-1.06, p=0.13 respectively). Likewise, no differences in OS and DFS were observed in the indirect comparison between poli-chemotherapy and observation (HR=1.09, IC95%: 0.87-1.36, p=0.45, and HR=1.03, IC95%: 0.8-1.32, p=0.84 respectively).

Conclusions: Our Data do not support use of adjuvant chemotherapy after neoadjuvant chemo-radiotherapy in patients with LARC.

F09

CLINICIANS' ATTITUDE TO DOUBLET PLUS ANTI-EGFR VERSUS TRIPLET PLUS BEVACIZUMAB AS FIRST LINE TREATMENT IN PATIENTS WITH LEFT-SIDED RAS AND BRAF WILD-TYPE METASTATIC COLORECTAL CANCER: A MULTICENTRE, "REAL-LIFE" STUDY

Parisi A.[1], Salvatore L.[2], Avallone A.[3], Filippi R.[4], Nigro O.[5], Gelsomino F.[6], Leo S.[7], Dell'Aquila E.[8], Roselló Keränen S.[9], Lombardi P.[10], De Petris I.[11], Giampieri R.[12], Morelli C.[13], De Tursi M.[14], De Galitiis F.[15], Troiani T.[16], Garajova I.[17], Ghidini M.[18], Spinelli G.P.[19], Porzio G.[20]

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Background: A doublet+anti-EGFR treatment is widely considered the preferable first-line regimen in left-sided *RAS/BRAF* wild-type mCRC patients, resulting superior in terms of activity and efficacy compared to a doublet+bevacizumab. However, data comparing doublet+anti-EGFR and triplet+bevacizumab are lacking, and the relative benefit of an intensive regimen plus an antiangiogenic backbone in this population is debated.

Methods: This multicentre, retrospective study is aimed at evaluating clinicians' attitude to triplet+bevacizumab and doublet+anti-EGFR as first-line regimen in left-sided *RAS/BRAF* wild-type mCRC patients treated in clinical practice in 22 European Institutes from March 2012 to October 2020. A random case-control matching was performed to compare activity (ORR), and effectiveness (PFS, OS, secondary resection rate of metastases with curative intent) between triplet+bevacizumab and doublet+anti-EGFR, based on ECOG-PS, age, gender, and burden of disease.

Results: The median period of follow up for the overall population was 33.8 months (95%CI: 29.9-108.6), while among the doublet+anti-EGFR and the triplet+bevacizumab cohort was 33.4 months (95%CI: 29.1-108.6) and 41.6 months (95%CI: 30.4-68.8), respectively. ORR, PFS, and OS of the doublet+anti-EGFR cohort were 71.3% (95%CI: 65.2-78.2), 12.3 months (95%CI: 11.3-13.2), and 32.3 months (95%CI: 28.6-35.9), respectively.

After random case-control matching, 32 patients from each cohort were paired according to all the selected variables. Median PFS of the doublet+anti-EGFR was 13.6 months (95%CI:8.9-31.7; 26 events), while median PFS of the triplet+bevacizumab was 16.1 months (95%CI:12.1-36.8; 28 events, p=0.621). Median OS of the doublet+anti-EGFR was 30.2 months (95%CI: 14.4-69.5; 18 events) while median OS of the triplet+bevacizumab was 38.1 months (95%CI: 33.1-101.1; 15 events, p=0.028).

The ORR was 65.6% and 90.6% in the doublet+anti-EGFR and the triplet+bevacizumab cohort, respectively (p=0.016). Secondary resection rate differed significantly between the doublet+anti-EGFR and the triplet+bevacizumab cohorts (18.8% and 46.9%, respectively, p=0.016)

Triplet+bevacizumab cohort was associated with a higher incidence of G3-4 neutropenia (25.0% vs 12.5%, p=0.041).

Conclusions: Although doublet+anti-EGFR remains the recommended upfront regimen in left-sided *RAS/BRAF* wild-type mCRC patients, our real life data suggest triplet+bevacizumab might be at least equally active and effective in properly selected cases.

F10

MTHFR, TSER AND DPYD GENE MUTATION IS ASSOCIATED WITH TOXICITY AND RESPONSE IN PRE-OPERATIVE CHEMO-RADIOTHERAPY FOR LOCAL ADVANCED RECTAL CANCER

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Background: Radiotherapy and 5 FU based chemotherapy is the most common pre-operative regimen used for cT3-T4, N1 rectal cancer (RC). Evaluation of predictive markers of response and toxicity to radio-chemotherapy is a challenging approach for patients (pts) and drug selection. In the present experience we have analyzed the predictive role of the genetic polymorfisms (MTHFR, TSER and DPYD) on toxicity and response to pre-operative radio-chemotherapy. The usefulness of determining the MTHFR mutation C677T is the evaluation of the efficacy / toxicity risk during therapies with drugs such as methotrexate and 5 fluorouracil that act on the metabolic pathways in which the MTHFR enzyme is involved.

Materials and methods: We have enrolled twenty five patients with locally advanced RC treated with pre-operative radiotherapy and fluoropyrimidines base chemotherapy.

Genetic polymorphisms of MTHFR C677T, MTHFRA 1298C, DPYD IVS 14+1G>A, DPYDA 2846T, DPYD T 1679 G, TSER 28 bp VNTR were analyzed by PCR and pyrosequensing of genomic DNA extracted from peripheral blood samples. Genetics markers were correlated with toxicity to treatment (chemotherapy and radio-chemotherapy) and clinical response.

Results: Patients characteristics were: male 18 pts, female 7 pts, median age 66 years, ECOG PS 0-1 all pts. We found DPYD IVS 14+1 G>A G/G homozygous wilde type, DPYD A2846T, T/T homozygous wilde type and DPYD T1679 g, T/T homozygous wilde type in 100% of pts, homozygous wilde type MTHFR C677T in 10% of pts, MTHFR C677T homozygous mutated in 50% of pts, heterozygous MTHFR A1298C in 60% of pts and homozygous wilde type MTHFR A 1298C in 40% of pts. G3-G4 advers events (diarrhea, neutropenia, asthenia, mucositis) were observed in 60% of pts with heterozygous MTHFR A 1298C and in 10% of pts with homozygous mutated MTHFR C 677t. Treated with chemo radiotherapy combination. DPYD homozygous wilde type was not associated with severe toxicity. Rectal surgery with TME/TEM will be performed 8 weeks after the end of pre-operative chemo-radiotherapy. We obtained 8 patological complete response and 17 partial patological response.

Conclusions: Concomitant assesment of genetic polymorphisms of MTHFR and DPYD is promising to predict severe toxicity during preoperative chemo-radioterapy approach for pts with locally advanced rectal cancer. This result does not exclude the need to consider other non-genetic factors that might influence the individual enzyme activities.

F11

A BAYESIAN APPROACH FOR REPORTING EFFICACY FROM AN OBSERVATIONAL STUDY OF REAL-LIFE TREATMENT WITH TRASTUZUMAB PLUS LAPATINIB IN HER2-POSITIVE METASTATIC COLORECTAL CANCER

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Background: HER2 positivity is found in 3-5% of metastatic colorectal cancer (mCRC). The phase II HERACLES-A trial showed that dual anti-HER2 therapy with trastuzumab plus lapatinib (T+L) has a 30% response rate (RR) in HER2+ RAS wt mCRC after the failure of standard care (Sartore-Bianchi 2016). These data led to the inclusion of T+L regimen in NCCN guidelines while in the absence of confirmation by large trials comparing treatments, AIOM considers its use within trials or off-label only. Large controlled trials, especially for an uncommon biomarker-defined subset, would require efforts often unbearable in the frame of independent clinical research. We designed this study to confirm HERACLES-A safety and efficacy through a Bayesian approach allowing monitoring longitudinally RR and toxicity (Tox, defined as adverse event G3) of T+L in the practice setting.

Methods: We adopted a Bayesian design for an observational cohort study in order to report the RR of T+L in HER2+ mCRC by updating the prior probability of response observed in the HERACLES-A trial with the likelihood of the RR in all consecutive patients with the same characteristics treated at Niguarda Cancer Center after the HERACLES-A closure. We simultaneously monitored RR and Tox using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee, and Yuan 2017), with futility boundaries for both endpoints (RR=10% and Tox=30%, H_0) and a total sample size of 40 patients. We planned 3 interim analyses at 10, 20, and 30 patients evaluable for RR. Type I = II error was ~10%, calculated after 10000

simulations under H_0 and H_1 (RR = 35% and Tox = 20%) scenario.

Results: From May 2019 to Jan 2021, we collected data of HER2+ mCRC patients treated with off-label T + L according to HERACLES-A inclusion criteria (Valtorta et al, 2015; Sartore-Bianchi et al. 2016). Patients were followed for RR and AEs. On May 1st 2021, at the first interim analysis, 2/10 evaluable patients had PR according to RECIST criteria, with an updated likelihood of response of 26.2% and a 95% credible interval of 13.7-39.2%. No AE G3 drug-related were reported.

Conclusions: At the first planned interim analysis, treatment with T + L for HER2+ mCRC was confirmed to be safe and effective. A Bayesian approach, allowing monitoring results accounting for previously available data, can support the process of approval by regulatory authorities for treatments targeted to uncommon biomarker-defined subsets such as HER2+ mCRC.

F12

POTENTIAL EMERGING ROLE OF LIQUID BIOPSY IN CLINICAL PRACTICE IN METASTATIC COLORECTAL CANCER (MCRC) TREATMENT

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Background: Liquid biopsy could become a useful mean in mCRC patients (pts) in order to weigh tumor heterogeneity. In this study we aimed to investigate the clinical utility of circulating exosomes DNA (exo-DNA) and the role of some cytokines in the management of mCRC during the first-line of chemotherapy.

Methods: Exosomes analysis at different steps (basal, post-therapy and at progression) was assessed in 70 mCRC, in 60 pts KRAS mutational status on exo-DNA was evaluated at baseline (BL) and progression (PD). In 90 pts, 45 all-wild-type (WT) and 45 with a RAS or BRAF mutation (MT) the expression of 5 cytokines (CD44, IL-6, IL-8, CD147 and progranulin) was analysed at different time-points.

Results: Plasma exosomes levels have been significantly modified during the three disease steps, also in an only-liver metastatic disease subgroup which received hepatic resection (p=0,012). Levels significantly correlated with the extension of metastatic sites (p=0,0019) and they were significantly higher in MT compared to WT pts (p=0,026). CEA expression and liver metastasis were correlated with KRAS status and fractional abundance. KRAS-WT (>125 copies) and KRAS-MT (>37 copies) BL levels were related to worse OS (p=0,001; p=0,008). At BL one WT patient and 4 KRAS-MT pts on tissue resulted respectively KRAS-MT and KRAS-WT on exo-DNA. At PD other 4 mutations were revealed in WT cohort and KRAS mutation disappeared in 5 pts in MT cohort.

The MT and WT subgroups expressed different CD44, IL-8 and progranulin levels statistically significant in the analysed steps. CD147 and IL-6 concentration was significantly modified during the treatment and at PD only in the WT cohort. Only IL-8 BL expression was identified as a prognostic factor for OS in MT-group (p=0,0135).

Conclusions: In a prospective cohort of mCRC pts, we have shown how exosome-based liquid biopsy and some cytokines analysis might provide relevant clinical information to therapeutic stratification that must be investigated in wide studies.

F13

MONOCYTES TO RED BLOOD CELLS RATIO (MRR): AN INNOVATIVE HAEMATOLOGIC PROGNOSTIC PARAMETER IN METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH FOLFIRI-AFLIBERCEPT - A SUBGROUP ANALYSIS FROM THE DISTINCTIVE STUDY - A GISCAD TRIAL

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Background: Recently, laboratory parameters have been explored as potential prognostic biomarkers in several tumour types. We present our findings in the population enrolled in the interim analysis of the DISTINCTIVE study (NCT04252456), a prospectively stratified, biologically enriched phase II trial of second-line FOLFIRI-aflibercept in RAS wild type (wt) metastatic colorectal cancer (mCRC) patients (pts) with progression after first-line anti-epidermal growth factor receptor (EGFR) agents.
Material (patients) and methods: RAS wt mCRC pts resistant to first-line oxaliplatin-based chemotherapy plus an anti-EGFR monoclonal antibody 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 and angiogenic factors levels. Clinical and laboratory data are collected in order to assess their correlation with outcome. Statistical analysis is performed with MedCalc (survival distribution: Kaplan-Meier; survival comparison: log-rank test; cut off: ROC curves).
Results: Overall, 73 pts were enrolled from 04/2018 to 06/2020; 44 were eligible for interim analysis. Among the laboratory values assessed, monocytes (M), red blood cells (RBC) and M/RBC ratio (MRR) were found of particular interest. Longer OS was related to lower ($\leqslant 0.7x10^3/\mu l$) M count (14.2 months [95% CI: 10.4-14.2] vs 6.8 months [95% CI: 0.5-6.8], HR 0.003, p=0.0002) and higher ($>3.81x10^6/\mu l$) RBC count (14.2 months [95% CI: 10.4-14.2] vs 6.8 months [95% CI: 0.5-9.1], HR 0.005, p< 0.0001). Improved PFS was correlated with lower M count (8.5 months [95% CI: 5.3-24.2] vs 4.2 months [95% CI: 3.9-5.8], HR 0.18, p=0.0266) and higher RBC count (8.5 months [95% CI: 5.7-24.2) vs 2.5 months [95% CI: 2.1-4.2], HR 0.04, p=0.0007). Lower MRR ($\leqslant 1528$) was related to longer OS (14.2 months [95% CI: 10.4-14.2] vs 6.8 months [95% CI: 0.5-6.8], HR 0.004, p=0.0003) and PFS (8.5 months [95% CI: 5.3-24.2] vs 4.2 months [95% CI: 3.9-5.8], HR 0.24, p=0.0492).
Conclusions: Our findings confirmed the prognostic role of some haematologic parameters and suggested an innovative and easy-to assess ratio in RAS wt mCRC pts receiving FOLFIRI-aflibercept in the second-line setting.
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F14

THE ROLE OF SITE OF METASTATIC RESECTION (MR) IN METASTATIC COLORECTAL CANCER (MCRC) PATIENTS (PTS): A MONO-INSTITUTIONAL COHORT STUDY

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Background: Approximately 50%-60% of CRC pts developed metastases, usually to liver and lung. When feasible, MR is the only potentially curative option in the multimodal management of mCRC pts. We retrospectively analyzed mCRC pts, underwent radical lung and/or liver resection at our Institution, investigating the impact of resection site on overall survival (OS).
Material (patients) and methods: mCRC pts underwent radical liver (group [gp] 1), lung (gp 2) or liver and lung (gp 3) resection were included. The following variables were collected: age (> vs = 65 years); gender (male vs female); primary tumor site (right vs left); synchronous vs metachronous; RAS/BRAF status; number (N) of MR (1,2 or $\geqslant$3); chemotherapy (CHT) treatment (No treatment vs Post-operative vs Peri-operative/pre-operative treatment) and CHT regimen (5FU monotherapy, Oxaliplatin-based, Irinotecan-based regimen, FOLFOXIRI, Bevacizumab, Anti-EGFR). The association of MR site and OS was evaluated. Univariate and multivariate analyses for OS were performed.
Results: A total of 191 mCRC pts underwent radical MR was included in the analysis: 112 (59%) pts in gp 1, 38 pts (20%) in gp 2, 41 pts (21 %) in gp 3. 145 (76%) pts had a left-sided tumor and 46 (24%) a right-sided tumor. Out of 156 evaluable pts, 73 (47%) pts harbored a RAS mutation, while out of 136 evaluable pts, 4 (3%) pts had a BRAF mutation. Regarding the N of MR, 125 pts (65%) underwent 1 MR, 43 (23%) pts 2 MR and 23 (12%) $\geqslant$3 MR. In the overall population, median OS (mOS) was 77.2 months. According to MR site, mOS was 59.4, not reached (NR) and 99.1 months, in gp 1, 2 and 3 (p=0.075). At the multivariate analysis no significant association with OS was shown for MR site, while the N of MR and RAS status were indipendently associated with OS. mOS was 58.5, 97.7 months and NR in pts underwent 1, 2 and $\geqslant$3 MR, respectively (p=0.02). mOS was 58.5 and 83.1 months in RAS mutated and RAS wild-type pts (p=0.12).
Conclusions: Despite the limited number of pts and the retrospective nature of our study, these results confirmed that surgery represents the only option with curative intent for mCRC pts, independently of metastatic site (liver vs lung vs liver and lung). A higher number of MR is associated to long-term survival and this could be explained with an accurate selection of pts that could benefit from multiple MR. A multidisciplinary approach is essential for the

management of mCRC pts and surgery should be evaluated and performed independently of site of MR.

F15

HEALTH EQUITY AUDIT BEFORE AND AFTER THE START OF A DIAGNOSTIC-THERAPEUTIC PATHWAY FOR THE MANAGEMENT OF RECTAL CANCER

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Background: Rectal cancer treatment has evolved during the past 40 years thanks to the advancements in imaging, pathology, surgical treatments, radiotherapy, and chemotherapy, within a multidisciplinary team approach providing an optimum health care. Many studies have demonstrated how the social environment can affect the treatment and outcome in neoplastic patients. The primary endpoint of this study was to compare the Health Equity Audit (HEA) before and after the establishment of a structured pathway for the management of neoplasms of the rectum.

Methods: This was a retrospective study carried out at the University Hospital of Ferrara, Italy, on selected patients with rectal cancer stage < IIIb, who were diagnosed and treated in the year 2012 (Group 1:35 patients), before the start of the rectal cancer multidisciplinary team, and in the year 2020 (Group 2: 35 patients), after the setting up of the rectal cancer multidisciplinary team.

For each patient we considered different social variables: age at time of diagnosis, gender, distance in km from the centre of treatment, level of education. We analysed the following indicators: Indicator 1: time between the first symptoms and diagnosis; Indicator 1b: % of patients coming from screening programs; Indicator 2: time between the communication of diagnosis and the beginning of the treatment; Indicator 3: adherence to treatment; Indicator 4: time between the end of neoadjuvant treatment and surgery.

Results: The characteristics of the patients at baseline were well balanced between the two groups.

Indicator 1 goal was achieved in 64% of the patients in group 1 and in 73,9% of the patients in group 2.

Indicator 2 goal was achieved in 35,3% of group 1 and 55,6 % of group 2. In group 1, 71% of patients who lived less than 30 km away from our center met the indicator 2 criteria while only 33% of patients who lived more than 30 kms away had the same result. In group 2, 53% of patients who lived less than 30 km away from our center met the indicator 2 criteria while none of the patients who lived more than 30 kms away did. In addition, we found out that in group 1 the rate of patients who met indicator 2 goal increased with level of education.

These preliminary results demonstrated that equality seems to have improved after 8 years despite the Covid pandemic in 2020.

Conclusions: The introduction of a dedicated treatment pathway appears to have improved Health Equity for patients with rectal cancer.

F16

CD44 EXPRESSION IN METASTATIC COLORECTAL CANCER: NEW PROGNOSTIC BIOMARKER?

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Background: The transmembrane glycoprotein CD44, the major hyaluronan (HA) receptor, has been proven to regulate cell growth, survival, differentiation, and migration and is thereby widely considered to be involved in carcinogenesis. CD44 might potentially represent a new therapeutic molecular target, and it is being assessed in ongoing clinical trials. The prognostic value remains controversial. Here, we aimed to investigate the correlation between CD44 expression and the clinicopathological features and survival of metastatic colorectal cancer (mCRC) patients (pts)

Patients and methods: Data from 65 mCRC pts of the Medical Oncology Department of the University Hospital of Cagliari were retrospectively collected from 2008 to 2021. The immunohistochemical analysis was performed at the Pathology Department of the University Hospital of Cagliari on 3 μm thick sections obtained from paraffin blocks. Paraffin-tissue sections were immunostained using anti-human CD44 Rabbit monoclonal antibody (clone SP37). The immunointensity was subclassified into four groups as shown in the table. Statistical analysis was performed with MedCalc© (survival distribution: Kaplan-Meier; survival comparison: log-rank test, association between categorical variables: Fisher's exact test)

Results: Pts median age was 66 years (range 49-85). Regarding CD44 expression: score was 0 in 18 pts, 1+ in 16 pts, 2+ in 17 pts and 3+ in 14 pts. Median Overall Survival (mOS) was 28.1 months (m) (95%CI: 21.3-101). Overexpressed CD44 (3+) was correlated with poor prognosis (p=0.0011; HR=0.2), with a mOS of 15.4 m (95% CI 8.5-35.9) versus 28.8 m (95%CI:24.8-101) in low CD44 expression (0, 1+, 2+). CD44 strong expression was

associated with clinical poor prognostic features: 58.3% were = 70 years old (p=0.03); 58.3% had inoperable disease (p=0.01); 91.7% had stage IV at diagnosis (p=0.1); 75% had synchronous metastases (p=0.4); BRAF was mutated in 9% of CD44 non-overexpressed vs 25% of CD44 3+ pts (p=0.1)

Conclusions: CD44 markedly correlated with aggressive tumor behavior and contributed to the progression of mCRC, thus suggesting its role as a novel prognostic marker and potential therapeutic target for mCRC pts

CD44 expression	Score
Negative or weak membrane staining (MS) in less than 10 % of tumor cells (TC)	0
Weak MS in at least 10 % of TC or moderate MS in less than 10% of TC	1
Moderate MS in at least 10% of TC or intensive MS in less than 10% of TC	2
Intense MS in at least 10% of TC	3

F17

VITAMIN D DEFICIENCY IN METASTATIC COLORECTAL CANCER (MCRC) WORSENS SURVIVAL AND CORRELATES WITH SIGNIFICANT PERIPHERAL INFLAMMATORY/IMMUNE CELL CHANGES

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Background: Vitamin D (Vit.D) deficiency is a poor prognostic factor in mCRC patients (pts). To evaluate if this is attributable to an impaired immunity boosting effect, we analysed peripheral inflammatory/immune components in Vit. D deficient mCRC pts.

Methods: Pts eligible for 1st line chemotherapy were tested for serum Vit.D levels and association of Vit.D with OS was analyzed (Kaplan Meier and Cox regression methods). Differences in 24 peripheral inflammatory/immune variables [i.e.: white blood cells (WBC), neutrophils (N), lymphocytes (L), NL ratio (NLR), platelet/L ratio, monocytes, sum of mononuclear cells, systemic inflammatory index, CRP, LDH, albumin, albumin-to-globulin ratio, D-Dimer, different subsets of lymphocytes] between Vit.D deficient (<10 ng/dL) vs non-deficient (>10 ng/dL) pts were analyzed (Mann-Whitney-Wilcoxon test).

Results: 135 pts were included [74 males, median (m) age 64 yrs, range 30-84]. mVit.D was 14.8 ng/ml (range 3-160); mOS for Vit D <10 ng/mL (63 pts) vs >10 ng/mL (70 pts) was 12.3 vs 24.5 months, respectively [HR 2.03, p 0.002]. Vit.D deficient pts had a significant increase in mN (69% vs 65%, p 0.04), mNLR (3.5 vs 2,9, p 0.05) and CD4+/L (48% vs 40%, p 0.04) and a significant decrease in CD19+/L (4% vs 7%, p 0.03) as compared to non-deficient pts. In Vit.D deficient pts, N count could further stratify prognosis: mOS for < vs > 6000/µl was 19.1 vs 8.1 [HR 2.76, p 0.006]. No significant difference in survival between Vit.D deficient pts with low N and non-deficient pts was observed (p 0.07).

Conclusions: Vit.D deficiency is confirmed to be a poor prognostic factor in mCRC pts and correlates with meaningful inflammatory/immune changes. The observed increase in T helper cells (CD4+) might be restricted to Th1 activation with a possible surge in proinflammatory cytokine production reflected, peripherally, by higher N and NLR values. Further evaluation of the Th1/Th2/Th17/Treg balance and effector cytokines is underway. The observed B cell (CD19+) depletion might be due to the lack of Vit.D-induced differentiation.

F18

SKIN TOXICITY MANAGEMENT IN LEFT-SIDED RAS AND BRAF WILD-TYPE METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH FIRST-LINE ANTI-EGFR-BASED DOUBLET REGIMEN: A MULTICENTER STUDY

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Background: Skin toxicity in patients affected by metastatic colorectal cancer (mCRC) in treatment with anti-EGFR is a well-known issue. However, ad hoc ESMO guidelines have been published only recently.

Methods: The aim of this retrospective, multicenter, observational study, was to assess safety and effectiveness in the management of anti-EGFR-related skin toxicity, in a real-life context, in left-sided RAS/BRAF wild-type mCRC patients treated with doublet (FOLFOX or FOLFIRI) plus anti-EGFR (Cetuximab or Panitumumab) as first-line regimen, distinguishing between two different therapeutic approaches: pre-emptive (i.e. a primary prophylaxis with minocycline or doxycycline from the first day of antineoplastic therapy for at least two weeks, with or without non-pharmacological measures) or reactive (any treatment administered at the time of skin toxicity onset). The measured clinical outcomes were: treatment-related adverse events, PFS, OS, and ORR.

Results: 515 consecutive patients treated from March 2012 to October 2020 in 22 European Institutions have been included in the present analysis. Among these, 173 (33.6%) received a pre-emptive treatment, while 342 (66.4%) a reactive treatment. The median age was 64 years (range: 28-84) and the male/female ratio was 64.3/35.7%. A lower incidence of any grade skin rash both in the overall population (78.6% vs 94.4%, $p<0.001$) and in patients treated with panitumumab (76.1% and 93.7%, $p<0.001$) or cetuximab (83.3% and 94.5%, $p=0.004$) was found in the pre-emptive compared to the reactive cohort. A higher rate of anti-EGFR dose reduction was required during induction treatment in the reactive cohort (20.3% vs 14.5%, $p<0.001$). At a median period of follow up of 30.0 months (95%CI: 26.1-33.9) for the overall population, no difference was found between the pre-emptive and the reactive cohort in terms of ORR (69.2% vs 72.8%, respectively), mPFS (12.3 vs 13.0 months, respectively, $p=0.127$), mOS (28.8 vs 33.5 months, respectively, $p=0.118$).

Conclusions: Although recommended by international guidelines, a pre-emptive approach to the anti-EGFR-related skin toxicity in mCRC patients still appears less adopted in daily clinical practice compared to a reactive management. A wider reception and application of this indication is desirable to potentially improve quality of life of patients without impair continuity in antineoplastic therapy.

F19

TRIFLURIDINE/TIPIRACIL OR REGORAFENIB FOR LATE-LINE METASTATIC COLORECTAL CANCER PATIENTS: A MULTICENTER RETROSPECTIVE OBSERVATIONAL REAL-LIFE STUDY

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Background: Compared with best supportive care, Trifluridine/tipiracil (FTD/TPI) and Regorafenib (REG) have been shown to prolong survival in refractory metastatic colorectal cancer (mCRC). Real-world data or head-to-head trials comparing these 2 agents are lacking. The aim of our study was to evaluate the efficacy and safety profiles of FTD/TPI and REG in real-life daily practice.

Materials and methods: Clinical variables of all patients diagnosed with mCRC treated with FTD/TPI or REG between 2015 and 2020, were retrospectively collected from 8 institutes in Lazio Region. Adverse events (AEs), overall survival (OS), progression free survival (PFS), overall response rate (ORR) and disease control rate (DCR) were compared between the 2 groups.

Results: We had available data for 80 patients (pts), 51.2% (n=41) treated with FTD/TPI and 48.7% (n=39) with REG (48 males and 32 females). Median age was 68 (42-83); median duration of follow-up in FTD/TPI-treated pts was 6 (1-31) vs 4 months (mos) (1-45) of the REG group ($p=0.06$). PS ECOG ranged between 0 (n=10; 12.5%) and 2 (n=22; 27.5%). 20 pts (25%) received previous active 3 lines of treatment, 59 pts (73.7%) 2 lines and 1 pt (1.2%) 1 line. A reduction in drug doses due to the appearance of AEs was carried out in 57.1% of cases (n=24) with FTD/TPI versus 42.8% with REG (n=18). The most reported grade III/IV AEs with FTD/TPI included haematological toxicities (46.7%, n=36), asthenia (10.3%, n=8) and gastrointestinal disorders (3.8%, n=3); in the REG-treated pts we observed asthenia (10.3%, n=8), hand-foot skin reaction (10.3%, n=8), gastrointestinal (9%, n=7) and haematological toxicities (7.7%, n=6). The FTD/TPI pts showed a longer OS than the REG pts: 13 (CI95%=4.6-21.4) vs 5 mos (CI95%=4.2-5.8) respectively ($p=0.09$). Best 1-y survival rate was observed with FTD/TPI (29.2% vs 5.1% of REG). PFS was the same: 4 (CI95%=2.4-5.6) vs 3 mos (CI95%=2.5-3.5) in the FTD/TPI and REG group respectively ($p=0.17$). ORR was twice higher in REG pts (5.2% vs FTD/TPI 2.6%); 1 complete response was achieved with REG. DCR was greater in FTD/TPI pts (42.1% vs 34.2%) ($p=0.99$).

Conclusions: With the limit of sample size, our study has confirmed the efficacy of FTD/TPI and REG in the real-life setting. Despite a higher ORR achieved in REG-treated pts, statistically not significant, we can underline that treatment with FTD/TPI, even if worse tolerated due to haematological toxicities, could allow a longer OS and a greater control of the disease.

F20

CIRCULATING TUMOUR DNA (CTDNA)-GUIDED RETREATMENT WITH ANTI-EGFR-BASED THERAPY IN RAS WILD-TYPE (RASWT) METASTATIC COLORECTAL CANCER (MCRC): EVIDENCE FROM THE CLINICAL PRACTICE

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Background: ctDNA analysis holds great promise for monitoring tumour response, detecting acquired resistance and studying clonal dynamics in mCRC. Notably, RAS status in ctDNA has been shown to predict the efficacy of anti-EGFR rechallenge, though until now only clinical criteria have been used to guide treatment decision in the clinic. We applied ctDNA-based extended RAS genotyping to clinical criteria to aid in molecularly selecting patients (pts) eligible for anti-EGFR-based retreatment in a real-world setting.
Material and methods: ctDNA testing for RAS status was prospectively applied to tissue-based RASwt mCRC progressed after first-line anti-EGFR-containing regimen and at least one further line and deemed candidates for retreatment with EGFR blockade based on clinical judgment. Blood samples were taken at unique time-point before retreatment and RAS status was analyzed using PCR or NGS. A cohort of RASwt mCRC retreated with EGFR blockade only based on clinical criteria was identified to make comparison. The co-primary endpoints were the objective response rate and the PFS.
Results: Overall, 8 pts were included in the analysis between February-November 2020. The median age was 59 years and 89% had an ECOG PS of 0-1. All pts had left-sided CRC and 6 (67%) had metachronous disease. The median PFS to anti-EGFR-containing first-line was 16 months. 5 pts (62%) received $\geqslant$2 prior lines. The mean turnaround time for RAS status was 5.5 days (range 1-6 days). The anti-EGFR retreatment was administered combined with chemotherapy in 6 pts (75%) and as single-agent in 2 pts (25%). Among 7 evaluable pts, the objective response rate was 100%: 5 (71,4%) partial and 2 (28,5%) complete responses. The duration of response was 4 months. The median PFS and 0S were 6 and 8.5 months. Notably, anti-EGFR-based retreatment is still ongoing in 4 pts. When compared with the historical cohort (n=10) selected for anti-EGFR retreatment solely based on clinical criteria, ctDNA-driven approach resulted in a higher chance of achiving an objective response (p=0.03) and a longer PFS ($p<0.001$).
Conclusions: Blood-based RASwt status may enrich for mCRC more likely to benefit from anti-EGFR-based retreatment. RAS genotyping in ctDNA represents a feasible, fast, and cost-effective tool to be implemented in the clinic for advancing precision medicine. Prospective randomized trials are underway to evaluate efficacy and optimal timing of ctDNA-guided retreatment with EGFR inhibitors in mCRC.

F21

PROGNOSTIC IMPACT OF ANTI-EGFR MONOCLONAL ANTIBODIES (MOABS) DOSE REDUCTION DUE TO SKIN TOXICITY IN METASTATIC COLORECTAL CANCER (MCRC): A RETROSPECTIVE SINGLE CENTRE EXPERIENCE

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Background: Treatment of RASwt mCRC includes anti-EGFR moAbs in combination with chemotherapy, although skin toxicities (ST), occurring in 90% of cases, often require drug reductions. Previous evidence showed that ST from anti-EGFR inhibitors relates to favourable prognosis and increased responses, probably due to EGFR intron-1 polymorphisms. Nowadays, it is still unknown whether a dose reduction could adversely affect the therapeutic efficacy of anti-EGFR drugs. Here, we conducted a single centre retrospective analysis to assess the correlation between dose reduction and clinical efficacy of anti-EGFR moAbs.
Material and methods: Patients with RASwt mCRC treated at our centre between January 2018 and December 2020 with anti-EGFR moAbs ± chemotherapy as 1st line therapy were included. Skin toxicity was established according to the "Common Terminology Criteria for Adverse Events" (CTCAE v4.0) and treatment response evaluated with RECIST criteria as per clinical practice. The study population was divided into two groups according to ST-related anti-EGFR moAbs dose reduction (Group A) or not (Group B). Objectives of the study were the disease control rate (DCR), progression free survival (PFS) and overall survival (OS). The Fisher exact test and the Man-Witney were used to investigate differences in terms of DCR and dose intensity reduction, while the Kaplan–Meier method explored survivals.
Results: Forty-one patients were enrolled in the study, including 16 patients (39%) in group A and 25 (61%) in group B. All patients in Group A had ST, including G1-2 events in 87.5% (n=14) and G3-4 in 12.5% (n=2);

conversely, 26% (n=7) of patients in Group B had G1-2 while no one had G3-4 ST. Comprehensively, patients in Group A experienced an average dose-intensity reduction due to ST of 9% (range 3-14%). The DCR was 62.5% in Group A and 52% in Group B (p=0.53). Finally, both PFS (HR 0.36; CI 95% 0.13-0.98; p=0.04) and OS (HR 0.31; CI 95% 0.12-0.082; p=0.01) resulted significantly improved in A as compared to B.

Conclusions: Our data endorse previous scientific reports about the prognostic role of ST in anti-EGFR therapy, confirming the favorable impact also in patients undergoing dose reductions of anti-EGFR moAbs. Hence, in case of ST, our data suggest dose reductions to preserve quality of life without affecting treatment efficacy.

F22

LONGITUDINAL ANALYSIS CAN IMPROVE THE ACCURACY OF TUMOR BIOMARKERS FOR COLORECTAL CANCER DIAGNOSIS

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Background: Tumor biomarkers for cancer diagnosis have been assessed with disappointing results. But there is evidence that repeated measurements instead of a single measurement could be more useful, as they allow the early identification of exponential growth. We investigated if longitudinal analysis of CEA and CA19.9, conducted over a short period of time, could increase their accuracy for the diagnosis of colorectal cancer.

Matherial and Methods: Two measurements of CEA and CA19.9 were taken 2 to 5 weeks between each, in 48 patients with newly diagnosed non metastatic colorectal cancer and 45 healthy controls. A positive result at the single test was given if values were above normal levels at the first sample (5 ng/ml for CEA and 32 mIU/ml for CA19.9). Both samples were included in a dual test and a positive result was given if both values were above normal levels or when the value increased with a doubling time less than 180 days. This doubling time threshold was chosen as the most effective at increasing sensitivity without affecting specificity. If both samples were below a lower threshold (2 ng/ml for CEA and 15 mIU/ml for CA19.9) dual test was considered negative regardless of the doubling time. Sensitivities and specificities were calculated and compared with N-1 corrected chi square test.

Results: Sensitivities and specificities for the single test were respectively 42.2% and 95.6% for CEA and 13% and 97.7% for CA 19.9. The dual test for CEA led to the identification of 10 more patients and sensitivity significantly increased to 63.8% (p = 0.039) and correctly identified 1 false positive subject in the control group, for a specificity of 97.7% (p=0.865). No significant differences in both sensitivity and specificity were seen between the two tests for Ca 19.9, nor its addition modified the results of CEA alone.

Conclusions: Our data suggest that longitudinal analysis can improve the diagnostic accuracy of at least some tumor biomarker, leading to improved sensitivity and possibly also specificity. Times and modalities of such assessments need to be better characterized. Theoretically, this approach could improve the accuracy of a wide set of biomarkers and deserves further investigations.

F23

IRINOTECAN PLUS OXALIPLATIN: A SALVAGE COMBINATION THERAPY FOR RELAPSED COLORECTAL CANCER

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Background: Irinotecan, a topoisomerase I inhibitor, has proven to be effective in both chemonaive as well as previously treated patients. Oxaliplatin, a 1,2 diaminocyclohexane platinum compound, has demonstrated activity as first-line therapy as well as previously treated patients in terms of response rate and time to progression.

The irinotecan/oxaliplatin combination showed synergistic activity in vitro, and the optimal dose safety profile has been explored in several phase I-II studies.

A recent randomized phase II study revealed that the irinotecan/oxaliplatin combination has a manageable toxicity profile Neutropenia and diarrhea were the dose-limiting toxicitie. The recommended dose of irinotecan/oxaliplatin in every-2-week and every-3-week schedules ranged from 150–200 mg/m2 and 85 mg/m2, respectively.

Materials and methods: We have studied eight eligible patients (pts) with metastatic colorectal cancer, with disease progression, bidimensional measurable disease,

PS< 2 and adeguate haematological, hepatic, renal and cardiac functional, of which three whith rigth colon cancer and five with left colon cancer, treated with EGFR inhibitors panitumumab, VEGF inibitors bevacizumab and various lines of chemotherapy.

Patients with median age of 60 years (range 46-74) were treated for a median of six cycles (range 1-13 cycles) with oxaliplatin 85 mg/m2 following by irinotecan at the dose of 125 mg/m2 with peg-filgrastin rescue. Treated patients were previously sensitive to chemotherapy treatment with schedules containing oxaliplatin and / or irinotecan.

Results: Out eight evaluable patients for response, we obtained 4 stable disease and 1 disease progression in the left colon cancer and 3 disease progression in the right colon cancer. The duration of stable disease varies between 84 days and 273 days. The haematologic toxicity was modeste. Three patients (pts) experienced grade 3-4 neutropenia without fever, 5 pts anemia, three pts experienced thrombocytopenia grade 2 and 1 patient hypertransaminasemia grade 2. Additional non-hematologic toxicities experienced include mild nausea/vomiting, hair change, pruritus, mucositis, xerosis and peripheral paraesthesia.
Conclusions: Salvage treatment with oxaliplatin and irinotecan in heavily pretreated patients demonstrated modest activity. This activity was most evident in left colon cancers.

F24

OPTIMIZING THE MULTIDISCIPLINARY TEAM CANCER CARE: THE CASE MANAGER ROLE

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In many health care systems globally, cancer care is driven by multidisciplinary cancer teams (MDTs). In particular, patients with gastrointestinal cancer (GIC) require integrated treatments that must be shared and ensured in a short time. For this reason, the implementation of MDTs cancer care is of fundamental importance. The MDT of the Francavilla Fontana Hospital, active since December 2020, has identified the case manager as a central figure to improve cancer care and team work. The case manager is a professional specifically trained to manage one or more clinical cases on the basis of a predefined path in a given space-time continuum. From December 2020 to April 2021, 26 patients were included in the case management project of the gastrointestinal MDT (GIMDT). Study endpoints were the timing between patient entry in the MDT and staging (CT scan, MRI) and cancer treatment starting (surgery, radiotherapy, chemotherapy) and patients reported outcomes (PROs). All these paths were led by the case manager. The median age was 69 years (37-89); 50% were female (13 patients) and 50% male (13 patients). The site of disease was the colon in most patients (54%); followed by stomach (19%); rectum (12%); pancreas (4%) and other sites (11%). Most patients underwent surgery followed by chemotherapy (46%); 39% received only surgery; 11% surgery plus chemotherapy and radiotherapy; 4% received best supportive care. Median time from GIMDT entry to disease staging was 7 days (2-10); median time from GIMDT entry to surgery was 10 days (5-18); median time from GIMDT entry to chemotherapy was 9 days (3-12); median time from GIMDT entry to radiotherapy was 30 days (10-30). Many patients are still receiving anti-cancer treatments and therefore definitive PROs data are not yet available. This ongoing study shows that the case manager plays a central role in the improvement of inter-professional collaboration in multidisciplinary teams and guarantees time-limited pathways for cancer diagnosis and therapy.

G – Gastrointestinal (non-Colorectal) Cancers

G01*

EXPLORING SECOND-LINE THERAPY OUTCOME IN PANCREATIC DUCTAL ADENOCARCINOMA (PDAC) PATIENTS WITH GERMLINEBRCA1-2 PATHOGENIC VARIANTS (GBRCA1-2PV)

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Background: Pancreatic Ductal Adenocarcinoma (PDAC) harboring germlineBRCA1-2 pathogenic variants (gBRCA1-2pv) is emerging as a distinct entity, benefitting from specific treatments (platinum agents, PARP-inhibitors). Information on second-line therapy (2LT) outcome in this setting is lacking.
Methods: Clinical data of stage IV PDAC patients (pts) carrying gBRCA1-2pv receiving a 2LT were retrospectively collected from 23 Italian Centers and descriptively analyzed, focusing on RECIST response and survival outcome. Progression-free and Overall survival$_2$ (PFS_2 and OS_2) were calculated from 2LT start to 2nd progression or death, respectively.
Results: 49 out of 63 pts treated with first-line therapy (1LT) between December 2008 and July 2020 had Progressive Disease (PD) at time of database lock: 7 pts (4 treated without platinum) did not receive subsequent therapies, while 42 (86%) started a 2LT, whose outcome was assessable in 40 pts (2 had immature follow-up). ECOG

Performance Status at diagnosis was ⩽1 in 38 (95%) pts, 32 (80%) had liver metastases, median age was 62 (39-84) years. RECIST responses of the 19 and 18 pts receiving platinum- and non-platinum-based multidrug 2L were 47% vs 28% partial responses, 21% vs 33% stable diseases and 32% vs 39% PD, respectively. Median PFS for 1LT ($mPFS_1$), $mPFS_2$, mOS_2 and total median OS (mOS_{tot}) are shown in Table 1.

Conclusions: Keeping in mind the small sample size of our series, gBRCA1pv and > 65 years pts yielded limited benefit from 2LT. Platinum-based 2LT obtained longer PFS_2 and OS_2 as opposed to platinum-free 2LT. Pts with $PFS_1 \leqslant$ 6 months had longer PFS_2 and OS_2, but shorter OS_{tot} if compared to pts with $PFS_1 >$ 6 months. Overall, 2L data confirm that platinum is the backbone of treatment for gBRCA1-2pv stage IV PDAC pts, but first-line use should be preferred.

Table 1. Clinical characteristics and survival outcomes.

Variable	N	$mPFS_2$ (mo)	mOS_2 (mo)	$mPFS_1$ (mo)	mOStot (mo)
All patients	40	5.3	9.8	7.5	19.9
Germline BRCA pathogenic variant					
1	8	3.0	6.0	5.3	12.7
2	32	6.6	11.3	7.9	20.9
Gender					
male	17	6.2	10.4	8.5	17.4
female	23	4.3	8.4	6.2	20.1
Age (years)					
⩽ 65	29	6.5	12.5	8.5	21.1
> 65	11	3.1	6.8	5.9	12.8
I line chemotherapy					
Nab-paclitaxel + Gemcitabine	18	8.1	11.8	6.0	19.9
(m)FOLFIRINOX/PAXG/PEXG	14	5.3	11.4	11.6	26.8
GEMOX/FOLFOX	6	2.6	2.8	5.3	10.8
Gemcitabine	2	2.4	3.6	3.9	8.1
II line chemotherapy					
Platinum	19	8.7	12.0	5.9	21.1
NO Platinum	18	5.3	7.4	9.5	18.7
Gemcitabine or Capecitabine	3	2.4	4.9	3.5	9.7
Previous PFS_1 (mo)					
⩽ 6	16	6.8	10.6	–	14.7
> 6	24	5.3	8.8	–	21.5

mo: months.

G02*

PRIMARY CILIUM-ASSOCIATED GENES BY MOLECULAR INTEGRATIVE ANALYSIS AS NOVEL KEY DRIVERS IN BILIARY TRACT CANCER (BTC)

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Background: Biliary tract cancer (BTC) is an aggressive and highly lethal cancer arising from the epithelium lining the biliary tree. The mechanisms underlying cholangiocyte malignant transformation and BTC progression are largely unknown. Genomic and transcriptomic profiling can offer a deeper understanding of disease biology in BTC. We performed large-scale integrative analyses on a clinically-annotated cohort of BTC patients to identify novel key-genes driving BTC initiation and progression as well as drug-resistance.

Material and Methods: We analyzed 100 resected specimens from a well-annotated cohort of BTC patients from the University of Modena. Overall, whole-exome sequencing (WES) was performed on 40 samples, RNA sequencing (RNAseq) on 80 samples, and small RNA sequencing on 30 samples. Somatic alterations, transcriptomic and epigenetic profiles of tumours and stromal area were identified for each sample, and searched for driver genes. By using a bio-informatic pipeline, we integrated somatic mutation patterns and epigenetic features defined at the spatial level to identify novel target genes in the tumour microenvironment. Functional studies in 2D and 3D culturing models were conducted to investigate candidate genes linked to BTC progression.

Results: A total of 3392 and 6315 DEGs (Differentially expressed genes) were respectively observed in BTC comparing tumour (T), normal (N) and stromal (ST) areas with the criterion of false discovery rate <0.05. In top-ranked differentially regulated gene sets, we identified primary cilium-associated genes (PC). OFD1, CNGB1, AURKA, CENPF, STIL, STK39, RAB23 and OSR1 were found based on the criteria of fold change >2.5 and P< 0.01. We started also to clarify at molecular level the role of PC in BTC pathogenesis and progression. A therapeutic approach targeting OFD1 in BTC cells was also investigated.
Conclusions: We performed large-scale genome sequencing analysis of 100 BTC samples from Italian populations. Among top-ranked dis-regulated gene sets we identified ciliary-associated genes. Loss of PC is frequently observed in BDC, suggesting that the absence of this organelle may promote tumorigenesis through aberrant signal transduction and the inability to exit the cell cycle. We investigated the molecular mechanisms underlying the cilia loss and test whether may be potential therapeutic target. These findings could be useful to establish treatment and diagnostic strategies for BTCs based on genetic information.

G03

EFFICACY AND SAFETY OF PEMIGATINIB IN EUROPEAN PATIENTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC CHOLANGIOCARCINOMA: A FIGHT-202 SUBGROUP ANALYSIS

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Background and Aims: Pemigatinib, a potent and selective oral fibroblast growth factor receptor (FGFR) 1-3 inhibitor is approved in the US, Europe, and Japan for previously treated advanced CCA harbouring *FGFR2* fusion/rearrangements based on results from FIGHT-202 (NCT02924376; objective response rate [ORR], 35.5%; disease control rate [DCR], 82%; median duration of response [mDOR], 7.5 months; progression-free survival [mPFS], 6.9 months; overall survival (mOS, not mature), 21.1 months) [Abou-Alfa. *Lancet Oncol.* 2020;2:671-684]. We conducted a post-hoc subgroup analysis of European patients enrolled in FIGHT-202.
Methods: Patients with advanced disease and progression after ⩾1 prior treatment were assigned based on confirmed *FGF/FGFR* status to cohort A (*FGFR2* rearrangement), B (other *FGF/FGFR* genetic alterations [GAs]), or C (no *FGF/FGFR* GAs). Patients received pemigatinib 13.5 mg QD (21-day cycle; 2 weeks on, 1 week off) until disease progression/unacceptable toxicity. The primary endpoint was centrally confirmed ORR in cohort A.
Results: Of 147 patients enrolled in FIGHT-202 at data cutoff (Mar 22, 2019), 35 (24%) were from Europe (cohort A, n=32; B, n=3; C=0; France, n=10; Italy, n=8; other country, n=17; median (range) age, 59 (34-77) years; ⩾2 prior therapies, 46%). Of the 35 patients, 25 discontinued treatment (disease progression, 84%); 10 continued treatment (all cohort A). In cohort A, ORR (95% CI) was 40.6% (23.7-59.4) with 1 complete response; mDOR was 7.5 months (5.5-7.5), DCR was 87.5% (71.0-96.5), mPFS was 6.9 months (4.8-9.1), and mOS was 14.7 months (11.7-not reached). In cohort B, 2 patients had stable disease (mPFS, 2.1 and 4.0 months). Common adverse events (AEs) were diarrhoea (80%), alopecia (66%), and hyperphosphataemia (60%); 14%, 60% and 3% of patients had hypophosphataemia, nail toxicities, and retinal detachment, respectively. AEs led to dose reductions and interruptions in 20% and 57% of patients.
Conclusions: Efficacy and safety of pemigatinib in European patients enrolled in FIGHT-202 were similar to published findings in the total study population.

G04

THE IMPACT OF FIRST-LINE CHEMOTHERAPY IN ELDERLY PATIENTS (PTS) WITH ADVANCED PANCREATIC CANCER (APC): A MONO-INSTITUTIONAL RETROSPECTIVE STUDY

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Background: Pancreatic cancer median age at diagnosis is 70 years old. However, elderly pts are underrepresented in clinical trials and chemotherapy efficacy and safety data in this population are limited. Herein, we present a retrospective analysis of an elderly population treated at our Institution.
Material (patients) and methods: Pts aged ⩾70 years old receiving a first-line chemotherapy for APC were included. The primary end-points were progression-free survival (PFS) and overall survival (OS). The following variables were collected: gender; age (⩾70 and <75 years vs ⩾75 years); baseline ECOG PS (0-1 vs 2-3); site of primary tumor (head/uncinate process vs body/tail); disease stage

(locally advanced vs metastatic); baseline CA19.9 (< vs ⩾200); chemotherapy regimen; comorbidities (yes vs no); number of comorbidities (0-1 vs ⩾2). Univariate and multivariate analysis for PFS and OS were performed.

Results: 169 APC pts aged ⩾70 years old, receiving first-line chemotherapy between March 2015 and August 2020, were included. The median age was 76 years (70-89), ECOG PS was 0-1 in 77% of pts; 70% were metastatic; 70% of pts had a head/uncinate process primary tumor; 25% had baseline CA19.9 ⩾200; 9.4% of pts had no comorbidities and 50% had ⩾2 comorbidities. The majority of pts received gemcitabine nab-paclitaxel (60%), other regimes included gemcitabine (28%), FOLFIRINOX (5%), capecitabine (4%), FOLFOX (2%) and FOLFIRI (1%). The median PFS and OS were 6.5 (median follow-up 19.1 months) and 11 months (median follow-up 21.8 months), respectively. Out of 164 pts evaluable, 38 (23%) pts achieved a partial response and 58 (35%) a stable disease. At the multivariate analysis, ECOG PS 0-1 resulted independently associated both with improved PFS (p 0.005) and OS (p 0.0084). At the multivariate analysis for PFS, also locally advanced stage resulted significantly associated with better PFS (p=0.036). In pts with ECOG PS 0-1 vs 3-4 the median PFS was 6.7 vs 3.3 months (p 0.0004) and median OS was 11.3 vs 5.5 moths (p 0.003), respectively.

Conclusions: Despite the retrospective nature of the analysis and the limited sample size, we observed that elderly APC pts can benefit from a first-line treatment. On the basis of our results, the baseline ECOG PS can be considered a prognostic factor for both PFS and OS. In conclusion, elderly pts should not be precluded from an active treatment and careful patient selection, mainly according to baseline ECOG PS, should guide treatment indication.

G05

IMMUNE-RELATED ADVERSE EVENTS AND CLINICAL OUTCOMES IN UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC): A SINGLE INSTITUTE RETROSPECTIVE ANALYSIS

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Background: Immune checkpoint inhibitors (ICIs), as monotherapy or in combinations, have broadened the treatment landscape of unresectable HCC, both in first-line and in further lines. The prognostic role of multikinase inhibitors-induced adverse events has been proven in HCC patients (pts) and the development of immune-related adverse events (irAEs) has been associated with improved outcomes in other cancer types, such as melanoma and non-small cell lung cancer. However, whether or not irAEs can predict outcomes in unresectable HCC is still under evaluation.

Material and methods: In this retrospective analysis we aimed to assess the association between grade (G) =3 irAEs and efficacy outcomes (overall response rate (ORR), overall survival (OS), progression-free survival (PFS)) among pts with unresectable HCC treated with ICIs. ORRs were calculated as the sum of complete and partial responses per RECIST 1.1 and compared using chi-squared test. OS and PFS were estimated using the Kaplan–Meier method and survival curves were compared using log-rank test. Statistical significance was set at p=0.05 and all reported p values are two-sided.

Results: From August 2015 to March 2021, 110 pts with unresectable HCC received ICIs within clinical trials available at our Institution. 58 pts (52.7%) received ICIs as first-line systemic treatment and 36 pts (32.7%) received single-agent ICI. Overall, 38 pts (group A) developed G⩾3 toxicities whereas 72 pts (group B) experienced no or G<3 toxicities. The most common G⩾3 AEs were hepatic (28.9%), dermatological (13.2%) and gastrointestinal (7.9%) toxicities. ORR was 18.4% in group A and 11.1% in group B (p=0.96). Median PFS was 6.9 and 3.9 months (HR 0.66, 95% CI 0.43-0.99, p=0.04) and median OS was 17.6 and 9.1 months (HR 0.52, 95% CI 0.32-0.84, p=0.04) in group A and B, respectively.

Conclusions: Despite the small sample size and the retrospective nature, our analysis suggests that the development of G⩾3 irAEs might correlate with survival outcomes in unresectable HCC. Prospective analyses are needed to confirm these results and hopefully provide further insights on possible predictive biomarkers.

G06

WHOLE-GENOME NEXT GENERATION SEQUENCING (WG-NGS) IN ADVANCED PANCREATIC CANCER (PC)

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Background: PC has still a poor prognosis and clinical impact of targeted therapies is limited[i]. For this setting, NCCN recommends tumour gene profiling to detect actionable mutations (MUT)[ii]. In Europe, multigene determination is not recommended, but available in clinical trials. Foundation Medicine (FM) is a WG-NGS assay. We aimed to describe PC MUT profiles and the clinical impact of sequencing results in our practice.

Materials and methods: We enrolled metastatic (MTS) or unresectable locally advanced (ULA) PC patients (PTS) tested for NGS at our institution in 2020. For each patient, tumour characteristics, treatments and results of NGS performed on primitive or MTS tissue were collected. Descriptive statistics were performed; survival analyses of PFS and OS were obtained with log-rank test comparison of kaplan-meier curves.
Results: Cohort comprises 56 PTS with 16.5 [95%IC: 16.5-27.4] months of mOS and 6.5 [95%IC: 5.4-9.7] months of mPFS; 54 were ductal adenocarcinomas (3 with mucinous and 2 with squamous aspects), 1 pseudopapillary tumor and 1 acinar carcinomas. About half of PTS had an oncological-positive familiar history, of whom 19% positive for hereditary-suspected neoplasia (i.e. pancreatic, breast and ovarian cancers in first-degree relatives). Eighty-eight percent of samples (67% from primary tumor and 33% from metastases) were evaluable for NGS. All but three patients were MTS at the determination; 56% of tests were requested at first line-treatment, 21% at second-line and 19% in further-lines. Median MUT per patient were 4; occurring MUT>10% were KRAS (84%, of which 42% G12D, 30% G12V, 21% G12R, 5% amplifications, 2% G13P), TP53 (62%), CDKN2A (42%), SMAD4 (20%), CDKN2B (16%) and MTAP (14%). Homologue-deficiency repair (HDR) pathway associated MUT were 14% (of which one BRCA2 MUT); all samples have microsatellite stable and median TMB was 1.47. We found only three MUT (EGFR, BRCA2 and FGFR rearrangement) potentially targetable with available drugs. No prognostic role was found for any MUT, except for a trend toward better OS for HDR MUT PTS (37 vs 16 months, p=0.5).
Conclusions: NGS determination is feasible for MTS/ULA PC, despite a 13% sample failure rate. Consistently with other case series, the prevalence of targetable alterations was low and potential access to drugs unfeasible. Hence, clinical applicability of NGS profiling is still limited for PC PTS. HDR PTS' subgroup may warrant further evaluation in clinical trials.

G07

CHEMOTHERAPY TOXICITY AND DOSE INTENSITY IN PATIENTS WITH PANCREATIC DUCTAL ADENOCARCINOMA AND GERMLINEBRCA1-2 PATHOGENIC VARIANTS (GBRCA1-2PV)

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Background: GermlineBRCA1-2 pathogenic variants (gBRCA1-2pv)-related Pancreatic Ductal Adenocarcinoma (PDAC) have increased sensitivity to DNA cross-linking agents. However, limited data are available on chemotherapy (CT) toxicity and dose intensity (DI) in this subset of patients (pts).
Methods: A descriptive analysis of CT toxicity and DI in gBRCA1-2pv PDAC pts of any clinical tumor stage, who completed a first CT, was performed. RECIST response and survival outcomes were also analyzed.
Results: 82 gBRCA1-2pv PDAC pts treated in 23 Italian Centers (December 2008 - July 2020) were enrolled. Toxicity and DI of CT regimen subgroups including ⩾10 pts are reported in Table 1. Characteristics of these 60 pts were: median age 59 (34-76) years, 32 (53%) female, 59 (98%) ECOG Performance Status ⩽1, 46 (77%) gBRCA2pv, 42 (70%) stage IV. Among 18 stage I-III pts, 5 and 13 received adjuvant and primary CT, respectively. When compared to the literature, FOLFIRINOX-related toxicity was unmodified to the price of consistently reduced DI. Nab-paclitaxel + gemcitabine (AG) DI and toxicity were as expected. On the contrary, DI of PAXG was preserved to the price of greater hematological and gastro-intestinal grade 3-4 toxicity. Among stage IV pts, platinum-based 3-and 4-drugs CT yielded higher response rates ((m) FOLFIRINOX: 77%, PAXG: 70%, AG: 47%) and longer median progression-free survival (PFS): (m) FOLFIRINOX: >13.5 (4.8-24) months, PAXG >10.2 (3-14.6) months, AG: 6.3 (2-12) months. Albeit still immature, data on overall survival seem to parallel those on PFS.
Conclusions: In our retrospective series, platinum-containing CT provoked either an increased toxicity on proliferating cells when DI was maintained or an as-expected toxicity, when DI was reduced. Furthermore, apparently improved outcome was observed with platinum-based triplets or quadruplets.

Table1. Chemotherapy DI and Grade 3-4 toxicity [N (%)].

Regimen	N	DI (%)	Neutropenia	Anaemia	Thrombocytopenia	Diarrohea	Nausea/ Vomiting
AG	22	A 72 G 78	7 (32)	2 (9)	1 (4)	1 (4)	1 (4)
FOLFIRINOX	15	O 64 I 58 FU 35 FU c.i. 63	7 (47)	0	0	0	0
mFOLFIRINOX	11	O 86 I 80 FU c.i. 88	3 (27)	2 (18)	0	1 (9)	0
PAXG	12	P 75 A 73 X 73 G 65	8 (66)	2 (17)	2 (17)	3 (25)	3 (25)

A: Nab-paclitaxel; G: gemcitabine; O: Oxaliplatin; I: irinotecan; FU: fluoruracil; c.i.: continuous infusion; mFOLFIRINOX: modified FOLFIRINOX; P: cisplatin; X: capecitabine.

G08

THE DOSE ADJUSTMENT OF GEMCITABINE PLUS NAB-PACLITAXEL AS FIRST LINE CHEMOTHERAPY IN ADVANCED PANCREATIC CARCINOMA CAN AFFECT THE EFFICACY OF THE TREATMENT? ANALYSIS FROM "REAL WORLD" DATA OF A SINGLE INSTITUTION

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Background: Gemcitabine plus Nab-paclitaxel represents a standard first line treatment for advanced pancreatic cancer (APC). Unselected patients require dose adjustment more often than patients from Clinical Trials. We retrospectively collected the data of our six years experience with particular interest on the effects of dose reduction on Response Rate and Survival.

Patients and methods: From May 2015 to May 2021 118 patients with histologically confirmed metastatic or inoperable locally APC were treated with the standard dose Gemcitabine plus Nab-paclitaxel combination. Treatment was administered on days 1, 8, and 15 every 4 weeks, until disease progression. There were 71 males and 47 females; median age was 67 (39-83). ECOG PS was 0 in 61, 1 on 54 and 2 in 3 pts. Ninety-three pts had metastatic disease and 25 locally advanced inoperable cancer. The disease involved the head of pancreas in 88 pts, the body in 17 and the tail in 13. Response Rate was evaluated using RECIST 1.1 Criteria and the chi-square test was used to compare the two groups in terms of activity. Overall survival (OS) and progression-free survival (PFS) were expressed by Kaplan-Meier method and OS values were compared using log-rank testing and Cox regression.

Results: We administered in total 511 courses of CT (range 1-13; median 4). More frequent non-hematological toxicities were fatigue (73), alopecia (54) and neuropathy (31) while hematological toxicities were: G3 neutropenia (156 episodes); G4 neutropenia (53 ep); G3-4 thrombocytopenia (48 ep). Febrile neutropenia was seen in 5 pts. A dose reduction has been necessary in 66 pts (55.9%) mainly during the first (12 pts), the second (35 pts) and the third (9) course. The most frequent causes of dose reduction were fatigue (23), neutropenia (22), PS decline (7) and thrombocytopenia (5). In this moment 112 patients are evaluable for response. Overall Response Rate was 32.1% (2 CR + 34 PR) and Disease Control Rate was 62.5%. A disease progression was seen in 42 pts. Median PFS was 5.98 (95% c.i. 4.83-7.49) months and OS was 10.49 (95% c.i. 8.94-12.66) months. The survival rate was 30% at 1 year, and 6% at 2 years. We didn't detect differences between groups with or without dose reduction in ORR (p 0.119) and in OS (p 0.113).

Conclusions: This retrospective analysis confirms the efficacy of this combination even in unselected patients. The dose adjustment, more frequent in real world patients, doesn't significantly impact on the treatment results.

G09

A PILOT STUDY OF MIRNA EXPRESSION PROFILE IN SURGICALLY RESECTED PANCREATIC DUCTAL ADENOCARCINOMA: INITIAL REPORT FROM A BI-INSTITUTIONAL COHORT

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Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal human malignancies: novel therapeutic approaches beyond conventional chemotherapy are still lacking and prognosis remains poor, even for resectable patients (pts). Furthermore, there is an almost complete absence of validated predictive factors. Consequently, robust biomarkers for the early diagnosis and the prognostic stratification are urgently needed in clinical practice, especially in the context of neoadjuvant and adjuvant settings. In the last years, evidence revealed the crucial role of miRNAs in cancer initiation and progression, as well as in the chemo-resistance mechanisms, suggesting their use as clinical biomarkers.
Material and methods: In this pilot study, we performed a microarray analysis to characterize global miRNA expression profile from surgical tissue samples collected from 20 resected PDAC pts pooled into 4 groups according to different clinico-pathological features: nodal metastases (N+/N-) and tumor grading (G2/G3).
Results: According to expression patterns, we identified, among 384 miRNAs, a significant different modulation for 11 miRNAs associated to G2 vs G3 and for 7 miRNAs in N+ vs N- disease, suggesting a possible specific signature reflecting histological grade and nodal metastasis occurrence, respectively. We focused on 2 up-regulated (miR-138-5p and miR-518-3p) and 3 down-regulated (miR-215-5p, miR-519a-3p and miR-576-5p) miRNAs in N+ pts, and on 3 up-regulated (miR-1-3p, miR-31-5p and miR-205-5p) in G3 pts, in order to verify their possible implication in the molecular changes behind tumor differentiation and spread, as well as their potential use for prognostic and therapeutic purpose. A bio-informatic analysis was also performed, using different *in silico* tools, to study both high affinity miRNA targets and cross-regulated pathways among the up- and down-regulated miRNAs. The results identified several associated targets involved in multiple signaling pathways commonly dysregulated in cancer. Finally, BRCA1/2 and RB1 miRNAs-mediated-modulation is actually ongoing, considering the pivotal role of these genes in some PDAC pts.
Conclusions: These preliminary data provide a strong rationale to further investigate miRNAs expression in larger cohorts of PDAC pts, possibly integrating validated tissue miRNAs data with circulating miRNAs, in order to identify strong (and easily accessible) potential biomarker(s) with prognostic and/or predictive significance.

G10

HEPATOCARCINOMA NEW ERA: REAL LIFE ANALYSIS TWO YEARS AFTER NEW TKI, WAITING FOR IMMUNO-ANTIANGIOGENIC COMBO

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Background: For years, the only therapeutic option for a patient with hepatocarcinoma no longer susceptible to local treatments was Sorafenib. In Italy, the treatment indication obtained by Regorafenib in 2018 and by Cabozantinib in 2020 has opened up new treatment options for patients progressing after sorafenib.
Patients and methods: They were included in the study all patients followed at our center over the past four years, suffering from hepatocellular carcinoma stage B and C, with Child Pugh A at the beginning, who were subjected to systemic treatment.
Results: within the study 24 patients were enrolled retrospectively, all undergoing systemic treatment. Of these, 12 patients were treated between January 2016 and June 2018 and had BSC as the only option for systemic treatment after progression from Sorafenib. Patients had a 4:1 M:F ratio and a mean age of 72 years; Three patients had a survival from the start of treatment of less than 3 months. The other 9 presented an 11-month mOS. All of them died at the time of data processing. The other 12 patients were treated between July 2018 and April 2021. They all received sorafenib on the front line; patients had a 4:1 M:F ratio and mean age 77 years; three of them had a survival from the start of treatment of less than 3 months. The other 9 patients received 2 (6 patients) or 3 lines of treatment with TKI (3 patients) with a mOS of 22.4 months. Six patients are still alive and on treatment.
Conclusions: The results of our analysis suggest a trend for a better prognosis for advanced HCC patients with the recent availability of the new drugs Regorafenib and Cabozantinib after progression with Sorafenib. It will be very interesting to designa a new therapeutic algorithm in the advanced HCC treatment with the new and imminent

availability of the immuno-antiangiogenic combo as first line approach.

H – Head and Neck Tumours

H01

ROLE OF GERIATRIC ASSESSMENT IN TAILORING TREATMENT OF LOCALLY ADVANCED HEAD AND NECK CANCER: THE ELDERLY STUDY

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Background: Approximately 45% of head and neck squamous cell carcinoma (HNSCC) patients are ⩾65 years old, and this rate is expected to increase. We prospectively evaluated the role of comprehensive geriatric assessment (CGA) as a tool to personalize therapeutic approach in the elderly with locally advanced (LA) HNSCC.

Methods: We enrolled patients aged ⩾65 years old, with stages III-IVb HNSCC according to the AJCC 7th, and potentially suitable for curative treatment. At first, the HN multidisciplinary team (HN-MDT) defined a therapeutic indication driven by clinical judgement and standard evidence-based recommendations, and a geriatrician performed CGA, preceded by a G8 screening tool. Later, the same HN-MDT re-discussed the curative strategy in light of the CGA results. Primary objective was to define the proportion of changes in therapeutic indications after CGA. Secondary aims were to assess the distribution of elderly LA-HNSCC patients into three geriatric categories (fit, vulnerable, and frail) according to CGA and the accuracy of the G8 geriatric screening tool in this setting.

Results: Between December 2017 and March 2021, in eight Italian centers we enrolled 101 patients: 33.7% were fit, 39.6% vulnerable, and 26.7% frail. After geriatric assessment, the major therapeutic strategy changed in 12 cases (11.8%): in 7 it was de-intensified, in 4 intensified, and in one it changed from surgery to chemoradiation. Furthermore, CGA resulted in an increased demand for certain supportive care needs, such as nutritional (27.7% at first HN-MDT evaluation vs. 49.5% after CGA), psychological support and psychiatric treatments (3.9% vs. 19.8%), and chronic therapy modification (1% vs. 9%). G8 score >14 corresponded to fit patients at CGA in 83.3%, whereas ⩽14 to vulnerable/frail in 87.3%. G8 score with cut-off ⩽14 had sensitivity and specificity of 92.5% and 73.5%, respectively.

Conclusions: Geriatric intervention changed major therapeutic choices in about one out of 10 patients. In addition, CGA played an important role in tailoring elderly patients supportive care needs. G8 can be used as a screening tool in LA-HNSCC, with a good sensitivity in identifying unfit patients who then need a complete geriatric evaluation, even if with limited specificity. Geriatrician should be an integral part of HN-MDT to better modulate needs of HNSCC elderly patients.

H02

RETROSPECTIVE ANALYSIS ON THE ROLE OF BIOMOLECULAR MARKERS IN LOCO-REGIONALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMAS, TREATED WITH CHEMORADIOTHERAPY OR RADIOTHERAPY AND CETUXIMAB, PRECEDED OR NOT BY INDUCTION CHEMOTHERAPY

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Background: Ancillary study to the GSTTC trial aimed to verify the correlations between clinical outcomes and molecular biomarkers.

Materials and methods: The GSTTC study is a non-profit, Italian, multicentre, phase III factorial trial in which 414 patients with loco-regionally advanced Head and Neck Squamous Cell Carcinomas (LAHNSCC) were randomized to receive radiotherapy plus concomitant chemotherapy or cetuximab, preceded or not by induction docetaxel, cisplatin and 5- fluorouracil (TPF). Tissue samples were collected for IHC staining of p16 (integrated by molecular qualitative assessment of HPV DNA), PD-L1 (CPS score), amphiregulin, epiregulin, bax, bcl2, survivin and tubulin antibody. The prognostic value of biomarkers on progression free survival (PFS) and overall survival (OS) was analyzed by Cox regression models.

Results: 117 patients, representative of the whole group in the GSTTC trial, were included. Median age was 61.2, 78.6% were males and 85.5% had an ECOG PS = 0. Most of the patients (65%) had stage IV disease, with 65% T3-4 and 87.2% nodal involvement. The primary site of disease was oropharynx (OPC) in 59.8%, oral cavity in 22.2% and hypopharynx in 17.9% of the patients. HPV (p16) was detected in 31.6% of the samples (43% in OPC). PD-L1 CPS was ⩾ 1 in 52.0% and ⩾ 20 in 17.3% of the samples. Amphiregulin was expressed in 80.4%, bax in 74.2%, bcl-2 in 52.6%, epiregulin in 58.8%, survivin in 62.2% and tubulin in 75.3%.

Median PFS and OS was 20.0 and 29.3 months, respectively. Adjusting for clinical factors, only HPV+ [HR 0.44, p=0.007 for PFS, HR 0.35, p=0.003 for OS] and score 3+ of bcl-2 [HR 0.54, p< 0.001 for PFS, HR 0.45, p < 0.003 for OS] were associated with a better prognosis. At the multivariate analysis HPV positivity, PD-L1 <1, PS = 0, stage T1-2 and IC were correlated with better PFS and OS.

Main G3-4 toxicities were hematological (27.6%, -neutropenia 10.3% -anemia 4.3%), neurological (18.1%) and oral mucositis (44%). A significant correlation was found between G3-4 oral mucositis and immunoreactivity for bax, whose direct activation and overexpression can render normal cells less sensible to the effect of chemotherapy.

Conclusions: HPV positivity and bcl-2 overexpression significantly correlated with PFS and OS in LAHNSCC. It is of interest the role of PD-L1 as, in its absence, immunotherapy loses most of its effectiveness while chemotherapy, in the context of PD-L1 negative cells, acquires the maximum ability to kill cancer cells.

H03

THE SARCOPENIA SKELETAL MUSCLE MASS INDEX (SMI) HAS A THREE-TIER SURVIVAL EFFECT IN HNSCC, WHICH CAN BE PREDICTED BY HEMOGLOBIN (HB), LYMPHOCYTES (LY) AND CREATININE (CRE)

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Background: In cancer, sarcopenia is an important predictor of adverse outcome and treatment-related toxicity. SMI is an established surrogate of sarcopenia for advanced head and neck squamous cell carcinoma (aHNSCC) patients (pts). However, ideal cut-off values for prognostication and biochemical predictors of SMI are under reported for pts approaching a first-line chemotherapy.

Methods: SMI was calculated as per standard at the baseline CT scan in consecutive aHNSCC pts candidate for a first-line chemotherapy. Hazard Ratio Smoothed Curve (HRSC) analysis was used to identify ideal SMI cut-off values. Multivariate logistic regression (MLR) with LASSO analysis was performed to identify biochemical predictors of poor SMI. Survival was reported in months (mo).

Results: HRSC revealed a three-tier prognostic effect of SMI in 83 included pts: SMI <31 (poor risk, mOS 9.2 mo), SMI 31-44 (intermediate risk, mOS 33.1 mo), SMI >44 (good risk, mOS not reached after a mFollow-Up of 38.6 mo), HR of 11.4 (p 0.0003) and 4.2 (p 0.02) for poor and intermediate risk, respectively, taking as a reference SMI >44. Twenty biochemical variables were analyzed with MLR-LASSO and Hb <12 g/dL, Ly <1.5/mL and Cre <0.8 mg/dL were all found to be independent predictors of poor SMI: Odds Ratio (OR) 13.7 (p 0.004), 12.9 (p 0.009) and 14.9 (p 0.03), respectively. These three variables were used to build a model with a discriminatory power of 92% (C-statistics). The prevalence of poor SMI was for all three predictors unfavorable, mixed unfavorable/favorable and all three favorable of 66% (OR 29860.7), 13% (OR 2132.8) and 0% (reference), respectively, p <0.0001.

Conclusions: SMI was confirmed to be a powerful prognostic factor in HNSCC patients with three distinct risk categories. We built a model based on 3 routinely available biochemical parameters that can identify those sarcopenic patients with a poorer outcome.

H04

PROGNOSTIC VALUE OF NEUTROPHIL–LYMPHOCYTE RATIO AND PLATELET–LYMPHOCYTE RATIO IN PATIENTS WITH RECURRENT/METASTATIC AND PLATINUM-REFRACTORY HEAD AND NECK SQUAMOUS CELL CARCINOMA TREATED WITH NIVOLUMAB

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Background: Anti PD-1 monotherapy (Nivolumab or Pembrolizumab) is the standard of care for patients with platinum-refractory recurrent/metastatic Head and Neck

squamous cell carcinoma (R/M HNSCC). High neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR) have been associated with poor prognosis in several tumor types.

Aim of the present study was to investigate the relationship between pre-treatment NLR and PLR and survival of patients with platinum-refractory R/M HNSCC treated with Nivolumab monotherapy.

Patients and Methods: We retrospectively reviewed the data of 48 platinum-refractory patients with R/M HNSCC treated with Nivolumab between January 2018 and March 2021 at the Istituto Oncologico Veneto of Padua. Nasopharyngeal carcinomas were excluded from the analysis due to differences in prognosis compared to squamous cell carcinomas of other sub-sites.

Pre-treatment NLR and PLR were evaluated on blood samples collected within 20 days before treatment start. The cut-off values of NLR and PLR were determined according to receiver operating characteristic (ROC) curve using as endpoint the 12 months overall survival (OS). OS and Progression free survival (PFS) were estimated using the Kaplan-Meier method. Univariate and multivariate Cox proportional hazard models were used to compare survival outcomes.

Results: 40 patients were eligible for the study: three patients were excluded because of incomplete data and five due to nasopharyngeal primary tumor site. Primary sites were oropharynx (37.5%), hypopharynx (27.5%), oral cavity (17.5%), larynx (12.5%) and nasal cavity (5%). Median follow-up was 5.9 months. The median PFS and OS for all patients were 2.5 (95% CI 2.1 – 3.0) and 6.7 (95% CI 5.0 – 8.4) months, respectively. The cut-off values to discriminate between low and high NLR and PLR were 3.36 (AUC 0.688) and 280 (AUC 0.813), respectively. High pre-treatment NLR and PLR values correlated with a shorter OS: median OS was 6.5 vs 12.5 months (P=0.007) for high vs low NLR and 3.9 vs 12.5 months (P<0.0001) for high vs low PLR. Multivariate analysis demonstrated a significant correlation between PLR > 280 and OS (P=0.001).

Conclusions: In our study, high pre-treatment NLR (>3.36) and PLR (>280) values were associated with a worse OS in patients with R/M HNSCC treated with Nivolumab. Large prospective trials are required to further investigate the prognostic role of pre-treatment NLR and PLR.

H05

TOXICITY PROFILES IN A REAL-WORLD COHORT OF HEAD AND NECK CANCER PATIENTS TREATED WITH NIVOLUMAB 240 MG EVERY 14 DAYS AND/OR 480 MG EVERY 28 DAYS DURING THE COVID-19 PANDEMIC

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Background: Anti-PD-1 inhibitor Nivolumab (N) is approved for recurrent/metastatic head and neck carcinoma (R/M HNC) at the dose of 240 mg every 14 days (240q14); in Italy, N 480 mg every 28 days (480q28) is approved only in melanoma and renal carcinoma. During the COVID-19 pandemic, health authorities allowed the prescription of N 480q28 also for HNC to limit hospital access and patients (pts) infective risk. Available data on the safety of 480q28 derive from two subanalysis of mixed-histology clinical trials and pharmacokinetic models. Currently, there are no real-world data comparing immune-related adverse events (irAEs) between the two schedules in HNC pts. We conducted a retrospective study addressing this issue.

Methods: We identified HNC pts consecutively treated with N at our HNC Oncology Unit between November 2018 and May 2021. Inclusion criteria were age = 18 years, R/M HNC (squamous cell HNC, sinonasal and nasopharyngeal cancers) diagnosis, ECOG PS 0-2, at least 2 N cycles. We collected clinical data and graded irAEs according to the CTCAE v.5. We compared the frequency of irAEs in pts treated either only with 240q14 cycles (A) or at least with one 480q28 cycle (B).

Results: 47 cases were retrieved: schedule was A in 26, B in 21 pts (6 received 480 mg only, 12 switched from 240 to 480 mg, 3 from 480 to 240 mg). Median age was 61 y.o. (range 28-83), with male prevalence (72%). Median follow-up was 14.4 months and median treatment duration was 4.9 mo (0.5-23.4). Overall, all-grade irAEs occurred in 39 pts (83%), G3-4 in 5 pts (11%): 1 (4%) in A vs 4 (19%) in B group (p=0.16). The observed G3-G4 irAEs were pemphigoid (2 pts: 1 A, 1 B), lipase increase, atrial fibrillation, AST/ALT increase (1 each). No G3-G4 irAEs occurred in 6 pts (13%) who started N with low-dose prednisone (=10 mg) as concomitant medication. Among pts who started N in B schedule, 33% switched to A in order to optimize the clinical monitoring due to clinical conditions, not for G3-G4 irAEs.

Conclusions: Aside from the COVID-19 pandemic contingency, a confirmation of N 480q28 approval for R/M HNC pts would optimize the treatment feasibility, particularly for the subgroup of fit patients who do not strictly require a q14 clinical monitoring. However, due to the trend towards an apparent higher toxicity with 480q28 schedule, special caution should be paid in selecting the most fit R/M HNC pts potentially benefiting from a monthly schedule in 2nd line. Further observation is needed to confirm these results.

H06

SELPERCATINIB EFFICACY AND SAFETY IN PATIENTS WITH RET-ALTERED THYROID CANCER: A CLINICAL TRIAL UPDATE

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Background: We report an update of selpercatinib's (a highly selective and potent RET kinase inibitor) efficacy and safety results in *RET*-altered thyroid cancer, with a longer follow up (30-Mar-2020 data cutoff vs 16-Dec-2019) and additional enrolment.

Material (patients) and methods: Patients (pts) with *RET*-mutant medullary thyroid cancer (MTC) and *RET*-fusion positive thyroid cancer (TC) were enrolled in global (16 countries, 89 sites) Phase 1/2 LIBRETTO-001 trial. Primary endpoint: objective response rate (ORR). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), clinical benefit rate (CBR; CR+PR+SD ⩾16 weeks), and safety. The integrated analysis set (IAS, n=143) includes efficacy evaluable MTC pts previously treated with cabozantinib and/or vandetanib (cabo/vande). The primary analysis set (PAS), a subset of IAS, is the first 55 enrolled pts. Cabo/vande naïve MTC pts (N=112) and TC pts with prior systemic treatment (N=22) were also analyzed. Safety population includes all pts who received ⩾1 dose (MTC N=315; TC N=42) by data cutoff.

Results: For MTC patients, ORR% (95%CI) was 69.2 (61.0, 76.7) for IAS (n=143), 69.1 (55.2, 80.9) for PAS (n=55), and 71.4 (62.1, 79.6) for cabo/vande-naïve MTC pts (n=112). ORR% (95%CI) for TC pts (n=22) was 77.3 (54.6, 92.2). Most treatment-emergent adverse events (TEAEs) were low grade; most common (⩾25% MTC and/or TC pts treated with selpercatinib) were dry mouth, diarrhea, hypertension, fatigue and constipation for both MTC and TC pts, increased ALT/AST, peripheral edema and headache in MTC pts and nausea in TC pts. 4.8% MTC and TC pts discontinued selpercatinib due to TEAEs; only 1.9% with MTC and none with TC discontinued due to treatment-related adverse events.

Conclusions: Selpercatinib continues to show marked and durable antitumor activity in pts with *RET*-altered thyroid cancers. It is well tolerated and no new safety concerns are identified. A global, randomized, phase 3 trial (LIBRETTO-531) evaluating selpercatinib vs cabo/vande in kinase inhibitor-naïve MTC pts is ongoing.

H07

IMPACT OF DAILY INTRAVENOUS HYDRATION ON RADIO-CHEMOTHERAPY COMPLIANCE IN HEAD AND NECK CANCER PATIENTS

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Introduction: Concurrent radio-chemotherapy (RCT) improves overall survival in resected high risk or locally advanced head and neck squamous carcinomas (HNSCCs). RCT can be a challenging treatment burdened by high toxicities, resulting in a discontinuation rate of 20-40%. Poor compliance to RCT affects negatively outcomes. We hypothesize that daily intravenous hydration during RCT could improve treatment adherence and handle toxicities, such as anorexia and weight loss.

Methods: We retrospectively collected clinical data from 35 patients (pts) with stage II-IV HNSCCs treated with RCT from January 2017 to December 2020 in our institution. They received cisplatin 100 mg/mq d1w21 and daily intravenous 1000 ml saline solution, infused from day 10 after the start of RCT until the end of treatment. Here we report the clinical impact of daily hydration during RCT.

Results: Pts were affected by larynx (28%), oropharynx (22%) and oral (17%) squamous carcinoma. The majority of pts had stage IV (77%) and III (14%) HNSCCs. The median age was 63 years (range 42-77), with 74% of male. At least 2 cycles of chemotherapy were administered in 94% of pts. A cumulative cisplatin dose of 200 mg/mq was reached in 46% of pts, with a median cumulative dose of 199 mg/mq. The optimal radiation dose was administered in 89% of pts, with a 20% of radiotherapy (RT) interruption. Only 14% of pts discontinued RT, mostly for toxicity, and in 80% of cases they had oropharynx carcinomas. Only 23% and 40% of pts suffered from oral mucositis CTCAE G3 and anorexia G3 respectively, without leading to treatment discontinuation. During RCT, 54% of pts had a performance status (PS) worsening: moving to PS 1 ECOG in 79% of cases and to PS 2 in 21% of cases. There were no hospitalizations during RCT. Intravenous steroids and analgesic therapy were administered in 80% and 49% of pts, respectively. Only 31% of pts received tube feeding

or total parenteral nutrition. The majority of pts (77%) underwent hydration supportive treatment with home care assistance.

Conclusions: Daily intravenous hydration during RCT could improve compliance and toxicity management, especially for anorexia, dehydration and weight loss. In our real-life experience we reached a relevant cumulative cisplatin dose in almost half of pts and low RT discontinuation rate. No hospitalizations were reported and the majority of pts underwent supportive treatment with home care assistance, a meaningful aspect during SARS-COV2 pandemic.

M – Melanoma and Skin Cancers

M01

5-YEAR OVERALL SURVIVAL (OS) IN COLUMBUS: A RANDOMIZED PHASE 3 TRIAL OF ENCORAFENIB PLUS BINIMETINIB VERSUS VEMURAFENIB OR ENCORAFENIB IN PATIENTS (PTS) WITH BRAF V600-MUTANT MELANOMA

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Background: Combined BRAF/MEK inhibitor therapy has demonstrated benefits on progression-free survival (PFS) and OS and is standard of care for the treatment of advanced *BRAF* V600-mutant melanoma. Here we report a 5-year update from the COLUMBUS trial.

Methods: In Part 1 of COLUMBUS, 577 pts with advanced/metastatic *BRAF* V600-mutant melanoma, untreated or progressed after first-line immunotherapy, were randomized 1:1:1 to encorafenib 450 mg QD + binimetinib 45 mg BID (COMBO450), encorafenib 300 mg QD (ENCO300), or vemurafenib 960 mg BID (VEM). An updated analysis including PFS, OS, objective response rate (ORR; by blinded independent central review), and safety was conducted after minimum follow-up of 65.2 months (mo). Data are as is; study is ongoing.

Results: At data cut-off (Sep 15, 2020), there were 131 (68%), 117 (60%), and 145 (76%) deaths in the COMBO450, ENCO300, and VEM treatment arms, respectively. The median OS (95% CI) and 5-year OS rate (95% CI) with COMBO450 were 33.6 (24.4–39.2) mo and 34.7% (28.0–41.5), respectively (median follow-up: 70.4 mo). The 5-year OS rate (95% CI) in COMBO450 pts who had normal lactate dehydrogenase (LDH) levels at baseline was 45.1% (36.5–53.2). Median OS and 5-year OS rates for ENCO300 and VEM, as well as for pts with normal and high LDH levels and $>$ 3 organs involved at baseline, are shown in the table. For COMBO450, ENCO300, and VEM, the 5-year PFS rate was 22.9%, 19.3%, and 10.2%; ORR (95% CI) was 64.1% (56.8–70.8), 51.5% (44.3–58.8), and 40.8% (33.8–48.2); and the median duration of response (DOR) was 18.6, 15.5, and 12.3 mo, respectively. Safety results were consistent with the known tolerability profile of COMBO450. Additional efficacy and updated safety analyses will be presented. Following study drug discontinuation, the most common subsequent treatment in all arms was checkpoint inhibitors.

Conclusions: Updated OS and DOR results with COMBO450 demonstrate continued long-term benefits in pts with *BRAF* V600-mutant melanoma. Clinical trial information: NCT01909453

	COMBO 450			ENCO 300			VEM		
	Events/pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)	Events/ pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)	Events/ pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)
All pts	131/192 (68.2)	33.6 (24.4–39.2)	34.7% (28.0–41.5)	117/194 (60.3)	23.5 (19.6–33.6)	34.9% (27.9–42.0)	145/191 (75.9)	16.9 (14.0–24.5)	21.4% (15.7–27.8)
LDH normal	81/137 (59.1)	51.7 (36.8–67.3)	45.1% (36.5–53.2)	79/147 (53.7)	35.3 (23.7–60.5)	41.8% (33.3–50.1)	95/139 (68.3)	24.5 (18.6–29.1)	28.4% (20.9–36.4)
LDH high	50/55 (90.9)	11.4 (9.0–17.4)	9.1% (3.3–18.4)	38/47 (80.9)	9.2 (7.0–16.2)	13.8% (5.6–25.6)	50/52 (96.2)	9.6 (8.5–11.5)	4.0% (0.7–12.1)
$>$ 3 organs involved	35/42 (83.3)	11.6 (9.1–20.8)	–	32/44 (72.7)	15.7 (7.9–19.7)	–	39/45 (86.7)	10.9 (8.6–15.7)	–

*Unstratified Cox regression model.

M02

COMPARISON BETWEEN FIRST LINE IMMUNOTHERAPY AND TARGETED THERAPY IN DIFFERENT PROGNOSTIC CATEGORIES OF BRAF V600 MUTANT METASTATIC MELANOMA PATIENTS

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Background: AntiPD1 immunotherapies (IT) and BRAF and MEK inhibitors target therapies (TT) are available first-line treatments for BRAF v600 mutant metastatic melanoma patients (pts). ECOG PS (E), baseline LDH (L), baseline number of metastatic sites (N)are well known clinical prognostic markers that identify different prognostic categories of pts. Direct comparison between first-line TT and IT in different prognostic categories could help in first line treatment decision.

Methods: This is a retrospective analysis conducted in 14 Italian centers. We analyzed data about 454 metastatic melanoma pts (without brain metastasis), Pts were divided in three different prognostic risk categories: group A: pts with E=0, L within normal range, and N less than 3; group B: pts not included in group A or C; group C: pts with E>0, L over the normal range, and N more than 3. For each prognostic group we compared TT and IT in terms of PFS, OS, DCR.

Results: In table 1 we report the comparison between TT and IT in groups A, B, C, in terms of PFS, OS, DCR.

Conclusions: In good prognosis group A (baseline ECOG PS 0, LDH within normal range, <3 metastatic sites) TT showed statistically significant better PFS than IT, also in a long term period, suggesting that TT can be a good first line option for this pts category. Only in Group B we observed a crossing of the survival curves after the 3rd year of observation in favor of IT. Few pts were enrolled in group C, so few conclusion can be made about it, even if TT showed grater efficacy. DCR was better for TT in all groups.

Table 1.

	Group A (better prognosis)		Group B (intermediate prognosis)		Group C (worse prognosis)	
	TT	IT	TT	IT	TT	IT
N° patients	140	36	196	38	41	3
mPFS (months)	36	12	11,5	5	6,4	1,8
HR (95%IC)	1,949 (1,180-3,217)		1,535 (1,036-2,275)		4,860 (1,399-16)	
p value	0,009		0.033		0,013	
PFS at 1y (%)	70	48	40	29	18	nr
PFS at 2y (%)	57	43	30	23	nr	nr
PFS at 3y (%)	48	37	22	23	nr	nr
PFS at 5y (%)	43	nr	12	23	nr	nr
mOS (months)	Not Reached	55	19	20,5	9	5,5
HR (95%IC)	1,195 (0,602-2,373)		0,886 (0,546-1,437)		3,443 (0,991-11,9)	
p value	0,610		0,623		0,052	
OS at 1y (%)	88	80	64	75	28	nr
OS at 2y (%)	80	77	48	48	10	nr
OS at 3y (%)	65	63	36	37	5	nr
OS at 5y (%)	55	43	27	30	nr	nr
Disease control rate (CR+PR+SD) (%)	99%	75%	85%	47%	66%	33%
P value	<0.001		<0.001		0.258	

M03

EFFECT OF CONCOMITANT ENCEPHALIC RADIOTHERAPY (RT) WITH ANTI-PD1 OR TARGETED THERAPY IN MELANOMA BRAIN METASTASES (BM): A RETROSPECTIVE SINGLE INSTITUTIONAL STUDY

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Background: Development of BM in cutaneous melanoma (CM) is considered a poor prognostic factor. Recent evidence underlies the efficacy of combo-immunotherapy (IT) in asymptomatic patients resulting in high rate of intracranial response. Further studies are required to clarify whether RT can be avoided in this subset of patients in order to spare neurocognitive side effects. To date, combo-IT is not still available in Italy. So, the aim of this study is to explore a real-life evaluation of the RT role for the improvement of life-expectancy in BM melanoma patients according to the addition of combo-targeted or IT despite the presence of symptoms.

Patients and Methods: This retrospective study includes 43 patients with CM and BM who were treated at University of Bari Medical School from 2012 to 2021. Median overall survival (mOS) after BM diagnosis and intracranic progression free survival (iPFS) were analysed by Kaplan-Meier method.

Results: In our cohort, neurologic symptoms occurred in 32% of pts. In the symptomatic group, first-line therapy after BM diagnosis included IT in 67% and targeted therapy (TT) in 33% of cases. Regarding the asymptomatic pts, 53% was treated with IT and 47% with TT. Comparing asymptomatic patients who underwent TT and RT to those who did not perform RT, both mOS (14.9 vs 9.2 months p= 0.32) and iPFS (6 versus 7 months, p =0.87) did not show significant differences. Instead, in the same subgroup, RT combined with IT showed as both mOS (10.9 vs 4 months, p <0.001) and iPFS (6 vs 2 months, p=0.04) resulted more favourable. Same evidence in symptomatic patients, indeed RT combined with TT seemed to not improve survival (mOS 3.5 versus 5.1 months, p=0.87 and median iPFS 3.1 vs 3.5 months, p=0.46). While, symptomatic pts who underwent IT benefit from RT (mOS after BM diagnosis 9.2 vs 4.8 months 4.8 months, p =0.04 and median iPFS 12 vs 2.1 months, p=0.006).

Conclusions: Our data demonstrated the efficacy of combination of RT and IT instead of TT and RT even if in presence of neurologic symptoms. This evidence, if validated in prospective trials, could support RT sparing in melanoma patients with BM treated with TT, thus avoiding neurocognitive side effects.

M04

SECOND PRIMARY MELANOMA: INCIDENCE RATE AND RISK FACTORS

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Background: It is well known that melanoma patients have an increased risk to develop second primary melanomas (SPMs). Objective of our study is to report our experience regarding the incidence rate, characteristics and risk factors associated with the development of SPM in melanoma patients.

Material (patients) and methods: This retrospective analysis included patients with melanoma history followed at the Melanoma Unit of the University of Federico II, Naples, from January 2014 to December 2018. The ethics approval was waived. Patients with a recently diagnosed cutaneous melanoma of any stage were enrolled, after having completed the treatment and staging procedure. Patients with familial melanoma and extracutaneous melanoma were excluded. Age, sex and Breslow thickness were recorded. Phototype (I–II vs. III–IV), phenotype (hair colour, eye colour), clinical signs of severe sunburns (photoaging, photoelastosis with numerous solar lentigos), total nevi count (<100 vs. >100) were also evaluated. The cumulative risk of SPM within 5 years from the index melanoma was calculated.

Results: A total of 773 melanoma patients (400 males and 373 females; male–female ratio: 1.07: 1) with a mean age at baseline of 56.3 years (M: 60.9; F: 51.5) were included. Melanoma index was invasive in 476 (62%) patients (mean Breslow: 0.97 +/- 1.48) and in situ in 297 (38%). Sixty-four out of 773 patients (8.2%) developed a SPM; of them, six developed a third, five a fourth, one a fifth and one a sixth primary melanoma within the study period. Interestingly, 68% (59/87) of new primary melanomas were in situ and 32% (28/87) were invasive with a mean Breslow thickness of 0.39 mm. Overall, 46/64 (71.9%) of patients were phototype I–II and 18/64 (28.1%) were phototype III–IV. There were a higher number of patients with blond or red hair (44/64; 68.7%) and clear eyes (49/64; 76.6%). The majority of patients (39/64; 61%) presented clinical signs of severe sunburns and 33/ 64 (51%) had a total nevi count >100.

Conclusions: In our retrospective study, a percentage of 8.2% was registered during 5-year study period. These results, in agreement with previous studies, confirmed the importance of rigorous controls in melanoma patients and

in high-risk people. Limitations of our study were the retrospective design and the lack of a control arm.

M05

A DIGITAL COMPANION FOR PATIENTS WITH BRAF-MUTANT ADVANCED MELANOMA TREATED WITH TARGETED THERAPIES: TAVIE SKIN APP

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Background: Patients with advanced melanoma are facing questions regarding their disease, their treatment, or potential signs and symptoms that are common, though predictable. Strategies to control symptoms include targeting patient education and unhealthy behaviors. In the context of an increasingly digital healthcare system, it is worth considering the role of mobile health applications (mHealth) as patient empowerment tools for routine care, patient education and treatment management. To support patients in their daily-life, a digital solution, called TAVIE Skin, was developed; dedicated to all BRAF-mutant unresectable or metastatic melanoma patients who are treated with targeted therapies.
Methods: The intended goal of the TAVIE Skin app is:

I to deliver the necessary information and education support to the patient in regards with their disease and medications, through virtual nurse coaching,
II to keep track of medications to improve adherence,
III to assist patients in identifying side effects using the virtual nurse coaching and side effects library, and
IV to engage them towards sustainable healthy behaviors thanks to lifestyle interventions, health trackers and real time coaching.

In addition, an optional patient survey is incorporated into the TAVIE Skin app to assess patient reported outcomes, after an e-consent is signed via the app. Ethics approval will be obtained before data collection as per local regulations.
Results: The application is available in France since January 2021 and will be available in 5 additional European countries throughout 2021. The survey will include 400 patients and will allow for describing the users' profile of TAVIE Skin app, for assessing HRQoL, including physical, emotional, social, and functional well being, treatment adherence, as well as work productivity and activity impairment upon targeted therapy. The patients' satisfaction toward their melanoma treatment, and toward the application will be also assessed.
Perspectives: To the best of our knowledge, TAVIE Skin is the first mHealth application dedicated to patients with BRAF-mutant advanced melanoma. At this year's AIOM Congress, a description of the app, the survey and their objectives will be presented.

N – Neuroendocrine Tumours

N01

THE PSYCHOLOGICAL IMPACT OF COVID-19 PANDEMIC ON PATIENTS WITH NETS: BETWEEN RESILIENCE AND VULNERABILITY

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Background: The COVID-19 pandemic has dramatically changed lifestyles and quality of life (QoL) of the global population. Little is known regarding the psychological impact of the COVID-19 outbreak on patients with gastroenteropancreatic (GEP) or bronchopulmonary (BP) neuroendocrine tumors (NETs).
Methods: We prospectively evaluated seven specific constructs (depression, anxiety, stress, QoL, NET-related QoL, patient-physician relationship, psychological distress) by using validated screening instruments including the Depression anxiety stress scale-21 (DASS-21), the EORTC QLQ-C30, the EORTC QLQ GI.NET21, the patient doctor relationship questionnaire 9 (PDRQ9) and the Impact of event scale-revised (IES-R). Mental symptoms and concerns of patients with any stage, well-differentiated GEP or BP-NET were surveyed twice, during the plateau phase of the first (W1) and second epidemic waves (W2) in Italy.
Results: We enrolled 197 patients (98 males) with a median age of 62 years (G1/G2: 96%; pancreas: 29%; small bowel: 25%; active treatment: 38%). At W1, the prevalence of depression, anxiety and stress was 32%, 36% and 26% respectively. The frequency of depression and anxiety increased to 38% and 41% at W2, with no modifications in the frequency of stress. By ordinal logistic regression analysis, female patients showed more severe forms of stress at W1 (OR=0.45±0.14; p=0.01),

while the educational status was associated with the levels of anxiety at both W1 (OR=1.33±0.22; p=0.07) and W2 (OR=1.45±0.26; p=0.03). An improvement of the physical (p=0.03) and emotional functioning domains (p=0.001) was observed over time. Both nausea/vomiting (p=0.0002), appetite (p=0.02), treatment related symptoms (p=0.005), disease-related worries (p=0.0006) and sexual function (p=0.02) improved between W1 and W2, suggesting that NET patients were able to cope with the perturbations caused by the pandemic. No difference was seen between W1 and W2 in the mean score (>4/5) of the PDRQ9. By IES-R, post-traumatic stress disorder was observed in 53% of patients at W2.

Conclusions: The implementation of psychological interventions within NET clinics might favor the emergence of functional coping strategies, attenuating the psychological distress caused by the COVID-19 pandemic.

N02

PROGNOSTIC FACTORS IN MEDULLARY THYROID CANCER: A SINGLE CENTER EXPERIENCE

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Background: Many factors have been associated to medullary thyroid cancer (MTC) prognosis. However, data on large cohorts with long-term follow-up are still limited. The aim of the study was to identify prognostic factors associated to progression free survival (PFS) and overall survival (OS) in our patients.

Patients and Methods: This is a retrospective study enrolling 111 patients affected by histologically proven MTC, followed for at least 12 months. Data on demographic, pathological and clinical parameters have been extracted from medical records. The Cox proportional hazards model has been used to conduct univariate and multivariate models to evaluate the impact of the parameters of interest on survival outcomes. The study was approved by local review board.

Results: Patients had a median age of 56 years (range: 10-85) and the 63% were females. The 9,1% of cases harbored germinal RET mutation. Median duration of follow-up was 92 months (range: 12-489). Patients presenting the following stage at diagnosis: stage 1: 49%; stage 2: 11%; stage 3: 18%; stage 4: 22%. Female gender was associated to longer PFS (HR: 0.32, 95% CI (0.17-0.62); p<0.001). Comparing sexes, we found a difference in only in RET mutation prevalence (p=0.012). Other factors associated to PFS by Cox regression models were higher preoperative serum calcitonin (CT) values (HR=5.58, 95% CI (2.09-14.9); p=0.001), TNM stage 3-4 (HR=20.28, 95% CI (6.12-67.15); p<0.001), presence of lymph nodes metastases at diagnosis (HR: 11.97, 95% CI (4.12-34.80), p<0.001) and multifocal disease (HR=4.73, 95% CI (1.53 14.60), p=0.009), but only the TNM stage was confirmed in multivariate models (adjusted HR=11.31 95% CI (2.54-50.37); p=0.001). A reduction in the CT serum levels between 1-3 months post-surgery seems to be associated to a longer PFS, even complete statistical significance was not achieved (HR=0.23 95% CI (0.05-1.01); p=0.052). Factors associated to OS by Cox regression models were age at diagnosis (HR=1.07, 95% CI (1.01-1.12); p=0.013) and the number of relapses (HR=1.66, 95% CI (1.18-2.34); p=0.004). Both factors were confirmed by multivariate cox regression models (adjusted HR=1.07, 95% CI (1.00-1.14); p=0.048 and HR=1.74, 95% CI (1.21-2.51); p=0.003, respectively).

Conclusions: The study confirmed that higher pre-operative CT values, male sex, lymph nodes metastases at diagnosis, TNM stage 3 and 4 and multifocal diseases were all associated to lower PFS. The higher number of relapses and age at diagnosis were associated to OS.

N03

PREDICTIVE FACTORS OF ADVERSE EVENTS ONSET IN GEPNET PATIENTS TREATED WITH PRRT

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Background: PRRT side-effects prediction is a crucial point in the managment of GEPNET.

Material and methods: Metastatic GEPNETs patients treated in our centre with PRRT (177Lu-Oxodotreotide, 4 administrations,7.4 GBq/each) from 04-2019 to 12-2020 were considered. Haematopoietic, liver and renal toxicities were collected during PRRT and graded according to CTCAE v5. The population was subdivided as midgut/foregut and G1/G2, according to WHO2019. Patients were categorical grouped according with ECOG-PS, number of metastatic sites, previous treatment lines (1 or ⩾2) and therapies received before PRRT (splenectomy, Everolimus, alkylating chemotherapy). To test independence between CTCAE onset and patient characteristics Pearson/Fisher and K-Wallis test were assessed. Logistic regression with Firth correction and bootstrap were performed to determine predictability of clinical features and previous therapies for CTCAE onset.

Results: 67 (31(46.3%) males, 36(53.7%) female, mean age 63) patients were considered. Thirty-eight (56.7%) were classified as midgut, 29(43.3%) as foregut, 24 (35.8%) G1 and 43(64.2%) G2. Alkylating chemotherapy and Everolimus were the previous treatments in 13(19.4%) patients, in both cases. Patients were treated with PRRT as third or further lines in 34.3% (23) of the whole population, 48.3% (14) of foregut cohort. All the patients showed at least one G1-G2 CTCAE during PRRT, in particular anaemia (46,68.6%), thrombocytopaenia (32,47.8%) and leukopaenia (30,44.8%). G3-G4 were rare events, reported in 5(7.5%) cases considering haematological alterations (2 neutropaenia, 1 anaemia, 2 thrombocytopaenia) and 2(3%) cases for liver (1 ALT and 1 INR alteration). Anaemia and thrombocytopaenia occurred in the same patient, causing discontinuation. In all the other cases G3-G4 were transitional. No G3-G4 renal toxicities were reported. Logistic regression showed that line of PRRT administration was the most powerful predictor of thrombocytopaenia (log Odds Ratio (logOR): 1.54,CI 0.24 -3.03, p:0.019), anaemia (logOR 5.63,CI 1.19-12.84, p:0.004) and GGT alteration (logOR 1.88, CI 0.29-3.53, p: 0.02). Primary tumour histology (midgut versus foregut) was a good predictor of ALT/GPT (logOR 1.24, CI 0.045-2.48, p: 0.04) and GGT alteration (logOR 1.34, SE 0.73,CI -0.02- 2.87, p: 0.05).
Conclusions: Line of PRRT administration is a strong predictor of CTCAE onset during PRRT. These results, if confirmed in large- cohort studies, can have a huge impact on everyday PRRT decision-making.

N04

THE CLINICAL UTILITY OF NETEST: A REAL-WORLD EXPERIENCE

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Background: The NETest is a mRNA-based multianalyte assay developed for clinical use in patients with neuroendocrine tumors (NETs). It evaluates by PCR mRNA transcripts derived from 51 genes characteristically expressed by gastroenteropncreatic (GEP) or bronchopulmonary (BP) NETs.
Methods: We investigated the clinical utility of the NETest in a real-world cohort of patients with any stage, any grade NETs seen at our institution between July 2019 and April 2021. Enrolled patients were subjected to a single blood drawn and blood samples were analyzed at Sarah Cannon Molecular Diagnostics, London, UK in a blinded fashion. NETest scores were interpreted as follows: 0-20, absence of disease; 21-40, low disease activity; 41-79, intermediate disease activity; 80-100, high disease activity.
Results: We included 67 patients (52% females) with a median age of 62 years. The majority of patients harbored G1/G2 tumors (93%), while poorly differentiated neuroendocrine carcinomas were diagnosed in 5 patients (7%). Most frequent tumor primary sites included small intestine (38%), pancreas (37%) and lung (13%). At the time of the blood drawn, 48% of patients had metastatic disease. The NETest showed a diagnostic sensitivity of 91%. Among patients who underwent radical surgery, 10 relapses were documented. The post-operative NETest scored positively in 9/10 patients who developed disease recurrence. Among patients with radiologically documented disease progression (n=13), stable disease (n=26) or partial/complete response (n=28) the median NETest score was 40, 26.7 and 26.7 respectively. After a median follow-up of 6 months, patients with a NETest score $\leqslant 40$ and >40 showed a 1-year OS rate of 100% ($\pm 0\%$) and 85.2% ($\pm 9.8\%$) respectively (p=0.14).
Conclusions: The NETest is characterized by high sensitivity and is able to capture disease recurrence in the post-operative setting. A longer follow-up is needed to draw reliable conclusions on the prognostic impact of the NETest.

N05

PROGNOSTIC VALUE OF INFLAMMATORY BIOMARKERS NEUTROPHIL-LYMPHOCYTE AND PLATELET/LYMPHOCYTE RATIOS IN NEUROENDOCRINE NEOPLASMS

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Background: In the last years neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have been extensively studied as predictive factors of cancer survival in solid tumors, but with limited evidence in NEN. They are important biomarkers of the tumor-induced systemic inflammatory response and they have been shown to

correlate with poor prognosis. The aim of the study was to assess the impact of systemic marker of inflammation on outcomes in patients with NEN.

Materials and methods: Clinicopathological data of 131 patients with NENs were collected and analyzed retrospectively. We calculated their basal NLR and PLR. The associations between these two blood biomarkers (categorized both according to their median value in "low" and "high", as well as evaluated as continuous variables) and clinicopathological features and their impact on overall survival (OS) were assessed.

Results: The median age was 64 years. Tumor primary location was pancreas in 26 cases (21%), gastrointestinal in 23 (17%), lung in 49 (37%), others in 33 (25%). In 43.5% of cases a well-differentiated morphology (WD) was found. Median NLR for all cases was 2.6 (0.6-16.5) (in WD tumors: median 2.4 (0.6-16.5); in PD median 3.0 (0.69-16)) and median PLR for all cases was 145 (33-1169) (in WD tumors: median 137.0 (57-670); in PD tumors: 154.0 median (33-1169). NLR (*p=0.038)* and PLR *(p=0.005)* were significantly lower in WD than in PD tumors. Lower NLR correlated with grade 1-2 vs 3 (*p=0.028)* and ki67< 20% vs >20% (*p=0.026)*. Median follow-up was 25.7 months (1-265.9), 2-years OS rate was 75.5% and 5-years was 68.8%. Lower age, lower ki67, WD morphology, grade 1-2, lower NLR and PLR correlated with longer OS (*p=0.007*, *p<0.001*, *p=0.008* and *p=0.001*, *p=0.003, p<0.001*, respectively). No association was found between primitive disease site and NLR (*p=0.129*) OR PLR (*p=0.717*). At the multivariate analysis, PLR was identified as a statistically significant factor.

Conclusions: Data from this study suggest that NLR and PLR could be a reliable and manageable prognostic markers for NENs and may serve as valuable markers to stratify NEN patients for the best therapeutic strategy and clinical trial enrollment.

N06

CLINICAL OUTCOMES OF PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITORS (ICIS) FOR ADVANCED MERKEL CELL CARCINOMA (MCC): A REAL-WORLD ANALYSIS

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Background: MCC is a rare neuroendocrine neoplasm with poor prognosis and limited therapeutic options. Recently, the introduction of ICIs has produced a paradigm-shift in the therapeutic landscape of advanced MCC, with a relevant proportion of patients experiencing durable disease control.

Material and methods: We retrospectively analyzed clinical characteristics and outcomes of patients with advanced MCC treated with ICIs at a tertiary cancer center (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy) from March 2015 to May 2021.

Results: A total of 31 patients were included. Male accounted for 81% of patients (25/31). Median age was 71 years (range 41-87). At the time of ICI start, 45% of subjects had ECOG PS 0, 42% had PS 1 and 13% had PS =2. Sixty-one percent of patients (19/31) had visceral metastases, whereas 39% (12/31) had limited cutaneous/nodal involvement. Overall, 71% of patients (22/31) received ICIs upfront, whereas 29% (9/31) received ICIs in subsequent lines.

Median follow up was 11.5 months (95% confidence interval [CI] 8.0-15.0). In the overall population, median overall survival (OS) was 18.7 months (95%CI 13.6-23.8). Median progression-free survival (PFS) was 4.1 months (95% CI 0.0-9.8). No significant differences were found in terms of OS (p=0.180) and PFS (p=0.834) between patients treated with ICIs upfront vs those receiving ICIs in subsequent lines.

Overall, 19% of patients (6/31) had complete response (CR), 13% (4/31) partial response (PR) and 10% (3/31) had stable disease (SD) as best irRECIST response, with a disease control rate of 42%. OS was significantly improved in patients achieving disease control (CR+PR+SD) vs those experiencing disease progression as best response (mOS: 47.6 vs 7.3 months, Hazard Ratio 21.5, 95%CI 2.8 -166.7, p<0.0001). Median duration of response was 19.5 months (95% CI 0.0-39.9).

Treatment proved tolerable, with a 29% incidence of grade (G)1-2 and a 10% incidence of G3-4 immune-related adverse events.

Conclusions: In our real-world experience, ICIs provided significant responses and durable clinical benefit in a relevant proportion of advanced MCC patients, along with a favorable toxicity profile. For patients experiencing primary refractoriness, the identification of clinical and molecular determinants of resistance still represents an unmet clinical need.

N07

KI-67 CAN PREDICT RADIOSENSIBILITY IN NET TUMORS? RETROSPECTIVE ANALYSIS OF A MULTIDISCIPLINARY CENTRE

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Background: Predictive biological markers of radio-sensitivity in NETs are not yet known and the true impact of radiotherapy in NETs is still unknown. This is a retrospective analysis of the correlation between Ki-67 expression and radiotherapy (RT) response in our series of consecutive patients.
Material and methods: Data on patients with NETs underwent radiotherapy between 2015 and 2020 at the Radiotherapy Department of the European Institute of Oncology in Milan were retrospectively collected. Cox proportional hazard regression models was applied. Informed consent to scientific research and the study was required. The study was notified to our Ethical Committee.
Result: Among 43 patients, there were 36% GEP-NENs, 36% pulmonary NENs, and 29% were NENs from other sites. The Ki-67 was < 3% in 9/45 patients, 3-20% in 9/45 and >20% in 14/33 patients. Almost all patients were metastatic at the time of radiotherapy. The purpose of the radiotherapy was symptoms control (43%) or cytoreductive (44%), in association or not with analogs therapy (48%) or with other systemic therapy (41%).
The RT technique were: 3DC (24%), IMRT (19%) and SRT (52%). The most frequent sites were the bone level (44% between spines and other bones) and extra-regional lymph-nodes (24%). At a median time of 3 months follow up (FU) there was local complete response in 9 patients (14%), a local partial response in 17 (27%), stable disease in 23 (37%) and local progression disease in 14 treatments (22%). At 1.9 years median FU, there were not statistically significant differences in terms of overall survival based on grading based on Ki-67 (p-value =0.770). Moreover, in a Cox proportional hazard regression models with Ki-67 in continuous, +10% increase shows an HR (95% CI): 1.14 (0.82-1.59), p-value =0.44. There was not statistically significant correlation between the objective response rate (ORR) and Ki-67 in an unadjusted model considering all the lines of the therapies. There was not correlation also in an adjusted model taking into account the systemic therapies and schedules and in an adjusted model with Ki-67 in continuous, +10% shows an ORR: 1.17 (p-value =0.19).
Conclusions: This retrospective study does not seem to suggest a possible correlation between Ki67 and the response to RT at the first interim analysis even using a categorical or continuous scale. However, considering the bias in selecting population, further studies are needed in a more homogeneous population to explore this purpose.

N08

ANALYSIS OF SYSTEMIC INFLAMMATORY BIOMARKERS IN NEUROENDOCRINE CARCINOMAS OF THE LUNG: PROGNOSTIC AND PREDICTIVE SIGNIFICANCE OF NLR, LDH, ALI, AND LIPI SCORE

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Background: Lung neuroendocrine carcinoma (NEC) is characterized by aggressive clinical behavior and lack of treatment advances. We evaluate the prognostic and the predictive roles of systemic inflammatory biomarkers in patient circulating blood: neutrophil-lymphocyte ratio (NLR), lactate dehydrogenase (LDH), advanced lung cancer inflammation index (ALI), and the Lung Immune Prognostic Index (LIPI) score.
Methods: A total of 120 patients with small-cell lung cancer (SCLC) (n = 110) and large cell neuroendocrine carcinoma (LCNEC) (n = 10) were enrolled. Overall survival (OS) was evaluated by Kaplan-Meier estimator and univariate and multivariate Cox proportional hazard analyses were performed to determine prognostic factors associated with OS while $\chi 2$ test was used for categorical data.
Results: NLR cutoff value was 1.93. NLR was measured before and after first-line chemotherapy; 25 (21%) patients had higher NLR (delta NLR >1), whereas NLR was lower in 37 (31%). At the univariate analysis, median OS was 12 months: OS for SCLC and LCNEC were 11 months and 14 months, respectively. OS had a prognostic positive value in patients with pre-treatment NLR <1.93 (p = 0.0002), LDH <600 U/L (p = 0,03) and ALI ?34 (p = 0,0065). At the multivariate analysis, Eastern Cooperative Oncology Group performance status, LDH levels and response after first-line chemotherapy were independently associated with OS. Median OS for good, intermediate, and poor LIPI was 15 months, 11 months, and 9 months, respectively (p = 0.091). Patients with higher NLR (>1.93) had an increased probability of tumor progression (p = 0.045, $\chi 2$ test).
Conclusions: This study demonstrated that systemic inflammatory biomarkers could facilitate the understanding of survival differences in the clinical management of lung NEC patients, underlying the need for prospective biomarker-driven studies in the immune checkpoint inhibitors setting.

N09

CLINICAL MANAGEMENT OF PATIENTS WITH MERKEL CELL CARCINOMA: OUR EXPERIENCE OF A SINGLE INSTITUTION

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Background: Merkel cell carcinoma (MCC) is an aggressive primary neuroendocrine cutaneous carcinoma. Treatment requests multidisciplinary management based on radiotherapy, surgery, chemotherapy and immunotherapy. MCC is

associated with poor prognosis in patients with advanced disease.

Material and Methods: From March 2019 to May 2021, we observed 13 patients (8 women, 5 men), median age was 74,15 years (range 42-92 years). Three patients had localized disease, 10 patients had advanced disease. All patients (13/13 patients) received surgery, 5/13 patients received radiotherapy. In advanced setting 2/10 patients received chemotherapy with platinum etoposide regimen, one in first the other in second line treatment; 10/10 patients received treatment with avelumab 800 mg total dose by 1 hour intravenous infusion every 2 weeks until disease progression or unacceptable toxicity (9 in first line, 1 in second line); among these patients receiving avelumab, two started treatment in other centres on 2017 and 2018.

Results: About patients receiving chemotherapy, the one treated in second line received only 2 administrations and died because of clinical worsening, the other treated in first line received 4 administrations and stopped because of disease progression. About patients receiving avelumab, no severe toxicity was reported. One patient presented G1 rush cutaneous rapidly resolved with topic medications. Only one patient showed pyrexia afther first administration despite premedication with paracetamole 1000 mg, chlorphenamine 10 mg. The symptom was resolved with paracetamole 1000 mg and betametasone 4 mg. As results, all patients presented stable disease with pain control. The median progression free survival was 12,4 months (range 1-41 months) with a patient showing a long lasting response of 41 months, in first line setting; in second line setting the patient received avelumab for 38 months.

Conclusions: in our experience, multidisciplinary management of MCC is necessary for adequate control of disease with avelumab showing promitting results both in first and successive lines, with stabilization of disease and long lasting responses.

P – Sarcomas

P01

ROLE OF CIRCULATING IMMUNE CHECKPOINTS IN KIT-MUTATED METASTATIC GASTROINTESTINAL STROMAL TUMOR (GIST) PATIENTS

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Background: Circulating immune checkpoints and type of KIT mutations have recently been shown to correlate with shorter survival in gastrointestinal stromal tumor (GIST). Our study was aimed to understand if soluble forms of immune checkpoints, such as sPD-1, sPD-L1, sBTN3A1, and pan-sBTN3As, and type of KIT mutations may be predictors of survival for metastatic GIST (mGIST) patients, in order to obtain useful information about the clinical evolution of disease.

Patients and Methods: We performed a retrospective study including a cohort of 30 mGIST patients enrolled from February 2015 to June 2017. All patients harboring a KIT exon 11 pathogenic variant (PV) were treated with first-line imatinib 400 mg/day: 16 patients (53.3%) harbored KIT exon 11 deletion or delection/insertion, and 14 (46.7%) carried other PV types (duplication, insertion, or single nucleotide variant). The plasma PD-1, PD-L1, BTN3A1, and panBTN3As concentrations were measured in peripheral blood by specific ELISAs, not yet commercially available.

Results: Plasma levels of sPD-1, sPD-L1, sBTN3A1, and pan-sBTN3As, age at diagnosis, and type of KIT exon 11 PV were found to be statistically significantly associated with progression-free survival (PFS) in univariable analyses, while in the final multivariable Cox regression model, only the plasma levels of sPD-L1 $\leqslant$ 0.7 ng/mL (HR: 0.01; 95% CI: 0.001 to 0.18; $p = 0.001$) and pan-sBTN3As $\leqslant$ 5.0 ng/mL (HR: 4.45; 95% CI: 0.96 to 20.5; $p = 0.05$), and the absence of KIT exon 11 Del or Delins at codons 557 and/or 558 (HR: 0.05; 95% CI: 0.007 to 0.31; $p = 0.003$) were statistically significant. The absence of KIT exon 11 deletions or delins at codons 557 and/or 558 and expression levels of sPD-L1 $\leqslant$0.7 ng/mL and pan-sBTN3As $\leqslant$ 5.0 ng/mL were independent prognostic factors associated with a longer PFS in mGIST patients harboring a KIT exon 11 PV prior to imatinib therapy.

Conclusions: Our study revealed that sPD-1, sPD-L1, sBTN3A1, and pan-sBTN3As could be used as prognostic factors in mGIST patients because individuals treated with imatinib with baseline immune checkpoint expression values below the respective thresholds showed improved clinical outcome and longer PFS than those with plasma levels above the cut-offs.

P02

METASTATIC OSTEOSARCOMA AT DIAGNOSIS: ANALYSIS OF 92 CASES FROM A SINGLE INSTITUTION (2000-2018)

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Background: Metastatic Osteosarcoma (MOS) with synchronous metastases (MET) at diagnosis account 20-25%

of all new cases of osteosarcoma. The 5-yrs Overall Survival (OS) of MOS ranges from 11 to 40%. In a previous study from our Institution on 57 pts <40 years old (1995-2000) the 2- and 5-yrs OS were 55% and 18%. Data of patients with pathologic and radiologic confirmed MOS with adequate follow up were reviewed. Time-to-event outcomes were estimate with Kaplan-Meier method and compared between groups with log-rank test and Cox model.

Patients and Methods: From Aug 2000 to Oct 2018, 92 patients had a diagnosis of MOS: median age 16.5 yrs (6-73, twelve pts >40), gender rate was M51/F41, axial primary tumor in 15 cases, extremity in 77. Lung only MET were described in 66 (71.7%) cases. In 75/90 cases primary tumor was surgically removed, 43 (46%) cases had at least one surgical metastasectomy. All patients received chemotherapy: preoperative only in 6 cases, postoperative in 6, and pre and postoperative in 66 patients. The 1st line chemotherapy was a combination of drugs: adriamycin in 91/92 pts, Cisplatin in 89/92, Ifosfamide in 88/92, Methotrexate in 83/92; 59 patients received 2nd line chemotherapy, 34 pts received a 3rd line; most employed regimen were Gemcitabine-Docetaxel, Ifosfamide 15 gr/m2, Cyclophosphamyde-Etoposide, TKI (Pazopanib, Sorafenib),few received experimental drugs.

Results: Complete remission (CR) was obtained in 26/92 (28%) in 19 cases after surgical metastasectomy. In 30 pts the information of PGP (P- glycoprotein) was available, pts with positive PGP (19/30) had a worst overall survival compared to negative PGP (P=0.038). The 2-yrs OS for all 92 pts from diagnosis was 66% (95%CI 55-75) and 5-yrs OS was 26% (95%CI 16-37). From the end of treatment, for those who reached a Complete Remission the 5-yrs OS was 57% and only 9% for those who did not reach the Complete Remission (P<0.001). At univariate analysis, primary tumor site (2-yOS 48% axial vs 72% extremity, P<0.001), type of MET (2-yOS 74% only lung vs 48% other, P=0.004) were significantly associated to OS. The OS worsened significantly also as the number of lung nodules increased (P=0.007). At multivariable analysis, only site of metastases (other vs. only lung HR=2.26, 95%CI: 1.21-4.22) and number of lung nodules (⩾10 nodules vs ⩽3 HR=2.44, 95%CI: 1.24-4.81) were confirmed as significant for OS.

Conclusions: Compared to our previous report, 2-year OS was 66% vs 55% and 5yrs OS was 26% vs to 18%, slightly improved but still unsatisfactory.

P03

TRABECTEDIN IN SOFT-TISSUE SARCOMA PATIENTS IN ITALY: ANALYSIS OF REAL-WORLD DATA FROM A NATIONAL REGISTRY

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Background: Trabectedin (Yondelis®) is a marine-derived drug with anticancer activity approved for the treatment of patients with advanced soft-tissue sarcomas (STS) previously treated with at least one line of therapy. In Italy, the use of trabectedin for STS patients has been monitored since 2013 through a registry run by the national drug regulator, i.e. the Italian Medicines Agency (AIFA). We assessed real-world data generated thereby on the use of trabectedin in sarcoma patients in Italy over a time lapse of 8 years.

Methods: Data on STS patients treated with trabectedin in Italy were prospectively collected from January, 2013 to December, 2019. They included: baseline patients characteristics (including histology), dose of trabectedin administered at each cycle, reasons for treatment discontinuation, region(s) of treatment and treating center. Time-to-off-treatment (TToT), defined as the time occurring between the initial prescription and the date of treatment discontinuation for any cause, were investigated using Kaplan-Meier's estimator and were presented as median value (95% Confidence Intervals, CI). The impact of the different covariates on TToT was evaluated using an accelerated failure time (AFT) model with log-logistic distribution.

Results: In total, we analyzed data from 2,633 sarcoma patients and 14,950 individual cycles of trabectedin. The median number of cycles of trabectedin received per patient was 3 (2-7), with a positively skewed distribution. The most common initially administered dose of trabectedin was the standard, i.e. 1.5 mg/sqm (719/2633, 27.3%). Likewise, 32.8% of patients received at least one cycle of trabectedin with a lowered dose. Trabectedin treatment was associated to inter-regional mobility. Overall, the median TToT was 93 days (95% CI 89-100). Considering main histological sarcoma subtypes, the median TToT was 104 days (95% CI 96-112) for leiomyosarcoma, 161 days (95% CI 120-188) for well differentiated/dedifferentiated liposarcoma and 123 days (95% CI 100-158) for myxoid liposarcoma. In the final AFT model, the variables significantly associated to TToT were gender, ECOG PS, histological subtype, and being a reference center.

Conclusions: In Italy the use of trabectedin was associated to inter-regional mobility. There were considerable variations of dosage across cycles. Median duration of treatment was in the range of 3-6 months for all the main sarcoma histologies in which the drug is recommended.

P04

A NEW TREATMENT OPTIONS FOR CLASSIC KAPOSI'S SARCOMA: A PILOT STUDY TO EVALUATE EFFICACY AND TOXICITY OF GEMCITABINE

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Background: Kaposi's Sarcoma (KS) is a rare, multifocal, endothelial cell neoplasm with an inflammatory component, and highly heterogenous clinical behaviour. Previous infection by human herpes virus-8 (also called KS herpes virus) is mandatory to develop KS. Four clinical subtypes are known: classic, endemic, epidemic (HIV-related) and iatrogenic. Classic KS typically occurs in elderly people of specific areas, such as the Mediterranean; it usually featured by skin lesions, often at lower limbs, without visceral involvement, and has a chronic course that require systemic chemotherapy for locally aggressive extensive disease. Very few evidence, in small populations, exist on classic KS. Pegylated liposomal doxorubicin (PLD) and paclitaxel are, actually, the recommended systemic regimen.

Methods: This is a pilot study to evaluate the efficacy and toxicity of gemcitabine in classic KS patients. The patients with HIV-related KS were excluded from the outcome analysis. From January 2016 to February 2021, the KS patients were treated with gemcitabine 1.000 mg/m2 on day 1 & 8, with cycles repeated every 21 days. The treatment was administered as I or II line.

Results: Twenty-seven (27) patients were included in the study. The median age was 74 years (range, 54-88); 22 patients were men (81.5%) and 5 were women (18.5%). Ten (11) patients (40.7%) were treated with gemcitabine as I line, and 16 patients (59.3%) as II line. The overall response rate was 88.8% (90% in I line patients, and 87.5% in II line patients). Four (4) patients (14.8%) had a complete response (CR) of skin lesions as best response, 1 patient (3.7%) had stable disease (SD) and 19 patients (70.4%) had a partial response (RP). The median duration of response was 19.2 months. Five (5) year survival rate was 85.2%. The safety profile was good with 19% of grade I or II neutropenia.

Conclusions: Classic Kaposi's Sarcoma is a chronic neoplasm, where disease control and toxicity profile of drugs are major objective of KS treatment. Prospective trials are rare, and very few data are available on the benefit and tolerance of KS-specific treatment beyond PLD and paclitaxel. Gemcitabine provided good tolerability and high response rate to treat these patients.

P05

OSTENONECROSIS OF THE JAW (ONJ) AFTER DENOSUMAB IN GIANT CELL TUMOR OF BONE (GCTB): A SINGLE INSTITUTION ANALYSIS OF PATIENTS WITH RESECTABLE AND UNRESECTABLE TUMORS ENROLLED IN A PROSPECTIVE, INTERNATIONAL STUDY 20062004

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Background: Giant cell tumor of bone (GCTB) is a progressive osteolytic tumor with proven response to denosumab when unresectable or at high surgical risk. We report on incidence of suspected and adjucated osteonecrosis of the jaw (sONJ or aONJ) in cases from a single institution treated with denosumab within a phase 2 study, NCT00396279.

Methods: Skeletally mature patients (pts) were enrolled within 2 cohorts: unresectable GCTB (Cohort 1), and resectable GCTB with planned high morbidity surgery (Cohort 2). Denosumab was given 120 mg SC every 4 weeks with loading doses on days 8 and 15. The primary endpoint was safety: aONJ and sONJ rate; efficacy endpoints included proportion of Cohort 2 pts without surgery, and progression-free survival (PFS)/ relapse-free survival (RFS) for cohort 1 and 2 respectively.

Results: 52 pts included: 30 (58%) women, median age 39 years (range 17-76); stage localized in 50 cases (96%), unresectable 9 cases (17%), pelvis/sacrum 15 (29%) patients, radius 12 (23%) and tibia 11 (12%)

Median follow-up was 103 months (95%CI 55-126) in Cohort 1 and 105 months (95%CI 9 in Cohort 2.

Of 9 Cohort 1 pts, 1 ended denosumab for GCTB progression after 70 months of follow up. Overall Kaplan Meier (KM) estimates (95% CI) for GCTB progression-free in these pts was 88% (39-98%).

23 Cohort 2 pts (53%) ended denosumab without GCTB progression, and 20 (47%) recurred with a KM estimate of 67% (51-79) at 24 months, and 52% (36-66%) at 60 months. Median time of denosumab therapy was 80 months in Cohort 1 and 14 months in Cohort 2 (Table 1). ONJ rate is reported in Table 1.

Within Cohort 2 pts with planned surgery, 88% underwent surgery and 12% continued with denosumab only. Following surgery, recurrence occurs higher after curettage than resection (47 vs 5%).

Table 1.

	Cohort 1 Unresectable (N=9)	Cohort 2 Resectable (N=43)
Median months on denosumab (range)	80 (39-141)	14 (4-119)
aONJ, n (%)*	2 (22)	0 (0)
sONJ, n (%)*	3 (33)	1 (2)
5-year PFS/RFS	100%	52% (36-66%)

aONJ Positively adjudicated.
sONJ Suspected.
PFS progression-free survival.
RFS relapse-free survival.

Conclusions: Denosumab was generally well tolerated with excellent long-term disease control in unresectable patients. A 47% recurrence rate following surgery was seen in this high-risk, selected, resectable population. ONJ rate increased with longer drug exposure.

P06

CALDESMON EXPRESSION IS A POSSIBLE BIOMARKER OF TRABECTEDIN EFFICACY IN LEIOMYOSARCOMAS

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Background: Trabectedin is an effective treatment for soft-tissue sarcomas (STSs), such as leiomyosarcomas (LMSs), where it is a standard of care in patients that have already been treated with previous anthracycline-based chemotherapy. However, no validated efficacy biomarkers are known. Caldesmon is a calmodulin-binding protein involved in the inhibition of smooth muscle contraction and is a marker for smooth muscle differentiation in pathology. Our study aims at understanding if the immunohistochemical expression of caldesmon was correlated with clinical benefit from the use of trabectedin.
Material (patients) and methods: We performed a retrospective analysis of all patients treated with trabectedin for LMS at our centre from January 2018 until September 2020. We stratified patients according to the immunohistochemical expression of caldesmon and compared the positive group versus the negative one. In particular, we correlated caldesmon expression with progression-free survival (PFS) and overall survival (OS) derived from the use of trabectedin. PFS and OS were calculated using the Kaplan-Meier analysis estimation.
Results: 23 patients were included in the analysis. 13 (56.5%) were affected by uterine LMS, 6 (26.1%) by retroperitoneal LMS, and 4 (17.4%) by LMS of the limbs. Most patients (18, 78.3%) were diagnosed at a localized setting and then received a radical excision for their initial disease, whereas 5 (21.7%) were diagnosed with advanced, unresectable disease. 11 patients (47.8%) had an expression of caldesmon in their pathology tissue. Positive vs negative patients were balanced in terms of the stage at diagnosis, site of metastases, number of previous chemotherapy lines, and number of trabectedin cycles. PFS was 18.03 months in the caldesmon-positive population versus 3.93 months in the negative population (*log-rank* p = 0.0242). OS was 34.03 months in the caldesmon-positive population versus 6.23 months in the negative population (*log-rank* p = 0.001).
Conclusions: With the limit of a retrospective analysis, our study demonstrates that caldesmon expression is a possible biomarker of trabectedin efficacy in LMSs. Caldesmon-positive patients are associated with a statistically significant longer PFS and OS with trabectedin. Our data should be validated in an *ad hoc* prospective trial.

P07

ESTABLISHMENT OF A NOVEL MYXOFIBROSARCOMA CELL LINES FOR SCREENING OF INNOVATIVE TREATMENT

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Myxofibrosarcoma (MFS) is a malignant soft tissue sarcoma (STS) that affects patients after the 5th decade of age. MFS patients have a lower risk to develop distant metastasis compared with other STS. However, MSF is characterized by high frequency of local recurrence. MFS can recur more than once, therefore, the patient is subjected to several local surgeries and frequently to amputation. Furthermore, when the tumor recurs generally has a higher grade, decreased response to radio and chemotherapy and increased tendency to form metastases. Taking in consideration the increasing age of the population in most of the countries, the incidence of MFS is likely to rise in the future. Thus, a better understanding of MFS is required to address this clinical problem. Primary cell cultures have been a basic tool to investigate molecular mechanism of cancer progression, to identify receptors and to study the effect of anticancer drugs at cellular and subcellular level. However, few MFS models are currently available. We established a new cell lines named MF-R 7C from a

41-year-old MFS patient that underwent surgical removal of the tumor at our Institution. This cell line had continuous growth for more than 200 days in culture performing more than 100 population doublings. We established the ability of anchorage-independent growth, index of aggressiveness, by the soft agar colony formation assay. The MFR-7C cell line showed a soft agar colony formation efficiency of 4,1 %. MF-R 7C cells were also able to be propagated as cell aggregates in 3D cultures. Another key characteristic of MFS is the ability to migrate into surrounding tissues for several centimetres. We demonstrated in a wound healing assay that these cells were able to close the gap in 48 hours, compared to 24 hours required to close the gap by the aggressive sarcoma cell line 143B. In conclusion, we established a novel MFS cell line, which could be used to study innovative treatments for MFS.

R – Brain Tumours

R01

REGORAFENIB IN RECURRENT GLIOBLASTOMA PATIENTS: A LARGE REAL-LIFE EXPERIENCE

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Introduction: Regorafenib (REG) showed encouraging benefit in recurrent GBM patients enrolled in the randomized, phase 2 REGOMA trial. We investigated the clinical outcome and safety of REG in a real-life population of recurrent glioblastoma patients treated at Veneto Institute of Oncology as off-label use.
Material and Methods: Patients receiving REG were entered prospectively on a clinical database. Data were retrospectively analyzed. The primary endpoints were overall survival (OS) and safety. The major inclusion criteria were: histologically confirmed diagnosis of GBM, disease progression as defined by RANO criteria after surgery followed by radiochemotherapy with temozolomide, ECOG PS = 2; PTS with = 2 prior lines of therapy were excluded. Patients received REG 160 mg once daily for the first 3 weeks of each 4-week cycle until disease progression, death, unacceptable toxicity, or consent withdrawal. Kaplan-Meier method was used to estimate the survival curves, CTCAE v5.0 for drug related adverse events.
Results: From February 2018 to September 2020, 54 consecutive patients were treated with REG and enrolled in this study: median age was 56, ECOG PS 0-1 in 91% of patients, MGMTmet in 53%, second surgery at relapse were performed in 30% of enrolled patient, 41% of patients underwent steroids at baseline. At the time of analysis, median follow-up was 11.1 ms, 30 PTS (56%) had died and 50 PTS (93%) had progressed. Median OS was 10.2 ms (95%CI 6.4-13.9), 12mOS was 43%; median PFS was 2.3ms (95%CI 1.3-3.3) and 6mPFS was 18%. All patients were evaluable for response: disease control rate (DCR) was 46.3%; stable disease was reported in 38.8% and partial response in 7.4%. Age, MGMT status and corticosteroid use at baseline were not statistically significant on multivariate analysis for OS. Grade 3 drug-related adverse events (AEs) occurred in 10 patients (18%) and the most frequent were hand-foot skin reaction, asthenia and increased lipase and transaminases; 1 PT (2%) reported a grade 4 AE (rash maculo-papular). AEs led to REG dose reductions in 37% of patients and, it was permanently discontinued in 5%. No death was considered to be drug-related.
Conclusions: We reported a large, mono-institutional "real world" experience of REG in recurrent glioblastoma patients. Overall, results are close to those reported in REGOMA trial although, we showed a longer OS. Toxicity was moderate and manageable. Encouraging clinical benefits of REG in recurrent GBM population were confirmed.

R02

METRONOMIC TEMOZOLOMIDE THERAPY IN HEAVILY PRETREATED PATIENTS WITH RECURRENT GLIOBLASTOMA: A LARGE MONO-INSTITUTIONAL RETROSPECTIVE STUDY

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Background: Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Despite advances in surgical and first-line treatment, all pts relapse.
The aim of this study is to evaluate the benefit of metronomic Temozolomide (mTMZ) for recurrent GBM.
Material and Methods: All pts treated at Veneto Institute of Oncology from September 2013 to March 2021 were retrospectively reviewed. Major inclusion criteria were: first-line therapy with Stupp protocol, relapse after first or subsequent line of therapy, treatment with mTMZ schedule (50mg/m2 continuously), hystologically confirmed diagnosis of GBM. RANO criteria and CTCAE v 5.0 were used for response and toxicity assessment.
Results: 120 pts were enrolled. Median follow-up was 15.6ms. Median age was 59ys (range 18-81), ECOG PS was 0-2 in 107 patients (89%) and 3 in 11 (9%). MGMT

was methylated and IDH mutated in 66 of 105 (62%) and in 9 of 106 (8%) evaluable pts, respectively. Median number of prior lines of treatment was 2 (range 1-7) and 41% of pts received the therapy beyond the third line. Median time between the last standard maintenance TMZ (sTMZ) cycle and the mTMZ administration was 6ms (range 1-50) and 40% of pts started mTMZ after 3ms from sTMZ. All pts were evaluable for response: 3 (2%) and 48 (40%) showed PR and SD. mOS from the start of mTMZ was 5.4ms (95% CI 4.3-6.4), mPFS was 2.6ms (95% CI 2.3-2.8).

On univariate analysis, MGMTmet and MGMTunmet pts had a mOS of 5.6 and 4.4ms (p=0.03); mOS for patients with ECOG PS $>$ or $\leqslant$2 was 2.3 and 6.0 ms ($p<0.001$); number of prior lines of therapies, time between sTMZ and mTMZ and age were not significant. On multivariate analysis, MGMT methylated status (HR=2.3, 95% CI, p=0.004) and ECOG PS (HR=0.5, 95% CI, p=0.017) remained statistically significant for PFS, while ECOG PS (HR=0.4, 95% CI, p=0.001) was the only factor significantly associated with OS.

The most common grade 3 and 4 hematologic toxicities were lymphopenia (10%) and thrombocytopenia (3%). Grade 3 and 4 nonhematologic toxicities were uncommon.

Conclusions: Rechallenge with mTMZ can be a well tolerated treatment option for recurrent GBM, even in heavily pretreated pts. Pts with MGMTmet and good ECOG PS might report the major benefit.

R03

NON-CANONICAL IDH 1 AND IDH 2 MUTATIONS AND SURVIVAL OF PATIENTS WITH GLIOMAS: RESULTS OF A META-ANALYSIS

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Background: Non-canonical isocitrate dehydrogenase (IDH) mutations are unusual between patients with grade 2 and 3 gliomas and their prognostic significance is still unclear.

Methods: We performed a meta-analysis aimed to assess the prognostic impact of IDH1 and IDH2 non-canonical mutations. We searched English-written articles published on PubMed/Medline, Cochrane library, and Scopus until the 1st May 2021. Keywords adopted for the research were: ''IDH'' OR ''IDH1'' OR ''IDH2'' OR ''Isocitrate dehydrogenase'' AND ''glioma''

Results: Overall, we selected 13 of 3513 studies reporting data of 4007 patients with a diagnosis of grade 2 and grade 3 including 3091 patients with a molecular proven IDH 1 or IDH 2 mutations. Between patients with IDH mutated gliomas, 479 (15.5%) patients showed non-canonical IDH 1 or IDH 2 mutations.

The presence of IDH 1 non-canonical mutation occurred in younger age and in non codeleted 1p19q as compared to canonical IDH 1 mutation. However, patients with IDH 2 mutations showed more frequently 1p19q codeletion as compared to those with canonical IDH 1 mutated glioma. Four studies reported complete data survival for patients with non-canonical (n= 160) and canonical mutations (n= 1019). The pooled HR of these studies was 0.47 (95% CI, 0.28-0.81) confirming a positive prognostic role for non-canonical IDH 1 and IDH 2 mutations.

Conclusions: Non-canonical IDH 1 and IDH 2 mutations identify a specific subgroup of gliomas occurring at younger age and associated to improved survival. Patients with a non-canonical IDH 1 mutation showed less frequently 1p19q codeletion as compared to those harboring a canonical or IDH 2 mutation.

R04

THE EVOLUTION OF AUTONOMY IN THE PATIENT WITH BRAIN NEOPLASM: A SYSTEMATIC REVIEW OF THE LITERATURE

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Background: Brain neoplasm is not very common within the population, but it is one of the types of cancer that most affect the individual's functional autonomy and their ability to carry out activities of daily living (ADL). The main purpose of the research is to report the evidence available in the literature on the subject of the evolution of the functional autonomy of the patient undergoing surgery for brain cancer.

Materials and Methods: A systematic literature review was conducted. The research was performed on Pubmed and CINAHL databases between December 2019 and March 2020. Studies with an adult population (age $\geqslant$ 18 years), with confirmed brain neoplasia, undergoing neurosurgery and eventual chemotherapy or concomitant radiotherapy were included. The keywords and mesh terms used were: "Brain neoplasm" / "Brain tumor"/"Brain Cancer", "Surgery", "Pathology", "Glioma"/"Glioblastoma", "Karnofsky Performance Status", "Activities of Daily Living"/"ADL", "Functional Status", "Treatment Outcome", "Functional

Outcomes"/"Functional Outcome Measures"/"Treatment Outcome", "Quality of life".
Results: The research identified 756 and included 23 studies in the review. Most of the studies were observational. The results show how, in an early post-operative phase, most patients are subject to an initial improvement in autonomy and self-care, and then demonstrate a gradual functional decline in the following months. Studies indicate that the following characteristics are the determining factors of autonomy: a) of the person (age, comorbidities, presence of epileptic seizures); b) of the neoplasm (histology, size, localization); c) of the intervention/treatment (time from diagnosis, extension resection, acquired deficits). Furthermore, it has been shown that a better functional outcome is closely related to an increase in survival and quality of life.
Conclusions: The study invastigate the trend of clinical history in terms of functional outcomes, the related determinants and potential outcomes. An awareness of these factors can help the nurse to identify priorities / needs and plan interventions aimed at improving sensitive outcomes (quality of life and survival). Health professional's focus on patients autonomy can improve patients and caregivers experience.

R05

PREDICTIVE VALUE OF MGMT PROMOTER (PMGMT) METHYLATION STATUS ON PSEUDOPROGRESSION (PSP) IN GLIOBLASTOMA MULTIFORME (GBM) PATIENTS: A RETROSPECTIVE SINGLE INSTITUTIONAL ANALYSIS

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Background: Glioblastoma is the most common and aggressive primary brain tumor. Conventional therapies, such as maximal extension of surgery followed by radiotherapy (RT) and chemotherapy with Temozolomide (TMZ) have not resulted in major improvements in terms of patients' outcome. In this context, radiological response assessment after radiotherapy remains challenging due to the potential effect of radionecrosis, often mimicking tumor progression. Differentiation between PsP and true progression is required to avoid further unnecessary surgeries or the premature discontinuation of TMZ. It is well known that pMGMT methylated patients benefit better to chemotherapy than unmethylated counterpart, so, tumor cells necrosis can be enhanced in this setting. The aim of the study is to observe the correlation between pMGMT methylation status and the incidence of PsP in GBM patients at the first radiological evaluation after RT.
Materials and methods: Patients with histologically diagnosis of GBM from 2017 to 2021 and availability of pMGMT methylation status were enrolled. PsP was radiologically defined at first brain MRI after RT in case of increasing size of the enhancing component and of peritumoral oedema that remain stable or decrease after anti-oedema therapy, such as a clinical improvement.
Results: We analysed 55 GBM patients, 35 (64%) displayed pMGMT methylation whereas 20 (36%) resulted pMGMT unmethylated. PsP was evident in 29 patients (53%), all of them showed methylation of pMGMT. In our analysis, none of pMGMT unmethylated patients experienced PsP. Regarding survival outcome for pMGMT methylated patients, our analysis shows a mPFS of 8.7 (95% CI: 5-10) months versus 9.3 (95%CI: 4.6-12.3) months in methylated and unmethylated respectively (p=0.87).
Conclusions: Methylation status of pMGMT showed to be predictor of PsP in GBM patients. If validated, this information could be very useful to guide clinicians in differentiating PsP from true progression. To date, our survival analysis regarding PFS showed no statistical difference among methylated patients with respect to the presence or absence of PsP. Thus, PsP seems not to be a marker of responsiveness to common treatment in this subgroup. Further prospective data are needed to validate our results.

S – Simultaneous Care

S01

EFFECTIVENESS OF EARLY PALLIATIVE CARE: MONO INSTITUTIONAL EXPERIENCE OF CARDINALE PANICO HOSPITAL

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Introduction: Early palliative care (EPC) represents a pivot in the integrated approach to solid tumors. The aim of the study was to introduce access to EPC in an orphaned territory, evaluating the frequency of access to the emergency room and the satisfaction of patients (pts) in terms of perceived quality of care as efficacy indicators.
Methods: From October 2018 to December 2020, 120 pts were evaluated and 600 palliative care visits were performed. The access to the clinic has been subordinate to

the clinical evaluation by the oncologist or by the multidisciplinary team.

Results: During the clinical monitoring activities (14 months), a progressive enhancement in the selection of pts was highlighted. The pts who died in less than 3 months were respectively the 60% of the pts who performed the first palliative care visit (PCV) in the first quarter, the 35% of pts who performed the first PCV in the second quarter, the 20% of pts who performed the first PCV in the third quarter and 15% of patients who accessed in the fourth quarter. Moreover, a progressive increase in the number of pts sent by oncologists to EPC and a progressive enhancement in life expectancy during this period was observed (about 60% of pts had an expectation of life more than 6 months in the last 2 quarters). Only 10% of the pts had abnormal access to the emergency room, and none of the 120 pts died in the hospital. The table below summarizes the analyzed data.

	PCV Twice a week	PCV monthly	Hospice Hospitalization in advanced stage	Hospice Hospitalization for adjustment therapy	Access in emergency room	Death in Hospital	Death at home	Death in Hospice	Reduction pain from NRS 10 to NRS 6 at third visit	Reduction pain from NRS 10 to NRS 3 at third visit
Early PC	30%	70%	40%	30%	10%	5%	30%	65%	30%	70%
Late PC	70%	30%	60%	5%	0%	5%	30%	65%	70%	5%

Finally, the 74% of pts described as "excellent" (maximum score expected) the satisfaction in terms of assistance received.

Conclusions: In our experience, EPC has significantly reduced the access number to the emergency room and hospital deaths. Despite the barriers to the involvement of EPC in the care of pts with advanced cancer, strong evidence now supports integrated palliative and oncology care. Our study suggests that future efforts should be directed to ensure the EPC access throughout national territory in order to offer an integrated treatment that includes care of physical and psychological symptoms, decision-making about cancer treatment, and care at end of life.

S02

DELIVERY OF ONCOLOGIC CARE AT HOME: READY FOR "ONCOHOME" ERA

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Background: During COVID pandemic, many cancer patients (pts) refused to come to hospital, suspending therapies, with ominous consequences. Based on positive (+) results of DOMONCOVID, our homecare project for COVID+ cancer pts, we created a new model of assistance, ONCOHOME, delivering cancer care at home to immune-compromised pts. We aim to provide data on feasibility, efficacy and costs of this innovative model.

Material and Methods: ONCOHOME is a multicenter project involving 3 Cancer Center (CC) of the North of Italy: National Cancer Institute, San Raffaele in Milan and Cremona CC. We created an organizational homecare model based on a medical and nursing team with a car equipped for home visits and a secretariat managing patient calls, with a dedicated phone number. The team administers cancer care at home and provides pts with the same assistance usually delivered in hospital. Patient-reported outcome (PRO) assessment is performed.

Results: From August 3rd 2020 to May 5th 2021, 79 cancer pts were assisted at home by Cremona team, receiving oral (62 pts), subcutaneous (10pts) or intravenous therapy (7 pts). All types of cancer were included. 77% of pts had a metastatic disease, 88% had a PS ECOG 0-1. Median duration of assistance was 126 days [range 2-270 days]. Most of the pts received oral chemotherapy (41pts). TKIs (25 pts), hormonal therapy (12 pts), supportive care with denosumab and zolendronic acid (5 pts) and immunotherapy (1 patient, pt) were successfully administered at home, too. 13 pts required hospitalization due to clinical complications. In this group, only 2 pts were admitted to hospital due to severe toxicity; in particular, 1 pt treated with trifluridin/tipiracil developed febrile neutropenia and 1 pt treated with gefitinib reported Grade 3 diarrhea. Both pts were discharged and continued to be assisted at home.

Conclusions: ONCOHOME showed that inpatient or outpatient cancer drug administration could be successfully replaced by home administration, for appropriate therapies and selected pts. This model is feasible at an affordable cost. The project is ongoing, planning to accrue other 100 pts for each center. ONCOHOME will be implemented with electronic devices for PRO evaluation, certified telemedicine service and non-invasive wearable smart tissue monitoring physiological parameters devices.

S03

ONCOLOGY SPECIALIST VISITS ONLINE WITH HOME PALLIATIVE CARE

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Background: Oncological home visits for non-transportable patients are guaranteed at home for patients with oncological disease in progress. In some selected cases, treatments began at hospital oncology centers and continued at home, without the need to access to hospital facilities. At home, intravenous treatments were replaced by oral, subcutaneous or intramuscular ones. In other cases, the patient was visited by the specialist directly in the home environment since the first time and on this occasion a specific oncological treatment was prescribed. In most cases, on the other hand, the oncological visit was only a further step to access the palliative care network in a gradual and less traumatic way.

Material (patients) and methods: From January 2011 to December 2020, 395 patients affected or treated for various oncological pathologies were evaluated at home (and in a few cases the patients were evaluated to make a differential diagnosis about the presence or absence of active oncological pathology), with a total of 987 specialist visits. The average age was 69 years; the males were 53% in percentage. The diagnosed oncological pathologies were: lung cancer (NCLC and SCL) 15.6%; colorectal cancer 16.2%; liver, pancreatic and biliary tract cancer 15.3%; prostate, bladder and kidney cancer 10.7%; breast cancer 10.5%; haematological neoplasms (myeloma, leukemia. . .) 7.3%; stomach cancer 6.1%; head and neck cancer 3.7%; cancer of the gynecological organs 2.8%; brain tumor 3.2%; skin cancer 4.2%; cancer of unknown origin 2.2%; other malignant forms 2.2%.

Results: The oncological examinations carried out were divided according to these types:

1) by primary diagnostics (oncological pathology: yes or no; relapse or recurrence of disease for patients in follow-up; indication of specific treatment not practicable at home; diagnosis of non-oncological pathology) 7%
2) for secondary diagnostics or follow-up 2%
3) for supportive care after specific surgical treatments, radiotherapy or chemotherapy 4%
4) for specific treatments (patients in good condition and without symptoms related to oncological disease): 10%
5) for simultaneous care (specific and supportive / palliative treatments, simultaneously) 11%
6) for palliative care tout court 66%

Conclusions: We can deduce from this report that the activity of the territorial oncologist specialist was in the "real world".

S04

INFLUENZA AND PNEUMOCOCCAL VACCINES IN CANCER PATIENTS ON ACTIVE THERAPY: A PROSPECTIVE STUDY

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Background: Due to immunosuppression, influenza virus and S. pneumoniae infections in cancer patients (pts) are responsible of a 4 times higher morbidity and mortality rates. Inadequate data are available about efficacy, safety, timing and immunogenicity of influenza (I) and pneumococcal (P) vaccine (vax) in pts undergoing active oncologic treatment. Nevertheless, the main Oncology societies recommend I and P vax in cancer pts and their family members (FMs).

Materials and Methods: This is a single institution prospective study conducted at L. Sacco Hospital (Milan) between Sept 20 and Apr 21. The aim was to evaluate efficacy and safety of vax. Pts with diagnosis of tumor, age>18ys, in active antineoplastic treatment and FMs age>18ys were included. Each pt received I+P vax on the same day of therapy. Pts were compared with a control group of FMs, with age- and gender-adjusted logistic regression. Monthly monitoring was scheduled to register any Adverse Events (AEs) after injection (local and systemic AEs), episode of Influenza Like Illness (ILI), pneumococcal infection, access to Emergency department (ED) or Hospital admission (HA) and delay of treatment (DT).

Results: 194 pts (63y median age, 67.5% female) and 140 FMs (59y median age, 49% female) were enrolled. CANCER: 92% solid and 8% hematological malignancy, 69% metastatic stage. TREATMENTS: 54% =1 previous line of therapy; 38% chemotherapy, 31% target, 17% chemo+target, 14% hormone therapy. VAX: 47% pts and 72% FMs received I-vax for first time. I+P-vax were administered in 100% pts and 49% FMs. LOCAL AEs: I-vax: 34% pts and 19.6% FMs (p=0.01), P-vax: 35.7% pts and 20.7% FMs (p=0.11). The most common was pain in site of injection. SISTEMIC AEs: 19.6% pts and 8.5% FMs (p=0.11); the most frequent was fatigue. EFFICACY: ILI were recorded in 8.8% pts (3 had a HA and 1 a DT) and 3.6% FMs (p=0.04). No PI was recorded. Type of therapy,

previous treatment and the use of steroid don't significantly impact on vax safety and efficacy.
Conclusions: Despite the atypical season, I+P vax are safe and effective in cancer pts. The limited number of ILI events observed could be referred to vax but also to COVID-19 risk prevention and mitigation measures. No differences in efficacy and safety were observed between the 2 groups, except for local I-vax AEs. Moreover, the vax administration in the Oncology department, a wide vaccination coverage was achieved (>70% of cancer pts), reducing the pressure on territorial healthcare system.

S05

SIMULTANEOUS CARE IN ONCOLOGY: EXPERIENCE FROM THE UNIVERSITY MEDICAL ONCOLOGY UNIT OF BARI

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Background: Recent evidence suggests that integration of anti-cancer treatment with early supportive care improves both patient outcomes and quality of life, although this new model of care is still underused in routine clinical practice. Here we present our single-centre experience on Simultaneous Care in Oncology (SCO).
Patients and methods: We retrospectively evaluated 60 patients referring to the Medical Oncology Unit of the University Hospital Policlinico (Bari) and undergoing anti-cancer treatment (e.g. chemotherapy, targeted therapy, immunotherapy) for at least 3 months. 30 patients received early integrated supportive care (group A), while the remaining underwent anti-cancer therapy only (group B). For each group, we identified the following events: drug dose reduction, treatment delay, discontinuation and grade⩾ 2 toxicities.
Results: The patients were well balanced in the two groups as for gender, age, ECOG PS, primary tumor site, disease stage and ongoing treatment (Table 1). The whole number of events was 17 for group A vs 40 in group B (p=0.002). Patients in group A experienced a significantly lower number of treatment discontinuations (2 vs 9, p=0.02); in addition, both dose reductions (4 vs 11) and treatment delays (11 vs 20) were less frequent in group A than in B. 13 patients in group A (43.4%) and 26 patients in group B (86.7%) experienced at least one event (p=0.001), with 4 and 11 patients (13.4 vs 36.7%) presenting more than 2 events in the two groups, respectively. Major toxicities were hematological (41%), mucocutaneous (17%) gastrointestinal (11%) and fatigue (11%).
Conclusions: Our preliminary data confirm that SCO improves patient adherence to antineoplastic therapy and hopefully outcomes.

Table 1. Patients' characteristics.

	GROUP A	GROUP B
N of pts	30	30
Gender M:F	1:1	1:1
Mean age (range)	62 (40-82)	64 (39-79)
ECOG PS		
0	8 (27%)	8 (27%)
1	17 (57%)	16 (53%)
2	5 (16%)	6 (20%)
Primary tumor		
Gastrointestinal	11 (37%)	11 (37%)
Genitourinary	4 (13%)	4 (13%)
Gynecological	3 (10%)	3 (10%)
Thoracic	3 (10%)	3 (10%)
Soft tissue	3 (10%)	3 (10%)
Liver	2 (7%)	2 (7%)
Head-Neck	2 (7%)	2 (7%)
Brain	1 (3%)	1 (3%)
Breast	1 (3%)	1 (3%)
Stage		
II	2 (7%)	1 (3%)
III	1 (3%)	3 (10%)
IV	27 (90%)	26 (87%)
Ongoing treatment		
CHT	15 (50%)	12 (40%)
TT	5 (17%)	6 (20%)
CHT+TT	8 (27%)	9 (30%)
CHT+IT	1 (3%)	1 (3%)
IT	1 (3%)	2 (7%)

Group A= pts on both supportive care and antineoplastic treatment; Group B= pts on antineoplastic treatment only; ECOG PS= performance status according to ECOG; CHT= chemotherapy; TT= targeted-therapy; IT= immunotherapy

S06

FIRST STEP FOR SIMULTANEOUS MULTIDISCIPLINARY CARE OF CANCER PATIENTS IN A SPOKE HOSPITAL OF THE NORTH WEST PIEDMONT CANCER NETWORK

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Background: Multidisciplinary patient (Pts) care is main basis of the modern therapeutic approach to cancer treatment. Simultaneously undertaking a PDTA by a multidisciplinary care group remains a very difficult challenge and requires a multistep path that the Oncology hospital team of ASLVC in Vercelli has started involving other hospital Units. The first goal is certainly to share the contents of Pts clinical history.
Materials and methods: Since 2019 an electronic oncology folder (ONCOSYS) has been implemented, integrated

with the existing hospital's information system, for the management of all Pts related to the structure. In 2020 a project started with Bocconi University of Milan and with the Hospital Quality Unit to involve other specialist units in the use of ONCOSYS. In order to assess the real collaborative will and motivational drive, it was decided to avoid the obligation to join. The Coordinators of the Multidisciplinary Care Groups (GIC) were asked to identify a doctor and a nurse referents for the project and educational meetings were scheduled by online platform for participants with subsequent support path.

Results: Contacts of GIC who voluntarily joined the project with related nurses were: 3 gynecologists, 1 neurologist, 1 dermatologist, 5 surgeons, 1 dentist,1 urologist. Two oncologists prepared 4 educational meetings by online platform with the referents instructing them on how to compile the folder. All medical doctors and their nurses joined meetings. After the first 10 successful visits they can in turn extend the experience to other colleagues participating in the GIC. Two indicators have been defined for the proposed intervention assessment. One on accuracy in information management with formula: cases of medical records with minimum shared requirements/total controlled medical records; another on perceived quality.

Conclusions: To fill a digital oncology medical record by GIC specialists in a spoke hospital is feasible and represents the first step to ensure a simultaneous multi-specialist Pts care, to draw up a truly shared PDTA and, last but not least, to build an interdisciplinary structural as well as virtual oncology area.

S07

EFFICACY OF HIGH-DOSE CORTICOSTEROIDS IN THE TREATMENT OF CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA

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Background: Chemotherapy-induced thrombocytopenia (CIT, platelet [PLT] count = 100,000/μL) is a common side effect with an incidence ranging from 16.5% to 21.8% in the global population, but higher than 30% in the patients treated with platinum- or gemcitabine-based regimens. Several agents for its treatment have been studied with unsatisfactory results. Corticosteroids (CSs) are commonly used, even if low evidence is available. The present study aims to observe whether CSs have a positive impact on the outcome of CIT.

Material (patients) and methods: We retrospectively reviewed all the cases of patients experiencing thrombocytopenia after chemotherapy administration at the Centre of Thoracic Oncology of our institution from 2015 to 2021. We excluded all those cases with possible other causes, such as concurrent radiotherapy, extensive bone marrow involvement, the recent introduction of other thrombocytopenia-inducing treatments (e.g. antibiotics), and the development of immune thrombocytopenia (ITP). We analysed whether patients received CSs or not and observed the median duration of CIT in treated vs untreated patients, comparing them with the unpaired *t*-test. We also focused on patients affected by severe CIT (PLT count = 50,000/μL) and made the same comparison. We finally analysed data on the homogenous population who received methylprednisolone (MPDN) 40 mg/day until recovery (the most used treatment scheme) and compared them to untreated patients.

Results: 174 patients experienced any-grade CIT. 132 (75.9%) patients experienced mild-to-moderate CIT, whereas 42 (24.1%) experienced severe CIT. 82 (47.1%) patients received CSs. The mean duration of CIT was 5.12 (SD 4.16) days in the CS-treated group and 6.95 (SD 6.6) in the non-CS-treated group ($p = 0.03$). Considering only the cases of severe CIT, 32 (76.2%) received CSs and 10 (23.8%) did not. The mean duration of severe CIT was 6.78 (SD 5.66) days and 7 (SD 3.13) in the CS-treated and non-CS-treated group, respectively ($p = 0.91$). Finally, 63 (36.2%) patients received MPDN 40 mg/day. The mean duration of CIT in this population was 4.98 (SD 4.01), shorter than untreated patients ($p = 0.036$).

Conclusions: With the limit of a retrospective evaluation, we observed that CSs might have a benefit in mild-to-moderate CIT, whereas they seem to be ineffective in case of severe CIT. Our analysis supports the use of high-dose CSs, such as MPDN 40 mg/day until recovery. Validation in *ad hoc* prospective trials is needed.

S08

CANCER TREATMENT AT HOME, THE PROJECT "HER HOME"

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Background: In December 2020, thanks to the collaboration among the U.O.C. Oncologia, Roche Italia, and our Association, was set up a project for the domiciliation of antiblastic treatment titled "HER Home", at the ASP 7 Ragusa in Sicily. The project involving patients with HER2 positive breast cancer concerns treatment at home with subcutaneous antiblastic therapy. Aims include the enhancement of patients' quality of life reducing the need for travel and visits to the hospital and making them more comfortable to receive the therapy. During the current pandemic situation, this means a greater safety for patients

who are fragile subjects and may be more exposed to the risk of infection; and, also, the improvement in organizational efficiency.

Materials and methods: Admission of patients takes place according to the evaluation of the Medical Oncologists who establish the schedule of treatments and prescribe the drug. The drug is prepared and dispensed by the hospital pharmacy. Our Association, already active for home palliative care, deals with the transport of the drug from the hospital pharmacy to the patients' home, where our Doctor, after a clinical evaluation of the patient, administers the drug. The project foresees the participation of 20 women and about 240 administrations. Quality of life will be assessed at baseline and every 4 administrations, using patient's self-reported outcome measures (PROMs).

Results: To date, have been assisted 4 patients and carried out 13 administrations. No adverse events have occurred and no organizational criticalities were recorded. All administrations were performed safely, within the foreseen times and methods.

Conclusions: The project has allowed the patients involved to have more free time since there are no needs for transfers and waiting times in the Day Hospital and so allowing them don't change the course of their daily routine; we, also, expect a measurable improvement in the quality of life. For the regional health system, this project achieved a simplification of the pathways and a reduction in the crowding of the Hospital, both essential during the COVID-19 pandemic. From the economic point of view, the project reduced costs and resources applied for about 30% less. The potential shown by this preliminary project could be fully realized in the evaluation of the possibility of home administration of other antiblastic therapies favoring above all the patients who lead a very active working and family life.

T – Miscellanea

T01*

THE CLINICAL SIGNIFICANCE OF TELOMERASE REVERSE TRANSCRIPTASE (TERT) PROMOTER MUTATIONS, TELOMERE LENGTH AND O6-METHYLGUANINE DNA METHYLTRANSFERASE (MGMT) PROMOTER METHYLATION STATUS IN NEWLY DIAGNOSED AND RECURRENT IDH- WILDTYPE GLIOBLASTOMA (GBM) PATIENTS (PTS): A LARGE MONO-INSTITUTIONAL STUDY

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Background: The clinical significance of TERT promoter mutations, telomere length and their interactions with MGMT methylation status in patients with IDHwt GBM patients remain unclear. We performed a large mono-institutional study to better investigate their impact and their nteraction on clinical outcomes.

Methods: TERT promoter mutations (C228T, C250T), relative telomere length (RTL) and MGMT status were assessed in 278 newly diagnosed and in 65 recurrent IDHwt GBM PTS which were treated at Veneto Institute of Oncology from Dec 2016 to Jan 2020. We have retrospectively explored association between gene characteristics and neuroradiological response (RANO criteria), progression-free survival (PFS), overall survival (OS). Telomere length was measured by monochrome multiplex PCR and RTL values were calculated as a telomere/single-copy gene ratio.

Results: Characteristics of newly diagnosed GBM PTS were: median age 63 ys, ECOG PS 0-1 in 71% of PTS, radical surgery in 38%, 78% received radiotherapy plus TMZ, MGMT was methylated in 53%, TERT promoter was mutated in 80% (75% C228T, 25% C250T), median RTL was 1.57 (range 0.4-11.37). ORR was reported in 15% of PTS, mOS was 15ms (95% CI 13-18), mPFS was 8ms (95% CI 7-9). At multivariable analysis, TERT promoter mutations and RTL were not associated with clinical outcomes; about OS, TERT promoter mutations and RTL reported a HR of 1.05 (95% CI 0.64-1.64) and 0.99 (95% CI 0.89-1.10), respectively; MGMT methylated tumors showed significant improved PFS and OS with a HR of 0.54 (95% CI 0.40-0.71) and 0.47 (95% CI 0.34-0.64), respectively. All interactions among MGMT status, TERT mutation status and RTL were not statistically significant. Characteristics of recurrent GBM PTS were: median age 55 ys, ECOG PS 0-1 in 60% of PTS, MGMTmet in 37%, TERT promoter mutations in 75% (75% C228T, 25% C250T), RTL was 1.67 (range 0.68-8.87). At multivariable analysis, only MGMT methylated tumors resulted significantly associated to prolonged OS (HR 0.16; 95% CI 0.07-0.40). No gene interaction was significant.

Conclusions: For the first time worldwide, we analyzed the impact of TERT promoter mutations, RTL and MGMT status in both newly diagnosed and recurrent IDH-wildtype GBM PTS. TERT promoter status and RTL were not associated with clinical outcomes at both diagnosis and relapse. MGMT promoter methylation status was the only prognostic factor in both cases. No significant interaction was demonstrated between TERT promoter mutations, RTL and MGMT status.

T02*

CLINICAL AND HISTOLOGICAL PROGNOSTIC FACTORS OF MALIGNANT TRANSFORMATION IN A LARGE SERIES OF ORAL POTENTIALLY MALIGNANT DISORDERS (OPMDS)

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Background: Despite optimal primary surgical resection, Oral Potentially Malignant Disorders (OPMD) show a rate of malignant transformation varying from 3% to 17.5%. We analyzed the clinical and pathological characteristics of patients with OPMD and their impact on the risk of malignant transformation.

Material and methods: We retrospectively evaluated 106 OPMDs cases treated with curative surgery at Spedali Civili, Brescia, from 1996 to 2019. The following clinical and histological characteristics were recorded: age at diagnosis, gender, alcohol and tobacco consumption, immunodeficiency status, comorbidities (according to Charlson Comorbidity Index), history of previous cancer, characteristics of dysplasia (localization, clinical aspect, OPMDs type, grade, state of surgical margins), and type of surgical treatment. We then evaluated the eventual dysplasia relapse (number, site, grading and treatment) and/or malignant transformation (number of oral cancers developed, site, grading, TNM staging, treatment).

Results: The cohort gender distribution was substantially equivalent (F/M, 55/51), with a median age of 64 years (30-94) and a previous diagnosis of head and neck squamous cell carcinoma occurred in 31% of cases. Grading was SIN1, SIN2, SIN3, and CIS (carcinoma in situ) in 46.2%, 30.2%, 14%, and 9% respectively. During a median follow up of 40.5 months (1-234), in 30% of patients dysplasia relapsed, while malignant transformation occurred in 24%, of which 44% had more than one carcinoma diagnosis. Median time to malignant transformation was 32 months (7-192). Only female gender (p 0.016 OR 3.2 1.3-8.6) and a previous cancer diagnosis (p 0.05 OR 2.6 1.0-6.7) were related to higher incidence of dysplasia relapse, while female gender (p 0.015 OR 3.7 1.4-11.7) was the only prognosticator of malignant transformation.

Conclusions: In this large series of OPMDs, just female gender was associated with higher risk of malignant transformation. Given the lack of clinical/pathological prognostic data, we advocate molecular characterization of OPMDs to better stratify the risk of malignant transformation and consequently define an enriched population who could benefit from preventive strategies within clinical trials.

The Impede trial (NCT04504552), coordinated by ASST Spedali Civili of Brescia, represents the first European trial administering immunotherapy in OPMDs at high risk of malignant transformation selected by LOH.

T03*

CLASSIFICATION OF MOLECULAR ALTERATIONS IN THE RATIONAL STUDY BASED ON THE ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

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Background: The Register of Actionable Mutations (RATIONAL) collects Next-Generation-Sequencing (NGS)-based tumor profiling data from patients enrolled in 34 Italian centers. The purpose of the study is to facilitate the identification of subgroups of patients who might benefit of targeted therapies. The ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) classification stratifies molecular alterations based on their value as clinical targets. We performed a classification of molecular alterations collected in the register based on the ESCAT scale.

Material and methods: The RATIONAL study is an Italian multicenter, observational and prospective clinical trial. The primary aim is the description of the frequency of actionable mutations in the cohort of enrolled patients. The study enrolled patients who already had available a NGS-based profiling of the tumor *(Pathway A)* or underwent a comprehensive tumor profiling with the FoundationOne CDx assay within the trial *(Pathway B)*.

Results: Genomic profiles of 611 patients, including 194 patients enrolled in Pathway A and 417 in B are collected in the register. The most common tumor types are lung cancer

(46% of cases), tumors of the biliary tract (18%), colorectal (8%), gastric (4%), pancreatic (3%) and breast (3%) cancers. Cancers of unknown primary (CUP) account for 9% of the cases. Among the 611 registered patients, 2594 genomic alterations in 254 genes were identified. The most frequently altered gene was *TP53* (53% of cases), followed by *KRAS* (27%), *EGFR* (12%), *CDKN2A/B* (11%) and *PIK3CA* (10%). We classified mutations according to the ESCAT scale for 457 cases belonging to lung carcinoma, cholangiocarcinoma, colorectal, gastric, breast and pancreatic ductal cancers. We found that 21.0% (96/457) of patients had genomic alterations classified in level I. Molecular alterations classified in level II were present in 12.91% (59/457) of patients, whereas 11.38% (52/457) of patients had genomic alterations classified in the level III. In 47% of patients with CUP, NGS profiling revealed at least one genomic alteration for which approved drugs for different indications are available.

Conclusions: The RATIONAL study allows clustering patients based on their molecular profile. The ESCAT scale might help categorize clinically relevant molecular alterations to select the best therapeutic strategies for patients undergoing comprehensive genomic profiling.

T04*

PATIENTS' SATISFACTION WITH BREAKTHROUGH CANCER PAIN THERAPY: A SECONDARY ANALYSIS OF IOPS-MS STUDY

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Background: Cancer pain is one of the most important symptoms for patients. Pharmacological control is central for clinical management and to ensure well-being. In cancer patients, the management of Breakthrough Cancer Pain (BTcP) is also crucial. This study aims to identify factors that can predict poor satisfaction with pain relief for BTcP.
Methods: This was a secondary analysis of the IOPS-MS study, a large, multicenter, national study where thirty-two centers were involved to explore BTcP management. Clinical and pathologic features were recorded, as well as the patients' degree of satisfaction with BTcP medications classified as dissatisfied (not or indifferent satisfied) versus satisfied (or very satisfied). Frequency distributions and the chi-squared test of independence were performed. A multivariate Cox hazard model was carried out by selecting significant variables upon univariate analysis.
Results: From the original 4,016 patients enrolled, 3,840 were available for the study purpose. The majority were male and the mean age was 64.6 years. Seventy-one per cent of patients declared satisfaction with BTcP medications. Young age, non-metastatic cancer stage, high Karnofsky performance status, the absence of anticancer treatment, the NSAIDs/paracetamol use for background pain and an high BTcP interference in activities of daily living resulted positively correlated with dissatisfaction in the multivariate analyses (Table 1). Also, the setting of care affects BTcP therapy satisfaction.
Conclusions: We have identified the key points to be considered in the pharmacological management of BTcP, useful to predict patients satisfaction and to ensure optimal quality of life.

Table 1. Univariate and Multivariate analyses for dissatisfaction with BTcP medications.

Variables	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	p	HR (95% CI)	p
Age <65 vs ⩾65 ys	1.38 (1.20-1.59)	< 0.001	1.29 (1.12-1.50)	< 0.001
Cancer Stage Locoregional vs metastatic	1.45 (1.19-1.78)	< 0.001	1.53 (1.22-1.91)	< 0.001
KPS >40 vs ⩽40	1.71 (1.42-2.07)	< 0.001	1.63 (1.33-1.99)	< 0.001
Anticancer Treatment No vs yes	1.35 (1.14-1.59)	< 0.001	1.42 (1.19-1.69)	< 0.001
Type background pain Neuropathic/mixed vs nociceptive	1.23 (1.05-1.44)	0.01	1.17 (0.81-1.67)	0.41
Type BTcP Neuropathic/mixed vs nociceptive	1.21 (1.04-1.41)	0.02	1.03 (0.72-1.48)	0.86
NSAIDs/paracetamol use Yes vs no	1.68 (1.44-1.95)	< 0.001	1.56 (1.34-1.82)	< 0.001
BTcP interference ADLs High vs low	2.46 (1.92-3.14)	< 0.001	2.34 (1.81-3.01)	< 0.001

T05

AWARENESS OF RISK OF PROSTATE CANCER REMAINS POOR IN FAMILIES WITH GERMLINE MUTATIONS IN DNA-REPAIR GENES

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Background: Prostate cancer (PCa) is the most commonly diagnosed cancer in men and the fifth most common cause of cancer death in Western countries. About 5-10% of PCas correlate with an inherited susceptibility; germline mutations in DNA-repair genes (DRG) were found in approximately 5% of localized PCas and in 12% of metastatic castration-resistant PCas. As DRG mutations correlate with PCa aggressiveness there is an urgent need to test individuals suspected to be carriers who eventually most benefit from early diagnosis and personalized therapies. The aim of the present study is to investigate the awareness of risk of PCa in families with germline mutations in DRG.

Patients and methods: This is a prospective, monocentric study about families with DRG mutations. BRCA1/2+ families were selected from all families of women with breast and/or ovarian cancer treated in the last 5 years at our tertiary University Hospital. To test the awareness of risk of PCa in BRCA1/2+ families we used the ratio between the number of families, where at least one man was present, that were offered the test for BRCA1/2 genes and families that were really tested as proxy. Healthy men with BRCA1/2 mutations were enrolled in a dedicated annual PCa screening consisting of digital rectal examination (DRE), blood test for Prostate Health Index (PHI) and multiparametric MRI with software assisted target biopsy plus systematic biopsy in suspected cases.

Results: We reviewed the genealogical trees of all breast/ovarian cancer patients who attended our Genetic Counselling Clinic from January 2016 to May 2021 and identified, over 1083 families, 132 positive for mutations in DRG. Over 132 families, we found that male members of 62 rejected to be tested, in 24 original parent branch of mutation was unknown and limited the interest in male relatives, in 9 no male relatives were present, in 5 men were already tested negative and in 8 men were missed. Finally, we selected 29 families (25%) with at least one male relative interested to be tested. Overall we identified 59 positive men, of whom 27 met the study inclusion criteria. They all accepted to be enrolled and started the annual screening with DRE and PHI.

Conclusions: Our analysis shows that only 25% of families with at least one man with high-risk of developing PCa received a genetic profile and could access to dedicated PCa screening. This observation strongly supports the urgent need to implement awareness of genetic risk for PCa within male population.

T06

ONCOLOGIC DRUGS APPROVAL IN EUROPE: FEATURES OF CLINICAL TRIALS

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Background: Drug development in oncology is changing rapidly. Here we describe the methodological features of clinical trials supporting the registration of anti-tumour drugs in Europe.

Methods: We included all the indications for solid tumours issued by European Medicines Agency (EMA) between 2015-2020. We extracted data from European Public Assessments Reports, including setting, primary and other endpoints.

Results: In the considered period, EMA issued 129 indications with 80 indications' extensions. The most common tumour types were non-small-cell lung cancer (NSCLC), breast cancer and melanoma (Table 1).

Overall, most of the indications were for the advanced disease (91.5%) and front-line therapy (62%). More than half were issued for immune checkpoint inhibitors (ICIs) and signal transduction inhibitors.

Out of 129 indications, 22 (17%) were approved on the basis of a single-arm study and 3 based on a phase 1 trial. Overall survival (OS) was evaluated as a primary endpoint in 40.3% of all the indications granting marketing authorisation. The remaining indications were supported by trials with a surrogate outcome or pharmacokinetics as primary endpoint. Quality of life (QoL) was never a primary endpoint of the pivotal trials.

Finally, we found that the average Hazard Ratio for OS and PFS were 0.7 (SD 0.105) and 0.57 (SD 0.164), respectively, with no difference according to treatment lines or across years of approval.

Conclusions: In this analysis, we intended to offer a picture of the recent drug authorisation in oncology. Most of the efforts led to broadening indications of pre-existing molecules and almost 20% of the drugs being approved without a randomized trial. Moreover, we show that most of the drugs entered the market without evidence of OS or QoL benefit but based on surrogate outcomes.

Table 1.

Setting	Localized	11	8.5%
	Advanced	118	91.5%
Class of drugs	ICIs	40	31%
	Signal transduction inhibitors	39	30.2%
	Angiogenesis inhibitors	16	12.5%
	Cell cycle and DNA repair	18	14%
	Chemotherapeutic agents	8	6%
	Hormonal therapy	7	5.5%
	Radiometabolic agent	1	0.8%
Disease	NSCLC	32	25%
	Breast Cancer	20	15.5%
	Melanoma	13	10%
	Ovarian Cancer	10	8%
	Other	54	41.5%
Phase	1	3	2.4%
	2	29	22.4%
	3	97	75.2%
Randomisation	Yes	107	83%
	No	22	17%
Primary Endpoint	OS	52	40.3%
	PFS	41	31.8%
	Other Survival Outcomes	9	7%
	ORR	25	19.4%
	PK	2	1.5%

T07

BRCA1/2 VARIANTS WITH UNCLEAR CLINICAL SIGNIFICANCE (VUS) IN HBOC SYNDROME: HUNTING FOR NOVEL POTENTIALLY PATHOGENIC VARIANTS

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Background: About 10-20% of hereditary breast and/or ovarian (HBOC) cancer patients undergoing germline *BRCA1/2* genetic testing harbour Variants of Uncertain Significance (VUS). Poor is the knowledge about the prevalence of germline *BRCA1/2* VUS in HBOC patients of Southern Italy. Our study is aimed at describing the spectrum of these variants detected in HBOC patients in order to improve the patient's stratification with the identification of potentially high-risk *BRCA* variants helpful for patient clinical management.

Patients and Methods: 874 breast (BC) or ovarian (OC) cancer patients, enrolled from October 2016 to April 2021 at the "Sicilian Regional Center for the Prevention, Diagnosis and Treatment of Rare and Heredo-Familial Tumors" of University Hospital Policlinico "P. Giaccone" of Palermo, were genetically tested for germline *BRCA1/2* variants through Next-Generation Sequencing analysis.

Results: The screening results showed that 639 (73.1%) out of 874 patients were BRCA-wild-type, whereas 67 (7.7%) were carriers of germline *BRCA1/2* VUS and 168 (19.2%) harboured germline *BRCA1/2* Pathogenic/Likely Pathogenic Variants. Overall, the mutational analysis revealed the presence of 59 different VUS detected in 67 patients, 46 of which affected by BC and 21 by OC. Twenty-one (35.6%) out of 59 variants were located on *BRCA1* gene, whereas 38 (64.4%) on *BRCA2*. We have identified six alterations in *BRCA1* and two in *BRCA2* with unclear interpretation of clinical significance. Familial anamnesis of a patient harbouring *BRCA1*-c.3367G>T suggests for this variant a potential of pathogenicity as well as the *BRCA1*-c.4963T>G variant identified in three unrelated OC patients.

Conclusions: Understanding clinical significance of germline *BRCA1/2* VUS could improve the identification of potentially high-risk variants useful for clinical management of BC/OC patients and family members. Reclassifying these variants could make them useful for predictive, prognostic and preventive purposes in clinical practice. Advances in molecular biology, such as the use of multigene panels, exome sequencing and/or RNA-seq, are increasing the amount of data in the field of research about VUS. Further linkage analyses will be able in the future to provide additional information useful for understanding inherited variants of unclear clinical significance associated with HBOC.

T08

SCREENING OF DELETERIOUS DPYD VARIANTS IN PATIENTS WITH GASTROINTESTINAL TUMORS: DATA FROM A SINGLE INSTITUTION IN ITALY

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Background: Dihydropyrimidine dehydrogenase (DPYD) gene encodes for DPD, involved in fluoropyrimidines (FP) catabolism. The identification of variants associated with

deleterious enzyme activity and increased risk of toxicity is recommended before treatment initiation [c.1905+1G>A(*2A); c.1679T>G(*13); c.1129-5923C>G, c.1236G>A(HapB3); c.2846A>T) or during treatment in case of adverse drug reactions [c.2194G>A (*6)]. The prevalence of DPYD deficient genotypes in the European population is estimated <8%.We aimed at determining the prevalence of DPYD deficient gene variants in patients with GI tumors treated at our department.

Methods: A consecutive series of patients diagnosed with GI tumors at our department from 15th June to 15th April 2021 and candidate to a FP-based therapy was assessed for germline DPYD testing before treatment initiation. The following variants were examined: c.1905+1G>A(*2A); c.1679T>G(*13); c.1129-5923C>G, c.1236G>A(HapB3); c.2846A>T; c.2194G>A(*6).

Results: 358 patients were included in the analysis: 261 patients with colorectal [CRC], 43 gastro-esophageal [GEC], 41 biliopancreatic [BPC], 10 other GI cancer (i.e. anal, NET), and 3 had a double-tumor diagnosis (CRC/GEC, GEC/BPC). 59 (16%) cases were carriers of a deleterious DPYD variant whereas 299 patients (84%) had DPYD wild type (WT) status. Among positive cases, 48 (81%) had CRC, 6 BPC (10%), 3 GEC (5%), 1 other GI tumor-type (2%) and 1 had a CRC and GEC (2%). No association was observed between DPYD status and tumor-type (p=0.33). Overall, 60 deleterious variants were observed in 49 subjects: c.2194G>A(*6) in 45 cases (12%); c.1905+1G>A(*2A) in 7 (2%); c.1129-5923C>G in 5 (1%); c.2846A>T in 2 (<1%); c.1679T>G(*13) in 1 (<1%).In 43 cases (12%) the recommended FP total dose (TD) was 85%, in 12 (3%) was 50%, in 4 ranged from 50 to 75% (1%), no variation was recommended in patients with WT status (TD 100%) (N=299, 84%).Of interest, 77 patients were enrolled in phase II or III clinical trials including FP treatment: 10/77 subjects (13%) showed a gene variant requiring a FP-dose reduction.

Conclusions: In our cohort the prevalence of DPYD deleterious variants was more frequent than in reported data. DPYD*6 c.2194G>A was the most frequent genotype requiring dose adjustments. According to our data, the assessment of deleterious DPYD variants and consequent FP-dose adjustment should be included in clinical trials protocols including FP treatment to prevent adverse drug reactions and to adequately describe toxicity and patients' quality of life.

T09

DIABETES THERAPY BURDEN AS PROXY OF IMPAIRMENT OF IMMUNE CHECKPOINT INHIBITORS EFFICACY

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Background: Chronic hyperglycemia is known to induce immune dysfunctions and multiple studies has identified resistance/adherence to insulin therapy as barriers to achieving an optimal glycaemic control in patients with diabetes mellitus (DM) after front line metformin failure. How DM affects the efficacy of immune checkpoint inhibitors (ICI) is yet to be defined.

Methods: We evaluated the impact of DM in a retrospective cohort of patients with advanced cancer treated with ICI at 22 Institutions. The diabetes medication burden (DMB) at ICI initiation was used as a proxy of long-term/poorly controlled DM. Patients with a high DMB were on high dose metformin (> 1000 mg daily) either alone or in combination with insulin therapy and/or other oral antidiabetics. Patients with low DMB were on oral antidiabetics/insulin therapy either with or without low dose metformin. In a subgroup of 133 patients the inter-relationships between the median baseline glycemia (MBG) (computed upon up to 3 fasting blood glucose tests within 3 months of ICI initiation) and the neutrophil-to-lymphocyte ratio (NLR) were assessed.

Results: From June 2014 to November 2020, 1395 patients treated with CTLA-4 (2.5%) and PD-1/PD-L1 (97.5%) inhibitors were included. Median age was 68 years; male/female ratio 888/507. Primary tumours were: NSCLC (54.7%), melanoma (24.7%), renal cell carcinoma (15.0%) and others (5.6%). 148 (10.6%) and 78 (5.6%) were on low and high DMB, respectively. The DMB was proportionally associated to both an increasing MBG (5.6, 7.5 and 9.5 mmol/L) and median NLR (3.8, 4.1 and 5.6). After adjusting for gender, age, BMI, primary tumour, treatment line, burden of disease, performance status and corticosteroids, patients on high DMB were confirmed to have shorter progression free survival (PFS) (HR 1.39[95%CI: 1.09-1.78] p=0.0075) and overall survival (OS) (HR 1.44 [95%CI:1.09-1.90] p = 0.0087) as compared to non-DM.

MBG significantly predicted for the NLR [F(1,131) = 4.09, p = 0.04), R2 of.030], and was associated to a high NLR (⩾ 4) even after adjusting for corticosteroids (OR = 1.68[95%CI: 1.23 – 2.29], p = 0.0011).
Conclusions: Long-term/poorly controlled diabetes may impair ICI efficacy. Strategies to improve glycaemic control should be strongly pursued in oncological patients about to start an immunotherapy.

T10

DEDICATED BREAST CANCER SCREENING IN A COHORT OF NEUROFIBROMATOSIS 1 WOMEN: PRELIMINARY DATA OF A 3-YEARS FOLLOW-UP

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Background: Neurofibromatosis type 1 (NF1) is a genetic condition characterized by a complex and heterogeneous multiorgan disease. It is also a well-known tumor predisposing condition. Recently several studies have established an association between NF1 and breast cancer (BC), especially for women under 50 years old, with an up to five-fold increased risk compared to the general population. Due to these findings, enhanced breast cancer screening is recommended for NF1 patients
Patients and Methods: In 2018 we started to offer a dedicated breast cancer screening to our cohort of NF1 women. Annual ultrasound breast examination beginning at 25 years of age, associated with annual mammography at 40 years old, with oblique reconstructions in tomosynthesis. Breast magnetic resonance imaging (MRI) was not performed in the diagnostic routine, but only for selected cases.
Results: One hundred fifty-nine women (age from 25 to 71 years old), without previous history of breast cancer, were screened for breast cancer in our Institution from February 2018 to April 2021. Sixty-one patients under 40 years old underwent ultrasound breast examination only. The most frequent findings were lesions radiologically compatible with dysplastic/benign nodules [16/160 (10%), among these lesions fibroadenomas, fibrolipomas and neurofibromas-like], and microcalcifications among patients screened with mammograms [16/98 (16%)]. At the first mammography examination, a result of BIRADS 3 or BIRADS 4 was reported respectively in 3/97 (3%) and 1/97 (1%), but none of these patients were diagnosed with cancer. The only case of BC has been diagnosed in a 43 years old patient, who missed radiological screening in 2020 (in 2021 an increased number of microcalcification clusters *versus* 2019 and a 2-cm nodule were observed, with core biopsy positive for ductal invasive cancer).
Conclusions: The increased risk for BC, and the younger age at diagnosis in comparison with the general population, are the main factors driving enhanced BC screening in NF1 women. It is likewise important to stimulate the adhesion to such a program, as well as to recommend a regular breast self-examination.

T11

CTLA-4 AND PD-1 BLOCKING AGENTS-INDUCED CARDIOTOXICITY IN CELLULAR AND PRECLINICAL STUDIES THROUGH MYD88-NLRP3-IL1 PATHWAYS

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Background: Several strategies based on immune checkpoint inhibitors (ICIs) have been developed for cancer therapy, opening to advantages in cancer outcomes. However, several ICIs-induced side effects emerged in these patients, especially a rare but clinically significant cardiotoxicity with high rate of mortality. We studied cytotoxic and pro-inflammatory properties of Ipilimumab and Nivolumab, underlying pathways and cytokine storm involved.
Methods: Co-cultures of human cardiomyocytes and lymphocytes were exposed to Ipilimumab or Nivolumab; cell viability and expression of leukotrienes, NLRP3, MyD88 and p65/NF-kB were performed. C57 mice were treated with Ipilimumab (15 mg/kg); analysis of fractional shortening, ejection fraction, radial and longitudinal strain were made before and after treatments through 2D-echocardiography. Expression of NLRP3, MyD88, p65/NF-kB and 12 cytokines have been analyzed in murine myocardium.
Results: Nivolumab and Ipilimumab exert effective anticancer but also significant cardiotoxic effects in co-cultures of lymphocytes and tumor or cardiac cells. Both ICIs increased NLRP3, MyD88 and p65/NF-kB expression compared to untreated cells, however the most pro-inflammatory and cardiotoxic effects were seen after exposure to Ipilimumab. Mice treated with Ipilimumab showed a significant decrease of fractional shortening and radial strain with respect to untreated mice coupled to a significant increase of myocardial expression of NLRP3, MyD88 and several interleukins.
Conclusions: Nivolumab and Ipilimumab exert cytotoxic effects mediated by NLRP3/IL-1β and MyD88 pathways leading to pro-inflammatory cytokine storm in heart tissue.

T12

DAPAGLIFLOZIN REDUCES ANTHRACYCLINE AND TRASTUZUMAB-INDUCED CARDIOTOXICITY THROUGH MYD88, NLRP3 AND MTORC1 /FOX01/3A MEDIATED PATHWAYS

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Introduction: The clinical trial "DECLARE-TIMI 58" (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58), demonstrated that dapagliflozin, a Sodium glucose cotransporter 2 inhibitor, reduces the composite end point of cardiovascular death/hospitalization for heart failure in a broad population of patients with type 2 diabetes mellitus. We aimed to study if dapagliflozin could exerts cardioprotective effects in doxorubicin and trastuzumab-induced cardiotoxicity through the analysis of multiple biochemical mechanisms.
Methods: HL-1 adult cardiomyocytes were exposed to subclinical concentration of doxorubicin and trastuzumab (100 nM) alone or in combination with dapagliflozin at 50 nM. Determination of cell viability was performed through analysis of mitochondrial dehydrogenase activity and the study of lipid peroxidation (quantifying cellular Malondialdehyde and 4-hydroxynonenal), and of intracellular Ca2+ homeostasis. Moreover, anti-inflammatory studies were also performed (activation of NLRP3 inflammasome; expression of TLR4/MyD88; transcriptional activation of p65/NF-κB and secretion of cytokines involved in cardiotoxicity (Interleukins 1ß, 8 and 6). Moreover, mTORC1 /Fox01/3a expression studies were performed through western blot.
Results: Dapagliflozin increases significantly the cardiomyocytes viability during exposure to doxorubicin and trastuzumab. Its cardioprotective properties are explainable by the reduction of intracellular Ca2+ overload (-47,6% vs cells treated only to anticancer drugs; $p<0,001$), of the lipid peroxidation (mean reduction of 35-43 % compared to cells exposed only to anticancer drugs; $p<0,001$). Moreover, cardiomyocytes exposed to dapagliflozin during anticancer drugs have a reduced expression of pro-inflammatory cytokines (- 37,3 % for Interleukin-1ß; -39,5 for Interleukin 8; -41,3 % for Interleukin 6; $p<0,001$ for all). Notably, dapagliflozin reduces p65-NF-κB activation (- 36,5% vs cells treated only to anticancer drugs) and inhibits of 27,8 % the expression of NLRP3. mTORC1 / Fox01/3a expression were also reduced after treatment with dapagliflozin, an aspect directly involved in the reduction of cardiomyocyte apoptosis
Conclusions: Dapagliflozin demonstrated for the first time cardioprotective properties during doxorubicin and trastuzumab exposure. The main biochemical effects of dapagliflozin are related to MYD88, NLRP3 complex, Leukotrienes/Interleukin 6 axis and mTORC1 /Fox01/3a mediated apoptosis.

T13

RISK-ADAPTED PREEMPTIVE TOCILIZUMAB TO PREVENT SEVERE CYTOKINE RELEASE SYNDROME AFTER CD19 CAR T CELLS: THE HUMANITAS CANCER CENTER EXPERIENCE

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Background: CAR T-cell therapy has revolutionized treatment for patients with relapsed/refractory Diffuse Large B Cell Lymphoma (DLBCL) or Primary Mediastinal B Cell Lymphoma (PMBCL). Cytokine release syndrome (CRS) immune effector cell–associated neurotoxicity syndrome (ICANS) are the most notable toxicities of CAR T-cell therapy.
Materials: We report about 20 patients with DLBCL (n= 15) and PMBCL (n=5) treated with CAR T-cells at Humanitas from November 2019 to April 2021, according to AIFA restrictions. The aim of the study is to evaluate the effectiveness of risk-adapted preemptive Tocilizumab administration in preventing severe (grade 3-4) CRS. Patients received a dose of Tocilizumab at the time of developing persistent grade 1 CRS, defined as fever (TC =38°C) for a 24-hour period. ASCT grading system was used to grade CRS and ICANS. Patients characteristics are listed in Table 1.
Results: Seventeen (85%) patients developed CRS: CRS was graded as G1 in 8 patients, G2 in 8 patients and G3 in 1 patient. No patients developed grade 4 CRS. Median time to CRS onset was 3 days (range, 0-8). Tocilizumab was administered in 15 cases and only 3 patients received steroids. ICANS was observed in 3 patients (15%). Median time to ICANS onset was 8 days (range, 7-10). ICANS grading was G2 in 1 patient, G3 in 1 patient and G4 in 1 patient. All patients with ICANS were treated with steroids with resolution of symptoms. Intensive care unit (ICU) admission was required for only 3 patients, 2 of them with severe ICANS and one with severe pleural effusion due to uncontrolled progressive disease. Two patents developed infections: one probable pulmonary aspergillosis and one Pneumocystis Carinii pneumonia. Non relapse mortality was 0%. The best overall and complete response rates were 70% and 60%, respectively. The progression free survival and overall survival at 12 months were 48% and 62%, respectively.
Conclusions: In conclusion, although the small number of patients analyzes, we found that preemptive administration of Tocilizumab decreased the expected incidence of severe CRS and ICU admission with no impact on neurotoxicity or infections and no death from CAR-T toxicity.

Patients characteristics	N=20	%
Age, median (range)	54 years (26-68)	
Disease		
DLBCL	15	75
PMBCL	5	25
ECOG performas status at apheresis		
0	18	90
1	2	10
Stage at apheresis		
I-II	6	30
III	1	5
IV	13	65
Prior ASCT		
no	15	75
yes	5	25
CART type		
Tisagenleucel	15	75
Axicabtagene ciloleucel	5	25

T14

PERFECT CONCORDANCE BETWEEN BLOOD-BASED AND NORMAL TISSUE-BASED DIHYDROPYRIMIDINE DEHYDROGENASE (DPYD) POLYMORPHISMS SUGGESTS THAT PHARMACOGENETIC SCREENING COULD BE CONTEXTUAL TO TUMOUR MOLECULAR PROFILING

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Background: 5 – fluorouracil (5-FU) represents the chemotherapy backbone of almost all GI cancers. Important 5-FU-related toxicities have been traced back to impaired or reduced enzymatic catabolism secondary to DPYD allelic polymorphisms. International guidelines recommend pharmacogenetic DPYD test prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine, and this usually requires an additional blood draw. The aim of our work was to evaluate the concordance of DPYD allelic variants detection from blood and normal tissue derived DNA in order to make the pharmacogenetic screening contextual to tumor mutation screening.

Patients and Methods: 5 standard DPYD gene polymorphisms (IVS14+1G>A, c.1905+1G>A; c.1679T>G, p I560S; c.2846A>T, p. D949V; c.1129–5923C>G, IVS10C>G; c.2194G>A, V732I) were tested both in blood-derived and normal formalin embedded tissue-derived cell DNA of consecutive GI cancers patients with Realtime Polymerase Chain Reaction (PCR) (Easy PGX ready DPYD – Diatech Pharmacogenetics). The adequacy of normal tissue availability on biopsy or surgical material had to be declared before testing by two dedicated pathologists (G.P and E.D.). Concordance of paired results was retrospectively evaluated.

Results: Nine Colorectal, 2 Esophago-Gastric Junction and 1 Pancreatic cancer patients were enrolled. Tissue samples were obtained from previous surgery or endoscopic biopsies. Pharmacogenetic evaluation was made before treatment start. Heterozygosis of rs1801160 polymorphism (c.2194G>A, V732I) was found in 4 out of 12 patients. Evaluation of heterozygous cases on paired blood and tissue samples showed a 100% overall agreement (Pearson's coefficient = 1). Concordance between blood and tissue-based results was also confirmed for the remaining 8 wild-type homozygous patients. As for international guidelines, 5 – FU administered dose was reduced by 15% in heterozygous patients. No grade > 1 fluoropyrimidine-related adverse events were reported in the whole cohort.

Conclusions: The fully concordant results in DPYD assessment between blood and tissue samples support the testing with Realtime PCR for genotyping of DPYD polymorphisms of GI patients on normal tissue when adequately available in routine clinical practice concomitantly with tumor genetic profiling (e.g. concomitant to RAS and BRAF mutation screening), thus avoiding the distress of an additional blood draw.

T15

RENAL FUNCTION IN CANCER PATIENTS UNDERGOING REPEATED ADMINISTRATIONS OF IODINATED CONTRAST MEDIUM (CM): A MULTICENTRIC RETROSPECTIVE STUDY

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Introduction: Contrast-enhanced computed tomography (CECT) is the imaging of choice for the diagnosis, staging, response evaluation, and follow-up of cancer patients; in fact, 47% of all CECTs are prescribed by Oncologists. Comorbidities, concomitant nephrotoxic (oncological and non-oncological) medications, as well as chronic dehydration from different causes, expose these patients to a higher risk of developing acute kidney injury (AKI) from CM. Risk factors, definition (PC-AKI vs CI-AKI), as well as preventive measures have been recently reconsidered, ultimately downsizing the incidence of this adverse event.

Materials and methods: The purpose of this study was to assess the effects of multiple and repeated CM administrations on the renal function in cancer patients on active treatment, collected from 5 Italian oncology departments. We have thus retrospectively evaluated 407 patients, who underwent at least 3 CECT (on the average 3.5) within one year (Table I).

Results: According to our study, neither significant differences in eGFR values, calculated with the CKD-EPI formula, between the baseline and the different post-CECT timepoints, nor AKI cases (defined according to the RIFLE criteria), were recorded.

Conclusions: Repeated and frequent CM administrations in cancer patients did not lead to a worsening of renal function, confirming that CI-AKI has a significantly lower incidence than previously thought; furthermore, 80% of the patients examined were found to be at low-risk. In concordance with the most recent guidelines, the administration of CM in oncological patients could be freely used, even in patients at higher risk.

Tab. I. Main characteristics of the population studied.

Age	>65	183 (45%)
	<65	224 (55%)
Sex	Male	228 (56%)
	Females	179 (44%)
Heart disease	Yes	79 (20%)
	No	274 (67%)
	Unknown	54 (13%)
Nephrectomy	Yes	171 (42%)
	No	236 (58%)
Diabetes	Yes	73 (18%)
	No	313 (77%)
	Unknown	21 (5%)
Hypertension	Yes	195 (48%)
	No	196 (48%)
	Unknown	16 (4%)
Kidney failure	Stages I and II	281 (69%)
	Stadio Iiia	85 (21%)
	Stadio Iiib	33 (8%)
	Stage IV	8 (2%)
	Stage V	0 (0%)
Type of tumor	Genitourinary	199 (49%)
	Gastro-intestinal	57 (14%)
	Lung	45 (11%)
	Head-neck	3 (0,8%)
	Cute	16 (4%)
	Udder	41(10%)
	Other	46 (11,2%)
Type of oncology therapy	Cytotoxic chemotherapy	175 (43%)
	Drugs with molecular target	134 (33%)
	Immunotherapy	142 (35%)
	Hormone therapy	16 (4%)

T16

PCSK9 INHIBITOR EVOLOCUMAB REDUCES CARDIOTOXICITY AND INFLAMMATION INDUCED BY DOXORUBICIN-TRASTUZUMAB THROUGH MYD88/NF-KB/MTORC1 PATHWAYS

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Introduction: Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as a novel therapy to treat hypercholesterolaemia and related cardiovascular diseases. Evolocumab, a PCSK9 inhibitor, reduced the risk of cardiovascular events in patients with atherosclerotic cardiovascular diseases when added to maximally tolerated statin therapy (± ezetimibe), and recent data from the ODYSSEY OUTCOMES trial indicate that alirocumab added to maximally tolerated statin therapy (± other lipid-lowering drugs) reduces the risk of cardiovascular events in patients with a recent acute coronary syndrome. Considering the expression of PCSK9 in heart tissue, we aimed to study for the first time the direct biochemical effects of evolocumab in cardiomyocytes during exposure to doxorubicin, trastuzumab, their sequential treatments.

Methods: Human fetal cardiomyocytes (HFC cell line) were exposed to subclinical concentration of doxorubicin, trastuzumab, sequential treatment of both (all 100 nM), alone or in combination with evolocumab (50 nM) for 48h. After the incubation period, we performed the following tests: determination of cell viability, through analysis of mitochondrial dehydrogenase activity, study of lipid peroxidation (quantifying cellular Malondialdehyde and 4-hydroxynonenal), intracellular Ca2+ homeostasis. Moreover, pro-inflammatory studied were also performed (activation of NLRP3 inflammasome; expression of TLR4/MyD88; mTORC1 Fox01/3a; transcriptional activation of p65/NF-κB and secretion of cytokines involved in cardiotoxicity (Interleukins 1ß, 8, 6).

Results: Evolocumab co-incubated with doxorubicin alone or in sequence with trastuzumab exerts cardioprotective effects, enhancing cell viability of 35-43% compared to untreated cells ($p<0,05$ for all); Evolocumab reduced significantly the cardiotoxicity through MyD88/NF-KB/cytokines axis and mTORC1 Fox01/3α mediated mechanisms.

Conclusions: We demonstrated, for the first time, that the PCSK9 inhibitor evolocumab exerts direct effects in cardiomyocytes during doxorubicin and trastuzumab exposure turning on a new light on its possible use in cancer patients.

T17

ECONOMIC IMPACT OF COMPASSIONATE USE OF CANCER TREATMENTS

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Background: The economic impact of clinical trials in the perspective of trial sites has been already investigated. Instead, there is no evidence on the economic net benefit of compassionate use programs for medicines (CUP). This research aims to fill the information gap, investigating the economic consequences of 12 CUP in Italy carried out from May 2015 to December 2020 in the hospitals' perspective. Eight programs concern cancer treatments: alectinib for first and second line non-small cell lung cancer – NSCLC; atezolizumab, for locally advanced or metastatic urothelial carcinoma, locally advanced or metastatic NSCLC and, in combination with nab-paclitaxel, unresectable locally advanced or metastatic triple-negative breast cancer; entrectinib for ROS1 NSCLC; polatuzumab vedotin for refractory DLBCL; trastuzumab emtansine TDM-1, for HER2 positive breast cancer.
Material and methods: Economic net benefit includes avoided costs for standard of care (SoC) the patient would have received if he/she has not joined the CUP and costs not covered by the pharmaceutical industry and sustained by the hospital hosting CUP. The latter include costs of adverse event (only severe sides effects generating hospitalisation and ascribed to medicines used in CUP), combination therapies and diagnostic procedures not covered by the sponsor and that would be not used with the SoC. SoC costing relied on publicly available estimation. Adverse events and diagnostic procedures were retrieved from the CUP and monetized using the relevant fee for episode.
Results: 1640 patients were treated in eight cancer CUPs (the overall number of recruited patients in the 12 CUPs was 2713). The SoC mean cost per patient ranges from €13555 to €28235 for all cancer drugs. The total cost of the SoC ranges €22.2 through €46.3 million. The mean cost per patient covered by hospitals hosting CUP was equal to €2694 for cancer drugs, with a total cost of €4.4 million. The net economic benefit ranges from €17.8 million to €41.9 million for cancer treatments.
Conclusions: Despite its limitations this paper illustrates for the first time the net economic impact of CUP in oncology patients in the perspective of payers. Additional evaluations are ongoing to better understand the prospective effects of CUP implementation, i.e. the economic value of the comparative benefit profile of medicines used in CUP versus the SoC, including potential effects on indirect costs.

T18

ONCOLOGIC TREATMENT IN THE LAST 30 DAYS OF LIFE: A SINGLE CENTER REPORT

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Background: End of life medical treatment is an issue widely discussed in Oncology. There is little data about the indications for decision making between active treatment versus best supportive care. In this report we present our experience in patients (pts) who received oncologic treatment within the last 30 days of life.
Material and methods: We retrospectively collected data of pts who have been hospitalized in the Medical Oncology Department of Istituto Nazionale Tumori of Milan receiving oncologic treatment from the 15th of November 2020 to the 15th of May 2021. We considered this period to mitigate the confusing effect of the SARS-Cov2 pandemic on the increase of mortality. We selected pts affected by any stage of cancer, who received any line of active cancer therapy within 30 days from death. We collected: age, sex, Performance Status according to the Eastern Cooperative Oncology Group (PS), type of cancer, line and type of treatment, Hemoglobin (Hb), White Blood Cells (WBC), Neutrophils (N), Platelets (PLT), Lactate Dehydrogenase (LDH), modified Glasgow Prognostic Score (mGPS) calculated with Albumine and C Reactive Protein, and cause of death.
Results: In total 263 pts were hospitalized. Of these, 166 have received oncologic treatment. Of them, 9 pts (5.4%) died within 30 days of treatment. Among them, the mean age was 64 years, 4 pts were women (44%) while 5 were men (56%). Three pts were PS 1 (33%), 3 pts were PS 2 (33%) and 3 pts were PS 3 (33%). All pts were affected by advanced cancer; 7 pts had lung cancer (78%), 1 gastric cancer (11%) and 1 breast cancer (11%). Four pts (44%) received first line therapy and 5 pts (56%) further line therapy. Five pts were treated with chemotherapy (56%), 3 pts with immunotherapy (33%), 1 with chemo-immunotherapy (11%). Considering the blood tests, median WBC count was 9680/μL (1080 - 33820), median N levels were 8860/μL (3780 – 31520), median Hb was 11.2 g/dL (9-15), median PLT count was 314 000/μL (196 000 - 413 000) and median LDH was 216 U/L (150 - 1372). mGPS were 2 in 5 pts (56%), 1 in 2 pts (22%) and 0 in 2 pts (22%). Causes of death were progression (78%), toxicity (11%) and other causes (infection, 11%).
Conclusions: Our study is consistent with available literature about end of life oncologic treatment. Based on our data, pts' selection according to PS and mGPS should not be the only parameter to consider for treatment decisions.

A comprehensive characterization of the pts treatment must be studied.

T19

CHANGES IN THE SECRETOME INDUCE RESISTANCE TO INHIBITORS OF DOWNSTREAM B CELL RECEPTOR (BCR) SIGNALING IN MARGINAL ZONE LYMPHOMA (MZL)

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Background: The PI3Kδ-inhibitor (i) idelalisib (IDE), the PI3Kα/δ-i copanlisib (COPA) and the BTK-i ibrutinib (IBRU) are FDA approved to treat indolent lymphomas including MZL. However, not all patients respond and some relapse after an initial response. We have generated MZL cell lines with acquired resistance to IDE, COPA, and IBRU providing insights on resistance and allowing the identification of novel therapeutic approaches.
Materials and Methods: VL51 and Karpas1718 (K1718) lines were exposed to IC90 doses of IDEL, COPA or IBRU for several months until acquisition of specific drug resistance (RES). In parallel, parental cell lines were cultured upon similar conditions with no drug (PAR). Resistance was confirmed as stable by keeping cells for 2-weeks in drug-free culture. Multi-drug resistance phenotype was ruled out. Cells underwent multi-omics characterization and pharmacological screening. Cytokines secretion was evaluated by ELISA in cell lines and patient serum samples.
Results: RES models exhibited from 15- to 50-fold times higher IC50s than PAR. VL51-IDEL-RES showed activation of p-ERK, p-STAT, higher surface PDGFRA and IL6 secretion. Pharmacological or genetic inhibition of IL6 or PDGFRA restored sensitivity to IDEL. K1718-IDE-RES exhibited elevated p-AKT and p-ERK, enrichment of ERBB signaling, and HBEGF secretion. Combination with the ERBB-i lapatinib was beneficial in K1718-IDE-RES. VL51-IBRU-RES exhibited increased levels of p-AKT, p-ERK, NF-kB and RAS-RAF pathways and secretion of IL16 and CXCL10. IL16 blocking recovered sensitivity to IBRU in VL51-IBR-RES and in cell lines with primary resistance and high IL16. Serum of patients not responding to IDEL, or IBRU, exhibited higher levels of IL6, HBEGF, or IL16 compared to clinically-matched responding patients. VL51-COPA-RES showed up-regulation of negative regulators of apoptosis, MAPK, NF-kB and JAK/STAT signaling, along with IL1A and IL1B secretion. Finally, cross-resistance among IDE, COPA, and IBRU was observed in the different models.
Conclusions: The development of models of acquired of resistance to IDEL, COPA and IBRU led to the identification of novel potentially active therapies for lymphomas with acquired resistance to these agents. Importantly, these models, driven by different biologic processes, are useful tools to run pharmacological screens.

T20

IMMUNE-RELATED ADVERSE EVENTS (IRAE) OCCURRENCE AMONG CANCER PATIENTS ACCESSING THE EMERGENCY DEPARTMENT (ED) DURING TREATMENT WITH IMMUNE CHECKPOINT INHIBITORS (ICIS)

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Background: Cancer therapy is continuously evolving, with an increasing number of new drugs available. Among these, ICIs have an important role. Effective treatments cause the number of long-surviving patients to grow. These patients, throughout the history of their disease, are cared not only by oncologists, but also by other health professionals, such as general practitioners and emergency physicians, who often lack an adequate knowledge about the most common side effects. We were interested in assessing the incidence of cancer patients undergoing treatment with ICIs that are referred to the ED with clinical conditions potentially related with IRAE.
Patients and methods: We retrospectively analyzed the accesses to the ED of patients with lung cancer and head and neck cancer from the first ICI administration until one month following the last one, during a period of two years in a single hub hospital. Presenting symptoms and the final diagnosis were classified as unrelated, potentially related or definitely related with ICIs. Data were retrieved from the health records of the Medical Oncology and of the ED departments.
Results: 78 ICIs treated patients were included in the analysis (69.6% male, median age 70 years). In the examined period there were 64 referrals to the ED. 48,7% had at least one access to the ED Patients referred to the ED were in red code in 1,5% (1), in yellow code in 46,8% (30) and in green or white code in 51,5% (33). Access to the ED was

followed by hospitalization in 60.9% of cases. In 70,3% (45) the presenting symptom was potentially related with ICIs and in only 1 case was clearly an IRAE (liver toxicity); in 39,0% (25) also the discharge diagnosis (from the ED or from the admission Unit) was potentially related with ICIs.

Conclusions: Patients treated with ICIs frequently need access to the ED. Although the incidence of IRAEs is low, the possibility of an IRAE enters in the differential diagnosis in a substantial fraction of emergency evaluations. This data support a widespread initiative aiming at increasing knowledge and at transferring useful informations among emergency physicians.

T21

THE COMBINATION OF A NEPRILYSIN INHIBITOR (SACUBITRIL) AND ANGIOTENSIN-II RECEPTOR BLOCKER (VALSARTAN) IMPROVES EJECTION FRACTION AND LONGITUDINAL STRAIN IN MICE EXPOSED TO DOXORUBICIN THROUGH NLRP3 INFLAMMASOME AND PRO-INFLAMMATORY CHEMOKINES

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Background: Doxorubicin-mediated- adverse cardiovascular events are among the leading causes of morbidity and mortality in breast cancer patients. Sacubitril-valsartan (LCZ 696) is a combination drug, made up of neprilysin inhibitor sacubitril and angiotensin II receptor blocker valsartan, used for the treatment of heart failure in patients with a reduced ejection fraction. Here, we aim to assess whether LCZ 696, administered during doxorubicin, reduces in vitro anticancer drugs-related cardiotoxicity compared to Valsartan (V), used as a control drug.

Methods: Human fetal cardiomyocytes (HFC cell line) were exposed to subclinical concentration of doxorubicin (at 200 nM) alone or in combination with LCZ-696 (100 mM) for 72 h. After the incubation period, we performed the following tests: determination of cell viability, through analysis of mitochondrial dehydrogenase activity, study of lipid peroxidation (Malondialdehyde and 4-hydroxynonenal), intracellular Ca2+ homeostasis. Moreover, pro-inflammatory studied were also performed (activation of NLRP3; TLR4/MyD88; mTORC1 Fox01/3a; p65/NF-κB and secretion of cytokines (Interleukins 1ß, 8, 6). C57Bl/6 mice were untreated (Sham, n=6) or treated for 10 days with doxorubicin (DOXO, n=6), LCZ-696 (LCZ, n=6) or doxorubicin combined to LCZ-696 (DOXO-LCZ, n=6). DOXO was injected intraperitoneally. Ejection fraction, radial and longitudinal strain were analyzed through transthoracic echocardiography (Vevo 2100). Cardiac tissue expression of NLRP3 inflammasome, Myd8, NF-kB and chemokines and cytokines were quantified.

Results: LCZ 696 co-incubated with doxorubicin exerts cardioprotective effects, enhancing cell viability of 48-54.6% compared to only doxorubicin-treated cells ($p<0,001$ for all); LCZ 696 reduced significantly the cardiotoxicity through MyD88/NF-KB/cytokines axis and mTORC1 Fox01/3α mediated mechanisms. In preclinical study, LCZ 696 improved significantly the EF and prevented the reduction of radial and longitudinal strain after 10 days of treatment with doxorubicin. A reduced expression of pro-inflammatory cytokines, NLRP3, MyD88 and NF-kB in heart tissues was also seen in DOXO-LCZ group compared to DOXO mice ($p<0.001$).

Conclusions: We demonstrated, for the first time, that the LCZ696 exerts direct effects in cardiomyocytes and preclinical models during doxorubicin exposure, turning on a new light on its possible use in cancer patients to reduce cardiovascular side effects.

T22

BRIDGING RADIOTHERAPY TO CAR-T CELL THERAPY IN REFRACTORY NON-HODGKIN B LYMPHOMA: SINGLE-CENTER EXPERIENCE

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Background: Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy is an effective option for the treatment of relapsed/refractory diffuse large B-cell lymphoma. In order to control lymphoma progression during the manufacturing period, a bridge therapy regimen is required for most patients. Radiotherapy (RT) may be used for patients with localized chemorefractory disease as a bridge therapy.

Patients: Here we report a case series of 6 patients (1 primary mediastinal, PMBCL, and 5 diffuse large B-cell lymphoma, DLBCL) treated with radiotherapy as bridge to CAR-T. (Figure 1 summarizes the treatment history). Four patients received tisagenlecleucel (tisa-cel), and one axicabtagene-ciloleucel (axi-cel); one patient died before reinfusion of CAR-T.

Results: The dose of RT was 30 Gy in 15 fractions, the site was mediastinum for pt 001, abdominal adenopathy for pt 002, 003 and 005, inguinal adenopathy for pt 004, laterocervical adenopathy for pt 006). Median volume of irradiation was 210 ml (avg. 270 ml, min 79,6 ml, max 635 ml). Response to bridging RT was achieved in 3/6

patients (2 PR, 1 CR), one patient had stable disease, and one patient ha disease progression at the time of CAR-T infusion. One patient died for severe Covid19 pneumonia before receiving the planned CART infusion. The outcome is favorable at the time of writing for all infused patient but one, who died for progression 3 months after infusion (the one with progressive disease at the time of infusion). Toxicity was manageable, with no grade 3-4 CRS; maximum CRS grade was 2 in 3 cases. Only one patient receiving axi-cel needed admission at ICU for grade 4 ICANS, with complete resolution after treatment with high dose steroids.

Conclusions: We showed in this report that RT is feasible and effective as bridging therapy for patients with localized disease before CAR-T therapy.

T23

WHAT DO MESOTHELIOMA PATIENTS AND THEIR CAREGIVERS REALLY CARE ABOUT THEIR CURE: AN EXPLORATIVE STUDY (POINTINME_EXPLOR)

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Objective: This study aimed at evaluating the pleural mesothelioma (PM) patients' and caregivers' expectations on treatment outcomes, their understanding of the information given during the visits and their perception of the role of the general practitioners (GP) in their clinical pathway in the area of Casale Monferrato, at very high incidence of PM. Since 2012 a Mesothelioma Unit have been created to manage the whole diagnostic and therapeutic pathway.

Methods: Patients and caregivers were asked to fill in a multiple-choice questionnaire after the first visit or the clinical review for treatment planning asking what is most important as the result of treatment, how much the oncologist was clear in communicating the diagnosis, the therapeutic options, the side effects, the role of the GP in supporting the care pathway and the trust-relationship with both the referral oncologist and the GP.

Results: From March to August 2019, 31 consecutive patients, 18 males and 13 females, median age 71 (IQR 66-75) and 29 caregivers, 7 males and 22 females, median age 63 (IQR 49-67) were enrolled. Improving survival was the most relevant expected outcome in 48% and 69% of patients and caregivers, respectively followed by maintenance of the quality of life (38% and 17%), having the minimal number of visits as possible (8% vs 4%) and improving symptoms (6% and 10%). Seventy-seven% of patients and 72% of caregivers stated that the communication of the diagnosis was very clear, 74% of patients and 72% of caregivers stated that explanations about treatments were very clear, 90% of both patients and caregivers stated that the communication of side effects was clear. Ninety% of patients and 86% of caregivers are completely satisfied about the relationship with the referral oncologist whereas 58% of patients and 55% of caregivers are completely satisfied with the support given by the GP. Ninety-three% of patients think that having a referral caregiver is of utmost importance.

Conclusions: This study highlights that in the high incidence area of PM of Casale Monferrato, only half of advanced MPM patients and less that 2/3 of caregivers think that improving survival is the most relevant treatment outcome. The majority of patients and caregivers state to have clear information about diagnosis, treatment and related side effects and feel satisfied about the relationship with the specialists of the Mesothelioma Unit.

T24

THE SGLT-2 INHIBITOR DAPAGLIFLOZIN EHNANCED THE ANTICANCER ACTIVITIES AND EXERTS CARDIOPROTECTIVE EFFECTS DURING EXPOSURE TO IPILIMUMAB THROUGH NLRP3 –IL1-IL-18 PATHWAYS

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Background: The clinical trial "DECLARE-TIMI 58" demonstrated that dapagliflozin, a Sodium glucose cotransporter 2 inhibitor, reduces the composite end point of cardiovascular death/hospitalization for heart failure in a broad population of patients with type 2 diabetes mellitus. Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment. However, ICIs are associated with immune-related adverse events involving cardiotoxicity. We aimed to study if dapagliflozin could affect ipilimumab-induced anticancer efficacy in human breast cancer cells and reduces its cardiotoxicity.

Methods: Co-culture of hPBMCs and human cardiomyocytes or estrogen-responsive and triple-negative breast cancer cells (MCF-7 and MDA-MB-231 cell lines) were exposed to ipilimumab (200 nM) alone or combined to SGLT-2 inhibitor (dapagliflozin) for 72h. After the incubation period, we performed the following tests: determination of cell viability, study of lipid peroxidation (quantifying cellular Malondialdehyde and 4-hydroxynonenal), intracellular Ca2+ homeostasis. Moreover, pro-inflammatory studied were also performed (activation of NLRP3; TLR4/MyD88; p65/NF-κB and secretion of cytokines (Interleukins 1β, 8, 6).

Results: Dapagliflozin increases significantly the cardiomyocytes viability during exposure to Ipilimumab. Indeed, in breast cancer cells, dapagloflozin showed an opposite behavior with a significant increase in cell mortality and apoptosis ($p<0.001$ vs only ipilimumab). Cardioprotective properties of dapagliflozin are explainable by the reduction of intracellular Ca2+ overload (-56,8 % vs only ipilimumab; $p<0,001$), of the lipid peroxidation (mean reduction of 42,1-48,6 % compared to cells exposed only to ipilimumab; $p<0,05$). Moreover, cells exposed to dapagliflozin during ipilimumab reduced the protein expression of pro-inflammatory cytokines involved in cardiotoxicity and resistance to anticancer effects of ICIs (- 47,2 % for Interleukin-1β; -48,7 for Interleukin 6; -32,1 % for Interleukin 8; $p<0,001$ for all vs only ipilimumab groups). Notably, dapagliflozin reduces p65- NF-κB activation (- 46,3 and – 49,3 % vs only ipilimumab, $p<0.05$) and inhibits of 43,2-53,7 % the expression of NLRP3, $p<0.05$ for all).

Conclusions: Dapagliflozin demonstrated cardioprotective properties during Ipilimumab exposure in co-culture model of hPBMCs and cardiomyocytes. Dapagliflozin improves Ca2+ homeostasis and inhibits the pro-inflammatory "NLRP3-NF-κB –cytokines" pathways in cardiac cells.

T25

ANALYSIS OF DEVIATIONS AND NON-CONFORMITIES IN A PHASE I UNIT: THE EXPERIENCE OF NIGUARDA CANCER CENTER

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Phase 1 clinical trials are the most delicate phase of drug development and require a special attention on quality assurance and risk management aspect according to AIFA law 809/2015. In this setting it is necessary to manage all the deviations and non-conformities occurred during phase 1 studies with the implementation of corrective and preventive actions. The analysis of most frequent deviation causes at experimental site is also very important to prevent future findings and to improve quality standards.

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Deviations and Non-Conformities (D/NCs) of 18 phase 1 clinical trials, conducted at Niguarda Cancer Center (NCC) between 2019 and 2020, were analyzed according to GCPs. All D/NCs were evaluated in blind by QA manager and then by a study coordinator using two score ratings: the first score establishes the influence between human and organization factors, while the second allows to evaluate the influence of a lack of communication, staff oversight, work stress, staff motivation and lack of technical skills (using a classification in 4th quarter of influences, from very low to high). The analysis was stratified for minor and major findings.

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Overall 349 minor D/NCs were identified between 2019 and 2020 (average 19,4 per study) and 17 majors findings (average 0.94 per study). No critical findings were found. Organizations factors highly influences all findings, even if human factors are strongly involved too, especially in informed consent procedure and drugs management findings. Lack of communication was the main cause of D/NCs and it ranks in the 3th quarter of influence for minor and in the 2nd quarter for major deviations. Communication lack mainly affected nursing procedures and study's procedures that requires and high levels of coordination between professionals. Overall the impact of technical skills on D/NCs was low. Moreover deficiency of oversight and high level of work stress showed to impact especially in causing minor deviations (ranking from 1st and 2nd quarter of rating scale).

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Communication between professionals represents a crucial aspect to achieve high standards of quality, and should be improved to reduce minor and major findings in phase 1 clinical trials. Moreover data suggest to work on stress reduction and PI oversight improvement to mitigate incidence of minor findings. Despite several limits, all these aspect should be attended by the QA manager and by the NCC leadership to improve continuously phase 1 unit's performances.

T26

PRELIMINARY RESULTS OF AN INNOVATIVE EDUCATIONAL METHOD ON LIFESTYLES FOR CANCER PREVENTION IN SECONDARY SCHOOL

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Background: Teenagers are at age when they start making decisive choices. Without adequate information on correct lifestyles they run health risks, particularly with regard to future cancers. However, they have curiosity, interest and strong desire to learn in medical issues. This trial was developed to promote knowledge of cancer development and prevention program by informing students about correct lifestyles by teaching, playing an educational game, involving them interactively both in presence and on digital platform.

Methods: Since September 2019, medical oncologists with teachers from 2 first grade classes in two schools started a shared teaching path. Educational meetings were held for class presenting slides on neoplasms development and wrong lifestyles causing their onset. Slides were illustrated with comics. Students built with comics some of 90 boxes of a pathway similar to game of goose, set in their country in Middle Age. Players were two classes competing throwing dices to reach box number 90,equal to the years of cancer-free life expectancy conquered with correct lifestyle. Each box corresponded to a card like "tarot cards", prepared to slow down the path, if it represented a wrong conduct or event, and to speed up otherwise. During the second year of class, lessons illustrated H&N with gastrointestinal cancers. Impact of course was evaluated through a questionnaire prepared by a dental hygienist and proposing a healthy snack at least once a week at school.
Results: We performed 40 educational meetings of 30 minutes, followed by 20 minutes of play. Six medical oncologists, 1 psychologist, 1 dietician, 1 dental hygienist, 4 teachers actively contributed; 4 classes joined the initiative, 92 teenagers participated in 15 in-presence meetings and 25 on online platform during COVID19. All contributed to build and enjoyed the game. They wanted to start following course directions by bringing to school a snack proposed by dietician once a week. Ten of them offered to participate in the peer education course in other classes. Fifty-two questionnaires were completed at the beginning of the course and re-proposed at the conclusion. Students answered: 52/52(100%) knew tumors of oral cavity, 37/52(71%) knew color of precancerous lesions, 42/52(79%) knew risk factors, 48/52(92%) replied they would never start to smoke.
Conclusions: Teaching teenagers correct lifestyle preventing cancer by innovative method playing an educational game is achievable and can give results.

T27

DETECTION RATE OF DIGITAL BREAST TOMOSYNTHESIS IN HIGH RISK BREAST CANCER WOMEN: OUR EXPERIENCE

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Background: Breast cancer is both the most commonly occurring cancer and the commonest cause of cancer death among women. Survival is determined on both stage and molecular subtype. Early detection is an important strategy to improve outcomes. Multiple randomized clinical trials have demonstrated that screening mammography reduces the mortality from breast cancer by 20/22%. A large proportion of cancers were, in retrospect, visible on the previous screening mammograms. The introduction of digital breast tomosynthesis (DBT), in which multiple projections of the breast are obtained over a limited angular range to reconstruct a three-dimensional data set of mammography images, is only a partial solution. The Genetic Counseling in Oncology and Mammographyc Center collaborated for the follow-up of women at high risk of breast cancer. A high risk of breast cancer is conferred by a history of multiple breast/ovarian cancer cases in first- and second-degree relatives and the hereditary trait (BRCA1/2 mutation).
Patients and results: we evaluated, retrospectively, radiological examinations of the last five years (2016-2020) of 130 healthy women, aged 55 to 65 years, with family history of breast and ovarian cancer, without BRCA genetic test. For these patients, it was planned an annual mammography; however we observed that in the last two years DBT was performed on almost all patients. All breast cancer diagnosed (4), in this years were detected with DBT. The comparison between DBT and mammography imaging (performed for histological diagnoses) showede significant differences.
Conclusions: In these 130 healthy women, aged 55 to 65 years, with family history of breast and ovarian cancer, without BRCA genetic test, the DBT improved the early lesion detection rate. The DBT shows the same cancer detection rate in both dense and fatty breasts.

	Age at diagnosis	Histotype	Tumor	Radiological breast configuartion	Mammography	DBT
1	54	CDI, RE+, Her0, G1	0.6 cm	Dense	– Minimal asymmetry – Minimal distortion	– Dense distortion with spiculated margins
2	58	CLI, RE+, Her1+, G2	1 cm	Dense	– Minimal asymmetry – Minimal distortion – Partialy regular margin	– Dense node with spiculated margins
3	61	DCIS, G2	0.7 cm	Fatty	– Minimal distortion – Partialy regular margin	– Little dense distorion with irregular margins
4	54	CLI, RE +, Her3+, G2	0.7 cm	Fatty	– Minimal asymmetry – Minimal distortion – Partialy regular margin	– Little dense distortion with spiculated margins

T28

MANAGEMENT OF SINGLE SITE LOCALIZED EARLY RELAPSE AFTER CART CELL THERAPY IN DLBCL: A SINGLE CENTER EXPERIENCE

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Background: Anti-CD19 Chimeric Antigen Receptor (CAR) T-cell immunotherapy is the best option for large B-cell lymphoma refractory or relapsed after two or more lines. Nevertheless, some patients receiving CAR-T still experience relapse or progression. Treatment of post-CAR-T relapse is not standardized.
Patients: Between November 2019 and April 2021, we treated 20 patients affected by large B-cell lymphoma (DLBCL 15; PMBCL 5) with commercially available CAR-T cell (tisa-cel 15, axi-cel 5). After a median follow-up of 6 months (1-17), 12 achieved a durable remission, 8 had a disease relapse or progression after CAR-T. Table 1 summarizes the characteristics of the two groups.
Results: No statistically significant association was found between relapse after CAR-T and the condition of relapsed vs. refractory lymphoma. Median time of relapse was 61 days after CAR-T (min. 30 for 3 refractory patients - max. 167). Out of 8 relapsed patients, 6 died because of progression. Median time from relapse to death was 67 days. Two patients with a single-site localized relapse are alive. Both received radiotherapy (30 Gy in 15 fractions) on the site of relapse; one of them underwent consolidation with allogeneic stem cell transplantation. Out of the other 6 patients, two died without receiving any further treatment because of rapidly progressive disease and death. One patient with PMBCL was treated with nivolumab+brentuximab with no response (death after 1 cycle). Three patients were enrolled into clinical trials and received experimental treatment.
Conclusions: Relapse of non-Hodgkin B lymphoma after CAR-T cell is a major issue, leading to a very unfavorable outcome. CD19+ loss in confirms to be a mechanism of CART failure in real life. Despite the retrospective nature and the small number of patients, our study suggests that single–site localized relapse after CAR-T may be rescued with combined strategy. Otherwise disseminated relapse have a very poor outcome, and probably experimental trial could be the right choice.

T29

SELF-EVALUATION SCREENING FOR EMOTIONAL DISTRESS IN CANCER OUTPATIENTS RECEIVING SYSTEMIC THERAPY: A PROSPECTIVE SURVEY AT THREE ONCOLOGY CARE UNITS

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Background: Emotional distress is high among cancer patients and their caregivers during the course of disease and this need can be difficult to detect by the oncologists. In such cases, issues related to emotional burden that contribute to limit patient's quality of life are likely to be addressed reactively rather than proactively. In the present survey, cancer patients were screened for emotional suffering to facilitate referrals to the psychologist for full assessment.
Methods: A new patient-oriented questionnaire was developed as part of this project. All outpatients referred to three oncology care units were asked to fill-in the self-evaluation questionnaire focused on their emotional status to gain insights into patient's reaction to cancer diagnosis, cognitive response to disease, caregiver support, use of psychotropic medication or utilization of emergency room for psychical symptoms. The questionnaires were analyzed by two experienced psycho-oncologists.
Results: From April 2021, 200 patients who were receiving systemic therapy for any cancer were asked to fill-in the questionnaire from oncology nurses, with 20 patients refusing to complete it. Fifty-seven percent of patients were female and the median age was 70 years. One-hundred and twenty (60%) patients rated their emotional distress to such an extent that they were referred to the psychologist for full assessment. After counseling, 30 (25%) patients started a psychology supportive care; 3 caregivers also required this support. Only 9 (5%) of the 180 screened patients had been previously referred to the psychologist by the treating physician.
Conclusions: This preliminary analysis indicates that a patient-oriented, self-evaluation questionnaire as screening tool is potentially a feasible option for proactively address emotional distress in cancer patients. The survey is still ongoing.

T30

CANCER PATIENTS' AWARENESS ABOUT CLINICAL RESEARCH - THE ELPIS STUDY PRELIMINARY RESULTS

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Background: The reasons for low recruitment in clinical trials have been classified in three main sources of obstacles: physician, patient, system. A primary role is played by a low patient awareness, which often leads to a lack of confidence in science and to a substantial inability to estimate the benefits deriving from trial participation. This trend is also aggravated by widespread fake news that circulate uncontrollably on the web, jeopardising the doctor-patient relationship.
Methods: Starting from April 2019 an academic prospective observational study was initiated in 9 Italian Medical Oncology Units. The study aimed at investigating the level of understanding of cancer patients towards clinical research and their expectations of inclusion in a trial and to evaluate the level of comprehensibility of informed consent and the extent of the fake news phenomenon. After signing the informed consent, patients were asked to complete a set of multiple choice and Likert-score questions.
Results: As of April 2021, 123 patients were enrolled, with a balanced sex distribution and a prevalence of age > 55-years (78%). Regarding the previous knowledge about clinical research, the average score was 3.3 (range 1-5). The vast majority of respondents (87%) had already started experimental drug and many of them constantly used internet (65.9%) and social networks (30.9%). More than half (56.1%) stated the interview with the physician was sufficient for a full understanding of informed consent. In case of doubt, very few (1.6%) relied on the web. The average score attributed to doctor-patient relationship was 8.82 (range 1-10). Respondents were quite confident in their ability to independently search for information, discriminate fake news and identify reliable sites (average score 3.20, 3.23, 3.03 respectively, range of 1-5). The scores related to the presumed ability to understand the results of a clinical study and to actively collaborate to produce research were high (4.67 and 4.36 over a range 1-5).
Conclusions: Preliminary data from ELPIS study show a good level of patients' awareness and a fine ability to understand information, discerning real from fake news. Continuing and implementing the training initiatives of the population in the health sector will certainly contribute to further improvement, hopefully obtaining an even greater involvement of patients in the early phases of research.

T31

ASSOCIATION BETWEEN PSYCHOLOGICAL DISTRESS AND CANCER TYPE IN PATIENTS REFERRED TO LILT STUDY "NEW LIFE"

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Background: Routine screening for distress is a recommended standard for good cancer care. The objective of our study is to assess the differences/variations in level of distress in oncological patients (pts) undergoing active treatments or follow-up, and evaluate the relationship between distress and cancer type as well as the relationship between these factors and the main clinical and socio-anagraphic features (1).
Methods: This study involved all pts of LILT project "New Life" of the Oncology Centers of Termoli (CB) and San Benedetto del Tr. (AP) from Nov. 2019 to Feb. 2021. Psychological distress was measured through Psychological Distress Inventory (PDI), at the first assessment and in subsequent evaluations by dedicated psychologists, in order to assure personalized programs. Socio-anagraphic and clinical variables were evaluated.
Results: We enrolled in "New Life" IT database 338 pts, of these 300 pts completed PDI questionnaire (91 males/209 females; average age: 62 years old) with diagnosis of solid or hematological cancer. The tumors reported were: breast cancer (110 pts; 36,7%), colon-rectum cancer (50 pts; 16,7%), high gastrointestinal cancer (esophagus, stomach, liver, pancreas 46 pts; 15.3%). At baseline administration of questionnaire: 132 pts (44%) had metastatic disease, 159 pts (53%) were undergoing chemotherapy treatment; 53 pts (17,7%) were undergoing adjuvant treatment and 64 pts (21,3 %) resulted in follow up, 24 pts followed at other centers. In addiction: the 39% of pts have a high school diploma, 16,7% have a degree, 38,3% have an elementary or middle school license, 45.3% are retired, 26.3 % are employed, 13.3 % are housewives, 9.3% are unemployed. Results in PDI >30 was reported in pts with high gastrointestinal cancer, lung cancer, urinary cancer and breast cancer. Higher levels of distress (PDI > 35) was reported in high gastrointestinal cancer during active treatment, adjuvant and oncological follow up. In our investigation distress seemed not related to stage of cancer, education and employment. Women experience a greater distress than men.
Conclusions: The study allowed to identify distress of pts in different stages of treatment in order to activate a

personalized psychological service in the target hospitals. We reported higher distress in pts with high gastrointestinal cancer in all stage of disease, therefore it could be a good practice to assure those pts with psychological evaluation and specific programs.

T32

SHORT TERM PRIMARY THROMBOPROPHYLAXIS IN NOT SURGICALLY TREATED INTRA-LUMINAL GASTROINTESTINAL CANCER PATIENTS (PTS) UNDERGOING FIRST LINE CHEMOTHERAPY: A PRELIMINARY SINGLE INSTITUTION SAFETY REPORT

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Background: in cancer patients (pts) undergoing chemotherapy the occurrence of venous thromboembolism (VTE) is a remarkable concern for the oncologist who in addition must pay careful attention to the possible major bleeding in patients carrying gastrointestinal cancer. Direct Oral Anticoagulants (DOACs) should not be used or used with caution in patients carrying not surgically treated intra-luminal gastrointestinal cancer. To date several CAT (Cancer Associated Thrombosis) risk scores such as Khorana and PROTECHT score have been employed to identify the cancer population at high-risk for VTE. Consensus guidelines recommend to consider the use of low molecular weight heparin (LMWH) for primary thromboprophylaxis in high-risk patients.

Patients and methods: We report on our retrospective case series of 18 intra-luminal gastrointestinal cancer patients, at high risk for VTE in accordance with a modified PROTECHT score by addition of central venous catheter (CVC) as a further risk factor. The patients with a score $\geqslant 3$ and undergoing first line chemotherapy had been administered short term LMWH based thromboprophylaxis. A prophylactic dose of LMWH was administered just before starting the chemotherapy cycle and until 48 hours after its completion. We mainly aimed to report occurrence of clinically perceptible gastrointestinal bleeding events.

Results: Eighteen pts were administered LMWH. Mean age: 58 (range 42-79). Gender: male 12. Tumor type: stomach (15); gastro-esophageal junction (2); colon (1). Duration of heparin treatment: the total treatment duration was 282 days; mean 15 days (range 5-45); nadroparin: mean 14 days (range 5-45); enoxaparin: mean 13 days (range 5-35); parnoparin: a total of 5 days. None patient experienced perceptible gastrointestinal bleeding.

Conclusions: Intra-luminal gastrointestinal cancer is a clinical condition demanding additional caution when using anticoagulants and DOACs should not be used or used with wariness. Short term LMWH based thromboprophylaxis did non trigger any major bleeding in the scrutinized patients. However the small number of patients included in this retrospective study does not permit any definitive conclusion and further research is needed.

T33

A SINGLE-CENTRE SURVEY ON THE ADHERENCE TO COLORECTAL CANCER SCREENING (CRCS) IN APULIA: IMPACT OF THE ORGANIZED REGION SCREENING STRATEGY (ORSS)

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Background: A great disparity in CRCS adherence exists between the various Regions of Italy, ranging from 98% (North) to 44% (South). The AIRTUM report in 2019 counted almost 2900 new CRC diagnosis for the Apulian Region, while CRCS adherence was inferior to 5%. To counterbalance this trend, an ORSS has been started since September 2019, consisting in an invitation to faecal occult blood tests for people aged 50-70 years. The effects of this strategy have not yet been quantified, while SARS-COV2 pandemic interference is unknown. The aim of our study was to evaluate the percentage of patients with recent CRC diagnosis by screening in a period across the start of the ORSS and unravel the reasons for patient refusal.

Material and methods: Patients aged >50 years and residing in Apulia with CRC diagnosis made at the Division of Medical Oncology in "A.O.U. Consorziale Policlinico di Bari" between May 2018 and April 2021 were interviewed by phone. Hereditary or IBD related CRC were both considered exclusion criteria. We collected data about the cause of diagnosis, knowledge of CRCS, how the subjects were informed about screening and reasons for non-adhesion. Close relatives were also asked if had joined or intended to take part in CRCS since they were considered a very sensitized population.

Results: We enrolled 130 patients, including 60 diagnosed before and 70 after September 2019. Overall, 10% of patients had received a diagnosis of CRC by screening. Of these, 1% was diagnosed before the start of the ORSS and 9% after. Only 23% of participants were sufficiently learned of CRCS across the study period, while invitation was received from ORSS in 14% and from general practitioners (GP) in 6%. The major reasons for CRCS denial were "diffidence" (65%) and "futility" (35%). Among

close relatives of people with recent CRC history, a 24% of CRCS adherence was observed, while another 50% of them said that intended to take the test.

Conclusions: We found an inadequate adherence to CRCS mainly due to poor consciousness of CRC disease and prevention, while it significantly increased in sensitized people. Moreover, the higher percentage of CRC diagnoses made by CRCS since 2019 may represent a direct effect of the ORSS, although the number of persons invited is still not enough. These data confirm the gap of the Apulia from other Italian Regions regarding the reluctance to carry out CRCS and suggest greater investments in awareness campaigns for the population and GP.

T34

PLACE OF DEATH OF FRAIL ELDERLY CANCER PATIENTS (PTS)

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Background: Home is the preferred place of death for most cancer pts, but many determinants may modify this choice and particularly pts and their caregivers characteristics and an early collaboration between oncologists and palliativists.

Material (patients) and methods: From February 2019 to March 2021, aged >70 years hospitalized pts were screened by G8 questionnaire and evaluated by Comprehensive Geriatric Assessment (CGA) to identify frail ones and define the most appropriate end-of-life setting with palliativists.

Results: By G8 questionnaire we screened 182 patients who were evaluated with the CGA and we identified 81 frail. Among these pts: 41 (50%) died in Hospice, 24 (30%) at home, 8 (10%) during hospitalization, 7 (9%) were lost to follow-up and 1 (1%) is alive.

Among 41 pts died in Hospice 24 (59%) male and 17 (41%) female median age was 80. Median score IADL/ADL (Instrumental/Activities Daily Living) was 2, median daily drugs taken was 7 and the median number of geriatric syndromes was 2. Malnutrition was present in 29 pts (70%), MMSE (Mini Mental State Examination) was normal in 5 pts (12%) and comorbidity index of CIRS (Cumulative Illness Rating Scale) was 1. The caregiver was identified for 25 (61%) patients and median survival in Hospice was of 33 days.

Among 24 pts died at home 15 (62%) male and 9 (38%) female median age was 82. Median score IADL/ADL was 4, median daily drugs taken was 7 and the median number of geriatric syndromes was 2. Malnutrition was present in 12 pts (50%), MMSE was normal in 7 pts (29%) and comorbidity index of CIRS was 1. The caregiver was identified for 24 (100%) patients and median survival at home was of 56 days.

Conclusions: In the presence of an adequate caregiver and an active collaboration with palliativists early identification of the frail patient can allow to 30% of pts to die at home. Pts who died at home are predominantly male who have a better functional, cognitive and nutritional status than pts who died in Hospice.

T35

ENDOCRINE TOXICITY IN CANCER PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS - A MONOCENTRIC PROSPECTIVE STUDY

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Background: Endocrine toxicity, especially thyroid dysfunction, is the most frequent immune-related adverse event (irAE) reported in cancer patients treated with immune checkpoint inhibitors (ICI). A better understanding of the underlying mechanisms could lead to a better management or even, to prevent these adverse events.

Methods: This monocentric prospective study includes patients treated with ICI, as monotherapy or in combination with chemotherapy or targeted therapies. Patients included have never received prior immunotherapy. Together with endocrinologists, we selected the relevant biological parameters to be measured at the initial assessment and during the follow-up: parameters were performed before the onset of treatment, and then, at every two cycles. In case of biological abnormalities, endocrinologists were contacted and came to Day Hospital to discuss the management of the treatments and visit the patient together to explain the endocrine therapy adaptation. Herein, we present the preliminary results of our study.

Results: Between January 2021 and May 2021, 14 patients were included in our study, 9 men (64 %) and 5 women (36 %). The median age at first administration of immunotherapy was 67.1 years (range 53-84). Patients were treated for lung cancer (n=7, 50%), skin cancer (n=4, 29%), head and neck cancer (n=2, 14%) and kidney cancer (n=1, 7%). Eight patients (57%) received a monotherapy, five patients (36%) received a combination with chemotherapy, and one patient (7%) received a combination with tyrosine-kinase-inhibitors. Immunotherapy was stopped in only 1 patient after 3 cycles of Nivolumab due to the development of hyperthyroidism with high thyroglobulin antibodies levels.

Conclusions: A multidisciplinary approach to the monitoring and management of endocrine immune-related adverse events allows an earlier detection and a quick adaptation of the treatments.

T36

SEX DIFFERENCES IN CANCER IMMUNOTHERAPY EFFICACY, OUR EXPERIENCE

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Background: Immunotherapy, represented by immune checkpoint inhibitors (ICIs), has revolutionized the treatment of cancer. However, the majority of patients still do not respond to ICIs.
Consequently, it is of great interest to examine the potentially predictive factors influencing the to ICI response.
Despite the acknowledged sex-related dimorphism in immune system response, little is known about the effect of patients' sex on the efficacy of ICIs.
The aim of our study was to correlate sex with treatment effectiveness, in NSCLC treated with Nivolumab.
Patients and methods: We have retrospectively analyzed the correlation between sex and the effectiveness of immunotherapy in terms of response rate (RR), progression free survival (PFS) and overall survival (OS) in 75 patients (pts) (48 men and 27 women) with advanced NSCLC treated with Nivolumab since April 2017 to April 2020. Mean age was 68 years (48-84).
RR: complete response (RC), partial response (RP), stable disease (SD), progression disease (PD), disease control rate (DCR) (RC+RP+SD), overall response rate (ORR) (RP+RC).
PFS is defined as the time from entry into the study to the first objective evidence of PD or death for any cause.
OS is defined as the time from entering the study to the death of the patient or loss during follow-up.
Results: We did not find statistically significant differences in RR between males and females (ORR 18.8% Vs 18.5% p 0.98; DCR 56.3% Vs 37% p 0.11) while in PFS and OS it appears as the benefit of treatment is in favor of the male sex (PFS: 4 months vs 2.2 months p 0.04; OS: 12 months vs 9.2 months p 0.03).
Conclusions: Our results suggest that male patients obtain more benefits from ICIs vs control compared with female patients.

T37

CHYMASE EXPRESSION OF MAST CELLS CORRELATES WITH NEOVASCULAR BED EXTENSION IN PANCREATIC CANCER TISSUE: A NOVEL POSSIBLE ANTI-ANGIOGENETIC TARGET?

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Background: Mast cells (MCs) are known to be involved in several physiological and pathological processes in humans and animals. Recently, their role in tumor development, with special regard to angiogenesis, has been investigated, arising interesting results to be potentially applied in clinics. Mast cells' granules contain a huge quantity of protease enzymes that, through different mechanisms, induce the formation of new microvessels, feeding tumor burden. Among them, tryptase and chymase are the most represented in the granules, but if tryptase is well known for its multiple activities, the role of chymase in pancreatic cancer angiogenesis has not been investigated yet.
Patients and methods: This paper aims to correlate each other four different tissue parameters, MCs density positive to Chymase, MCs area positive to Chymase, microvascular density and endothelial area, with angiogenesis and the main clinical-pathological characteristics in 52 patients surgically resected for pancreatic ductal adenocarcinoma, employing immunohistochemistry, image analysis system, and subsequent statistical analyses.
Results: All studied tissue parameters match to confirm the correlation between chymase and angiogenesis also in pancreatic cancer.
Conclusions: This evidence gives strength to a new potential therapeutic route by the evaluation in possible clinical trials of chymase inhibitors, as a novel anti-angiogenetic strategy in pancreatic cancer patients.

T38

PROGNOSTIC MARKERS TO IMMUNE CHECKPOINT INHIBITORS (ICI) IN GOOD RESPONDER PATIENTS (PTS): A RETROSPECTIVE ANALYSIS

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Background: Tools to predict immunotherapy response are a relevant unmet need in clinical practise. N/L (neutrophil/lymphocytes) ratio>3, P/L (platelets/lymphocytes) ratio>170, LDH>upper level (UL) and EC (eosinophil count)>500/microL were reported as inflammatory biomarkers (IB) associated with worse outcome in pts treated with ICI. Basing on these data, we conducted a retrospective study in order to evaluate the correlation between IB and a good response to ICI.

Material and Methods: From Jan 2018 to May 2021, all consecutive pts treated with ICI were enrolled. Good responders were defined as pts who achieved a complete (CR) or partial response (PR), according to RECIST criteria. Age, ECOG performance status (PS), PD-L1 expression, smoking status, cancer site, treatment planning, clinical response, adverse events (AE) and survival were recorded. Pre-treatment IB in good responders (N/L, P/L, EC and LDH) were matched with response rate (RR) and overall survival (OS). Pts were stratified in 2 groups according to the number of IB, group A (0-1) and group B (2-4), and subsequently matched with RR and OS.
Results: Among a group of 72 pts, 24(34%) with CR or PR were selected. 19 were NSCLC (15 adenocarcinoma + 4 squamous), 4 Kidney and 1 Head&Neck cancers. Pts: Median age 68 ys (range 41-83), 19 males, 8% no smokers. PDL-1 score was 1-49% in 18 pts and > 50% in 6 pts. PS was 0-1 in all pts. Six pts underwent ICI as first line treatment (2 combo with chemo), 18 as second line and 11 had also a palliative radiotherapy. Nivolumab was administered in 14 pts, Pembrolizumab in 8 pts and Atezolizumab in 2 pts. Median number of cycles was 15 (range 6-38). Duration of treatment was <12 months (m) in 8 pts, 12-24m in 10 pts and >24m in 6 pts. Four pts dead, 6 ruled out for AE while 14 ones are still ongoing. OS was 50% at 24m and 25% at 36m with 20 alive pts. Six pts stopped therapy for G3/4 AE as pneumonia, mucositis, muscle pain, adrenal failure and psoriasis reactivation. IB: N/L ratio was >3 in 13 (54 %) pts, P/L ratio was >170 in 12 (50%) pts, LDH >UL in 8 (33%) pts and EC >500 cells in only 1 pt. Group A included 45% (11/24) of responder pts and 75% (9/12) of long survivors, with predictive value of 82%.
Conclusion: This study cannot confirm the prognostic value of N/L ratio, P/L ratio, LDH and EC because of few pts enrolled, but it represents a good proof of concept for a subsequent prospective study that could clarify the role of IB in pts treated with ICI.

T39

PALMITOYLETHANOLAMIDE AND POLYDATIN REDUCES INFLAMMATION IN CARDIAC AND VASCULAR ENDOTHELIAL CELLS EXPOSED TO DOXORUBICIN THROUGH PPAR-A AND NLRP3-RELATED PATHWAYS

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Background: Palmitoylethanolamide is an endogenous fatty acid mediator that is synthetized from membrane phospholipids by N-acyl phosphatidylethanolamine phospholipase D. Polydatin is a nutraceutical agent derived from trans-resveratrol with established anti-inflammatory and anti-atherogenic properties. We aimed to assess whether palmitoylethanolamide combined to polydatin, co-incubated during doxorubicin, reduces anti-cancer drugs-related cardiotoxicity in cellular models.
Methods: Human fetal cardiomyocytes (HFC cell line) and vascular endothelial cells were exposed to subclinical concentration of doxorubicin (at 100 and 200 nM) alone or in combination with formulation composed by palmitoylethanolamide combined to polydatin (500 nM and 50 μM, respectively) for 48h. After the incubation period, we performed the following tests: determination of cell viability, through analysis of mitochondrial dehydrogenase activity, study of lipid peroxidation (quantifying cellular Malondialdehyde and 4-hydroxynonenal), intracellular Ca2+ homeostasis. Moreover, pro-inflammatory studied were also performed (activation of NLRP3 inflammasome; expression of peroxisome proliferator-activated receptor-α; mTORC1 Fox01/3a; transcriptional activation of p65/NF-κB and secretion of cytokines involved in cardiotoxicity (Interleukins 1β, 8, 6).
Results: Palmitoylethanolamide combined to polydatin co-incubated with doxorubicin exerts cardioprotective and vasculoprotective effects, enhancing cell viability of 48.4-58.7% compared to untreated cells ($p<0,001$ for all). The formulation reduced significantly the cardiotoxicity through peroxisome proliferator-activated receptor-α –related pathways and NLRP3 inflammasome but without the involvement of calcium homeostasis.
Conclusions: The present study demonstrates that palmitoylethanolamide and polydatin protects against cardio and vasculotoxicity of doxorubicin by promoting an anti-inflammatory phenotype, representing a new therapeutic approach to resolve doxorubicin-induced cardiotoxicity and inflammation.

T40

THE QUALITY OF MOTHER-INFANT INTERACTION IN A SAMPLE OF MOTHERS WITH A PREVIOUS CANCER DIAGNOSIS AND THEIR 4 MONTHS INFANTS

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Background: There is a paucity of data on the impact of having received a previous diagnosis of cancer on the quality of mother-infant interaction.

Methods: Our multicentric and longitudinal study was designed to assess maternal psychological well-being (Profile of Mood States - POMS), prenatal attachment with the foetus (Prenatal Attachment Inventory - PAI, and Maternal Antenatal Attachment Scale - MAAS), and quality of mother-infant interaction between 2 and 5 months postpartum (Global Rating Scale - GRS). Twenty-two dyads took part in the research (N=9, clinical group, N=13, age and parity matched controls). Two mothers in the clinical group had gynaecological cancer, 5 had breast cancer, 2 had skin cancer. And all of them had at least one treatment including chemotherapy, radiotherapy, or surgical intervention. Our sample varies in terms of level of education, and mothers are generally in stable relationships (87% lives with their partner or husbands) and work situation (87% of the sample, with the 78.3% on maternity leave at recruitment). Sixty-nine percent of woman were primiparous and 69% of the infants were female.
Results: Mann Whitney U test were performed to compare the two groups. Groups did not differ significantly in their psychological profile and levels of attachment with the foetus, but significant differences emerged in some of the scales used to assess the quality of mother interaction. While dimensions such as maternal sensitivity, warmth and intrusiveness, and infant distress and attentiveness did not differ between the two groups, in the clinical group, mothers were more remote ($p<.05$) and less absorbed in the infant ($p<.05$), and infants showed fewer positive communications ($p<.05$) compared to the control group.
Conclusions: Mothers with a previous cancer diagnosis seemed to engage with their foetuses and infants similarly to mothers without cancer, and they did not experience higher psychological stress compared to controls. However, during mother-infant interactions they seemed to show some defensive behaviours such as difficulties to remain engaged with their infants and being self-centred, possibly leading to less communicative infants. This preliminary data call for focused interventions to support mothers with a previous cancer diagnosis.

T41

THE EXPERIENCE OF CANCER PATIENT'S CAREGIVER

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Background: People with cancer are more and more in the world and to accompany them along the path of the disease there is almost always a caregiver. Experiment themselves in this role means for caregivers to reach out to important changes that often result in a negative experience with significant implications on a physical and emotional level and a reduction of perceived quality of life.
Purpose: This study is aimed at investigating experiences of cancer people's caregivers. It sought to understand needs of this people, their emotions, life changes, challenges and peculiar difficulties. The goal is to update and enrich knowledge on the subject by ensuring a current description of the phenomenon.
Methods: Research of articles was conducted by consulting three biomedical databases, MEDLINE / PUBMED, CINAHL and SCOPUS, in the period between May and July 2020. The articles found were selected based on the relevance of title, abstract and analysis of full text, identifying articles that met inclusion criteria.
Results: Research identified a total of 675 articles; of these, at the end of the selection process, 18 were included in the study. Five major themes emerged: emotions and feelings experienced by caregiver, changes of life, positive implications related to the assistance activity, difficulties or challenges of caregiving, expressed needs of caregivers.
Conclusions: Caregivers experience a major emotional storm throughout the care process of their loved ones. Most of these are negative emotions that are difficult to manage, but there are also feelings of hope and satisfaction. Life changes are manifolds, both practical and emotional, and require a particular adaptation effort on the part of caregiver. Numerous positive aspects related to caring activity emerged, described mainly as a personal change in relationship with others and a maturation of new priorities and virtues to be pursued. The difficulties expressed concern expectations caregiver has towards the socio-health professionals, management of physical limits, coexistence of multiple roles and responsibilities to be ensured, time management and practical difficulties of caregiving. Needs emerged refer to the desire to be supported and accompanied along the path of care by professionals and by the family.

T42

"ELECTRONIC INFORMED CONSENT: THE NEED TO REDESIGN THE CONSENT PROCESS FOR THE DIGITAL ERA"

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Background: The conscious involvement of the patient is a prerogative for her/his successful participation in a

clinical trial. The Electronic Informed Consent (eIC) was introduced with the aim of optimizing time and costs in an easy-to-use format thus enhancing patient understanding.
Material and methods: During 2020, the Working Group "Clinical Research Coordinators" of the Italian Medical Oncology Association (AIOM) has developed a survey on the knowledge, use and opinion of eIC. It was an anonymous web-based survey, consisting of 16 multiple-choice questions, aimed at clinical research stakeholders and disseminated through AIOM social channels.
Results: The survey was completed by 99 professionals: 49 physicians, 41 study coordinators, 4 research nurses, 5 others. Only 17,2% has a personal experience with the eIC (the 64,7% with Tablet and 17,6% with Smartphone). According to respondents opinion, 40.4% of patients did not express any difference in dealing the eIC compared to the paper version; 41,4% reported initial perplexities, overcome after an interview with the Physician, while for 6,1% the initial doubts did not subside throughout the study; only 12,1% had no experience with eIC. Major difficulties are related to patient age and computer literacy as well as a reduced attention by the physician. Finally, the attitude of the medical staff compared to the paper form, was more favorable in 37% of the answers.
Conclusions: Despite not jet popular, the eIC could certainly represent a valid tool to increasing patient participation and adherence to trial procedures thus reducing the probability of withdrawal and poor understanding.

T43

CLINICAL RESEARCH AND ISO 9001:2015 QUALITY STANDARDS: PERSPECTIVES AND EXPECTATIONS OF CLINICAL TRIAL CENTERS

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Background: In the last decade many clinical research centers in Italy have increasingly implemented and improved their quality standards and effectiveness of processes thought the adoption of a quality management system (QMS). In this context, the ISO 9001:2015 certification provides a QMS model focused on a risk-based approach and on a continual improvement driven by objective measurements. The aim of this project is to evaluate expected benefits and barriers of ISO 9001 certification for a Clinical Trial Center (CTC).
Material and Methods: On April 2021, the Italian Group of Data Manager and Clinical Research Coordinator spread an anonymous online survey to healthcare professionals operating in clinical research and quality management systems at experimental sites. The questionnaire consisted of 15 multiple choice questions about the importance of implementating the ISO 9001 certification in a CTC.
Results: A total of 84 professionals have completed the survey (51.2% from north Italy, 36.9% south and 12% central). Most of them were clinical research coordinators (66.7%) followed by physicians (8.3%), researchers (4.8%) and QA managers (3.6%). Oncological CTC are highly represented (59%) and almost all (92.9%) respondents conduct routinely at least phase II/III trials. A Good Clinical Practices' QMS is present in 81% of cases, but only in 74.7% is in compliance with ISO 9001:2015 standards requirements. The most used electronic tools are Client/server or web based software (57.1%) and organizational databases (42.9%). Reported benefits of ISO-oriented QMS adoption include continual improvement and better quality processes (77.1%), assuring corrective actions (65.5%), planning internal audits (61.9%) and risk management approach (60.7%). The most important barriers to QMS implementation are increased logistical and/or organizational activities (43.4%) and insufficient training about quality programs (30%), while only 48.2% of professional have not perform QMS trainings at least in the last year.
Conclusions: Implementing a quality management system represents a challenge for the CTC and helps to improve quality standards and risk management approach. The adoption of electronic tools is low and it could be increase in the future. Lastly, improvement of continuous QMS trainings should be necessary for updating professionals and to optimize activities at CTC.

T44

AMERICAN GINSENG AS TREATMENT FOR FATIGUE IN METASTATIC BREAST CANCER PATIENTS BEING TREATED WITH CDK 4/6 INHIBITORS

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Background: Cancer-related fatigue (CRF) is a frequent symptom in metastatic breast cancer patients who are being treated with CDK 4/6 inhibitors (40-60% in recent clinical trials). Despite the identification of multiple causes and some treatments to counter it (especially corticosteroids and antidepressant drugs), CRF remains an underestimated symptom that is not treated properly.
Aim of this study is to evaluate the effects of American Ginseng (Panax quinquefolium) on consecutive metastatic breast cancer patients presenting CRF, through the Revised Piper Fatigue Scale (RPFS), a self-assessment questionnaire of 22 items that assesses cognitive (6 items), behavioral (6 items), affective (5 items) and sensory/psychological (5 items) domains.
Material and Method: Ten patients presenting cancer-related fatigue and undergoing CDK 4/6 inhibitors since January 2020 were consecutively included in this study. A self-administered RPFS questionnaire was dispensed to these patients by nurses at the baseline and every 2 weeks for a total of 2 months. In this period patients received a product containing American ginseng (500 mg per day continuously).
Results: At baseline 4 patients reported mild CRF, 4 moderate CRF and 2 severe CRF. At 2 months total scores of RPFS have improved in 6 patients and in particular in 2 patients there was a transition from severe fatigue to moderate fatigue (total score 45 vs 27 and 46 vs 26 respectively). In 4 patients with mild CRF we obtained none CRF at the final score. 4 patients had stable scores during the treatment period.
Conclusions: The CRF is one of the most important factors that negatively affect quality of life of advanced cancer patients and is often present during CDK 4/6 inhibitors, standard of care of hormone receptor-positive, HER2-negative metastatic breast cancer. Our results suggest a positive correlation between the use of american ginseng and improving RPFS score (6 of 10 patients). Even if this study have some limits (small sample size, heterogeneous biological and clinical characteristics of breast cancer), the analysis of the data obtained allows to take into consideration the possibility of treating CRF through a therapeutic approach with american ginseng in order to improve the quality of life and the global patient care.

T45

USING MINDFULNESS IN PSYCHO-ONCOLOGY AS A MEANS OF COPING WITH STRESS AND ANXIETY

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Background: In recent years, psycho-oncology has focused on the growing awareness of the incidence of cancer on all dimensions of the human sphere. When patients receive a cancer diagnosis they are often confronted with their own mortality for the first time. They are then forced to cope with new emotions and stressors that can make them feel powerless and overwhelmed. This is a stressful and anxiety-provoking time not only physically, but also emotionally, spirituality and financially for them and their families.
There is growing evidence supporting the benefits of Mindfulness practice for cancer patients. They often have to learn a new skill set on how to cope with uncertainty and the stressors that a cancer diagnosis and treatment bring. Meditation as a practice of mindfulness involves the mental training of deliberately focusing on the here and now without judging our feelings as good or bad. Meditation relies on the experience of focusing on a neutral point and bringing our thoughts back as our minds wanders. Developing awareness this way helps to settle the mind and to minimize distractions.
Materials and Methods: In our psycho-oncological program we have created meditation sessions for cancer patients, survivors and for their caregivers, the goal was to offer support to patients, but also to improve the relationship between patient and caregiver.These were 90-minute weekly meetings, in each session we included the activity of coloring the mandala, a form of active meditation that invites the person to keep attention on the present moment but at the same time invites them to give expression to their creativity, tibetan yoga, visualization and listening to relaxing music. We created gruop of 10 partecipants (patients, survivors, caregivers).
Results: To identify the effects of the training, a semi-structured questionnaire was administered before and after 8 meetings. The participants found that coloring mandala helped them how to focus on one thing at a time, improving concentration, they also appreciated the meditation and the visualization helped them on creating positive images about their therapy. It also helped emotional well-being by decreasing stress and anxiety, and helping create a more positive outlook on life. There was a decreased of the perception of stress, they also feeld slowing breathing, learn to be more present in the moment.

T46

MUSIC AND CHOIR-SINGING AS A THERAPY: THE FUCKCANCER CHOIR EXPERIENCE

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Background: Music therapy in cancer patients and their caregivers can improve pain control and anxiety, enhance

relaxation, facilitate expressive skills and contribute in managing emotions, being of support also during the disease and mourning experience. Based on this preliminary evidence in current literature we aimed at testing in our oncological unit the choral singing.

Material and methods: In September 2019 we founded the FuckCancer Choir composed by 20 among cancer patients, their caregivers and some healthcare professionals. The choir met twice a month for rehearsals, and performed in many local public events. During the pandemic, the choir continued its activity at distance, recording many songs also collaborating with famous Italian singer. In March 2021, in order to evaluate the impact of this experience and if it was worth to be pursued, we performed a survey asking choir singers to describe their feelings with the choir through a free text, highlighting positive and negative aspects.

Results: Seventeen singers (85%) accepted to participate to the survey, all the experience collected were strongly positive confirming that choral singing is associated to psychosocial benefits, not only in patients and caregivers, but also in healthcare professionals. Patients and caregivers included in this project feel part of a cohesive group able to share similar emotions and understand the concerns of their fellows. They described the relationship within the group as "friendly" and "funny". Since the start of its activity, the choir experienced the loss of two singers and the group support was greatly appreciated by the families. For health professionals, singing with their patients and sharing relaxed moments or even the "stage fright" is a unique opportunity to maintain their empathy and reduce the risk of burnout.

Conclusions: In our hands, the FuckCancer Choir represents a positive experience both for patients and caregivers and for the healthcare professionals. The choir is continuing its activity, and we are planning new initiatives also aimed at better understanding and objectifying the benefits coming from this experience.

U – Oncology Nursing

U01*

WHAT ARE THE CHALLENGES FOR NURSES WHEN PROVIDING END-OF-LIFE CARE TO SURGICAL PATIENTS? FINDINGS FROM A DESCRIPTIVE PHENOMENOLOGICAL STUDY

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Background: Even today, many terminally ill patients die in high-tech, care-oriented acute hospital settings. To promote high-quality palliative care, the role of nurses is crucial. As professionals, they take care of the physical and psychological needs of the patient until the end of life, and they are at the bedside during the dying process. However, if not adequately trained and prepared, nurses who have to deal with the death of patients under their care can live complex and painful experiences. This study aims to investigate the lived experience of a group of nurses in delivering end-of-life care of oncology patients in surgical units.

Material and methods: A descriptive phenomenological study was conducted in 2019 with a purposive sample of 26 nurses working in six different surgical units at a teaching hospital located in the North-East of Italy. Individual semi-structured interviews based on open-ended questions were analyzed in-depth, adopting Colaizzi's descriptive analysis framework.

Results: Based on the participants' interviews, three main themes were identified embracing various aspects of the nurses' lived experiences: "Managing care and emotional complexity"; "Working in synergy for a common purpose" and "Improving the quality of care to guarantee the dignity of death." Overall, the emotional involvement of professionals who take care of terminally ill patients is very high, especially for those with less work experience. The need to share experiences and emotions in a structured way during the care of these patients is very high. There is an intense desire among nurses to improve their knowledge and skills concerning end-of-life needs and issues. Their wish is to guarantee quality care for terminally ill patients and their relatives, promoting a multi-professional approach.

Conclusions: To improve the quality of care of the terminally ill patient in surgical settings, it is essential that the organization recognizes and supports the centrality of the nurse in terms of training, care and emotions. Further studies are needed to better understand the care experience of other professionals to develop effective collaborative strategies. Surgical-specific end-of-life care education, training, and guidelines are also recommended to promote high-quality patient-centred care.

U02*

CASE MANAGER NURSE (CMN) AND MANAGEMENT OF LOCALLY ADVANCED RECTAL CANCER (LARC): A MONOISTITUTIONAL EXPERIENCE OF CARDINALE PANICO HOSPITAL

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Introduction: In the treatment planning of LARC the coordination of several professionals and the complexity of tumor staging significantly increase the "downtime" and the delay of care. In this context, the figure of CMN has been developed to improve the quality and the management of the care given to patients (pts). The aim of this research was to evaluate the efficiency of the CMN in the multidisciplinary team and the compliance with regional guidelines.
Methods: Several endpoints were investigated: time to preparation for treatment, as regional guidelines (42 days: 14 days for the histological diagnosis, 14 days for staging disease, 14 days for multidisciplinary review and start of therapy); time to start of treatment (within 45 days); time to restaging after radiochemotherapy neoadjuvant treatment (6-8 weeks); time to surgery (6-12 weeks). A prospective, observational and descriptive study was performed. The path of these pts was managed independently by the CMN and was discussed in a multidisciplinary setting at Time 0 (diagnosis), at Time 1 (after re-staging), and at Time 2 (after surgery).
Results: From January 1, 2019 to December 31, 2020, 107 patients (pts) with rectal cancer (RC) were treated. 45 of these pts with LARC were included in our analysis. The median age was 73 years (45 to 91), with a prevalence of males (78%) compared to females (22%). The stage at diagnosis was cT3-4 in 95.6% of cases, cN + in 86.7% of cases. The median time from first healthcare visit to histological diagnosis was 6 days (3-14), from first healthcare visit to complete staging was 10 days (1-47), from first oncological visit to start of treatment was 30 days (6- 85), from the end of treatment to the restaging was 7.9 weeks (4.7-11.7) and from the end of treatment to surgery 10.0 weeks (6.3-15.9) (Table 1).
Conclusions: Our preliminary experience confirms as the CMN has a pivotal role in the management of the PDTA. The result in terms of start of treatment complies with regional guidelines suggesting how the integration of effective communication and collaboration between different specialist figures is the key to the promotion of patient safety. These support the necessity to implement the training of case manager figures in order to optimize pts safety by facilitating effective care transitions.

Table 1.

Endpoint	Cardinale Panico	PDTA regione Puglia	results
Histological diagnosis	6gg	<14gg	+
Start of treatment	30gg	<45gg	+
Time of Restaging	7,9w	6-8w	+
Time of surgery	10w	6-12w	+

U03*

THE COMPARISON BETWEEN THE ORAL AND WRITTEN EDUCATIONAL INFORMATION AND ORAL INFORMATION IN REDUCING NAUSEA AND VOMITING IN PATIENTS UNDERGOING CHEMOTHERAPY

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Background: Chemotherapy-induced nausea and vomiting (CINV) is a frequent adverse event affecting 37% to 70% of patients undergoing chemotherapy, which greatly impacts on quality of life. CINV is difficult to control because of the subjectivity of the symptom, limited understanding of physiopathology, lack of validated instruments for measurement, inadequate reporting by the patients, nurses failing to assess its impact on patients' life. Despite the great number of studies on different antiemetic drugs for CINV reduction, no study focused on patients' educational programs through written information on CINV; nurses may play a role in this context. Therefore, a phase III randomized trial is being conducted on the efficacy of written and oral information (arm A) versus oral information alone (arm B) in CINV reduction.
Material and methods: Consecutive patients undergoing first-line chemotherapy in the Multidisciplinary Day Hospital at CRO Aviano are randomized to either arm A (information brochure and verbal information on CINV) or arm B (verbal information alone). Inclusion criteria include: age 18-80 years; signed informed consent. Exclusion criteria include: life expectation <6 months; previous psychiatric or neurologic disease; visual impairment. The study is designed to enroll 384 patients (192 per arm) to estimate a reduction of CINV from 60% to 45% (a=0.05; b=0.20). Adverse events were evaluated according to CTCAE 4.03. The FLIE Questionnaire is used to assess CINV impact on daily life activities 4 weeks after the first chemotherapy administration. The study, designed to enrol patients for 36 months, started January 2019.
Results: At this stage of the trial, 120 patients (31%), out of 384 planned ones, have been enrolled. No differences between study arms emerged for sociodemographic and clinical features, or in the depression level (measured through Hamilton Anxiety Rating Scale) at enrollment. Although no statistical significance was found, patients in arm A reported lower frequency of nausea (1.7% and 11.3% in arm A and B, respectively; p=0.10) and in the impact of nausea in daily life activities (1.7% versus 9.6%; p=0.16). No difference in vomiting frequency was found between study arms.
Conclusions: Although not significant, these preliminary results suggest that written information helps patients to

control nausea. These study findings, if confirmed at trial completion, will support the nurses' involvement in educational program to prevent CINV.

U04*

CLINICAL RESEARCH NURSE COORDINATOR: FROM PROFESSIONAL TO MANAGEMENT STATUS

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Background: Scientific literature has illustrated how the presence of a Clinical Trial Nurse (CTN) creates a positive impact on the quality of data harvesting and the safety of the research participants due to her range of experience as well as excellent decision-making skills.
Clinical studies are generally managed by a variety of professional figures and the quantity and diversity of tasks are often unevenly distributed, causing a less than efficient work strategy. Process analysis and activity mapping make it possible to reorganize and optimize tasks.
The Research Nurse Coordinator (RNC) could act as a key figure in ensuring homogenous distribution of activities, thus promoting high quality standards.
Materials and Methods: A quantitative Study was conducted at Fondazione IRCCS "Istituto Nazionale dei Tumori" (INT). In this study, the Clinical Trials Nursing Questionnaire (CTNQ) was issued to 14 CTNs to identify their activities and how they perceive their role.
Results: The studies followed by CTNs are: 78% sponsored studies, 50% no-profit studies and 71% Phase I studies.
In the part of the questionnaire related to activities, the CTNs responded, using the 5 point Likert scale. Low point scores (< 2) indicated a marginal contribution, while scores >2 indicated greater involvement.
The CTN works less with Protocol Planning and Data Management due to the presence of the other research team members. Instead, the CTN is more actively involved in Protocol Assessment, Informed Consent Process, Investigational Product, Implementation/Evaluation and Nursing Role Performance. 85,71% of the CTNs were satisfied with their role, however 78% reported a high workload and 86% considered their role to be poorly defined.
Conclusions: All CTNs adhere to the INT job description, but the latter alone is not sufficient to solve the issue of un-homogenous task distribution and overlapping roles. It is therefore essential that all processes be analysed and flow diagrams drawn up, clearly defining task distribution and respective responsabilities. As cited by the literature, the position of a research coordinator is often undertaken by a professional figure with no
Background: in healthcare and, because of this, the real nature of nursing work is often misunderstood and undervalued. The introduction of a coordinator into the CTN team with nursing experience would enhance the performance of each individual team member and the dynamics of the group as a whole.

U05

NURSES' EXPERIENCES DURING COVID-19 PANDEMIC: COPING AND RESILIENCE STRATEGIES IN ONCOLOGY SETTING. A MULTICENTER MIXED-METHODS STUDY

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Background: The study stems from the need to identify the resilience and coping mechanisms that oncology nurses adopted during the period of the COVID-19 pandemic and explore their individual experience.
Little information is available to date on nurses about this topic, therefore, we designed a mixed-methods study to evaluate these strategies in nurses working in the oncology setting.
Material and methods: A multicenter, sequential explanatory mixed-methods study will be conducted, in which quantitative and qualitative data will be collected and analyzed sequentially and individually. The study will begin in June 2021 and be conducted for 4 months in two Oncology Departments in Northeastern Italy (National Cancer Institute of Aviano and Teaching Hospital of Udine). The quantitative study will be based on the accuracy of estimating resilience with a 95% confidence interval and a standard deviation of 20% and 95%. Two questionnaires in Italian will be mailed to 276 nurses who have been working during the COVID-19 pandemic. Data will be collected through an electronic procedure (REDCap). The study findings will support the development of an interview guide for the qualitative study. Here, semi-structured interviews will be conducted involving a purposeful sampling until saturation. Interviews will be transcribed verbatim and the Colaizzi framework (1978) will be used for content analysis with the NVivo program.
Results: Data collection has not yet started, but the results of both the quantitative and qualitative studies will be available by the time of the conference.
Conclusions: We expect that this study will provide information about difficulties, resilience, and coping strategies adopted by oncology nurses who are working on the frontlines during the COVID-19 pandemic. The results will

help the organization and nursing managers develop effective strategies to cope with future emergency situations.

U06

THE EFFECTIVENESS OF EDUCATION IN REDUCING ANXIETY AMONG ONCO-HEMATOLOGICAL PATIENTS UNDERGOING CHEMOTHERAPY: A SYSTEMATIC REVIEW

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Background: Anxiety is a peculiar emotion understood as an anticipation of a future worry associated with the manifestation of signs and symptoms that invade both the physical and psychological spheres. In onco-hematological contexts, anxiety affects up to 30% of patients with cancer and in particular, among chemo-treated patients, anxiety can reach percentages of 77.8%. Anxiety inexorably impacts the physical, psycho-social, marital and sexual dimensions, often leading to the abandonment of treatments and resulting in an effective reduction in the quality of life. In clinical settings, the nurse plays an emblematic role in preventing and managing the development of complications related to anxiety by applying various strategies including educational interventions that can improve the emotional state and general well-being of the person. This study aims to analyze studies that identify educational interventions effective in reducing anxiety among patients undergoing chemotherapy.
Materials and methods: A systematic review of the literature was conducted by consulting the main scientific databases. Primary studies were included from which evidence of anxiety reduction efficacy through educational interventions was derived.
Results: We included 8 articles that met the inclusion criteria, specifically, 5 clinical trials, 2 quasi-experimental studies and a cohort study. The review found that the educational interventions consisting of individual sessions led by the nurse, personalized lessons, listening to audiotapes and psychoeducational interventions, proved to be statistically significant in reducing the outcome assessed, namely anxiety in patients undergoing chemotherapy. The analysis of the studies also shows that the oral educational approach integrated with paper material is effective in reducing anxiety and that the increase in the knowledge provided also determines an increase in resilience and self-efficacy.
Conclusions: Education has increased the safety of patients, their ability to self-care and retention of information; it has helped patients to understand and apply adaptive strategies towards the disease, promoting greater confidence and awareness, essential to better manage anxiety symptoms, with a positive impact on the quality of life.

U07

COMPLEX AND EMOTIONALLY STRONG WORK SITUATIONS: PEER SUPPORT IN THE NURSING TEAM

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Background: Having knowledge, skills and competences, even if of a high level, are often not enough to perform a task ideally. Often we realize that something is missing within the performance. This something is work experience. The Nurse, who possesses knowledge, skills and competences, and a strong professional experience, will have a high performance especially in those conditions in which he has to react to difficulties or new tasks in emergency conditions or finds himself resisting complex and emotionally strong work situations. Nurses (students, new hires, transfers from other departments) who do not have a past work experience or emotion management tools, can use the experience of others. Nurses within their own working context talk about them, their work, their difficulties, their path and the activities in which they are engaged, also underlining the weaknesses or shades of uncertainty that are encountered in this path. This research or just talking to others becomes the point of reference in which the phenomenon of peer support is established. Peer support also provides the opportunity to share emotions, feelings, perplexities and thoughts and to receive emotional and psychological support, especially with a view to preventing stress and complications from the point of view of mental health. Material and Methods: during the six months of the project all peer support behaviors implemented and encouraged, especially in the management of complex and highly emotional work situations. For the evaluation of peer support, an observational grid was used at the end of the project that analyzed the interactions between Nurses (use of peer support, empathy, hope for the future, authenticity, lifelong learning) and an interview used to search for elements of Stress or Burnout in the Nurses.
Results: 18 Nurses and 6 Nursing Students from the Medical Oncology Unit of the University of Cagliari were included in the project. 80% of Nurses voluntarily and frequently resort to peer support to manage emotions and stress while students only for 40%. 90% of Nurses implement peer support behaviors towards students in dealing with the complex work situations to which they are exposed. Conclusions: The results conclude that those who use peer support possess better coping strategies in solving work problems, improve their performance and better manage strong emotional situations, giving Nursing Students a viable and useful model to pursue in their future careers.

U08

ANTI-SARS-COV2 VACCINE PROJECT IN ONCO-HAEMATOLOGICAL PATIENTS IN PIACENZA

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Background: Onco-haematological patients are considered a vulnerable group with early access to SARS-CoV-2 vaccination. The Onco-Hematological Department of Piacenza has activated a dedicated vaccination program, with appropriate timing. We selected patients on active injection therapy with extreme immune fragility or undergoing haematopoietic stem cell transplantation. The project has created a path for access to vaccination, with reservations on a dedicated agenda and departmental vaccination point, has allowed patients to be vaccinated before starting therapies, start a clinical study of immunological surveillance, feed a departmental database by recording the number of vaccinated patients and any adverse events, favor vaccination in a known, familiar, comfortable context.

Materials and methods: The staff underwent training on the preparation, administration, registration of the vaccine, observation and management of any adverse events. On the basis of the identified criteria, the patients who had to carry out the vaccination were selected. The programming was carried out by the referring physician who delivered the informed consent and who checked the medical history. During the vaccination sessions, the patients were managed by the Department team who took care of all the planned vaccination phases. The data were recorded on a regional IT platform. Each vaccination session was coordinated by a nurse and a vaccinating doctor.

Results: The vaccination sessions were organized from 20/03/2021 for a total of 13 vax days. 426 patients were vaccinated, 230 F (53.99%) and 196 M (46.01%), mean age 63.38 ± 11.35, range 20-86, of these 415 (97.42%) completed the two scheduled vaccination doses, 11 patients (2.58%) did not receive the second administration due to worsening of the clinical picture. To evaluate the perceived quality and make suggestions, 10 posts were published on the FB page, totaling 2217 likes, 93 comments and 97 shares. The comments were positive, in particular the family environment, the presence of the treating team and the adequate waiting times were appreciated.

Conclusions: Experience has made it possible to vaccinate the category of vulnerable patients ensuring safety, appropriateness, effectiveness, efficiency, satisfaction and user loyalty, without delaying or interrumpting oncological treatment.

U09

HOPE: NURSING CLINIC

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Background: There are diseases that hurt us more than others, touch our souls, because they not only make us feel bad and fear for our life, but also put a strain on our identity, the image we have of ourselves. Cancer is one of these, especially when it affects women, and it does so in the organs that culturally represent femininity in all its meanings: maternal, erotic, symbolic. The creation of a dedicated nursing clinic could be a solution.

Methods: People diagnosed with non-ovarian gynecological cancer come to the nursing outpatient clinic for advice and / or any surgical treatment. The outpatient is activated through a first meeting between the patient and the Case Manager of the oncological pathways, who through a careful assessment and assessment of the woman, explaining the diagnostic-therapeutic and care process, establishes a relationship of knowledge and trust that will allow during the treatment path to face together the various needs that may arise through a multi-professional sharing of the socio-health needs highlighted. The methodologies used to develop the various organizational problems and supervised by the case manager can be represented by:

- Informative meetings between the woman and the multi-professional group dedicated to analyzing the real or potential problems that may develop during the treatment process to make the same aware and unravel possible doubts and misunderstandings
- Targeted interviews between patient and / or family and specialist professional
- Couple meetings with a dedicated professional specialist
- Self-help sessions with other women who live or have experienced this health problem
- Sharing with voluntary associations of alternative strategies to support women in the care path

Results: The expected results for patients with uterine cancer treated by the nursing clinic should include:

- Early detection of disease recurrence
- Instruction / education and support to the patient throughout the treatment process

- prevention and reduction of the psychosocial, physical and existential consequences of the disease and its treatment through the complete care of the person and his problems by providing psychologists, sexuality therapists, physiotherapists, dieticians, midwives
- Evaluation of the long-term outcomes of new care strategies
- Control of satisfaction of women the quality of life.

Conclusions: The nursing clinic could represent an aid to improve the quality of life of woman.

Late Breaking Abstracts

LBA01*

FOLFOXIRI PLUS BEVACIZUMAB (BEV) PLUS ATEZOLIZUMAB (ATEZO) VERSUS FOLFOXIRI PLUS BEV AS FIRST-LINE TREATMENT OF UNRESECTABLE METASTATIC COLORECTAL CANCER (MCRC) PATIENTS: RESULTS OF THE PHASE II RANDOMIZED ATEZOTRIBE STUDY BY GONO

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Background: FOLFOXIRI/bev is an upfront therapeutic option for selected mCRC pts. Immune checkpoint inhibitors (ICIs) reported remarkable achievements in dMMR but not in pMMR mCRC. The association of cytotoxics and bev may promote the sensitivity to ICIs increasing the exposure of neoantigens, inducing immunogenic cell death, and increasing the immune infiltration in tumor microenvironment while reducing the activity of Tregs.

Methods: AtezoTRIBE was a prospective, open label, phase II, comparative trial in which initially unresectable mCRC patients, irrespective of MMR status, were randomized 1:2 to receive up to 8 cycles of FOLFOXIRI/bev (arm A) or FOLFOXIRI/bev/atezo (arm B), followed by maintenance with 5-FU/bev or 5FU/bev/atezo until disease progression. The primary endpoint was PFS. Assuming a median PFS of 12 months in arm A, 201 patients and 129 events were required to detect a HR of 0.66 in favour of arm B with 1-sided α and β errors of 0.10 and 0.15. Trial info: NCT03721653.
Results: From November 2018 to February 2020, 218 pts were enrolled (arm A/B: 73/145) in 22 Italian sites. Main pts' characteristics were (arm A/B): right-sided 44%/44%, synchronous metastases 89%/86%, liver-only 22%/22%, RAS mutant 71%/73%, BRAF mutant 14%/8%, dMMR 7%/6%. At a median follow up of 19.9 mos, 159 (arm A/B: 60/99) PFS events were collected. A significant advantage by the addition of atezo was observed in PFS (13.1 vs 11.5 mos, HR 0.69, 80%CI 0.56-0.85, p=0.012), but not in ORR (59% vs 64%, p=0.412). No safety issues were evident. Significant interaction effect between MMR status and treatment arm was found (p=0.010). In the pMMR subgroup (N=199, arm A/B: 67/132), 147 (arm A/B: 54/93) PFS events were collected. Significantly longer PFS was reported in arm B (12.9 vs 11.4 mos, HR 0.78, 80%CI 0.62-0.97, p=0.071).
Conclusions: The primary endpoint was met: the addition of atezo to FOLFOXIRI/bev prolongs PFS of mCRC patients. While the magnitude of benefit is significantly higher in dMMR tumors, signals of efficacy are reported also in the pMMR subgroup. Translational analyses to identify predictive biomarkers are ongoing.

ELBA02

EFFICACY OF SARS-COV-2 VACCINATION IN CANCER PATIENTS DURING TREATMENT:A PROSPECTIVE OBSERVATIONAL STUDY (ANTICOV TRIAL)

Passalacqua R.[1], Ratti M.[1], Pan A.[1], Testa S.[1], Faliva A.[1], Molteni A.[1], Tonoli S.[1], Mainardi E.[1], Saleri J.[1], Gobbi A.[1], Nanni N.[1], Bacciocchini N.[1], Donati G.[1], Marchi R.[1], Pogliacomi G.[1], Cattaneo M.[1], Gnocchi N.[1], Grizzi G.[1], Brighenti M.[1], Maglietta G.[2], Caminiti C.[2]

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Background: Cancer patients (pts) have higher risk of serious COVID-19 symptoms, morbidity and mortality than general population. SARS-CoV-2 vaccine trials excluded patients with metastatic cancer or undergoing immunosuppressive therapies; therefore, the effectiveness of vaccines are unknown in this population. Hence, there is an urgent need to understand the correlation between cancer type, its treatment and vaccine efficacy.
Material and Methods: This is a prospective study conducted by the Oncology Unit of Cremona Hospital,

enrolling pts from Oncology, Hematology, Radiotherapy and Palliative Care divisions.
The trial aims to evaluate effectiveness of mRNA vaccines [BNT162b2 (Pfizer) and mRNA-1273 (Moderna)], incidence of symptomatic COVID-19 infection, antibodies (Abs) response in a consecutive population of 300 cancer pts, undergoing antiblastic therapies, starting from March 2021.
Primary endpoint: Number of symptomatic pts affected by COVID-19, diagnosed 7-60 days after the 2nddose of vaccines.
Secondary endpoints: Abs variation at different timepoints; duration of abs; correlation between effectiveness of vaccines and antiblastic treatments.
Statistical Analysis: The primary objective will be tested by non-inferiority one-single proportion test, compared with the value of 95% observed in the vaccine registration trials. The hypothesis of vaccine inferiority in the trial population is rejected if a rate of protection conferred by the vaccine is observed in 89% of the sample size.
Results: 356 patients received mRNA anti-COVID-19 vaccines. None of them reported symptomatic COVID-19 infection after vaccination. Whereas almost all patients (95.6%) with solid tumors developed an antibody response, only 77% of patients with hematological malignancy demonstrated anti-COVID-19 antibody production after vaccination. The different antiblastic treatments didn't have a significant impact on the antibody response. In particular, patients treated with immunotherapies and with chemotherapy developed antibodies against COVID-19 in 98% and 92% of cases, respectively.
Conclusions: Vaccination against COVID-19 demonstrated to be effective and to prevent symptomatic COVID-19 infection in patients with solid and hematological tumors during antiblastic treatment. The depth of antibody response resulted different between patients with solid and hematological malignancies. Different antiblastic therapies didn't significantly impact on the development of the antibody response.

ELBA03

EFFICACY AND SAFETY OF COVID-19 VACCINE IN CANCER PATIENTS

Biasini C.[1], Madaro S.[1], Citterio C.[1], Toscani I.[1], Cremona G.[1], Muroni M.[1], Muroni L.[1], Bacchetta N.[1], Lis A.[1], Cavanna L.[1]

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Background: Cancer patients are presumed a frail group at high risk of contracting coronavirus disease (COVID-19), and vaccination represents a cornerstone in addressing the COVID-19 pandemic. However, data on COVID-19 vaccination in cancer patients are fragmentary and poor.
Material (patients) and methods: An observational study was conducted to evaluate the seropositivity rate and safety of a two-dose regimen of the BNT162b2 or mRNA-1273 vaccine in adult patients with solid cancer undergoing active anticancer treatment or whose treatment had been terminated within 6 months of the start of study. The control group was composed of healthy volunteers. Serum samples were evaluated for SARS-COV-2 antibodies prior vaccinations and 2-6 weeks after the administration of the second vaccine dose. Primary endpoint: seropositivity rate. Secondary endpoints: safety, factors influencing seroconversion, IgG titers of patients versus healthy volunteers, COVID-19 infection.
Results: Between 20 March 2021 and 12 June 2021, 293 consecutive cancer patients with solid tumors underwent a program of COVID-19 vaccinations: of these, 2 patients refused vaccination, 13 did not receive the second dose of the vaccine due to cancer progression and 21 had COVID-19 antibodies at baseline and were excluded. The 257 evaluable patients had a median age of 65 years (range 28 - 86), 66.15% with metastatic disease. Primary endpoint: seropositivity rate in patients was 75.88%, versus 100% in the control group. Secondary endpoints: no grade 3 - 4 side effects, no COVID-19 infections were reported. Patients median IgG titer was significantly lower than in the control group, male sex and active anticancer therapy influenced negatively seroconversion.
Conclusions: BNT162b2 or mRNA-1273 vaccines were immunogenic in cancer patients, showing good safety profile.

ELBA04

COVID-19 VACCINE IN HEMATOLOGIC PATIENTS: PRELIMINARY SAFETY AND EFFECTIVENESS RESULTS

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Background: From March to May of the current year, the Department of onco-hematology of "Guglielmo da Saliceto" hospital of Piacenza vaccinated 108 haematological patients with a m-RNA vaccine, either Pfizer-BionNTech or Moderna. The aim of this study is to investigate the efficacy and safety of COVID-19 vaccine
Materials and methods: This is an observational study. We analyzed the humoral immune response by antibody titer (IgG) at baseline (T0) and 4-6 weeks after the first dose of vaccine (T1). We evaluated whether age, sex, hematologic disease, previous bone marrow transplant, past COVID-19 infection and antitumor treatments interfere with the development of the humoral immune response evaluated with an anti-SARS-CoV-2 IgG ChemiLuminescent ImmunoAssay (LIAISON SARS-CoV2 S1/S2 IgG-DIASORIN Inc.) measured in AU/ml. An antibody level ^{3}15 AU/ml was considered relevant.

Results: From the 108 patients enrolled, 87 patients with median age of 65 years (IQR 58-71) have T1 IgG determination available of which 51 patients (58,62%) seroconverted, with IgG median value of 254 AU/ml (IQR 98,1-385 AU/ml), whereas 36 patients (41,38%) did not, with IgG median value of 3.8 AU/ml (IQR 3.8-4,5 AU/ml). Being on active anticancer treatment at the time of vaccination (p 0,03), especially on anti-CD20 monoclonal therapy (p 0.001), showed a statistically significant effect on seroconversion in univariate analysis, while age over 60 years and sex (male vs female) are near to be significant (respectively p 0.05 and p 0.06). Hematologic disease and previous bone marrow transplant (without differentiate between allo-HSCT and auto-HSCT) seem not to influence the immune response. In multivariate analysis, only anti-CD20 monoclonal therapy deeply reduces the probability of seroconversion (99,97%, p 0.003). The latter does not seem to be influenced by age, sex and active therapy (including all the remaining immunomodulant or immunosuppressor treatments). None of the patients had adverse reactions to vaccine, neither allergic nor immunological.
Conclusions: More than half of the patients seroconverted. Active antitumor therapy, especially anti-CD20 monoclonal antibody, seems to have a negative effect on seroconversion. We are actually testing the cell-mediated immune response to prove the efficacy of COVID vaccination also in those immunocompromised subjects who did not seroconverted. The m-RNA vaccines seem to be safe in patients with immune deficiency.

ELBA05

ANTIBODY IMMUNORESPONSE TO ANTISARS-COV2 VACCINE IN CANCER PATIENTS

Schena M.[1], Alliod V.[1], Cucchi M.[1], Alvaro M.R.[1], Mozzicafreddo A.[1], Trogu A.[1], Stella A.[1], Di Benedetto M.[1], Delvescovo G.[1], Malossi A.[1]

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Background: There is unanimous agreement that oncological patients (pts) should be offered anti covid-19 vaccine, due to the risk of severe infection and serious complications caused by Sars-CoV-2. Little is known about efficacy of covid-19 vaccine in oncological and onco-haematological pts, as they weren't enrolled in clinical trial. Recently evidence of lack of immune response in pts affected by LLC undergoing to mRNA vaccine has been reported.
Methods: In our Oncological DH we administered anticovid-19 mRNA vaccine (Comirnaty, Pfizer) to all pts on anticancer treatment, except to anti CD20 MoAb treated pts, according to guidelines. From 30/3 to 8/5/2021 we vaccinated 236 pts, for a total of 425 doses. Median interval between first and second dose was 21,25 days (range 21-28 days); pts with a diagnosis of Covid, 3-6 months before received a single vaccine dose. 196/236 (83%) pts were affected by solid cancer and 40/236 (17%) were affected by haematological malignancies. Most (34%), were treated with chemotherapy (CT), 23% were treated with a target therapy, TKI or CD4/6i (TT), 10% with immunotherapy (IT), 12% with hormonal therapy (OT) and 4% with immunosuppressors. SARS-CoV-2 Trimerics IgG test was performed in 195/236 pts, 164 with solid tumors, 31 with haematological malignancies. The median interval between the last vaccine dose and sierological test was 61 days (range 29-133 days). A cut-off > 33 BAU/ml was assumed for positive test.
Results: None of the pts developed clinically meaningful adverse events after vaccination, but lymphadenopathy ipsilateral to the injection site was evident for at least one month after vaccination in CT and PET scan, complicating interpretation of restaging imaging. 184/195 (94%) pts had a sierological positive response to vaccine. Among them 68 were treated with CT, 54 with TT, 21 with IT and 12 with OT. 11 pts (11/195, 6%) were non-responders: 9 pts had haematological malignancy (9/31, 29%) and 2 had solid tumors (2/164, 1,2%). Among responders, CT treated patients showed SARS-CoV-2 IgG levels significantly lower than IT treated pts (p=0,014) and than TT treated pts (p=0,002), while no difference was evident between TT and IT pts.
Conclusions: Most oncological pts on active treatment in our DH showed antibody response to anti SARS-Co-V2 vaccine; non-responders were mostly detected among haematological pts and CT treated pts; the latter showed also lower antibody production respect to TT and IT treated pts.

ULBA06

UNICO STUDY. PREDICTORS OF POOR SEROCONVERSION AND ADVERSE EVENTS TO SARS-COV-2 MRNA BNT162B2 VACCINE IN CANCER PATIENTS ON ACTIVE TREATMENT. ROLE OF THE RESEARCH NURSE

Buttiron Webber T.[1], Provinciali N.[1], Musso M.[1], Magnani M.[1], Paciolla F.[1], Menghini N.[1], Briata I.M.[1], Cevasco I.[1], De Censi A.[1]

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Background: mRNA-based vaccines have shown 95% protection from SARS-COV-2 disease in healthy populations. Initial findings in cancer patients suggest a lower seroconversion and greater toxicity possibly related to myelo-immunosuppressive therapies.
Material and methods: We conducted a prospective study to assess factors predicting poor seroconversion and adverse events following immunization (AEFI) to the BNT162b2 vaccine in cancer patients on active treatment. Blood samples were collected by the research nurse for

serum IgG, C-Reactive Protein (CRP), blood cell count, D-dimer and cytokine panel measurement at baseline first dose (visit 1), second dose at 21 days (visit 2), after 42 days (visit 3) and after 6 months (visit 4). At visit 1, 3 and 4 all participants will receive questionnaires about their psychological status: Hospital Anxiety and Depression Scale (HADS) and Distress Thermometer. The primary endpoint was poor seroconversion (IgG<25 AU/mL) after 21 days from second dose. Patients who ended treatment >6 months on active surveillance served as controls. Multivariable logistic model and mixed effect models for repeated measures investigated independent factors associated with poor seroconversion and AEFI, adjusting for confounders.

Results: Between March 15 and July 21, 2021, 320 subjects were recruited and 291 were assessable for IgG response. The lack of seroconversion at 42 days was 1.6% (95% CI, 0.4-8.7) on active surveillance, 13.9% (8.2-21.6) on chemotherapy, 1.4% (5.1-21.3) on hormone therapy, 21.7% (7.5-43.7) on biological therapy and 4.8% (0.12-23.8) on immunotherapy. Compared to controls, risk of no IgG response was greater for chemotherapy (P=0.023), biological therapy (0.009) and hormonotherapy (P=0.052). Older age and advanced stage also predicted poor seroconversion. Overall, 43 patients (14.8%) complained of AEFI, mostly of mild grade. Risk of AEFI was greater in females (P=0.001) and younger patients (P=0.009). There was a trend to a D-dimer increase in IgG responders (p=0.01).

Conclusions: Except for immunotherapy, chemotherapy, biological therapy and hormone therapy as well as increasing age and advanced stage predict poor seroconversion after two doses of BNT162b2 in up to 20% of patients, indicating the need for a booster dose and long-term serological testing in vaccine non-responders. AEFI occur much more frequently in women and younger subjects who may benefit from preventive medications.

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