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Abstract Book

Guest Editor: Stefania Gori

XXI CONGRESSO NAZIONALE AIOM 2019

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TJ | Tumori Journal

Abstract Book of the 21th National Congress of Italian Association of Medical Oncology (AIOM)

25-27 October, 2019 - Rome, Italy

Guest Editor

Stefania Gori
Director of Oncology Department IRCCS Cancer Care Center "Sacro Cuore - Don Calabria", Negrar, (VR)
President, Italian Association of Medical Oncology (AIOM)


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

TJ | Tumori Journal

Stefania Gori
Medical Oncology
IRCCS - "Sacro Cuore Don Calabria" Hospital, Negrar (VR)
Italy

Dear Colleagues,

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

The abstracts are published in a special issue 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.

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, 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 meeting!

The Board of Directors for the years 2017-2019 includes:

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We are looking forward to seeing you in Rome.

Dott. Stefania Gori
(President of the Congress)

This abstracts book will be available on-line and will also be freely available to subscribers to the following website congresso.aiom.it from October 28, 2019

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Plenary Session

01*

INCIDENCE, REPRODUCTIVE AND DISEASE OUTCOMES OF PREGNANCY AFTER BREAST CANCER IN PATIENTS CARRYING A BRCA MUTATION: RESULTS FROM AN INTERNATIONAL COHORT STUDY

Lambertini M.[1], Ameye L.[2], Hamy A.[3], Zingarello A.[4], Poorvu P.D.[5], Carrasco E.[6], Grinshpun A.[7], Han S.[8], Rousset-Jablonski C.[9], Ferrari A.[10], Paluch-Shimon S.[11], Cortesi L.[12], Senechal C.[13], Miolo G.[14], Pogoda K.[15], Pérez-Fidalgo A.[16], De Marchis L.[17], Del Mastro L.[1], Peccatori F.A.[18], Azim Jr. H.A.[19]

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Background: Very limited data are available on the safety of pregnancy and reproductive outcomes in *BRCA*-mutated patients with prior breast cancer history. We report the results of the largest study to date addressing these questions.
Material and methods: This international, multicenter, hospital-based, retrospective cohort study included consecutive patients with invasive early breast cancer (stage I-III) diagnosed between January 2000 and December 2012 at the age of=40 years and carrying a deleterious germline *BRCA* mutation. Primary endpoints were pregnancy rate and disease-free survival (DFS); overall survival (OS) and pregnancy outcomes were secondary endpoints. To account for guarantee-time bias, we performed two survival analyses: 1) Case-control approach matching pregnant and non-pregnant (1:3) patients for classic prognostic factors (each non-pregnant control had a disease-free interval =than the time elapsing between breast cancer diagnosis and date of pregnancy of the matched pregnant case); 2) Extended Cox model with occurrence of pregnancy as time-varying covariate including all patients.
Results: 1,252 *BRCA*-mutatedbreast cancer patients (811 *BRCA1*,430 *BRCA2*, 11*BRCA1&2*) were included from 30 centers worldwide, of whom 195 patients had a pregnancy (pregnancy rate=16% [95% CI 14-18]) after a median 4.5 years (range 3.1-6.7 years) following breast cancer diagnosis. Pregnant patientswere younger and had more ER-negative tumors (all p<0.01). 16 (8.2%) and 20 (10.3%) patients had an induced and spontaneous abortion, respectively. Among the 150 (76.9%) patients who conceived (n=170 babies), pregnancy complications and congenital anomalies were described in 13 (11.6%) and 2 (1.8%) cases, respectively.Median follow-up was 8.3 years (range 8.1-8.7 years). In the case-control analysis, pregnant patients had better DFS (HR 0.71; 95% CI 0.51-0.99; p=0.045), with no difference in OS (HR 0.86; 95% CI 0.44-1.67; p=0.65). Subgroup analysis suggested that the superior outcome was restricted to *BRCA1*-mutatedpregnant patients(p-interaction<0.01). Similar results were obtained in the second supportive analysis.
Conclusions: Pregnancy following breast cancer is safe in *BRCA*-mutated patients, particularly those with *BRCA1*-mutations, with no detrimental impact on maternal prognosis or fetal outcomes. These findings are of paramount importance for fertility counseling in young *BRCA*-mutated breast cancer patients.
ClinicalTrials.gov Identifier: NCT03673306

02*

UPDATED RESULTS OF TRIBE2, A PHASE III, RANDOMIZED STRATEGY STUDY BY GONO IN THE FIRST- AND SECOND-LINE TREATMENT OF UNRESECTABLE mCRC

Rossini D.[1], Cremolini C.[1], Lonardi S.[2], Antoniotti C.[1], Pietrantonio F.[3], Cordio S.S.[4], Bergamo F.[2], Marmorino F.[1], Maiello E.[5], Passardi A.[6], Masi G.[1], Tamburini E.[7], Santini D.[8], Grande R.[9], Zaniboni A.[10], Granetto C.[11], Murgioni S.[2], Aprile G.[12], Boni L.[13], Falcone A.[1]

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Background: In the phase III TRIBE study FOLFOXIRI/bev significantly improved Response Rate (RR), PFS and OS when compared with FOLFIRI/bev as initial treatment of mCRC. However, the actual advantage by the triplet could be lower when compared with a pre-planned sequential strategy of doublets (FOLFOX, FOLFIRI). TRIBE2 (NCT02339116) is a phase III trial in which unresectable mCRC pts were randomized 1:1 to FOLFOX/bev followed by FOLFIRI/bev after PD (arm A) or FOLFOXIRI/bev followed by the reintroduction of the same regimen after PD (arm B). A pre-planned interim analysis showed a significant advantage for arm B in terms of PFS2, primary endpoint of the study, defined as the time from randomization to PD on any treatment given after first PD or death (PD2).

Methods: The study had 80% power to detect a HR for PFS2 of 0.77 in favor of arm B with an overall 2-sided-a error of 0.05 (0.0131 and 0.0455 for the interim and final analyses, planned at 303 and 466 PFS2 events, respectively). Secondary endpoints included RR, 1st-PFS, i.e. the time from randomization to the first evidence of PD or death (PD1), 2nd-PFS, i.e. the time from PD1 to PD2, and OS.

Results: From February 2015 to May 2017, 679 pts (arm A/B: 340/339) were enrolled in 58 Italian sites. Main pts' characteristics were (arm A/B): right side 38%/38%, synchronous mets 89%/89%, RAS mutant 65%/63%, BRAF mutant 10%/10%. At a median follow up of 30.6 mos, 514 (arm A/B: 272/242) PD2, 594 (arm A/B: 303/291) PD1 and 408 (arm A/B: 217/191) OS events were collected. A significant advantage by upfront FOLFOXIRI/bev was confirmed in terms of PFS2 (19.1 vs 16.4 mos, HR 0.74, 95%CI 0.62-0.88, $p<0.001$), RR (62% vs 50%, OR 1.61, 95%CI 1.19-2.18, $p=0.002$) and 1st-PFS (12.0 vs 9.8 mos, HR 0.75, 95%CI 0.63-0.88, $p<0.001$). A significant OS benefit for pts in arm B was also observed (27.6 vs 22.6 mos, HR: 0.81, 95%CI: 0.67-0.98, $p=0.033$). Out of 594 pts with a PD1 event, 470 (79%, arm A/B: 251/219) received a treatment after PD. In the per-protocol analysis ($N=323$), pts in arm B showed significantly longer 2nd-PFS (6.5 vs 5.8 mos, HR 0.76, 95%CI 0.59-0.97, $p=0.024$).

Conclusions: Upfront FOLFOXIRI/bev followed by the pre-planned reintroduction of the same agents after PD provided a statistically significant and clinically relevant PFS2 and OS benefit when compared with the pre-planned sequential administration of FOLFOX/bev and FOLFIRI/bev in unresectable mCRC patients. A median OS of 27.6 mos was reached despite the high percentage of pts with poor prognostic features.

03*

BENEFIT FROM LETROZOLE AS EXTENDED ADJUVANT THERAPY AFTER SEQUENTIAL ENDOCRINE THERAPY: A RANDOMIZED, PHASE III STUDY OF GRUPPO ITALIANO MAMMELLA (GIM)

Del Mastro L.[1], Mansutti M.[2], Bisagni G.[3], Ponzone R.[4], Durando A.[5], Amaducci L.[6], Fabi A.[7], Frassoldati A.[8], Michelotti A.[9], Pazzola A.[10], Valle E.[11], Sanna G.[12], Gori S.[13], De Placido S.[14], Garrone O.[15], Donadio M.[16], Bruzzi P.[17], Bighin C.[18], Lambertini M.[19], Poggio F.[18]

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Background: The effect of extended adjuvant endocrine therapy (ET) with aromatase inhibitors (AI) after sequential ET with tamoxifen followed by AI for 5 years is still controversial. We conduct a clinical trial to assess different durations of ET with letrozole after tamoxifen.

Methods: The GIM4 LEAD (Gruppo Italiano Mammella 4- Letrozole adjuvant therapy duration study, ClinicalTrials.gov:NCT01064635) was a prospective, randomized, phase III, Italian multicentric trial. Post-menopausal patients (pts) with hormone receptor positive early breast cancer free of recurrence after 2-3 years of adjuvant tamoxifen, were randomized in a 1:1 ratio to receive 3-2 years (short arm, S) or 5 years (long arm, L) of letrozole. The primary study end point was disease-free survival (DFS) in both arms. Results: Between August 2005 and May 2010, 2056 pts were randomly assigned to receive 3-2 years ($n=1030$) or 5 years ($n=1026$) of letrozole. Main patients characteristics in the S and L arms were, respectively: median age 60 vs 61 years, node negative 56 vs 56%, (neo)adjuvant chemotherapy 53.4 vs 54.1%. The median follow-up was

10.4 years (IQR range: 8.8-11.4). In the intention to treat (ITT) population the 8-year DFS was 82.2% (95% CI:79.5-84.9.) and 86.8% (95% CI:84.4-89.1) in the S and L arm, respectively. In a land-mark univariate Cox analysis, in which events occurred while patients in the 2 arms received the same therapy (i.e. 2/3 years after randomization) were excluded, the Hazard Ratio (HR) for DFS was 0.81 (95% CI 0.65-1.00; p=0.051). This effect did not change in a multivariate Cox model that included nodal status, tumor size, grading, age and previous chemotherapy (HR 0.81; 95% CI 0.66-1.01; p=0.06). Among 1960 pts evaluable for toxicity, osteoporosis was diagnosed in 47 (4.8%) in the S arm and 81 (8.3%) pts in the L arm (chi-square=9.88; p=0.002). Bone fractures occurred in 5 (0.5%) and 9 (0.9%) pts in S and L arm, respectively (p=0.29, Fisher exact test).

Conclusions: After 2-3 years of adjuvant tamoxifen, extended treatment with 5 years of letrozole improved DFS compared to the standard duration of 2-3 years of letrozole.

A - Gastrointestinal (Colorectal) Cancers

A01*

CLINICAL RELEVANCE OF MUCINOUS AND POORLY DIFFERENTIATED COLON ADENOCARCINOMAS ON THE OUTCOME OF PATIENTS WITH STAGE II: A TOSCA SUBGROUP ANALYSIS

Rosati G.[1], Galli F.[2], Cantore M.[3], Lonardi S.[4], Banzi M.[5], Zampino M.G.[6], Pelliccioni S.[7], Pella N.[8], Ronzoni M.[9], Antista M.[10], Tamberi S.[11], Marchetti P.[12], Bozzarelli S.[13], Marsico V.A.[14], Bochicchio A.M.[15], Artioli F.[16], Labianca R.[17], Galli F.[2], Bilancia D.[1], Bregni G.[18]

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Background: Although it has been proven for many years that adjuvant chemotherapy is the standard of care for stage III colon cancer (CC) after resection, there is no sufficient evidence that its role on stage II patients get the same benefit. ASCO and ESMO guidelines have identified inadequate sampling of lymph nodes, pT4 primary tumors, obstruction or perforation, lymphovascular and perineural invasion, and poorly differentiated tumors as negative prognostic factors supporting the clinicians in treating this subgroup of patients. However, the influence of histological subtypes on the risk of death or disease recurrence remains controversial.

Patients and methods: The phase III, multicenter, randomized TOSCA trial compared 3 versus 6 months of fluoropyrimidine-oxaliplatin adjuvant chemotherapy in 3,759 patients with high-risk stage II or stage III CC. Objective of this sub-study was to investigate the role of the histological subtype [(mucinous adenocarcinoma (MUC) or non-mucinous adenocarcinoma (NMUC)] on the impact of the treatment duration in terms of relapse-free survival (RFS) and overall survival (OS) in the subgroup of patients with high-risk stage II and grade 3 CC.

Results: Out of 3,614 patients from 130 centres enrolled in the per-protocol population defined in the TOSCA trial, 85 MUC and 389 NMUC patients were included in this analysis. No statistical differences were found between 3 versus 6 months groups in both histological subgroups in terms of baseline characteristics, except for tumor side. After a median follow-up of 62 months, 60 progression/deaths and 38 deaths were observed. A significant interaction between treatment duration and histology was observed on both RFS (p=0.027) and OS (p=0.017). In the subgroup of patients with MUC, worse RFS (adjusted hazard ratio [HR], 3.95; 95% confidence interval [CI], 1.03–15.17; p=0.045) and OS (HR, 9.56; 95% CI, 1.14–79.98; p=0.037) were detected for patients treated in the 3 months arm. No statistically significant differences were detected in the subgroup of patients with NMUC.

Conclusions: Both MUC and poorly differentiated subtypes identify unfavorable clinical characteristics. Patients with MUC, grade 3, stage II CC require special attention and may need 6 months of oxaliplatin-based chemotherapy. Larger studies are required to clarify the possible negative effect of the histological subtype to improve the prognosis of these patients.

A02*

BEVACIZUMAB (BV) MAINTENANCE (M) AFTER FIRST-LINE CHEMOTHERAPY (CT) PLUS BV FOR METASTATIC COLORECTAL CANCER (mCRC) PATIENTS (pts): A META-ANALYSIS OF INDIVIDUAL PTS DATA (IPD) FROM 3 PHASE III STUDIES

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Background: Although CAIRO3 and AIO KRK 0207 trials have demonstrated the benefit of BV and fluoropyrimidine as M regimen after induction CT plus BV, the role of BV alone is not clear. Indeed, SAKK 41/06 and PRODIGE 9 trials failed to demonstrate the superiority of BV alone in comparison to no M, while AIO KRK 0207 showed the non-inferiority of BV alone vs combo M. Thus, in order to evaluate the magnitude of the eventual benefit of M with BV alone in comparison to no M, an IPD meta-analysis of randomized trials prospectively investigating such issue was performed

Patients and methods: Trials whereas mCRC pts were prospectively randomized to receive BV M or not were considered eligible. Primary end-points were Progression-Free and Overall Survival (PFS/OS), both from the start of induction and M. Univariate and multivariate analyses for PFS and OS were performed, with the following variables: baseline ECOG PS; age (> vs=65 years); RAS and BRAF status; LDH and CEA baseline level; RR (PR or CR vs SD) during induction; induction CT (oxa- vs iri-based); resected primary tumor; primary tumor side; synchronous vs metachronous; adjuvant treatment; number of metastatic sites.

Results: IPD of 1,064 pts enrolled in the PRODIGE 9, AIO KRK 0207 and SAKK 41/06 trials were collected. Considering the different timing of randomization in PRODIGE 9 (at the start of induction) vs AIO KRK 0207 and SAKK 41/06 (at the start of M), IPD of pts not progressed during induction and starting M phase entered the analysis. 909 pts were included, 457 (50%) received BV M. Median PFS from induction start was 9.6 and 8.9 months in BV group vs no M group, respectively (HR 0.78; 95%CI: 0.68-0.89; $p<0.0001$). At the multivariate PFS analysis, BV M, resected primary tumor and number of m sites were significant. No difference in terms of OS between the two groups was observed.

Conclusions: This is the first IPD meta-analysis investigating the role of BV alone M vs no M after first-line induction CT plus BV in mCRC pts. Despite results demonstrated a significant PFS improvement in favor of BV M, the absolute benefit appears limited, and without a clear clinical relevance. Based on these findings, we can't conclude that BV alone can be a M therapy option for the overall population, but we need to identify pts most likely to benefit from BV alone.

A03

EFFICACY OF RETREATMENT WITH ANTI-EGFRS IN mCRC IS NOT PREDICTABLE BY CLINICAL FACTORS RELATED TO PRIOR LINES OF THERAPY: A MULTI-INSTITUTIONAL ANALYSIS

Zucchelli G.[1], Pagani F.[2], Pellino A.[3], Dell'Aquila E.[4], Liscia N.[5], Bensi M.[6], Germani M.M.[7], Masi G.[7], Moretto R.[7], Santini D.[4], Salvatore L.[6], Scartozzi M.[5], Lonardi S.[8], Rossini D.[7], Ongaro E.[7], Vannini F.[7], Colombo C.[7], Falcone A.[7], Pietrantonio F.[9], Cremolini C.[7]

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Background: Retrospective analyses and phase 2 studies suggest that administering an anti-EGFR in advanced lines may be effective in mCRC pts who achieved benefit from a 1st-line anti-EGFR containing regimen. The identification of clinical features associated with benefit from anti-EGFR re-treatment (re-tx) in pts experiencing PD during 1st-line anti-EGFR (rechallenge) or after its interruption (reintroduction), is a major clinical need.

Methods: A real-life data-base including a total of 5530 pts treated at 6 insitutions from December 2010 to October 2018 was queried. Pts retreated with anti-EGFRs, with RAS/BRAF wild-type status on tissue samples, who had received a 1st-line anti-EGFR-based tx with at least SD as best response, and at least one further line of therapy before anti-EGFR re-tx, were included. The association with RECIST response (RR), PFS and OS was investigated for the following variables: RR (PR or CR vs SD) and PFS during 1st-line; time from the last anti-EGFR administration to 1st-line PD (i.e. re-introduction vs rechallenge); reason for anti-EGFR discontinuation in 1st-line (PD vs. other); number of anti-EGFR-free lines of therapy before re-tx; anti-EGFR free interval (time between the last anti-EGFR administration in 1st-line and the time of re-tx); primary tumor side; time from the diagnosis of metastatic disease to re-tx (=vs. < 18 mos).

Results: Data from 86 patients were retrieved, 56 (65%) and 30 (35%) received anti-EGFR rechallenge or reintroduction, respectively. Median anti-EGFR free interval was 15.1 mos. The RR during re-tx was 19.8%, with a DCR of 46.5%. Median PFS and OS were 3.8 and 10.2 mos, respectively. No significant association of investigated features with RR and PFS was observed. No differences in RR or PFS were observed among patients receiving anti-EGFR re-tx as rechallenge or reintroduction (20.4% vs 23.1%, p=0.99; median PFS: 3.5 vs 5.0 mos, p=0.61). Patients with left-sided tumors had longer OS (HR: 0.50, 95%CI: 0.26-0.93, p=0.005).

Conclusions: Clinical factors that are generally believed to affect the efficacy of anti-EGFR re-tx are not confirmed in our series. Therefore, clinicians should not rely on those characteristics in their decision-making on anti-EGFR re-tx, and adequate studies for implementing liquid biopsy in clinical practice are urgently needed.

A04

TREATMENTS (TX) AFTER PROGRESSION TO FIRST-LINE FOLFOXIRI + BEVACIZUMAB (BEV) IN METASTATIC COLORECTAL CANCER (mCRC) PATIENTS (pts): A POOLED ANALYSIS OF TRIBE AND TRIBE-2 STUDIES BY GONO

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Background: FOLFOXIRI + bev is regarded as a valuable option in the first-line tx of mCRC pts. A possible concern for the adoption is the feasibility and efficacy of tx after progression, and especially the reintroduction of the same agents used upfront. The aim of the study was to evaluate the efficacy of tx after progression among pts treated with first-line FOLFOXIRI + bev in the phase III TRIBE (NCT00719797) and TRIBE2 (NCT02339116) studies. The impact of the oxaliplatin and irinotecan free interval (OIFI), defined as the time from the last administration of oxaliplatin and irinotecan to disease progression, on the efficacy of tx after progression was also investigated.

Methods: Data about tx received after progression including 2ndPFS (i.e. the time from 2nd line tx start to disease progression or death) were collected. The efficacy of tx after progression according to the duration of the OIFI was explored. A cut-off value of 4 months was adopted

Results: Out of 586 pts treated with upfront FOLFOXIRI + bev, 520 progressed. Among 409 (79%) pts who received a tx after progression, 168 (41%) received FOLFOXIRI ± bev (Group A) and 241 (59%) received other tx (Group B), including FOLFOX or FOLFIRI ± bev or other agents not used in first line in 124 and 117 cases, respectively. Anti-EGFR moAbs were administered in 68 cases. Pts in Group A experienced significantly longer 2nd PFS than pts in Group B (median 2nd PFS: 6.1 vs 4.2, HR 0.76, 95%CI 0.62-0.94; p=0.012). Pts with an OIFI ⩾ 4 mos (n=279) had longer 2nd PFS than those with an OIFI < 4 mos (n=130) independently of the second-line tx (6.1 vs 3.7 mos: HR 0.54, 95% CI 0.42-0.69; p<0.001). In the subgroup of pts with an OIFI ⩾ 4 mos FOLFOXIRI ± bev (n=125) was associated with longer 2nd PFS compared to other tx (n=154) (7.2 vs 5.5 mos; HR 0.75, 95% CI 0.58-0.97; p=0.029). Conversely, in pts with an OIFI < 4 mos no significant difference was shown between Group A (n=43) and B (n=87) (4.4 vs 3.2; HR 0.94, 95% CI 0.65-1.36; p=0.75).

Conclusions: Tx after progression to first-line FOLFOXIRI + bev were feasible. Pts with longer OIFI showed better 2nd PFS and seemed to derive more benefit from the reintroduction of the triplet.

A05

HOW TO DEAL WITH SECOND LINE DILEMMA IN METASTATIC COLORECTAL CANCER? A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Monoclonal antibodies targeting epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) have demonstrated efficacy in combination with chemotherapy as second line for metastatic colorectal cancer (mCRC). However, there is still a paucity of evidence or guidelines suggesting the right sequential treatment in all RAS (KRAS/NRAS) wild type(wt) mCRC. Therefore, we aimed to evaluate the impact of these targeted therapies by reviewing literature data.

Methods: We used Cochrane, EMBASE and Medline databases to select phase III clinical trials containing efficacy and safety data about chemotherapy (CT) or CT + targeted

agents combination (Anti-VEGF and Anti-EGFR) in second line mCRC setting. We performed direct comparisons to obtain pooled data for anti-VEGF + CT versus CT and anti-EGFR + CT versus CT comparisons. Then we performed indirect comparisons between anti-EGFR and Anti-VEGF. Outcomes were disease control rate (DCR), response rate (RR), progression-free survival (PFS), overall survival (OS) and most common G3-G5 toxicities.

Results: Eight eligible RCTs (6793 pts) were included: 5 studies compared anti-VEGF + CT and 3 anti-EGFR + CT combinations to CT. After direct comparisons, pooled indirect results showed significantly improved OS (HR 0.83, 95% CI 0.72 – 0.94) and DCR (HR 1.27, 95% CI 1.04 – 1.54) favouring anti-VEGF combinations in overall population; however, no statistically significant differences in all RAS wt patients was observed (HR 0.87, 95% CI 0.70 – 1.09). Additionally, anti-EGFR combinations significantly increased ORR in all patients (RR 0.54, 95% CI 0.31 – 0.96), showing a trend in all RAS wt patients (RR 0.63, 95% CI 0.48 – 0.83) too. Furthermore, no significant difference in PFS and DCR all RAS was registered. Anti-VEGF combination significantly increased the risk of asthenia difference (RR 1.34, 95% CI 1.03 – 1.75).

Conclusions: At our knowledge, our indirect comparisons between anti-VEGF and anti-EGFR combinations showed for the first time better OS and DCR for anti-VEGF combinations, whereas better RR is observed for anti-EGFR combinatory regimens, defining a role of both targeted agents in second line mCRC setting, according to mutational status, clinical conditions and toxicities.

A06

RARE BRAF MUTATIONS (MTs) IN METASTATIC COLORECTAL CANCER (mCRC): A BI-INSTITUTIONAL RETROSPECTIVE ANALYSIS (REBUS STUDY)

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Background: Recently, 3 classes of BRAF MTs have been described. BRAF V600 MTs, which identify mCRC with poor prognosis and not benefitting from anti-EGFR drugs, belong to class 1. Class 2 and 3 include BRAF non-V600 MTs, which occur in about 1-2% mCRC and are associated to favourable prognosis and specific clinicopathologic features. Class 2 and 3 differ in kinase activity and sensitivity to anti-EGFR: class 2 are activated and RAS-independent MTs; class 3 are kinase-dead and sensitive to inhibition of activated RAS. This study aims to retrospectively evaluate features and prognostic role of rare BRAF non-V600 compared to BRAF V600E MTs in mCRC pts treated at 2 Italian Institutions.

Methods: mCRC pts harboring BRAF MTs, assessed by means of NGS, pyrosequencing or RT-PCR, treated between Jan-13 and Dec-18 at 2 Italian Institutions, were retrospectively analyzed. Clinico-pathological and treatment characteristics and survival data were collected.

Results: 55 pts bearing BRAF MTs were identified. Of those, 46 (84%) harbored a V600E and 9 (16%) a non-V600 MT. Within the non-V600 group, 3 MTs (K601E, G469A, G469R) belonged to class 2, while 5 MTs (G466E, G466A, 2 D594G, D594N), belonged to class 3. One pt harboured a T599I MT, whose kinase activity is unknown. Compared to BRAF V600E mCRC, BRAF non-V600 mCRC were more frequently left-sided (*p.017*) and displayed a lower grade (*p.045*). In addition, non-V600 mCRC pts had a lower tumor burden (involving one metastatic site) (*p.026*) and underwent more frequently to resection of metastases with radical intent (77.7 vs 18%; *p.000175*). mOS was significantly longer in the non-V600 compared to the V600E group (61.3 *vs* 20.4 m; HR 0.41, 95%CI 0.18-0.93; *p.05*). No difference in activity and efficacy of anti-EGFR agents was observed between class 2 and 3.

Conclusions: Despite the small size of our retrospective analysis, the results were consistent with previous evidences. BRAF non-V600 MTs identified a subgroup of mCRC, differing both in terms of clinicopathologic characteristics and prognosis from BRAF V600 mCRC. Interestingly, the better prognostic features allowed more frequently radical resection of metastases, positively impacting on survival.

A07

UPDATED RESULTS OF THE PHASE 2 TRUST TRIAL OF TOTAL NEOADJUVANT APPROACH IN LOCALLY ADVANCED RECTAL CANCER (LARC)

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Background: Induction chemotherapy (CT) followed by chemoradiotherapy (CRT) represents a promising strategy in LARC. TRUST is a phase 2 trial in which LARC patients were treated with 6 cycles of induction with GONO FOLFOXIRI plus BV regimen followed by CRT plus BV and surgery with total mesorectal excision (TME). TRUST met its primary end-point with a 2-year disease-free survival (DFS) of 80.45% (Masi et al. EJC 2019). Neoadjuvant rectal (NAR) score is a composite short-term endpoint that seems to predict outcome in locally advanced rectal cancer treated with preoperative CRT. The aim of this analysis is to provide an update of DFS and overall survival (OS) at a longer follow up and to validate NAR score in TRUST cohort.
Materials and methods: NAR score was calculated as previously reported. The cT category of the NAR score formula was obtained from the MRI performed before induction chemotherapy. NAR was applied to 44 patients treated per-protocol. According to the score, patients were divided into low, intermediate, or high risk of relapse or death. For statistical analysis, we performed Kaplan-Meier curves, log-rank tests, and Cox regression analysis.
Results: 48 patients were included in per-protocol analysis; 45 completed CRT and 44 underwent surgery. After a median follow up of 60.6 months, 13 patients had experienced disease progression. Median DFS was not reached. Updated DFS at 2 and 3 years was 80.51% and 71.8%, respectively. Median OS was not reached and 3y-OS was 86.9%. Of the 44 patients undergoing surgery, NAR score was low (<8) in 22 patients (50%), intermediate (8-16) in 13 patients (29.5%) and high (>16) in 9 patients (20.5%). DFS was significantly better in patients with low NAR score (3y DFS: 95.4%) compared to those with intermediate (3y DFS: 54.5%, HR 0.133 [95% CI: 0.021-0.842]; p=0.032) and high NAR score (3y DFS: 33.3%, HR 0.024 [95% CI: 0.004-0.145]; p<0.0001). The difference between intermediate and high NAR score in terms of DFS was not statistically significant (p=0.097). Three-year OS was 100% in low NAR score compared to 84.6% (p=0.09) in patients with intermediate and 75% (HR 0.093 [95% CI: 0.013-0.648]; p=0.016) in those with high NAR score, respectively.
Conclusions: Effect of induction therapy with FOLFOXIRI plus BV followed by CRT plus BV seems promising at a longer follow up. We confirmed the prognostic role of NAR score in an independent cohort of patients treated with total neoadjuvant approach.

A08

P53 EXPRESSION AND CLINICAL OUTCOME IN RAS/BRAF WILD TYPE METASTATIC COLORECTAL CANCER PATIENTS RECEIVING LATER-LINE IRINOTECAN-CETUXIMAB: A RETROSPECTIVE ANALYSIS

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Background: Preclinical and clinical data support that p53 might modulate the EGFR activity and as a consequence it might influence response/resistance to anti-EGFR monoclonal antibodies. However, the association between p53 status and clinical outcome has not been clarified yet. In our study we evaluated the role of p53 expression in RAS/BRAF wild type (WT) metastatic colorectal (mCRC) patients (pts) receiving irinotecan-cetuximab by using a validation cohort.
Patients and methods: p53 immunohistochemical expression was retrospectively analysed in tumour samples of RAS/BRAF WT mCRC pts treated with second-third line irinotecan-cetuximab. Our aim was to evaluate the correlation between p53 expression and OS, PFS and RR. Statistical analysis was performed with the MedCalc package. Survival distribution was assessed by the Kaplan-Meyer method and comparison of survival curves was performed with log-rank test.
Results: Globally 120 RAS/BRAF WT mCRC pts were included in our analysis, 88 in the exploratory cohort and 32 in the validation cohort. 36/88 and 14/32 pts had p53 normal expression, whereas 52/88 and 18/32 showed p53 overexpression. In the exploratory cohort, RR was 61.1% in pts with p53 normal expression versus (vs) 3.8% in pts overexpressing p53 (p<0.0001); median OS (mOS) was 18 months in pts with normal p53 (95% CI 17-20) vs 8 months (95% CI 5.9-9; p<0.0001) and median PFS (mPFS) was 8 months in pts with p53 normal status (95% CI 6.98-8.10) vs 3 months in pts with abnormal p53 (95% CI 2.90-3.63; p<0.0001). These results were confirmed in the validation cohort: RR was 56.2% in pts with normal p53 and 43.7% in pts with abnormal p53 (p=0.4830); mOS was 30.1 months in pts with p53 normal status (95% CI 22.42-53.31) vs 13.4 months in pts with p53 overexpression (95% CI 12.04-24.84; p=0.03) and mPFS was 9.8 months in pts with normal p53 (95% CI 7.51-12.55) vs 7.9 months in pts with abnormal p53 (95% CI 5.32-8.21; p=0.02).
Conclusions: In our study p53 normal expression was associated with better outcome in RAS/BRAF WT mCRC

pts receiving irinotecan-cetuximab, as confirmed by the validation cohort. Further prospective studies are needed to validate the role of p53 in these pts and to investigate its cross-talk with EGFR.

A09

METASTATIC COLORECTAL CANCER AND PIK3CA MUTATION: ASSOCIATION WITH CLINICO-PATHOLOGICAL FEATURES AND OUTCOME

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Background: Mutations in *PIK3CA*, an EGFR downstream effector, and the subsequent activation of AKT pathway plays an important role in colorectal carcinogenesis. Considering the frequent co-occurrence of *PIK3CA* and *RAS* mutations, conflicting data exist about its impact on prognosis of metastatic colorectal cancer (mCRC) patients (pts) and its predictive role to anti-EGFR therapy. However, PI3K inhibitors have been developed and are currently under investigation in mCRC.

Material and methods: Data from mCRC pts treated at Azienda Ospedaliero-Universitaria Pisana from 1 Jan 2005 to 31 Dec 2017, whose tumours had been analysed per clinical practice by means of MALDI-TOF MassArray were retrieved. Association between *PIK3CA* mutation and clinico-pathological features was analysed by $\chi 2$ test; OS curves were estimated with Kaplan-Meier method and compared by log-rank test.

Results: Tumours from 90 (17%) out of 542 pts included in the present analysis were *PIK3CA* mutated (mut), mostly in exon 9 (58.9%) or 20 (21.1%). Other mutations involved exon 1 (10%), 7 (3.3%), and 4 (2.2%); a double mutation was found in 4 pts: exon 1+20 (3.3%) and exon 1+7 (1.1%). Compared to *PIK3CA* wild-type (wt) tumours, mut ones were more often *RAS* mut (p=0.006), MSI high (p=0.008), and right-sided (p=0.0004). Among 53 pts for whom *PIK3CA* status was available on both primary tumours and metastasis, the concordance was 92.4%. *PIK3CA* mutations were not associated with OS (36.4 vs 35.9 mos, HR 1.17, 95%CI 0.85-1.62, p=0.3), with no difference among those affecting exon 9 and exon 20 (36.4 vs 27.5 mos, HR 0.77, 95%CI 0.39-1.54, p=0.44). In *RAS/BRAF* wt (N=188) and in *RAS* mut (N=299) subgroup, no difference in terms of OS was reported between pts bearing *PIK3CA* mut and wt tumours (38.1 vs 44.4 mos, HR 1.22, 95%CI 0.60-2.48, p=0.55 and 27.5 vs 34.4 mos, HR 1.26, 95%CI 0.85-1.86, p=0.22, respectively), though *PIK3CA* mut had shorter OS. In *BRAF* mut subgroup (N=54), *PIK3CA* mut pts had longer OS compared to *PIK3CA* wt (not reached vs 14.4 mo, HR 0.37, 95%CI 0.16-0.85, p=0.09). Among 39 chemorefractory *RAS/BRAF* wt pts evaluable for response to an anti-EGFR agent, only 2 harboured exon 9 *PIK3CA* mutations and achieved stable disease.

Conclusions: *PIK3CA* mut tumours displayed specific clinico-pathological features and a strong concordance was found between primary tumours and paired metastases. Interestingly, a different impact on prognosis of *PIK3CA* mutation in *RAS/BRAF* wt, *RAS* mut or *BRAF* mut mCRC pts was observed and deserves validation.

A10

IMPACT OF AGE AND GENDER ON SAFETY AND EFFICACY OF FIRST-LINE FOLFOXIRI/BEVACIZUMAB IN METASTATIC COLORECTAL CANCER: A POOLED ANALYSIS OF TRIBE AND TRIBE2 STUDIES

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Background: FOLFOXIRI/bevacizumab (bev) is a valuable upfront option in mCRC based on results of phase III TRIBE and TRIBE2 studies: 1187 patients (pts) aged 18–70 years with ECOG-PS=2 or between 71–75 years with an ECOG-PS=0 were randomized to receive first-line FOLFOXIRI/bev or a doublet (FOLFIRI in TRIBE and mFOLFOX6 in TRIBE2)/bev. We aimed at assessing the effect of the intensification of the upfront chemotherapy (CT) (triplet versus doublets) in terms of safety and

efficacy in pts aged<70 vs 70-75 years and in females vs males.

Methods: Subgroup analyses for ORR, PFS, G3/4 overall adverse events (AEs), CT-related and bev-related AEs were performed according to baseline age and gender.

Results: Among 1187 pts enrolled in TRIBE and TRIBE2 studies, 85% and 15% were aged<70 and 70-75 years respectively; 58% and 42% were males and females respectively. The benefit provided by the intensification of the upfront CT was independent of the age and gender subgroup in terms of both ORR (p for interaction >0.05 for age and gender) and PFS (p for interaction >0.05 for age and gender). In the safety population, the risk of overall and CT-related G3/4 AEs was increased with the triplet independently of age (p for interaction: 0.74 and 0.79) and gender (p for interaction: 0.63 and 0.33). Overall, pts aged 70-75 experienced a higher rate of overall G3/4 AEs (70% vs 57%, p<0.01) as compared with younger pts, and females had a significantly higher risk of overall G3/4 AEs compared with males (65% vs 55%, p<0.01). In the FOLFOXIRI/bev arm, elderly pts reported a higher incidence of G3/4 diarrhea (27% vs 17%, p=0.02) and febrile neutropenia (16% vs 6%, p<0.01) than younger pts, while females had a higher risk to experience any grade of vomiting (50% vs 34%, p<0.01) and nausea (68% vs 59%, p=0.03) as compared with males.

Conclusions: The activity and efficacy of FOLFOXIRI/bev are independent of gender and age, with a relative increase in the risk of overall and CT-related AEs similar among age and gender subgroups. However, elderly and females pts are more likely to experience AEs regardless of the treatment arm. Considering the increased incidence of febrile neutropenia and diarrhea with FOLFOXIRI/bev, the use of G-CSF as primary prophylaxis or an initial dose reduction of irinotecan and 5-fluoruracil might be considered in this population. In females treated with FOLFOXIRI/bev the high incidence of nausea and vomiting may suggest the need for an intensification of the antiemetic prophylaxis.

A11

DRUG HOLIDAYS FOR PATIENTS WITH METASTATIC COLORECTAL CANCER: ASSOCIATION TO OVERALL SURVIVAL

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Background: Patients with metastatatic colorectal cancer (mCRC) have improved their overall survival (OS), over the last decade. Patients with stable disease can currently undergo programmed temporary treatment discontinuations called drug holidays (DH), in order to limit toxicity. Since a full demonstration of OS benefit of continuous treatment over DH was not proven, we studied the real world association of DH to OS.

Patients and Methods: The study included 754 consecutive pts treated in first line for mCRC, at University Hospital of Udine and IRCCS CRO of Aviano from 1/1/2005 to 15/03/2017. A first line interruption of 56 or more days was considered a DH. We performed a uni- and multivariate Cox regression analyses to find association between DH and OS. Kaplan-Meier curves were used to estimate OS.

Results: Continuous treatment was given to 459 (60.9%) pts, while DH to 255 (33.8%) (5.3% missing data). Univariate analysis found associated to OS: KRAS (HR 1.39; 95%CI 1.17-1.66; p<0.001) and BRAF mutation (HR 1.39; 95%CI 1.02-1.90; p=0.035), nodes (HR 1.92; 95%CI 1.49-2.46; p<0.001) peritoneum (HR 1.72; 95%CI 1.38-2.15; p<0.001), bone (HR 1.93; 95%CI 1.93; 1.02-3.64; pp=0.043) and brain (HR 13.51; 95%CI 5.94-30.74; p<0.001) involvement, ECOG PS (1 vs 0: HR 1.84; 95%CI 1.35-2.50,p<0.001; 2 vs 0: HR 2.87; 95%CI 1.89-4.33, p<0.001), metastatic sites >1 (HR 1.61;95%CI 1.36-1.91; p<0.001), DH (HR 0.43; 95%CI 0.36-0.52; p<0.001), metastasectomy (HR 0.32; 95%CI 0.24-0.44; p<0.001), left sidedness (HR 0.70; 95%ICI 0.58-0.86; p<0.001), rectal tumor (HR 0.71; 95%CI 0.58-0.88; p=0.002) and thermo-ablations (HR 0.34; 95%CI 0.25-0.47; p<0.001).

After multivariate analysis, worst survival was associated to BRAF mutation (HR 1.82; 95%CI 1.15-2.87; p=0.010); ECOG PS 1 (HR 2.08; 95%CI 1.29-3.35; p=0.003) and 2 (HR 3.57; 95%IC 1.91-6.63; p<0.001). Better OS was associated to DH (HR 0.44; 95%CI 0.35-0.57; p<0.001), metastasectomy (HR 0.33; 95%CI 0.20-0.55; p<0.001), thermo-ablations (HR 0.44; 95%CI 0.28-0.70; p=0.001) and left sidedness (HR 0.72; 95%CI 0.55-0.95; p=0.018). After median follow-up of 68.6 months, median OS was 23.15 months. Interestingly, median OS was 35.3 months for DH and 18 months for continuous therapy.

Conclusions: In our study, DH seems to be an independent prognostic factor, suggesting that DH could be a safe treatment strategy in accurately selected patients.

A12

OLD PATIENTS MANAGEMENT IN COLON-RECTAL CANCER POPULATION: A MONOCENTRIC EXPERIENCE

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Background: In patients (pts) aged over 70 years colon-rectal cancer (CRC) is the second cause of death. The Italian Society of Gerontology and Geriatrics (SIGG) proposes a new definition of old age for population due to prolongation of life expectancy. Now we can define as old people aged 75 years and over, in contrast with the previous threshold of 65 years. Unfortunately this part of population is poorly represented in clinical trials so data are poor. We report the experience of our oncology unit in the management of patients aged ⩾75 years underwent surgery for CRC.

Patients and Methods: We included 406 consecutive pts with diagnosis of CRC candidate for surgery (at least stage II) and evaluated in our institution between 2009 and 2018. Age of pts ranged from 75 to 92 years at the time of first visit. Patients were divided in two subgroups: group A (214 pts, aged 75-79) and group B (192 pts, aged = 80). Main subgroups characteristics are summarized in table below. 81 (38%) pts in group A and 72 (38%) in group B were candidate for adjuvant chemotherapy related to their tumor risk. From these 59 (73%) pts in group A received an adjuvant treatment versus 20 (10%) in the group B ($p<0.0001$). 27% vs 72% of pts in respectively group A and B didn't perform adjuvant chemotherapy. The main causes of exclusion in group B were comorbidity/PS (71%) and patient refuse (25%). 52 (69%) out of 75 metastatic patients in group A started a first line treatment versus 22 (41%) out of 54 patients in group B ($p=0.0028$). In the group B an higher proportion of patients didn't start follow-up program: 31 (18%) in group A vs 68 (39%) in group B ($p<0.0001$).

Conclusions: In old patient it's important to consider comorbidities, PS and patient preferences in therapy decision making. Pts aged = 80 receive less adjuvant/ first line therapies and have a more drop-out in the follow-up respect younger counterpart. Age anyway remains an important factor to consider in decision-making.

PATIENT CHARACTERISTICS	GROUP A n. 214 (%)	GROUP B n. 192 (%)
Gender M:F	129:91	108:88
Adjuvant chemo indication n. (%)	81 (38)	72 (38)
Adjuvant chemo performed n. (%)	59 (73)	20 (28)
Completed	45 (76)	15 (75)
Interrupted for toxicity	14 (24)	5 (15)
Metastatic patients n. (%)	75 (35)	54 (28)
Synchronous metastases	40 (53)	19 (35)
Metachronous metastases	35 (47)	35 (65)
First-line treatment performed	52 (69)	22 (41)
Follow-up not started	31 (18)	v

A13

AXL EXPRESSION IN PATIENTS WITH RAS WILD TYPE METASTATIC COLORECTAL CANCER IS PREDICTIVE OF POOR PROGNOSIS AND OF LACK OF EFFICACY OF BOTH ANTI-ANGIOGENIC AND ANTI-EPIDERMAL GROWTH FACTOR RECEPTOR DRUGS

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Background: AXL receptor is a tyrosine kinase member of the TAM family, key mediator of epithelial to mesenchymal transition. AXL is overexpressed in several human cancers, including CRC (colorectal cancer).

Methods: AXL expression was evaluated by immunohistochemistry in tumor samples from 346 mCRC patients (pts) treated at three Institutions and enrolled in different clinical trials (CAPRI, MACBETH, MOMA, TRIBE2). *In silico* data of AXL RNA levels were obtained from GSE5851 dataset, including 80 pts with advanced mCRC treated with cetuximab in a later line.

Results: AXL expression in tumor was found in 61 out of 346 cases (18%), with no difference among RAS cohorts. In stroma, that was assessable in 334 samples, AXL was expressed in 268 cases (80%), with no difference in RAS groups.

In the RAS WT cohort, a worse mPFS was registered in AXL positive pts, whether treated with chemotherapy (CT) + anti-angiogenic agent [6.7 m (CI95% 8.9- 19.3) vs 14.1 m (CI95% 9.4– 13.0) p 0.007] or CT + anti-EGFR drug [6.2 m (CI95% 4.2- 8.2) vs 12.1 m (CI95% 10.6 – 13.6) p 0.012], whereas in RAS mutant pts no impact on PFS was observed. AXL expression in tumor cells correlated with worse mOS in both cohorts; notably, in RAS WT pts mOS was 19.9 m (CI95% 10.5- 29.2) vs 37.6 m (CI95% 31.1– 44.1) p 0.006.

AXL expression in stroma was associated with worse mOS in both cohorts [in RAS WT pts: 49.8m (CI95% 40.6 – 59.0) vs 33.5m (CI95% 29.3- 37.7) p 0.03; in RAS mutant: 35.5m (CI95% 24.2- 46.5) vs 24.7m (CI95% 21.8- 27.6) p 0.056)].

Intriguingly, taking into account AXL levels in both tumor and stroma, AXL double positive expression (+/+) correlated with shorter mOS; in particular, RAS WT pts (+/+) had a mOS of 19.9 m (CI95% 8.0- 31.7) vs (-/-) 50.1 m (CI95% 43.9- 56.2) p 0.004].

In silico analyses showed high AXL RNA levels in 50% of pts. Moreover, in this population treated with cetuximab in later line, in the KRAS exon2 WT cohort (N=43) AXL high pts had worse mPFS [1.9 m (CI95% 1.7 -2.0) vs 3.8 m (CI95% 0.7-6.7) p 0.59].

Conclusions: AXL expression in tumor and stroma might have a negative prognostic relevance in mCRC, irrespective of RAS status. In RAS WT pts, AXL expression might represent a predictive biomarker of lack of efficacy for both anti-EGFR and anti-angiogenic agents.

A14

A METABOLOMIC RECURRENCE SCORE AS PROGNOSTIC BIOMARKER IN ELDERLY PATIENTS (pts) WITH EARLY COLORECTAL CANCER (eCRC)

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Background: Adjuvant management of eCRC is guided by pathological staging and risk stratification, but a significant proportion of pts who receive chemotherapy derive no benefit, particularly in elderly population. Metabolomics measures multiple cancer-related metabolites which may identify new prognostic and predictive biomarkers, potentially enabling a personalized approach to curative therapy.We have previously shown that serum metabolomics can separate pts with eCRC from pts with metastatic CRC (mCRC). In order to evaluate this potential prognostic role in eCRC, we performed a retrospective evaluation of serum metabolomics in a cohort of elderly pts with CRC.

Methods: Serum samples from a cohort of 103 pts aged=70(55 with eCRC, 48 with mCRC) were pooled from four clinical trials (follow up: 5 years). Samples were retrospectively analyzed via proton nuclear magnetic resonance (1H NMR), to evaluate each metabolomic fingerprint. A Random Forest (RF) classification model was built using a training set of eCRC pts free from relapse at 5 years (N=30) and all mCRC pts (N=48). This model was then applied to a validation set made of the remaining eCRC pts (10 relapse-free; 15 with relapse). A risk-of-recurrence score was built on the basis of the likelihood of a sample being misclassified as metastatic.

Results: In the overall eCRC group, 44% (n=24) received adjuvant chemotherapy. Over a quarter (27%; n=15) experienced relapse. In the training set, the RF model split CRC from mCRC with an accuracy of 74.4%.The RF risk of recurrence score correlated with relapse, with an AUC of 0.754 in ROC analysis. By maximizing specificity and sensitivity in the training set, a threshold for the RF score was set at 0.55. In the validation set, using this threshold, an AUC of 0.727 in ROC analysis, and a prediction accuracy of 76% (73.3% sensitivity, 80% specificity) were obtained in predicting relapse.

Conclusions: Metabolomic fingerprinting of post-operative sera from elderly pts with eCRC identifies pts with higher risk of relapse with good accuracy. This may represent a tool to refine risk stratification in this population, to maximize the benefit from adjuvant chemotherapy. Analysis of an additional cohort drawn from a prospective trial of elderly pts is ongoing to confirm this data. Based on these results, a larger prospective, multicenter trial has recently opened to accrual (Liquid BIopsy and METabolomics in CRC-LIBIMET), with a focus on high-risk disease.

A15

COLORECTAL CANCER LUNG-LIMITED METASTASIS: CLINICO-PATHOLOGICAL FEATURES AFFECTING PROGNOSIS, OUTCOME AND TREATMENT STRATEGY

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Background: Unlike liver metastases, the role of surgery in colorectal cancer lung-limited metastasis (CCLM) is not yet established and data are still poor. We conducted a retrospective analysis to evaluate the management of CCLM at our Centre, prognostic factors and their impact on survival.
Material and method: We retrospectively analyzed patients (pts) with CCLM treated at our Institution from Jan-2006 to Jan-2019. Aim of the study was to evaluate the impact of clinical and pathological features on survival outcomes (DFS and OS). Differences were compared with the use of log-rank test andstatistically significant (p value <0.5) parameters at univariate analysis were included in the multivariate analysis.
Results: One-hundred and forty-four pts were included in the analysis. 70 pts received a preoperative chemotherapy (pCT), 56 an adjuvant chemotherapy (a)CT, while 18 underwent up-front surgery without CT. Seventy-three patients also received liver surgery, 57 before and 16 after lung surgery. In the whole population median DFS (mDFS) was 24 m (20-34) and median OS (mOS) 54 m (46-82), while mDFS and mOS were 20 m (13-34) and 53 m (33-82) for pts undergoing pCT and 23 m (15-31) and 65 m (42 – 204) for those receiving aCT respectively, without statistically significant differences. Among patients receiving both liver and lung surgery, mDFS and mOS were 21 and 54 months respectively. Age, gender, PS, disease-free interval (DFI) ($>$ or $<$18 months), primary tumor sidedness, mucinous histology, grading, *RAS* status, timing of lung metastasis (metachronous *vs* synchronous), number of lesions ($>$2), metastasis location (uni *vs* bilateral) and liver resection were evaluated at univariate and multivariate analysis. At univariate analysis, DFS was correlated with DFI $>$ 18m ($p=0.047$), timing ($p=0.03$) and number ($p<0.0001$) whereas OS was associated to number ($p=0.0005$) and *RAS* status ($p=0.05$). At multivariate analysis, number of lesions was the only factor correlated to DFS ($p<0.0001$) and OS ($p=0.0233$).
Conclusions: Our study, although retrospective and small-sized, strongly suggests that surgery of lung metastasis prolongs survival, since mOS is much higher when compared to that of patients treated in a metastatic setting in phase III randomized studies. These data strengthen the role of a multidisciplinary management to allow pts with lung-limited metastasis to achieve surgery whenever possible, even regardless of previous liver surgery and *RAS* status.

A16

AN ITALIAN OBSERVATIONAL, MULTICENTER, RETROSPECTIVE STUDY IN PATIENTS WITH STAGE IV RIGHT-SIDED COLON CANCER

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Background: Colorectal cancer is one of the leading cause of cancer death worldwide. Recently, primary tumor location has emerged as one of the factor that may influence prognosis and treatment response in the metastatic setting. Right-sided tumors are less prevalent than left-sided counterpart and seem to be associated with worse survival and resistance to anti-EGFR therapy.
Methods: this retrospective analysis investigated clinical outcomes of a population of patients (pts) with advanced right-sided colon cancer. PFS and OS were compared between 3 groups (group 1 RAS mut/BRAF WT, group 2 RAS WT/BRAF mut, group 3 RAS WT/BRAF WT) by using log-rank test.
Results: 194 pts were included in the analysis. Median age was 66.6 y/o. 104 pts (53.6%) were RAS mut/BRAF WT, 43 (22.2%) were RAS WT/ BRAF mut and 47 (24.2) were RAS WT/BRAF WT. In first-line 93 (47.9%) pts were treated with chemo plus bevacizumab, 43 (22.2%) with chemo plus anti-EGFR and 58 (29.9%) with chemo alone. Globally, 75 (38.7%) pts had an objective response (OR), median PFS and OS were 8.5 and 19.9 months, respectively. No statistical differences were observed in OR rate, median PFS and OS between group 1 and 3, while pts in group 2 had inferior outcomes. 17/32 (53.1%) pts treated with anti-EGFR in first-line (group 3) had an OR. No statistical difference were observed in PFS and OS according to first-line treatment.
Discussion: a relevant proportion of pts were treated in a real-world setting with chemotherapy alone. This can be due both to clinical (performance status, older age) and economic reasons. A significant proportion of patients with metastatic right-sided colon cancer were RAS WT/BRAF WT. These patients seem to benefit from the use of anti-EGFR in term of OR, while the choice of first-line treatment does not have any impact on survival. These data could be of particular interest in patients with potentially resectable disease who need tumor shrinkage.

Table. Summary of results.

Treatment	OR	Median PFS (months)	Median OS (months)
All patients	75/194 (38.7%)	8.5	19.8
Group 1	37/104 (35.5%)	9.5	22.3
Group 2	12/43 (27.9%)	6.0	13.4
Group 3	23/47 (48.9%)	8.0	19.2

A17

HEMOSTATIC BIOMARKERS PREDICT PROGNOSIS IN PATIENTS WITH METASTATIC GASTROINTESTINAL CANCER: RESULTS FROM THE HYPERCAN STUDY

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Background: Laboratory evidence of hypercoagulability and high incidence of thromboembolic events are often associated with low response to chemotherapy and disease progression (DP) in patients with gastrointestinal (GI) cancer, particularly in metastatic condition. In a cohort of patients with newly diagnosed metastatic GI cancer participating to the HYPERCAN study (ClinicalTrials.gov ID#NCT02622815), we aimed to prospectically assess whether the pre-chemotherapy levels of thrombotic biomarkers may predict for resistance to first line chemotherapy.
Materials and Methods: The study cohort included 160 consecutive cancer patients (100 colorectal/60 gastric) with a median age of 65 (41-78) years. Clinical data were recorded at enrollment and during scheduled follow-up visits for at least two years. DP was monitored by imaging at each time point. Fibrinogen, D-Dimer, and thrombin generation (TG) were measured at diagnosis, before starting any curative chemotherapy. The study protocol has been approved by the local Ethics Committee. Informed written consent was obtained from all study subjects.
Results: At diagnosis, patients presented with a hypercoagulable state, as shown by significantly ($p<0.01$) higher plasma levels of fibrinogen, D-Dimer and by increased endogenous TG potential (ETP) as compared to healthy control subjects. In the cohort of patients, cumulative incidence of disease progression after six months of follow-up was 23.7% (CI 95% 17-30.1). Analysis of thrombotic biomarkers according to DP, showed that patients with DP ($n=38$) were characterized by significantly ($p<0.05$) greater pre-chemotherapy levels of ETP compared to patients with no DP [2,050 vs 1,699 nM*min]. Furthermore, by multivariate Cox regression analysis, plasma levels of D-Dimer (HR = 1.08) and TG ETP (HR = 1.01), together with gastric cancer diagnosis (HR = 2.2), were identified as independent risk factors for DP.
Conclusions: Our data show that elevated levels of circulating thrombotic biomarkers and increased TG potential are associated with chemotherapy failure and DP in GI cancer patients. The possible role of these biomarkers for DP prediction is of utmost importance for treatment decision making and a more personalized approach to each patient. Further analysis are warrant to confirm the role of these biomarkers in DP prediction by a clinical risk assessment score model.
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A18

THE POTENTIAL PROGNOSTIC ROLE OF METABOLOMICS IN EARLY COLORECTAL CANCER (eCRC)

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Background: The prognosis of early colorectal cancer (eCRC) differs according to the stage of disease, informing the choice of adjuvant therapy. A significant proportion of patients (pts) who receive adjuvant chemotherapy derive no benefit from treatment. Therefore, biomarkers to improve risk stratification are urgently needed. Metabolomics allows to concurrently study multiple metabolites in body fluids, including serum. We used metabolomics to explore the potential prognostic role of metabolomic profiles in a prospective cohort of patients with eCRC (METCOLON Study).
Material and Methods: Pts with histologically proven stage I-III CRC, candidate for radical resection were prospectively enrolled in the study. Blood serum samples were taken from each patient before surgery (T0) and after surgery (T1) and these samples were analyzed using 1H-NMR spectroscopy to characterize the metabolomic profile. To investigate the differences of metabolomic profiles before and after surgery mPLS was applied.
Results: A total of 41 pts (11 stage I, 13 stage II, 17 stage III) were enrolled into the study between May 2017 and September 2018. At the time of the analysis pts median follow-up was 15 months. Tumor relapse was observed in 5 pts. Using the mPLS, serum samples were correctly classified between pre-operative (T0) and post-operative (T1), and showed significant differential clustering, with good separation of the two groups with the all 3 spectra CPMG, NOESY and DIFFUSION. Three metabolites were found to differ significantly ($p < 0.05$) between the pre- and post-operative metabolomic profiles: pyruvic acid was found higher in the T1 samples and the acetone and 3-hydroxybutyric acid in the T0 samples.
Conclusions: Metabolomic analysis correctly classifies pre- and post- operative serum samples of patients with

eCRC, suggesting that this methodology can identify tumor-related specific metabolites with a potential role for biomarkers in the adjuvant setting. The limited number of observed relapse events prevents our possibility of inferring prognostic information. With further maturity of the data, we plan to correlate intra-patient differences in metabolomic spectra between T0 and T1 with clinical outcome. A larger prospective clinical trial testing the prognostic role of metabolomics in patients with early and metastatic CRC is currently ongoing (LiBiMet).

A19

SAFETY AND EFFECTIVENESS OF REGORAFENIB (REG) IN ITALIAN PATIENTS WITH METASTATIC COLORECTAL CANCER (mCRC): A SUBGROUP ANALYSIS FROM THE PROSPECTIVE, OBSERVATIONAL CORRELATE STUDY

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Background: REG (160 mg daily, 3 weeks on/1 week off) is approved for the treatment of patients with mCRC refractory to standard therapies.CORRELATE (NCT02042144) evaluated the safety and effectiveness of REG for mCRC treatment in real-world clinical practice. Here we present the final results of the Italian patient subgroup.

Patients and methods: CORRELATE was a prospective, observational study conducted in 13 countries across Europe, Latin America, and Asia, and included patients with mCRC who were previously treated with approved therapies and for whom the decision to use REG was made by the treating physician according to the local health authority approval. The primary aim was to assess safety (treatment-emergent adverse events [TEAEs]; NCI-CTCAE v4.03). Secondary endpoints included overall survival (OS) and progression-free survival (PFS).

Results: Of 1037 patients, 193 (19%) were treated in 32 centers in Italy: 56% were male, the median age was 67 years (range: 30–84), most patientswere ECOG PS 0–1 (86%), and 62% had KRASmutations. Patients had received a median of 3 prior systemic treatments. The median REG treatment duration was 2.7 months (range: 0.03–13.4). The REG starting dose was 160 mg in 68% of patients, 120 mg in 18%, and 80 mg in 13%. Overall, 39% of patients had dose reductions,52% had an interruption/delay, while 33% had no dose modifications. Most dose modifications were due to AEs (69%). TEAEs of any grade and grade ⩾3 occurred in 94% and 59% of patients, respectively; REG related TEAEs of any grade and grade ⩾3 occurred in 78% and 39% of patients, respectively. The most common grade ⩾3 TEAEs were fatigue (15%), hypertension (10%), blood bilirubin increased (9%), and hand–foot skin reaction (8%). Grade 5 TEAEs occurred in 10% of patients, none of which were considered REG related. Median OS was 8.9 months (95% CI 6.5, not reached) and median PFS was 3.4 months (95% CI 3.1, 3.8).

Conclusions: The safety profile in this real-world, observational study was generally consistent with the known safety profile of REG in mCRC. Most patients started at the approved starting dose (160 mg/day). Outcomes were in the range of those previously observed in phase 3 trials.
Clinical trial registration: NCT02042144

A20

EXOSOMES AS NOVEL PROGNOSTIC BIOMARKER IN POTENTIALLY RESECTABLE COLORECTAL CANCER LIVER METASTATIC (CCLM) PATIENTS

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Background: Target therapies and new surgical strategies deeply modify CCLM history. Several prognostic scoring systems have been developed but no one is able to identify patients (pts) who should be excluded from a potentially useless surgery. The current goal of research is to identify early biomarkers able to discern pts who could benefit from an aggressive approach. Exosomes are arising as promising biomarkers in cancer. The aim of this pivotal study was to analyze the association among exosome levels during CCLM-pts treatment, clinical outcomes and Kras status.

Material and Methods: We enrolled 22 pts with CCLM candidate to preoperative chemotherapy (pCT) and subsequent liver surgery. A blood sample was collected before pCT, after surgery, monthly during follow-up and at progression (PD). Exosomes were isolated by ultracentrifugation and characterized by standard methods. Exosomes concentration was assessed by Bradford assay. We adopted ddPCR™ KRAS G12/G13 Screening Kit to evaluate the status of Kras in exosomal DNA (e-DNA).
Results: 22 CCLM pts received pCT and underwent liver surgery: 5 major hepatectomies and 17 multiple liver resections. Changes in exosomes plasma levels were found to correlate with each treatment step, resulting reduced after pCT and surgery and increased at PD, respectively ($p=0.0026$). Pts with higher baseline exosome levels experimented shorter PFS than those with lower levels ($p=0.0033$ HR 0.2). No association was found between exosome levels after liver surgery and disease free interval nor overall survival. RAS status on e-DNA was evaluated on 10 pts in baseline, in pCT, after surgery, and in PD samples. In 8 out of 10 pts e-DNA displayed the same mutational status than the one detected on tumor DNA. Changes in e-DNA Kras copies were found statistically significant in pCT vs surgery and pCT vs PD ($p=0.039$; $p=0.04$).
Conclusion: Our study suggests a prognostic role of exosome levels in CCLM pts. Moreover, we showed that Kras mutational status could be monitored during the post-surgery follow up by analyzing e-DNA. Overall, our data confirm the potential role of exosomes in liquid biopsy tool to monitor molecular changes during the treatment of CCLM pts.

A21

CORRELATION BETWEEN VALUES OF SPECIFIC BIOMARKERS AND OUTCOME IN METASTATIC COLORECTAL CANCER (mCRC) PATIENTS TREATED WITH REGORAFENIB

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Background: Regorafenib is an oral small-molecule multiple kinase inhibitor indicated as third-line treatment for metastatic colorectal cancer (mCRC) patients. Regorafenib has shown significant benefits in Overall Survival (OS) and Progression-Free Survival (PFS) compared to placebo in mCRC patients in two phase III trials. This study aims to evaluate the role of specific biomarkers potentially involved in the clinical activity of regorafenib.

Material and methods: We determined the concentration of 6 proteins of interest in plasma samples collected from 17 mCRC pts before starting regorafenib (baseline).The proteins selected are: VEGF, TNF-a, TGF-ß, CCL2, CCL4, and CCL5. They were analysed with ELISA test.The values obtained were compared with the values of 7 healthy controls, in order to evaluate the differences in the concentration of the cytokines examined. All analysis were performed using GraphPad (Version5). Additional ongoing analysis include other cytokines.
Results: We found that plasma basal level of TNF-α ($P=0.011$), TGF-β ($P=0.031$) and CCL-5 ($P=0.31$) are significantly higher in Non responders compared to Responders (complete response $n=1$, partial response $n=1$ or Stable Disease SD $n=3$). Moreover, plasma basal levels of CCL-4 are lower in NR compared to R patients. NR patients have also shown slightly higher level of VEGF and CCL-2 compared to R. Plasma concentration of VEGF, CCL-2, CCL-4, CCL-5 are higher in R compared to healthy controls. Furthermore, TGF-β negatively correlates with PFS ($P=0.038$). According to ROC analysis, there was also improvement in PFS (5.2 vs. 2.57 months, $P=0.005$). We observed also significant better OS in the same patterns (16.6 vs. 7.3 months, $P=0.010$). These results might discriminate mCRC patients that will respond better to the treatment.
Conclusions: Our data show that in R pts the baseline cytokine signature approaches the values observed in healthy volunteers. On the contrary, pts that do not benefit by the treatment can be identified by a different cytokines profile. However, it must be stressed that our population is small and data should be verified on a larger number of pts. It might also be of interest to extend analysis to other cytokines and cells population not yet determined in our study.

A22

PREDICTIVE AND PROGNOSTIC FACTORS IN LOCALLY ADVANCED RECTAL CANCER PATIENTS: A USEFUL TOOL FOR PERSONALIZED TREATMENT SELECTION?

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Background: Neoadjuvant chemoradiation (CRT) is the standard treatment of locally advanced rectal cancer (LARC). However, although beneficial for most patients, a significant fraction derives no response from CRT. Knowledge of predictive and prognostic factors at the time of diagnosis is scant.

Methods: Data of LARC patients treated at Candiolo Cancer Institute between Oct 2010 and Apr 2017 were retrospectively analysed to assess the correlation of a diverse variables with median overall survival (OS) and with pathologic response to CRT assessed by Mandard tumor regression grade (TRG, considering TRG=2 a good response and=3 a poor response).
Clinicopathologic variables embraced age, sex, BMI, distance of the neoplasm from the anal margin (AM), standard pathological report, time interval between CRT and surgery, adjuvant chemotherapy, site of progression and pre- and post-CRT carcinoembryonic antigen (CEA), pre-CRT platelet count and neutrophil/lymphocyte ratio (NLR).
Radiological and nuclear variables - from pre- and post-CRT MRI and pre- CRT PET scan - included tumor circumferential extension, mesorectal fascia (MRF) involvement, metabolic volume (MV), total glycolytic volume (TGV) and median standardized uptake value (mSUV).
Results: Data from 75 clinical histories were retrieved; median follow-up was 36 months.
Age ⩽65 years (P=0.02), pre-CRT MRI tumor circumferential extent ⩽50% (P=0.01), pre-CRT CEA ⩽5.0 ng/ml (P=0.015) and mSUV <4.9 (P=0.03) independently predicted good response on multivariate analysis. On univariate analysis only, distance from AM>5 cm was a positive predictor, while MV>55 and TGV>215 predicted poor response.
Good responders (n=28) experienced longer OS than poor responders (n=47; P=0.01). OS was 81, 79 and 41 months in TRG⩽2, 3 and 4 groups, respectively.
While the pathological finding of vascular invasion was significant on univariate only, post-CRT MRF involvement (P=0.039), an elevated (>4) NLR (P=0.037), grade=3 tumor (P=0.001) and positive resection margins (P=0.01) retained a significant adverse prognostic impact on multivariate analysis.
Conclusions: To our knowledge, this is the first attempt to evaluate diverse classes of features for a prediction study in LARC. A limited number of predictors of response to CRT and a non-overlapping set of prognostic factors were identified. Upon validation on a larger dataset, these factors may help to personalize the therapeutic algorithm in LARC.

A23

CHEMOTHERAPY-INDUCED CARDIOTOXICITY AND RISK FACTOR CORRELATION IN PATIENTS WITH COLORECTAL CANCER RECEIVING FLUOROPYRIMIDINE TREATMENT

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Background: Fluoropyrimidines (FP), 5-fluorouracil (5-FU) and capecitabine, are essential agents in the treatment of colorectal cancer (CRC). Despite being considered well-tolerated drugs, cardiotoxicity represents a rare but potentially fatal adverse event. The reported incidence of cardiovascular (CV) events during 5-FU or capecitabine administration varies greatly among different studies in patients treated with FP. The most frequently reported symptoms are chest pain, palpitations, dyspnea and hypotension. The mere presence of these symptoms is sufficient in most studies to ascribe the case to fluoropyrimidine-induced cardiotoxicity (FIC). Moreover, the correlation between presence of CV risk factors (CV-RF) or cardiac comorbidity and incidence of FIC is not clear.
Primary objective: The aim of this study is to evaluate prospectively the incidence of FIC in cancer patients treated for the first time with FP and to identify predisposing risk factors.
Study design: FP-naïve CRC patients (pts) treated at our Institute were evaluated for CV-RF and preexisting CV comorbidities and treated before starting chemotherapy (CT). Patients were followed during FP treatment with seriated electrocardiograms, questionnaires on the symptoms and analysis of troponine I (TnI) and brain natriuretic peptide (BNP) measurements at day 1 and 3 of the first 3 cycles of CT (observation period).
Result: Data from the first 101 patients enrolled from January 2016 to April 2019 are presented 43.3% had 3 or more CV-RF (among BMI >25, smoker, heavy drinker and sedentary life-style) and 77,5% had at least one CV comorbidity at screening. During the treatment period 19 pts (18.8%) experienced FIC: 1 acute coronary syndrome (ACS), 1 coronary vasospasm, 1 paroxysmal supraventricular tachycardia (PSVT), 1 complete left bundle branch block (LBBB), 2 syncope, 4 typical chest pain, 6 sudden wheezing 3 sudden palpitations. After treatment of the CV events, only 3 pts discontinued FP (ACS, LBBB and PSTV). No further cardiac events occurred in patients who resumed treatment after being diagnosed with FIC. No difference in FIC incidence was observed according to sex or CT type (capecitabine vs 5-FU) (all Fisher's exact test p>0.05).
Discussion: Preliminary data suggest the lack of excess risk of FIC in patients with CV-RF or cardiac comorbidities and the safety of the reintroduction of FP after a CV event.

A24

LIQUID BIOPSY FOR RAS ASSESSMENT IN METASTATIC COLORECTAL CANCER (MCRC) PATIENTS USING HIGH-AFFINITY PLASMA DNA-BINDING MAGNETIC BEADS AND QUALITATIVE REAL-TIME PCR PRECEDED BY MUTANT ALLELE ENRICHMENT

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Background: Plasmatic RAS testing of cancer cell free DNA is increasingly being used to rapidly assess mCRC mutational status and monitor biological evolution of the disease during the course of treatment.
Methods: Broadly available kits of plasma DNA-binding magnetic beads (MagCore® Plasma DNA Extraction Kit) and post-mutant allele enrichment qualitative Real-Time PCR for RAS mutations (EasyPGX® ready KRAS and NRAS Kit) were used to assess at baseline circulating RAS status and compare it to the gold standard (tumor tissue RAS status) in consecutive mCRC patients. Sensitivity, specificity and prognostic value of the liquid biopsy were determined. Either tissue or plasma BRAF mutated patients were excluded from the analysis
Results: Enrolled mCRC patients (n=21, female 6, male 15) had a median age of 63 years (range 38-83), and were all candidate for first-line standard chemotherapy. According to liquid biopsy, the prevalence of RAS mutation was 33% (7 mutated cases=3 of KRAS codon 12, 1 of KRAS codon 13, 1 of KRAS codon 61, 2 of NRAS codon 61). As compared to the gold standard of tissue mutations, only two cases of discordant results were observed (1 NRAS codon 61 mutation in the plasma but not in the tissue and 1 KRAS codon 13 mutation in the tissue but not in the plasma). All RAS concordant cases were also concordant for the specific RAS mutation subtype. Sensitivity and specificity of the liquid biopsy were 86% and 93%, respectively. Determined AUC was 0.893. Positive and negative Likelihood Ratios were 12.000 (1.772-81.261) and 0.154 (0.025-0.950), respectively. Positive and negative predictive values were 86% and 93%, respectively. After a median follow-up of surviving patients of 8.7 months, progression free survival (PFS) was shorter in liquid-biopsy defined RAS mutated patients as compared to wild type patients (median PFS 5.6 vs 9.8 months, respectively, Hazard Ratio 1.92, p value non significant because of the small sample size)
Conclusions: Liquid biopsy for RAS mutations using broadly available kits of high-affinity plasma DNA-binding magnetic beads and qualitative Real-Time PCR preceded by mutant allele enrichment was feasible and yielded high sensitivity and specificity testing performance. Liquid biopsy-determined RAS status was confirmed to be of prognostic value even though sample size needs further increase. The value for monitoring disease biological evolution requires further investigation.

A25

TOXICITY SYNDROMES, PATIENT-RELATED CLINICAL INDICATOR OF TOXICITY BURDEN INDUCED BY INTENSIVE TRIPLET CHEMOTHERAPY-BASED REGIMENS IN METASTATIC GASTROINTESTINAL CANCERS

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Background: Cancer treatments induce symptoms/signs superimposing on clinical and cancer-related status of individual patient, determining heterogenous toxicity syndromes (TS). We reviewed intensive first line triplet chemotherapy-based regimens developed in fit metastatic gastro-intestinal cancers (mGI), based on FIr/FOx schedule including fluorouracil and weekly alternating irinotecan/oxaliplatin, to point out clinical relevance of integration of limiting TS (LTS).
Patients and methods: Metastatic colo-rectal (mCRC), pancreatic ductal adenocarcinoma (mPDAC), gastric carcinoma (mGC) patients were enrolled by careful decision-making in real life phase II studies: FIr-B/FOx adding bevacizumab (B) in overall, FIr-C/FOx-C adding cetuximab (C) in KRAS/NRAS wild-type mCRC; FIr/FOx in mPDAC; FD/FOx adding docetaxel (D) in mGC. Toxicity, and individual LTS, classified as limiting toxicity alone (LTS-single site, LTS-ss) or associated to other limiting or G2 toxicities (LTS-multiple sites, LTS-ms) were evaluated and compared by chi-square test. More, in FIr-C/FOx-C study, 5-fluorouracil/irinotecan pharmacogenomic biomarkers, specifically 5-fluorouracil degradation rate (5-FUDR), Single Nucleotide Polimorphisms (SNPs) ABCB1, CYP3A4, DYPD, UGT1A1 were evaluated and related with LTS occurrence.
Results: FIr-B/FOx and FIr-C/FOx-C in mCRC, FIr/FOx in mPDAC, FD/FOx in mGC, respectively showed activity, efficacy, limiting toxicities similar to reported triplet chemotherapy-based regimens. Reported LTS: in mCRC FIr-B/FOx 44%, LTS-ms 24% and LTS-ss 20%, in young elderly (yE) 46%, LTS-ms significantly increased vs LTS-ss; in KRAS/NRAS wild-type mCRC FIr-C/FOx-C

65.5%, significantly increased LTS-ms vs LTS-ss, in yE 83%; in mPDAC FIr/FOx 27.5%, mostly LTS-ms, in yE 38.4% all LTS-ms; in mGC FD/FOx 30%, all LTS-ms, in yE 25%. Reduced FUDR, SNPs CYP3A4, UGT1A1, >1 positive pharmacogenomic biomarkers were prevalent in patients with gastrointestinal LTS.

Conclusions: LTS met the need of an innovative clinical parameter of patient-related toxicity burden, indicating global and individual toxicity, including differential spectrum/intensities of TS related to cancer treatment, according to clinical status of individual patient. LTS integrated with conventional toxicity can also represent the proper indicator to evaluate predictive relevance of pharmacogenomic biomarkers to properly select patients fit for intensive medical treatments in mGI cancers, at risk of limiting gastrointestinal toxicity.

A26

GENDER-RELATED CUT-OFF DEFINITION AND PROGNOSTIC ROLE OF MONOCYTE-TO-LYMPHOCYTE RATIO (MLR) IN METASTATIC COLORECTAL CANCER

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Background: Gender-related immune system composition influences immune response and, subsequently, efficacy of immunotherapy in cancer patients (pts). The purpose of this study is to investigate the gender-related prognostic role of MLR in metastatic colorectal cancer (mCRC) pts, defining at the same time a gender-specific cut-off value.

Material and methods: This retrospective study analyzed a consecutive cohort of 490 mCRC pts treated in 2004-2017 at the Oncology Departments of Aviano, Pordenone (training set) and Udine (validation set), Italy. Association analysis was explored by Chi-squared or Kruskal-Wallis test, as appropriate. The prognostic impact of MLR on overall survival (OS) was evaluated with uni- and multivariable Cox regression models. The best cut-off value to predict survival was determined through a ROC analysis.

Results: We identified 288 males and 202 females; 324 pts (67%) had a left-sided cancer and 161 (33%) a right-sided one. Sex was significantly associated with MLR ($p = 0.004$). The obtained cut-off value for MLR in females was 0.27 and in males was 0.49. Univariate analysis of the training set showed a poorer OS for females when MLR was >0.27 (HR 1.95, $p = 0.003$) and in males when MLR was >0.49 (HR 2.65, $p = 0.010$); this was confirmed in the validation set for the values of MLR >0.27 in females (HR 2.21, $p = 0.010$) and MLR >0.49 in males (HR 2.99, $p = 0.002$). Overall, high MLR was more frequently detected in females than in males (41% vs 9%). At univariate analysis on overall population, MLR >0.27 in females (HR 2.07, $p \leq 0.001$), MLR >0.49 in males (HR 2.87, $p \leq 0.001$), KRAS (HR 1.37 $p = 0.008$) and BRAF mutations (HR 1.69 $p = 0.009$), sidedness (right vs left HR 1.59, $p \leq 0.001$) and peritoneal metastases (HR 2.32, $p \leq 0.001$) were associated with shorter OS. Conversely, primary tumor resection (HR 0.37 $p \leq 0.001$) was associated with prolonged OS. Multivariate analysis confirmed the association of MLR >0.27 in females (HR 2.77, $p = 0.002$), MLR >0.49 in males (HR 5.39, $p \leq 0.001$), BRAF mutation (HR 3.38, $p \leq 0.001$) and peritoneal metastases (HR 2.50, $p = 0.003$) with worse OS.

Conclusions: Our findings suggest that the impact of high MLR as unfavorable independent prognostic factor is significant both in males and females. Higher MLR was found more frequently in females. Further prospective studies are needed to confirm these data.

A27

SQUAMOUS CELL CARCINOMA ANTIGEN (SCCAG) AND CARCYNOEMBRIONIC ANTIGEN (CEA) AS PROGNOSTIC BIOMARKERS IN ANAL SQUAMOUS CELL CARCINOMA (ASCC): THE EXPERIENCE OF A SINGLE RESEARCH CANCER CENTER

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Background: Many efforts are ongoing to individuate biological characteristics suitable for targeting new medical approaches for ASCC. Currently different biomarkers emerged, but their ability to predict clinical outcome is still unclear. Among them, SCCAg firstly identified in malignant cervical tissue was also found in anal tumors, with conflicting data about its correlation with survival. Serum CEA level was evaluated also in patients with ASCC undergoing combined chemoradiotherapy, without demonstrating any correlation with outcome.

Patients and methods: We performed a retrospective study on 53 consecutive patients affected by non-metastatic ASCC and treated with cisplatin (CDDP) or mitomycin

Table 1. Patient characteristics for stage and biomarkers levels (N = 53).

	Normal CEA	High CEA	Normal SCCAg	High SCCAg	Normal CEA+ SCCAg	Normal CEA, high SCCAg	High CEA, normal SCCAg	High CEA+ SCCAg
stage								
I	1 F (MMC-5FU)*	_____	1 F	_____	_____	1 M (C)*	_____	_____
II	1 M, 5 F	_____	6 F	3 F	1 M (C)*	_____	_____	_____
IIIA	1 M, 4 F	2 F	4 F	1 M, 1 F	1 M, 1 F	1 F	_____	_____
IIIB	5 F (1 MMC-C)*	1 F	3 F	2 F	1 F	6 F	_____	_____

*All patients received CDDP-C except for 4 cases. F: female; M: male.

(MMC) plus 5-fluorouracil (5FU) or capecitabine (C) concomitant to pelvic Intensity-Modulated Radiation Therapy (IMRT) for curative intent, with the aim to evaluate the prognostic role of baseline SCCAg and CEA serum values in this setting.

Results: Patient characteristics are shown in Table 1. At a median follow up of 48 months, among 32 evaluable patients the Complete Response (CR) obtained at the 6-month time-point was 86% (25/29) in the group with normal basal CEA and 0% (0/3) in the group with high CEA (p = 0.007). Hazard ratios (HRs) resulted 0.30 for Disease-free Survival (DFS) (95% CI 0.02-3.41; p = 0.03) and 0.34 for Overall Survival (OS) (95% CI 0.01-8.65; p = 0.27) in favor of normal values, respectively.

Among 33 evaluable patients, the CR at the 6-month time-point was 89% (16/18) in the group with normal basal SCCAg and 93% (14/15) in the group with high SCCAg (p = 1.0). HRs resulted 0.38 for DFS (95% CI 0.1-1.45; p = 0.13) and 0.10 for OS (0.006-1.69; p = 0.11) in favor of normal values.

Conclusions: SCCAg and CEA appear interesting biomarkers in ASCC and in our setting CEA levels more markedly seem to correlate with response and survival. Further prospective studies are necessary to confirm these observations.

A28

PROGNOSTIC ROLE OF K-RAS MUTATION RATE IN STAGE II-III CRC PATIENTS

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Background: No data about the prognostic value of K-Ras mutation rate, defined as the percentage of mutated alleles/tumor sample, are available in stage II-III CRC, while it has been already investigated in metastatic stage. We aimed to retrospectively evaluate the correlation between K-Ras mutation rate and DFS in a cohort of relapsed K-Ras mutant stage II-III CRC pts.

Material and Methods: 80 relapsed stage II-III CRC patients from 2 Italian cancer centers were enrolled but only 66 patients (21 pts affected by radically resected rectal cancer and 45 colon cancer pts) were fully evaluable. K-Ras mutation rate was assessed in each center by pyrosequencing on tumor tissue specimen derived from resection of primary tumor. We investigated prognostic significance of different cut-off values of mutation rate corresponding to the first quartile, median value and 25%. Pts with less than 40% of cancer cells in tumor tissue were excluded.

Results: The median KRas mutation rate in the entire cohort was 36.75% and no significant correlation has been evidenced with DFS and OS at univariate analysis. We explored the prognostic role of K-Ras mutation rate according to different cut-offs. More in details, the univariate analysis revealed that CRC pts with K-Ras mutation rate < 29% (n = 15), corresponding to the first quartile cut off, had worse DFS comparing to pts = 29% (n = 51) (12.9 vs 18.3 months, log-rank p = 0.03); moreover CRC pts with KRas mutation rate < 25% (n = 11) maintained a worse DFS comparing to pts = 25% (n = 55) (12.3 Vs 19 months, log-rank p = 0.002). A subgroup univariate analysis exploring the value different cut-offs of K-Ras mutation rate in colon cancer pts (n = 45), who did not received any preoperative treatment, confirmed that low K-Ras mutation rates (< 29.55% or < 25%) correlate with worse DFS. There was no correlation between OS and the previously examined cut-offs.

Conclusions: Our retrospective study, for the first time in literature, showed that low K-Ras mutation rate could be a negative prognostic factor in K-Ras mutant stage II-III CRC pts. Moreover, low K-Ras mutation rate could represent an indirect estimation of high intratumoral stroma and mutational heterogeneity, which are interesting factors affecting prognosis of stage II and III CRC. These data deserve to be verified in larger studies.

A29

RETROSPECTIVE STUDY ON REAL-WORLD USE OF REGORAFENIB IN COLORECTAL CANCER IN THE EMILIA-ROMAGNA REGION: CORE-GI-01 PRELIMINARY RESULTS

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Background: Regorafenib is a multitargeted inhibitor that blocks angiogenesis, oncogenesis and stromal protein kinases and is approved for the treatment of colorectal cancer. To date there are limited data on the real-world adherence to treatment.

Methods: This is a multicentric retrospective study on patients (pts) with colorectal cancer previously treated with regorafenib in any setting in Emilia-Romagna Region. The aim of the study was to evaluate adherence to treatment, effectiveness and safety. Descriptive statistics are reported for patient/tumor/treatment characteristics, and observed Adverse Events (AEs) were graded by CTCAE v. 4.03. The Kaplan-Meier analysis was used for duration of treatment (DT) and overall survival (OS).

Results: 144 pts were treated from December 2013 and June 2017. Of these, 81.3% had non-mucinous histology, 45.1% had tumor located in left colon, 29.2% in rectum, 54.2% were KRAS mutated. Median age was 63 years (range 28-85), and 79.9% of pts had Performance Status 0-1. 68% of pts had liver metastasis. The median of previous systemic anticancer therapies was 2.6 (range from 1 to 5), and the trend shows that in 2016-2017 regorafenib was mostly used in third- and fourth-line treatment. Precisely 7% were in second-line, 47.6% third-line, 28.7% fourth-line, 11.9% fifth-line, and 4.9% sixth-line. 69.4% of pts started treatment at full dosage of 160mg/day, while 17.4% started at 120mg/day. There was no need for treatment reduction in 49.3% of pts. Patients reduced treatment due to all grades of toxicities: hand-foot syndrome (6.9%), fatigue (6.9%), diarrhea (6.2%), mucositis/stomatitis (4.2%). Treatment was interrupted due to disease progression (75.7%) and toxicity (8.3%). Median duration of treatment was 3.2 months (CI95% 2.7-3.8 months). Median overall survival was 5.5 months (CI95% 4.3-6.7 months). Grade 3-4 toxicities were experienced in 30.5% of patients. The most frequently observed G3-4 AEs include fatigue (6.9%), hand-foot syndrome (5.5%), and diarrhea (3.5%).

Conclusions: The frequency and severity of AEs were consistent with the known safety profile of regorafenib. OS was similar to reports of phase III trials. Over time, the management of adverse events in daily practice has improved. We learned to better select patients by anticipating the use of the drug in earlier lines. In this way, with the best management of adverse events, it was possible to avoid dose reductions at the beginning as well as in subsequent cycles.

A30

ROLE OF GENETICS POLYMORPISMS OF MTHFR AND DPYD IN PREOPERATIVE 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 to select the best chemotherapy or chemo-radiotherapy tratment for the individual patient (pz) and the best surgical tretment. 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.

Materials and methods: We have enrolled twenty- four patients with locally advanced RC treated with pre-operative radiotherapy and 5- fluorouracil based 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. This genetics markers were correlated with toxicity to treatment (chemotherapy and radio-chemotherapy) and clinical response.

Results: Patients characteristics were: male 21 pts, female 3 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 15% of pts, MTHFR C677T homozygous mutated in 50% of pts, heterozygous MTHFR A1298C in 70% of pts and homozygous wilde type MTHFR A 1298C in 40% of pts. G3-G4 advers events (diarrhea, neutropenia, asthenia, mucositis,

bleeding) were observed in 50% of pts with heterozygous MTHFR A 1298C and in 10% of pts with homozygous mutated MTHFR C 677t. treated with chemo and/or 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 13 clinical complete response and 11 partial clinical response. Adjuvant chemotherapy has been planned especially in patients with partial remission of disease and was well tolerated without G3-G4 adverse events. Ten pts with patological complete respose were treated with Transanal Endoscopic Microsurgery (TEM) and they are currently in close follow-up.

Conclusions: Concomitant assesment of genetic polymorphisms of MTHFR and DPYD is promising to predict severe toxicity during preoperative treatment approach for pts with locally advanced rectal cancer.

A31

SURVEY ON TREATMENT WITH TAS 102 IN PATIENTS WITH METASTATIC COLORECTAL CANCER

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Introduction: Trifluridine/tipiracil (TAS102) is a new drug that has been shown to have a moderate activity and efficacy with an acceptable toxicity profile in the treatment of metastatic colon cancer beyond the second lines. In Sicily TAS102 has been used since July 2018. We conducted a survey in 18 Sicilian oncological centers to evaluate from July 2018 how oncologists employ this drug and which type of toxicity was experienced by patients (pts).

Materials and methods: We asked the oncologists to evaluate six questions: how many pts they have treated or are still on treatment with TAS 102, how many pts were over 75, how many pts received the drug on the third line, which drug they were more likely to use on the third line, which G3/G4 toxicity they have detected and which dose of TAS102 they use.

Results: The survey showed that in 18 centers 223 pts with mCRC received TAS102. 52% were over 75 years old (117), 60% (134) of the pts received the drug as third line. 89% of interviewed Sicilian oncologists prefer to use TAS 102 as third line (11% Regorafenib) and 67% of these start with the standard dose. Detected toxicity =G3 was mostly hematologic with neutropenia 38% and anemia 11%.

Conclusions: Thanks to this survey we have tested the Sicilian oncological network and it has been proved that TAS 102 is adequately and correctly used, although it was introduced later than in other Italian regions. No unexpected toxicity emerged from this real life experience on the use of this drug and it also seems to be well tolerated by elderly pts (over 75) who represent about half of the examined population.

A32

CLINICOPATHOLOGICAL FEATURES IN RELATION TO TUMOR LOCATION IN ELDERLY PATIENTS (⩾ 70 YEARS OLD) WITH METASTATIC COLORECTAL CANCER (mCRC): A RETROSPECTIVE SINGLE-INSTITUTE ANALYSIS

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Background: Aging is one of the factors we need to take into account in defining a comprehensive strategy of CRC treatment. Elderly patients (pts) with CRC tend to be under-presented in clinical trials and undertreated in clinical practice.

Materials and methods: We retrospectively reviewed the records of mCRC pts who underwent first-line therapy from 2011 to 2018 at our institute. We also examined the subgroup of pts aged ≥70 years. The aim was to analyse the correlation between the clinicopathological features and tumor location in terms of gender, RAS status, grading, T, N, adjuvant therapy, metastatic pts at diagnosis, chemotherapy regimens and monoclonal antibodies (Abs) use.

Results: Overall, 130 pts were considered eligible: 93 left-sided CRC (LCC) and 37 right-sided CRC (RCC). We analyzed the subgroup of pts aged 70 or over (36 pts) too: 15 RCC and 21 LCC. M/F = 19/17, median age 76 years (y) (70-82). 21 LCC (8 RAS-wt, 11 RAS-mut, 2 not tested) and 15 RCC (6 RAS-wt, 8 RAS-mt, 1 not tested). There were no significant differences in terms of grading and T3-T4 status (33.3% G3, 60.0% T3 and 26.6% T4 vs 38.0% G3, 61.9% T3 and 33.3% T4, respectively). The highest incidence of N+ in RCC pts was confirmed (86.6% vs 76.1%). We noted a higher percentage of LCC in elderly pts (58.3% vs 41.6%), particularly in the males (57.1% vs 46.6%) whereas a higher incidence of RCC was confirmed in the females (53.3% vs 42.8%). The principal tumor site

was rectum-sigmoid junction (19.4%). There were no significant differences about metastatic pts at diagnosis (27.7% RCC vs 33.3% LCC) while 13.8% RCC pts vs 25% LCC pts underwent prior adjuvant therapy. Liver only metastases were more observed in RCC pts (40% vs 23.8%), liver + other metastases more in LCC pts (28.5% vs 13.3%); no differences about all the other metastatic sites (27.7% vs 33.3%) had been found. The most used chemotherapy regimens were doublets compared to fluoropyrimidines alone (particularly in LCC pts 85.7% vs 14.2%). Bevacizumab use has prevailed in both sides.

Conclusions: With the limit of the sample size, considering the increased fragility of elderly patients caused by multiple pathophysiological factors and comorbidities, our data confirm that age is not necessarily an absolute contraindication to adjuvant or palliative combination chemotherapy and the use of targeted therapies. Further studies are needed about tumor location in this population in order to develop a standardized treatment of elderly patients with CRC.

A33

DEPARTMENT OF ONCOLOGY (DO) OF AZIENDA USL TOSCANA NORD OVEST (ATNO): TRIFLURIDINE/TIPIRACIL (T/T) (LONSURF ®) EXPERIENCE IN METASTATIC REFRACTORY COLORECTAL CANCER PATIENTS (mr-CRC-P)

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Background: The DO of ATNO with its 5 Divisions of Medical Oncology, covers a catchment area of more than one million and three hundred thousand of people, over a third of the Tuscan population. The possibility of having a large and unique database allows for extensive analysis, crossing the data from the department of the drug and the pathological anatomy with those from clinical setting. In this report, we report our initial experience with T/T in an unselected population of mr-CRC-p.

Patients and methods: We considered the first group of patients treated with T/T. All patients included in this analysis were not candidates for further treatment with available therapies, due to a progressive disease within three months from the end of the last treatment.

Results: A total of 28 mr-CRC-p were included, 18 (64%) males and 10 (36%) females; median age was 67 years (range 30-80); performance status ranged between 0 and 1; median number of cycles was 2 (range 1-6); RAS mutation was in 12 (42%) patients. A stable disease was observed in 11 (39%) patients, a partial response in 3 (11%) and 14 (50%) patients experienced a progression of disease. Of note, the patients with the partial response were previous heavily treated with chemotherapies and refractory to fluoropyrmidines. Median progression-free survival was 2.5 months (range 1-7+); at median follow-up of 8,5 months, median overall survival was 7.5 months (range 2-9+). Treatment was generally well tolerated and T/T was interrupted only for a disease progression. G3 neutropenia was the most frequent adverse event, observed in 14 (50%) patients.

Conclusions: These results seem to confirm those reported in literature when mr-CRC-p are treated with T/T. However, more than 50% of patients interrupt treatment too early. So, more efforts needed to better select patients candidate to T/T. For this reason, taking into account that many other patients are expected to be treated in ATNO in a short time, we have planned a Next Generation Sequencing (NGS) analysis with a 45-gene panel to investigate possible molecular predictive factors to improve response to T/T.

A34

PROGNOSTIC ROLE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) AND PATHOLOGICAL RESPONSE (PR) IN LOCALLY ADVANCED RECTAL CANCER (LARC) TREATED WITH NEOADJUVANT CHEMORADIOTHERAPY (CRT)

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Introduction: In Italy Colorectal cancer (CRC) is still one of the most common malignancy with 51.000 new cases observed in 2018. About 30% of these new cases are rectal cancers. Preoperative chemoradiotherapy (CRT) is the standard treatment for locally advanced rectal cancer (LARC) before surgery. Few studies have reported data of the prognostic significance of neutrophil-to-lymphocyte ratio (NLR) in patients with rectal cancer. A lot of studies relates the raise of NLR to the poor survival of patients

with rectal cancer (RC). Nowadays, the greatest number of scientific publications regards the Asian population. We retrospectively investigated the relationship between NLR and response to neoadjuvant treatment.
Material and methods: From July 2017 to April 2019 we consecutively treated 39 patients (pts) with LARC with capecitabine (825 mg/mq/bid) and concomitant RT. Subsequently patients received radical surgery. Baseline clinical and radiological staging was T4N0 for one patient (pt); T3 N1 for 17 pts, T3N0 for 18pts, T2N1 1 pt and T2N0 for 2 pts. Before starting CRT (baseline), we collect white blood cell count (WBC), absolute neutrophil count (ANC) and absolute lymphocyte count (ALC). NLR was calculated as ANC/ALC. NLR = 3 was defined high. NLR was related to patological tumor response (sec.AJCC/CAP). We made a comparison between pre-CRT NLR and post-CRT NLR, gathering pts in four subgroups.
Results: At baseline NLR was < 3 in 24/39 (62%) and a NLR = 3 15/39 (38%) respectively. A 0 TRG was recorded for 7 pts with NLR = 3 (46%) and for 13 pts with NLR < 3 (54%). The percentage of lymphocytes in the total WBC population was higher in pts with pCR than that without pCR. One pt with NLR = 6 showed disease progression, in this case percentage of lymphocytes was low (13%).
Conclusions: Our data suggest that baseline low NLR could be an indication of a good pathological response but our cohort is too small to have statistical relevance. Other studies with numerous samples are needed to validate the prognostic meaning of NLR as prognostic marker in pts with LARC who received CRT.

A35

CIRCULATING-FREE DNA ANALYSIS FROM LONG-TERM SURVIVING METASTATIC COLORECTAL CANCER PATIENTS UNDERGOING SURGERY FOR RESECTABLE DISEASE

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Background: Liquid biopsies (LB) allow monitoring of genetically different and co-occurring cancer cell clones present in primary tumor and all metastatic sites in parallel. In metastatic colorectal cancer (mCRC), circulating-free DNA (cfDNA) can be relevant for monitoring treatment and identification of molecular alterations resulting in disease relapse often earlier than radiological examinations.
Patients and methods: Patients with mCRC at diagnosis and treated with chemotherapy (CT) in combination with antibodies (bevacizumab, cetuximab or panitumumab) before undergoing surgery for resectable disease were included in this study. LB were collected before therapy start, every four weeks during treatment, within ten days of radiological disease evaluation, at radiological relapse and until two months after relapse. Next generation sequencing based on plasma samples was performed (testing for mutations and copy number variations covering 77 genes).
Results: From February 2016 to October 2018, 14 patients having surgery after first line treatment were included herein; median follow-up was 21.5 months. Five of them had RAS wild-type disease and received CT plus anti-EGFR treatment, while nine RAS mutated mCRC patients received bevacizumab. Surgery was radical in 10 cases, with no further treatment. In four cases, surgery was not radical and required further treatment. Disease relapse happened in seven cases, with subsequent death in three cases. In six out of seven cases, gene alterations were already detected in the pre-operative cfDNA. In the seven cases without disease relapse, gene variants were detected even after the surgery in two patients despite receiving radical resection. Median number of gene variants was two. Beside the well-established mutations in TP53 gene, both APC and ROS1 gene mutations were frequent, while further evaluations are required for the other variants detected.
Conclusion(s): Evaluation of cfDNA mutations in LB from mCRC may be a useful tool for monitoring clinical response and predict treatment outcome. Moreover, this molecular analysis can help to subgroup patients with regard to risk of relapse after radical surgery. Indeed, cfDNA mutations present before surgery seem to be an indication for a higher risk of post-surgery disease relapse.

A36

CDX2 PROGNOSTIC VALUE IN STAGE II/III RESECTED COLON CANCER IN ELDERLY PATIENTS

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Background: Loss of CDX2 expression has been proposed as a prognostic biomarker in patients (pts) with stage II and III colorectal cancer (CRC). The elderly population is poorly represented in large randomized trials, due to specific characteristics of geriatric patients: comorbidities, concomitant therapies, poor adherence to therapy and increased risk of developing toxicity. The aim of his study is the assessment of the impact of CDX2 on the prognosis of elderly pts with stage II and III CRC and the assessment of the impact of the loss of CDX2 expression on the efficacy of adjuvant therapy.
Patients and methods: We retrospectively reviewed clinical data on pts with stage II-III CRC treated with adjuvant chemotherapy or with exclusive follow up in Clinical

Oncology Unit of the University Hospital of Ferrara. The immunohistochemical analysis of CDX2 expression was performed using a specific monoclonal antibody. Cases classified as CDX2 + had an intense nuclear signal in all or almost all the tumor cells, while the negative cases had complete absence or a weak signal which was present in few cells. We performed survival analysis with a univariate analysis according to the Kaplan-Meier method. In addition, a multivariate analysis was performed to confirm the independent prognostic value of the statistically significant data.
Results: We conducted an analysis on 98pts aged 65 or older with stage II-III CRC. 77 pts were treated with adjuvant chemotherapy between January 2010 and December 2014.
A group of 8 of 98 tumor samples (8,2%) lacked CDX2 expression. Thecorrelation with Loss of CDX2 expression in the univariate analysis is associated with DFS ($p < 0.0001$) and OS ($p < 0.034$); the multivariate analysis confirmed CDX2 as an independent prognostic factor for survival ($p < 0.05$). Subpopulation analysis of stage III CRC pts treated with adjuvant chemotherapy, showed a significant worsening in DFS ($p < 0.0001$) and OS ($p < 0.039$) in patients CDX2- negative.
Conclusions: Lack of CDX2 expression can be considered an adverse prognostic factor in the elderly pts with stage II-III CRC. CDX2 would also appear to be a bad prognostic factor in OS in stage III patients undergoing chemotherapy. It indicates a cohort in which innovative treatments must be developed, or where the utility of adjuvant treatment may be questioned. The latter hypothesis must also be supported by an analysis of the prognostic value of CDX2 by randomized studies.

A37

HIGH-DOSE CONFORMAL RADIATION THERAPY IN REFRACTORY METASTATIC COLORECTAL CANCER

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Background:, In this study we have retrospectively analyzed the survival and relapse free-survival after high-dose radiation in patients with unresectable intrahepatic metastatis in refractory metastatic colorectal cancer.
Material and Methods: Between May 2016 and December 2018, 12 patients with unresectable chemotherapy-refractory metastatic colorectal cancer have been treated at the Department of Hemato-Oncology, AOPC, Catanzaro and at Operative Unity of Medical Oncology, Hospital N.Giannettasio, Rossano ASP Cosenza, Three-dimensional conformal high-dose radiation therapy was delivered in 12 patients, The radiation dose was based on a normal-tissue complication probability model and subjected the patient to an estimated maximum risk of radiation-induced liver disease of 10% to 15% Figg 1,2).
Results: The median radiation dose delivered was 5000 cGy (1.25-Gy fractions bid). At a median follow-up time of 11 months (22 months in patients who were alive) the median survival was 11.8 months (95% CI, 10.3 to 15.3 months). The actuarial 2-year survival was 11%. The total dose was the only significant predictor of survival. Overall toxicity was acceptable, with 3 patients (21%) and 1 patients (8%) developing grade 3 and 4 toxicity, respectively.
Conclusions: The results suggest that high-dose focal liver irradiation prolongs survival in patients with unresectable chemotherapy-refractory metastatic colorectal cancer. This provides a rationale for intensification of local therapy for integration of this regimen with newer systemic therapy for patients with metastatic/refractory colorectal cancer.

A38

REAL LIFE EXPERIENCE ABOUT THE USE OF TAS-102 AND REGORAFENIB IN THE DAILY CLINICAL PRACTICE FOR PATIENTS WITH REFRACTORY METASTATIC COLORECTAL CANCER

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Background: TAS 102 and Regorafenib showed to be superior to placebo plus best supportive care in refractory metastatic colorectal cancer (mCRC) and these drugs appeared to have similar efficacy but a different toxicity profile. No studies have directly compared both drugs. Giving the lack of standard options, we performed a retrospective analysis of our clinical experience in the use of TAS 102 and Regorafenib in the treatment of patients with refractory mCRC. Here we report the efficacy and safety of these two drugs in a series of refractory mCRC patients treated at our Colorectal Cancer Unit.
Patients and methods: Patient's data and data about response rate and toxicities were collected from December 2016 to January 2019. A retrospective analysis was conducted on 38 consecutive mCRC patients. 25 (66%) were treated with TAS 102 and 13 (34%) were treated with Regorafenib. Median age was 60 yrs. Male/Female 23 (60%)/ 15 (40%). PS ECOG 0 70%, PS ECOG 1 30%. 28 (74%) patients received active 3L and 10 (26%) patients 4L treatment prior TAS-102 or Regorafenib.
Results: Globally since 2016, 38 patients received TAS 102 or Regorafenib at our Colorectal Cancer Unit for refractory mCRC. A median of three cycles per patient were administered.

We observed in term of hematological toxicity neutropenia grade 3-4 in 10 (26%) patients. The most frequent non hematological toxicities were: decreased appetite G3/4 in 4 (10%) patients, fatigue G3/4 in 5 (13%) patients and HFSy G3/4 in 3 (8%). Any treatment related deaths have been observed. There were 1 patient (3%) that achieved partial response, while 4 (10%) patients showed stable disease and 33 (87%) had progressive disease. Median time to progression was 2,8 months.

Conclusions: Our results suggest that TAS-102 or Regorafenib represent a possible option of palliative treatment in daily clinical practice for fit "trials ineligible" patients with refractory pretreated mCRC. The use of these drugs in this advanced setting can bring a clinical benefit and the choice among them must take into account their different toxicity profile.

B - Gastrointestinal (non-Colorectal) Cancers

B01*

RANDOMIZED PHASE 3 STUDY OF ADJUVANT CHEMOTHERAPY WITH FOLFOXIRI COMPARED TO GEMCITABINE IN RESECTED PANCREATIC CANCER: THE "GRUPPO ITALIANO PANCREAS" GIP-2 STUDY

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Background: Even at early stage, 80-90% of resected pancreatic cancer patients show recurrence. Adjuvant gemcitabine increases the probability of cure of about 10-15%. FOLFIRINOX prolonged survival compared to gemcitabine in metastatic pancreatic cancer patients and, recently, also in adjuvant setting. FOLFOXIRI demonstrated activity also in this setting. The phase 3 multicenter randomized national GIP-2 trial (NCT02355119) aimed therefore to evaluate FOLFOXIRI as adjuvant treatment in resected pancreatic cancer.

Methods: Patients aged 18-75 years, with ECOG PS 0-1, radically resected pancreatic adenocarcinoma and Ca19.9=2.5 x ULN were randomized 1:1 within 12 weeks after surgery to receive adjuvant FOLFOXIRI (irinotecan 165 mg/ m^2; oxaliplatin 85 mg/ m^2; folinate 200 mg/ m^2; 5-Fluorouracil 3200 mg/ m^2in 48 hours, every 14 days) for 12 cycles or gemcitabine (1000 mg/m^2days 1, 8 and 15 every 28 days) for 6 cycles. Primary endpoint was DFS; OS and toxicity were secondary endpoints. Expecting a median DFS with gemcitabine of 13.4 months, 253 events were required to detect a HR of 0.70 in favour of FOLFOXIRI with overall 2-sided-a and ß errors of 0.05 and 0.20, respectively. On June 2018, considering the results of PRODIGE24 trial, the accrual was early stopped.

Results: From 1/2015 to 5/2018 a total of 77 patients were randomized in 18 centres. Median age was 61 years (range 39-73), 91% of patients had PS0 and 83% had tumour on pancreatic head; pathological stage was II or III in 94% of cases, 77% had positive nodes, 95% had grade (G) 2 or 3. Adjuvant chemotherapy was initiated after a median of 8 weeks after surgery (range 3-12). FOLFOXIRI increased the risk of G 3-4 neutropenia (53 vs 23%; p=0.007) even if no neutropenic fever occurred. No major differences have been observed among other G 3-4 toxicities. After a median follow up of 26 months, 56% of patients had progressive disease and 31% died. Median DFS was 11.4 months with gemcitabine and 30.4 months with FOLFOXIRI, p=0.038; HR 0.53 (95%CI:0.28-0.97). Median OS resulted 19.3 months in control arm while was not reached with FOLFOXIRI with survival proportions at 2 and 3 years of 83% and 69%, respectively, compared to 44% and 33% with gemcitabine.

Conclusions: Even if GIP-2 study was early stopped, adjuvant FOLFOXIRI seems to prolong DFS and OS in resected pancreatic cancer patients. GIP-2 results are in line with those from PRODIGE24 trial and support the use of this triple-drug regimen in this setting.

B02*

THE OUTCOME OF METASTATIC (M) OR LOCALLY ADVANCED (LA) GASTRIC CANCER (GC) IS NOT IMPROVED BY A NEW DOCETAXEL (DOC)-BASED TRIPLET REGIMEN AS COMPARED WITH AN EPIRUBICIN (EPI) STANDARD TRIPLET REGIMEN: A GISCAD TRIAL

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Background: In advanced gastric cancer EOX (EPI + oxaliplatin-OHP + capecitabine-CAPE) is one of the standard regimens, but the role of EPI is under discussion and DOC substituted it in many centers. An innovative DOC-based regimen was developed, aiming at increasing the outcome vs EOX without the important side-effects of the conventional DOC combination.
Methods: From 1/2013 to 11/2018, 169 chemo-naive patients (pts) with M (87,6%) or LA GC were randomized by 23 institutions between low-TOX (arm A) and EOX (arm B): Arm A: DOC: 35 mg/m2 iv, d 1 and 8 + OHP: 80 mg/m2 iv, d 1 + CAPE: 750 mg/ m2 x2 daily p.o. for 2 weeks; Arm B: EPI: 50 mg/m2 iv, d 1 +OHP: 130 mg/m2 iv, d 1 +CAPE: 625 mg/m2 x2 daily p.o. for 3 weeks. Both regimens recycled q 21 days.
If no PD or heavy toxicity, pts were programmed on therapy for a maximum of 5 (if CR) or 6 courses (if PR or SD). The primary endpoint was PFS, the secondary OS, ORR, DCR and tolerability. The study was designed to detect a 35% (80% power at a two side 5% significance level) PFS increase with low-TOX and an interim analysis for futility was planned after the first 127 events (75% of expected).
Results: At the cut-off date of interim analysis, 164 pts (median age 62 y; 63,9% male; ECOG PS: 0 in 75,7%) have available data for primary efficacy analysis. The median PFS was 5.8 months (m) (95% CI: 5.0 – 7.8) in arm A vs 6.5 m (95% CI: 5.0 – 8.9) in arm B, without statistical difference (NS). Also OS was comparable: 12.2 (95% CI: 8.6 -16.0) vs 12.8 m (95% CI: 9.1-21.0). ORR were 22% and 35.4% and DCR 59.8% and 65.9%, again NS.
The median number of courses per pt was 6 and treatment modification was higher in arm A (90,2% vs 78%) with a weakly higher number of CTC $\geqslant$ 3 AE in arm A (54 vs 41).
Conclusions: On the basis of these results, it is unlikely that low-TOX regimen can reach the target of improvement vs EOX, both in efficacy/activity and in tolerability. Therefore, if clinicians decide for a triplet (i.e. in aggressive or very symptomatic disease), EOX could remain a standard option.

B03

THE PROGNOSTIC NUTRITIONAL INDEX (PNI) IS AN INDEPENDENT PREDICTOR OF SURVIVAL IN ADVANCED BILIARY CANCERS (ABC) RECEIVING FIRST-LINE CHEMOTHERAPY (1L)

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Background: ABC portend a dismal prognosis despite standard chemotherapy treatment. A proper risk-stratification is key to optimize the benefit-to-risk ratio of palliative treatment. The PNI is an immune-inflammatory and nutritional indicator showing to be prognostic across a number of malignancies. We aimed at investigating the impact on survival of the PNI in ABC patients (pts) treated with 1L.
Methods: Electronic medical records of pts diagnosed with ABC and treated with 1L between 2002 and 2018 at the Modena Cancer Centre were retrospectively reviewed. Clinical, pathological and biochemical variables of potential interest were collected. The PNI was calculated as follows: 10 $\times$ serum albumin concentration (g/dL) + 0.005 $\times$ peripheral lymphocyte count (number/mm2) and dichotomized using the ROC analysis with 36.7 as the cut-off value. Univariate and multivariate analysis were performed to assess the impact of covariates on overall survival (OS). Kaplan-Meier survival curves were generated and log-rank testing was used to make comparisons.
Results: Overall, 114 pts fulfilled the inclusion criteria and were included in the analysis. 51% (n=58) were female and 49% (n=56) had an ECOG PS of 0. 35% (n=40) of pts received a platinum/gemcitabine doublet, while 65% (n=74) were treated with other regimens. The median OS in the cohort was 8.1 months. At the univariate analysis the following covariates were associated with OS: PNI ($P<0.0001$), CA19.9 ($P=0.0063$), CEA ($P=0.0004$), LDH ($P=0.0360$), alkaline phosphatase ($P=0.0308$), monocyte count ($P=0.0124$), neutrophil count ($P=0.0013$), ECOG PS ($P<0.0001$), neutrophil/lymphocyte ratio (NLR) ($P<0.0001$). Interestingly, the PNI retained a statistical significance ($P=0.0011$) also at the multivariate analysis, together with NLR ($P=0.0046$) and ECOG PS (<0.0001). The median OS in pts with a PNI $>$ 36.7 and $<$ 36.7 was 12.1 months and 5.4 months, respectively.
Conclusions: We demonstrated an independent prognostic role for the PNI in a cohort of ABC treated with 1L. Since it is based on easy-to-collect and inexpensive parameters it should be implemented in the clinical practice to improve the accuracy of current available tools.

B04

MULTICENTRIC PROSPECTIVE STUDY OF VALIDATION OF ANGIOGENESIS-RELATED GENE POLYMORPHISMS IN HEPATOCELLULAR CARCINOMA PATIENTS TREATED WITH SORAFENIB(S): FINAL RESULTS OF INNOVATE STUDY

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Background: In two retrospective studies we analyzed endothelial-derived nitric oxide synthase (*eNOS)* and angiopoietin-2 (*ANGPT2*) polymorphismsand patients with *eNOS*-786*CC*+*TC*genotype and *ANGPT2*rs55633437 GG genotypes had significantly higher median PFS and OS compared to those with other genotypes. On the basis of these preliminary results, our aim is to validate in a prospective study these data in patients with HCC treated with sorafenib (NCT02786342).

Methods: The primary outcomes were PFS. 160 total sample size were planned with the aim to confirm a HR of 0.58. Event-time distributions were estimated using the Kaplan-Meier method and survival curves were compared using the log-rank test.

Results: 165 patients in 9 Italian hospital were enrolled in the study between 03/2015 and 06/2018.

Median OS was 13.1 months (95% CI 10.4-15.7) and median PFS was 4.2 months (95% CI 3.2-5.3).

At univariate analysis, we confirmed that *eNOS*-786 CC+CT genotype was significantly associated with a higher median PFS (2.4 vs 5.9 months, HR 0.43, 95% CI 0.26-0.70 $p=0.0007$) and OS (15.7 vs 8.6 months, HR 0.38, 95% CI 0.24-0.60 $p<0.0001$) than the other genotypes. At univariate analysis, we not confirmed that *ANGPT2*rs55633437 GG genotypes were significantly associated with a lower median OS ($p=0.55$) and PFS ($p=0.13$).

No differences were found between *eNOS-786 TT*and *eNOS-786 CT/CC*genotypes in term of disease control rate and best response. No correlation were found between eNOS polymorphisms and toxicity.

Following adjustment for clinical covariates positive in univariate, multivariate analysis confirmed *eNOS*as only independent prognostic factor predicting OS ($p=0.0072$).

After progression to S in all population we highlight that patients with *eNOS*-786 CC+CT genotype was significantly associated with a lower median OS (HR 0.56, $p=0.0343$) and a trend was found for patients treated with Regorafenib (HR 0.13 $p=0.0573$).

Conclusions: Our Italian multicenter, prospective study meet the primary end point and we confirmed that*eNOS*-786 TT genotype may be capable of identifying a subset of HCC patients who have a lower median OS and PFS. For the first time in ten years of sorafenib research our study confirms the prognostic role of a biological marker in a prospective study.

B05

AEROBIC GLYCOLYSIS ENZYMES GENE EXPRESSION ANALYSIS IN GASTRIC CANCER (GC) AND SELECTIVE METABOLIC ADVANTAGE IN THE CLINICAL PROGRESSION OF PATIENTS WITH METASTATIC DISEASE TREATED WITH TAXOL-RAMUCIRUMAB

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Background: Invasive cancer cells mostly produce lactate even in the presence of sufficient levels of oxygen (AG). This metabolic shift promotes a survival advantage in proliferating cells and it makes them insensitive to transient or permanent hypoxia. This phenomenon may cause secondary resistance to anti-angiogenic compound and identify new targets in cancer metabolism. We analyzed mRNA expression of AG key-enzymes in primary tumor (PT) of GC pts who underwent second-line therapy with paclitaxel/ramucirumab. This setting was chosen for verifying the possible clinical impact of adaptive hypoxia with AG against a prevalent anti-angiogenic regimen.

Methods: Tissues of pts were retrospectively studied by RT-qPCR for mRNA expression of the following AG-related genes: HK1, HK2, PKM2, LDH-A, GLUT-1, VDAC1. The relative mRNA expression of each candidate gene was expressed as the DCt =Ct(target gene) – Ct(reference gene). By comparing DCt values between the tumor sample and the normal counterpart the differential expression was estimated. A doubled mRNA expression ($DCt \geqslant 1$) in all AG "core" enzymes (HK1/HK2 PKM2 LDH-A) identified high glycolytic score (HGS) samples, otherwise as having low glucolytic sore (LGS). Data of HGS and LGS were associated with clinical outcomes.

Results: A retrospective series of 50 pts from the RAMoss study (Di Bartolomeo et al, Target Oncol, 2018), treated

with second-line Paclitaxel/Ramucirumab was analyzed. The median age was 60 years (range 38-60) with prevalence of ECOG performance status 0 (55%), multiple sites of metastatic disease (65%), male gender (65%), peritoneal involvement (40%) and time-to progression on first-line treatment > 6 months (66%). At the time of writing of this paper, results are available for 30 pts with 9 having HGS. Median PFS were 2.3 and 5 months in pts with HGS and LGS, respectively ($p<.001$). Median OS were 4.4 and 9.6 months in pts with HGS and LGS, respectively ($p<.01$). Multivariate analysis will be performed in the final dataset.

Conclusions: GC displaying an aerobic glycolysis metabolic profile may tolerate the unfavorable microenvironment determined by anti-angiogenic therapies. This feature may explain secondary resistance to anti-angiogenic therapies in subset of patients and it deserves further investigations for potential innovative treatment strategies. Final data will be presented at the meeting and results in the whole sample size would allow additional analyses in combination with GLUT-1 and VDAC1.

B06

NAB-PACLITAXEL (NAB) PLUS GEMCITABINE (G) IS MORE EFFECTIVE THAN G ALONE IN LOCALLY ADVANCED, UNRESECTABLE PANCREATIC CANCER (LAUPC): THE GAP TRIAL, A GISCAD PHASE II COMPARATIVE RANDOMIZED TRIAL

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Background: The role of a combination therapy is defined in metastatic pancreatic cancer but not in LAUPC. Lacking dedicated randomized trials, evidence mostly comes from retrospective or phase II studies. G alone remains the standard option following a subgroup LAUPC analysis of a GERCOR/GISCAD trial (J Clin Oncol 2005).

Methods: GAP is a multicentre, open-label, randomized, comparative phase II trial testing the efficacy of NabG vs G. Patients ⩽75 years, PS 0-1, were randomized 1:1 to Nab/G (Nab 125 mg/mq plus G 1000 mg/mq on days 1, 8 and 15 every 28 days for 3 cycles) or G (same schedule and doses). Patients not progressing after 3 cycles had to receive capecitabine plus radiotherapy for 5 weeks. Disease progression rate (DPR) according to RECIST 1.1 after 3 cycles of chemotherapy is the primary endpoint. With 80% power in detecting a reduction of DPR from 40% to 20%, one-tailed alpha=0.05, 124 patients were required. Progression-free survival (PFS) is a secondary endpoint; with 109 events the study has 80% power, with one-tailed alpha=0.05, to detect a 0.62 hazard ratio of PFS.

Results: 124 patients were enrolled in this trial (4 withdrew consent after randomization in the G arm). Most of the patients were PS 0 (65.8%), and women (56.7%). The study met its primary endpoint DPR, with a reduction from 45.6% with G to 25.4% with Nab/G.

There was no unexpected toxicity. One patient died during treatment with G due to a stroke.

Conclusion: NabG reduces the rate of LAUPC patients who progress after 3 cycles of chemotherapy compared with G, especially in terms of distant relapses, positively affecting PFS and overall survival. Nowadays it should be the therapeutic option in this setting.

ClinicalTrials.gov Identifier NCT02043730. The study was supported by Celgene.

B07

ADJUVANT CHEMOTHERAPY IN RESECTED BILE DUCT CANCER: A METANALYSIS OF RANDOMIZED TRIALS

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Background: Despite improvements in surgical resection techniques and multidisciplinary management, patients suffering from bile tract cancers (BTC) have a poor prognosis.

Arm	Patients	DPR	One-tail chi square	Median PFS (102 events)	HR of PFS	Progression at distant site	Median OS (82 events)	HR of OS
G	57	26 (45.6%)	P=0.01	5.1 mos	0.71	18/26	10.7 mos	0.65
NabG	63	16 (25.4%)		7.6 mos	(90% CI 0.51-0.99)	6/16	13.1 mos	(90% CI 0.44-0.94)

About 50% of them will develop disease recurrence after curative surgery, and the 5-year survival rate accounts for 10-40%. The role of adjuvant chemotherapy (ACT) is still unclear and no specific adjuvant treatment is recommended by international guidelines given conflicting results from the available clinical trials. We performed a meta-analysis of randomized clinical trials (RCTs) to better define the clinical benefits and the risk of ACT or observation in resected BTC.

Method: A systematic literature search of Pubmed, Embase, and the Cochrane Library was carried out up to April 2019. Phase II/III prospective randomized controlled trials comparing ACT or observation in BTC patients were eligible for the metanalysis. Overall survival (OS) and recurrence free survival (RFS) were co-primary end-points. Hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and RFS, as well as Risk Ratio (RRs) for ⩾ G3-G4 adverse events (AEs) were calculated for each trial. A pooled analysis was carried out using the random effects model. A pre-specified subgroup analysis was performed to assess OS in patients with node positive or positive surgical margins (R1). Results: Three RCTs including 866 BTC patients (435 ACT arm vs 431 observation arm) were eligible for the metanalysis. A trend toward better OS (HR: 0.91, 95% CI 0.75-1.09) and a statistically significant difference in RFS (HR: 0.83, 95% CI 0.69-0.99) was reported among patients who underwent ACT. Similarly, a trend toward better OS in ACT arm was reported in node positive subgroup (HR: 0.84, 95% CI 0.65-1.08), whereas there was no difference in R1 subgroup (HR: 0.95 95% CI 0.69-1.31). The use of ACT was characterised by a significant increase of ⩾G3-G4 AEs (RR: 3.03, 95% CI 2.22-4.15).

Conclusions: This metanalysis showed for the first time that ACT meaningfully improved RFS in resected BTC patients' and led to longer OS than observation alone in overall population and node positive subgroup, although the difference was not statistically significant. As expected, ACT caused treatment-related toxicities which offsets benefits.

B08

THE MANAGEMENT OF BILIARY TRACT CANCER: A NEW PROGNOSTIC SCORE SYSTEM

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Background: Biliary tract cancers (BTCs) are heterogeneous tumours with poor prognosis and limited therapeutic options.Innovative predictive and prognostic factors are urgently needed in order to improve the global management of BTC patients (pts).

Methods: From August 2001 to March 2019, clinical and demographic data of advanced BTCs pts attending the Medical Oncology Department of Cagliari, Modena, Meldola and Macerata University Hospitals, were retrospectively collected.All pts underwent at least one line of chemotherapy.The aim of our research was to investigate the correlation between clinical data and outcomes in order to identify a prognostic index, clustering pts in low and high-risk subgroups.The score was validated by a confirmation-cohorts (Medical Oncology Department of Pisa, Torino, Candiolo and Alba). Survival analysis were performed using the Kaplan-Meyer method and log-rank test, ROC curves were applied to define cut off values for Ca19.9

Results: Exploratory cohort and validation cohort considered data of 256 and 294 advanced BTCs pts respectively. In exploratory cohort median overall survival (mOS) was 9,23 months. Clinical parameters correlating with OS were primary tumour site, age, ECOG PS, biliary stenting and baseline Ca19.9 values.The intrahepatic cancer mOS was 11,6 months, 9,16 months in extrahepatic subgroup and 8,1 in gallbladder tumours($p=0,04$). Age=70 years and the presence of biliary stent were associated to a lower OS [(12,3 vs 7,8 months; $p=0,0006$) and (12,3 vs 7,9 months; $p=0,0342$) respectively]; ECOG-PS0-1 was associated with longer survival than ECOG-PS>1 (12,3 vs 3,23 months;$p<0,0001$); pts with Ca19.9 levels=305 U/ml had a mOS of 12,6 months, while those with higher levels showed a mOS of 7,63 months ($p<0,0001$). A unitary value was assigned to each significative prognostic factor, in order to stratify pts in 2 prognostic groups. We found a statistical significative difference between pts located in the 0-2 score group and pts in the 3 score group in terms of OS (12,3 vs 7,6 months respectively, $p<0,0001$). Confirmatory results were obtained by the same analysis in the validation cohort with a mOS of 14,43 and 11,16 months in pts with low (n=127) and high-risk group (n=167) respectively ($p=0.0001$).

Conclusions: Prognostic score including primary tumour site, ECOG PS, age, presence of biliary stent, baseline Ca19.9 values, was significantly correlated with survival in BTCs.Further studies with larger sample size are needed to confirm our results.

B09

TARGETING DNA REPAIR IN BILIARY TRACT CANCER (BTC): ARE IDH AND MGMT NEW THERAPEUTIC TARGETS?

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Background: Biliary Tract Cancers (BTC) are molecularly heterogeneous malignancies with significant molecular differences between intrahepatic (ICC) and extrahepatic (ECC) cholangiocarcinoma and gall bladder (GB) cancer. DNA Damage Repair (DDR) is relevant to BTC proliferation and apoptosis and DDR deficiency can lead to sensitivity to novel therapies, such as Poly(ADP-ribose) polymerases inhibitors (PARPi), due to synthetic lethality. Among DDR genes, *IDH1/2* mutations (~15% of CC) convert a-ketoglutarate (aKG) into 2-hydroxyglutarate (2HG) and drive a homolougus repair (HR) defect, and consequently sensitivity to PARPi in preclinical models. Another DDR gene, *MGMT*, is responsible of alkyl groups' elimination from the O6-position of guanine. Reductions in MGMT expression and *MGMT* promoter methylation result in diminished DNA-repair of O6-alkylguanine adducts and enhanced sensitivity to alkylating agents, such as Temozolomide (TMZ). Here we present data on these DDR alterations tested in BTC pts at our center.

Methods: Formalin-fixed paraffin-embedded (FFPE) tissue samples were examined using Next Generation Sequencing (50 genes "Hotspot Cancer Panel, Ion Torrent®"). *MGMT* promoter methylation was studied via methyl specific PCR (EZ DNA Methylation-Gold™ KIT), while protein expression was assessed via immunohistochemistry (IHC).

Results: Archived FFPE tissue sections from 100 pts admitted at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan, from October 2017 to February 2019, were analyzed. Amongst the 89 samples with adequate tissue, 73% were ICC, 16% were ECC and 8% were GC. We found IDH1/2 mutations in 15% (all ICC). 34 pts (38%) had *MGMT* promoter methylation, while low/negative MGMT protein expression was found in 45 pts (50%). Of note, *MGMT* methylation was identified in each soubgroup of pts, with 38% of ICC, 26% of ECC and 62% of GC. Amongst *MGMT* methylated pts, 4 (11%) had concomitant IDH1/2 mutations, which are reported to be associated with CpG Island Methylator Phenotype.

Conclusions: Evidence supporting the role of *IDH1/2* mutations and *MGMT* methylation in leading to sensitivity to PARPi and TMZ is increasing. In our single-center experience, *IDH1/2* mutations and *MGMT* promoter methylation were found in 15% and 38%, respectively, of patients with BTC. More data are needed, but there is definitely a definitely an interest in exploring the prognostic role of *IDH1/2* mutations and *MGMT* methylation in BTC and novel therapies targeting these DDR genes.

B10

RETROSPECTIVE SURVIVAL ANALYSIS IN METASTATIC PANCREATIC CANCER PATIENTS AFFECTED BY TYPE 2 DIABETE MELLITUS

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Background: The association between pancreatic ductal adenocarcinoma (PDAC) and type 2 diabetes mellitus (DM2) has long been evaluated, some studies had described diabetes mellitus 2 as a risk factor for the development of PCAD or as its epiphenomenon. The objective of the present study was to investigate the correlation between overall survival (OS) and DM2-PDAC versus not DM2 PDAC.

Methods: We retrospectively analyzed an exploratory cohort from Medical Oncology of Cagliari University Hospital and a validation cohort from Medical Oncology of Modena University Hospital. All patients had stage IV disease and received at least 1 line of chemotherapy treatment for metastatic disease. Statistical analysis was performed with MedCalc package. Our aim is to evaluate the correlation between DM2 and overall survival (OS), and subsequently investigate the differences between insulin and metformin therapy in relation to OS. Survival distribution was assessed by the Kaplan-Meyer method.

Results: 86 pts of Cagliari University Hospital and 45 pts of Modena University Hospital were included in our analysis. 63/86 (73.3%) and 31/45 (68,9%) pts were not affected by DM2, instead 23/86 (26.7%) and 14/45 (31,1%) pts were affected by DM2. Median OS (mOS) was significantly improved in DM2 pts versus (vs) not DM2 pts (24 months, 95% CI 0.19-0.59 vs 8 months, 95% CI; $p<0,0005$); in validation cohort mOS was improved in DM2 pts vs not DM2 pts (11 months, 95% CI 0.21-0.72 vs 6 months, 95% CI; $p<0,001$).

Within the DM2 group of exploratory cohort 16/23 (69.6%) pts were insulin treated and 7/23 (30.4%) with metformin; mOS was significantly improved in the metformine subgroup (30 months, vs 24; $p<0,005$). In the DM2 group of validation cohort 9/14 (64,3%) pts were insulin treated and 5/14 (35,7%) pts were metformin treated; mOS was significantly improved in metformin subgroup (11 months vs 10.5 months; $p<0,01$).

Conclusions: PDAC patients with DM2 have shown better OS than non-DM, as demonstrated by the validation cohort. Furthermore, the role of metformin in improving OS was

confirmed in PDAC patients of both cohorts. However, if the molecular mechanism of metformin in improving OS has been investigated and partially explained, the mechanism by which the DM2 not metformin treated can improve the OS should be investigated.

B11

MGMT METHYLATION IN PANCREATIC CANCER (PAC): A NEW TARGET?

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Background: Pancreatic adenocarcinoma (PAC) is a devastating disease with few therapeutic options. O6-methylguanine-DNA methyltransferase (*MGMT*) is a key DNA repair gene and *MGMT* alterations are described in various gastrointestinal cancers, including colorectal cancer. Reports regarding the frequence and the role of *MGMT* methylation and/or low protein expression by immunohistochemistry (IHC) in PAC are conflicting. It is established that low MGMT expression and *MGMT* promoter methylation are related to reduced DNA-repair of O6-alkylguanine adducts. In fact, there is increasing evidence of the activity of alkylating agents, such as temozolomide (TMZ), in these patients (pts). This report presents data on *MGMT* testing PAC pts admitted at our center.
Methods: Formalin-fixed paraffin-embedded (FFPE) tissue samples were examined via methyl specific PCR (EZ DNA Methylation-Gold™ KIT), to assess *MGMT* promoter methylation, and IHC, to assess protein expression. Furthermore,
Next Generation Sequencing (50 genes "Hotspot Cancer Panel, Ion Torrent®" and "Oncomine BRCA Research Assay") and PCR analysis of microsatellite instability (MSI) were performed.
Results: Archived FFPE tissue sections obtained from 90 pts admitted at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan from October 2017 to April 2019 were analyzed. By May 2019, 60 samples (66%) had adequate tissue for *MGMT* status analyses. We identified *MGMT* promoter methylation in 21 pts (35%), of which 13 (61%) had low/negative MGMT protein expression. Of note, amongst *MGMT* methylated pts, there were 5 (23%) *BRCA1/2* somatic mutant and 2 (9%) MSI, which may suggest possible genomic instability in this subset of pts. It is worth considering *BRCA1/2* somatic mutations (VUS or pathogenic) and microsatellite instability (MSI) were identified in 9 (15%) and 2 (3%) pts, respectively.
Conclusions: In our single center experience, *MGMT* methylation was found in 35% of patients with PAC. This data warrant further confirmation; nevertheless, considering the role of MGMT alterations in glioblastoma and other gastrointestinal cancers, there is definitely a rationale in investigating *MGMT* methylation as a predictive and prognostic biomarker in PAC.

B12

ANALYSIS OF ACCRUAL IN GIP-2 STUDY, AN ITALIAN MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING FOLFOXIRI VERSUS GEMCITABINE AS ADJUVANT TREATMENT FOR RESECTED PANCREATIC CANCER

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Background: Adjuvant chemotherapy with gemcitabine increases survival over surgery alone in resected pancreatic cancer. Modified FOLFIRINOX demonstrated higher survival compared to gemcitabine in this setting. However, this triple-drug combination may be more aggressive and not all patients could be eligible to this treatment. No data regarding screening failure were presented in PRODIGE 24 trial. The GIP-2 trial recently investigated FOLFOXIRI versus gemcitabine in the same setting. We decided to analyze the number of screened patients and reasons for ineligibility.
Methods: A retrospective analysis of clinical data of patients with resected pancreatic cancer evaluated at the centers enrolling patients in GIP-2 trial during the time the study was conducted in order to evaluate the population of patients not included in the trial and the reasons for ineligibility. To avoid risks of overweighting screening failure rate, we decided to include only patients evaluated in active centers who enrolled at least one patient in the trial.

Results: A total of 77 patients were enrolled in GIP-2 study in 18 centers from 1/2015 to 5/2018, with an accrual rate of 1.25 patients/center/year that was similar to those of other adjuvant trials in pancreatic cancer (PRODIGE 24: 1.42; ESPAC-4: 1.33). In the same period, a total of 461 resected pancreatic cancer were evaluated in the 18 centers; the 77 enrolled patients represent about 17% of all the assessed patients.
Main reasons of ineligibility to the study were:

- age (>75 years or 70-75 years and ECOG Performance Status 1), 111/384 (28.9%)
- slow recovery after surgery, 69/384 (18%)
- patient refusal, 43/384 (11.2%)
- physician decision, 30/384 (7.8%)
- metastatic disease at postsurgical restaging, 29/384 (7.6%)
- comorbidity, 23/384 (6%)
- other neoplasia within 5 years, 18/384 pts (4.7%)
- CA19.9 > 2.5 x upper limit of normal range, 17/384 (4.4%)
- previous neoadjuvant chemotherapy, 17/384 (4.4%)
- enrollment in competitive trial, 11/384 (2.9%)
- time from surgery >12 weeks, 9/384 (2.3%)
- histology, 7/384 (1.8%)

Conclusions: Patients enrolled in phase III trials of adjuvant chemotherapy for resected pancreatic cancer are selected for good performance status, age, with no evidence of metastatic disease after surgery, having a good recovery after surgery. These results are crucial for design of possible future clinical trials investigating chemotherapy in different settings (preoperative versus postoperatitve) for resectable pancreatic cancer.

B13

USER-FRIENDLY SCORING SYSTEM AND NOMOGRAM TO PREDICT RELAPSE-FREE SURVIVAL (RFS) IN WESTERN PATIENTS (pts) WITH RESECTED GASTRIC CANCER (GC)

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Background: Despite multimodality treatment, in the Western world >50% of GC pts relapse following curative-intent surgery. The absolute survival benefit of perioperative or adjuvant chemotherapy ranges from 6 to 15% at 5 years and must be balanced against treatment-related toxicities. Reliable tools to risk-stratify patients are lacking. The aim of this study was to build a practical tool to guide daily decision-making and clinical trial design.
Methods: Data of pts undergoing curative-intent surgery for T2-4 and N-positive GC between 2008 and 2018 at the Modena Cancer Centre were retrieved. Clinico-pathologic and biochemical parameters deemed of potential interest were collected. The cut-off value for continuos variables was assessed at 75° percentile. Univariate and multivariate Cox proportional-hazard models were used to assess the prognostic value of covariates. Based on the multivariate model, a nomogram to predict 2- and 3-year RFS was developed with a corresponding number of points assigned to a given magnitude of the variable.
Results: A total of 157 pts were eligible for the analysis. 51% (n=80) were female and 88% (n=139) had an ECOG PS of 0-1. Only 6% of cases were gastroesophageal cancers. 13% (n=20), 25% (n=40), 62% (n=97) presented at diagnosis with stage I, II and III, respectively. Adjuvant chemotherapy was administered to 49% of patients. Out of 15 covariates tested, the following were independent predictors of outcome in the multivariate analysis and therefore included in the nomogram: ECOG PS (HR 2.51; p=0.006), nodal status (HR 3.04; p=0.078), angioinvasion (HR 2.62; p=0.005) and logNeutrophil/Lymphocyte ratio (HR 3.50; p<0.001). Moreover, by assigning to each of them weight equal to 1, a scoring system was devised that differentiates 3 prognostic groups: low- (0-1 factors), intermediate- (2 factors) and high-risk (3-4 factors) group with a mOS of 35, 22 and 8 months (p<0.001), respectively.
Conclusions: We built an easy-to-use prognostic score and a nomogram to estimate 2- and 3-year individual RFS probability in resected GC. Interestingly, these tools incorporate variables reflecting patients characteristics (ECOG PS), tumour aggressiveness (nodal status and angioinvasion) and immune-inflammation status (NLR). Both the scoring system and the nomogram could assist clinicians in discussing with patients prognosis and risk-to-benefit ratio of systemic treatment as well as the design of future trials.

B14

EFFICACY, SAFETY, AND CANCER-RELATED SYMPTOMS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA WITH ALPHA-FETOPROTEIN GREATER THAN OR EQUAL TO 400NG/ML: A POOLED ANALYSIS FROM REACH AND REACH-2 STUDIES

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Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death. Advanced stage is associated with symptoms and poor quality-of-life. Ramucirumab (RAM) shows survival benefits in patients with alpha-fetoprotein (AFP) ⩾400 ng/ml who failed prior sorafenib treatment. We present efficacy, safety, and cancer-related symptoms in HCC patients with AFP ⩾400 ng/ml.

Material and methods: This meta-analysis included individual patient-level data from REACH and REACH-2. Both studies had the same eligibility criteria (except AFP⩾400 ng/ml in REACH-2): prior sorafenib treatment, advanced HCC (BCLC-C), Child-Pugh score <7, ECOG PS 0-1. Patients received RAM (8 mg/kg) or placebo (PBO) on day 1 every 14 days. Functional Assessment of Cancer Therapy (FACT) Hepatobiliary System Index (FHSI)-8 assessed cancer-related symptoms. Time-to-deterioration (TTD) was time from date of randomization to date of first FHSI-8 deterioration (3+ point worsening). Efficacy assessment included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and safety.

Results: 542 patients with AFP ⩾400 ng/ml pooled from REACH (n=250) and REACH-2 (n=292) were treated with RAM (n=316) and PBO (n=226). Patients treated with RAM had improved OS (RAM=8.1 months; PBO=5.0 months; HR=0.694; 95% CI=0.571-0.842; p<.0002), PFS (RAM=2.8 months; PBO=1.5 months; HR=0.572, 95% CI=0.472-0.694; p<.0001), and ORR (RAM=5.4%; PBO=0.9% [p<.004]). TTD of FHSI-8 total score was delayed in patients treated with RAM (3.3 months) vs PBO (1.9 months; HR=0.725, 95% CI=0.559-0.941). Overall, 9.5% (RAM) and 3.6% (PBO) of patients discontinued due to adverse events (AEs). Hypertension (RAM=12.0%; PBO=3.6%) and hyponatremia (RAM=5.1%; PBO=2.2%) were the grade ⩾3 treatment-emergent AEs occurring in ⩾5% in RAM.

Conclusions: RAM significantly improved OS, PFS, ORR, and delayed deterioration of cancer-related symptoms in HCC patients with AFP>400ng/ml, with an acceptable safety profile.

B15

A CLINICAL SCORE IDENTIFIES PROGNOSTIC CLASSES IN CHOLANGIOCARCINOMA (CCA) TREATED WITH FIRST-LINE CHEMOTHERAPY

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Background: The first-line treatment of CCA relies on palliative-intent chemotherapy with median overall survival (mOS) hardly exceeding 12 months. Hence, the trade-off between efficacy, toxicity and quality of life must be carefully evaluated. However, it exists an unmet need for factors aiding risk-stratify CCA in both the clinic and trials. We aimed at evaluating the impact on OS of clinical, pathologic and biochemical factors to develop a prognostic tool assisting in treatment decision.

Methods: Medical records of patients affected by unresectable locally advanced and metastatic intrahepatic, perihilar and distal CCA who received first-line chemotherapy from 2006 to 2018 at the Modena Cancer Centre and Cremona Cancer Centre were retrospectively reviewed. Variables of potential interest were collected. Kaplan-Meier survival curves were generated and differences between covariates were addressed with the log-rank test. Univariate and multivariate Cox proportional-hazard models were used to assess the prognostic value of covariates.

Results: Amongst 122 CCA included in the analysis, 53% were female and 55% had an ECOG PS of 0. 87% of patients presented with stage IV disease. Tumour site was iCCA, pCCA and dCCA in 60%, 22% and 18% of cases. The mOS in the overall population was 11.5 months and 1-year OS was 52%. Globally, 24 variables deemed of potential interest were evaluated in the univariate analysis. ECOG PS > 0 (p<0.001), age > 75 years (p=0.009), NLR > 3.0 (p<0.001), CEA > 9.5 (p<0.001) and stage IV (p=0.001) remained independently associated with worse survival in the multivariate analysis. By assigning to each of these five variable weight equal to 1 and grouping together the patients based on their presence, we identified a low- (0-1 factors), intermediate (2 factors) and high-risk (3-5 factors) group, respectively. The mOS differed significantly in the three groups being 19 months in the low-risk group (p<0.001), 11 months in the intermediate-risk group (p<0.001) and 3 months in the high-risk group (p<0.001).

Conclusions: We developed a clinical score based on readily-available and inexpensive parameters that risk-stratifies CCA treated with first-line chemotherapy in three significantly different prognostic classes. Although an external validation is required, this score could be a

valuable tool to guide clinical decision-making and patient stratification.

B16

EPSTEIN-BARR VIRUS (EBV) ASSOCIATED METASTATIC GASTRIC CANCER (GC) AND ITS CORRELATION TO CLINICAL OUTCOMES

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Background: EBV-associated gastric cancer (EBVaGC) has been recently categorised as a specific subgroup of gastric cancer (GC), harbouring a remarkable sensitivity to immune-checkpoint inhibitors. As today, few evidences are available on the prognosis of this subgroup and its sensitivity to chemotherapy in the metastatic setting, especially in the non asian population. This study aims to investigate the prevalence, the clinical-pathological characteristics and the prognosis of metastatic EBVaGCs in a single centre population.
Methods: Formalin-fixed, paraffin-embedded tumour samples from 170 stage IV GC treated at Istituto Nazionale dei Tumori of Milan from April 2009 to April 2019 were examined. Ventana Benchmark *in situ* hybridization (ISH) system was used for EBV-encoded RNA (EBER) ISH. Patients were considered EBV positive when the presence of EBV in tumour cells was detected in EBER-ISH analysis. Medical records were reviewed to obtain data on clinical characteristics and survival outcomes.
Results: One-hundred-seventy stage IV GC patients were analyzed: EBV infection was found in 3 cases (1.8%). After a median follow up of 23.4 months, median overall survival (mOS) was 15.83 months in the EBV negative population, while it was not reached in EBVaGC cases. At the univariate analysis, EBV infection was significantly associated with high grade tumours (66.7% vs 50%, $p<0.001$) and the presence of distant nodal metastases at diagnosis, without liver and /or peritoneal lesions (100%, $p<0.001$).
Conclusions: Our single institution retrospective analysis shows that the prevalence of EBVaGC metastatic patients is small, lower than expected based on data derived from asiatic population series. Indeed, our results suggest that this patients subgroup is characterized by extraordinary long survival, even in the pre-immunotherapy era. Further investigations are warranted in larger patient series.

B17

PLASMATIC CXCL8 IS A MARKER FOR TGFß-ACTIVATED KINASE 1 (TAK1) ACTIVATION WHICH MAY PREDICT RESISTANCE TO NANOLIPOSOMAL IRINOTECAN (nal-IRI) IN GEMCITABINE-REFRACTORY PANCREATIC CANCER (PC) PATIENTS

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Background: PC remains one of the most lethal solid tumors, mainly because of its intrinsic chemoresistance. We recently identified TAK1 as a central hub integrating the most relevant signals sustaining PC chemoresistance. nal-IRI is a novel standard of care for metastatic PC patients who had been previously treated with a gemcitabine-based therapy.We endeavoured to identify circulating markers for TAK1 activation predicting chemoresistance in this clinical setting.
Methods: In vivo activity of nal-IRI was validated in an orthotopic nude mouse model of PC cells expressing TAK1- specific shRNA or a scramble sequence as control. Using multiplex xMAP/Luminex technology, the samples from 77 metastatic PC patients progressing after gemcitabine and prospectively enrolled to receive nal-IRI + 5FU/LV were analysed for the plasma concentration of 20 different TH1and TH2cytokines. The optimal cut-off thresholds able to significantly predict patient outcome were obtained based on the maximization of the Youden index.
Results: A significant tumor volume reduction in mice bearing shTAK1 PC treated with nal-IRIwas detected, whereas controls were resistant to this agent. Differential gene expression profiling revealed CXCL8 as the most significantly downregulated gene coding for secreted proteins in shTAK1 PC cell lines. After a 27 month median follow-up, in the overall population the median progression-free survival (PFS) was 3.3 months (95% CI=3.039-3.561) and the median overall survival (OS) was 7.3 months (95% CI=5.487-9.113). Cox proportional hazard regression multivariate analysis confirmed CXCL8 as the circulating factor most significantly correlated with survival outcomes. Patients with CXCL8 higher than 16.68 pg/mL cut-off value had a PFS of 2.8 vs 3.4 months (HR=2.61, 95% CI=1.42-4.79, p=0.0014), and an OS of 5.3 vs 8.9 months (HR=3.7, 95% CI=1.93-7.11, p=2.6e-05), respectively.
Conclusions: We identified CXCL8 as the most significant circulating marker of TAK1 activation. Our study candidates CXCL8 as a potential predictive biomarker of resistance to nal-IRI in gemcitabine- refractory PC patients.

B18

RELATIONSHIP BETWEEN CHANGE IN A-FETOPROTEIN (AFP) AND PATIENT (pt) SURVIVAL IN HEPATOCELLULAR CARCINOMA (HCC): A REAL-WORLD ELECTRONIC MEDICAL RECORDS (EMR) DATABASE STUDY

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Relationship between change in AFP and OS

Observed AFP change during 1L	N	Median OS (95% CI), months	Cross-ratio	Kendall's Tau
Decrease (≥) to <400 from ⩾400 ng/mL	20	14.3 (4.8–30.9)	1	0
↓ ⩾20 ng/mL	85	7.4 (5.7–11.9)	1	0
↓ ⩾7 ng/mL/month	68	6.8 (5.0–12.7)	1	0
↓ ⩾20%	98	11.1 (7.3–13.2)	1	0
↓ ⩾50%	51	12.2 (7.3–18.2)	1	0
Increase (≥) to ⩾400 from <400 ng/mL	18	5.9 (3.6–7.4)	1.506	0.202
↑ ⩾20 ng/mL	140	4.8 (3.7–5.5)	1.902	0.311
↑ ⩾7 ng/mL/month	124	4.5 (3.1–5.2)	2.006	0.335
↑ ⩾20%	141	5.2 (4.1–6.5)	1.841	0.296
↑ ⩾50%	109	5.4 (4.5–6.9)	1.755	0.274

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Background: Serum AFP levels are used as diagnostic and prognostic markers for pts with HCC. Assessment of clinical relevance of changes in AFP over time outside of clinical trials is lacking. This study explored the relationship between changes in AFP levels and overall survival (OS) in a real-world setting.

Material and methods: This retrospective analysis used the IMS Oncology EMR database (US patients 12/01/2007-12/31/2014). Eligible pts were diagnosed with HCC, 18+ years old, had ⩾1 AFP test recorded 60 days prior to 180 days after diagnosis and received anticancer therapy ⩽180 days after diagnosis. Survival analyses were by Kaplan-Meier method. The gamma-frailty model was used to correlate AFP change utilizing previously reported definitions of AFP change (above/below 400 ng/mL, ⩾20 ng/mL, ⩾7 ng/mL/month, ±20%, ±50%) and OS.

Results: 907 pts met eligibility criteria (77.3% male, median 65 years). Of 697 pts with AFP prior to start of first-line therapy (1L), 453 (65%) with baseline AFP <400 ng/mL had an OS of 4.2 months and 244 (35%) with ⩾400 ng/mL an OS of 2.9 months. An increase in AFP was associated with a decrease in OS in 278 patients with baseline and 1L AFP (Table). Of the 101 pts with an AFP test before start of second-line therapy, 32.7% had AFP ⩾400 ng/mL.

Conclusions: Increases and decreases in AFP during 1L, regardless of AFP change definition, were generally associated with shorter and longer OS, respectively. Conclusions are limited by the risk of immortal time and selection bias, as not all patients had multiple AFP measures recorded.

Disclosure: This was an unfunded research project. Eli Lilly and Company provided employee time and database access.

B19

PREOPERATIVE NUTRITIONAL STATUS AS A PREDICTIVE FACTOR OF SURVIVAL FOLLOWING RESECTION FOR PANCREATIC DUCTAL ADENOCARCINOMA

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Background: Nutritional derangements and loss of skeletal muscle mass are common hallmarks of pancreatic ductal adenocarcinoma (PDAC). Their early detection and management are usually overlooked in routine practice, so their impact on outcome is poorly described. Therefore, this study aimed to investigate the prognostic value of nutritional status in patients (pts) undergoing surgery for PDAC.

Patients and methods: Clinical data of non-consecutive pts submitted to surgery for PDAC from November 2015 to January 2018 at General and Pancreatic Surgery Unit, Pancreas Institute, University Hospital of Verona, were prospectively collected. Nutritional screening was performed according to the standard of Nutritional Risk Screening (NRS)-2002. Body composition was evaluated using Bioelectrical Impedance Vector Analysis (BIVA) the day before the scheduled surgery. Clinical, pathological and nutritional data were correlated to disease-free/overall survival (DFS/OS) using a Cox and logistic regression model. Kaplan-Meier curves were compared with Log-Rank.

Results: Overall data from 73 patients (41 males [56.2%], 32 females [43.8%]) were gathered. The

median age was 65 years [range 37-81] and the median follow-up was 11 months [range 1-40]). The majority (80.8%) were at risk of malnutrition (NRS-2002⩾3), despite median BMI was 23.9 kg/m^2. At multivariate analysis, stage (HR 4.30, 95% CI 1.03-17.92, *p = 0.045*), NRS-2002 (HR 6.51, 95% CI 1.39-30.38, *p = 0.017)*, fat-free mass (FFM) (HR 1.08, 95% CI 1.02-1.14, *p = 0.013*) were significant independent predictors for OS. Particularly, patients with preoperative NRS-2002 ⩽3 had significantly longer 2-year OS than those with NRS-2002>3 (94% vs 75%, *p = 0.02*). Conversely, BMI did not affect OS. Twenty-four patients (32.9%) were treated with neoadjuvant therapy. NRS-2002 was significantly higher in this subset of patients (*p = 0.026*), with a significant difference according to chemotherapy regimens (Folfirinox vs. Gemcitabine/Nab-paclitaxel) (*p = 0.035*). In pts treated with adjuvant chemotherapy (n=33, 45.2%) FFM correlated with worse DSF and OS (*p = 0.039* and *p = 0.039*, respectively).

Conclusions: Our analysis suggests that preoperative malnutrition and FFM have a detrimental impact on OS in PDAC. Therefore, preoperative nutritional screening and, possibly, targeted nutritional intervention may improve outcomes in resectable PDAC pts, particularly in those who are candidate to neoadjuvant therapy.

B20

RAMUCIRUMAB (RAM) AS SECOND-LINE TREATMENT IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC) AND ELEVATED BASELINE A-FETOPROTEIN (AFP): AN ANALYSIS OF AFP KINETICS IN THE PHASE 3 REACH-2 STUDY

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Background: REACH-2 demonstrated a significant survival benefit with RAM vs placebo in the second-line treatment of patients with advanced HCC and AFP ⩾400 ng/mL. This analysis investigated changes in AFP during treatment, as well as potential relationships with survival or progression.

Material and methods: Patients were randomized (2:1) to RAM 8 mg/kg IV or placebo Q2W plus best supportive care until disease progression or unacceptable toxicity. Serum AFP levels were measured at baseline and every 3 cycles. Percent change in AFP from baseline was analyzed at each time point up to Cycle 12 with descriptive statistics and Wilcoxon rank sum test between treatment arms. AFP response was defined as ⩾20% decrease from baseline. The association between AFP progression and radiographic progression in each time interval was assessed by odds ratio (OR) and Fisher's exact test. Time to AFP progression and time to radiographic progression (TTP) were evaluated by the Kaplan-Meier method and compared between treatment arms using a stratified log-rank test. AFP progression was defined as ⩾20% increase from baseline. Hazard ratio (HR) was generated using a stratified Cox regression model.

Results: AFP response was significantly higher with RAM compared with placebo (42.1% vs 10.5%, p<0.0001). Overall survival (OS) was longer in patients with AFP response (13.5 months) than in patients without (6.7 months), irrespective of treatment (HR 0.470, p<0.0001). The median percent increase in AFP level from baseline was smaller in the patient population treated with RAM (0.4%, 6.1%, 15.4%, 10.8%) than with placebo (45.7%, 98.5%, 122.2%, 91.3%) at Cycles 3, 6, 9 and 12, respectively. Time to AFP progression (HR 0.422, p<0.0001) and TTP (HR 0.427, p<0.0001) favored a RAM benefit; subsequent analyses demonstrated a strong association between AFP progression and radiographic progression at 6 weeks (OR 2.44, p<0.0084) and at 12 weeks (OR 1.89, p=0.0430).

Conclusions: Changes in AFP levels were associated with TTP and OS. RAM prolonged both time to AFP progression and radiographic TTP, and appeared to slow the rate of AFP increase during treatment.

B21

INTERIM ANALYSIS OF BI-CAUSE STUDY (BILIARY CANCER IN ITALY: A STUDY ON CHOLANGIOCARCINOMA CAUSES AND RISK FACTORS)

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Background: Cholangiocarcinoma (CC), partitioned in intrahepatic (ICC) or extrahepatic (ECC) subsites, is a rare cancer in Italy, whose etiology is still largely unexplained. The majority of the existing etiologic studies is based on Eastern populations and is inherently biased by patient selection, retrospective nature, small sample size or inappropriate grouping with other cancers, such as gallbladder and ampullary cancer.

Patients and Methods: The BI-CAUSE trial is an ongoing multi-centre, observational, prospective study aimed to depict the etiologic landscape of CC in Italy. Per protocol, CC patients admitted to oncologic care are administered an interview on life-style and concomitant conditions and undergo additional laboratory testing at the beginning of chemotherapy; moreover, clinical and pathology informations are collected.

Results: We hereby present results from the first 90 enrolled patients (pts) (male 60.0%; caucasian 98.9%; median age 65 years). ICC were 58.5% of the sample, ECC 41.5% (perihilar 12.2%, distal 29.3%). M:F ratio was numerically higher in ECC than in ICC (2.1:1 vs 1.1:1, p=0.15), whereas median age of onset was identical. The main histology was adenocarcinoma (88.7%), further defined as papillary, mucinous or desmoplastic in 2 cases (2.5%) each; combined hepatocholangiocarcinoma was 3.8% (7.1% of ICC cases).
Active or former smokers were 59.5% of the sample, and most (46.2%) had cumulated a moderate or high exposure (⩾10 pack-years); 33.7% were at least moderate drinkers (⩾2 alcohol unit/day). Only 29.1% did not meet any of the lab criteria of dyslipidemia; 17.0% had type-2 diabetes mellitus; 41.4% had a BMI ⩾25 Kg/m^2, including 13.1% with BMI ⩾30 Kg/m^2. One pt had a history of ulcerative rectocolitis, while none of Crohn's disease, primary biliary cholangitis (PBC) or primary sclerosing cholangitis; however, 7.5% were positive for anti-mithocondrial antibodies (AMA). HBcAb+ pts were 19.9% [ICC 27% vs ECC 7%, p=0.058], of whom 2.7% were HBsAg+ (1 with detectable HBV-DNA) and 2.7% co-infected with HCV.

Conclusions: In this interim analysis, a high incidence of alcohol consumption, smoke, and features of dismetabolic state (diabetes mellitus, dyslipidemia, excess weight), was observed. The etiologic role in CC of viral hepatitis B -already demonstrated in Countries with high incidence of both entitites- appears confirmed, particularly for ICC. The novel finding of serum AMA in the absence of clinical PBC deserves further investigation.

B22

OXALIPLATIN-BASED THERAPY AND ECOG PERFORMANCE STATUS (PS) ARE PREDICTIVE OF SURVIVAL IN SECOND-LINE ADVANCED PANCREATIC CANCER (PC) AFTER GEMCITABINE PLUS NAB-PACLITAXEL TREATMENT

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Background: The most effective chemotherapeutic regimen in patients (pts) affected by PC in the second-line setting has not been defined yet. In two phase 3 randomized trials, doublet chemotherapy provided a survival benefit compared to monotherapy, showing the superiority of OFF (oxaliplatin + fluorouracil) regimen and nal-irinotecan (nal-IRI) + fluorouracil/leucovorin (FU/LV) over FU/LV. Clinical decision is mainly based on persistent toxicities by first-line treatment, and patients preference.
The aim of this analysis is to evaluate different second-line regimens in a real-world population of pts progressing under gemcitabine plus nab-paclitaxel first-line treatment.

Material and methods: Clinical data of pts affected by advanced PC receiving a doublet chemotherapy regimen in the second-line setting between January 2015 and December 2018 were retrospectively reviewed. All pts received at least 3 cycles of gemcitabine and nab-P as first-line therapy.
Median progression free survival (PFS) and overall survival (OS) were estimated with Kaplan-Meier method with 95% CI (confidence interval). Cox-regression model was applied to the data with univariate approach.

Results: 136 pts were included in our analysis. The median age was 65 (35-79). 55.9% had head primary tumor location. The majority of pts had an ECOG PS=0 (65.1% PS 0, 28.7% PS 1, 6.3% PS 2) at the beginning of second line. About one third of pts (33%) previously underwent surgery. Half of pts (48.6%) received a third or further lines of treatment.
Second-line PFS and OS were 3.25 (95%CI 3.01-3.49) and 9.14 (95%CI 7.82-10.47) months, respectively. We measured a significant longer OS in pts receiving an oxaliplatin-based therapy (FOLFOX/XELOX) compared that in pts receiving irinotecan-based chemotherapy (FOLFIRI/nal-IRI+5-FU) (13.75 vs. 8.04 months, p=0.014). Pts with ECOG PS=0 had a better OS compared to ECOG PS

1 pts (10.5 vs. 7.79 months respectively, p=0.044). No difference was detected in PFS.
Conclusions: Pts receiving an oxaliplatin-based chemotherapy and with PS ECOG=0 had a longer OS in the second-line setting. However, no differences have been shown considering PFS and no analyses have been performed regarding different regimens (e.g. irinotecan versus nal-IRI) because of the limited number of pts included. Further possible predictive factors could be investigated by expanding the population analyzed.

B23

TUMOR MICROENVIRONMENT (TME) IN RESECTED PANCREATIC CANCER (PC): EVALUATION OF FIBROSIS, TUMOR-INFILTRATING LYMPHOCYTES (TILS), AND ANGIOGENESIS

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Background: Inflammation may promote cancer development and, in turn, an immune suppressive TME with abundant fibrosis may favor tumor progression. Aim of the study was to evaluate the association of fibrosis, TILS (CD4+ and CD8+), blood and lymphatic vessels, within the PC TME, with other PC pathological features, and their impact on disease-free survival (DFS).
Material and methods: The study included 37 consecutive patients (pts) who underwent surgery for PC from January 2012 to December 2017 at the University Hospital of Udine, Italy. Immunohistochemical analyses for CD4, CD8, ERG (blood vessels), D2-40 (lymphatic vessels) and Masson's Trichrome stain were performed. CD4+ and CD8+ lymphocytes were evaluated as the mean value derived from five counts in hot spot High-Power Field; ERG and D2-40 as the average in 3 fields at 10x magnification; fibrosis as proportion to the total neoplastic mass, clustering every ten percentiles. The prognostic impact on DFS was analyzed through Cox regression model. Associations were explored by Wilcoxon rank-sum test or Kruskal-Wallis test, as appropriate.
Results: Median age was 67.5 years; 19 (51%) pts were male. R0 resection was observed in 28 (76%) pts whereas 9 (24%) pts achieved R1 resection. The median percentile of fibrosis was 30-40%; median number of blood vessels was 13; median number of lymphatic vessels was 5; median CD4+ and CD8+ lymphocytes were 43 and 33, respectively. A higher number of CD4+ was associated (p=0.016) with pathological nodal involvement (pN1). Higher CD8+ lymphocytes count was associated (p=0.056) with higher tumor grade (G3 vs G2/G1). No association was shown with pts age, tumor size, vascular or neural invasion, PC site (head vs body vs tail), and site of further disease progression. No association was observed between fibrosis and TILS. No prognostic value was shown for neither fibrosis nor angiogenesis nor TILS.
Conclusions: In resected PC, intriguing association was observed between TILS and nodal involvement. Further investigations and validation on larger case-series are needed to better explore the prognostic impact of TME in pts with resected PC.

B24

NIVOLUMAB IN METASTATIC GASTRIC CANCER PATIENTS PROGRESSED AFTER TWO OR MORE CHEMOTHERAPY LINES: DATA FROM A WESTERN POPULATION

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Background: The phase III ATTRACTION-2 trial showed that Nivolumab is a new treatment option for unselected Asian patients (pts) with advanced gastric (GC) and gastro-oesophageal (GEJ) cancer progressed after two or more previous chemotherapy regimens. However, still today there is a lack of evidence about its efficacy in non-Asian pts. The aim of this analysis was to evaluate the safety and efficacy of Nivolumab in a real-life western population.
Materials and methods: Pts progressed after two or more chemotherapeutic regimens for advanced disease with performance status of 0 or 1 according to ECOG and without ongoing or previous autoimmune disease were eligible for treatment. Pts were unselected for PD-L1 tumor expression or microsatellite status. All pts received Nivolumab 3mg/Kg every 14 days until progression or unacceptable toxicities. Statistical analysis was performed by SPSS 21.0 software.
Results: 15 pts were treated with Nivolumab as off-label treatment from September 2017 to April 2019. Pts received Nivolumab as third (80%) or fourth line of treatment (20%). The safety profile was in line with the literature and only 6.6% of pts showed unacceptable toxicities, requiring the discontinuation (prolonged anemia and thrombocytopenia G3). Best overall responses were complete response in 2 pts, partial response in one pts and stable disease in 2 pts. Median duration of response was 2 months (range: 2-15 months).

Eleven pts discontinued Nivolumab due to PD, worsening of conditions or death, whereas treatment is ongoing in 4 pts. With a median follow-up of 17 months (95% CI: 6.2-27.7), median OS was 6 months (95% CI: 0.5-11.5) and median PFS was 3 months (95% CI: 0.47-5.5). Median OS was 6,18 and 19 months in responders pts. Median treatment duration was 4 months (range:1-19 months). Data for PD-L1 and microsatellite status were retrospectively collected for 10 pts as following: MSS/MSI: 7/3; PD-L1 positive (⩾1%)/negative: 3/7. Although no statistically significant difference in OS or PFS was reported according to PD-L1 expression, neutrophil/lymphocyte ratio or microsatellite status, however all responders had PD-L1 positive or MSI status.
Conclusions: Our results showed that Nivolumab is feasible and effective in real-life unselected western pts affected by advanced GC and GEJ. Moreover, these results might suggest that PD-L1 expression and microsatellite status could be predictive factors for nivolumab efficacy after confirmation in a larger sample.

B25

FOLFIRINOX VERSUS GEMCITABINE-NABPACLITAXEL AS NEOADJUVANT STRATEGIES IN LOCALLY ADVANCED PANCREATIC CANCER: A RETROSPECTIVE MONOCENTRIC STUDY

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Background: Pancreatic Ductal Adenocarcinoma (PDAC) is an aggressive disease, being the 4th leading cause of cancer mortality, expected to achieve second place by 2030. Around one third of cases are diagnosed as locally advanced (LA-PDAC), for which the therapeutic strategy is still unclear.
Methods: Retrospective analysis of patients with LA-PDAC, at least 18 years of age, treated between October 2014 and April 2019, with either FOLFIRINOX or Gemcitabine-NabPaclitaxel as neoadjuvant treatments. The information collected at baseline included the patients' age, gender, performance status assessed following ECOG scale (PS ECOG), CA19.9, pancreatic lesion site (head vs body/tail), staging (TNM). At the end of treatment, all of the above variables were assessed again.
Results: A total of 73 patients were diagnosed with LA-PDAC during the observation time: 18 patients were offered best supportive care or monotherapy treatment, 35 patients FOLFIRINOX (FFN) and 20 patients Gemcitabine Nab-Paclitaxel (GemNab). At the time of analysis, 2 patients in the GemNab arm were still on treatment. The population characteristics were similar in the two treatment groups. Eighteen patients of the 55 evaluated underwent surgery (32.7%), 13 in the FFN group (37.14%), 5 in the GemNab group (25%). Resection margins were positive in 4/13 and 1/5 patients, in the FFN and in the GemNab groups respectively. The median Disease Free Survival (mDFS) was 70.4 weeks in the resected population; 70.4 weeks in the FFN group and 85.9 weeks in the Gem Nab group ($p=0.96$). The median Overall Survival (mOS) for unresected patients was 57 weeks, 73.6 weeks for the FFN group and 57 weeks for the GemNab group ($p=0.26$).
Conclusions: The results from our study showed that LA-PDAC patients can be addressed to neoadjuvant strategies with the objective of R0 resections: 18 of the 55 patients evaluated underwent surgery and in more than 70% of cases the margins were negative. A survival benefit can be observed: mDFS of resected patients (70.4 weeks) is even longer than mOS of the unresected population (57 weeks). The OS substantial difference will be appreciated with a longer follow up.

B26

IMMUNE CHECKPOINTS INHIBITORS IN PRE-TREATED GASTRIC CANCER PATIENTS: RESULTS FROM A LITERATURE-BASED META-ANALYSIS

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Background: Immunotherapy has recently changed the treatment of several cancers. We performed a literature-based meta-analysis of randomized controlled trials to assess the efficacy of the novel immune check-point inhibitors (ICIs) in metastatic gastric cancer.
Materials and methods: The primary outcome was overall survival. We planned a subgroup analysis for OS according to PD-L1 status, age (65 years was the cut-off), tumour location (gastric versus gastro-oesophageal junction), sex and ECOG performance status (1 versus 0).
Results: Three studies were included in the analysis for a total of 1456 cases (811 cases were in the experimental group and 645 cases in the control group). The pooled analysis showed improved OS in the experimental arm, in the absence of statistical significance (HR = 0.87, 95%CI: 0.64-1.18; P = 0.37). The subgroup of patients with PD-L1 positive tumours (HR = 0.82 vs 1.04) and gastroesophageal junction cancer (HR = 0.82 vs 1.04) showed a statistically significant advantage.
Conclusions: This study doesn't support the efficacy of immune check-point inhibitors in unselected patients with metastatic gastric cancer. Future studies are needed with the aim of identifying reliable predictive biomarkers of ICIs' efficacy.

B27

ROLE OF CHEMORADIATION (CRT) IN THE ADJUVANT TREATMENT OF RADICALLY RESECTED PANCREATIC CANCER (PC) PATIENTS (pts): A MONO-INSTITUTIONAL RETROSPECTIVE ANALYSIS

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Background: To date, the standard of care for resectable PC pts is upfront radical surgery followed by adjuvant chemotherapy (CT). The role of CRT in this setting remains controversial and often it is reserved for PC pts with a high risk of local relapse, due to positive margins and/or positive lymph-nodes.
Method: Radically resected PC pts receiving adjuvant CT and CRT at our Institution were retrospectively collected. The objective of the analysis was to evaluate the role of postoperative CRT in terms both of disease-free survival (DFS) and overall survival (OS). The association with rate of local recurrence, DFS and OS was evaluated for both margin (R0 vs R1/R2) and nodal status (pN0 vs pN1/2) and also for the combination of these two variables (R0 and pN0 vs R1/2 and/or pN1/2).
Results: From January 2000 to April 2018, a total of 106 radically resected PC, treated with postoperative CT and CRT, were identified. Pts median age was 62 years (range 41-83); 45% of pts were females. Tumor characteristics were the following: head tumor location 81%; stage I, II and III was 6%, 58% and 14%, respectively, not applicable (NA) in 22% of cases; margin status was R0 in 68%, R1 in 21%, R2 in 3% and NA in 8% of pts; 95% of pts had ductal adenocarcinoma; pN0 and pN1/pN2 was 43% and 56%, respectively (NA 1%); grading G1 was 2%, G2 54% and G3 30%; pT1 2%, pT2 17%, pT3 69%, pT4 12%. Adjuvant gemcitabine was administered to 75% of pts; RT technique was intensity modulated RT and 3D RT in 22% and 75% of cases, respectively. Disease progression (PD) was observed in 66% of pts: local and distant recurrence occured in 35% and 47% of cases, respectively. Median DFS was 19.2 months, median OS was 36.7 months. No significant association of margin and nodal status with local recurrence, DFS and OS was observed.
Conclusions: Our analysis, although limited by the small sample size, its retrospective nature and the lack of pts treated with a more efficacious adjuvant CT such as FOLFIRINOX, might suggest a possible role of postoperative CRT in maximizing adjuvant treatment of radically resected PC pts, in particular of those with poor prognostic factors such as positive margins and/or positive lymph-nodes.

B28

FOLFIRINOX AFTER FIRST LINE GEMCITABINE BASED CHEMOTHERAPY IN METASTATIC PANCREATIC CANCER: A MONO-INSTITUTIONAL EXPERIENCE

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Background: Pancreatic adenocarcinoma represents the fourth cause of death among both males and females. For many years the standard of care for the locally advanced or metastatic setting was Gemcitabine-based chemotherapy. There are only few data on the safety and efficacy of FOLFIRINOX or fluoropyrimidine (5FU)-based chemotherapy after Gemcitabine-based first line's failure.
Methods: From February 2013 to August 2018, a total of 102 locally advanced or metastatic pancreatic patients, who progressed from Gemcitabine-based first line chemotherapy, were candidate to receive a second line chemotherapeutic treatment based on 5-FU. The goal of this study was to evaluate the progression free survival (PFS); overall survival (OS), and safety were also analyzed.
Results: At the time of the analysis, out of 102 patients with metastatic pancreatic adenocarcinoma that underwent first-line chemotherapy with gemcitabine-based schedules (92.5% of these patients were treated with Gemcitabine-NabPaclitaxel), only 37 of them succeeded to receive a second line 5FU-based treatment and only 26 of them succeeded to receive 4 cycles of chemotherapy, at least. The schedules used were FOLFIRINOX (11 patients), FOLFOX (7 patients), FOLFIRI (8 patients). Median PFS was longer in the FOLFIRINOX group compared to FOLFOX (32.1vs23 weeks, $p=0.03$) and FOLFIRI (32.1vs15.8 weeks, $p=0.004$), while there was no difference between the FOLFOX and FOLFIRI groups (23vs15.8 weeks, $p=0.34$). As well as the PFS, the median OS, calculated as the overall survival from the start of second-line treatment, was significantly higher in the FOLFIRINOX group compared with FOLFOX (11.6vs6.9 months, $p=0.01$) and FOLFIRI (11.6vs6.4 months, $p=0.001$). Main grade 3/4 adverse events were anemia and neutropenia, and they were higher in the FOLFIRINOX and FOLFOX group. Moreover, there was no difference among the three groups of treatment for age, sex, stage of disease, adjuvant treatment performed, and the presence of biliary

stent. However, patients enrolled in the FOLFIRINOX group had better performance status (ECOG0 = 80%) compared with FOLFOX and FOLFIRI (ECOG1 = 80%).
Conclusions: FOLFIRINOX is efficacy and a well tolerated chemotherapeutic schedule as second-line treatment in patients with advanced pancreatic cancer after gemcitabine-based first line. Patients should be selected according to performance status, comorbidities and previous toxicities reported during first line.

B29

FLOT REGIMEN AS PERIOPERATIVE TREATMENT IN RESECTABLE GASTRIC CANCER: SAFETY UPDATE AND PROGNOSTIC FACTORS ANALYSIS FROM A MONO-INSTITUTIONAL EXPERIENCE

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Background: FLOT-4 is a new standard of care for resectable gastric (GC) and gastroesophageal (GEJ) cancer. Our retrospective analysis aims to evaluate safety and efficacy of FLOT in a real-life population and to identify potential prognostic factors.
Methods: from January 2015 to April 2019, 45 patients (pts) received FLOT (docetaxel 50 mg/mq d1, oxaliplatin 85 mg/mq d1, leucovorin 200 mg/mq d1, and 5FU 2600 mg/mq as 24h infusion all q14) as perioperative treatment. All pts received PEG-G-CSF. Based on our previous data on Neutrophil to lymphocyte ratio (NLR) in GC (Petrillo A, Future Oncology 2018), we evaluated this factor from pretreatment blood count.
Results: median age was 62 years (range 36-78), male/female: 31/14, PS ECOG 0: 97.8%, 1: 2.2%; tumor location: Siewert I: 15.5%; Siewert II/III: 33.3%, stomach: 51.2%; adenocarcinoma with signet ring cells (SRC): 37.8%; Lauren's type: intestinal 24.4%, diffuse 28.9%, unknown 46.7%; stage: IB: 4.5%, II: 55.5%, III: 40%. Most frequent adverse events (AE) were fatigue G1 (60%), nausea G1 (70%) and neurotoxicity G1 (22%); most common grade 3 AE was neutropenia (2.2%). No grade 4-5 toxicity has been described. Perioperative treatment is ongoing in 8.9%, while 80% underwent surgery. R0 and R1 resection were achieved in 84.4% and 15.6% respectively. Among evaluable pts, 11% reported TRG1, 14% TRG 3, 25% TRG 4, 11% TRG5 and TRG was not reported in 39% of cases. The majority of TRG 4/5 were diffuse with SRC component (54%). With a median FUP of 14 months (mo) [95% CI: 11.5-16.6], mOS and mPFS were not reached. OS was higher in pts with no SRC tumors [NR vs 14 mo, p = 0.35] and in pts with intestinal type [NR vs 18 mo, p = 0.5]. 32% of the 28 pts who received adjuvant treatment did not complete the 4 postoperative cycles due to poor tolerability; these pts had a worse PFS and OS trend when compared to pts who completed treatment: 16 mo vs NR [p = 0.056] and 18 mo vs NR [p = 0.291]. Pretreatment NLR (median value 2.6) did not show a significant correlation with OS and PFS.
Conclusions: Our results showed that FLOT is well tolerated in GC perioperative treatment. Diffuse histology and the presence of SRC component are associated with a worse outcome and TRG. NLR does not correlate with outcome, while a suboptimal adjuvant treatment could be associated with worse prognosis.

B30

ANALYSIS OF NEW POTENTIAL PROGNOSTIC FACTORS IN ADVANCED PANCREATIC ADENOCARCINOMA PROGRESSING TO FIRST-LINE CHEMOTHERAPY: THE EXPERIENCE OF NATIONAL CANCER INSTITUTE OF MILAN

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Background: Metastatic pancreatic adenocarcinoma (mPAC) is one of the most poor-prognosis cancers, with limited therapeutic options. In the second-line (2L) setting, except for ECOG performance status (PS) and CA 19.9, there is no clear evidence on factors that could predict patients (pts)' survival. The aim of this monocentre, retrospective study was to investigate the association between other candidate clinical prognostic variables, as neutrophil-to-lymphocyte ratio, modified Glasgow Prognostic Score, BMI, Khorana score, and overall survival (OS).
Methods: Data records of pts affected by mPAC progressing to 1L chemotherapy and treated between 1/08/2008 and 31/08/2018 were reviewed. We considered pts who received at least one administration of 2L therapy (group A) and pts who did not receive any oncologic active treatment by clinical judgement (group B). The statistical analysis was performed separately for each subgroup. OS was defined as the time elapsed between the start of 2L therapy and death (A), or between disease progression and death (B). Cox regression model was used in univariate and multivariate analysis. P-values for interaction are reported in the results section.
Results: Groups were homogeneous for characteristics: 57 out of 63 (90%) pts and 65 out of 67 (97%) pts were respectively dead in group A and group B at the end of follow-up period. Median OS time was 6.2 months in group A and 0.4 months in group B. ECOG PS >= 2 [A: HR = 7.23 (95%CI

2.66-19.60); B: HR=2.54 (95%CI 1.32-4.88); p: 0.09], mGPS=2 [A: HR=4.00 (95%CI 1.88-8.51); B: HR=2.57 (95%CI 1.39-4.76); p: 0.37], NLR >=3.5 [A: HR=2.56 (95%CI 1.44-4.58); B: HR=1.44 (95%CI 0.82-2.54); p: 0.16], Khorana > 2 [A: HR=2.32 (95%CI 1.26-4.29); B: HR=1.91 (95%CI 1.13-3.25); p: 0.646], were significantly related with worse prognosis. Conversely, CA19.9 and BMI did not appear to increase death risk [A: HR=1.00; B: HR=1.00; A: HR=1.12 (95%CI 0.95-1.32); B: HR=1.12 (95%CI 0.95-1.32); p: 0.13]. In the multivariate analysis point estimates were confirmed, although statistical association was weaker.

Conclusions: In a setting of mPAC progressing to 1L therapy, our analyses confirm several clinical variables as related to a worse outcome and add NLR and Khorana as possible factors conditioning the possibility to receive a 2L therapy. For this instance, we emphatize the importance to conduct prospective studies in order to develop and validate reliable and feasible prognostic nomograms.

B31

IMPACT OF BASELINE CA19.9 LEVELS ON OUTCOMES OF PATIENTS WITH BORDERLINE RESECTABLE AND LOCALLY ADVANCED PANCREATIC CANCER: A RETROSPECTIVE ANALYSIS

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Background: Almost 40% of pancreatic cancer have inoperable, loco-regional tumor at diagnosis with extension to surrounding vasculature or structures. Management of locally advanced tumor (LAPC) and borderline resectable tumor (BRPC) is often heterogeneous and no prognostic or predictive markers are achievable in clinical practice.

Patients and methods: This retrospective analysis included 52 not operable LAPC and BRPC treated at Sant'Orsola-Malpighi Hospital between 2012 and 2017. After data collection we performed an univariate analysis of clinic-pathological and anthropometrics parameters using log-rank test. Survival outcomes were estimated with Kaplan-Meier curves.

Results: Forty patients were included in final analysis. Median age was 65.8 year and 95% had ECOG PS >=1. At baseline the median tumor marker carbohydrate antigen 19-9 (CA 19-9) levels were 1274.25 U/ml (range 0.8-10000). About 47.5% of patients received FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) schedule as first line of therapy, while in 37.5% of cases was given a combination gemcitabine-based chemotherapies and 15% received gemcitabine monotherapy. In 47.5% of cases were given a second-line, whereas in 27.5% received third- or more line therapies. Eighteen patients (45%) were treated with subsequent radiotherapy. The median progression free survival (PFS) and median overall survival were 8.7 months and 11.5 months respectively.

In univariate analysis the factors that significantly influenced PFS were ECOG-PS (p=0.001), baseline CA19.9 levels (p=0.034) and radiotherapy treatment (p=0.033), while only baseline CA19.9 levels (p=0.033) were significantly associated with OS.

Conclusions: Baseline CA 19-9 levels are significantly correlated with overall survival of patients affected by LPAC and BRPC, suggesting that this evaluation could improve their clinical management and the decision making. Further investigations and multivariate analysis are needed to confirm these data.

B32

HEPATIC ARTERIAL INFUSION OF CHEMOTHERAPY FOR ADVANCED BILIARY TRACT CANCERS

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Background: Treatment outcomes and survival for patients with biliary tract cancers (BTCs) have improved little over the past three decades. Approximately half of untreated patients die within 3–4 months of presentation from the indirect effects of local tumor progression, bile duct obstruction, liver failure or sepsis from cholangitis and abscesses. Hepatic arterial infusion of chemotherapy (HAI) gets better pharmacokinetics outcome with some compounds that have a very high vascular extraction ratio on first pass removal.

Patients and methods: This is an observational, single-center, retrospective analysis of HAI associated to systemic fluoropyrimidines-based chemotherapy (sCT) for patients with locally advanced or metastatic BTCs. HAI provided the loco-regional infusion of epirubicin and cisplatin.

Results: From 2000 to 2015, 142 patients were treated with HAI associated to sCT (43% female, 57% male). The median age was 62. Primary tumor were intrahepatic, extra-hepatic, or gallbladder in 102 (72%), 18, (13%) and 22 (15%) cases, respectively. HAI was administered as

first-line or second-line in 116 (82%) and 26 (18%) patients, respectively. Extra-hepatic metastases were present in 58 (40%) patients. In 37 (25.5%) cases a curative surgery was performed before the recurrence. There were no difference in median progression-free survival (mPFS) and overall survival (OS) according to primary tumor site. With HAI as first-line the overall response rate (mORR) was 16% with a disease control rate (DCR) of 65% with 5.5 and 13 months of mPFS and mOS. As second-line, the ORR was 19% with DCR of 50% with 3.8 and 20.1 months of mPFS and mOS. Nine (6%) patients have been converted to surgery after HAI, with mOS of 50.3 months. After HAI, liver progression was documented in 81% of patients.
Overall, pre and post treatment median performance status and median CA19.9 level were 1 and 0 – 151.5 and 95.5. Patients that underwent to curative surgery had better survival (p: < 0.0001) – mOS were 50.3, 28.9, and 11.5 months in converted to surgery after HAI group, previous curative surgery group, and no surgery group, respectively.
Conclusions: In our series most of patients were treated with HAI as first-line treatment before the evidence of efficacy of cisplatin and gemcitabine doublet. However, this analysis has demonstrated an interesting activity of HAI associated with sCT despite the line of treatment, and confirms the fundamental role of surgery for a good outcome in BTCs.

B33

MODIFIED FOLFIRINOX FOR UNRESECTABLE LOCALLY ADVANCED/ METASTATIC PANCREATIC CANCER. A REAL-WORLD COMPARISON OF AN ATTENUATED WITH A FULL DOSE IN A SINGLE CENTRE EXPERIENCE

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Metastatic pancreatic adenocarcinoma has a very poor prognosis. Although irinotecan, oxaliplatin and leucovorin-modulated fluorouracil (FOLFIRINOX) significantly increases survival in advanced pancreatic cancer, compared to employing only gemcitabine (GEM), toxicities have tempered enthusiasm for its use. This study analyses in a retrospective study the real-world clinical practice with full and attenuated doses of FOLFIRINOX in unselected patients with locally advanced unresectable or metastatic pancreatic cancer, treated at an Italian general hospital. Efficacy, tolerability and toxicity were evaluated, and Overall Survival (OS) and Progression-Free Survival (PFS) were estimated by Kaplan-Meier method. Fifty consecutive patients with advanced (13 patients)/metastatic (37 patients) pancreatic adenocarcinoma were treated with FOLFIRINOX at the Medical Oncology Unit, Piacenza General Hospital, North Italy. The first enrolled consecutive eighteen patients (36%) of this series started the treatment with a full dose of the regimen, while the subsequent thirty-two (64%) consecutive patients received dose attenuation (-20% bolus fluorouracil and -25% irinotecan). In the entire group, the response rate (RR), median OS and median PFS were 30%, 10.1 months, and 5.6 months respectively, with no differences in objective response in the 32 patients that received an attenuated dose compared with the 18 patients receiving a full dose of chemotherapy. However neutropenia, anemia, fatigue and vomiting were statistically increased in the 18 patients receiving a full dose compared with the 32 patients receiving an attenuated dose of FOLFIRINOX ($p<0,05$). This study demonstrates the efficacy and tolerability of modified FOLFIRINOX in advanced/metastatic pancreatic cancer.

B34

COMPARISON BETWEEN FOLFIRINOX AND GEMCITABINE-NABPACLITAXEL FOR METASTATIC PANCREATIC CANCER: A MONOCENTRIC RETROSPECTIVE COHORT STUDY

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Background: Metastatic pancreatic cancer (PC) has a dismal prognosis, with a median overall survival (mOS) of about 6 months without systemic therapy. FOLFIRINOX (FFN) and Gemcitabine plus nab-paclitaxel (GnP) are actually used as first-line treatments in metastatic pancreatic cancer, but there are no head-to-head randomized trials available supporting the optimal choice between these two regimens. The aim of our study is to evaluate the efficacy and the toxicity profile in patients treated with these therapies in a real word setting.
Methods: We retrospectively evaluated 89 chemotherapy-naïve metastatic PC patients treated with FFN or GnP, at the Oncology Department of Federico Ii University of Naples, between September 2011 and March 2018. We compared the patients' clinical characteristics, and efficacy and tolerability of FFN and GnP.
Results: In our study, 31 patients were treated with FFN and 58 patients with GnP as first line therapy. Baseline characteristics (FFN/GnP) were as follows: median age 56/61.6 years, ECOG performance status (0-1): 100%/96%, gender (female): 31%/44%, median number of cycles: 9.22/6.48 respectively. Objective response rate (41% vs. 43%) and disease control rate (64% vs. 82%) were similar in both groups. Median PFS was 34.86 weeks (95% CI:

0.43-1.12) in FFN and 24.43 (95% CI: 0.89-2.28) in GnP [p=0.02]. Median OS was 48.6 weeks (95% CI: 0.58-1.50) in the FFN group and 51.9 weeks (95% CI: 0.66 – 1.71) with GnP [p=0.31]. The frequency of grade 3 or higher adverse events were reported as follow: neutropenia (44% vs. 39%), anaemia (0% vs 18%), thrombocytopenia (6% vs 10%), thrombocytosis (0% vs 50%), elevated transaminases (13% vs 8%), diarrhoea (0% vs. 6%), asthenia (0% vs. 3%), lower extremities oedema (0% vs 58%) and peripheral neuropathy (44% vs. 39%), respectively in FFN and GnP groups.

Conclusions: Patients treated with FFN achieve statistically longer PFS compared to GnP, however OS was similar and response rates were comparable between the two groups of treatment. Only one patient treated with GnP reached a complete response. Incidence of major adverse events (G3 or more) appears similar in both the FFN and GnP groups, excluding anaemia, lower extremities oedema and thrombocytosis which are more frequent or even exclusive in the GnP group.

B35

PHASE 3 (COSMIC-312) STUDY OF CABOZANTINIB IN COMBINATION WITH ATEZOLIZUMAB VERSUS SORAFENIB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (aHCC) WHO HAVE NOT RECEIVED PREVIOUS SYSTEMIC ANTICANCER THERAPY

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Background: Cabozantinib inhibits tyrosine kinases involved in tumor growth, angiogenesis, and immune regulation, including MET, VEGFR, and TAM kinases (Tyro3, AXL, MER). Cabozantinib is approved in the United States and Europe for treatment of aHCC after prior sorafenib based on improved overall survival (OS) and progression-free survival (PFS) versus placebo in the phase 3 CELESTIAL trial (Abou-Alfa NEJM 2018). Cabozantinib may promote an immune-permissive tumor environment, which could enhance response to immune checkpoint inhibitors. Cabozantinib in combination with the anti-PD-L1 antibody atezolizumab is being evaluated in multiple tumor types including HCC in a phase 1 study; recommended dose, preliminary clinical activity, and safety of the combination have been demonstrated in aRCC (Agarwal Ann Oncol 2018). Atezolizumab in combination with bevacizumab, an anti-VEGF antibody, has shown preliminary clinical activity in first-line aHCC (Pishvaian Ann Oncol 2018). Here, we present the study design of a phase 3 trial of cabozantinib + atezolizumab versus sorafenib in patients with aHCC who have not received prior systemic therapy.

Patients and methods: This global, randomized, open-label phase 3 trial (NCT03755791) is evaluating the efficacy and safety of cabozantinib + atezolizumab versus sorafenib as first-line treatment for aHCC. Eligibility criteria include age ⩾18 years, BCLC stage B or C, Child-Pugh A, ECOG PS ⩽1, and measurable disease per RECIST 1.1. Patients are randomized 2:1:1 to an experimental arm of cabozantinib (40 mg qd) + atezolizumab (1200 mg infusion q3w), a control arm of sorafenib (400 mg bid), and a cabozantinib monotherapy arm (60 mg qd). 740 patients are planned to be enrolled at ~250 sites globally. Randomization is stratified by disease etiology (HBV [with or without HCV], HCV [without HBV], or other), region (Asia, other), and the presence of extrahepatic disease and/or macrovascular invasion (yes, no). PFS and OS for cabozantinib + atezolizumab versus sorafenib are primary endpoints, and PFS for cabozantinib versus sorafenib is a secondary endpoint. Additional endpoints include safety, pharmacokinetics, and correlation of biomarker analyses with clinical outcomes. The first patient was enrolled in December 2018, and enrollment is ongoing.

B36

SECOND-LINE CHEMOTHERAPY WITH GEMCITABIN+VINORELBINE (GEMVIN) IN ADVANCED ESOPHAGEAL CANCER (AEC)

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Background: Esophageal cancer is a very aggressive tumor, most patients are often not fit enough to receive second line chemotherapy, and even in this case results are dismall with poor response and short survival.

A retrospective analysis of all consecutive patients with AEC followed at the our Medical Oncology Unit between from February 2017 and January 2019 was performed.

Methods: a total number of 14 AEC patients treated with one chemotherapy line were eligible for the analysis. Histological type was Squamous cell carcinoma 8SCC) in all patients.

Results: patients characteristics were: male/female 10/4, median age 67 (55-75). ECOG performance status was 0/1/2 in 2/9/3 cases. Mestastatic site of disease were: lung/liver/peritoneum/bone/nodes/brain in 9/5/4/1/14/2 cases.

First line chemotherapy regimen were platinum/5FU based. The schedule of treatment was as follows: Gemcitabin 1000 mg/ mg i.v. on days 1 and 8, Vinorelbine 25 mg/ m2 on days 1 and 8 both of them every 3 weeeks. We observed 5 stable disease, 4 progressive disease and 5 objective response. Median time to progression was 5.1 months. All patients was evaluable for survival (median overall survival 8.3 months). No life threatening event occurred. Teatment was well tolerated from the great part of patients and the main toxicities were low-grade (G1-G2). Few patients reported severe (G3-G4) adverse events such as fatigue (2 pts), thrombocytopenia (1 pts), peripheral neuropathy (2 pts).

Conclusions: the study suggest that GEMVIN schedule in effective and well tolerated, and may prolog survival with a relatively good quality of life in patients with AEC previously exposed to one chemotherapy line.

B37

THE REAL-LIFE EXPERIENCE WITH PERIOPERATIVE CHEMOTHERAPY (FLOT) IN THE TREATMENT OF LOCALLY ADVANCED GASTRIC AND GASTRO-OESOPHAGEAL CANCER (GEC)

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Introduction: GEC is the fourth most common cancer and the second leading cause of cancer-related deaths worldwide. Until not long ago, surgery was considered the only curative treatment for GEC. However, the results are still unsatisfactory, due to the high rate of metastasis and relapse. Chemotherapy together with surgery has shown promising results. Randomized studies proved that perioperative chemotherapy provides a survival benefit over surgery alone and should be considered the standard of care in potentially operable GEC. However, 5-year survival rates are still in the range of just 35-45%.

Materials and methods: From March 2017 to January 2019, 20 fit patients(pts) with operable GEC were treated in our centre with 4 pre- and 4 postoperative cycles of infusional 5-FU 2600 mg mq 24/h, Folinic Acid, Oxaliplatin 85mg/mq and Docetaxel 50 mg/mq every 2 weeks.

Results: treated pts included 10 female and 10 males with median age 64 years (range 36-74) and PS ECOG 0. 8/20 tumors were gastroesophageal junction, 11 were intestinal, 5 diffuse and 4 mixed histotype. All tumors were cT3 and/or N+.19/20 pts have completed the 4 pre-operative cycles while 17/20 have also completed the 4 postoperative. TRG (tumour regression grade sec.AJCC/CAP) was: 10% TRG0,21% TRG1,31% TRG2,36%TRG3. 2/7 non responder (TRG3) were MMRD to IHC (confirmed results by Idylla Biocartis assay). The treatment was well tolerated with only grade 3 neutropenia in 20% and thrombocytopenia in 10% of pts.

Conclusions: Our real-life experience shows that the perioperative FLOT appears to be effective and safe. It would be useful to evaluate prospectively the microsatellite instability as predictive factor to treatment response.

B38

RISE-HEP PROJECT PART 1: TREATMENT SEQUENCES EVALUATION IN HEPATOCELLULAR CARCINOMA CELL LINES

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Background: For over ten years the most stimulating results in systemic therapy for advanced HCC derived from the use of sorafenib (S). But in the last two years several drugs, in particular other multikinase inhibitors like lenvatinib (L), regorafenib (R), cabozantinib (C), proved to be effective both as an alternative or a sequential therapy to sorafenib. In this widened and rapidly increased scenario, without any head-to-head trial, clinicians struggle to define the best drug and the best treatment sequence. Aim of the first part of this project is to evaluate the activity of different treatment sequences in HCC cell lines to pave the way to a future clinical trial investigating their efficacy.

Methods: Compounds of S, R, L and C were dissolved in DMSO and aliquoted. HepG2 cell line, obtained from ECACC (Salisbury, UK), was seeded at the density of 3 x 104 cells/ml. After 24 h of incubation, compounds or vehicle (DMSO) were added. Treatments were performed in single administration and six replicates were carried out for each dose. At 48h post-treatment, cells were fixed and stained with acid solution. The absorbance was measured at 520 nm using an ELISA reader (BioTek Instruments, USA). The assay was also performed with the sequences of: S-R, S-C, L-R, L-C (first line treatments for 48h followed by the second compound for 48h). Higher doses than the minimum inhibiting one were tested.

Results: S showed superior activity than L as first line compound. In the sequence assay S-C and S-R seems to have the best results in terms of cell viability. After L the best compound appears to be R. See table.

Conclusions: Our results showed relevant variations in cell viability with different drug sequences. Already

Sequences (ng/ml)	% Viability
S 2000 + R 2000	14.5
S 4000 + R 2000	11.2
S 2000 + C 1000	16.8
S 4000 + C 1000	10.1
L 250 + R 2000	34.2
L 500 + R 2000	31.0
L 250 + C 1000	53.3
L 500 + C 1000	47.9

planned analyses in the RISE-HEP project in vivo and in humans are mandatory to confirm which sequence would have the highest efficacy.

B39

REAL-LIFE DATA ON THE PERIOPERATIVE FLOT REGIMEN IN LOCALLY ADVANCED RESECTABLE GASTRIC/GEJ ADENOCARCINOMA

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Background: Gastric cancer is one of the most frequent neoplasias with an aggressive behavior. Long-term outcome after surgery alone is poor, therefore a combined treatment approach is the standard of care. Perioperative FLOT showed to improve OS in locally advanced, resectable gastric/GEJ adenocarcinoma. Here, we report the results of efficacy and safety of FLOT regimen in our real-life experience. We also evaluated neutrophil-lymphocite ratio (NLR), marker of inflammation associated with worse OS in solid tumours.
Patients and methods: We analysed 18 patients (pts) with locally advanced, resectable gastric/GEJ adenocarcinoma (stage I-III) treated between March 2017 and April 2019 with perioperative FLOT at the Oncology Unit of University Hospital of Cagliari. Pts had the following charactheristics: ECOG PS 0-1. Median age 64 years (range 49-79). 6 were ⩾70 years old. 38,9% had GEJ adenocarcinoma and 61,1% had stomach adenocarcinoma. 5,6% had a clinical stage cT1-2, 72,2% cT3-4 and 22,2% had missing cT. 61,1% had cN+. 22,2% had signet ring cells (SRC). 11,1% had diffuse type. The median duration of treatment was 4 cycles. The cut-off of NLR was evaluated with ROC curves and survival analysis with Kaplan-Meier estimate.
Results: Median OS (mOS) in our whole population is not reached. We observed a significantly higher mOS in pts with cT1-2 (17.83 m) vs cT3-4 (8.53 m) ($p=0.01$) and in pts without SRC (not reached) vs pts with SRC (8.53 m) ($p=0.02$). We observed a trend toward a higher mOS in pts with cN- vs cN+ and in pts with low NLR (<2,375) vs high NLR (⩾2,375), but these were not statistical significantly (respectively $p=0.47$ and $p=0.08$). We obtained a similar result in pts <70 years vs ⩾70 years ($p=0.21$). DCR was significantly higher in pts without SRC (100%) vs pts with SRC (50%) ($p=0.04$). We observed only G1-2 adverse events (AE): fatigue in 38,9% of pts, nausea in 27,8%, neuropathy in 16,7%, diarrhea in 11,1%, thrombocytopenia in 11,1%. No case of neutropenia was registered. All pts received peg-G-CSF. No patient interrupted chemotherapy due to toxicity. Were not differences in terms of AE between young and elderly pts. Surgery was performed in 66.7% of pts. Preoperative FLOT is ongoing for 2 pts.
Conclusions: Despite the limited sample size, our real-life experience confirm that perioperative FLOT is an effective and well tolerated regimen with a significant benefit in survival outcome and a good safety profile, in line with the results of FLOT trial.

B40

NLR (NEUTROPHIL/LYMPHOCYTE RATIO) AND SECOND LINE CHEMOTHERAPY WITH FOLFIRI FOR PATIENTS WITH METASTATIC PANCREATIC CANCER: OUR EXPERIENCE

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Introduction: Pancreatic cancer (PC) is the fifth most lethal cancer.Metastatic PC still has an estimated 5-year survival rate of 7%, even considering new strategies on treatment. Identifying prognostic factors is important to layer individual risk. Several studies have analyzed FOLFIRI regimen in 2nd line treatment The progression free survival (PFS) varies from 2 to 5 months. The overall survival (OS) varies from 4,2 to 13,2 moths. Neutropenia and diarrhea are the most frequent toxicities. Several evidences suggest that a high NLR is related to an adverse outcome.
Materials and Methods: From December 2015 to March 2019 we evaluated pts with metastatic PC treated with Nab-paclitaxel-Gemcitabine as first line and with standard FOLFIRI regimen as 2nd line. Our endpoints were: the prognostic role of NLR at baseline, safety, PFS and response rate (RR) in second line. FOLFIRI consists of irinotecan 180 mg/m2 on day 1 and leucovorin 400 mg/m2 followed by 5-fluorouracil (5-FU) 400 mg/m2 bolus, then 5-FU 2400 mg/m2 as a 46-h infusion, biweekly.
Results: At time of data analysis among 57 pts with PC treated with Nab-paclitaxel-gemcitabine, 18 pts (31,5%) received 2nd line FOLFIRI chemotherapy (CT). All 18 pts

had a NLR<5. Baseline characteristics of 18 pts receiving 2nd line CT were: median age 67,5 (range 45-76), M/F: 7/11. They received a median of 6,5 (range 1-24) drug administrations. mPFS was 3 months (range 1-14) mOS was 11 months (range 2-30). Among the 18 pts, 2 pts (11%) had a partial response (PR) and 7 (38%) a stable disease (SD),with a disease control rate (DCR) of 49%. Detected toxicity G3-4 was neutropenia and diarrhea in 3 and 1 patients, respectively.

Conclusions: Our experience shows that Nab Paclitaxel-Gemcitabine in the first line is an active and well tolerated regimen, allowing about a third of the patients to receive a second-line treatment. FOLFIRI regimen in 2nd line showed a modest activity and discrete tolerance in this setting.NLR <5, in our experience, is correlated to a better prognosis. We are expecting new prognostic factors could be a guidance to choice the treatment.

C - Breast Cancer

C01*

EFFICACY OF DOSE-DENSE (DD) ADJUVANT CHEMOTHERAPY (CT) IN HORMONE RECEPTOR POSITIVE/HER2-NEGATIVE EARLY BREAST CANCER (BC) PATIENTS (pts) ACCORDING TO IMMUNOHISTOCHEMICALLY (IHC) DEFINED LUMINAL SUBTYPES: AN EXPLORATORY ANALYSIS OF THE GIM2 TRIAL

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Background: DD adjuvant CT improves disease free survival (DFS) and overall survival (OS) in high-risk, hormone receptor positive BC. Luminal A and luminal B subtypes have different sensitivity to (neo)adjuvant chemotherapy; however, their role in predicting DD efficacy in clinically high-risk setting is uncertain. This exploratory analysis of the GIM2 trial (Del Mastro et al, Lancet 2015) evaluated DD efficacy according to IHC defined luminal subtypes.

	% 8-year DFS SI	% 8-year DFS DD	HR (95% CI)
Luminal A-like	81.6	80.6	0.86 (0.56–1.30)
Luminal B-like	66.8	74.7	0.74 (0.55–0.98)
	% 8-year OS SI	% 8-year OS DD	
Luminal A-like	92.9	90.6	0.88 (0.47-1.67)
Luminal B-like	80.8	89.4	0.61(0.40-0.93)

Methods: In the GIM2 trial, pts with node-positive early BC were randomized to receive 4 cycles of (fluorouracil) epirubicin/cyclophosphamide every 2 (DD) or every 3 (standard interval [SI]) weeks followed by 4 cycles of DD or SI paclitaxel. Luminal A-like and luminal B-like BC were identified according to 13h St Gallen definition as having a Ki67<20% and a PgR>/=20% (luminal A-like), and a Ki67>/=20% and/or a PgR<20% (luminal B-like). Pts with HER2-positive BC were excluded. The efficacy of DD CT in terms of DFS and OS was compared between the two subtypes.

Results: Out of 2,003 pts enrolled in the GIM2 trial, 401 had luminal A-like and 657 luminal B-like BC. After a median follow-up of 8 years, DFS was 81.1% (95% Confidence Intervals [CI] 76.6-84.7) and 70.6% (66.6-74.1) in luminal A-like and luminal B-like BC, respectively, and OS was 91.6% (88.1-94.1) and 85% (81.7-87.7), respectively. There was no significant interaction between treatment and luminal subtypes ($p_{interaction}$=0.416 for DFS and $p_{interaction}$=0.313 for OS); however, the effect of DD CT appeared to be greater in luminal-B like BC (see table below).

Conclusions: These long-term results confirm the prognostic value of IHC-defined luminal subtypes, with luminal B-like bearing a worse prognosis. In clinically high-risk, hormone receptor positive BC, luminal B-like subtype benefits more from DD CT both in terms of DFS and OS.

C02*

NON-ADHERENCE TO TAMOXIFEN ADJUVANT THERAPY THROUGH PLASMA LEVEL ASSESSMENT AMONG EARLY BREAST CANCER PATIENTS IN NORTHERN ITALY

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Background: Non-adherence to Tamoxifen (TAM) was shown to considerably impact on the risk of recurrence and mortality of women with breast cancer and efforts should be made to ensure therapeutic adherence during clinical follow-up.
Patients and Methods: (pts) age has been suggested as an important factor in adherence to TAM. The TAM study is an Italian multicenter prospective longitudinal study that enrolled around 1000 patients affected by early breast cancer and treated with adjuvant tamoxifen for at least 3 years after surgery. Two blood samples, at least 3 months apart, were obtained by each patient after reaching the steady state and TAM plasma levels were measured by an HPLC system. According to standard definitions, non-adherence to TAM has been defined if TAM plasma levels < 60 ng/mL (<150 nM).
Results: We present here the results of TAM plasma assessment in 580 patients in steady state.Overall, 224 (18.2%) pts appeared not adequately adherent to TAM: 162 (13.2%) non-adherent and 62 (5.0%) poorly-adherent. Matching with pts' self-declaration and clinical determinants of non-adherence will be presented.
Conclusions: At steady state, around 5% had low TAM plasma measurements, indicative of not adequate adherence to this treatment. Poorly-adherent pts could benefit from metabolic and pharmacogenetic investigations. Identification of pts at risk of non-adherence allows early targeted interventions to promote adherence in this unique population.

C03*

TUMOR INFILTRATING LYMPHOCYTES (TILS) IN ER+/HER2- BREAST CANCER

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Background: The prognostic role of TILs in ER+/HER2- breast cancer (BC) is debated. We evaluated the association of TILs and clinico-pathological features with DDFS in a large series of patients with ER+/HER2- BC.
Methods: Our initial cohort of 9415 pts included all women who underwent surgery for early ER+/HER2- BC at IEO. Then, the cohort was restricted to 3986 pts in the period 1998-2002, and with whom long-term follow-up available. A case-cohort was built by randomly selecting approximately 17% of the above cohort (680 pts). 307 additional pts with an event were added to this cohort. TILs were assessed for 987 cases. TILs were considered both as continuous variable, and dichotomized in low ($<5\%$) vs high ($\geqslant 5\%$). The main outcome was DDFS. Median follow-up was 7.5 years (0.1-10). Differences between BC subtypes were assessed using the log-rank test. Univariable and multivariable Cox proportional hazards regression with inverse sub-cohort sampling probability weighting were used to evaluate the risk across groups.
Results: Median TILs was 2%. Higher TILs were positively associated with pN ($p=0.003$), tumor grade ($p<.0001$), peritumoral vascular invasion ($p=.003$), Ki-67 ($p=.0001$), luminal B ($p<.0001$), and chemotherapy ($p<.0001$), while they were inversely associated with ER expression ($p<.0001$) and age ($p=.02$). There was no association with type of endocrine therapy. In multivariable regression analysis, only Ki-67 expression retained significant association with TILs. Age and ER showed a trend towards negative association with TILs. In univariate Cox regression, TILs expression ($=5\%$ vs. $<5\%$) was not associated with DDFS ($p=.62$). At stratified cox exploratory analyses, high TILs were correlated with low risk in very young women ($p=.03$) and G3 tumors ($p=.047$), and high TILs with worse outcome in G1 tumors ($p=.05$). We evaluated TILs by treatment group (chemo vs no chemo). TILs were not associated with DDFS in the no-chemotherapy group. Instead, in the chemotherapy group, high TILs were associated with better DDFS ($p=.006$), particularly in the group with ki67 $=20\%$ ($p=.01$).
Conclusions: High TILs in ER+/HER2- BC are significantly associated with several clinico-pathological features of dismal outcome. In this group, treatment escalation might be worthy. Our findings suggest that this subgroup might be more immunogenic, thus deserving the exploration of immunotherapy approaches. The prognostic value of TILs seems to be different in patients treated with or without chemo.

C04*

ROLE OF A SET OF GENE POLYMORPHISMS IN THE ONSET OF NEUROPATHY (N) IN METASTATIC BREAST CANCER (MBC) PATIENTS (pts) TREATED WITH ERIBULIN IN THE PAINTER STUDY (POLYMORPHISM AND INCIDENCE OF TOXICITY IN ERIBULIN TREATMENT)

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Background: MBC is an incurable disease and therefore treatment focuses mainly on prolonging pts survival and improving quality of life. Eribulin (E) is a microtubule inhibitor that increases overall survival in pretreated pts. E peripheral N is reported in 4-35% of cases. PAINTER main objective was to survey tolerability of E in real life in MBC, while secondary endpoints were to investigate the relationships between specific genetic polymorphisms and incidence and severity of peripheral N.

Patients and methods: This is a multicenter, interventional, single-arm, phase IV study, that enrolled pts who received E (dose 1.4 mg/m^2 day 1 and 8 every 21 days) after taxanes and antracyclines. Genomic DNA was isolated from whole blood samples (Maxwell whole blood DNA kit. Promega). 15 SNPs (Single Nucleotide Polymorphisms) were genotyped by Taqman specific assays. For SNPs analysis, we selected pts with available genomic data and who started E treatment. N was evaluated by medical examination. The associations between peripheral N and the selected polymorphisms were evaluated with Fisher exact test.

Results: From May 2014 to June 2018, 180 pts were enrolled from 20 Italian hospitals and 159 were evaluated for genetic analysis. Pts and tumor characteristics were as follow: median age 60 years, ductal carcinoma 75.9%, visceral disease 68.6%, luminal type 63.2%, Her2 positive 18.8%, triple negative 18.1%, median of previous treatment lines for MBC 5, previous N reported in 17.8% of pts (all N were sensory and 22.2% were also motor). N (all grades) during E treatment was reported in 33.9% of patients (G2-G3-G4: 15%). Among the selected SNPs, the allelic variant T of the polymorphism rs2233335 in NDRG1 gene ($p < 0.001$) and the allelic variant C of the polymorphism rs7214723 in CAMKK1 gene ($p = 0.04$), showed a higher and statistically significant N occurrence; see table below.

rs2233335 - NDRG1	G0 n(%)	G1 n(%)	G2 n(%)	G3 n(%)
G/G	25 (78.1)	2 (6.3)	3 (9.4)	2 (6.3)
G/T	54 (77.1)	10 (14.3)	4 (5.7)	2 (2.9)
T/T	26 (45.6)	18 (31.6)	12 (21.1)	1 (1.8)
rs7214723 - CAMKK1	G0 n(%)	G1 n(%)	G2 n(%)	G3 n(%)
C/C	32 (68.1)	8 (17.0)	5 (10.6)	2 (4.3)
C/T	32 (68.1)	12 (18.2)	3 (4.5)	3 (4.5)
T/T	23 (52.3)	10 (22.7)	11 (25.0)	0 (0.0)

Conclusions: The results suggest that the SNP rs2233335 (G/T and T/T) in NDRG1 gene and rs7214723 (CC and CT) in CAMKK1 gene are associated with E induced N. These data, if corroborated, will allow a tailored treatment with E. Clinical trial registration: NCT0286403

C05

IMPACT OF BODY COMPOSITION PARAMETERS ON TUMOR RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN OPERABLE BREAST CANCER PATIENTS

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Background: Overweight is a known risk factor for various health disorders, including breast cancer (BC). Preclinical evidence shown how endogenous factors released from fat tissue are involved chemo resistance and cells survival. Sarcopenia seems to be a negative prognostic factor too. Computed tomography (CT) imaging instead of body max index (BMI) gives a reliable measure of muscles mass and body fat distribution. The impact of body composition parameters (BCPs) on chemo sensitivity is still debated. We examined the associations between BCPs and tumor response to neoadjuvant chemotherapy (NC) in patients treated for operable breast cancer (BC).

Patients and methods: BMI value, Visceral Fat Area (VFA), Subcutaneous Fat Area (SFA), Lumbar Skeletal Muscle Index (LMCI), Liver/Spleen Ratio (L/S) were collected, besides clinical parameters. BCPs were calculated from pre-treated CT scan images, and correlated to pathologic complete response (pCR) and with survival outcomes.

Results: 407 patients were included in the study: 55% with BMI < 25 and 45% with BMI >25. 137 of them had pre-treatment CT scan imagines. Overweight was significantly associated with postmenopausal status and older age. Hormonal receptor positive BC were more frequent in overweight patients ($p<0.05$). Postmenopausal women had higher VFA, fatty liver disease and obesity compared to premenopausal patients. 34% of patients had criteria for obesity disease while 48% of them were sarcopenic. Overall, 25% of women achieved pCR. No association between BMI classes and tumor

response was detected. High VFA and liver steatosis were negative predictive factors for pCR (pCR rate: 35% normal VFA vs 20% high VFA, no steatosis 32% vs steatosis 13%; $p<0.05$). Neither BMI classes nor BCPs significantly influenced overall survival and relapse free survival.

Conclusions: Visceral adiposity as well as steatosis were closely involved in chemo sensitivity in BC patients treated with NC. Their measures from clinically acquired CT scans provide significant predictive information that outperform BMI value. More research is require to evaluate relationship among adiposity site and survival outcomes.

C06

REAL WORLD EVIDENCE ON HR+/ HER2- METASTATIC BREAST CANCER: EPIDEMIOLOGY, CLINICAL PRACTICE AND DIRECT COSTS FROM A LARGE ITALIAN DATABASE

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Background: The epidemiology knowledge of different breast cancer types is crucial for planning and funding effective health services. The aim of this study was to estimate the burden of HR+/HER2- metastatic breast cancer (MBC) in Italy, in terms of incidence, prescription patterns, healthcare resource utilisation and costs for the National Health System (NHS).

Methods: A cohort study based on healthcare administrative data (ReS database), covering >10 millions of Italians, was performed. Incident cases of HR+/HER2- MBC were identified among adult women, in 2013. A woman was defined affected by MBC if she was hospitalized with concomitant diagnosis of "Malignant neoplasm of female breast" and "Secondary and malignant neoplasms". Incident cases were identified by excluding women responding to these criteria in the previous year. The cohort was followed-up for 2 years to describe healthcare utilisation and integrated costs (pharmaceuticals, hospitalisations and outpatients services) paid by the NHS. Prescription patterns were described as first-line choice and therapeutic changes. Specific changes of therapy were used as proxies of disease progression. A survival analysis was performed to estimate the time from diagnosis to first disease progression.

Results: Out of 5,174,723 adult women, 355 new cases of HR+/HER2- MBC were selected (incidence: 6.9 per 100,000). These generated a mean cost of €3,888 due to the diagnoses used to identify the cohort. During the 1st follow-up year, they on average costed €7,543, whereas €4,834 in the 2nd year. The 85.9% of the cohort received a monotherapy, while the 14.1% a combination therapy. The most used monotherapy was nonsteroidal aromatase inhibitors (45.9%), while the most prescribed combination was tamoxifen + LHRH analogues (6.2%). Therapeutic changes occurred in 45.4% of the cohort, especially from chemotherapy to nonsteroidal aromatase inhibitors, after on average 276.8 days from the first treatment. Disease progression was identified in 22.5% of patients and it occurred after a mean of 13 ± 6 months from diagnosis.

Conclusions: The study provided a detailed picture of HR+/HER2- MBC, by using real-world data. These findings could be helpful in health technology assessments and expenditure forecasts of future therapeutic strategies for HR+/HER2- MBC, particularly in the field of "precision medicine" or "personalized medicine".

C07

THE ROLE OF DOSE-DENSE (DD) ADJUVANT CHEMOTHERAPY (CT) IN HER2-POSITIVE (HER2+) EARLY BREAST CANCER (BC) PATIENTS (pts) BEFORE AND AFTER THE INTRODUCTION OF TRASTUZUMAB (T): EXPLORATORY ANALYSIS OF THE GIM2 TRIAL

Poggio F.[1], Lambertini M.[2], Bruzzone M.[3], Conte B.[4], Bighin C.[1], De Azambuja E.[5], De Placido S.[6], De Laurentiis M.[7], Cognetti F.[8], Fabi A.[9], Bisagni G.[10], Durando A.[11], Turletti A.[12], Defraia E.[13], Garrone O.[14], Puglisi F.[15], Montemurro F.[16], Ceppi M.[3], Del Mastro L.[17]

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Background: DD adjuvant CT is standard of care in high-risk early BC pts. However, the role of DD CT in HER2+ BC pts remains uncertain, particularly when T is administered. In this exploratory analysis of the GIM2 trial (Del

	% 7-year DFS SI	% 7-year DFS DD	HR (95% CI)
HER2+ NO trastuzumab	67.0	72.1	0.84 (0.56-1.24)
HER2+ with trastuzumab	72.3	70.4	0.80 (0.40-1.59)
HER2-/unk	73.3	79.9	0.72 (0.59-0.88)
	% 7-year OS SI	% 7-year OS DD	
HER2+ NO trastuzumab	78.6	85.2	0.67 (0.39-1.16)
HER2+ with trastuzumab	86.1	84.9	1.04 (0.36-3.00)
HER2-/unk	85.3	90.9	0.64 (0.49-0.84)

Mastro et al, Lancet 2015), we investigated the efficacy of DD CT in the subgroup of HER2+ BC pts with or without subsequent exposure to T.

Methods: Using a 2x2 factorial design, the GIM2 trial randomized node-positive early BC pts to receive 4 cycles of (fluorouracil)epirubicin/cyclophosphamide (F)EC every 2 (DD) or every 3 (standard interval [SI]) weeks followed by 4 cycles of DD or SI paclitaxel (P). The same number of cycles (4 (F)EC and 4 P) and doses (FEC 600/90/600 mg/m2, P 175 mg/m2) were used in all treatment arms. After the approval of adjuvant T, protocol was amended in April 2006 to mandate use of T for 1 year after CT completion in all HER2+ pts.

The efficacy of DD CT in terms of disease-free survival (DFS) and overall survival (OS) was compared between HER2+ pts with or without subsequent exposure to T and those with HER2-negative /HER2-unknown (HER2-/unk) status.

Results: Out of 2,003 pts randomized to DD or SI CT in the GIM2 study, HER2 status was positive in 452 (22.6%) pts, negative in 1,243 (62.0%) and unknown in 308 (15.4%). Among 452 pts with HER2+ disease, T was administered to 132 (29.2%) pts. Overall median follow-up was 8.1 years (interquartile range: 7.0-9.3).

No significant interaction between T therapy and the effect of DD CT, ($p_{interaction}$=0.603 for DFS and $p_{interaction}$=0.776 for OS) was observed; however, among pts treated with T, the effect of DD CT appeared to be smaller as shown in the table.

Conclusions: In HER2+ early BC pts, DD adjuvant CT appears to have a role only in pts without subsequent exposure to T.

C08

THE PREGNANCY AND FERTILITY (PREFER) STUDY: AN UPDATE ON FERTILITY-PRESERVING (FP) STRATEGIES IN YOUNG EARLY BREAST CANCER (EBC) PATIENTS (pts)

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Background: Young early breast cancer (EBC) patients relevant concerns are fertility issues due to oncology treatments. Limited data are available on pts and their oncologists attitude about FP strategies. The PREFER study was developed as a national comprehensive program aiming to optimize care and improve knowledge around this topic.

Methods: This is a prospective cohort study ongoing across 20 Italian centers affiliated to the GIM (Gruppo ItalianoMammella) study group. Oncologists offer the available FP strategies to young EBC pts undergoing (neo) adjuvant CT: oocyte cryopreservation (OC), ovarian tissue cryopreservation (OTC) and LHRH analogue (LHRHa) during CT. Eligible pts are premenopausal, ⩽ 45 years, no previously exposed to CT and/or radiotherapy. Primary objective is to obtain data about preferences and choices of young EBC pts on the FP strategies. Secondary objectives are to evaluate the success and safety of FP strategies, hormonal changes during CT and survival outcomes. The present analysis reports preliminary results of the study including pts enrolled at the coordinating center from November 2012 to May 2019, an update of previous data 2017.

Results: A total of 204 EBC pts were enrolled; median age was 38.77 years (24.80- 45.34). Patients interested in Fertility Preservation were 193 (94.61%); patients not interested were 11 (5.39%) Reasons for refusal were: no interest in fertility preservation 7 pts (3.43%); previous pregnancy 3 pts (1.47%), no interest in having children 1 pt (0.49%). FP strategies: 133 pts (65.19%) accepted only LHRH a, 2 pts (0.98%) counseling only, 57 pts (27.94%) both of them. Only 29 (14.22%) pts accepted OC or OTC after gynecologic counseling. Main reason for refusal of cryopreservation procedures was fear of delaying cancer treatment (3 pts). Median number of oocytes yielded was 13.50 (0-42); median number of mature oocytes yielded and cryopreserved was 10 (0-24).

Conclusions: LHRHa is the fertility-preserving strategy accepted by the majority of young early breast cancer patients, cryopreservation procedures are accepted by nearly 15% of patients.

C09

A PHASE 2 STUDY OF ABEMACICLIB IN PATIENTS (pts) WITH BRAIN METASTASES (BM) SECONDARY TO HR+, HER2- METASTATIC BREAST CANCER (MBC)

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Background: Abemaciclib is a selective CDK4 & 6 inhibitor approved to treat HR+, HER2- MBC pts on a continuous dosing schedule as monotherapy or in combination with endocrine therapy (ET). Clinical data demonstrate that abemaciclib penetrates the blood brain barrier resulting in comparable concentrations in tissues and plasma.

Materials and Methods: JPBO is a Simon 2-stage trial evaluating abemaciclib in 6 pt cohorts with BM secondary to HR+ MBC, non-small cell lung cancer, or melanoma. Here, we report on HR+, HER2- MBC pts. Eligible pts had ⩾1 new or not previously irradiated measurable BM ⩾10mm or a progressive previously irradiated BM. Pts receiving ET at the time of enrollment were permitted to continue the same ET provided that extracranial disease was stable ⩾3 months and the CNS progression occurred on the ET. Abemaciclib was orally administered 200mg BID. Primary endpoint was objective intracranial response rate (OIRR; [CR+PR]) based on Neuro-Oncology BM response assessment criteria (RANO-BM). Secondary endpoints included intracranial clinical benefit rate, PFS, and safety.

Results: 58 HR+, HER2- MBC pts were enrolled and 52 pts were evaluable. Pts had a median of 4 prior systemic therapies, 75% of pts had prior chemotherapies (0-6, median 2), and 71% of pts had prior ET (0-4, median of 1) in the metastatic setting. 50% of pts had prior whole brain radiotherapy, 39% stereotactic radiosurgery, and 8% surgical resection of BM. Median time from radiation to study enrollment was 9.4 months. Out of the 52 evaluable patients, 3 pts had a confirmed intracranial response (6% OIRR), and 38% of pts showed a decrease in the sum of their intracranial target lesions. Intracranial clinical benefit rate (CR+PR+SD persisting for ⩾6 months) was 25%. Median PFS was 4.4 months (95% CI, 2.6-5.5). Safety and tolerability were similar to previous reports for abemaciclib.

Conclusions: Abemaciclib demonstrated intracranial clinical benefit in heavily pretreated HR+, HER2- MBC pts with BM in this study. Further evaluations are ongoing to identify ABC patients with BM who might benefit most from abemaciclib.

C10

CORRELATION BETWEEN WEIGHT LOSS AND OUTCOME IN METASTATIC BREAST CANCER PATIENTS TREATED WITH EVEROLIMUS: RESULTS FROM A RETROSPECTIVE EXPLORATORY ANALYSIS OF A BALLET STUDY COHORT

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Background: Notwithstanding the encouraging results seen with everolimus in advanced BC, reliable biomarkers of response to mTOR inhibitors are yet to be identified. Drug-induced toxicities have raised interest as surrogate biomarkers of activity. Here, we present the results of a retrospective analysis evaluating the impact of BMI/weight variation during everolimus therapy on survival in a subgroup of patients recruited in the BALLET trial, whose disease progressed during the study.

Patients and Methods: BALLET evaluated the safety of everolimus plus exemestane in post-menopausal women with advanced hormone positive BC which recurred or progressed on NS-AIs. A total of 685 patients recruited on the trial in Italy were included in our analysis and BMI/weight recorded at baseline till end of treatment (EOT). Metabolic treatment-related adverse events (TrAEs) were considered of "special interest" and obtained at each time-point. BMI was calculated with the formula Kg/m2. The Wilcoxon matched-pairs test was used for the statistical analysis and the Kaplan-Meier to analyse the correlation between BMI/weight and overall survival (OS), defined as the time between the start of everolimus and death.

Results: we found no correlation between BMI measurements and outcomes. To look at weight, we divided the study population in four subgroups according to their absolute weight loss (Δ) during treatment: Δ pre-post ⩾0 kg; Δ >0⩽2 kg; Δ >2⩽5 kg; Δ >5 kg. 68.7% of patients showed a measurable weight-loss. We found a positive correlation between a Δ >5 kg and the outcome, with a median OS of around 180 days in comparison to 120 days for a Δ <5 kg or 0 (p=0.0). Cholesterol (C) and

NMA Comparisons	OR (95% CI)	Estimated pCR rates (95% CrI)	
D-CTA vs D-CT	0.88 (0.64-1.20)	D-CTA	58% (45-71%)
H-CTA vs H-CT	1.22 (0.77-1.92)	D-CT	54% (40-67%)
L-CTA vs L-CT	1.33 (0.77-2.30)	H-CTA	44% (35-54%)
D-CTA vs H-CTA	1.39 (1.03-1.87)	H-CT	36% (23-53%)
D-CT vs H-CTA	1.58 (1.06-2.38)	L-CTA	35% (23-50%)
H-CTA vs CTA	2.21 (1.47-3.33)	L-CT	26% (12-46%)
H-CT vs CTA	1.82 (0.99-3.35)	CTA	24% (13-42%)

Triglycerides (T): 85.8% of patients suffered at least a grade 1 TrAE during therapy with everolimus. The great majority were grade 1 or 2 events, with only 0.87% of patients developing a grade 3 AE and 0.14% a grade 4. We found a statistically significant difference between pre- and post-treatment values, with higher C and T recorded at EOT in comparison to baseline (C: 5.44 $\pm$ 1.04 at baseline vs 5.84 $\pm$ 1.27 at EOT, $p<0.001$; T: 1.36 $\pm$ 0.66 at baseline vs 1.77 $\pm$ 1.03 at EOT, $p<0.001$).

Conclusions: even with the limitations of an exploratory retrospective study, our analysis suggests weight-loss of more of 5 kg as a putative prognostic biomarker of everolimus efficacy in patients with metastatic BC. Prospective studies are needed to confirm the findings and validate the predictive/prognostic value of these biomarkers.

C11

ROLE OF ANTHRACYCLINES IN NEOADJUVANT ANTI-HER2 REGIMENS FOR HER2-POSITIVE BREAST CANCER (BC): A NETWORK META-ANALYSIS (NMA)

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Background: It is matter of current debate which would be the best chemotherapy backbone of neoadjuvant HER2-targeted therapy for HER2-positive BC. The TRAIN 2 trial showed no significant difference in terms of pathological complete response (pCR) when anthracycline-based (CTA) or anthracycline-free regimens (CT) were combined with dual HER2 blockade. However, it remains unclear how anthracyclines may influence the relative benefit across different anti-HER2 treatments.

Methods: A systematic review was conducted which included all phase II/III randomized clinical trials (RCTs) comparing different neoadjuvant regimens for HER2-positive BC. pCR (yT0/isN0) was the outcome of interest. Indirect comparisons of all combinations of anti-HER2 agents with CTA or CT were estimated with a random-effects frequentist NMA. Estimated pCR rates were inferred adopting a Bayesian NMA.

Results: 17 RCTs (3933 patients) were included. Overall, 8 arms were identified, comprising all possible combinations of CTA and CT with trastuzumab (H), lapatinib (L) and dual HER2 blockade (D) but also CTA and D only. Odds ratios (OR) for pCR and 95% confidence interval (CI) of selected NMA comparisons are shown in the table. Estimated rates of pCR for each treatment and 95% credible interval (CrI) are reported in the table.

Conclusions: In these indirect comparisons, we did not find a significant pCR gain for CTA vs CT when combined to D, H and L. Considering double vs single-agent anti-HER2 regimens, D-CT remains superior to H-CTA, supporting a possible omission of anthracycline when a dual anti-HER2 block is used. On the contrary, our pooled estimate suggests a more relevant role for anthracycline when comparing H-CT or H-CTA vs CTA. Moreover, we estimated a 4% pCR gain for D-CTA vs D-CT, and an 8% higher pCR rate for H-CTA vs H-CT.

C12

PALBOCICLIB-FULVESTRANT (PALBO-FUL) AND EVEROLIMUS -EXEMESTANE (EVE-EXE) FOR SECOND LINE HORMONAL TREATMENT (HT) OF METASTATIC BREAST CANCER (MBC) WITH LOBULAR HISTOLOGY: A PROPENSITY SCORE MATCHED ANALYSIS

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Background: In the last years, CDK4/6i showed to improve efficacy of HT in HR-positive/HER2-negative MBC patients (pts). Up to date, no data are available about the best sequence of HT according to MBC histotype. Alterations in the AKT pathway are known to be implied in acquired endocrine resistance and represent a main driver of proliferation in metastatic lobular breast cancer (MLBC). In this contest, the overexpression of cyclin E through the dysregulation of AKT may lead to an intrinsic resistance to CDK4/6i in MLBC previously exposed to HT. Instead, the inhibition of the AKT pathway could represent a better strategy in this setting. Thus, we performed a multicentric retrospective study to compare the efficacy of PALBO-FUL versus EVE-EXE as second line HT of MLBC.

Patients and Methods: From 2013 to 2018 patients with diagnosis od MLBC were collected from databases of 7 Italian centers. Progression free survival (PFS) was the primary endopoint. Results were adjusted through a propensity score (PS) for the final analysis of survival.

Results: Of 376 MLBC pts screened, seventy-four were elegible; 46 and 28 pts received PALBO-FUL or EVE-EXE as second line HT, respectively. Pts characteristics were well balanced between the two groups. Pts receiving EVE-EXE resulted to have significantly longer PFS than pts treated with PALBO-FUL (6.1 vs. 4.5 months, HR 0.58, 95% CI 0.35-0.96; $p = 0.025$). At the multivariate analysis, previous exposure to chemotherapy was significantly correlated with PFS (HR 0.41, 95% CI 0.24-0.72, p=0.002). Finally, the PFS benefit for EVE-EXE was confirmed independently from previous chemotherapy exposure and stage at diagnosis at the PS analysis (6.0 vs. 4.6 months, $p = 0.04$)

Conclusions: This retrospective analysis indicates a potential benefit of EVE-EXE in comparison with PALBO-FUL as second line HT of MLBC. The small pts' cohort calls for a larger and adequately sized prospective validation. However, these early data allow to speculate on the best hormonal therapeutic sequence in MLBC. Indeed, in this setting a late exposure to CDK4/6i might not allow to exploit its efficacy, while once hormonal resistance is acquired the inhibition of AKT/m-TOR pathway may represent the best option.

C13

NEXTMONARCH 1: PHASE 2 STUDY OF ABEMACICLIB PLUS TAMOXIFEN OR ABEMACICLIB ALONE IN HR+, HER2- ADVANCED BREAST CANCER

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Background: NextMONARCH 1 evaluated abemaciclib (2 monotherapy arms); 200mg Q12H abemaciclib +prophylactic loperamide to reduce incidence/severity of diarrhea and dose adjustments; and abemaciclib+tamoxifen as a strategy to overcome endocrine resistance.

Material and Methods: NextMONARCH 1 is a multicenter, randomized, open-label, Phase 2 study of abemaciclib or abemaciclib+tamoxifen in women with HR+, HER2- advanced breast cancer (ABC) who have progressed on or after prior endocrine therapy and previously received chemotherapy. Patients (Pts) were stratified by presence of liver metastases and prior use of tamoxifen in advanced setting. Randomization was 1:1:1 to abemaciclib 150mg Q12H+daily tamoxifen 20mg (Arm A) or abemaciclib 150mg Q12H (Arm B) or abemaciclib 200mg Q12H+prophylactic loperamide (Arm C). Key eligibilities: ⩾2 chemotherapy regimens, measurable disease & no prior treatment with CDK4&6 inhibitors. Primary objective: progression-free survival (PFS); key secondary objectives: objective response rate (ORR), clinical benefit rate (CBR) and safety. PFS analysis tested superiority of Arm A to C at one-sided alpha of.10 with ~110 events across the 2 arms assuming a hazard ratio (HR) of.667 to achieve ~80% power. Arm B would be considered non-inferior to Arm C if the observed PFS HR is <1.2.

Results: 234 pts were randomized to Arms A (n=78), B (n=79), C (n=77). PFS events: 166 (A:57/B:54/C:55); median PFS: 9.1 months (A)/6.5 (B)/7.4 (C; A vs C: HR=.815, 95%CI,.556-1.193, p=.293; B vs C: HR=1.045, 95%CI,.711-1.535 p=.811). Investigator-assessed ORR: 34.6%, 24.1% and 32.5% (confirmed ORR: 25.6%, 19.0%, 28.6%) and CBR: 61.5%, 49.4% and 51.9% in Arms A, B and C, respectively. Prophylactic loperamide reduced incidence and severity of diarrhea (C: 62.3%, Gr3: 7.8%) vs MONARCH 1 (90.2%, Gr3: 19.7%) resulting in similar rates of diarrhea with 150mg abemaciclib without prophylaxis (A: 53.8%, Gr3: 1.3%; B: 67.1%, Gr3: 3.8%).

Conclusions: NextMONARCH 1 confirmed single-agent activity of abemaciclib in heavily pretreated pts with HR+, HER2- ABC. Efficacy of abemaciclib monotherapy at 150mg was similar to 200mg. Abemaciclib+tamoxifen did

Summary of dose adjustments for diarrhea or neutropenia

Characteristics	MONARCH 1 Abemaciclib N = 132	MONARCH 2 Abemaciclib+F N = 441	MONARCH 3 Abemaciclib+NSAI N = 327
Diarrhea (any grade), n(%)	119(90.2)	381(86.4)	269(82.3)
Grade 3	26(19.7)	59(13.4)	31(9.5)
Incidences per patient, n(%)			
1	60(50.4)	185(48.6)	124(46.1)
2	29(24.4)	90(23.6)	52(19.3)
⩾3	30(25.2)	106(27.8)	93(34.6)
Outcome, number (%) of events	263	995	802
Not recovered/resolved	15(5.7)	106(10.7)	70(8.7)
Treatment change[a], n(%)			
Dose reduction of study drug	27(22.7)	83(21.8)	45(16.7)
Dose omission	32(26.9)	83(21.8)	51(19.0)
Antidiarrheal medication, n(%)	80(60.6)	333(75.5)	226(69.1)
Neutropenia (any grade), N(%)	49(37.1)	203(46.0)	143(43.7)
Grade ⩾3	32(24.2)	117(26.5)	78(23.9)
Treatment change, n(%)			
Dose reduction of study drug	14(10.6)	44(10.0)	42(12.8)
Dose omission	21(15.9)	72 (16.3)	57(17.4)

[a]Based on patients who had diarrhea

not demonstrate a statistically significant improvement in PFS vs abemaciclib monotherapy. Addition of prophylactic loperamide to abemaciclib 200mg resulted in diarrhea similar to 150mg without prophylaxis.

C14

MANAGEMENT OF ABEMACICLIB-ASSOCIATED ADVERSE EVENTS IN PATIENTS WITH HORMONE RECEPTOR-POSITIVE (HR+), HER2- ADVANCED BREAST CANCER: ANALYSIS OF THE MONARCH TRIALS

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Background: Abemaciclib demonstrated efficacy and acceptable safety profile in HR+, HER2- advanced breast cancer patients (pts) as monotherapy (MONARCH 1) and in combination with endocrine therapy; with fulvestrant (MONARCH 2) or non-steroidal aromatase inhibitors (MONARCH 3). We describe timing and management of common AEs in MONARCH trials.

Material and Methods: Study designs and key eligibility criteria of MONARCH 1,2,3 have been reported. Pts were advised to initiate antidiarrheal therapy at first sign of diarrhea and notify the investigator, drink fluids. If not improved within 24 hours to ⩽ grade 1, treatment was suspended until diarrhea resolved. Dose reductions required for grade ⩾3 or persistent grade 2 diarrhea. For grade 3 neutropenia, abemaciclib was held until ⩽ grade 2. Dose was reduced for recurrent grade 3 or 4 neutropenia.

Results: Across MONARCH, median time to onset of diarrhea was between days 6&8. First dose reductions for diarrhea occurred at a median of 28-41 days. Dose holds for diarrhea were brief, constituting 1.7-3.8% off total treatment time. Median time to onset of grade 3/4 neutropenia was 29-36.5 days, and resolved at a median of 11-15 days. AEs were managed by dose adjustments and/or supportive medication (Table).

Conclusions: The dose adjustment strategy used in the MONARCH studies was effective at managing AEs by dose adjustment and/or supportive medication. Understanding the safety profile of abemaciclib can inform AE management and can extend time on treatment.

C15

FERTILITY CONCERNS AND DESIRE OF PREGNANCY IN YOUNG BREAST CANCER PATIENTS: A SINGLE INSTITUTE EXPERIENCE

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Background: Although the use of adjuvant therapies with cytotoxic drugs can significantly reduce breast cancer (BC) mortality, it raises issues of the long-term toxicity, such as induction of an early menopause and fertility impairment in young women. The risk of infertility is a potential hardship to be faced by the patients following treatment of BC. Preservation of fertility in BC survivors of reproductive age has become an important issue regarding the quality of life. We conduct this prospectively observational study with the following aims: 1) to estimate the desire of pregnancy in young women with BC; 2) to evaluate the need to adopt appropriate fertility preservation techniques; 3) to evaluate the possible influence of pregnancies preceding the disease; 4) to analyze the implications of ovarian function recovery after adjuvant therapies.

Patients and Methods: We prospectively analyze pathological and clinical data about all consecutive patients younger than 40 years with diagnosis of invasive BC referred to our Institution from january 2013 to december 2017. All patients fill in a questionnaire at diagnosis and then once a year for 5 years after diagnosis that collect data about pregnancies, desire of maternity, using of fertility preservation techniques and menstruation history.

Results: 73 (5.7%) of 1265 patients referred to our Institution are included. The age at diagnosis correlates with the desire of pregnancy ($p=0.0018$). About 40% of them had no pregnancies before the diagnosis of BC, consequently more than 60% of patients reveal desire of maternity at the beginning of the treatments and decide to preserve fertility. LH-RH analogue and cryopreservation procedures are used to preserve fertility. However, at the end of the adjuvant therapies only 37% of patients preserve the desire of pregnancy. Among patients who have a free interval $\leqslant$24 months between the last pregnancy and the diagnosis of BC (23.3% of cases), tumors are predominantly ER-negative (60% of cases). Ovarian function recovery occurs early and more frequently in ER-negative BC patients ($p<0.0001$).

Conclusions: Our results reveal that an higher proportion of young BC women lost the desire of pregnancy during the adjuvant treatments; it may depends on type and duration of oncological therapies and side effects of treatments. A multidisciplinary approach and an adequate psychological support need to encourage young BC patients to pursuing their future aims, including motherhood.

C16

ABEMACICLIB WITH FULVESTRANT IN PATIENTS WITH HORMONE RECEPTOR POSITIVE (HR+), HER2- ADVANCED BREAST CANCER (ABC) THAT EXHIBITED PRIMARY OR SECONDARY RESISTANCE TO PRIOR ENDOCRINE THERAPY

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Background: Abemaciclib, a selective inhibitor of CDK4 & 6, dosed on a continuous schedule is approved for the treatment of HR+, HER2- ABC. In the intent-to-treat population, abemaciclib with fulvestrant (F) demonstrated improved progression-free survival (PFS) and objective response rate (ORR) compared to placebo (P)+F (16.4 vs 9.3 months, HR: 0.553; $P<.0000001$; ORR in measurable disease 48.1 vs 21.3%; $P<.001$). ET resistance (ETR) were classified into primary ETR, which includes patients (pts) whose disease relapsed while receiving the first 2 years of (neo)adjuvant ET or progressed while receiving the first 6 months of ET for ABC, and secondary ETR. Here, we compare the efficacy and safety of abemaciclib+F vs P+F in the primary and secondary ETR subgroups.

Material and Methods: MONARCH 2 was a phase 3 randomized, double-blind, placebo-controlled study of abemaciclib+F vs P+F in pts with HR+, HER2- ABC that progressed on ET. Key eligibility criteria were previously discussed. Pts received orally administered abemaciclib 150 mg Q12H + 500 mg F (per label) or P+F. Pts were stratified by sensitivity to ET. Primary objective was investigator-assessed PFS. Secondary objectives included efficacy, safety and tolerability.

Summary of PFS and ORR in primary and secondary ETR population.

	Primary Resistance		Secondary Resistance	
	Abemaciclib + F	Placebo + F	Abemaciclib + F	Placebo + F
PFS				
Median (months)	15.3	7.9	16.6	9.6
HR (95% CI)	0.45 (0.31, 0.67)		0.59 (0.46, 0.75)	
P-value	<.001		<.001	
ORR in measurable disease (%)	53.9	17.9	46.2	22.6
P-value	<.001		<.001	

Results: 169 pts (25.3%) had primary ETR and 489 pts (73.1%) had secondary ETR. Key efficacy endpoints are summarized (Table). The most frequent adverse events in primary and secondary ETR population are similar. For primary ETR, abemaciclib+F vs P+F were diarrhea (87.3 vs 22.4%), neutropenia (43.6 vs 5.2%), nausea (41.8 vs 25.9%), abdominal pain (36.4 vs 13.8%), and anemia (31.8 vs 5.2%), respectively.
Conclusions: Abemaciclib+F improved PFS and ORR in pts with primary and secondary ETR, and had a generally tolerable safety profile. Although pts with primary ETR typically have poor prognosis the benefit for abemaciclib+F was maintained in pts HR+, HER2- ABC.

C17

THE NEUTROPHIL-TO-LYMPHOCYTE, PLATELET-TO-LYMPHOCYTE AND MONOCYTE-TO-LYMPHOCYTE RATIOS PREDICT EFFICACY OF CDK 4/6 INHIBITORS IN WOMEN WITH HORMONE RECEPTOR-POSITIVE/HER2-NEGATIVE ADVANCED BREAST CANCER

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Background: Cyclin-dependent kinase (CDK) 4/6 inhibitors in combination with endocrine therapies are a mainstay of treatment for patients (pts) with advanced hormone receptor-positive breast cancer (HR+ BC). Preclinical evidence indicates that the ability of CDK 4/6 inhibitors to stimulate antitumor immunity may crucially contribute to their anticancer activity. Although peripheral blood-derived markers reflecting systemic inflammation and immune system activation, such as the neutrophil-to-lymphocyte ratio (NLR), the monocyte-to-lymphocyte ratio (MLR) and the platelet-to-lymphocyte ratio (PLR), have been associated with patient prognosis in several malignancies, their role in predicting CDK 4/6 inhibitor efficacy in HR+ BC pts remains unknown.
Patients and Methods: We performed a retrospective, monocentric study in advanced HR+ BC pts treated with CDK 4/6 inhibitors at our Institution. We assessed the association between NLR, MLR or PLR, as measured two weeks after treatment initiation or at the fist disease re-evaluation, and patient progression free survival (PFS). The threshold for NLR (2.5) was chosen on the basis of literature data, whereas MLR and PLR thresholds were calculated through maximally selected rank statistics. The impact of these parameters on PFS was evaluated at univariate and multivariable analysis by using Cox proportional hazard models.
Results: A total of 92 pts treated with palbociclib or ribociclib plus aromatase inhibitors or fulvestrant between January 2017 and December 2018 at our Institution were included in the analysis. When measured two weeks after treatment initiation, NLR, MLR and PLR were not associated with PFS. Conversely, high NLR ($>$ 2.5), high MLR ($>$ 0.19) and high PLR ($>$ 323), as measured at the first disease re-valuation, were associated with significantly higher risk of disease progression (HR 3.12; 95% CIs: 1.06-9.16; HR 2.38; 95% CIs: 1.06-5.34 and HR 3.89; 95% CIs: 1.53-9.9, respectively). Multivariable analysis confirmed an independent association between high MLR or PLR and lower PFS, and a trend towards statistical significance for NLR.
Conclusions: This is the first study to show a significant association between high NLR, MLR or PLR values and lower PFS in HR+ BC pts treated with CDK 4/6 inhibitors. Further studies are warranted to prospectively validate these biomarkers, and to investigate if patients with poorer predicted prognosis may benefit from alternative endocrine, cytotoxic or biological agents.

C18

BRCA MUTATIONS AMONG TRIPLE NEGATIVE BREAST CANCER, EARLY ONSET BREAST CANCER, MALE BREAST CANCER AND OVARIAN CANCER WITHOUT FAMILY HISTORY OF BREAST AND/OR OVARIAN CANCER: THE MODENA FAMILY CANCER CLINIC EXPERIENCE

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Because of the high costs associated with genetic analyses, BRCA-testing has traditionally been restricted to breast cancer (BC) patients having an a priori high risk of being a carrier. According to the National Institute for Health and Care Excellence (NICE) in the UK, BRCA testing should be offered to BC patients with a probability of having a mutation = 10%. Regardless of family history, International Guidelines include among the BRCA testing Criteria personal history of triple-nagtive BC (TNBC) diagnosed = 60 years, early onset BC (= 35 years according to the Italian Criteria), male BC and epithelian ovarian cancer (OC).
In the archives of the Modena Family Cancer Clinic, we identified 258 early onset BCs, 126 TNBCs $<=$ 60 years,

44 male BCs and 99 OCs without any breast and/or ovarian family history, which underwent BRCA-genetic testing. BRCA detection rate among eorly-onset BCs was 15.5% (12% BRCA1, 3.5% BRCA2), among TNBCs was 15.8% (14.3% BRCA1, 1.5% BRCA2), among male BCs was 18.2% (18.2% BRCA2) and among OCs was 19.2% (11.1% BRCA1, 8.1% BRCA2). BRCA-associated early-onset BC showed significantly higher MIB-1. The other clinical-pathological characteristics were equally distributed between carriers and non-carriers and will be detailed in the final presentation.

Our analyses highlighted a mutational rate greater than 10% in all the four categories considered. These results confirm the indication to test TNBC = 60 years, early onset BC (=35 years), male BC and epithelian ovarian cancer (OC) regardless their family history.

C19

FEASIBILITY OF AUTOMATED DATA EXTRACTION AND ELECTRONIC PHENOTYPING USING THE i2b2 PLATFORM FOR OUTCOMES RESEARCH ANALYSIS, IN A LARGE COHORT OF HER2+ EARLY-STAGE BREAST CANCER

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Background: With the widespread adoption of electronic health records, large repositories of structured and unstructured patient data are becoming available to conduct observational studies. This single-centre study aimed to evaluate the feasibility of the Harvard-academic, open-source, *i2b2 (Informatics for Integrating Biology & the Bedside)* platform to support an outcomes research study, through the automated reconstruction of individual pathways of care and long-term survival of a large cohort of HER2+/eBC, based on an electronic phenotyping approach.

Material and Methods: To test the *i2b2* platform, we identified a 10-year dataset of consecutive HER2+/eBC patients treated at Papa Giovanni XXIII Hospital (Bergamo), with an automated multiple temporal electronic phenotyping, according to the main clinico-pathological characteristics. In this unselected cohort of patients, the Kaplan-Meier estimates were used to evaluate cumulative incidence of relapse and survival, stratifying for the tumor burden (T, N) and tumor biology (Grade, ER). Multivariable Cox proportional-hazard models were apply to estimate HRs of relapse and death adjusting for potential confounders.

Results: From Sept 2007 to Sept 2017, 531 HER2+/eBCs, out of >5000 consecutive eBCs, were identified and the individual-data automatically analyzed through the *i2b2* open-source platform. At a first preliminary analysis, the 10-year OS of trastuzumab-treated patients (391) was 68.3%. According to the multiple electronic phenotyping, OS was significantly affected by lymph node involvement (N-: 79.0% vs. N+: 58.7%, p = 0.0001), tumor size (T1: 76.7% vs. T2-4: 68.4%, p = 0.039) and ER status (ER-: 63.2% vs. ER+: 69.7%, p = 0.012). Similarly, the 10-year cumulative incidence of relapse was mainly associated to lymph node involvement (N-: 26.5% vs. N+: 51.9%, p = 0.0001), ER status (ER-: 51.4% vs. ER+: 30.8%, p = 0.001) and tumor grade (G1-2: 20.7% vs. G3: 45.5%, p = 0.003). The adjusted multivariable analysis confirmed N+, ER- and age>65 as independent risk factors of BC relapse and death, in line with the previously reported evidences.

Conclusions: This real-life experience shown the exportable, open-source *i2b2* platform is able to automatically rebuilt the individual pathways of care and clinical outcomes of a large and unselected cohort of HER2+/eBCs. Actually, the *i2b2* platform supported the automated data extraction and the phenotyping approach and can be considered as a relevant tool for multiple outcomes research studies.

C20

IMPACT OF ESTROGEN RECEPTOR LEVELS ON OUTCOME AND PATHOLOGICAL COMPLETE RESPONSE IN TRIPLE NEGATIVE BREAST CANCER (TNBC) PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY

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Background: Although 1% has been proposed as cut-off for estrogen receptor (ER) positivity, the 10% cut-off is often used in clinical practice based on several studies showing that breast cancers with ER<1% have biological characteristics similar to those with ER≥1%&<10%. Our aim was to compare pathological complete response (pCR) rates and disease-free survival (DFS) according to ER level in a cohort of patients with HER2-negative, ER<10% and progesterone receptor <10% undergoing neoadjuvant chemotherapy (NACT).

Patients and Methods: Clinicopathological data of patients with triple negative breast cancer (TNBC, defined

as ER and progesterone receptor <10% and HER2-negative) treated at our Institution with anthracycline and taxane-based NACT were collected. Patients were categorized according to ER expression; <1% or ⩾1%&<10%. pCR was defined as ypT0/is and ypN0. DFS was calculated from the date of diagnosis to the date of relapse (locoregional or distant), death or last follow up.

Results: 184 patients were included: 157 with ER<1%, 27 with ER⩾1%&<10%. Main characteristics: median age 50 years, ductal histology 93%, grade 3 90%, cT>2cm 86%, cN+ 56%, median ki67 60%, BRCA mutated 9%. There was no significant difference in clinicopathological characteristics according to ER level. With regards to adjuvant therapy, 27% (n=50) of patients underwent chemotherapy after surgery: 29% in the ER<1% and 19% in the ER⩾1%&<10% cohort, p=0.317. More patients in the ER⩾1%&<10% cohort received adjuvant endocrine therapy (15% vs 6%, p=0.078). Reason to prescribe endocrine therapy in ER<1% patients was residual disease with ER⩾1%. pCR rate was similar in the two cohorts (38% in ER<1% cohort, 44% in ER⩾1%&<10% cohort, p=0.498). With a median follow up of 48 months, no difference was observed in DFS: 2-year DFS was 80.9% in ER<1% and 82.9% in ER⩾1%&<10% cohort (HR 1.04, 95%CI 0.46-2.3, p=0.928).

Conclusions: Early HER2-negative primary breast cancer with ER<10% behaves clinically like ER<1% breast cancer in terms of pCR after NACT and DFS. Our results support the definition of TNBC as HER2-negative breast cancer with ER<10% and PgR<10%, rather than <1%.

C21

AN ANALYSIS OF THE RELATIONSHIP BETWEEN ABDOMINAL FREE FLAP WEIGHT AND MASTECTOMY WEIGHT AND THE EFFECT OF ADJUVANT RADIOTHERAPY ON THE AESTHETIC OUTCOMES OF IMMEDIATE BREAST RECONSTRUCTION: A MULTICENTRE STUDY

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Background: Breast cancer is the most common malignancy in women (25% of all cancers). In the UK, its incidence has increased by 4% over the last 10 years, while it is estimated that in Italy 1 in 8 women will be affected by breast cancer in her life. It has however, the highest survival rate amongst all types of female cancers. In view of this and the fact that today breast reconstruction is a significant component of breast cancer treatment, improving reconstruction outcomes needs to be an ongoing goal.

Material and Methods: Between May 2004 and August 2018, 423 women, who underwent immediate abdominal free flap breast reconstruction (FFBR), were enrolled in our multicentre study (UK and Italy). Abdominal free flap weights were compared with mastectomy weights with a view to analysing the rates of contralateral balancing and ipsilateral revision surgeries based on the relative magnitudes of the weights. Patients were thus divided into two groups: Group A mastectomy weight > flap weight; Group B mastectomy weight < flap weight. The influence of post-mastectomy radiotherapy on the incidence of contralateral balancing and ipsilateral revision surgeries was also studied. Fisher's Exact test was used to analyse the comparative requirements for these aesthetic adjustment procedures.

Results: In Group A, the incidence of adjustment surgery was dominated by balancing surgeries on the contralateral breast (37%) versus 14% revisions of the reconstructed breasts. In Group B, the rate of contralateral balancing surgery was much less: 11% versus the above 37% (p value=0.00001). The revision surgery rate on the index breasts in Group A (14%) was double that of Group B (7%) [p value=0.003]. For all patients, post-operative radiotherapy significantly increased the number of ipsilateral revisions (p value=0.048) compared with contralateral balancing surgeries.

Conclusions: When performing immediate FFBR, where the flap weight is smaller than the mastectomy weight, surgeons can reasonably expect an increased need for subsequent adjustments on both the contralateral and ipsilateral breasts (revisions and balancing surgeries respectively). Furthermore, post-operative irradiation predisposes to ipsilateral revisions. We believe that these findings are important in patient counselling before and after reconstruction. They may also play a role in planning subsequent aesthetic refinements.

C22

NODE-NEGATIVE BREAST CANCER AND LONG-TERM PROGNOSIS

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Background: Early breast cancers (BC) are associated with a risk of relapse which may vary according to clinical-pathological features of disease. Thanks to a wider diffusion of screening, incidence of node-negative BC has increased in the recent decades and it is expected to further increase in the next future. Aim of our study was to evaluate prognosis of node-negative BC and to evaluate which factors are associated with an increased risk of relapse.
Methods: BC operated at our institution with evidence of negative nodes and with a potential follow-up of at least 5 years were retrospectively reviewed. OS was estimated by Kaplan Meier method and differences between groups by log-rank test. Cox proportional Hazard model was used to estimate Hazard ratio (HR) with 95% confidence intervals (CI). Significance was set at 0.05.
Results: We analyzed 1276 patients (pts) affected by node-negative BC, operated at our institution between April 1999 and December 2013. With a median follow-up of 71.6 months (range 1-227.2 months), we observed 159 events of relapse or death. Median PFS was 170 months. Median OS was 192 months. At univariate analysis, older age, negative hormonal receptors, larger tumor size and higher proliferation index (ki67) were significantly associated with worse PFS and OS ($p<0.05$); higher grading was significantly associated with worse PFS ($p=0.01$). At multivariate analysis for PFS, age, ki67 and tumor size confirmed their independent prognostic role (HR 1.035, 95% CI 1.021-1.048, $p<0.001$; HR 1.012, 95% CI 1.004-1.021, $p=0.005$; HR 1.020, 95% CI 1.004-1.037, $p=0.018$, respectively). At multivariate analysis for OS, age and positive hormonal receptors showed an independent prognostic role (HR 1.104, 95% CI 1.079-1.129, $p<0.0001$, HR 0.426, 95% CI 0.224-0.809, $p=0.0092$, respectively). In order to compare prognosis of triple negative BC (TNBC) with non-TNBC subtypes, a subgroup of 71 TNBC pts were matched according to age, ki67 and tumor size with 71 non-TNBC pts. We observed no statistically significant difference in terms of prognosis (72-months PFS 89.6% vs 92.9% in TNBC and non-TNBC, respectively, $p=0.232$; 72-months OS 90% vs 98% in TNBC and non-TNBC, respectively, $p=0.1779$).
Conclusions: In our retrospective analysis of node-negative BC, age, hormonal receptor status, tumor size and ki67 showed a significant association with prognosis. TNBC subtype was not associated with a statistically significant worse prognosis, compared to non-TNBC subtypes.

C23

EFFICACY AND SAFETY OF ORAL CAPECITABINE-VINORELBINE COMBINATION VERSUS SINGLE-AGENT CAPECITABINE OR VINORELBINE IN METASTATIC HER2-NEGATIVE BREAST CANCER: A RETROSPECTIVE, MONOCENTRIC STUDY

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Background: Despite the introduction of new treatments, chemotherapy (ChT) still plays a pivotal role in HER2-negative metastatic breast cancer (mBC). Although single-agent capecitabine (C) and vinorelbine (V) are effective agents in mBC treatment, the capecitabine-vinorelbine (CV) combination is frequently used despite the lack of data demonstrating its superiority over single-agent C/V. In this study, we retrospectively compared the efficacy and safety profile of CV and single-agent C/V.
Patients and Methods: We collected data of 310 patients (pts) with HER2-negative mBC treated between April 2012 and December 2018 with C 2000 mg/m2 on days 1-14 of every-three weeks cycles, V 60 mg/m2 on days 1 and 8 of every-three weeks cycles, or the CV combination. We compared progression-free survival (PFS), overall survival (OS) and rate of adverse events (AEs) in pts treated with CV or single-agent C/V. Subgroup analysis was conducted in pts with hormone receptor-positive (HR+) and triple negative breast cancer (TNBC). Propensity score analysis was used to confirm results of OS analyses in pts matched for clinical/tumor characteristics. As an exploratory analysis, we evaluated the impact of single versus combination treatments on the neutrophil-to-lymphocyte ratio (NLR) after one treatment cycle.
Results: We found no differences in median PFS between pts treated with CV vs. single-agent C/V, while CV was associated with significantly longer OS in pts with HR+ BC (27.6 vs. 22.7 moths; $p=0.016$). These results were confirmed at multivariable analysis when balancing for known prognostic factors in mBC, as well as after propensity score-based matching of pts with similar clinical/tumor characteristics. Pts treated with CV had higher incidence of any-grade and G3/G4 neutropenia, whereas the incidence of other AEs was similar in the two treatment groups. A NLR higher than 3.67 before treatment initiation was associated with worse OS; of note, the CV combination reduced the NLR significantly more than single-agent C/V.
Conclusions: When compared with single-agent C/V, the CV combination was independently associated with significantly longer OS in the subgroup of HR+ BC pts. However, this potential advantage comes at the cost of increased incidence of neutropenia. Prospective studies

are required to confirm the observed association between CV and better OS in HR+ BC patients, as well as to explore the potential immunomodulatory effect of this combination chemotherapy.

C24

LIQERBCEPT: INTERCEPTING MUTATIONAL TRAJECTORIES OF HER2+ BREAST CANCER PATIENTS UNDERGOING T-DM1 ADMINISTRATION

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Background: Trastuzumab Emtansine (T-DM1) is standard of care (SOC) in HER2+ breast cancer on progression following previous lines of HER2-targeted therapies. Despite clinical benefit, some patients display primary resistance, and the majority relapse within 1 year due to acquired resistance. The underlying mechanisms remain ill-defined. Liquid biopsy (LB) may help to uncover genomic alterations linked to T-DM1 resistance.

Methods: Tissue DNAs (tDNAs) from the latest available primary and/or metastatic lesions (n=23), and circulating tumor DNAs (ctDNAs) from plasma (n=157) were collected from 13 patients. tDNAs and ctDNAs were analyzed by ultra-deep NGS (IonTorrent S5) and dPCR (QuantStudio3D). Genomic data were matched with radiomics (PET/CT).

Results: Nine out 13 patients progressed within 1 year (mean 306±209 days). At least 1 mutation per patient (range=1-64) was identified in tDNAs, and multiple sequential tDNAs documented clonal selection prior to T-DM1 administration. At baseline, 9/13 patients showed at least 1 ctDNA (VAF=0.1-15.2%), and tDNA/ctDNA mismatches were common. Increases and *de novo* ctDNA appearance (indicative of primary and adaptive resistance, respectively) were seen by LB in 5/8 relapsing patients, 2.0 months on average before radiomic progression (range 0.7-2.8). The remaining 3 patients developed brain (n=2) or skin (n=1) metastases not captured by the available ctDNAs, that registered clonal regression instead. Remarkably, 6/8 relapsing patients displayed actionable (OncoKB levels ⩽3) ctDNAs. As to responders, outcome was anticipated in all (4/5) patients in whom a ctDNA was detectable at baseline. In two of them, ultra-fast ctDNA clearance (<2 months) of two HER2 mutations was observed. Finally, intersecting, divergent ctDNA trajectories were noted in a patient.

Conclusions: Although non-informative in 4/13 patients, our study provides proof of principle for tumor evolution, outcome anticipation, and divergent/accelerated clonal selection. Vulnerabilities only seen in blood may offer unprecedented non-SOC therapeutic opportunity upon T-DM1 progression.

C25

TOXICITY (T) OF ERIBULIN (E) IN METASTATIC BREAST CANCER (MBC) PATIENTS (pts). RESULTS OF THE PHASE IV PAINTER (POLYMORPHISM AND INCIDENCE OF TOXICITY IN ERIBULIN TREATMENT) STUDY

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AEs n=170	G1 n. (%)	G2 n. (%)	G3 n. (%)	G4 n. (%)	Severe T (G3+G4) % [%95%CI]
Neurotoxicity	31 (18.2)	20 (11.8)	5 (2.9)	0 (0.0)	14.7 [9.75 - 20.9]*
Neutropenia	15 (8.8)	11 (6.5)	16 (9.4)	10 (5.9)	15.3 [10.2 - 21.6]
Constipation	16 (9.4)	8 (4.7)	1 (0.6)	0 (0.0)	0.6 [0.02 - 3.23]
Alopecia	25 (14.7)	13 (7.6)	0 (0.0)	0 (0.0)	0.0
Asthenia	38 (22.4)	38 (22.4)	10 (5.9)	0 (0.0)	5.9 [2.86 - 10.6]
Nausea	19 (11.2)	6 (3.5)	0 (0.0)	0 (0.0)	0.0

*G2 for neoropathy was considered as severe T.

Background: MBC is a deathly disease. Treatments in this setting have a palliative aim, therefore the management of drug related adverse events (AE) is very important. E is a microtubule inhibitor, approved for the treatment of MBC. The most common AE reported in the literature are fatigue, neutropenia and peripheral neuropathy.
Material and Methods: PAINTER is a multicenter, interventional, single arm, phase IV study, aimed to survey the tolerability of E, at conventional dose, in an unselected population of pts with MBC. T was reported according to the NCI CTCAE v4.0.
Results: From May 2014 to June 2018, 180 pts were enrolled from 20 Italian centers and 170 were evaluated for the safety analysis. Pts and tumors characteristics were as follow: median age 60 years, ductal carcinoma 76.3%, visceral disease 68.8%, luminal type 64.7%, Her2 positive 18.3%, triple negative 17%, median previous treatment lines for MBC 5, median years from first diagnosis 6.1, mean BMI 25.5, with 27.2% overweight and 19.5% obese pts. Previous neuropathy was reported in 15.9% of pts. The table shows the incidence of expected AEs. Other G1-G4 toxicities were: gastrointestinal in 30.9% pts, dermatological in 8.6%, liver injury in 13.6%, pulmonary in 13.6%.
Interestingly, 40.7% of pts reported pain, especially osteomuscular, abdominal and in tumor site. 48.8% of pts experienced a schedule modification, mainly at the 2nd cycle, due to neutropenia (23.9%) and liver injury (12%). 37.3% had a modification of timing, mainly for logistic reasons (19.4%) or previous reactions (3.2%). Ten serious AEs were reported, only two E related. 5.2% of pts discontinued E for T and for pts refuse.
Conclusions: PAINTER study offers a wide spectrum of information about E tolerability. Asthenia, neuropathy and neutropenia were the most common T, but few pts experienced severe AEs. Schedule and dosage modifications were common, as expected in pretreated pts, but T rarely lead to treatment discontinuation.

C26

AGREEMENT BETWEEN THE MULTIDISCIPLINARY TEAM MEETINGS PROPOSAL AND FINAL THERAPEUTIC CHOICE IN EARLY BREAST CANCER

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Background: A multidisciplinary team meetings (MDMs) approach to breast cancer (BC) management is a standard of care. One of the roles of MDMs is to identify the best diagnostic and therapeutic strategies for patients (pts) with new diagnosis of early BC. The purpose of this study was to define whether there was agreement between the planned program (i.e. MDMs-based decision) and that actually applied. In addition, the study explored factors associated with discordance.
Methods: We conducted a retrospective study of a consecutive series of 291 pts with new diagnosis of early BC, discussed at MDMs at the University Hospital of Udine (Italy), from January 2017 to June 2018. The association between clinico-biological factors and discordance was explored through uni- and multi-variate logistic regression analysis.
Results: Median age was 62 years (range 27-88 years). Among invasive early BC patients, the most frequent phenotype was luminal A (38%), followed by luminal B (33%), HER2-positive (12%) and triple negative (5%). In situ carcinoma (DCIS) represented 12% of cases. Median time from MDMs discussion to first oncologic examination was 2 weeks. Rate of discordance between MDMs-based decision and final choice, during face to face consultation with the oncologist, was 15.8% (46/291). The most frequent reason for changing the MDMs-based program was clinical decision (87%). Follow-up was preferred to the chemotherapy (CT) proposed within the MDMs in 15% of cases, and to the endocrine therapy (ET) in 39% of cases (among these, 44.5% had diagnosis of DCIS). Therapeutic change from sequential CT-ET to Et alone was chosen in 16/46 pts (35%): among these pts, 7 had a luminal B disease and 6 had a HER2-positive disease. On univariate analysis, factors associated with discordance were values of Ki-67 14-30% (OR 3.91; 95%CI 1.19-12.9), age⩾70 years (OR 2.44, 95%CI 1.28-4.63), housewife/retired status (OR 2.35, 95%CI 1.14-4.85), polypharmacy (OR 1.95; 95%CI 1.02-3.72), postmenopausal status (OR 4.15; 95%CI 1.58-10.9), high Charlson Comorbidity Index (OR 1.31; 95%CI 1.09-1.57). Association with marital status, educational level, alcool and smoke habits, presence of caregiver, parity, grading, histotype and phenotype, stage were not statistically significant. On multivariate analysis, only ki-67 value maintained its statistical significance.
Conclusions: The results of our study could be useful for enhancing the role of MDMs in clinical decision making process in early BC.

C27

ASSESSING THE IMPACT OF 12 MONTHS LIFESTYLE INTERVENTIONS ON BREAST CANCER SECONDARY PREVENTION: A MODELING APPROACH

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Background: Healthy lifestyle, including caloric restriction, balanced diet and physical activity, is important in primary and secondary prevention of breast cancer (BC). Since January 2014, at our Institution we promoted a project named "Lifestyle Program" for high risk BC patients underwent to primary surgery. Here we presented the results of 12 months of "Lifestyle Program".

Patients and Methods: Since January 2014 we have prospectively enrolled all high risk patients between 18 and 70 years treated to our department for invasive early-stage breast cancer (stage I-III). High risk has been defined by one or more of the following inclusion criteria: body mass index (BMI)> 25, diagnosis of metabolic syndrome, increased level of blood testosterone and/or insulin. All high risk patients receive a periodical personalized educational intervention by a physiatrist for physical activity and by a nutritionist for a mediterranean diet low in animals fat and enriched of fibers, fruits and vegetables. All patients underwent to screening for anxiety and depression through HADS questionnaire scores.

Results: 98 BC patients were included; 21.4% of them had a metabolic syndrome. Median age was 56 years old (range 27-75). Most of patients enrolled had ER+ (85.7%), Her2/neu negative (79.6%), stage I (48%) BC. We observed a statistically significant reduction of BMI (BMI>25 in 94.9% of pts at baseline vs 63.2% after 12 months of lifestyle; p=<0.0001), glycemic (>110 mg/dl in 23.5% of pts at baseline vs 10.2% at 12 months; p=<0.0001), insulin levels (>27 uU/ml in 20.6% of pts at baseline vs 2.9% after 12 months; p<0.0001), testosterone (>1,2 ng/ml in 17.6% of pts at baseline vs 4.1% at 12 months; p<0.0001), cholesterol (>200 mg/dl in 46.9% of pts at baseline vs 35.7% at 12 months; p<0.0001), triglycerides (>170 mg/dl in 13.3% of pts at baseline vs 10.2% at 12 months; p<0.0001) and arthralgia (37.7% at baseline vs 17.3% at 12 months; p=0.0008). We also noted a significantly reduction of anxiety and depression after 12 months of lifestyle program (25.4% and 12% respectively at diagnosis vs 13.4% and 4.5% at 12 months respectively; p=0,0064 and p<0.0001).

Conclusions: Promoting healthy lifestyle can reduce risk factors involved in BC recurrence and ensure psychological benefit and compliance to endocrine therapy. A multidisciplinary approach allows greater adherence to healthy attitudes in BC high risk patients.

C28

BASELINE SUVMAX AS A PREDICTOR OF PATHOLOGICAL COMPLETE RESPONSE (pCR) FOR PATIENTS (pts) WITH BREAST CANCER (BC) TREATED WITH PREOPERATIVE SYSTEMIC THERAPY (pst)

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Background: PST is the standard of care for inoperable locally advanced or inflammatory BC and it is also an option for operable BC in order to improve breast conservation. Achieving a pCR to PST is associated with better DFS and OS. In this retrospective study, we assessed the potential role of baseline SUVmax as a predictor of pCR for BC pts treated with PST.

Methods: We retrospectively reviewed medical charts of pts with stage II-III BC who underwent a baseline FDG-PET/CT scan before PST. Categorical data were compared with chi-square test and a multivariate logistic regression analysis was performed to investigate the association of clinicopathologic variables and pCR. Kaplan-Meier method with log rank test was used for DFS analysis. Cox multivariate analysis was performed to evaluate the association of clinicopathological variables with DFS.

Results: From 2010 to 2019, 140 pts received a baseline FDG-PET/CT scan before starting PST for stage II-III BC. Among them, 30 (21%) achieved a pCR. pCR rates were 42% (24/57), 27% (6/22), and 0% (0/61) for pts with HER2+, TN and luminal A/B BC, respectively (p<0.001). Median baseline tumor SUVmax was 10, median post-treatment delta SUVmax was 68%: these were considered as cut-off values. SUVmax was more frequently high (=10) in HER2+ (57%) and TN (68%) than in luminal BC (24%, p=0.30). High SUVmax was associated with G3 (p<0.001) and Ki67=20% (p=0.001). At univariate analysis, pCR was significantly associated with HER2+ and TN subtype (HER2+ vs luminal, OR 89; p=0.002; TN vs luminal, OR 48; p=0.009), high grade (G3 vs G2, OR 6; p=0.002), and high baseline SUVmax (=10 vs <10, OR 1.6, p=0.001). At multivariate analysis, only BC subtype and SUVmax were significantly associated with pCR. After a median follow-up of 27 months, 28/140 pts relapsed locally (6) or at a distant site (22). No pts who achieved pCR had recurrence, and median DFS was NR vs 56 months (p=0.0011) for pts with pCR compared to those with no pCR. Among pts who did not achieve pCR, stage (III vs II, HR 30, p=0.007), grading (G3 vs G2, HR 3.7, p=0.045), HER2 status (HER2+ vs luminal, HR 0.28,

p=0.016) and deltaSUVmax (=68% vs <68%, HR 0.11, p=0.002), but not baseline SUVmax (=10 vs <10, HR 0.46, p=0.324), were significantly associated with DFS.
Conclusions: High baseline SUVmax (=10) and BC subtype could represent predictive factors of pCR for BC pts receiving PST. At a median follow-up of 27 months, no relapse was observed among pts who achieved pCR.

C29

CLINICAL PATHWAYS (PERCORSO DIAGNOSTICO-TERAPEUTICO-ASSISTENZIALE O PDTA) AND MULTIDISCIPLINARY APPROACH IN BREAST CANCER UNIT: A MODEL BASED ON CENTRO ACCOGLIENZA E SERVIZI (CAS) AND GRUPPI INTERDICIPLINARI E CURE (GIC) IN RETE ONCOLOGICA DEL PIEMONTE E VALLE D'AOSTA (ROPEVDA)

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Background: Detailed clinical pathways (PDTA) and multidisciplinary approach represent two instrument keys faced to improve local organizational model, healthcare [1] quality and clinical outcomes. At Parini's Hospital in Aosta, we implemented a Breast Unit with CAS and GIC activity in order to manage breast cancer patients(pts) across the entire process from diagnosis, staging and therapies, according to a shared PDTA. The aim of this study is to present a preliminary analysis of process indicators from our model of breast cancer management.
Patients and Methods: Pts were referred from the breast cancer screening program, the senologist or the [2] general practitioner. As indicated by the ROPeVDA, the oncologist or the surgeon performed the first clinical evaluation at CAS. In the meanwhile the CAS nurse collected clinical, pharmacological, social and personal informations and provided the correct planning of clinical and histological staging. The GIC discussion was performed after completing the first step evaluation defining the following therapeutic approach. The GIC was composed by oncologists, radiotherapists, surgeons, radiologists, pathologists, psicologists, palliative care medicine and a case manager nurse. **Results:** Here we report data of our activity in January-December 2018. We observed 120 women with hystologically proven breast cancer, median age 61 years. Hormonal receptor positive pts were 82%, Her2 positive 23%; triple negative 6%. Six pts had metastatic disease at diagnosis. 100 pts underwent surgical intervention as primary treatment; 21/100 pts had a pre-surgical GIC discussion, 79/100 were discussed after surgery. The median time from diagnosis to surgery was 36 days (range 19-67), from surgery to adjuvant chemotherapy or hormonal therapy was 46 days (35-60) and 36 day (20-73) respectively. 13 pts received neoadjuvant chemotherapy (neoadj CT) followed by surgery. All of them had a GIC discussion before CT. The median time from diagnosis to neoadj CT was 29 days (11-80), while from GIC discussion to neoadj CT it was 22 days (5-45).
Conclusions: The Breast Unit model based on CAS, GIC and PDTA allows to measure the time frame between the different steps of breast cancer management showing the respect of guidelines and PDTA parameters in most but not all patients. Further analysis of the delay reasons in single cases are needed in order to adopt corrective actions. [1]Healthcare quality and [2]General practitioner (medico di base).

C30

ITALIAN BONE METASTASES (BM) DATA BASE (DB): FIRST PROSPECTIVE DATA ON BREAST CANCER (BC) PATIENTS (pts)

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Introduction: BM are still the main cause of morbidity and morbility in cancer pts because of their complications defined as skeletal-related events (SREs).SREs reduce pts quality of life and are associated with an increasing in social and health costs.
Materials and Methods: This is a multicentric prospective observational study on pts with BM from BC with at least 6 months follow-up, enrolled into the BMDB. From October 2014 pts were recruited at the first BM occurrence by 14 Italian hospitals.The DB will allow to gather information on BM pts medical history using an online tailored software. The platform consists of 4 files containing information regarding pts demographics, primary tumors and BM characteristics and their evolution,in particular the onset and the types of SREs.Data are updated every 6 months by the participating centers and reviewed by coordinator center.The study was approved by ethical commitee.All pts have signed an informed consent.
Results: Since October 2014, 814 pts with BM from solid tumors were enrolled of whom 192 have BC as primitive site. Median age was 62 years (range 26-86). Median follow up was 34 months (range 6-149). At enrolment 97 pts (51%) had only BM, 67 (35%) had concomitant non-skeletal and BM

Table 1.

	N (192)	%
PS ECOG 0-1	144	75.0
Number of BM		
1	33	17.9
2-6	52	28.3
>6	99	53.8
Type		
Litic	98	60.1
Osteoblastic	42	25.8
Mixed	23	14.1
Pain at diagnosis	40	20.0
SRE at diagnosis		
Radiotherapy	49	24.5
Pathological fracture	21	10.5
Surgery	4	2.0
Spinal cord compression	1	0.5

and 28(14%) had previous non-skeletal metastases. Median time to first BM was 53 months (range 0-312). At first BM diagnosis, SREs were present in 75 pts (39%). Zoledronate was used in 51% and Denosumab in 21% of cases. Treatment was hormone-based (n=96, 52%) chemo-based(n=71, 39%) and chemo+ormono based therapy (n=15, 8%). During follow up,67 new SREs were observed.Pts' characteristics were resumed in table 1. Progression occurred mainly in skeletal sites (n=107, 73%). Median progression-free (PFS) and overall survival (OS) were 13.7 (95%CI 11.3-17.1) and 56.8 months (95%CI 46.4-72.4),respectively.The 2-year survival according to the presence of nonskeletal metastases and the time of BM appearance was 87.8% (95%CI 77.6-93.5) for BM only,78.9% (95%CI 56.6-90.7) for previous non-skeletal BM and 87.2% (95% CI 74.4-93.9)for concomitant nonskeletal and BM pts.

Conclusions: This study presents prospective data about a cohort of BC pts enrolled at the first BM occurrence and followed over the time, extrapolated by the multicentric observational BMDB.

C31

REAL-LIFE DATA ON THE SAFETY OF TRASTUZUMAB BIOSIMILAR IN HER2-POSITIVE BREAST CANCER PATIENTS IN DEPARTMENT OF ONCOLOGY (DO) OF AZIENDA USL TOSCANA NORD OVEST (ATNO)

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Background: Biosimilars are biologic products designed to mimic existing approved biologic agents. Trastuzumab biosimilars (TB) have been approved in the treatment of HER2-positive breast cancer (BC) based on the evidence of the same efficacy to trastuzumab originator (TRZ). Few data from real-life are available regarding toxicities associated with TB administration.

Methods: The DO of ATNO was established in 2016 and incorporates 5 Divisions of Medical Oncology. For what concern the oncologic field, ATNO presents an unique working group on breast cancer with a referring physician in each hospital. In order to offer an homogeneus service also in terms of therapeutic options, our clinical practice is based on specific predefined protocols, also named PDTA (Percorsi Diagnostici Terapeutici e Assistenziali). In our study we retrospectively collected all consecutive HER-2 positive BC patients (pts) treated with TB in the (neo)adjuvant or metastatic setting from 2018 to now in theoncology units of the DO, of Massa Carrara, Lucca, Livorno (including also Piombino, Portoferraio and Cecina units) and Versilia hospitals. We reported pts characteristics and adverse events (AEs) graded according CTCAE v 4.0.

Results: A total of 196 HER2-positive BC pts receiving a TB were analyzed. Median age was 56.3 years (range 29-83 years). 130 (66%) pts received TB in the (neo)adjuvant setting, 76 (34%) in the metastatic setting, among them 37 (19%) received TB in combination with pertuzumab as first line therapy. 90% pts had shifted from TRZ to TB, 10% received directly TB. The overall incidence of AEs was low. The most common AE reported was infusion related reaction (IRR), that was observed in 6 pts (3%): 3 pts G1, 1 pt G2, 1 pt G3, 1 pt G4; a permanent discontinuation of anti-HER2 therapy was required in case of G3-4 IRR. An asymptomatic left ventricular systolic dysfunctionwas observed in 2 (0.7%) pts; in both cases a complete resolution of the event was obtained with a temporary suspension of TB. Only one patient was shifted from TB to TRZ, due to the onset of a stomatitis G2. Interestingly no AE was observed when TB was administered in combination with pertuzumab.

Conclusions: In our real life experience TB showed a good toxicity profile, with a low incidence of AEs. Our

preliminary results confirm the safety of TB, despite the retrospective nature of the trial and the limited sample size.

C32

SAFETY OF ANTHRACYCLINES REGIMENS IN PATIENTS WITH EARLY BREAST CANCER AND GLUCOSE-6-PHOSPHATE-DEHYDROGENASE (G6PD) DEFICIENCY

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Background: Anthracyclines are considered a cornerstone in the adjuvant treatment of breast cancer. Due to their oxidative properties, they are contraindicated in G6PD deficient patients. Considering the high frequency of breast cancer and G6PD deficiency worldwide, there is little to no information about that.

The aim of this study is to evaluate the hematologic and non-hematologic toxicity of adjuvant treatment with anthracyclines in G6PD deficient patients affected by breast cancer.

Material and Methods: From July 2009 to May 2019, we enrolled 52 Caucasian female patients carrier of G6PD deficiency with early breast cancer. Anthracyclines' toxicities were evaluated with clinical assessments and blood test analyses. In this study, the median age of the patients was 52,5 years (28 to 69). As for adjuvant treatment, 23,1% of patients were treated with FEC regimen (Fluoruracil 500 mg/m^2 i.v., Epirubicin 75-100 mg/m^2 i.v., Cyclophosphamide 500-600 mg/m^2 i.v. every three weeks) for 6 cycles; 70% of the women received chemotherapy including anthracyclines and taxanes: 65,4% with EC regimen (Epirubicin 90 mg/m^2 i.v. and Cyclophosphamide 600 mg/m^2 i.v. every two weeks) for 4 cycles and Paclitaxel 80 mg/m^2 i.v. weekly for 12 cycles; 11,5% were treated with FEC regimen for 3 cycles and Docetaxel 100 mg/m^2 i.v. every three weeks for 3 cycles.

Results: Anemia of grade 1 (48,1%) or 2 (15,4%) occurred in 63,5% of patients. In 36,5% of patients no anemia occurred. None of them have had acute hemolytic anemia or G3 neutropenia/thrombocytopenia. Bilirubin levels were normal in all patients (0.2-1,2 mg/dl) such as reticulocytes count (0,5-1,5%). Haptoglobin levels (50-150 mg/dl) were normal too.

In 67,3% of cases LDH levels were lightly increased (200-500 U/L), but this result was due to a G-CSF injection.

A common trait that occurred in 100% of the patients was alopecia. Only 21,2% of patients reported fatigue of grade 1 while in 1,9% of cases fatigue G2 were reported; 34,6% reported nausea of grade 1 and 2; 3,8% of patients presented vomit; 5,8% of patients reported constipation of grade 1 or 2, 3,8% presented diarrhea of grade 1 and 2 and 7,7% of patients reported oral mucositis of grade 1 or 2.

Conclusions: Despite this is a retrospective study, anemia percentages reported are similar in patients with enzymatic deficiency and those who do not have any. Therefore, it appears safe to use chemotherapy regimens containing anthracyclines in G6PD- deficient patients.

C33

TEN-YEARS RETROSPECTIVE ANALYSIS ON THE EFFICACY OF SHORT-COURSE VS.STANDARD ANTHRACYCLINE-TAXANE-BASED NEOADJUVANT CHEMOTHERAPY IN TRIPLE NEGATIVE AND HORMONE RECEPTOR-POSITIVE BREAST CANCER

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Background: Neoadjuvant anthracycline-taxane-based chemotherapy is one standard treatment option for patients with stage II-III breast cancer (BC). Patients achieving pathological complete response (pCR) after neoadjuvant chemotherapy have significantly longer disease-free survival (DFS) and overall survival (OS) when compared to patients with residual disease. However, the optimal duration of neoadjuvant anthracycline-taxane chemotherapy has not been investigated so far.

Material and Methods: We retrospectively collected clinical data about patients with stage II-III TNBC and hormone receptor-positive (HR+) BC who were treated at our Institution between October 2007 and January 2018 with neoadjuvant AT (doxorubicin 60mg/m^{2}i.v. plus paclitaxel 175 mg/m^{2}i.v. every 3 week) for 3 cycles (group A: 5,5 months) or 4 cycles (group B: 7 months) followed by CMF (cyclophosphamide 600 mg/m^2 i.v. plus methotrexate 40 mg/m2 i.v. and 5FU 600 mg/m2 i.v. on days 1 and 8 every 4 weeks) for 3 cycles (group A) or 4 cycles (group B). The aim of our study was to assess the impact of neoadjuvant chemotherapy duration (group A vs group B) on pCR rate, DFS and OS in the whole patient population, as well as in patients with TNBC and HR+ BC.

Results: A total number of 209 patients were included in our analysis; of these, 62 had TNBC and 147 had HR+ BC. Median age was 50 years (range 30-74). 111 patients belonged to group A and 98 patients to group B. We observed a total of 29 pCRs (13,9%), of which 25 (40%) occurred in the TNBC subgroup and 4 (3%) in the HR+ BC subgroup (p=0.009). As expected, pCR was associated with better DFS and OS, with statistical significance

reached only in patients with TNBC (DFS: p=0.0012; OS: p=0.0025). We observed no differences in terms of pCR between patients in group A and group B (17 and 12 patients respectively, p=0.552). Local or distant relapse occurred in 56 patients (26,8%), with no significant differences between groups A and B when considering the whole patient population (p=0.62), as well as TNBC (p=0.22) and HR+ BC (p=0.56) patients. DFS and OS rates at 5 years were 74,8%/70,7% (group A/B) and 86,4%/85,7% (group A/B) respectively.

Conclusions: Shorter duration of neoadjuvant doxorubicin-paclitaxel followed by CMF chemotherapy was not associated neither with lower pCR rate nor with worse DFS/OS in TNBC and HR+ BC patients. Prospective studies are needed to evaluate if the duration of neoadjuvant anthracyclines-taxane-based chemotherapy can be shortened.

C34

THE EARLY CHANGES OF THE STANDARDIZED UPTAKE VALUES (SUVMAX) IS A PREDICTIVE MARKER OF RESPONSE AND OUTCOME IN EVEROLIMUS-BASED TREATED PATIENTS WITH BREAST CANCER

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Background: ^{18}F-Fluorodeoxyglucosepositron-emission tomography (^{18}F-FDG PET/CT) is one of the essential imaging modalities for establish the efficacy of breast cancer therapy and the measures of tumor burden showed promises to predict survival in patients with metastatic breast cancer (mBC). Everolimus inhibits mammalian target of rapamycin (mTOR) and leads to decreased protein synthesis, cell metabolism and cancer cell proliferation in solid tumors. Identification of predictive markers for everolimus-based treatment remains a major issue, but to date, no predictive markers have been established. The aim of this study is to evaluate an optimal SUV% [(SUV baseline-SUV 3 months)/SUV baseline] as a predictive factor of response and disease progression in patients with mBC receiving the combination of everolimus and exemestane in first line treatment.

Patients and methods: The study included 31 patients with a new diagnosed luminal B phenotype mBCs treated with everolimus and exemestane in ASST of Cremona and Istituto Nazionale Tumori of Milano between May 2013 and March 2108. The ^{18}F-FDG PET/CT and glycemia were performed at baseline and after three months of treatment. Patients who stopped treatment before 10 months were considered as in a progressive disease (PD) status, otherwise a duration of therapy > 10 months was scored as no PD. ROC analysis was performed to determine the optimal cut-off value of SUV% to differentiate PD from non-PD women using Youden Index. Time to progression survival (TTP) was estimated by Kaplan-Mayer method. Spearman's rank correlation coefficient (rho) was calculated to describe correlation between SUV% and glycemia.

Results: An optimal cut-off SUV% value of 29% was proposed for discriminate patients with PD from those without PD: patients with SUV%<29% had a median TTP of 3.11 months versus 9.29 months for patients with SUV%>29% (p=0.0036) and more frequently had PD within 10 months: 100% vs 53%, respectively (p=0.005). There was a negative correlation between SUV% and glycemia (rho=-0.32, p=0.15)

Conclusions: Our results showed that SUV> 30% tested with ^{18}F-FDG PET/CT after 3 months of treatment identified patients who had benefit from the everolimus-exemestane combination in term of response and TTP (>10 months). Moreover we have observed an inverse correlation between SUV and glycemia. These results warrant further validation with a potential integration with molecular biomarkers related to tumor metabolism and mTOR signalling.

C35

IDENTIFICATON OF HER2 POSITIVE PROGNOSTIC SUBGROUPS USEFUL FOR ADJUVANT THERAPY DECISION MAKING. RESULTS OF A MONOCENTRIC OBSERVATIONAL STUDY

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Background: The clinical magnitude of the benefit observed with the addition of Pertuzumab (P) to Trastuzumab (T) and chemotherapy (CT) in early HER2-positive (HER2+) breast cancer (BC) is debated, particularly in patients (pts) with 1-3 positive nodes (N1-3) or node negative (N-). In this retrospective study, we analyzed HER2+ BC pts with N1-3 and N- tumors treated with adjuvant CT and T at the Breast Unit of our Institute to identify possible eligibility criteria for adjuvant dual HER2 blockade.

Methods: From 1992 to 2016, 694 consecutive HER2+ early BC pts were registered in a monocentric observational

study. For this analysis we excluded pts who underwent neoadjuvant CT (113 pts), pts who were metastatic ab initio (21 pts), pts receiving treatment with adjuvant P or Lapatinib (31 pts), not receiving adjuvant T (81 pts), and missing baseline data (63 pts). 5-years (yrs) disease free survival (DFS) rates analyses were compared using Kaplan Meyer method to evaluate differences between the following groups: node positive vs N-, N1-3 and N- according to hormone receptor (HR) status.

Results: A total of 385 pts with HER2+ BC treated with adjuvant T was identified, with a median follow-up of 7 yrs (6.5-7.4). Median age was 56 yrs (28-85), 123 pts (32%) were premenopausal and 262 pts (68%) were postmenopausal. 201 pts (53%) were N- and 179 (47%) were N+. 114 pts (30%) were N1-3, 64 (17%) had more than 4 positive nodes. HR were negative in 127 pts (33%) and positive in 258 pts (67%). As expected, 5yrs DFS in N+ group was significantly lower (83.2%) than N- group (93.5%) ($p=0.005$). N1-3 HR- pts had a 5yrs DFS lower than N1-3 HR+ pts (86% vs 88%; $p=0.583$). The limited number of events didn't allow statistical analyses in N- subgroup according to HR status.

Conclusions: Our results confirmed that HER2+ BC N+ pts are at higher risk of relapse than N-. Moreover, among N1-3 pts, HR status seems not to give useful information to add single or dual HER2 blockade to CT.

Age, years	
Range	29 – 87
Median	53
Menopausal status	93 (65%)
Histology	
Ductal	107 (75%)
Lobular	33 (23%)
Others	3 (2%)
"Luminal subtype"	
Luminal A	70 (49%)
Luminal B	35 (24%)
Luminal HER2	18 (13%)
N.A.	20 (14%)
TNM Staging	
I	27 (19%)
II	61 (43%)
III	55 (38%)
Grading	
1	10 (7%)
2	64 (45%)
3	41 (29%)
N.A.	28 (19%)
Adjuvant hormonal therapy	
AI only	33 (23%)
TAM only	61 (43%)
AI + TAM	33 (23%)
No adjuvant hormonal therapy	16 (12%)
(Neo)Adjuvant chemotherapy	
Yes	102 (71%)
No	41 (29%)

C36

THE PARADOX OF AROMATASE INHIBITORS (AI) INDUCED BONE RESORPTION AND BONE RECURRENCE IN EARLY BREAST CANCER (EBC) PATIENTS: A SINGLE-INSTITUTION STUDY

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Background: Several trials of adjuvant bisphosphonates showed a disease-free survival improvement in early breast cancer (EBC) patients, treated with endocrine therapy. In a cohort of EBC "luminal-like" patients with bone recurrence, we found that median time to skeletal recurrence (TSkR) was shorter for those who received adjuvant AIs.

Patients and Methods: A retrospective analysis of EBC "luminal-like" patients with bone recurrence was performed, to evaluate the impact of adjuvant AI on the TSkR. Patients were categorized according to the adjuvant hormonal therapy: AI (exclusively), tamoxifen (exclusively), AI/tamoxifen, and no-treatment. Binary logistic regression and $\chi 2$ were used to evaluate relationships between age, menopausal status and adjuvant AI. Baseline TNM stage (AJCC 8th edition) was used as pre-planned adjusting factor in the multivariate analysis.

Results: From May 1995, to March 2019, 143 patients experienced bone recurrence (Table 1). There was a significant association between age and adjuvant AI ($\chi 2=20.9$, $p<0.0001$), and between menopausal status and adjuvant AI ($p=0.0067$). At median follow-up of 178 months, median TSkR and median Overall Survival were 54 months (95%CI: 45 – 65) and 120 months (95%CI: 99 – 147; 54 censored), respectively. Among patients who received adjuvant AI median TSkR was 35 months (95%CI: 25-54), while among patients who did not received adjuvant AI was 61 months (95%CI: 50-80) (HR = 1.45 [95%CI: 0.97-2.17], $p=0.0644$). After adjusting for TNM stage, adjuvant AI was significantly related to a shorter TSkR (HR = 1.60 [95%CI: 1.06-2.42], $p=0.0244$). Adjuvant Tamoxifen, adjuvant AI/Tamoxifen and no-treatment did not revealed to be associated to TSkR.

Conclusions: In our cohort (selected for bone recurrence), AI treatment is related to a shorter TSkR. AI-induced bone resorption could be the underlying mechanisms, thus antiresorptive adjuvant treatments should be always taken into account.

C37

THE ASSOCIATION OF IMMUNE CHECKPOINT INHIBITOR PEMBROLIZUMAB AND TRASTUZUMAB HAS ADDITIVE CARDIOTOXIC AND PRO-INFLAMMATORY EFFECTS IN PRECLINICAL MODELS

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Background: The association of Pembrolizumab and Trastuzumab was recently proposed for the treatment of Trastuzumab-resistant advanced HER2-positive breast cancer patients, with extremely interesting therapeutic perspectives. Although immunotherapies are frequently associated with a wide spectrum of immune-related adverse events, the cardiotoxicity has not been properly studied. We studied, for the first time, the putative cardiotoxic and pro-inflammatory effects of Pembrolizumab associated to Trastuzumab

Materials and Methods: Cell viability, intracellular calcium overload and pro-inflammatory studies (analyzing the production of Interleukin 1β, 6 and 8, the expression of NF-kB and Leukotriene B4) were performed in human fetal cardiomyocytes exposed to Pembrolizumab or Trastuzumab alone or in combination. Preclinical studies were also performed in C57BL6 mice treated with Pembrolizumab (10 mg/kg, i.p, for the first dose, followed by a dose of 5 mg/kg every 5 days until the study end point) or Trastuzumab (10 mg/kg/day, according to literature) alone or in combination. After treatments, we studied cardiac fibrosis (by quantifying collagen fibers) and expression of pro-inflammatory interleukins in heart tissues.

Results: The combination of Pembrolizumab and Trastuzumab leads to an increase of the intracellular calcium overload (of 3 times compared to untreated cells) and to a reduction of the cardiomyocytes viability (of 65 and 20-25%, compared to untreated and Pembrolizumab or Trastuzumab treated cells, respectively) indicating cardiotoxic effects. Notably, combination therapy increases the inflammation of cardiomyocytes by enhancing the expression of NF-kB and Interleukins. Moreover, in preclinical models, the association of Pembrolizumab and Trastuzumab increases the Interleukins expression of 40-50% compared to the single treatments; the expression of NF-kB and Leukotriene B4 was also increased. The histological analysis showed an increased amount of collagen fibers in mice treated with Pembrolizumab and Trastuzumab, compared to the single treatments.

Conclusions: Pembrolizumab associated to Trastuzumab leads to significant cardiac pro-inflammatory effects mediated by overexpression of NF-kB and Leukotriene B4 related pathways.

C38

EXPRESSION OF ER, PGR, HER-2, AND KI-67 IN CORE BIOPSIES AND IN DEFINITIVE HISTOLOGICAL SPECIMENS IN PATIENTS (pts) WITH LOCALLY ADVANCED BREAST CANCER (BC) TREATED WITH NEOADJUVANT CHEMOTHERAPY (NACT)

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Background: Pathologic response to NACT differ among BC subtypes and reported changes in expression of estrogen-receptor (ER), progesterone-receptor (PgR), HER-2 and Ki-67 following NACT. The aim of our study is to evaluate effect of NACT on expression of ER and PgR, Her-2 and Ki67.

Material and Methods: 93 pts with BC stages IIB, IIIA, and IIIB were treated with anthracycline and paclitaxel based NACT. In pts with HER-2 amplification, trastuzumab was added.ER, PgR, HER-2 and Ki-67 status were evaluated before and after NACT.

Results: Of 93 pts, 29% achieved a pathologic complete response(pCR). In pts luminal A(28%) pCR occurred in 15%; luminal B HER2 –(35%) in 28%; luminal B HER2+(15%) in 28%; HER2 +(8%) in 50% and triple negative (14%) in 46%.

We evaluated changes in hormone receptors, ki-67 and HER2 in 56 pts in correlation with pathological response, excluding pts with pCR.

ER modified expression from positive to negative in 8% pts and from negative to positive in 22%. Mean value of ER positivity remained unchanged before and after NACT(54,5% vs 54,7%).In pathological responders group (pPR) median value of 43,9% was observed before NACT and 43% after; in non-pPR median value of 62% was observed before NACT and 63% after. PgR changed from positive to negative in 21% cases and from negative to positive in 37%. Mean value of PgR positivity was different before and after NACT (36,7% vs 28%). In pts with

pPR, mean value was 28% before vs 16,5% after NACT; in pts non-pPR, mean value was 42,9% before vs 36,3% after NACT. Median Ki-67 value was 20,9% before NACT and 18% after. In pPR ki-67 median value was 25% before and 12,8% after NACT. In non-pPR median ki-67 was 18% before and 21,8% after NACT. HER-2 expression changed in 46% pts, 30,7% pts with HER-2 positive before NACT had HER-2 negative after.Conversely, 15,3% pts HER-2 negative became HER-2 positive.

Conclusions: We identified a Ki-67 reduction after NACT in pts whit pathological response. Ki-67 could predict pCR and identify pts most likely to benefit from NACT. NACT can change status of ER, PgR, Ki-67 and HER

2. After NACT, PgR+ expression decreased while ER positivity remained. We identified a prognostic role of decreased expression of PgR and Ki-67.

C39

LIFESTYLE ASSESSMENT IN EARLY-STAGE BREAST CANCER (EBC): RESULTS OF A TELEPHONE SURVEY

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Background: Weight gain, overweight and lack of physical activity (PA) are associated to an increased risk of recurrence and mortality in pts affected by EBC. This preliminary study explores the levels and the association of PA, emotional functioning, nutritional status in a sample of EBC pts.

Methods: A telephone survey was conducted in a sample of EBC pts by a trained staff. The eligible pts received a nutrition evidence-based tailored educational intervention by a skilled dietitian. The telephone questionnaire included anthropometric measures, the validated International Physical Activity Questionnaire (IPAQ) telephone short version, the Med-Diet 14 items (MDS), while the questions about emotional functioning (EF) were drawn from EORTC QLQ C30 Quality of Life questionnaire. Clinical and demographic variables were obtained by Hospital registry. Descriptive analysis, absolute frequencies and Spearman Rank Correlation test were used.

Results: With a response rate of 76%, 136 women (median age 52 years) were included in the analysis. The median time since diagnosis was 1.96 year. Nearly all the participants had received surgery (93%), 71% chemotherapy, 58% radiotherapy and 82% hormonotherapy. Over the half (55%) of patients were normal weight, 28% and 15% presented overweight and obesity status, respectively. With a median of energy expenditure for PA low/moderate [769.5 MET-min/week (metabolic equivalent of task)], 43% of women resulted to be in low category for PA, 40% in moderate and only 17% in high, according to IPAQ scoring protocol. The half of participants reported a high adherence at MDS (defines as a MDS $\geqslant$10), while 49% an average adherence (MDS 6-9). Increasing of PA level ($rs=0.17$; $p=0.04$), better scores of MDS ($rs=0.16$; $p=0.05$) and a decrease in sedentary time ($rs=-0.20$; $p=0.02$) were significantly related to high score of EF. Body mass index resulted inversely associated with PA ($rs=-0.16$; $p=0.05$) and correlated with time since diagnosis ($rs=0.20$; $p=0.01$). MDS was inversely associated with weight gain from diagnosis ($rs=0.22$; $p=0.01$).

Conclusions: Despite the validated importance of PA and weight control, a large portion of EBC pts did not engage in enough PA and nearly 45% were either overweight or obese. Healthy lifestyle modifications should be incorporate into EBC care, in order to increase PA levels, manage body weight control, allowing also an improvement in term of emotional functioning.

C40

CIRCULATING TGFß AND TNFA DURING ERIBULIN TREATMENT IN METASTATIC BREAST CANCER PATIENTS. THE TRANSERI PROJECT

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Background: Eribulin (E) is approved for the treatment of metastatic breast cancer (mBC) patients (pts) after failure of antracyclines and taxanes. E interferes with microtubule leading to apoptosis and G2/M cell cycle arrest. In human cancer cell lines and in mice, it reverses epithelial mesenchimal transition (EMT) and reduces metastases in mice. TGFβ, an immunosuppressive cytokine, acts as growth factor for cancer-associated fibroblasts (CAFs) and promotes EMT. TNFα synergizes with TGFβ to promote EMT. The TRANSERI study investigates the modifications of TGFβ and TNFα levels in 42 mBC pts treated with E.

Methods: Plasma levels of TGFβ and TNFα were determined by ELISA assay at baseline, before cycle (C) 3, 5 and at disease progression in mBC pts treated with E at 1.23 mg/m2, d 1–8 every 21 days. Statistical analysis of the changes in the longitudinal samples was performed by GraphPad 5. Clinical outcome was monitored according to standard internal follow up procedure.

Results: At baseline the median (M) TGFβ value was significantly higher in pts than in 7 healthy volunteers (203,4

pg/ml vs 113,0 pg/ml respectively; p<0.0001). At C 5, 17 pts had a decrease in TGFß with a M value approaching the one of healthy controls (152,8 pg/ml vs 113,0 pg/ml respectively). Twenty-five pts progressed before C 5. The M value of TGFß in pts at disease progression was 297,3 pg/ml. A significant difference of TGFß was observed between non progressed vs progressed pts (p=0.01). The M TNFα value at baseline was higher in pts than in healthy volunteers, even if in both groups it was close to the lower sensitivity cut-off of the assay. Intriguingly, at C 5, the TGFß/TNFa ratio was significantly lower in pts who did not progressed compared to the value at progression (p=0.01). We did not observe any relationship between the number of metastatic sites and the amount of circulating TGF-β. Similarly high tumor burden did not account for an increased level of TGF-β at baseline. Indeed the level of the cytokine, in patients who gained benefit from therapy, decreased irrespective of the objective response or disease stabilization.

Conclusions: TGFβ levels changed during treatment with E and correlate with outcome. We are evaluating the role of tumor burden in modulating the TGFβ/TNFα ratio.

C41

POTENTIAL IMPACT OF MIGRAINE ON THE COURSE OF BREAST CANCER PATIENTS: A PILOT SURVEY

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Background: Recently, large registry-based studies highlighted an interplay between breast cancer (BC) and migraine (M). In particular, M seems to be associated to a better overall BC prognosis, and menstrual migraine (MM) to luminal rather than triple-negative disease, albeit not in all studies. We aimed to investigate BC-M relationship in a clinical setting, with strict data check and clinical evaluation.

Methods: Consecutive BC patients filled a custom-made questionnaire to obtain a diagnosis of M according to Migraine-ID and International Headache Society (IHS) criteria. Clinical data on BC type, treatments and prognosis were collected together with phenotypic and clinical data on M. Parametric and nonparametric statistics were used according to data distributions to investigate differences in BC features between patients with and without M.

Results: Presently, 50 patients completed 1-year follow-up. Median age was 51.5 years (range, 27-79); 11 patients were diagnosed as Luminal A (LA), 9 as Luminal B (LB), 24 HER-2 positive (H2), and 6 as Triple Negative (TN). Thirty-eight (76%) patients had hormone-receptor positive disease. Thirty (60%) had a G3 BC, 18 (36%) G2 and 2 (4%) G1. M was diagnosed in 29 patients (18 with MM), tension-type headache (TTH) in 9 and no headache at all in 12; 19 out of 29 M patients still had migraine attacks at the time of the survey; 10 no longer had attacks. Seven patients had migraine with aura. All patients with migraine had an episodic pattern (less than 15 days/month), no one were under treatment for headache except acute treatments. Regarding demographics, patients with M were younger (48.4 ± 10.7 vs. 60.5 ±12, p<0.01) than patients without M. No association between migraine diagnosis and BC characteristics was found. However, patients with active M at recruitment had higher levels of HER-2 and ER expression than patients with prior M (p<0.05 for both).

Conclusions: Our preliminary survey showed no direct impact of M on the course of BC. However, patients with an active migraine at recruitment had higher ER and HER-2 expression levels; furthermore, BC patients with M were younger than BC patients without M, with no interaction with other variables. Results on HER-2 are in line with new researches on the use of EGFR inhibitors in pain management. Larger sample and longer follow-up are needed to confirm these preliminary results.

C42

BREAST CANCER IN WOMEN AGING 40 YEARS OLD AND YOUNGER: CLINICOPATHOLOGICAL PROFILE AND IMPLICATIONS ABOUT ADJUVANT TREATMENTS AND SCREENING

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Background: Differences in the clinical and biological characteristics between young and older breast cancer patients have been observed. Breast cancers (BCs) in young women are more often hereditary and express different genes compared with breast cancers in older patients. The purpose of this study was to evaluate the clinicopathological profile of BC in younger women (⩽ 40 years) and their implications on choosing adjuvant treatments and screening.

Patients and Methods: We prospectively analyzed pathological and clinical data about all consecutive patients younger than 40 years with diagnosis of invasive BC referred to our Institution from january 2013 to december 2017. All the patients'clinical data were collected at their first visit, and information about their pathological characteristics and treatment history was obtained after surgery and following subsequent visits.

Results: We selected 73 patients from a database of 1265 patients. Median age at diagnosis was 38 (range 26-40). 40% of them had no pregnancies before BC diagnosis.

84% of patients had invasive ductal carcinoma. The main pathological features were G3, ER+, HER2+ (74%, 65% and 30%, respectively). Interestingly, at diagnosis 56% of the patients had tumors size greater than 2 cm with an higher incidence of metastatic axillary nodes (53% of cases). Consequently the major part of patients (63%) underwent to adjuvant chemotherapy in addiction to endocrine therapy and anti-HER2-blockade treatment based on biological features of disease.

Conclusions: Our results confirmed that younger women tend towards an increased risk of developing biologically aggressive BC subtypes (especially HER2+ subtype tumors) with worse prognosis. Furthermore, this young population is actually excluded from the mammography screening programs making an early diagnosis very difficult to reach. The low percentage of pregnancies before BC needs a multidisciplinary approach to evaluate strategies to preserve ovarian function and the desire to become pregnant at the end of adjuvant therapies.

C43

ERIBULIN MESYLATE-TREATED METASTATIC BREAST CANCERS DEVELOP PROGRESSION MAINLY ON PRE-EXISTING LESIONS

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Background: Eribulin mesylate (EM) provided survival advantage in metastatic or locally advanced breast cancer (MBC) previously treated with anthracicline and taxanes, mainly in several subgroups like triple-negative ones. Epithelial-to-mesenchymal transition (EMT) is a crucial process in breast tumour progression; the adoption of EMT phenotype is responsible of enhancing invasivity and metastatic potentialities. In preclinical observations EM showed the ability to reverse EMT and consequently to reduce the capacities of in vitro migration and invasion of MX-1 cells xenografts.

Matherial and Methods: In the aim to find clinical implications of EM-induced inhibition of tumour cells ability to metastasize, we retrospectively analyzed the records of 38 pts with MBC that underwent EM administration. The median age of the series was 51 years (r. 33-74); ECOG-WHO PS distribution was 39.5, 57.9 and 2.6% for 0,1 and 2 respectively. Thirty-five (92.1%) of pts were ER and/or PgR positive, three (7.9%) were triple-negative and seven (18.4%) overexpressed Her-2. Twelve (32%) pts had only one site of disease,whereas 26 (68%) had more than one site of disease. At the time of the censorship of data, four patients were still on treatment.

Results: The entire series of pts had a median-overal survival (mOS) of 10.5 (r. 1 – 56) months, with a median progression-free-survival (mPFS) of 4 (r. 1-17) months. The 82% (28/34) of the pts developed progression of disease (PD) on a pre-existing lesion (PEL); 1/34 (3%) developed a new lesion in a pre-existing site of disease (PESD), and only 5/34 (15%) progressed on a site not previously involved by the tumor (NL).The mOS of the NL-progressive-pts was 9 months (r. 8-22), whereas the mOS of the PEL-progressive-pts was 15.5 months (r.2-56)

Conclusions: In our retrospective series, MBC pts exposed to EM developed progression of disease mainly on PEL showing a mOS of 15.5 months; only a minority of pts progressed on new sites, with a mOS of 9 months. This observation could be interpreted as being linked to an inhibition of the metastatic capacity of the tumor induced by the drug and is consistent with preclinical findings; furthermore, the better survival of PEL-progressive-pts could be interpreted as related to the acquisition of a more indolent phenotype caused by the exposure to EM. Further studies aimed to investigate the correlations between EM-induced bio-molecular modifications and clinical observations are needed.

C44

CARDIAC SAFETY OF ADJUVANT TRASTUZUMAB AND PACLITAXEL FOR HER2+ EARLY BREAST CANCER PATIENTS

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Background: Trastuzumab (T) improves outcomes of HER2+ early breast cancer (eBC) patients (pts). However, it may lead to left ventricular ejection fraction (LVEF) decline, mostly reversible. As anthracycline administration increases the risk of cardiac toxicity, anthracycline-free regimens, such as weekly paclitaxel (P)-T are increasingly used for low-risk HER2+ eBC. Little evidence exists regarding cardiac safety of this regimen in real-life pts. Here, we report cardiac outcomes of pts treated with adjuvant P-T in our institution.

Methods: We included HER2+ eBC pts planned to receive weekly P-T for 12 weeks followed by T up to 1 year between 2014 and 2019. LVEF assessment was performed by two-dimensional echocardiography at baseline and months 3, 6, 9, 12, as by clinical practice. LVEF reduction (% points from baseline) was calculated. Significance of changes in LVEF from baseline were determined by paired Wilcoxon test. Heart failure (HF) was defined by

	3 months	6 months	9 months	12 months
LVEF reduction from baseline	N (%)	N (%)	N (%)	N (%)
5-9%	25 (22%)	26 (27%)	23 (27%)	18 (20%)
10-15%	2 (2%)	2 (2%)	1 (1%)	1 (1%)
Not evaluated	16	33	41	37
Median (range)	63 (50-74)	62 (55-70)	62.5 (55-72)	63 (55-72)
Change from baseline (Wilcoxon test p-value)	0.001	<0.001	<0.001	0.007

New York Heart Association (NYHA) class (I asymptomatic, II-IV congestive HF [CHF]).

Results: Data from 127 HER2+ eBC were available. Pts characteristics were: median age 57 (range 26-87), postmenopausal 67%, Tumor≤2cm 90%, N0 86%, G3 67%, hormone-receptor positive 78%. Cardiovascular risk factors at baseline were: dyslipidemia 33%, hypertension 30%, history of tobacco use 24%, diabetes 10%, and BMI≥30 15%. Five pts (4%) had an history of arrhythmias and 49 pts (39%) were receiving cardiologic therapy. Median LVEF at baseline was 64% (range 55-73). Table 1 reports LVEF reductions from baseline. Overall, 2 pts (1.6%) presented CHF, while 3 (2%) presented NYHA I. As of April 2019, T was ongoing for 24 pts (18%). Three pts (2%) discontinued T due to cardiac toxicity.

Conclusions: LVEF decreases during adjuvant P-T. However, LVEF decrease of more than 10% points and HF are uncommon. These results confirm that P-T treatment retains cardiovascular safety even in real-life pts with cardiovascular risk factors.

C45

SAFETY AND EFFICACY OF CDK4/6 INHIBITORS IN PATIENTS WITH ADVANCED BREAST CANCER: A REAL WORD EXPERIENCE

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Background: CDK4/6 inhibitors plus endocrine treatments are the standard of care in hormonal receptors positive metastatic breast cancer (MBC) due to the positive results of Paloma, Monaleesa and Monarch trials. Our aim was to audit the real life experience of treating MBC with CDK4/6 inhibitors.

Methods: All patients receiving CDK4/6 inhibitors at the University Hospital of Modena were registered in a database. At the time of analysis, all women were evaluated for safety and efficacy. Treatment toxicities were graded according to CTCAE v5. Efficacy was assessed using routinely performed imaging.

Results: 87 patients have been treated with CDK4/6 inhibitors, in particular 78 with Palbociclib and 9 with Ribociclib. Considering first line setting, 43 patients received CDK4/6 inhibitors: 74% of them with aromatase inhibitors (AI) and 26% with fulvestrant, respectively. More than half of them received neo/adjuvant chemotherapy and 70% adjuvant endocrine therapy (ET) too. Only bone disease was present in 70% of patients. All patients were assessed for efficacy with 79% of them exhibiting ORR (CR+PR), 3% SD and 18% PD as best response. The clinical benefit rate (CBR: CR+PR+SD>6months) was 81%. At the time of the analysis, 9 patients (21%) progressed with a median time to progression of 5 months (2-7 months), all the others are ongoing. Regarding second line, 19 women were treated: 32% with AI and 68% with Fulvestrant. All women were pre-treated with ET in adjuvant setting and/or 1st line and more than half of them with chemotherapy too. 63% of patients had visceral disease. ORR was 53%, 11% SD and 36% PD. The clinical benefit rate was 68% Moreover, in naïve patients the CBR was 100% with no tumors progression. Neutropenia was the most common side effect observed in 95% of the patients. 60% were G3 with only 5% of febrile neutropenia. 65% and 40% of patients had delay in treatment administration and first dose reduction due to neutropenia, respectively. In 16% of them a second dose reduction was performed too. All other toxicities reported were all grade 1-2. Diarrhea and nausea determined dose reduction in 3% of women. No treatment discontinuation due to toxicity were observed.

Conclusions: CDK4/6 inhibitors administered outside the context of a clinical trial was safe, well tolerated and with significant efficacy. Our results were consistent with those published in the phase III clinical trials.

C46

EFFICAY OF ERIBULIN MESYLATE IN ELDERLY PATIENTS WITH BREAST CANCER: A POOLED ANALYSIS OF 5 REAL WORLD STUDIES

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Introduction: Eribulin Mesylate (EM) is a nontaxane microtubule inhibitor approved for the for use in in patients with metastatic breast cancer (BC).

This pooled analysis of retrospective published series aims to evaluate efficacy and toxicities of EM in elderly patients in the "real-world".

Material and Methods: A systematic review for studies reporting outcome and adverse events with EM in elderly BC patients (⩾70 years) was performed up to March 2019. Overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) were described and aggregated in a pooled analysis. Main toxicity rates (G1-2 & G3-4) were described.

Results: A total of 5 studies (3 retrospective, 1 observational and 1 pooled analysis of 3 prospective studies) were included for a total of 301 patients. Median age ranged from 69 to 74 years. Most patients had performance status 0-1. Estrogen receptor positive disease ranged from 79 to 89%. Triple negative BCs were 12%. The median number of administered cycles was 5. Overall the pooled ORR, median OS and PFS were 23.2%, 13.1 and 4.83 months. The disease control rate was 47%. Grade 3-4 neutropenia ranged from 0 to 49%, G3-4 anemia and thrombocytopenia were rare. Among nonhematological toxicities, the most frequent G3-4 adverse events were fatigue (range 5-16.5%) and neurotoxicity (range 0-10.1%). Dose reduction rate was reported in n = 3 studies and was provided in 40% of patients (range 18.6-84%).

Conclusions: This pooled analysis of 5 studies show that median OS is 13 months with an ORR of 23%. About 50% attained control of disease. Dose reduction was relatively frequent, but severe toxicities were rare. Treatment of elderly patients with EM is so feasible and reflects the results of the general population.

C47

REAL LIFE INCIDENCE AND MANAGEMENT OF ADVERSE EVENTS (AES) IN WOMEN WITH ESTROGEN-RECEPTOR (HR)–POSITIVE AND (HER2)–NEGATIVE ADVANCED BREAST CANCER TREATED WITH PALBOCICLIB: A SINGLE INSTITUTION EXPERIENCE

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Background: Palbociclib is selective CDK4/6 inhibitor a cyclin-dependent approved on results of Paloma 2 and Paloma 3 study for the treatment of locally advanced or metastatic breast cancer with hormonal-receptor (HR)–positive and negative human epidermal growth factor receptor(HER2). Inhibition of CDK4/6 prevents cell cycle progression from G1 to the S phase. We present the results on most common AEs, incidence of dose reduction and management in "real life" clinical practice.

Material and methods: We retrospectively reviewed records of all patients who were treated with palbociclib at our institution from 2017-2019. Our aim is to report our experience about the management of adverse event. A total of 51 females received palbociclib in various lines of treatment associated with hormonal therapy. We evaluated AEs, number of delayed cycles and incidence of dose reduction.

Results: About 51 patients analyzed, median age was 66. Histological exam revealed ductal carcinoma in 32 patients and lobular in 14. 26 patients had not performed previous treatment lines. Palbociclib was associated to aromatase inhibitor in 27 (53%) patients and to fulvestrant in 24 (47%). 5 patients had a biopsy-only as they were metastatic at the diagnosis, 7 (13,7%) had a previous neoadjuvant treatment. 19 patients had only one site of metastasis, 11 four sites. The only side effect of a high degree G3- G4 occurred was neutropenia in 21,6% (11) of the patients with a grade G3 and in 3,9% (2) with a G4; there was only 1 case of febrile neutropenia (2%). The other frequent AEs were grade G1-G2: fatigue in 41% (21), thrombocytopenia in 17% (9), anemia in 13,7% of pts (7), stipsis 6% (3), nausea 3% (2), diarrea 2% (1), mucositis 2% (1). 29 pts (56,8%) had to delay at least one subsequent therapeutic cycle, but only 10 out of 51 (20%) had to reduce the dosage of palbociclib.

Conclusions: The most common adverse events with Palbociclib are hematologic, particularly neutropenia.This neutropenia is rapidly reversible, reflecting a cytostatic effect on neutrophil precursors in the bone marrow. Most hematologic abnormalities seen with CDK4/6 inhibitors are not complicated and are adequately managed with standard supportive care and dose adjustments when indicated. Dose modification occur within the first two cycles. Older age does not affect palbociclib tolerance. Accurate patient monitoring and management of the side effects is crucial.

C48

BREAST CANCER: TIME BETWEEN ACCESS TO RECEPTION SERVICE CENTRE (CAS), INTERDISCIPLINAR TEAM (GIC) VISIT AND SURGERY IN A SPOKE HOSPITAL OF PIEDMONT ONCOLOGY NETWORK (ROP)

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Background: Delay of therapies in oncology is one of prognostic factors determining the outcome. The piedmont oncological network has proposed a new organisational model by setting the timing between visits cas and gic
These are affected by the mode of onset of neoplasia. Objective of the study is to assess the adherence to the

Priority	Definition	Time for Surgery	CAS	GIC
1	Strong suspicion of cancer or positive biopsy: the patient experiences symptoms or serious life-threatening signs, and illness or impending death without immediate intervention is high	Within 24 hours	NO	NO
2	High suspicion of cancer or positive biopsy: the patient has a high probability of having a highly aggressive neoplasm	Within 10 days	Yes	NO
3	All patients with high suspicion of cancer that does not meet the criteria of priority 1, 2 and 4	Within 30 days	Yes	Yes
4	All patients with an intermediate level of suspicion of cancer or patients with a positive biopsy, but with a high probability of an indolent (slow-growing) cancer	Within 40 days	Yes	Yes

indications of the rop and the interval between cas gic and surgery for breast cancer in the hospital spoke with the purpose to define classes of priorities for intervention.

Materials and Methods: We evaluated admissions for breast cancer present in reports sent to cas from the medical department of the hospital. We calculated the time between taking charge cas, gic and surgery and we divided into classes of priority related to the mode of onset.

Results: From january to december 2018 246 patients admitted for neoplasia were examined. 75/246 (30%) had breast cancer. 39/75 (52%) performed both cas and gic visits.

14/39 (36%) respected the 24 days waiting time between cas and gic visits as indicated by the rop. 5/75 (7%) had neither a cas visit nor a gic visit, 10/75 (13%) had only gic.

Conclusions: In this initial assessment only a third of patients had conditions indicated by the respected global timing rop. Efforts are needed to improve performance. However examination of medical records has allowed to divide cases into 4 groups related to disease onset.

C49

EVALUATION OF OVARIAN FUNCTION SUPPRESSION (OFS) IN PATIENTS (pts) TREATED WITH EXEMESTANE (E) AND TRIPTORELIN (T) IN PREMENOPAUSAL ADJUVANT SETTING. FROM TRIAL TO CLINICAL PRACTICE: SOMETIMES A CHALLENGE

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Background: TEXT and SOFT 8-year update demonstrates that E was superior to tamoxifen alone or plus LHRHa at preventing distant metastases among HER2-negative chemotherapy-treated patients (pts) with a lack of benefit in overall survival(OS), many hypothesis have been proposed to explain it. In SOFT and TEXT OFS was investigated only by amenorrhea, in a SOFT substudy one-third of pts had Estradiol level above 2,72pg/ml, with uncertain clinical implication. No definitive data are emerged to now about the need of monitoring hormone levels. The aim of our analysis is to evaluate OFS by measuring estradiol levels in pts treated with E and T in our Day Hospital

Patients and method: We analyzed the quarterly estradiol values and menstrual documentation of pts treated with E and T off-label, according to TEXT and SOFT criteria.

Results: Since January 2018 we treated 10 pts. Median age 41y (as in TEXT and SOFT trial), 33% were node positive; 78% HER2 negative. Six(67%) received chemotherapy. All are still receiving hormonal treatment. We measured estradiol level every three months since baseline, our laboratory upper limit is 5pg/ml: in two pts the value raised at three months, in one case the dosage fell within the limits at six month; we are waiting for the six-month value of the second pt. Two pts showed a fluctuation of estradiol at 6 months, one returned to normal at 9 month, the other one is ongoing. One patient switched to tamoxifen after six month due to persistent elevation of Estradiol level. All patients maintained amenorrhea despite elevation of estradiol

Conclusions: Preliminary 5-year data of SOFT and TEXT demonstrate a benefit in disease outcome with E plus LHRHa in high risk patients, unconfirmed at 8-year follow up. Through data in our small experience we documented a lack of inhibition of ovarian function in 40% of our pts, whose meaning cannot be fully examined, but it's not possible to exclude that such fluctuations might negatively affect the efficacy of treatment. Monitoring OFS with amenorrhea could be inaccurate, as we have seen elevations of Estradiol levels despite persistent absence of menses. We argue caution in translating results from trial population into clinical practice, we have to consider unanswered issues, as impact of incomplete OFS and the need of monitoring Estradiol value, pts compliance to scheduled blood examination and visits. Moreover intensifying treatment could increase side effect and reduce adherence to therapy.

C50

TREATMENT WITH ERIBULIN MESILATE(EM) IN NINETIES WOMEN (NW)WITH LOCALLY ADVANCED BREAST CANCER NOT RESPONDING TO ENDOCRINOTHERAPY(NRETH):TOXICIT Y EVALUATION

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Background: Cases of women about 90th with locally advanced breast neoplasms not responding to endocrinotherapy are more and more frequent: These subjects are mostly frail subjects.Therapy must therefore mainly take this condition into account. A synthetic analog of "halichondrin B," Eribuline Mesilate was defined also to prolong overall survival of heavily pretreated metastatic breast cancer(MBC) patients. Furthermore,the EM limited adverse events like slightly neutropenia, fatigue, and peripheral neuropathy are especially appreciate in the treatment of elderly population. Aim: We plain to use a modified EM schedule to evaluate if is more effective than conventional treatments also in NW withy LABC.
Methods: Treatment plan: EM 0.96-1.0 mg/sqm IV on d1 every 21 (it depend on evaluation of CCl according to Kintzel-Dorr's way, was delivered until progression or intolerable toxicity. Eligibility criteria: acquired written consensus; confirmed diagnosis of LABC -skin or visceral(one site) measurable lesion, medium age:88; Comprehensive Geriatric Assessment evaluation (CGA) permissive for chemotherapy, adequate renal function (CCl evaluation), proper bone marrow function; adequate liver function. Charlson's Score Comorbidity Scale 1-3 score points max Evaluations tools: Clinical Benefit (CB) as Stable Disease + Objective Response Rates (ORR) according to ESMO CB scale v.2a; Toxicity Profile using CTCAE v3.0 Criteria; Quality of Life (QoL) score EORTC QLQ-C30 questionnaire.
Results: From 2017 to 2018, 22 women with locally advanced breast cancer were treated.20 of these are still under maintenance therapy (2 pts discontinued treatment for personal reasons). A total of 759 cycles were delivered to pts: 9out of 22 develop G3-4 hematological toxicity, but no delay in therapy delivery was needed. QoL score shows no noticeable decline in comparison with baseline whereas Clinical Benefit was about 65-70%.
Conclusions: EM adj schedule in the treatment of LABC NRETh about ninety women shows good safety also in presence of comorbidity and frailty with 65-70% of Clinical Benefit.These data also show that subjects at a very advanced age better withstand this type of chemotherapy even compared to endocrine therapy [ic1] Authors suggest starting an enlarged polycentric study to confirm these outcomes.

C51

ASSESMENT OF IN VITRO CELL PROLIFERATION RESPONSES: A SINGLE BOUT OF MODERATE INTENSITY AEROBIC EXERCISE SERUM ON TRIPLE-NEGATIVE BREAST CANCER

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Background: Breast cancer (BC) is the most common invasive cancer in women of all age groups, and studies have shown that sedentary women who are overweight or obese, or suffering from metabolic syndrome are more likely to have unfavorable prognoses. The cellular and molecular mechanisms related to this evidence are still unknown. The purpose of the study is to examine if systemic responses to a single bout of vigorous intensity aerobic exercise in sedentary healthy women could modulate cell proliferation, including the Triple-Negative BC (TNBC) subtype.
Methods: Pre-menopausal women performed 65 min of moderate to baseline vigorous intensity aerobic exercise on a treadmill. First 20 minutes subjects run at a heart rate reserve (HRR; ≈42%) corresponding to 50% of their own estimated VO2max, then exercise intensity was increased to 65% of VO2max (60% HRR) and maintained for 45 minutes (Rundqvist H et al., 2013).
Blood samples were collected before exercise, immediately after the end of exercise, and 2h post-exercise. The TNBC MDA-MB-231 cell line was exposed to the three blood samples. TNBC cells were seeded at a density of 2500 cells/well in 96 well plates. After overnight incubation, culture medium was changed with red-phenol free DMEM (0.8 or 1.2 mg/mL glucose) conditioned with 5% of human serum, and cell proliferation was evaluated using MTS assay after 72 hours.
Results: Post exercise sera showed a control on cell proliferation in comparison to sera collected before exercise. Indeed, the proliferation of cells cultured with 2h post-exercise serum lowered about 10%. Data were statistically significant (One-way ANOVA, Bonferroni post-hoc test; $p<0.05$) with a physiological concentration of glucose (0.8 mg/mL).
Conclusions: The effect of a single bout of moderate-intensity aerobic in sedentary pre-menopausal healthy women, in particular 2h post exercise, reduced TNBC cell proliferation. Therefore, we consider important that even a single exercise session of prolonged moderate exercise seems to have the potential to add a positive effect to the

overall beneficial influence of exercise on TNBC. This protocol could be prescribed as MOVEMENT AND HEALTH CARE
STRATEGIES, MoviS within physical activity educational programs for cancer patients.
Rundqvist H et al., (2013) Plos One. 8(7):e67579.

C52

CLINICAL IMPACT OF PACLITAXEL INDUCED PERIPHERAL NEUROPATY (PIPN): MONOCENTRIC EXPERIENCE

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Background: Paclitaxel is one of the most used drugs in early and advanced breast cancer treatment. The incidence of all grades of neurotoxicity in patients (pts) treated with paclitaxel is high, ranging from 57%–83% overall and with severity in 2%–33% of patients. Peripheral neurotoxicity was the dose-limiting side effect mostly for weekly regiments. This could decrease total cumulative dose administered which may impair patients outcome as it is described in the literature. Patients receiving chemotherapy at relative dose intensity (RDI; received dose/planned dose) ⩾85% had better clinical outcome. We reviewed retrospectively the clinical impact of PIPN on our patients.
Material and Methods: We conducted a retrospective single institution analysis of 133 newly consecutive diagnosed breast cancer patients treated with paclitaxel-based neoadjuvant/adjuvant regimen (EC90 every 21 days for 4 cycles followed by weekly paclitaxel 80 mg/mq for 12 cycles). 89 pts and 44 pts were treated respectively in adjuvant and neoadjuvant setting.
Results: The median age of patients was 59 years (ranged 34-79). 89 pts (67%) were <65 years (ranged 34-64), 44 pts (33%) were ⩾65 years (ranged 66-79). 42 pts (31%) required discontinuation of paclitaxel for neuropathy (median of 10 cycles, ranged 4-11). 77 pts (58%) reduced paclitaxel dose (60 for PIPN, 17 for other causes). The median RDI for the 73 PIPN-induced dose reduction and/or treatment discontinued pts was 77%. 102 pts (77%) received a RDI ⩾85% while 29 pts (23%) received a RDI < 85%. In pts ⩾65 years (44 pts) 26 pts (59%) received RDI ⩾85% and 18 pts (41%) RDI<85%. In pts <65 years (89 pts) 76 pts (85%) received RDI ⩾85% and 13 pts (15%) RDI<85%.
Conclusions: These results add to a poor body of literature related to the frequency of taxane-associated dose reduction and its impact on the adherence to follow the planned treatment. PIPN seems to have an impact on RDI and maybe on patient outcome. This would seem even more true considering aging patients. Age seems an important factor to consider when we set up a taxane-based regimen above all in adjuvant/neoadjuvant setting even if there is for now controversial evidence of literature.

C53

PALBOCICLIB: CDK4/6 INHIBITORS: EFFICACY AND TOXICITY EVALUATION: OUR EXPERIENCE IN ADVANCED BREAST CANCER

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Introduction: Palbociclib (P) is a highly selective oral inhibitor of cyclin-dependent kinase 4/6 (CDK4/6). Cyclin D1 and CDK4/6 are downstream of signaling pathways that lead to cellular proliferation. Preduce cellular proliferation of estrogen receptor-positive breast cancer cell lines by blocking progression of the cell from G1 into the S phase of the cell cycle.
Methods: Between August 2017 to April 2019, 44 pts with MBC were treated with Palbociclib: 41 female and 3 male PS:0-2 (ECOG).Median age was 61 years (range:36-84). 18 pts received Palbociclib plus Letrozolo as first Line;15 pts received P plus Fulvestrant as first Line (after progression Adjuvant therapy with Aromatase Inhibitor) and 9 pts P plus Fulvestrant as second Line. 8 pts were in pre-menopausal, received LHRH agonist. 43% had visceral metastases; 32% had bone-exclusive metastases and 25% had multiple metastatic sites. HR: POS; HER2: NEG. Dose: P was administered at mg125/die (72% of pts) or 100/die (19% of pts) or 75/die (9% of pts) every day x os:1-21 every 28 days. Toxicity: Main observed toxicities were: neutropenia (G2-3):75% (33/44); thrombocytopenia (G1-2):22% (10/44); anemia (G1-2):27% (12/44); mucositis (G1-2):31% (14/44); fatigue (G2):40% (18/44); nausea (G1-2):34% (15/45); diarrhoea (G1-2):25%(11/44); emesis (G1):11% (5/44); arthromyalgie(G1):15% (7/44); dry skin (G1-2): 11% (5/44). No clinically relevant effect on the QTc interval. In pts with neutropenia G3: delayed treatment for 1 week.
Results: At a median follow-up of 20 months (until April 2019), median PFS was: First Line with P plus Letrozolo: 10,42 months: ORR was 78% (15/19); PR: 21% (4/19); CR: 10% (2/19); SD: 31% (6/19); PRO: 21% (4/19); First Line with P plus Fulvestrant: 11,3 months: ORR was 86% (13/15); PR: 53% (8/15); CR: 13% (2/15); SD: 20% (3/15); PRO: 13% (2/15). Second Line with P plus Fulvestrant: 7 months: ORR was: 50% (5/10); PR: 20% (2/10); SD: 30% (3/10); PRO: 50% (5/10).

Conclusions: Our experience confirm discrete tolerability and efficacy of PALBOCICLIB plus Letrozolo and even more with Fulvestrant. Moreover Palbociclib does not prolong QTc at the recommended therapeutic dosing regimen. Anyway is important to consider medications that could impact QTc, mostly in older pts.

C54

OBSERVATIONAL PROSPECTIVE ITALIAN STUDY ON BREAST CANCER - BRIDE STUDY

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Backround: Breast cancer (BC) represents the first leading cause of death for cancer disease in the female sex. In Italy, in 2018 were estimated about 52,000 new breast cancers. This can be ascribed to both implementation of screening campaigns and increasing health information. The knowledge of clinical and biological prognostic factors (pT, pN, G, ER, PgR, Ki67 or MIB-1, HER2) is important to evaluate appropriate treatments both in the early and metastatic stages.

The aims of BRIDE study are to evaluate prospectically: 1- the criteria with which the oncologist consider to decide to carry out an adjuvant or neoadjuvant therapy in patients with a stage I-II-III BC; 2- the treatments used in patients with in situ carcinoma; 3- the types of treatment used in stage IV "de novo" and in stage IV as first disease recurrence (locoregional and/or metastatic). Secondary objectives are: disease free survival (DFS), progression free survival (PFS), overall survival (OS) and the evaluation of implementation in the clinical practice of AIOM v. 2017 Breast guidelines.

Methods: BRIDE is an observational, prospective, multicentre study. The sample size chosen is 4,500 patients in the 30 Italian cancer Centers. The oncologic centers are selected according to the geographical distribution, type of institution, listed in the AIOM Report v.2016 and also on the basis of new cases afferent per years. The target population included female patients with age =>18 years with histological diagnosis of carcinoma in situ (DCIS, LCIS) or invasive BC; stage I-III and stage IV (according to TNM v. VII) "de novo" or stage IV as first disease recurrence (loco-regional or metastatic). Clinical characteristics, biological parameters (grading, ER, PgR, Ki67/MIB-1, HER2 on primary tumour and/or metastatic lesion), treatments and outcome of patients were recorded. The accrual period is two years.

Results: From January 2018 to April 2019, 589 patient were enrolled in 13 Italian centers: 365 patients were treated with adjuvant and 44 with neoadjuvant therapy. PFS and DSF will be analyzed. The end of the study is estimated by January 2024.

Conclusions: The BRIDE study is ongoing. The data collected will let know the percentage of stage I-II-III BC patients treated with a systemic adjuvant or neoadjuvant therapy, the parameters that influenced the physician choice and the types of chosen treatments. Moreover the implementation of the AIOM v. 2017 Breast guidelines will be evaluated.

C55

EVEROLIMUS (EVE) IN HORMONE RECEPTOR POSITIVE ADVANCED BREAST CANCER: RETROSPECTIVE REVIEW OF A SINGLE INSTITUTE EXPERIENCE

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Background: EVE is an mTOR inhibitor approved in association with exemestane for advanced breast cancer progressing after non-steroidal aromatase inhibitors (NSAIs). This retrospective analysis was aimed to evaluate clinical activity and tolerability in real life setting.

Material and Methods: Patients (pts) treated at the Oncology Unit of PG23 Hospital in Bergamo from January 2013 to January 2019 were included. We collected data about safety, drug exposure and efficacy.

Results: We treated 73 pts, median age 64 years, 36% had visceral involvement, 23% had ⩾ 3 metastatic sites, previous therapy included NSAIs (100%), fulvestrant (59%), chemotherapy for advanced disease (44%), 71% had a DFI >24 months. The most common grade 3 and 4 adverse events (AE) were stomatitis (7%), anemia (3%), pneumonitis (3%), grade 1-2 AE were stomatitis (67%), asthenia (46%), rash (31%), pyrexia (38%), cough (35%). A dose reduction to 5 mg of EVE was necessary for 47% of the pts, 57% temporary interrupted EVE. The most frequent reason of discontinuation was disease progression (71%). At the cutoff date (January 31,2019) 4 pts were still on treatment. The median duration of exposure of EVE was 6 months (range1-31+). Response rate was 17%, with 2 complete response and 10 (14%) partial response, stable disease was obtained in 44% of the pts. Median progression free survival was 6.5 months (range interquartile: 3.6-14.0).

Conclusions: EVE and exemestane combination is effective and manageable in real life setting, even if it is

Table 1. Adverse Events (%) any grade G3/G4.

	N°pts (%)	N°pts (%)
Stomatitis	48(67)	5(7)
Asthenia	33(46)	1(1)
Pyrexia	27(38)	1(1)
Cough	25(35)	0(0)
Rash	22(31)	0(0)
Pneumonitis	16(22)	2(3)
AST increased	16(22)	1(1)
ALT increased	15(21)	1(1)
Anemia	13(18)	2(3)
Hyperglycemia	13(18)	0(0)
Diarrhea	11(15)	1(1)
Decreased appetite	11(15)	0(0)
Nausea/vomiting	11(15)	0(0)
Arthralgia	11(15)	0(0)
Decreased weight	9(13)	0(0)
Thrombocytopenia	9(13)	0(0)

Table 2. Treatment.

	N°mo	N°pts (%)
months on treatment%	< 3	19(26)
	3-5	16(22)
	6-9	18(25)
	>9	20(27)
dose reduction (5 mg) %		34(47)
treatment interruption %		41(56)
	1	18(25)
	2	20(27)
	⩾ 3	3(4)
reasons for interruption %	PD	52(71)
	toxicity	13(18)

burdened with many side effects. We experienced that dose reductions and temporary interruptions of EVE, together with symptomatic therapies, can help to overcome toxicities and prolong a potential effective therapy.

C56

EFFICACY AND SAFETY OF RIBOCLICLIB AND LETROZOLE IN THE TREATMENT OF LOCALLY ADVANCED AND METASTATIC HR+/HER2 - BREAST CANCER: A REAL WORLD EXPERIENCE

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Background: Breast Cancer is the second most common type of cancer worldwide. Targeted therapies have revolutionized the treatment of metastatic breast cancer, improving the life expectancies of many women. Selective CDK 4/6 inhibitors are a new class of drugs that, in addition to hormone therapy in patients with advanced HR + / HER2- breast cancer, have been shown to improve the results obtained with hormone therapy alone and to prolong survival progression free, with a lower level of toxicity and less impacting side effects than the chemotherapy, offering a better quality of life, an early reduction of pain. In the past four years, the CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, received their first FDA approval for the treatment of Hormone Receptor (HR)-positive and (HER2)negative breast cancer after showing significant improvements in progression-free survival in the PALOMA-1, MONALEESA-2 and the MONARCH-2 randomized clinical trials, respectively.

Methods: From September 2018 to May 2019 in our hospital we have treating thirty women with metastatic or locally advanced breast cancer with expression of hormone receptors and HER2 not amplified with ribociclib 600 mg/day, (3 weeks-on/1 week-off), plus letrozole (2.5 mg/day continuous). Of these thirty patients, 8 have a diagnosis of locally advanced breast cancer not susceptible to surgery.

Results: In our experience, the treatment with ribociclib and letrozole was well tollereted, and the most common Grade 3/4 adverse events observed until today were neutropenia and leukopenia; incidence rates were similar to those observed in the full MONALEESA-2 population. In 40% of these patients, and in accordance with the result of the recording study, we found both a clinical and ultrasound imaging examination, after eight weeks of therapy, a volume reduction of breast lesions.

Conclusions: Ribociclib plus letrozole represents an effective and well tollerated therapeutic opportunity in postmenopausal women with HR+, HER2− de novo advanced breast cancer. This therapeutic approach translates into the possibility of administering to women in this setting a treatment that is not, as a first option,chemotherapy, but an oral therapy, with many advantages for patients in terms of quality of life, impact on everyday life and safety. These results, confirmed in our real life experience,open up new horizons, not only for the efficacy observed, but also for the quality of life that this change can offer.

C57

CARDIAC TOXICITY OF ADJUVANT TRASTUZUMAB IN BREAST CANCER PATIENTS AGED ⩾60 YEARS

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Background: Adjuvant trastuzumab in combination with chemotherapy is the treatment of choice for patients (pts) with human epidermal growth factor receptor positive (HER2+) early breast cancer (EBC). Cardiac toxicity became a major concern in trastuzumab-treated pts but, to date, the incidence of Trastuzumab-mediated cardiotoxicity in older patients is not well defined. Cardiac dysfunction appears to be related to both age and baseline left ventricular ejection fraction (LVEF) values.
Patients and Methods: We conducted a retrospective data analysis of 76 consecutive pts >=60 years (median age 67 years; range 60-87) with HER2+ EBC treated with adjuvant trastuzumab from June 2009 to December 2017 at our institution. Thirty-five pts received sequential trastuzumab according to HERA trial design, twenty-eight pts received trastuzumab with concurrent taxanes administration and thirteen pts did not receive any adjuvant chemotherapy but undertook adjuvant treatment with trastuzumab and letrozole. Adjuvant antracycline-based chemotherapy was administered in 52 pts. An assessment of LVEF by echocardiography was performed at baseline, and at 3, 6, 9, 12 months during trastuzumab. Pts with an LVEF value >=55% were eligible to receive therapy. Median LVEF at baseline was 68%.
Results: A total of 1.234 cycles of trastuzumab were administered and 64 pts (84.2%) completed one year of treatment. Seventeen pts (22.4%) interrupted treatment because of asymptomatic LVEF decrease > 10% but thirteen of these resumed trastuzumab after LVEF recovery. Definitive discontinuation occurred in only four pts (5.3%). No clinically significant congestive heart failure and no cardiac death occurred. Eight pts (10.5%) discontinued treatment for no cardiac causes: disease relapse, severe adverse skin reaction, liver toxicity, worsening of chronic renal failure, severe and prolonged asthenia. When compared for trastuzumab treatment duration, LVEF values at baseline, cardiological risk factors and previous exposure to anthracycline or to left-sided chests irradiation, pts who experienced LVEF reduction did not differ from those who do not.
Conclusions: Our results show that, with appropriate pts selection and systematic cardiac assessment, cardiotoxicity in adjuvant trastuzumab therapy is confirmed manageable also in older women. In our experience no serious cardiac events were observed and only 5.3% of pts permanently discontinued treatment because of cardiac toxicity.

C58

BEVACIZUMAB COMBINED WITH PACLITAXEL AS FIRST-LINE TREATMENT OF HER2-neg METASTATIC BREAST CANCER: MONOINSTITUTIONAL EXPERIENCE

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Background: Bevacizumab + paclitaxel represents a standard of care for HER2-neg metastatic breast cancer (MBC) and has shown an improved progression-free survival (PFS), despite the lack of clear overall survival (OS) benefit. We performed a retrospective analysis to evaluate the efficacy and safety of this combination in patients (pts) no previously treated with chemotherapy for HER2-neg metastatic breast cancer.
Materials and Methods: from October 2011 to April 2018 we identified 33 pts treated at our institution with paclitaxel 90 mg/mq on days 1.8.15 + bevacizumab 10 mg/mq on days 1,15 q28 until disease progression or intolerable toxicity. Patients' median age was 60.5 years (range 40-79) and 72.7% of them (24 pts) had visceral disease; 11 pts (33.3%) were previously treated with endocrine therapy for metastatic disease. Histology: ductal carcinoma 25 (75.8%), lobular carcinoma 8 (24.2%). Molecular subtype: triple negative 6 (18.2%). 11 pts received maintenance therapy with bevacizumab (4 pts), letrozolo (4 pts) or both (3 pts) after paclitaxel discontinuation due to progression or toxicity.
Results: All the pts were evaluable for toxicity and response. An objective response rate of 45.4% was reached in the whole population (4 complete responses, 11 partial responses), stable disease in 24.3% (8 pts), progression disease (PD) in 30.3% (10 pts). Median PFS was 10 months (range 3-61+), median OS was 23 months (range 9-61+); At 1 and 2 years PFS rates were respectively 39.4% and 18.2% and OS rates 75.8% and 42.5%. At the time of statistical analysis, 4 pts were still receiving maintenance therapy with letrozolo with a PFS of 26 to 61 months and 2 pts were still in treatment with bevacizumab + paclitaxel after 10 and 8 cycles respectively. After disease progression, further anticancer therapy was administered to 19 pts. Grade 3 adverse events occurred in 13 pts (39.4%) and the most common were neutropenia (6 pts), hypertension (5 pts) and peripheral neuropathy (2 pts); no grade 4 adverse events were detected. Five pts (15.1%) interrupted treatment for side effects: 2 because of G3 hypertension, 2 for prolonged G2 proteinuria and 1 for G3 neuropathy; neither vascular thromboembolism nor gastrointestinal perforation or congestive heart failure occurred.
Conclusions: Our small retrospective study conducted on HER2-negative MBC pts confirms the efficacy of bevacizumab-paclitaxel therapy. The regimen is well-tolerated and adverse events are fairly manageable.

C59

A NON STANDARDIZED QUESTIONNAIRE TO INVESTIGATE ADVERSE EVENTS DURING ENDOCRINE THERAPY IN PATIENTS WITH EARLY BREAST CANCER

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Background: Breast cancer is the leading neoplasia among women. Endocrine therapy is indicated in all patients with detectable ER expression (⩾1% of invasive cancer cells), irrespective of the use of chemotherapy and / or target therapy. In premenopausal patients, for 5 years is a standard the ovarian suppression with Gonadotropin releasing hormone (GnRH) in combination with Tamoxifen (T) 20mg/day or an Aromatase inhibitor (AI). The aim of this study is to analyse adverse events due to GnRH+T or GnRH + AI.

Material and Methods: From July 2005 to August 2018, we enrolled 90 premenopausal patients with non-metastatic breast cancer.

Patients were treated with adjuvant endocrine therapy (T+GnRH or AI + GnRH). Adverse events were evaluated with clinical assessments and blood samples. We also administered the patients a non-standardized questionnaire to investigate which were adverse events caused by endocrine therapy. The median age of the patients was 48 years (from 32 to 58). Of them, 98% were Caucasian women and 2% Asian women. Our population was split in 4 subgroups, respectively:1. Patients treated with AI+GnRH (62%); 2. Patients treated with T+GnRH (31%); 3. Patients initially treated with T+GnRH and subsequently treated with AI+GnRH for adverse events occurred (3%); 4. Patients initially treated with AI + GnRH, were switched to T+GnRH due to adverse events (4%).

Results:

	Group 1	Group 2	Group 3	Group 4
Hot flushes	91%	68%	33%	100%
Depression	34%	25%	33%	33%
Anxiety	2%	4%	33%	0
Irritability	9%	10%	33%	33%
Insomnia	77%	61%	33%	33%
Nausea	34%	11%	33%	0
Constipation	27%	36%	0	0
Headache	21%	29%	33%	33%
Vaginal dryness	64%	61%	66%	100%
Vaginitis	16%	18%	33%	33%
Libido decreased	70%	50%	33%	100%
Gain of weight	38%	50%	66%	100%
Joint pain	84%	32%	66%	33%
Paraesthesia	27%	0	33%	33%
No symptoms	48%	57%	0	0

Conclusions: These adverse events irremediably affect quality of life of patients treated with endocrine therapy. It would be advisable to use a standardized questionnaire to investigate adverse events due to endocrine therapy to improve quality of life of these patients.

C60

HEPATIC ARTERIAL INFUSION OF CHEMOTHERAPY IN PRETREATED LIVER METASTASES FROM BREAST CANCER

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Background: The presence of liver metastases in breast cancer is associated with poor outcome. Up to 20% of this patients, will die from hepatic failure. In literature there are limited experiences with hepatic arterial infusion of chemotherapy (HAI) for these patients, in particular without subcutaneous pumps.

Patients and methods: This is an observational, single-center, retrospective analysis of HAI in heavy pretreated patients with breast cancer liver metastases (with only liver metastases or in which disease progression was mainly on liver, or at risk of liver visceral crisis, but always without other organs at risk of visceral crisis). Patients were treated with the combination of 5-fluorouracil (1000 mg), epirubicin (50 mg), and mitomycin-C (10 mg), every 28 days.

Results: From 2011 to 2018, 23 female patients were treated with HAI. The median age was 65 (range 40-77) at treatment, 58 (range 38-71) at breast cancer diagnosis. The most frequent tumor biology was hormone receptors (HR) positive/HER2 negative (56%); triple positive, triple negative, or unknown occurred respectively in 13%, 9%, and 22%. The median Ki-67 was 20% (15-90). Extra-hepatic disease was described in 17 patients (74%). Before HAI patients received a median of 4 (range 2-6) previous lines of treatment for stage IV disease, with a median of 2 (range 1-4) lines of systemic chemotherapy.

Regarding HAI, a median of 3 cycles was administered (range 1-9). The overall response rate (ORR) on liver was 26%, with a disease control rate (DCR) of 56% and a clinical benefit rate (CBR) of 47%. A progressive disease (PD) in liver or other sites was reported in 44% of patients. The median progression-free survival (PFS) was 6,45 months on 20 patients (3 were not evaluable for survival). Response rates and PFS benefit were independent from the number of previous lines (p: 0.26 and 0.56). Grade 3-4 adverse events or injuries linked to the invasive procedure were not reported.

Conclusions: In this series of pretreated patients with breast cancer liver metastases, the treatment with HAI achieved a durable disease control in about one case out of

two. Most of them had a HR positive/HER2 negative tumor. Prospective confirmation in clinical trials in the "*cyclin inhibitors era*" is recommend.

C61

IMMUNOLOGICAL EFFECTS OF ERIBULIN MESYLATE ADMINISTRATION IN PATIENTS WITH ADVANCED BREAST CANCER

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Background: Anticancer chemotherapy (CT) has been traditionally considered to be strongly immunosuppressive. However, increasing evidences suggest that certain CT agents have the ability to stimulate the immune system, inducing anti-tumor immune responses that contributes to their clinical efficacy. Eribulin mesylate (EM) exerts multiple non-mitotic effects on tumor biology including: tumor vasculature remodeling, reversal of epithelial-to-mesenchymal transition and stimulations of some immune cell-mediated activities.

Patients and Methods: In a study project on the role of CT drugs on the immune system we have studied the effect of EM on different T-cell populations in advanced breast cancer (BC). Using high-resolution multicolor flow cytometry, FOXp3+ *Treg* populations, sub-populations of cytotoxic CD8+ T-cells and CD57+ NK cells were analyzed in 19 pts (median age 61, range 40-76 yrs) undergoing a 3rd or 4th line of treatment. Ten healthy subjects matched for sex and age were utilized as control.

Results: There was a progressive decrease in absolute numbers of leukocytes, lymphocytes and CD8+ T-cells during CT courses. Starting from the 3rd course, T*reg* populations, that initially were increased compared to the healthy controls ($p<.001$), significantly decreased ($p<.001$). Among the T-cells, there was a lower $CD8^-/CD8^+$ ratio in pts compared to controls. The proportion of $CD28^-CD57+$ cells also remained higher among pts with cancer throughout the study duration.The number of $CD28^+CD57^-$ and $CD28^-CD5^-$ cells decreased faster during CT than $CD28^+CD57^+$ and $CD2^-CD57^+$ cells.

Conclusions: In pre-treated advanced BC pts, EM elicit several changes of some immune-related parameters including the composition and phenotype of immune cells. In particular, during treatment, regulatory activities in T cells were increased through a decrease of Foxp3+*Treg* cells. These findings suggest a contribution of the immune cells to the antitumor activities of EM and may help to design relevant clinical protocols based on the combination of EM with immune checkpoint blockers.

C62

PROOF-OF-CONCEPT OF SERENITY TRIAL (SECOND LINE ERIBULIN FOR LOCALLY ADVANCED OR METASTATIC BREAST CANCER): FOCUS ON NEUROPATHY AND OVERALL TOXICITY

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Background: In heavily pre-treated locally-advanced / metastatic breast cancer (LA/MBC) patients, neuropathy frequently occur. This disabling symptom leads to drug delays, dose reductions and discontinuations in addition to a detrimental impact on health-related quality of life (HRQoL). Eribulin mesylate was studied as subsequent line in various murine model with induced paclitaxel neuropathy producing less neuropathy than did paclitaxel. The aim of this study is to assess the toxicity profile of 2nd line chemotherapy with eribulin in a cohort of LA/MBC patients treated in real life setting, focusing on neuropathy-related toxicity assessed by both physician and Patients Reported Outcomes (PROMs).

Patients and Methods: Serenity is a longitudinal, prospective, open label multicentric study investigating tolerability profile and efficacy in a real life setting of eribulin as 2nd line treatment for HER2- LABC/MBC. An overall series of 33 patients is estimated, including a 10% of patients drop out from the study. Eribulin (1.23 mg/m²) is administered as per local practice. Tumor response will be evaluated with clinical, laboratory and imaging evaluations following the local center policy. Peripheral motor and sensory neuropathy will be assessed after clinical examination, using NCI CTCAE (version 5.0). PROMs related to neuropathy will be assessed concurrently, through the following tools: EORTC QLQ-CIPN20, Clinical version of the Total Neuropathy Score clinical version (TNSc), mISS, Visual analog pain scale (VAS).

Results: This study aims to collect data to assess the toxicity profile, the mode and the effectiveness of treatment of LA/MBC with eribulin. Relevant parameters in this respect are the reasons for stopping eribulin as well as the toxicity profile during and after stopping the above-mentioned treatment. Outcome data will be collected, in particular, side effects using the NCI CTCAE v.4 scale. In addition, data will be collected regarding progression-free survival, subsequent therapy lines and time to recurrence.

Conclusions: This study aim observe prospectively heavily pre-treated LA/MBC patients treated with 2nd line eribulin. We want to describe a toxicity profile in detail, comparing clinical assessment and PROMs.

C63

IMMUNE CHECK POINT INHIBITORS IN METASTATIC BREAST CANCER: A REVIEW OF THE AVEILABLE DATA

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Background: Immune check point inhibitors have become a standard of care in some tumors, and are emerging as a new treatment modality also in breast cancer, where anti cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4), anti programmed death-1 (PD-1) and anti-programmed death ligand-1 (PD-L1) antibodies were developed later. Metastatic breast cancer (MBC) remains incurable, and some breast cancer subtypes have a higher TILs expression with greater immunogenic power, like triple negative breast cancer (TNBC), considered the most immunogenic subtype.
Materials and Methods: We review available data from clinical trials regarding safety and efficacy of immune check point inhibitors in MBC.
Results: Eighteen trials were founded, mainly phase I/II. Efficacy data are encouraging, especially in TNBC and in PD-L1+, and when immune check point inhibitors are used in combination with other therapies, like eribulin, radiotherapy like abscopal effect and poly(ADP-ribose) polymerase (PARP) inhibitors, or abemaciclib in hormone receptor (HR) positive tumors. Progression free survival (PFS) and overall survival (OS), in Impassion 130 phase III trial, were better in the nab-paclitaxel plus atezolizumab group, especially in PD-L1+, and atezolizumab has recently been approved by FDA for metastatic TNBC. Pembrolizuamb alone, in TNBC, demonstrated better responses in less pre-treated patients especially in PD-L1+, with a median duration of response higher than standard chemotherapy, also in pre-treated patients, while it demonstrated less efficacy in patients with poor prognostic factors. In human epidermal growth factor 2-neu (HER2) positive tumors there are less data and more controversial, Immune check point inhibitors were well tolerated and the main side effects were similar to those seen in studies conducted in other cancer types.
Conclusions: Available data regarding immune check point inhibitors use in breast cancer are promising, especially in metastatic TNBC. The main biases of the published studies are the small sample size and the early phase of the trials. These drugs are well tolerated, both alone or in combination, and reflect the toxicities already known from studies in other cancer types. Efficacy is interesting, especially in TNBC, early metastatic setting and PD-L1+, even if these drugs need further investigations, that are ongoing. Patients with poor prognostic factors should not be considered for therapy with immune checkpoint inhibitors alone.

C64

FROM AN HOSPITAL TO A NETWORK: SHARING OF AN INTERDISCIPLINARY AND MULTIPROFESSIONAL CARDIO-ONCOLOGY PATHWAY FOR THE MANAGEMENT OF BREAST CANCER PATIENTS IN AZIENDA USL TOSCANA NORD-OVEST (ATNO)

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Background: The impact of cardio-oncology issues in breast cancer patients management has become more and more relevant so making crucial to adopt a dedicated care pathway.
Materials and Methods: In late 2017 an ATNO interdisciplinary and multi-professional working group was established. The group was composed by selected medical oncologists, belonging to the Department of Oncology, cardiologists and nurse representatives from each different hospital. The aim was to create a shared cardio-oncology pathway based on an in-hospital cardio-oncology pathway previously active at Versilia Hospital. The process was divided into three phases: a) cardio-oncology census and inner organization of each hospital (if available); b) oncology-related workload; c) availability of trained and/or interested physicians. Final objectives were: 1) promote the Versilia model in the other hospitals of ATNO; 2) define a shared model to be applied across all ATNO hospitals, to take care of breast cancer patients from a cardiological point of view; 3) encourage clinical research in this unexplored area of clinical oncology.
Results: Baseline cardio-oncology service organization clearly differs among ATNO hospitals ranging from established pathway to no service. On the other hand, the amount of monthly oncology-related workload was relevant with a mean of 40-60 services/month/hospital. The

working group so defined cardiac risk toxicity categories, timing and type of cardiology visits and imaging and need for next-level diagnostic tests. The group also focused on network level activities by the identification of some centers with specific expertise on cardiac imaging (cardiac MRI and coronary-CT) and cardiac rehabilitation to be offered to all ATNO breast cancer patients.

Conclusions: A cardio-oncology pathway is now active at ATNO and breast cancer patients cardiac management is based on shared expertises at hospital network level.

D - Thoracic Cancers

D01*

SECONDARY ROS1 MUTATIONS AND LORLATINIB SENSITIVITY IN CRIZOTINIB-REFRACTORY ROS1 POSITIVE NSCLC: RESULTS OF THE PROSPECTIVE PFROST TRIAL

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Background: Lorlatinib, an ALK/ROS1 inhibitor, showed activity in ROS1+NSCLC pretreated with crizotinib. However, molecular events predictive for tumor response during lorlatinib treatment are largely unknown.

Material and Methods: The phase II PFROST trial included ROS1+NSCLCs refractory to crizotinib. Eligible patients received lorlatinib 100 mg daily until disease progression. Primary end point was response rate (RR). For all patients, pre-lorlatinib tumor tissue or blood sample collection was mandatory. At the time of lorlatinib failure liquid biopsy was recommended. The samples were then run with the NEOliquid assay, specifically designed for liquid biopsies, or NEOselect, a panel optimized for formalin-fixed paraffin-embedded (FFPE) tumor tissue, covering 39 cancer related genes.

Results: From June 2017 to April 2019, 22 ROS1+ crizotinib refractory lung adenocarcinoma patients were included in 10 Institutions. Median age was 56 years (range 39-82); male/female: 8/14; ECOG PS 0 (N=8; 36.4%), PS 1 (N=14; 63.6%); The majority had brain metastases at baseline (N=15; 68.1%), were never smokers (N=13; 59.1%) and received lorlatinib as third line therapy (N=16; 72.7%). In all cases crizotinib was the last therapy before lorlatinib. At the time of this analysis, trial completed its accrual and 13 patients are still receiving therapy. A total of 18 patients were evaluable for response and 7 had confirmed complete (N=1) or partial (N=6) responses for an overall RR of 38.8%. In 4 patients, response to therapy was not yet evaluated. A total of 10 tissue biopsies and 20 blood samples obtained after crizotinib and before lorlatinib therapy were collected. For 7 samples analyses are ongoing. Among responders, no patient harbored a secondary ROS1mutation. Conversely, no response was observed among patients with secondary ROS1 mutations (N=1 ROS1 S1861I, N=1 ROS1 V2054A, N=3 ROS1 G2032R). All patients harboring the ROS1 G2032R mutation rapidly progressed and maintained this aberration in liquid biopsy at the time of of lorlatinib failure.

Conclusions: In our study lorlatinib confirmed its efficacy in crizotinib resistant ROS1+NSCLC. Molecular profile of refractory patients suggests reduced efficacy in individuals harbouring crizotinib-induced secondary ROS1 mutations.

D02*

RELAY: A MULTINATIONAL, DOUBLE-BLIND, RANDOMIZED PHASE 3 STUDY OF ERLOTINIB (ERL) IN COMBINATION WITH RAMUCIRUMAB (RAM) OR PLACEBO (PL) IN PREVIOUSLY UNTREATED PATIENTS WITH EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION-POSITIVE (EGFRM) METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

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	RAM + ERL (n = 224)	PL + ERL (n = 225)	HR (95% CI)	p-value
PFS			0.591 (0.461–0.760)	<0.0001
Median, months (95% CI)	19.4 (15.4–21.6)	12.4 (11.0–13.5)		
Censoring rate	46%	30%		
ORR, % (95% CI)	76.3 (70.8–81.9)	74.7 (69.0–80.3)		0.7413
Number of responders	171	168		
DoR**			0.619 (0.477–0.805)*	0.0003*
Median, months (95% CI)	18.0 (13.9–19.8)	11.1 (9.7–12.3)		
Censoring rate	41%	24%		
PFS2			0.690 (0.490–0.972)	0.0325
Median, months (95% CI)	NR	NR		
Censoring rate	73%	65%		
Interim OS			0.832 (0.532–1.303)	0.4209
Median, months (95% CI)	NR	NR		
Censoring rate	83%	81%		

Median follow-up: 20.7 months; NR, not reached; * unstratified; **Ns are based on number of responders from the ITT population.

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Background: Dual blockade of EGFR and VEGFR pathways in EGFRm NSCLC augments anti-tumor efficacy vs EGFR inhibition alone. RELAY evaluated efficacy and safety of ERL, an EGFR TKI standard-of-care, plus RAM, a human IgG_1 VEGFR2 antagonist, or PL in 1L EGFRm metastatic NSCLC.

Materials and Methods: Eligibility included untreated metastatic NSCLC pts with Exon 19 deletion (del) or L858R and no CNS metastasis. Randomized (1:1) pts received ERL (150 mg/day) + RAM (10 mg/kg q2w) or ERL + PL, stratified by gender, geographic region (East Asia v other), EGFRm type (Ex19del v L858R) and EGFR testing method (Therascreen/Cobas v other). The primary endpoint was Investigator assessed progression free survival (PFS). Other objectives included ORR, DoR, PFS2, OS, safety, and plasma T790M mutation (Guardant NGS).

Results: 449 pts were randomized and characteristics were balanced between treatment arms: Asian 77%, Females 63%, Ex19del 54%. RAM + ERL significantly prolonged PFS, DoR, and PFS2 (Table). Grade >=3 TEAEs were greater with RAM (72%) vs PL (54%), largely driven by hypertension (24 vs 5%, no Gr4); with 1 treatment related on study death (hemothorax) in RAM vs 0 PL. EGFR T790M + rates at progression are forthcoming.

Conclusions: RAM + ERL led to superior PFS in 1L EGFRm metastatic NSCLC. Safety was consistent with the established safety profiles of the individual compounds.

D03*

GEFITINIB PLUS VINORELBINE IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) HARBORING MUTATIONS OF THE EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

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Background: Patients with advanced EGFR-mutant NSCLC are generally destined to experience disease progression in spite of initial benefit from EGFR Tyrosine kinase inhibitors (TKIs). In a preclinical study conducted within our Institution, the administration of vinorelbine followed by gefitinib resulted in increased activity due to synergistic effect of the combined drugs. Here we present the interim analysis of GEfitinib plus viNorelbine in Advanced EGFR mutated NSCLC (GENOA TRIAL), which was designed to investigate the role of oral

vinorelbine followed by gefitinib for the management of treatment-naïve patients affected by *EGFR*-mutant NSCLC (Clinicaltrials.gov: NCT02319577).

Methods: This was an open-label, randomized phase II trial designed to explore activity and tolerability of vinorelbine followed by gefitinib compared to gefitinib alone in patients with *EGFR*-mutant NSCLC. The estimated enrolment was equal to 80 patients; enrolled patients were randomized (1:1) to receive oral vinorelbine (60 mg/m^2) on days 1,8 followed by gefitinib (250 mg) on days 9-21 (Arm A) or gefitinib alone (250 mg) on days 1-21 (Arm B) in three-weekly cycles. The primary end-point of the study was the increase in terms of 6-month progression-free survival (PFS) rate in the experimental arm, while median PFS and median overall survival (OS) were secondary end-points.

Results: Data from 44 patients (Arm A=23; Arm B=21) are available for this interim analysis. All the patients had advanced lung adenocarcinoma with *EGFR* mutation (exon 18=2; exon 19=16; exon 21=21; multiple exons=5). The 6-month PFS rate was 48% for Arm A compared to 66% for Arm B (p=0.24). Median PFS was 6.2 months for Arm A vs. 9.5 months for Arm B (p=0.17), while median overall survival (OS) was 18.2 months for Arm A and not reached for Arm B (p=0.12). Response rate was 47% for Arm A vs. 55% for Arm B (p=0.76). Severe adverse events (AEs) were similarly uncommon in both arms: two patients in Arm A experienced grade 3 white blood cells reductions, and two patients in Arm B experienced grade 3 increase of liver alanine aminotransferase. No treatment-related deaths were reported.

Conclusions: At the interim analysis of GENOA Trial, the addition of oral vinorelbine to gefitinib was not associated with increased 6-month PFS rate; similarly, no differences in terms of response, median survival or toxicity was reported. The study was interrupted on the basis of this interim analysis.

D04*

CORRELATION BETWEEN MALIGNANT PLEURAL MESOTHELIOMA TREATMENT AND GENOMIC PROFILE: UPDATE RAMES STUDY

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Background: MPM is an aggressive tumor mainly caused by asbestos exposure, with a median overall survival ranging from 12 to 18 months. Platinum/pemetrexed regimen is the standard 1°-line chemotherapy (CHT) in advanced disease.

Methods: The RAMES Study evaluated the 2°-line efficacy of gemcitabine/ramucirumab treatment vs. gemcitabine/placebo. From December 2016 to July 2018 (end of enrolment), 164 pts were admitted to this study. We evaluated by NGS the mutational profile of a panel of 34 genes (gs) (ACTB, ACTG1, ACTG2, ACTR1A, BAP1, CDH8, CDK4, CDKN2A, CDKN2B, COL3A1, COL5A2, CUL1, DHFR, GOT1, KDR, KIT, MXRA5, NF2, NFRKB, NKX6-2, NOD2, PCBD2, PDZK1IP1, PIK3CA, PIK3CB, PSMD13, RAPGEF6, RDX, SETDB1, TAOK1, TP53, TXNRD1, UQCRC1, XRCC6). We reported the results of the 103 pts (63%) of both arms with specimen available for molecular analysis. Median age was 63 years (45-81), 24.3% (n=25) were females and 75.7% (n=78) males. Histotype was 83.5% (n=86) epithelioid and 16.5% (n=17) non-epithelioid. 37.8% (n=39) were stage IV, 60.2% (n=62) were stage III, and 1.9% (n=2) were unknown. In 1°-line platinum/pemetrexed CHT treated pts, the median PFS was 5.75 months (ms) (C.I. 95% 4.75-6.76). 50 pts had PFS <6 ms, while 50 pts had PFS >6 ms (n=3 not available).

Results: 260 functional somatic mutations were identified in 28 of the 34 gs analyzed. 75pts (72.8%) displayed mutations in 1 to 3 gs while 17 pts (16.5%) showed mutations in at least 4 gs. No mutated gs were detected for 11 pts (10.7%). The number of mutated gs was positively associated with higher stage and metastatic behavior (p=0.025) and increased 1°-line PFS (p=0.011). RDX (42.7%), MXRA5 (23.3%), BAP1 (13.6%), PIK3CB (10.7%) and NF2 (10.7%) were the most frequently mutated gs in our pts. Mutations in RAPGEF6 (p=0.013) and ACTG1 (p=0.01) were associated with non-epithelioid, while mutations in BAP1 (p=0.041) were associated with PFS >6 months. A positive trend of association was also observed between mutations in COL3A1 (p=0.052) and NFRKB (p=0.052) and stage IV.

Conclusions: In MPM the identification of molecular gene alterations could be an important starting point for understanding the main pathways involved in prognosis and sensitivity/resistance to therapy. In the RAMES Study, the mutation of gene BAP1 is related to a prolonged PFS at the 1°-line CHT (p=0.041).

D05

CRIZOTINIB IN ROS1 REARRANGED NSCLC: FINAL RESULTS OF THE METROS TRIAL

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Background: The METROS was a phase II, non-parallel, Italian trial, specifically designed to evaluate the activity of crizotinib in two different cohorts of oncogene addicted NSCLC (cohort A=*ROS1* rearranged; cohort B=*MET* amplified or *MET Exon14* mutated). Based on positive results obtained in ROS1cohort (Landi L, et al. AIOM 2016), we emended the study to include additional patients. Here we reported results of the whole *ROS1* population.
Material and methods Patients with advanced NSCLC and evidence of *ROS1* rearrangements on FISH test were treated with crizotinib 250 mg BID orally until disease progression. Primary end point was objective response rate (ORR).
Results: From December 2014 to August 2018, 64 *ROS1* rearranged NSCLC patients were included onto the study (N = 26 initial cohort; N = 38 expansion cohort). Median age was 55 years (28-86 years), most were females (65.5%), never/past smokers (90.6%) with ECOG PS 0 (57.8%). All but one case had adenocarcinoma histology and presented with >2 metastatic sites. The most common sites of disease were lung (92.2%), nodes (65.6%), liver (76.6%), bone (35.9%) and brain (26.6%). At data cut-off of 30 March 2019, 19 patients are still receiving treatment. ORR was 65.2%, including 2 (3.1%) complete and 41 (64.1%) partial responses. Twelve patients (18.8%) obtained a stabilization of the disease, resulting in an overall disease control rate of 86%. Depth of response, defined as the median percentage of reduction in target lesions from baseline, was -62% (IQR, -26% - -100%). With a median follow-up of 15 months (95% CI 1 – 52), median PFS was 16.5 months (95% CI 9.4-23.6), whereas median OS was 40.9 months (95% CI 23.1-58.7). Median time to response and median duration of response were 1.9 months (IQR, 1.1-37.8) and 14.9 months (95% CI 1.8 – 36.6), respectively. Safety profile of crizotinib was consistent with literature data and no new safety alert was reported.
Conclusions: Our results confirmed the marked activity of crizotinib in *ROS1* rearranged NSCLC. Biomarker analyses on plasma collected at baseline and during treatment are ongoing.

D06

CDKN2A/B GENE LOSS AND MDM2 ALTERATION AS A POTENTIAL MOLECULAR SIGNATURE FOR HYPERPROGRESSIVE DISEASE IN ADVANCED NSCLC: A NEXT-GENERATION-SEQUENCING APPROACH

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Background: Hyperprogressive disease (HPD) incidence ranges from 8% to 21% in patients treated with anti-PD-1/PD-L1 mAbs in NSCLC and is associated with poor survival. Previously published data underlined a link between HPD across different cancers types and specific genetic alterations, such as MDM2 amplification and EGFR aberrations. We present a single-center cohort of patients with NSCLC and PD-L1>50% treated with 1st-line pembrolizumab. We performed NGS, IHC and FISH analysis to evaluate genetic correlations with the clinical phenotype.
Methods: Clinical data from 20 patients with diagnosis of advanced NSCLC treated with 1stline immunotherapy pembrolizumab were retrospectively collected. HPD was defined by Time to Treatment Failure ⩽2 months and raising in Tumor Burden ⩾50% compared with basal CT-scan. MDM2 amplification was investigated by FISH on FFPE tissue sections using the MDM2/CON12 break apart FISH Probe. Positive cases were defined as those with >10% positive tumor cells. We performed IHC for MDM2 protein on FFPE tissue sections. The staining was semiquantitatively graded for the intensity as: 0, negative; 1+, weak positive; 2+, moderately positive; 3+, strongly positive, and for the extent as 0–<1% (negative), 1–50% (focal), and >50% (diffuse). We also performed NGS analysis (FoundationOne CDX, Foundation Medicine Inc.) on 324 preidentified genes.
Results: We identified 5 cases of HPD; all five cases showed *MDM2* amplification by FISH analysis and a focal protein expression by IHC with the strongest nuclear staining observed in the cases showing a higher degree of *MDM2* amplification (8/9 dots) and a weaker expression in those with a lower *MDM2* amplification (4/5 dots). NGS analysis showed *MDM2*amplification in 1/5 HPD patient and a loss of CDKN2A/B in 4/5 patients. None of the non-HPD patients had IHC expression of MDM2 or amplification of the gene. Among the non-HPD patients no genetic alterations regarding MDM2 and/or CDKN2A/B were found on NGS analysis.

Conclusions: Our data suggest a potential role of CDKN2A/B gene loss and alteration of MDM2 on the establishment of HPD in NSCLC patients treated with immunotherapy. Because the HPD logic is not yet clear, more data is needed to better understand the link between this genomic signature and the development of HPD.

D08

IMMUNE CHECKPOINT INHIBITORS IN THE ELDERLY WITH NON-SMALL CELL LUNG CANCER: EFFICACY AND SAFETY

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Background: Data about efficacy and safety of Immune Checkpoint Inhibitors (ICIs) in elderly patients (pts) with Non-Small Cell Lung Cancer (NSCLC) are scarce. However, NSCLC is often diagnosed in pts older than 70. Therefore, we aimed at investigating the topic of Immunotherapy (IO) in the elderly in a real-world case series.

Material and Methods: All consecutive pts with advanced or metastatic NSCLC treated with ICIs at Istituto Nazionale dei Tumori, Milan, between 04/2013 and 03/2019 were retrospectively reviewed. Cases were divided in the following three age classes: <70 year-old (yo), 70-79 yo, ⩾80 yo. Chi-square test was used to compare qualitative variables. Survival was estimated with Kaplan-Meier method. Log-rank test was used to compare curves.
Multivariate analyses were performed with Cox model.

Results: We identified 290 cases, whose median age was 67 (range: 29-89). The aforementioned three age classes included 180, 94 and 16 pts, respectively. IO consisted in anti-PD1 in 205 cases, in anti-PDL1 in 77 cases, in an anti-CTLA4 or in a combo-IO in 8 cases. Main clinico-pathological variables were well balanced among subgroups, except for a higher frequency of male gender (p 0.0228) and squamous NSCLC (p 0.0071) in the class 70-79 yo.
Response Rate (RR) did not show differences across subgroups (21.5% vs 22.3% vs 18.8% for pts aged<70 vs 70-79 vs ⩾80 yo, respectively; p 0.9470). Similarly, no difference was observed in median PFS (2.8 vs 3.5 vs 2.6 mos for pts aged<70 vs 70-79 vs ⩾80 yo, respectively; p 0.2020) and OS (9.1 vs 11.3 vs 9.6 mos for pts aged<70 vs 70-79 vs ⩾80 yo, respectively; p 0.9144), even after stratification according to gender (p 0.516 for PFS, p 0.5154 for OS) and histology (p 0.9057 for PFS, p 0.1002 for OS). Toxicity was comparable across age classes (grade⩾2 adverse events in 35.8% vs 32.7% vs 37.5% for pts aged<70 vs 70-79 vs ⩾80 yo, p 0.6493). At multivariate analysis, outcome was
affected by performance status (p<0.0001 for PFS, p 0.0192 for OS), number of metastatic sites (p 0.0842 for PFS, p 0.0235 for OS) and IO line (p<0.0001 for both PFS and OS), but not by age.

Conclusions: In our series, ICIs appeared safe and effective irrespective from age. Notably, with the limitation of the low number of cases, no toxicity concerns emerged even in pts aged >80. If these data were confirmed, IO should be considered as a valid treatment option for elderly pts with NSCLC, provided an adequate performance status.

D09

SOLUBLE PROGRAMMED DEATH LIGAND-1 (SPD-L1) IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH IMMUNO-CHECKPOINT INHIBITORS

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Background: Immuno-checkpoint inhibitors (ICIs) anti-PD1/PDL-1 have demonstrated to improve patient outcome in advanced NSCLC but predict treatment benefit still remain an unsolved problem. PD-L1 tissue testing is recommended for all patients with newly diagnosed advanced NSCLC, but sometimes is not feasible and, however, still represents a snapshot not a dynamic portrait. Therefore, here, we investigate the role of soluble PD-L1 (sPD-L1) in predicting clinical outcomes of advanced NSCLC patients (pts) treated with ICIs.

Material and Methods: Levels of sPD-L1 were tested in advanced NSCLC pts treated with ICIs. Serum sample was collected at baseline and analyzed with Human/Cynomolgus Monkey PD-L1/B7-H1 Immunoassay (R&D Systems) following the manufacturer's instruction. sPD-L1 levels were correlated with patients' characteristics and principle outcome measures.

Results: From March 2017 to February 2019, 80 advanced NSCLC pts treated with ICIs were consecutively enrolled. Median age was 72 years (range 41-85), 65% were males, 30% never smoker and principal histology was non-squamous (65%). Lines of therapy were first (13.8%), second (66.3%), third (8.7) and above (11.2%). ICIs were nivolumab in 70% of pts, pembrolizumab in 17.5%, atezolizumab in 10% and ipilimumab-nivolumab in 2.5%. Median progression-free survival (PFS) and time to treatment failure (TTF) were both 2.4 months, while overall survival (OS) was 4.9 months. Median value of sPD-L1 was 62.8 pg/ml (range 14.8-189.8 pg/ml). No statistically significant correlation was observed between levels of sPD-L1 and disease control rate. Cox regression analysis, corrected for therapy line, shown a statistically significant

inverse correlation between sPD-L1 level and OS and TTF (for both p 0.049). According to PFS and considering two opposite groups (PFS < 6 vs. > 12 months), patients with worse outcome showed higher levels of sPD-L1 (p 0.009).
Conclusions: From our preliminary results, higher level of sPD-L1 seems to be a negative prognostic factor. These results need to be investigated in a better stratified cohort for line of treatment, type of ICIs and with an adequate follow-up. In fact, survival outcome analysis were mature for PFS/TTF analysis but not for OS analysis. Despite this, sPD-L1 constitute as a promising circulating biomarker to explore.

D10

USING PLASMA MICRORNAS AS BIOMARKERS OF RESISTANCE TO IMMUNE CHECKPOINT INHIBITORS IN PD-L1 ⩾50% ADVANCED NSCLC

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Background: PD-L1 is the only clinically approved biomarker for cancer immunotherapy. However, a sizable proportion of PD-L1⩾50% NSCLC patients (pts) do not benefit of immune checkpoint inhibitors (ICIs). A plasma microRNA signature classifier (MSC), reflecting the immune cells switch towards an immunosuppressive profile, was able to identify NSCLC pts with worse prognosis after ICIs, irrespective of PD-L1 expression. In this work we prospectively evaluated the MSC role as biomarker of primary or secondary resistance to ICIs in PD-L1⩾50% advanced NSCLC.
Materials and Methods: Plasma samples, demographics data, baseline smoking history and ECOG PS were collected for 50 consecutive PD-L1⩾50% advanced NSCLC pts treated with ICI as first (n=32) or further line. Using the MSC test we distinguished high (H) vs intermediate/low (I/L) risk level pts. According to RECIST 1.1 criteria, we classified pts as responders (R), pts with stable disease (SD) and progressors (P). Objective Response Rate (ORR), Progression Free Survival (PFS) and Overall Survival (OS) in baseline MSC risk level strata were our endpoints. Additive, not mandatory, plasma samples were collected at the time of revaluations in 26 R or SD pts with extended follow-up. Changes in the probability of progressive disease after two consecutive MSC tests, considering all possible combinations, were evaluated to determine changes in the risk level during follow-up.
Results: Out of 50 pts, 17 (34%) were R, 17 (34%) pts with SD, 11 (22%) P and 5 (10%) not evaluable pts. At baseline 11 (22%) pts showed MSC H. ORR was 0% in MSC H vs 45% in other pts (p=0.0090). Median PFS was 2.3 vs 10.9 months in MSC H vs other pts (HR=0.38; 95%CI=0.17-0.84; p=0.0174). Median OS was 2.9 vs 22.0 months in MSC H vs other pts (HR=0.18; 95%CI=0.07-0.47; p=0.0004). Significance was maintained after adjusting for age, sex, pack-years and ECOG PS: PFS HR=0.31 (95%CI=0.13-0.73; p=0.0072) and OS HR=0.13 (95%CI=0.04-0.39; p=0.0003). Among 26 pts with longitudinal evaluation of MSC risk level, all the 12 pts progressed during ICIs showed an increase in the risk level (Sign-test p-value=0.0039). Conversely, 9/14 (64%) pts with SD or response to ICIs at the time of the analysis, showed a decrease in the risk level (Sign-test p-value=0.1655).
Conclusions: The MSC test may represent a useful biomarker of primary or secondary resistance in PD-L1>/=50% advanced NSCLC pts during ICIs. Ongoing trials are validating these results.

D11

SHORT AND MID-TERM OUTCOMES OF MULTIMODAL TREATMENT FOR LOCALLY-ADVANCED NON SMALL CELL LUNG CANCER IN ELDERLY PATIENTS

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Background: Multimodality treatments are effective for locally advanced non-small cell lung cancer (LA-NSCLC) and have demonstrated clinical benefits in terms of overall survival (OS) and disease-free survival (DFS). Nevertheless elderly patients are often excluded to these treatment options because of fears of fatal complications.
Methods: The objectives of this single institution retrospective study were: to investigate mortality, morbidity, short and mid-term oncological outcomes of pulmonary resection after induction chemotherapy (IT) for NSCLC in elderly patients treated from June 2014 to December 2018. We divided the study population into two groups based on age at time of the treatment: patients <70 years (group A) and patients >70 years (group B). Inclusion criteria was patients who received IT (+/- radiation therapy) and subsequent pulmonary resection. The multimodal treatment was established by a multidisciplinary team. To be identify factors associated with overall morbidity, including a set of variables chosen according to clinical relevance, a multivariable logistic regression was used.
Results: 77 patients underwent pulmonary resection after IT; among these, 27 were aged >70 years. The majority of patients were classified as clinical stage IIIA in both groups. Platinum-based chemotherapy was administered to 73

patients and chemo-radiation was used more frequently in group A (24% vs 3.7%; p=0.02). Surgical procedures were similar in both groups, although chest wall resections were more frequent in group A (20% vs 11%, p=0.52). Pathological stage didn't differ between the two groups and we had a total of 10 complete responses after IT.
In-hospital mortality (2% vs 0%) was similar, while the percentage of patients with complication (38% vs 48.1%, p=0.47) and the complication rate (50% vs 77%, p=0.01) were higher in group B, in particular we observed a significant higher incidence of atrial fibrillation (4% vs 25.9%; p<0.01) but the severity of complications was comparable between the two groups. The multivariable analysis demonstrated the absence of any significant factors associated with overall morbidity. At the median follow-up of 22 months, OS at 3 years and DFS at 2 years were not different between the two groups (61% vs 48.5% and 61.7% vs 44%).
Conclusions: Lung resection for LA-NSCLC after IT can be performed safely in appropriately selected elderly patients with favorable post-operative and mid-term oncological results.

D12

A RANDOMISED PHASE 3 STUDY OF CARBOPLATIN + NAB-PACLITAXEL WITH OR WITHOUT ATEZOLIZUMAB AS FIRST-LINE THERAPY IN ADVANCED NON-SQUAMOUS NSCLC: IMPOWER130

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Background: Atezolizumab, a humanised anti-PD-L1 antibody, improved overall survival (OS) *vs* docetaxel, regardless of PD-L1 status, when administered as monotherapy in 2nd/3rd line NSCLC patients in the OAK clinical trial. IMpower130 (NCT02367781) evaluated atezolizumab + Carboplatin/nabPaclitaxel (CnP) *vs* CnP as first line therapy (1L) in patients (pts) with measurable (RECIST v1.1) stage IV non-squamous NSCLC.
Methods: Patients (randomised 2:1) received atezolizumab (1200 mg IV q3w) + CnP (carboplatin: AUC 6 q3w; nab-paclitaxel: 100 mg/m^2 IV qw) (Arm A) or CnP (Arm B), for 4 or 6 21-day cycles and maintenance (Arm A: atezolizumab until loss of clinical benefit; Arm B: best supportive care or pemetrexed q3w until disease progression [PD]). Crossover to atezolizumab at PD was initially permitted for Arm B pts. Co-primary endpoints: investigator-assessed PFS and OS (ITT-WT population: *EGFR*-WT/*ALK*-negative). Secondary endpoints: OS and PFS (ITT population and by PD-L1 expression), response rate and safety. ITT population could be formally tested for OS/PFS if ITT-WT OS was positive.
Results: Overall, 723 ITT pts (679 ITT-WT) were enrolled. A statistically significant improvement in OS was observed both in ITT-WT (18.6 mo in Arm A vs 13.9 mo in Arm B; HR: 0.79) and in ITT population (18.1 mo in Arm A vs 13.9 mo in Arm B; HR: 0.80). Furthermore, study showed statistically significant improvements in PFS, both in ITT (7.0 mo in Arm A vs 5.6 mo in Arm B; HR: 0.65) and ITT-WT (7.0 mo in Arm A vs 5.5 mo in Arm B; HR: 0.64). PFS and OS benefit was observed in all PD-L1 subgroups (OS was 17.4 mo in Arm A vs 16.9 mo in Arm B with HR 0.84 in PD-L1 high; 23.7 mo in Arm A vs 15.9 mo in Arm B with HR 0.70 in PD-L1 low; 15.2 mo in Arm A vs 12.0 mo in Arm B with HR 0.81 in PD-L1 negative) and consistently across all subgroups, except in pts with liver metastases and *EGFR*/*ALK* genomic alterations. In treated pts, 73.2% (Arm A) *vs* 60.3% (Arm B) had grade 3–4 treatment-related adverse events.
Conclusions: IMpower130 showed statistically significant and clinically meaningful improvements in OS and PFS with atezo + CnP *vs* CnP, in 1L, stage IV non-squamous NSCLC, in this predominantly ITT-WT population. No new safety signals were identified.

D13

CLINICAL IMPLICATIONS OF RET REARRANGEMENTS IN NON-SQUAMOUS NSCLC PATIENTS: AN ITALIAN SINGLE-INSTITUTION STUDY

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Background: REarranged during Transfection (RET) gene rearrangements are described in <2% of non-small cell lung cancers (NSCLCs). The identification of RET as driver alterations in NSCLC increased its relevance as druggable

target, with a growing interest to understand the implications on clinical course of NSCLC patients (pts). The aim of this study is to determine the clinical-pathological characteristics of NSCLC pts harboring RET rearrangements.

Material and Methods: We performed a retrospective, single-institution study on EGFR, ALK and ROS1 wild type, non-squamous NSCLC pts, evaluated and treated at our Institution (IEO, Milan). All pts were tested for RET by next generation sequencing (using the Oncomine™ Comprehensive Assay, Thermo Fisher Scientific) with confirmatory *in situ* hybridization. Data on clinical-pathological features and progression-free survival (PFS) under first line (1L) treatment were retrieved from clinical records. Demographic and clinical-pathological features [age, sex, histology, PD-L1 expression (evaluated by tumor proportion score (TPS) immunohistochemistry), stage at presentation, metastatic sites, type of treatment] were analyzed using descriptive statistics. PFS was calculated using the Kaplan–Meier method. Differences between variables were assessed by the log-rank test.

Results: Of 578 NSCLC pts screened, RET rearrangements were detected in 21 cases (3.6%). Median age was 57 years (range 37-80, IQR 18), with >80% of pts younger than 65 years. Of 21 pts, 13 (61.9%) were females and 16 (76.2%) never smokers. 17/21 (81%) of pts presented with *de novo* stage IV NSCLC, including 4 pts with brain metastases at diagnosis. PD-L1 expression ⩾50%, was detected in 8/21 (38.1%) pts; all these patients received 1L pembrolizumab (IO). Conversely, pts with PD-L1<50% received standard 1L chemotherapy (76.9% platinum+pemetrexed, 15.4% platinum+gemcitabine, and 7.7% gemcitabine monotherapy). PFS after therapy in the 1L setting was significantly longer for RET-rearranged NSCLC pts receiving chemotherapy compared to IO (18.5 vs 2.9 month; log-rank p<.001). No significant differences in PFS were detected in the subgroup analysis.

Conclusions: In our cohort, RET-rearranged NSCLCs were more frequent in female, younger, and non-smoker pts, confirming the current available data. In addition, our results suggest that RET-rearranged NSCLCs seem to be poorly responsive to IO. These results need to be validated in a larger prospective cohort of NSCLC pts.

D14

DEMO SCORE: A PROSPECTIVE EVALUATION OF A PROGNOSTIC CLINICO-MOLECULAR COMPOSITE SCORE IN PATIENT WITH ADVANCED NSCLC TREATED WITH IMMUNOTHERAPY

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Background: The DiMaio (D), EPSILoN (E) and plasma microRNA signature classifier (MSC), are 3 different clinico-biochemical and molecular scores able to independently predict prognosis in advanced non-small cell lung cancer (aNSCLC) patients (pts) treated with immunotherapy (IO). By assessing the ability of each test a combined score called DEMo was developed. The study aims to prospectively evaluate the prognostic value of DEMo in aNSCLC pts treated with IO.

Methods: We included in the analyses 166 aNSCLC pts treated in first (n=47) and further-lines (n=119) with IO at Istituto Nazionale Tumori of Milan. For all pts we obtained complete necessary data for both clinical scores: D-clinic (sex, histology, ECOG-PS stage, uses of platinum-based therapy at first-line and response to first-line) and E-biochemical (ECOG-PS, Smoke, Liver, LDH, NL-ratio). MSC (molecular score) was prospectively evaluated in plasma samples collected at baseline IO and the risk level was assessed. Endpoints were median overall survival (mOS), progression-free survival (mPFS) and overall response rate (ORR). Kaplan-Meier was used to generate survival curves and also Cox hazard model to perform multivariate analyses.

Results: In multivariate analysis adjusted accroding age, sex, smoke and ECOG-PS each score (D-E-MSC) remain independently significant for both mPFS (D: HR=1.99, CI95% 1.21–3.03, p=0.007; E: HR=1.87 CI95% 1.12 – 3.10, p=0.016; MSC: HR=1.56, CI95% 1.03–2.37, p=0.0370) and mOS (D: HR=3.12, CI95% 1.80–5.41, p=0.0001; E: HR=2.21, CI95% 1.28–3.79, p=0.0041; MSC: HR=2.03, CI95% 1.30–3.17, p=0.0019). DEMo was able to separated patients in 4 different-risk groups (grs) based on the presence of 3–2–1–0 poor prognostic scores. Strata had 0%–7%–20%–46% 18-months (mo) PFS (p<0.0001) and 0%–23%–44%–78% 18-mo OS (p<0.0001). We further combined DEMo grs 3/2 and 0/1 to perform a multivariate analysis: mPFS and mOS for grs 3/2 vs 0/1 were 2.1 vs 6.4 mo (HR=2.06, CI95% 1.26–3.36, p=0.0038) and 4.1 vs 20.3 mo (HR 3.17, CI95% 1.91–5.24, p<0.0001). The ORR was 2.9 (CI95% 1.4–6.0) fold lower for gr 3/2 compare to 1/0 (p=0.0034).

Conclusions: In conclusion, we created a composite clinic- biochemical-molecular combined biomarker classifier able to better predict prognosis compared to each single score. In particular, DEMo where capable to select those patients who are less likely benefit from IO and thus could be a useful tool to guide choices in aNSCLC.

D15

PROGNOSTIC ROLE OF CD73 IN METASTATIC NON-SMALL CELL LUNG CANCER ACCORDING TO THE PRESENCE OF DRIVER ALTERATIONS

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Background: The enzyme CD73 is responsible of the conversion of extracellular Adenosine Monophosphate (AMP) into adenosine (Ad). Ad has an inhibitory function on T lymphocytes and can thus be implicated in tumor immune escape. Few data exist about the CD73 role in Non-Small Cell Lung Cancer (NSCLC), particularly in presence of genetic drivers.

Material and Methods: All cases of metastatic NSCLC with available tumor tissue sample treated according to clinical practice at Istituto Tumori, Milan, between 2010 and 2018 were reviewed and classified according to the presence or not of a genetic driver. CD73 expression was determined by immunohistochemistry (Ab133582 ABCAM). Semiquantitative H score (HS) was calculated multiplying the membrane intensity score (0-3) by the % of stained cells to yield a value of 0–300. Median value of HS was chosen as a cutoff. A gene expression profiling was performed on NSCLC datasets from Tumor Cancer Genome Atlas (TCGA, n=488), and cases were divided according to CD73 median level. A Cibersort analysis was performed in these series to profile the immune infiltrate.

Results: We identified 54 EGFR Mutated (EM) cases, 28 ALK Rearranged (AR) cases and 40 Wild Type (WT) cases. Median HS of these 3 subpopulations was 0, 100 and 0, respectively. Main clinical and pathological variables were well balanced between the subgroups. Although no significant differences in outcome were observed, EM cases with high HS had a trend towards a worse OS (23.4 vs 39.5 months, p.2237), while AR and WT cases with high HS had a trend towards a superior OS (53.3 vs 25.1 months, p.1263, and 59.6 vs 18.7 months, p.5063, respectively). Cibersort analysis highlighted some differences in immune cells infiltration among the CD73 high subgroups of TCGA cases: WT ones were enriched in Treg and resting Dendritic Cells (DCs), AR had abundance of M1 macrophages, EM had a reduction in activated NK cells along with an increase in activated DCs.

Conclusions: CD73expression seems to play a different prognostic role in EM, AR and WT metastatic NSCLC. Notably, the trend towards a better outcome in AR cases with high HS may find a biological rationale in the specific inflammatory infiltrate evidenced in the analysis on TCGA. Gene expression profile using nanostring platform is ongoing on our cases to confirm these findings.

D16

INCIDENCE OF T790M IN NSCLC PATIENTS PROGRESSED TO GEFITINIB, ERLOTINIB AND AFATINIB: A STUDY ON CIRCULATING TUMOR DNA

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Background: Insights into the mechanism of resistance to first generation EGFR-TKIs may provide important information for further patient management, including the choice of second-line treatments. T790M is a gatekeeper mutation of the ATP binding pocket of the EGFR kinase domain and is the most common mechanism of resistance to first-generation EGFR-TKIs. Owing to its biologic relevance in the response of NSCLC to the selective pressure of treatments, the present study investigated in circulating cell-free DNA (cfDNA) if the occurrence of T790M at progression differed among gefitinib, afatinib, and erlotinib.

Methods: This study included patients with NSCLC bearing EGFR activating mutation, and given gefitinib (G), erlotinib (E) or afatinib (A) as first-line treatment. Plasma samples for the analysis of cfDNA were taken at disease progression (PD) and analyzed by a ddPCR using the ddPCR EGFR Mutation Assay. In selected cases, a rebiopsy was performed to confirm the absence of the T790M in negative plasma.

Results: A total of 83 patients were enrolled; 42 patients received G/E and 41 received A. Patients' characteristics were comparable across the two groups. Median time to progression (TTP) was 14.4 in G/E vs 10.2 months in A group (p=0.09). Forty-seven out of 83 patients (56.6%) were positive for the T790M in plasma. There was a higher incidence of the T790M in patients who progressed to G/E than in patients treated with A: 33 (79%) vs 14 (34%), respectively (p<0.0001, OR: 7.1, 95% CI: 2.7-18.5). To confirm the absence of the T790M, a rebiopsy was feasible in 7 patients of the G/E group and in 23 of the A group. The analysis of the cytological sample confirmed the absence of the T790M, and PI3K mutation was found in both groups in 1 patient (2%). Three patients (7%) had MET amplification in the A group. Afatinib dosage was reduced in 15 patients to 30 mg; T790M was not correlated with the dose reduction, being detectable in 6 patients who needed the reduction and in 8 who received the full standard dose (p=0.54).

Conclusions: In conclusion, even though gefitinib, erlotinib, and afatinib belong to the same class of EGFR-TKIs,differences in the appearance of resistance mutation

are demonstrated in the present study and this finding may have implications in the choice of 2nd-line treatment.

D17

HYPERPROGRESSIVE DISEASE IN ADVANCED NON–SMALL CELL LUNG CANCER PATIENTS TREATED WITH IMMUNOTHERAPY

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Background: Hyperprogressive disease (HPD) is a paradoxical boost in tumour growth described in a subset of cancer patients treated with immune checkpoint inhibitors (ICIs).
Methods: We retrospectively collected data about all consecutive patients with advanced Non-Small Cell Lung Cancer (aNSCLC) treated with ICIs at our Institution between 04/2013 and 02/2019. Patients were classified according to our previously published clinical/radiological criteria for HPD (Lo Russo G, Clin Canc Res 2018). All ICIs administered for ⩾2 cycle were admitted. Chi-square test was used to compare qualitative variables. Survival was estimated with Kaplan-Meier method. Log-rank test was used to compare curves. Multivariate analyses were performed with Cox hazard model.
Results: We reviewed 309 cases and 268 were evaluable for response. On the basis of the clinical/radiological best response obtained, we identified four categories: responders (R, 59 cases, 22.0%), patients with stable disease (SD, 74 cases, 27.6%), progressors (P, 79 cases, 29.5%), and patients with HPD (56 cases, 20.9%). Clinical/pathological variables were uniformly distributed among groups, except for a higher rate of patients with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) >1 in HPD group (p=0.0141). After a median follow-up of 23.49 months (IQR 10.72–44.21 months), median Progression-Free Survival (mPFS) and median Overall Survival (mOS) were 14,2 vs 6,6 vs 2,2 vs 1,5 months ($p < 0.0001$) and 38,9 vs 17,8 vs 7,8 vs 4,1months ($p < 0.0001$) in R, SD, P and HPD group, respectively. The multivariate analyses, between P and HPD groups, adjusted for ICIs line, number of metastatic sites and ECOG-PS according to PFS (HR 2.551, 95% CI 2.247-2.950, p<0.0001) and OS (HR 2.525, 95%CI 2.132-2.985, $p < 0.0001$) confirmed the worse outcome of HPD group.
Conclusions: Our updated analysis confirmed patients with HPD as a distinct category that performs significantly worse than other groups, including P patients.The incidence of HPD in our cohort is relevant. The ICIs' detrimental effect has to be taken into account and further investigated.

D18

THE ROLE OF OPIOIDS IN PATIENTS WITH NSCLC TREATED WITH IMMUNOTHERAPY

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Background: Opioids seem to interfere with innate and adaptive immune response. The aim of our study is to analyse a real-world sample of advanced non-small cell lung cancer (NSCLC) patients treated with immunotherapy, focusing on the prognostic and predictive impact of opioids' treatment.
Patients and Methods: we retrospectively analyzed data about consecutive patients treated with immunotherapy at our Institution for advanced NSCLC, between August 2015 and December 2018. Tumour response was assessed using the Immune-related Response Evaluation Criteria In Solid Tumors (irRECIST). Progression-Free Survival (PFS) and Overall Survival (OS) were estimated using Kaplan-Meier method. A Cox regression model was carried out for univariate and multivariate analyses.
Results: sixty-six patients were enrolled, 50 males (75,8%) and 16 females (24,2%). Median age was 72 years (range 25-88) and the majority had a good Performance Status (PS) recorded at the start of immunotherapy according to the Eastern Cooperative Oncology Group (ECOG) system (ECOG-PS <2=84.4%). Thirty-one patients (47%) received opioids at the beginning and/or during immunotherapy.
Patients receiving opioids had a poorer prognosis (mOS 5.37 months vs not reached, $p=0,0009$; mPFS 3.83 months vs not reached, HR: 4.15, CI 95% 2.22−10.66, p=0,0001). Elevated neutrophil-lymphocytes ratio (cut off 9,53) resulted as a negative prognostic factor (mOS 2.97 months vs not reached; $p=0.0049$). Patient with ECOG-PS ⩾ 2 had a lower survival (mOS 3.23 months vs not reached, p=0.0059; mPFS of 1.7 months vs 3.8 months, p=0,0089). Sex, age (cut-off 70 years), smoking history, histology, lymphopenia and PD-L1 expression did not result as prognostic and predictive factors. At multivariate analysis treatment with opioids was confirmed as independent negative prognostic and predictive factor, while ECOG-PS ⩾2 as an independent negative predictive factor. Patients requiring higher opioids' doses or opioids switch for uncontrolled pain during immunotherapy had a lower survival (mOS 4.9 vs 16.5 months; p=0,0030). A trend of worse prognosis was observed in patients receiving morphine (mOS 4.1 vs 8.6 months, p=0.059) and fentanyl (mOS 4.17 vs 8.63 months).

Conclusions: this study showed that opioid treatment and its escalation at the beginning and during immunotherapy are negative prognostic factors in advanced NSCLC. Need for concomitant opioid treatment could be considered for treatment choice in NSCLC patients.

D19

NSCLC MOLECULAR PROFILE ACCORDING TO STEPWISE ALGORITHM IN MONOCENTRIC EXPERIENCE IN NORTHERN ITALY

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Objective: Characterizing the type and frequency of main genetic alterations in non-squamous NSCLC patients whose specimens were analyzed in our institution according to a stepwise, pragmatic algorithm that included a first screening with KRAS and EGFR mutation analysis. EGFR and KRAS wild type sample were subsequently analyzed for ALK translocations, ALK wild type tumors were analyzed for ROS 1 and, in case of "quadruple wildtype" tumors, BRAF, MET, HER2 and RET were analyzed singularly or within an NGS panel.
Materials and methods: This is a monocentric retrospective cohort study conducted at the Sant'Orsola-Malpighi University Hospital. All consecutive patients whose histological specimen were analyzed in our institution between January 2014 and November 2017 were retrospectively enrolled, and data were extracted from their clinical records.
Results: 642 patients' specimen were included. 100% of specimen eligible according to our algorithm were analyzed for EGFR, 90.3% for KRAS, 78.5% for ALK, 58.3% for ROS1 and 19-26% for rarer molecular alterations. The analysis lead to the finding of 110 patients (17.1%) with EGFR mutations (54% exon 19, 35% exon 21), 202 (31.5%) with KRAS mutation (44.6% G12C, 19% G12V, and G12D, 16.6%), 18 (7.7%) for ALK, 7 (5.6%) for ROS1. Of the 48 specimens analyzed for rare mutations, 16 alterations were found. The number of eligible specimens excluded from subsequent analysis increased at each step of the algorithm, probably due to sample material exhaustion or clinical deterioration of patients.
Conclusions: Our study showed a prevalence of more common alteration (EGFR, KRAS and ALK) similar to those previously reported in Caucasian populations, while the stepwise algorithm lead to an higher rate of discovery of rarer ones, but also to an increasingly higher risk of dropout and, of course, to the lack of recognition of co-mutations. Upfront NGS sample analysis and data collection is ongoing.

D20

IMMUNE-ONCOLOGY GENE EXPRESSION PROFILES ALLOW LUNG CANCER PATIENTS' STRATIFICATION AND IDENTIFICATION OF RESPONDERS TO IMMUNOTHERAPY

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Background: Immune-checkpoint inhibitors (ICI) represent a new standard of care for Non-Small Cell Lung Cancer (NSCLC) patients. Beyond tumor PD-L1 protein expression, other biological parameters are emerging as potential

		EGFR	KRAS	ALK	ROS1	MET ampl	MET mut	RET	BRAF	HER2
Patients eligible according to stepwise algorithm		642	642	298	216	119	119	119	119	119
Patients tested (% of eligible)		714 (100%)	580 (90.3%)	234 (78.5%)	126 (58.3%)	32 (26.7%)	28 (23.3%)	30 (25%)	27 (22.5%)	23 (19.2%)
Mutated or rearranged (% of tested)		110 (17.1%)	202 (31.5%)	18 (7.7%)	7 (5.6%)	9 (28.1%)	2 (7.1%)	3 (10%)	1 (3.7%)	1 (4.3%)
Not assessed		0 (0%)	63 (9.8%)	77 (24.4%)	83 (38.4%)	81 (68%)				
Mean age (range)		66,8 years (37-90)	66,9 years (37-89)	61,7 years (40-87)	68.8 years (67-72)	63.5 years (46-79)				
Sex	M	43 (32%)	126 (60%)	8 (44%)	4	5	1	1	1	1
	F	90 (68%)	85 (40%)	10 (56%)	3	4	1	2	0	0

predictive biomarkers. We evaluated high-throughput immune-related Gene Expression Profiles (GEP) in tumor tissue from ICI-treated patients, correlating immune activation data with clinical response to immunotherapy.

Methods: RNA was isolated from tumor tissues of 44 metastatic NSCLC patients treated with Nivolumab (as 2nd or 3rd line therapy) and collected from different Italian centers. The nCounter® PanCancer IO360™ Panel was applied on NanoString platform to analyze 770 genes involved in key immuno-oncology pathways. Clinical-pathological data, as well as best response to ICI treatment, have been collected.

Results: Patients were dichotomized as responders (7 Partial Response and 19 Stable Disease) and non-responders (18 Progressive Disease). A pre-identified T-cell inflamed signature was evaluated at single gene level and the expression of *CCL5, CD27, CD276, CMKLR1, CXCL9, CXCR6, LAG3, NKG7, PDCD1LG2, PSMB10, TIGIT* was higher in the responder group, although not reaching statistical significance. Moreover, higher *STING, CGAS* and *IRF3* genes expression level appeared to be more commonly associated with non-responder patients.

Considering the disease stage at the time of diagnosis, a different gene panel (CCL5, CD27, CD274, CD8A, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PSMB10, TIGIT) resulted to be more expressed in early and locally advanced (16 from stage I to IIIA) compared to metastatic (28 stage IV) tissue samples.

Conclusions: A trend in differential expression patterns was observed between responders and non-responders NSCLC patients treated with Nivolumab and additional analyses on this cohort could reveal specific pathways able to predict unresponsiveness to ICI treatment. Different disease stage seems also to influence immune-related GEPs.

D21

INFLUENZA VACCINE IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS (ICIS): A SINGLE INSTITUTION EXPERIENCE

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Background: In cancer patients we usually recommend influenza vaccination due to the risk to develop flu-complications. In these recent years immunotherapy has emerged and, right now, there aren't clear data about recommendation of this vaccine in patients (pts) with NSCLC. Some recently published studies report controversial results about vaccine in pts treated with ICIs and a possible increase of the Immune-related Adverse Events (IRAEs).

Material and Methods: We retrospectively collected data of consecutive NSCLC pts in our institution (Fondazione IRCCS, Istituto Nazionale Tumori of Milan) treated with ICIs and who underwent influenza vaccination between September and December 2018. We selected pts subjected to inactivate influenza vaccine before or within 30 days after ICI start. The aim of our study was to collect the occurred toxicities due to flu-syndrome and IRAEs potentially related to the vaccine.

Results: Of 75 pts treated with ICIs between October 2018 and January 2019, 21 received influenza vaccine. Of those 14 pts (66.6%) were adenocarcinomas, 3 squamous carcinomas (14.3%) and 4 had other histologies (19%). Of the 21 pts, 12 received pembrolizumab (57.1%), 4 atezolizumab (19%), 4 nivolumab (19%) and 1 durvalumab (4.8%). Most were metastatic pts (95.2%); 8 were treated with ICI in 1st line (38.1%), 12 (57.1%) in 2nd or further lines and 1 as maintenance therapy for 3rd stage NSCLC (4.8%). In our cohort 6 pts (28.6%) experienced a toxicity possibly related to influenza vaccine with 1 (4.8%) death due to a pneumonitis. Other toxicities were lung infection in 2 pts (9.5%) and 2 infection of the upper respiratory track (9.5%). Only 1 patient (4.8%) develop flu infection with complete resolution.

Conclusions: In our cohort we report a substantially good safety of using influenza vaccine in pts with NSCLC treated with ICIs. Of the 6 reported toxicities reported, 5 resolved with no further consequences, whilst 1 occurred death possibly related to vaccine assumption. Safety and utility of influenza vaccine in NSCLC during treatment with ICIs remains an unanswered question and further studies with a large sample is needed to correctly assess if this vaccine gives a benefit in this kind of pts or it has even a detrimental effect.

D22

PD-1/PD-L1 IMMUNE CHECKPOINT INHIBITORS FOR PRE-TREATED ADVANCED MALIGNANT MESOTHELIOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Despite recent advances in oncology, advanced malignant mesothelioma (aMM) still lags behind other diseases due to its rarity and modest activity of standard chemotherapy. Recently, immune checkpoint inhibitors

(ICIs) directed against PD-1/PD-L1 have been tested in clinical trials in chemotherapy pre-treated aMM patients, but their efficacy is still debatable as randomized trials results are not available and single studies were characterized by small sample size.

Materials and Methods: We searched PubMed and proceedings of major meetings, to perform a systematic review and meta-analysis of clinical trials testing ICIs in this setting, describing activity in terms of Objective Response Rate (ORR) and Disease Control Rate (DCR, defined as stable disease or objective response as best response). To explore the potential predictive role of PD-L1 expression, we also collected the ORR in subgroups of patients selected for PD-L1 expression (based on the highest cut-off used in each study).

Results: 6 studies were selected (4 phase II, 2 phase IB), including 273 patients, most with pleural MM; one registry study was excluded due to inclusion of treatment-naive patients. 220 patients (80.6%) were treated with anti-PD-1 (nivolumab [N] or pembrolizumab [P]), 53 (19.4%) with anti-PD-L1 (avelumab [A]). Overall, ORR was 19.8% (95% CI, 15.5-24.9%) with no significant difference among drugs (N 22.9%, P 21.4%, A 9.4%,p=0.10); DCR was 60.1% (95% CI, 54.2-65.7%) with no significant difference among drugs (N 57.3%, P 65.2%, A 58.5%; p=0.48). When restricting the analysis to patients selected for PD-L1 expression (n=91, based on cut-offs ranging from 1% to 50% in different trials), ORR was 34.1% (95% CI, 25.2-44.3%), ranging from 18.8% to 71.4% in different trials. In unselected patients, median progression-free survival ranged from 2.6 to 6.1 months, and median overall survival ranged from 10.7 to 17.3 months.

Conclusions: To our knowledge, this is the first meta-analysis synthesizing the evidence of activity of PD-1/PD-L1 ICIs in pre-treated aMM. ORR in unselected patients is encouraging compared to historical results with second-line chemotherapy, and DCR is promising. Selection based on PD-L1 expression could increase activity, but trials were heterogeneous for test and cut-off. Results of ongoing randomized trials are needed to drive more robust conclusions on the role of these agents in pre-treated aMM.

D23

SARCOPENIA AND IMMUNOTHERAPY RESPONSE IN PRETREATED ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: The loss of muscle mass – named sarcopenia – is a common condition in NSCLC. Previous studies evidenced its detrimental effect on survival outcomes of patients treated with chemotherapy. This retrospective study investigates whether sarcopenia has a predictive role in immune checkpoint inhibitors (ICIs) treatment.

Patients and methods: We included 110 patients affected by advanced NSCLC treated with ICIs (pembrolizumab or nivolumab) and at least one previous line of chemotherapy. Weight and height were obtained from medical records when immunotherapy was started. Skeletal muscle index (SMI) was measured by the analysis of electronically stored computed tomography images obtained before the start of ICIs; sarcopenia was defined using gender-specific cutoffs by international consensus. Kaplan-Meier method and Log-Rank test were used to determine the impact of sarcopenia on overall survival (OS) and progression-free survival (PFS). Exact Fisher test and Chi-squared test were used to establish the association between the presence of sarcopenia and other variables. Median follow-up time was 20.5 months, with a median OS of 10.1 months and median PFS of 3.7 months.

Results: Ninety-two out of 110 patients were sarcopenic (83.6%): 3 of them were under weight (BMI ⩽18.5), 32 overweight/obese (BMI⩾25), 57 had a normal weight. The median OS was shorter in sarcopenic when compared to non-sarcopenic patients (8.1 vs 16.2 months; p=0.045). Overweight/obese sarcopenic patients had a trend toward a longer OS when compared to normal-weight sarcopenic patients (11.3 vs 5.6 months; p=0.071) with an OS rate at 1 year of 49.8% vs 29.6%, respectively. A shorter PFS was found in sarcopenic compared to non-sarcopenic patients, although statistical significance was not reached (p=0.054; PFS rate at 1 year: 15.6% vs 36.1%); no differences were found between overweight/obese and normal-weight sarcopenic patients (p=0.214; PFS rate at 1 year: 16.2% vs 16.9%). At univariate analysis, sarcopenia was not associated to histologic subtype, fast progression during first-line chemotherapy or performance status.

Conclusions: Sarcopenia at baseline could be a predictor of worse outcome in patients with advanced NSCLC receiving ICIs.

D24

IMMUNE GENE PROFILING AND BAYESIAN NETWORK ANALYSIS IN ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH IMMUNOTHERAPY

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Background: Immune checkpoint inhibitors (ICIs) have revoluzionized the therapeutic paradigm for different types

of cancer including NSCLC. Clinical benefit, however, is limited to a minority of patients. The only adopted predictive biomarker, PD-L1 IHC testing, suffers from some limitations. A better understanding of biomarkers associated with response to ICIs is needed. Here, we studied immune gene expression profile and association with clinical response to immunotherapy in advanced NSCLC patients (pts) treated with ICI.

Material and Methods: A total of 37 Formalin-fixed, paraffin-embedded (FFPE) samples from advanced NSCLCs were analyzed by RNA-Seq using the Oncomine Immuno Response Assay (OIRRA) (ThermoFisher Scientific) to measure the expression level of 395 genes associated with 36 functional groups including checkpoint pathways, lymphocyte regulation and cytokine interactions, using the Ion Chef and Ion Torrent PGM. Gene level differential expression analysis were performed with the Torrent Suite and Transcriptome Analysis Console (TAC) 4.0 Software. Gene network analysis based on Bayesian algorithm was performed by GeneMANIA database querying with the genes selected through mRNA expression analysis

Results: Among 37 FFPE samples only 18 showed more than 300 OIRRA detectable target genes. In this subgroup, gene expression analysis revealed 7 genes (CCR2, CRTAM, FASLG, SELL, TIGIT, TNFRSF4, and TP63) up-regulated and one gene (CXCL8) down-regulated ($p<0.05$) in ICI-responders compare to ICI-no responders. Bayesian enrichment computational analysis of the eight gene expression signature showed a more complex network which involves other 10 genes (SIRPG, GZMK, XCL2, CD8A, CD2, IFNG, SIT1, TAGAP, PTPRC and GZMH), correlated with different functional groups. Three main immune-pathways were identified ($p<0.01$) (T cell activation, leucocyte activation and migration) involving TIGIT, TNFRSF4, CCR2 and CXCL8 genes among the gene expression signature identified

Conclusions: Our results revealed an immune response gene expression signature of 8 genes differentially expressed between ICI and ICI-no responders. Cancer systems biology analysis approach strengthen our findings identifying an immune molecular network and confirm the correlation of the gene expression signature with relevant immune regulatory functions. If validated, our results may have an important role for the development of a robust test to select patients properly and predict immune response to enable precision immunotherapy

D25

LIQUID BIOPSY FOR T790M ANALYSIS IN ADVANCED EGFR-MUTATED NSCLC PATIENTS PROGRESSED TO I-II GENERATION TKI: A MULTICENTER "REAL-LIFE" RETROSPECTIVE STUDY

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Background: In advanced EGFR-mutated (EGFR+) non-small cell lung cancer (NSCLC) patients (pts), progressed to I-II generation TKI (I-II gen TKI), liquid biopsy (LB) emerged as a valid non-invasive tool to evaluate the presence of EGFR T790M as mechanism of acquired resistance. The diagnostic accuracy of circulating tumor DNA (ctDNA) in NSCLC patients progressed to prior EGFR-TKIs is associated with a wide range of concordance rate with the tumor tissue analysis. The objective of this study was to asses a "real-life" picture of EGFR T790M detection in liquid biopsy.

Material and Methods: Results of LB performed between June 2016 and October 2018 in advanced EGFR+ NSCLC pts, at disease progression (PD) to I-II gen TKIs, were evaluated retrospectively in 5 centers (Piacenza, Parma, Reggio Emilia, Modena and Bologna). All molecular procedures were performed on site, ctDNA was extracted from plasma and tested with different commercial kit (Diatech, Qiagen and Roche), all similar in term of sensibility. Analysis of detection rate and correlation with patients' characteristics were performed.

Results: 116 advanced EGFR+ NSCLC pts underwent to LB were consecutively enrolled. Median age was 67 years, 67.2% were females, 62.1% never smoker and principal histology was adenocarcinoma (83%). Distribution of metastatic site was intra-thoracic (16.4%), extra-thoracic (28.4%) and both in 55.2% pts. Median progression-free survival to I-II gen TKI was 12 months (range: 1.1-75.3). Positivity for T790M was observed in 21 pts (18.1%) at fist LB and in 8 pts at subsequent liquid re-biopsies; the overall T790M detection rate on LB was 25%. Fifty-eight out of 87 (66,7%) LB negative pts underwent tissue re-biopsy and 55.2% pts resulted positive for T790M. The overall % of T790M in the study cohort was 50%. LB performed for clinical decision before formal PD according RECIST criteria was negative for T790M in all patients ($n=25$; p 0.006). No other significant correlation was observed between distribution of metastatic site and shedding status and no sensitivity measures were possible

considering that only 3 pts performed both liquid and tissue re-biopsy.
Conclusions: This retrospective study shows that the detection of T790M positive patients progressed to I-II gen TKI in "real-life" is similar to what expected according to literature data. This result is, however, obtained with an articulated clinical course, repeated liquid biopsies and tissue re-biopsy.

D26

DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN THE MANAGEMENT OF ADVANCED NON-SMALL CELL LUNG CANCER AMONG ITALIAN MEDICAL ONCOLOGISTS: A NATIONAL SURVEY

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Background: Molecular testing is crucial for the implementation of personalized therapy in patients with lung cancer. Whether routine biomarker testing and access to personalized therapies are limited in some Italian regions is unclear.
Methods: We conducted a national cross-sectional survey between April and May 2019 among Italian oncologists to determine differences in biomarker testing and access to personalized therapies for lung cancer. The anonymous online questionnaire included 23 items across 3 sections: demographics, diagnostics and therapeutics. Institutions with at least 2 of the following criteria were defined as referral center for the purpose of this study: ⩾50 new NSCLC patients treated/year, ⩾10 active clinical trials for NSCLC, ⩾10% patients referred from other regions.
Results: Based on GIMBE report n. 3/2018, 32 respondents (39.5%) were defined as belonging from budget deficit regions (BDRs) while 49 (60.5%) as from balanced/positive budget regions (BPRs). Respondents from thoracic oncology referral centers were 10/31 (32.3%) and 18/47 (38.3%) in the BDRs and BPRs group, respectively. At least 10% of patients were referred to an outside institution according to 28.6% and 62.5% of respondents from BPRs and BDRs respectively. Diagnostic assays for EGFR/ALK/ROS1 and PD-L1 were reported to be available in 43/47 (91.5%) and 22/30 (73.3%) centers from BPRs and BDRs, respectively (P=0.05). 37/49 (69.4%) and 16/32 (50.0%) respondents from BPRs and BDRs, respectively, reported that molecular assessment was available in <15 days from biopsy. 80/81 (98.8%) oncologists reported that ⩾75% of eligible patients received 1st line targeted therapies. Reason for not administering 1st line targeted therapies was defined as clinically-unrelated (molecular testing not available or incomplete, pharmacoeconomic issues) by 28/44 (63.6%) of respondents from BPRs and 25/31 (80.6%) from BDRs (P=0.13). Among PD-L1 ⩾50% NSCLC patients, ⩾75% were reported to receive 1st line pembrolizumab by 32/49 (65.3%) and 16/32 (50.0%) of respondents from BPRs and BDRs, respectively (P=0.24). Reason for not administering 1st line pembrolizumab was defined as clinically-unrelated by 11/45 (24.4%) of respondents from BPRs and 18/31 (58.1%) from BDRs (P=0.004).
Conclusions: Disparities in access to diagnostic assay and 1st line immunotherapy exist between BPRs and BDRs. Implementing timely diagnostic testing and granting access to high-cost treatments represent an urgent need.

D27

HOST METABOLIC FACTORS AND PROGNOSIS IN PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS FOR NON-SMALL CELL LUNG CANCER

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Background: An altered host metabolism has an impact on cancer outcome, possibly mediated by several mechanisms, including hyperglicaemia, hyperinsulinemia and presence of chronic inflammation. The aim of our analysis was to evaluate the correlation between host metabolism and clinical outcome in patients with advanced non-small cell lung cancer (NSCLC), treated with immune checkpoint inhibitors (anti-CTLA4, anti PD1 and anti PDL1).
Material and Methods: The relationship between body mass index (BMI) (normal < 25 kg/m2, overweight or obese >=25 kg/m2) at baseline and outcome was assessed in 93 patients treated with immune checkpoint inhibitors in two cancer centers from January 2016 to May 2019. We also analized the relationship between presence of type 2 diabetes mellitus (T2DM) and outcome in the same population. Progression-free survival (PFS) and Overall Survival (OS) were calculated by Kaplan-Meier estimator; multivariable Cox regression was performed according to age, gender and line of treatment.
Results: Median age at diagnosis was 68 years (range 47-81); sixty-nine were males (75%); forty-six (50%) patients had BMI < 25. Median PFS was 23 months in BMI >=25 vs 12 in BMI < 25(HR 2.16; 95%CI

1.30-3.57); median OS was 39 months in BMI >=25 vs 15 in BMI < 25(HR 2.11; 95%CI 1.21-3.67). Seventeen patients (18%) were diabetics at baseline. Median PFS was 13 months in non-diabetics vs 23 in diabetics patients (HR 0.50; 95%CI 0.26-0.98); median OS was 20 months in non-diabetics vs 34 in diabetics patients (HR 0.66; 95%CI 0.32-1.33).

Conclusions: The results of our analysis show that in patients with advanced NSCLC treated with immune checkpoint inhibitors, lower BMI is associated with a significantly worse PFS and OS, independently from, age and gender. Moreover, non-diabetics patients have worse PFS and OS.

D28

CYCLOOXYGENASE (COX) INHIBITION IMPACTS THE EFFICACY OF FIRST LINE SINGLE AGENT PD-1/PD-L1 INHIBITORS (ICI) IN ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC) PATIENTS (pts)

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Background: The role of COX as a therapeutic target in cancer is controversial. Although a non-selective COX-2 inhibition by non-aspirin (NA) non-steroidal anti-inflammatory drugs (NSAIDs) may reduce prostaglandin E2 level and negatively regulate PD-1 in tumor infiltrating lymphocytes, the impact of COX inhibitors (COXi) in ICI treated NSCLC pts is still unknown.

Material and Methods: We restrospectively analized aNSCLC pts treated with 1st line ICI in a single institution. We defined baseline chronic (BC) NSAIDs administration as assumption of NA-NSAIDs for at least 3 weeks, before or within 30 days after ICI start. BC-NSAIDs association with pts' characteristics was performed by chi-square. Median overall survival (mOS) and progression free survival (mPFS) were estimated using Kaplan-Meier and compared according to BC-NSAIDs administration by log-rank test. Multivariate analysis was performed using Cox hazard proportional regression model.

Results: 64 aNSCLC pts treated with 1st-line single agent ICI were included: 64% ⩾65 years, 62% male, 37% current smokers, 44% had tumor PD-L1 expression ⩾50%, 89% ECOG performance status (PS) 0-1. At a median follow-up of 9.2 months (95% CI 6.7-11.8), objective response rate (ORR), mPFS and mOS were 39%, 7.1 months (95% CI 4.6-9.6) and 22 months (95% CI NR-NR). BC-NSAIDs were administered in 12 pts (19%), all of them received acetaminophen and 2 (16%) assumed also other NSAIDs (ibuprofen or COX-2 selective inhibitors). BC-NSAIDs didn't correlate with PS or other characteristics but was associated with significantly worse mPFS (1.8 months, 95% CI 0.1-6.2 vs 11.4 months 95% CI 4.5-18.3, $p=0.0018$). No differences in ORR and OS were observed according to BC-NSAIDs. In a multivariate Cox hazard regression model (including ECOG PS, BC-NSAIDs, gender, smoking habits, PDL-1 expression), no BC-NSAIDs administration (HR 0.36, 95% CI 0.16-0.80, p=0.02) and ECOG PS 0-1 (HR 0.19, 0.06-0.57, p=0.003) were the only variables significantly associated with better PFS.

Conclusions: BC-NSAIDs are associated with significant worse PFS upon 1st-line ICI in aNSCLC pts. Further research is ongoing to characterize how COX inhibition is related to lack of benefit from ICI.

D29

IMMUNE-CHECKPOINTS INHIBITORS IN ADVANCED NON SMALL CELL LUNG CANCER WITH UNCOMMON HISTOLOGIES

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Background: Immune-checkpoints inhibitors (ICIs) have significantly improved outcome of patients (pts) with advanced non-small cell lung cancer (NSCLC). However their benefit is still uncertain in uncommon NSCLC histotypes (UH). This study aim was to evaluate ICIs efficacy in UH.

Patients and Methods: We retrospectively collected data from consecutive metastatic NSCLC pts treated with ICIs at a single Institution from 4/2013 to 2/2019. Objective response rate (ORR) and disease control rate (DCR) were assessed. Chi square test was used to compare ORR and DCR in UH versus common histologies (CH). Univariate and multivariate survival analyses were estimated by Kaplan-Meier and Cox progression hazard models, respectively.

Results: Of 292 pts, 61 (20.9%) had UH: 14 (23%) sarcomatoid, 12 (19.7%) mucinous adenocarcinoma (ADC), 10 (16.4%) pulmonary enteric ADC, 6 (9.8%) mixed histology other than adenosquamous (ADS), 5 (8.2%) ADS carcinoma, 4 (6.5%) large cell neuroendocrine carcinoma, 10 (16.4%) other UH (poorly differentiated, NAS carcinoma, colloid ADC, signet ring cells carcinoma, salivary gland type tumour). In UH group, median age was 65 years old (range 28-83), males were 50.8% and smokers 82.0%; ECOG PS was: 0 (32.8%), 1 (52.4%) and 2 (14.8%). PD-L1 < 1%, 1-49%, ⩾50% and unknown expression

were reported in 32.8%, 24.6%, 24.6% and 18.0% pts, respectively. Twenty-two (36%) pts received ICIs as first and 39 (64%) as second or further-line. ORR was 21.3% in UH, 21.2% in CH (p=0.999); DCR was 37.7% in UH, 51.1% in CH (p=0.059). After a median follow-up of 25.0 months (m) (95% CI 21.7 – 28.3 m), median progression-free survival (PFS) was 2.6 m (95% CI 2.2-3.0 m) in UH vs 2.9 m in CH (95% CI 2.3 – 3.5 m), with p-value 0.653; median overall survival (OS) was 8.8 m (95% CI 4.8-12.8 m) in UH vs 9.2 m (95% CI 7.1 – 11.3 m) in CH, with p-value 0.756. At multivariate analyses according to OS adjusted for age, sex, smoke, ECOG PS, PD-L1 status, line of therapy and histotype (UH vs CH), only low ECOG PS and first line treatment were independent prognostic factors (p < 0.001 and p=0.006, respectively) in overall population.

Conclusions: No significant differences in ORR, PFS and OS were detected between UH and CH groups treated with ICIs. CH seem to achieve a better DCR compared to UH. The limits of our study are its retrospective nature and the heterogeneous UH sample size. Awaiting for larger specific prospective studies to better clarify the ICIs role in UH NSCLC pts.

D30

BODY MASS INDEX (BMI) AND ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS (ANSCLC): WHAT IS ITS ROLE IN THE IMMUNOTHERAPY ERA? A MONOCENTRIC EXPERIENCE

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Background: BMI and circulating markers of inflammatory status, such as neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios (NLR; PLR), are easy to be accessed and known to predict survival in several malignancies. For NSCLC, results are contradictory, and few data are available since immune checkpoint inhibitors (ICIs) introduction. We evaluated association of BMI with clinical outcome and disease control rate (DCR) of aNSCLC patients (pts) undergoing ICIs.

Material and Methods: We reviewed clinical data of aNSCLC pts treated with ICIs at our Institution between August 2013 and December 2018. We calculated BMI, NLR and PLR before ICI treatment. Pts were classified according to BMI, following WHO definition. NLR and PLR were dichotomized into high (H) and low (L), using pre-identified cut-offs of 3 and 180.

Results: A series of 188 pts (83 women, 105 men) was evaluated: median follow-up was 17,1 months (m), range (r) 3,8-68,8m, median age 68 years (r: 39-83 years), 85% of them were smokers and had ECOG performance status (PS) 0-1 (81,3%). According to BMI, 6 (3,2%) pts were underweight, 88 (46,8%) normal, 70 (37,2%) overweight and 24 (12,8%) obese.

Median PFS and OS were 5,7m (95%CI: 4-7,3m) and 9,8m (95%CI: 7,4-12,3m).

BMI was not associated neither with PFS, nor with OS.

As previously described, low PS, low number of metastatic sites, L-NLR, L-PLR and onset of immune-related adverse events (irAEs) were positively associated both with PFS and OS. In multivariate analysis, PS and irAEs maintained association with PFS (HR 1,9; 95% CI: 1,3-2,9; p=0,001 and HR 0,3; 95%CI: 0,2-0,5; p<0,001) and OS (HR 2,6; 95% CI: 1,7-4,1; p<0,001 and HR 0,3; 95%CI: 0,2-0,5; p<0,001).

In terms of DCR, increased BMI was associated with higher rate of response to ICIs (OR 1,15; 95%CI: 1,05-1,25; p=0,001). In multivariate analysis, including other characteristics significantly linked with DCR, such as low PS, low number of metastatic sites, L-NLR, L-PLR, higher PD-L1 TPS and irAEs, BMI was confirmed as an independent predictor of response (OR 1,27; 95%CI: 1,08-1,49; p=0,003).

Higher values of BMI correlated with L-PLR (OR 0,89; 95%CI: 0,83-0,97; p=0,006), but not L-NLR, consistently with previous studies on non-oncologic pts.

Conclusions: BMI has no prognostic role in aNSCLC pts treated with ICIs, whereas it seems to predict response. Conflicting results on BMI and inflammatory indexes, may derive from the fact that inflammation may be linked more to BMI composition, rather than its mere quantification.

D31

FIRST REPORT ON FREQUENCY AND TYPES OF SECOND MALIGNANCIES IN A LARGE COHORT OF MALIGNANT PLEURAL MESOTHELIOMA (MPM) FROM THE HIGH ASBESTOS POLLUTED AREA OF CASALE MONFERRATO

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Background: MPM is a deadly and rare cancer related to asbestos exposure. The only approved treatment for advanced disease is the combination of pemetrexed with platinum-derived agents with median overall survival (OS)of approximately one year. To our knowledge data about the frequency of second malignancies in MPM patients (pts) and whether they impact on treatment and prognosis is lacking. We analzysed our series to describe this topic.

Patients and Methods: We reviewed our web-base registry and selected pts diagnosed between January 1st, 2012 and December 31st, 2017 and followed at the mesothelioma unit of Alessandria and Casale Monferrato Hospitals. We used Medcalc® version17.6.
Results: 385 pts, 134 (35%) female and 251 (65%) male where included in the analysis. Median age at diagnosis was 74 (IQR 67-90; range 20-96), histology was epithelioid in 298 (77%), biphasic in 50 (13%) and sarcomatoid in 37 (10%), median OS of the whole series was 15 months (CI 95% 13,8-16,7). Sixty-one pts (16%) had a second malignancy, 26 females (42%) and 35 (58%) males, median age of this subgroup was 74 years (IQR 69-81, range 29-89), histological subtypes were epithelioid in 50 cases (82%), biphasic in 8 (13%) and sarcomatoid 3 (5%). In all cases the second malignancy was diagnosed before mesothelioma; 4 pts (1 female and 3 male) had 2 second malignancies. The most frequent second malignancy in females was breast cancer (15 patients, 58%) and in males, prostate cancer (14 pts, 42%), other malignancies were hematological (10%), thyroid, gastrointestinal and genitourinary (7% each), sarcoma and skin cancer (5% each), lung cancer (3%). Median OS of pts with second malignancies was 15,8 months (10,7-21,7). Twenty-four pts (39%) received best-supportive care only, whereas thirty-seven pts (61%) received chemotherapy for mesothelioma.
Conclusions: In our series the frequency of second malignancies is 16% and the presence of a second malignancies does not seem to influence OS nor appears related to increased age, since the median age of this subgroup of pts is in line with that of the whole series. Being asbestos a known risk factor for both tumors we would have expected a higher number of lung cancers, on the contrary the high percentage of breast and prostate cancers could not be ascribed only to their high global incidence but could imply genetic alterations such as those affecting DNA repair machinery, which are currently being actively investigated in this disease.

D32

CEA AND CYFRA 21-1 AS PROGNOSTIC BIOMARKERS OF BENEFIT AND AS A TOOL IN TREATMENT MONITORING IN ADVANCED NSCLC TREATED WITH IMMUNE CHECKPOINT INHIBITORS (ICI)

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Objective: To assess the role of pre-therapy Carcinoembryonic antigen (CEA) and Cytokeratin-19 Fragments (CYFRA 21-1) blood levels as prognostic

Variable	Univariate		Multivariate		Internal Validation
	HR (95% CI)	p Value	HR (95% CI)	p Value	BCA HR (95% CI)
ECOG PS					
0-1	1 [Reference]	< 0.001		<0.001	
2	5.04 (3.375 -7.533)		3.72 (2.30 - 6.01)		(2.08 - 8.21)
Cyfra 21-1					
⩽ 3.5	1 [Reference]	< 0.001		0.006	
> 3.5	2.52 (1.59 -3.99)		2.03 (1.22 - 3.39)		(1.22 - 4.22)
Neutrophil Lymphocyte ratio					
< 4	1 [Reference]	< 0.001		0.010	
⩾ 4	2.24 (1.54 -3.27)		1.75(1.14 - 2.67)		(1.01 - 2.87)
Liver Metastasis					
No	1 [Reference]	0.002		0.015	
Yes	1.97 (1.28 - 3.04)		1.83 (1.12 - 2.97)		(1.14 - 2.80)
Bone metastasis					
No	1 [Reference]	0.032		0.153	
Yes	1.52 (1.04 -2.23)		1.38 (0.89 - 2.15)		
CEA					
⩽ 5	1 [Reference]	0.235			
> 5	1.25(0.86- 1.83)				
Brain Metastasis					
No	1 [Reference]	0.401			
Yes	1.22 (0.77 - 1.94)				

(Continued)

Variable	Univariate		Multivariate		Internal Validation
	HR (95% CI)	p Value	HR (95% CI)	p Value	BCA HR (95% CI)
Hystologic Subtype					
Non squamous	1 [Reference]	0.864			
Squamous	1.04 (0.70 - 1.54)				
Sex					
Male	1 [Reference]	0.962			
Female	0.99 (0.68-1.45)				
Stage					
IIIB	1 [Reference]	0.138			
IV	1.72 (0.84 - 3.54)				

marker in NSCLC patients treated with ICI, and their change as an early predictor of clinical benefit.

Material and Methods: This is a retrospective cohort study including patients with stage IIIB – IV NSCLC who received nivolumab, pembrolizumab or atezolizumab in first or advanced lines of therapy in 2 institutions in Italy, Ospedale Maggiore, Parma and Policlinico Sant'Orsola, Bologna. Overall Survival (OS) was chosen as endpoint.

Results: 201 patients' clinical record were retrospectively reviewed and 167 patients with baseline CEA and Cyfra 21-1 levels were included in the analysis. Cyfra 21-1 > ULN was correlated with OS both in univariate (HR 2.52, 95% CI 1.59 – 3.99, p<0.001) and multivariate analysis (HR 2.03, 95% CI 1.22 – 3.39, p 0.006). The other factors correlated with OS in multivariate were ECOG PS of 2 vs 0-1 (HR 3.72, 95% CI 2.30 – 6.01, p<0.001), Neutrophil to lymphocyte ratio ⩾ 4 (HR 1.75, 95% CI 1.14 – 2.67, p 0.010) and presence of liver metastasis (HR 1.83, 95% CI 1.12 – 2.97, p 0.015). The model was validated with a resampling bootstrap procedure (5000 replications). Early 20% reduction after 3rd cycle (n. 25 patients) was correlated with OS for CEA, HR 0.05 (95% CI 0.01–0.41), p 0,003 and borderline for CYFRA 21-1 (n. 29 patients), HR 0.29 (95% CI 0.09 – 1.01), p 0.052 for CYFRA 21-1.

Conclusions: Our data suggests that Cyfra 21-1 pre – therapy assessment may provide clinicians with further information on the prognosis of patients treated with ICI. CEA and CYFRA 21-1 repeated measures could be useful as an early surrogate marker of benefit.

D33

IMPACT OF TUMOR BURDEN IN ADVANCED NSCLC PATIENTS TREATED WITH IMMUNOTHERAPY

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Background: Characteristics of non-small cell lung cancer (NSCLC) patients who may benefit from immunotherapy are still controversial. We analyzed the prognostic role of tumor burden (TB) in a real-world sample of advanced NSCLC patients receiving immunotherapy.

Patients and Methods: we retrospectively collected data about consecutive advanced NSCLC patients treated with immunotherapy in first or second-line at our Institution, between August 2015 and February 2019. Tumor response was assessed using Immune-related Response Evaluation Criteria In Solid Tumors (irRECIST). TB was recorded at baseline considering: sites and number of metastases; thoracic or extrathoracic disease; measurable disease (MD) vs not-measurable disease (NMD); dimensional aspect both as the largest tumoral lesion's diameter (cut-off=3.7 cm) and the sum of the five largest lesions' diameters (cut-off=14.3 cm) calculated with ROC curve. Progression Free Survival (PFS) and Overall Survival (OS) were estimated using Kaplan-Meier method. A Cox regression model was carried out for univariate and multivariate analyses.

Results: sixty-five patients were enrolled, 50 males (77%) and 15 females (23%). Median age was 73 years (range 25-88). Nineteen patients received immunotherapy as first-line, 46 as second-line treatment. Women had a poorer mOS (4.9 vs 16.5 months, p=0.0363) and mPFS (3.9 vs 5.7 months, p=0.0248) compared to men. Poor performance status (PS-ECOG> 2) at the start of immunotherapy resulted as negative prognostic factor (mOS 1.9 vs 13.3 months; p<0.0001). Bone metastases (BM) had a negative prognostic and predictive impact (mOS 5.4 months vs not reached, p=0.0036; mPFS 3.0 vs 8.6 months, p=0.0037). Patient with NMD had a poorer prognosis (mOS 5.3 months vs not reached; p<0.0001), while MD was predictive of response to immunotherapy (mPFS 12.2 months vs 3.8, p=0.0199). Pulmonary, lymphatic, hepatic, cerebral, adrenal and pleural involvement had no impact on survival. Number of metastatic sites ⩾ 3 was a negative predictive factor (mPFS of 4.2 vs 24.2 months; p=0.0423). The dimensional aspect of TB, did not show a prognostic or predictive role. At multivariate analysis, sex,

ECOG-PS, BM, MD were prognostic factors ($p<0.0001$), while BM and sex were confirmed as predictive factor ($p=0.0015$).

Conclusions: although the definition of tumor burden is still controversial, our study underlined the impact of BM and MD on survival in advanced NSCLC patients treated with immunotherapy.

D34

FORCE (FOCUS ON RESEARCH AND CARE): A COMPREHENSIVE LIFESTYLE TEAMWORK INTERVENTION TO MODULATE IMMUNOLOGICAL STATUS AND TREATMENT OUTCOME IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Nutrition, physical activity, and psychological well-being profoundly impact on prognosis and treatment outcome. The hypothesis that a comprehensive lifestyle intervention may improve the outcome of immune checkpoint blockade (ICB), by modulating the cancer-immunity balance, represents a fascinating and unexplored research area.

Patients and Methods: The FORCE team, composed by oncology-trained dietitians, kinesiologists, and psychologists, provides: i) nutritional screening, assessment, and tailored counselling; ii) personalized physical exercise program; iii) psychosocial distress and anxiety assessment and control, using cognitive-behavioral techniques. We aim at evaluating whether such a comprehensive lifestyle intervention modulates tissue- and blood-based immunological parameters and improves ICB outcome in NSCLC.

Results: We are currently validating tissue- and blood-based immunological signatures, as potential intermediate biomarkers for sensitivity/resistance to ICB. Moreover, preliminary data demonstrate that: i) malnutrition has a detrimental impact on survival of NSCLC patients, including ICB-treated patients; ii) only 10% out of 405 of cancer patients are sufficiently active, while 80% would be willing to start a supervised training program; and iii) cognitive-behavioral therapy effectively controls anxiety, depression and distress levels in breast cancer and NSCLC. Based on these premises, we plan to prospectively evaluate whether an integrated lifestyle intervention (nutritional support, physical activity, psychological intervention), carried out by the FORCE team, modifies intermediate immunological parameters, as a proxy for ICB outcome, in advanced NSCLC patients. In parallel, potential mechanisms of immune modulation will be modelled in suitable animal models in preclinical trial(s). If the following premises: i) tissue/blood-based signatures effectively predict ICB outcome and ii) integrated lifestyle intervention modifies intermediate immunological biomarkers, are fulfilled, we will proceed to design a randomized trial to test whether a comprehensive lifestyle preconditioning affects outcome in advanced NSCLC undergoing ICB.

Conclusions: This project is unique in fact it combines a comprehensive approach to patients' well-being with a rigorous scientific method aimed at assessing the immune competence status, with the ultimate goal of improving ICB efficacy through a patient-centred approach.

D36

SAFETY OF COMBINED PD-1 PATHWAY INHIBITION AND INTRACRANIAL RADIATION THERAPY IN BRAIN METASTASTIC NON-SMALL CELL LUNG CANCER

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Background: Brain metastases are the leading cause of death and morbidity in lung cancer patients and are frequently managed with radiation therapy (RT). At the moment, however, the safety of this approach with immunotherapy (PD-1/PD-L1 inhibitors) is not yet established.

Material and Methods: All patients, affected from brain metastases from lung cancer who received PD-1/PD-L1 inhibitors and RT, from November 2015 to December 2018 were retrospectively reviewed. Adverse events related to radiotherapy were retrospectively evaluated and analyzed, not only in relation to radiotherapy treatment (cranial RT type and timing of RT) but also in relation to the immunochemotherapy treatment received.

Results: Of 33 patients analyzed, with a median of follow-up of 3 months, of these 18 cases were treated with PD-1/PD-L1 inhibitors. Overall, 30 (91%) and 3 (9 %) patients received whole brain RT (WBRT) and stereotactic radiosurgery (SRS) and/or whole brain RT (WBRT), respectively.

We found no significant differences in adverse events among patients treated with PD-1/PD-L1 inhibitors and patients not treated with PD-1/PD-L1 inhibitors and among patients treated with PD-1/PD-L1 inhibitors and with the various types of radiotherapy. Furthermore, no difference

was found on the time of PD-1/PD-L1 inhibitors administration and the RT.
Conclusions: The study shows that the combined treatment of intracranial irradiation with PD-1 / PD-L1 inhibitors is not associated with an increase in adverse events RT-related, although validation studies of this therapeutic option are needed.

D37

DURABLE RESPONSE TO NIVOLUMAB IN ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS: A MULTI-INSTITUTIONAL REAL LIFE EXPERIENCE

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Background: In pre-treated advanced NSCLC Nivolumab improved Ovearall Survival (OS) versus Docetaxel, as showed in two randomized phase III trials. Updated results confirmed long-lasting responses and higher survival rates in a subset of patients (pts) with different baseline characteristics.
Patients and Methods: we collected the data of advanced NSCLC pts treated with N for at least 24 months. Baseline parameters were available. Responses to treatment were evaluated according to Response Evaluation Criteria in Solid Tumors, version 1.1, and immune-related adverse events (irAEs) were reported according to Common Terminology Criteria for Adverse Events, version 5.0.
Results: From June 2015 to the time of analysis, 53 advanced NSCLC pts were selected. Median age was 68.2 years; males were 74%, females 26%; the majority of pts (92%) were current or former smokers and 55% had metastatic disease at diagnosis. PS ECOG was 0/1, squamous 47% and non-squamous 53%. No EGFR mutation or ALK rearrangement was recorded. 59% of pts had at least 2 metastatic sites at the start of N: bone in 20%, brain in 13%, adrenal in 9%, and liver metastasis in 0.5%. The majority of pts (80%) had a thoracic metastatic disease. Median number of N administrations was 62 (35-89); median time to best response was 6.4 months (2-20): 3 complete responses, 34 partial responses and 16 disease stabilizations were observed. At the time of the analysis, 47 pts (90%) are alive and 37 (70%) are still on treatment with N. N was interrupted in 16 pts: 7 disease progressions, 2 pulmonary and pancreatic severe adverse events and 7 other causes. No treatment-related deaths were observed. 3 pts (5%) had G3-4 irAEs (pulmonary, pancreatic and G3 glossitis), 40 (75%) had G1-2 irAEs (mainly skin toxicity, asthenia, diarrhoea and hypothyroidism). No irAE was reported in 20% of pts. Median Progression Free Survival was 30.7 months (16.8-42.4). Median OS from the start of N was 31.9 months (18.9-42.4). Median OS from the diagnosis of metastatic disease was 44 months (14.3-71.2). Six patients received further therapies.
Conclusions: This multi-institutional experience of pts treated with N monotherapy for at least 2 years, confirm the efficacy and safety of this drug, with an impressive long-term survival and durable responses in a peculiar subset of patients, mainly current or former smokers, with mutation-negative, squamous and non-squamous NSCLC. Further analysis of the present series are ongoing.

D38

EVALUATION OF THE CORRELATION BETWEEN DIVERTICULOSIS AND THE ONSET OF DIARRHEA IN PATIENTS WITH LUNG CANCER TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background: Immune checkpoint inhibitors anti-PD-1 (Nivolumab and Pembrolizumab) and anti-PD-L1 (Atezolizumab) represent a remarkable advance in non-small-cell lung cancer (NSCLC) treatment with impressive clinical activity and durable responses in some patients. However, immunotherapies generate new toxicity profiles called immune-related adverse events (irAEs) that require specific management. Gastrointestinal (GI) irAEs (diarrhea and colitis) are among the most common and if they are left unrecognised or untreated, they can become life threatening. Therefore, the identification of the risk factors for the development of diarrhea could be helpful for the prevention and management of GI irAEs. Among these, the presence of diverticulosis/diverticulitis could affect the onset of diarrhea.
Material and Methods: This retrospective analysis was conducted in 94 patients with metastatic NSCLC who received Nivolumab at the Papa Giovanni XXIII Hospital in Bergamo between 2015 and 2017. We evaluated the presence of diverticulosis/diverticulitis before the start of

immunotherapy, the onset, the degree and management of diarrhea during therapy and the correlation between the presence of diverticulosis and GI irAEs.

Results: All patients had previously been treated with chemotherapy. 90 patients (95.7%) received Nivolumab at a dose of 3mg/kg. The remaining 4.3% received Nivolumab flat dose of 240mg. The response rate was 14% and the disease control rate was 45%. The median PFS has not yet been reached. 19 of 94 patients (20%) had a radiological diagnosis of diverticulosis before the start of treatment and 11 of 94 patients (12%) developed diarrhea during the therapy. While of the 75 patients without diverticulosis only 7% developed diarrhea (5 total patients), 32% of patients with diverticulosis developed diarrhea (6 patients). The chi-square test was used for statistical analysis. GI irAEs were in most cases of grade 2 and were treated with benefit with steroid therapy without having to resort to other types of immunosuppressive therapy such as infliximab. No patient discontinued treatment due to adverse event.

Conclusions: In our population, the presence of diverticulosis/diverticulitis increases the risk of gastrointestinal irAEs. However, these patients can be treated with immunotherapy but they represent a risk class for the onset of diarrhea. Therefore, multicenter and prospective studies are needed to improve the management of this subgroup of patients.

D39

PROGNOSTIC VALUE OF LUNG IMMUNE PROGNOSTIC INDEX (LIPI) IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (aNSCLC) TREATED WITH FIRST-LINE PEMBROLIZUMAB

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Background: Immune checkpoint inhibitors (CPI) are playing a central role in the management of aNSCLC patients. However, the lack predictive of response biomarkers is challenging for oncologists in patients selection. A recent study reported that the pretreatment LIPI was related to worse outcomes of patients treated with CPIs (Mezquita L et al, Jama Oncol 2018).

Patients and methods: We retrospectively reviewed the clinical records of patients with aNSCLC who received pembrolizumab as first-line treatment from August 2017 to April 2019. The pretreatment complete blood cell (CBC) counts and LDH values were evaluated in order to calculate LIPI. The score was based on neutrophil/lymphocyte ratio, which was dichotomized by using three as cut-off (ratio $\leqslant 3$ and > 3 were scored 0 and 1, respectively), and lactate dehydrogenase (score 0 and 1 indicated values $\leqslant$ and $>$ upper limit of normality respectively). The LIPI score defined two prognostic groups: good (score 0) vs intermediate-poor (score 1 or 2). The primary endpoint was the overall survival (OS). The secondary end-point was the disease control rate (DCR).

Results: We considered a consecutive series of 28 patients with PDL1 $\geqslant$ 50% at immunohistochemical analysis. Most of them was male (60.7%), with adenocarcinoma (53.6%) and a performance status of 0 (71.4%). The median age at diagnosis was 72 (range 52-81) years. LIPI score was 0 in 16 pts, 1-2 in 12 pts. After a median follow-up of 7 months, the median OS was 16.4 (95% CI 12.4 – 20.4) months in the good prognosis group vs 11.8 (8.3 – 15.3) months in the intermediate-poor group ($p<0.385$). In the 22 patients evaluable for response, the DCR was 83.4% and 70% in the good and intermediate-poor prognosis group, respectively.

Conclusions: Although the small number of evaluated patients reduced the power of the present study, our preliminary data seem to confirm that higher LIPI score is related to worse survival and response outcomes for aNSCLC patients treated with pembrolizumab as first line, suggesting that LIPI might be a useful tool to select patients for immune checkpoint inhibitors treatment.

D40

BREATH ANALYSIS: NEW KEY-CHALLENGES FOR EARLY DETECTION OF LUNG AND PLEURAL NEOPLASMS

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Background: The growing interest about breath analysis relies on the need of tools to get an early diagnosis of respiratory pathologies with high mortality rate such as lung cancer (LC) and malignant pleural mesothelioma (MPM). Nowadays the key-challenge of the scientific community is the search for non-invasive diagnostic biomarkers able to identify patients at risk of developing cancer or with early stage cancer. The analysis of Volatile Organic Compounds (VOCs) pattern in human breath for early detection and follow-up of diseases such as cancer is low-cost, non-invasive and promising alternative to traditional exams.

Methods: This study is based on the development and validation of a methodological approach to identificate VOCs breath pattern to discriminate between patients affected by both LC and MPM, and healthy controls (CTRL). A total of 80 breath samples from 36 patients with LC, 14 patients with MPM and 30 CTRL have been collected into inert Tedlar bags, transferred to sorbent tubes (biomonitoring, Markes) and analysed by TD-GC/MS.

Results: Non parametric test as Wilcoxon/Kruskal Wallis tests (R version 3.5.1) allowed to identify the most

weighting variables in discrimination between LC, MPM and HC breath samples. On the basis of p-values lower than 0.05 (selection between CTRL and LC, and between CTRL and MPM) and current knowledge on metabolic processes, a multivariate statistics (Principal Components Analyses (PCA) -PAST 3.20) has been applied on breath samples, considering only selected variables. The preliminary statistical elaboration by PCA of data collected from the analysis of LC and CTRL samples have shown two principal components: PC1 characterized by higher loadings of benzoic acid, methylcyclohexane and hexanal, and PC2 characterized by high loadings for dimethyldecane, pentane and pentanal. Similar results were obtained by PCA applied to MPM and CTRL breath samples considering 2-methylpentane, cyclopentane, hexane and 2-butanone as discriminant variables.

Conclusions: PCA was able to discriminate between LC and CTRL and between MPM and CTRL breath samples. Leave-one-out cross-validation method was applied to calculate the prediction accuracy obtaining good sensitivity (88%), accuracy (86%) and specificity (92%).

Further investigation about breath analysis is strongly warranted, due to the need of biomarkers potentially useful both for the screening of high-risk subjects and for the early diagnosis of lung and pleural neoplasms.

D41

ACCURACY OF PATHOLOGIC DIAGNOSIS OF THYMIC EPITHELIAL TUMORS: A SINGLE INSTITUTION EXPERIENCE

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Background: Rare tumors often constitute a diagnostic challenge for Pathologists. Indeed, referral to a Center with a high expertise in the field is crucial in obtaining the right diagnosis. This is particularly true for Thymic Epithelial Tumors (TETs), whose treatment strategies vary widely according to specific histological subgroup. We aimed at evaluating the accuracy of pathologic characterization of TETs comparing the initial pathological diagnosis with the second opinion obtained in a reference Center.

Material and Methods: All the cases with a diagnosis or a suspicion of TET, which underwent a pathological second opinion at Istituto Nazionale dei Tumori (INT), Milan, between 2010 and 2019 were retrospectively reviewed. Descriptive statistics were used for qualitative variables. Concordance between diagnoses was estimated through Cohen's kappa (k).

Results: Two hundred seventy-eight cases was identified, for a total of 72 pathologic revisions. Of them, 5 cases were initially diagnosed as thymoma A, 3 as thymoma AB, 5 as thymoma B1, 15 as thymoma B2, 7 as thymoma B3, 8 as thymoma Not Otherwise Specified (NOS), 17 as thymic carcinoma, 8 as carcinoma NOS, 3 as carcinoma with different histology, one as lymphoblastic lymphoma. INT pathologic revision changed the diagnosis in 41 (56.9%) cases, with a potential shift in therapeutic approach in 32 (44.4%). In particular, 12 cases of carcinoma NOS or lymphoma were reviewed as thymic carcinoma (10 cases) or thymoma (2 cases); 11 cases of thymoma were reviewed as different thymoma subtypes (9 cases), or thymic carcinoma (one case), or diffuse large B cell lymphoma (one case); 9 cases of thymic carcinoma were reviewed as cases of thymoma (7 B3, 2 B2). Concordance between Pathologists was moderate for the initial diagnosis of thymoma (74.7%, k 0.447), while it was slight for the initial diagnosis of thymic carcinoma (60.5%, k 0.139).

Conclusions: A significant percentage of cases referred to INT for a presumptive TET received a different histological characterization by the pathological second look. A potential radical shift in therapeutic indication was not rare. Therefore, the experience of our Center underlines the importance of patients' referral to Institutions with high pathological expertise, for TETs as well as for other rare diseases.

D42

CLINICAL CHARACTERISTICS AND BIOLOGICAL PROFILE OF LUNG ENTERIC ADENOCARCINOMA

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Background: Lung Enteric Adenocarcinoma (LEA) is a rare variant of Lung Adenocarcinoma (LA), defined by an intestinal differentiation in ⩾50% of tumor and ⩾1 colorectal biomarker at immunohistochemistry. Due to its low incidence, clinical and biological characterization is scarcely known. We investigated this topic through a comparison between Institutional LEA series, and the cases of both LA and Colorectal Cancer (CC) derived from Tumor Cancer Genome Atlas (TCGA).

Material and Methods: All consecutive cases of LEA diagnosed at Istituto Nazionale dei Tumori (INT), Milan, between 01/2013 and 12/2018 were retrospectively reviewed. Next Generation Sequencing was performed with IonTorrent (ThermoFisher Scientific, Life Technologies) by using the commercial Hot Spot Cancer Panel (HCP) on DNA derived from on formalin-fixed paraffin-embedded tissues. ALK and ROS1 status was assessed with fluorescent in

Gene mutation	INT LEA (N = 38)	TCGA LA (N = 660)	TCGA CRC (N = 534)
	%	%	%
TP53	52.6	54.1	58.8
KRAS	34.2	32.4	40.8
STK11	23.7	15.8	1.1
CDKN2A	15.8	3.9	0.6
APC	7.9	4.8	72.5
CTNNB1	7.9	3.8	6.2
EGFR	7.9	15.8	2.8
KIT	5.3	2.1	4.9
PI3KCA	5.3	5.9	14.7
SMAD4	5.3	4.1	12.9
ATM	2.6	8.9	13.1
BRAF	2.6	8.2	11.6
FGFR3	2.6	0.8	3.2
NRAS	2.6	0.6	6.2
PDGFRA	2.6	7.4	5.1

situ hybridization. PDL1 was determined with DAKO22C3. The incidence of mutations in the genes analyzed by HCP were compared to that reported in TCGA for LA and CC.

Results: Thirty-eight cases of LEA were identified. As regards clinical variables, major differences from TCGA series were a higher prevalence of female gender (34.1% vs 51.9%) and advanced stage (stage III-IV 94.8% vs 9.0%); both case series were mostly composed by current or former smokers (76.3% vs 78.9%). The following table shows the comparison in the frequency of specific gene mutations between INT patients and TCGA case series.

No INT cases showed either ALK or ROS1 rearrangement. PDL1 expression was negative in 23 cases, 1-49% in 9, not evaluable (NE) in 6. All cases were microsatellite-stable except 3 cases with low instability and 3 NE.

Conclusions: The biological characteristics of INT LEA showed more similarities with the profile of LA than with that of CC. Nonetheless, we identified a higher incidence of STK11 and CDKN2A mutations, and a lower incidence of ATM, BRAF, PDGFRA and EGFR mutations than those reported in TCGA. Therefore, the profile of LEA seems partially different to that of common LA, deserving further investigation in large multicentric series.

D43

CHECK-POINT INHIBITORS (CKI) TREATMENT IN CLINICAL PRACTICE: WHERE DO WE STAND?

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Background: More and more data come available on real-life toxicity and efficacy of CKi in non-small cell lung cancer (NSCLC) patients (pts). However, insights on clinicians' attitude and adherence to international and national guidelines when using CKi are still missing. The main objective of this survey was to obtain a clean snapshot of physicians' personal attitude toward CKi use in daily practice and to compare it with (retrospective) real-life CKi data of these centres.

Methods: A selected group of physicians from high-volume European centres were requested to complete two sequential online questionnaires with 30 open and multiple-choice questions that assessed their (1) view and (2) to collect data on CKi treatment of all NSCLC pts who were treated, not in clinical trial, between 01-Jan and 30-Sep-2017. Descriptive statistical analysis was applied to assess the preliminary results.

Results: All fourteen centres (53.3% general, 20% university, 6.7% private hospital, 20% oncological centre) provided a response. The real-life data analysis is still ongoing. In most sites (6; 49.1%) CKi were administered as second line (80% or more of all treated pts). Before initiating CKi treatment, ECOG PS and PD-L1 expression were considered important by 100%, followed by concomitant steroids (86.1%) and interstitial lung disease (60%); 46.6% considered the smoking status and less than 15% considered age and tumor load. Most participants (86.1%) allowed pts on low dose steroids (less than 10 mg prednisone or similar); the majority (60%) allowed radiotherapy treatment either by applying a washout period (13.3%) or depending on the irradiated site (46.7%). Asymptomatic or stable brain metastases were no reason to exclude pts from CKi for 86.6%. CKi were mainly interrupted due to radiological (40%) or clinical progression (46.7%) while 46.7% continued treatment even beyond radiological progression. A worse outcome or toxicity than expected from clinical trials with CKi was perceived by 20% and 26.7%, respectively.

Conclusions: Even considering limitations due to the retrospective dataset, this is among the earliest reports on physicians'personal opinion and experience with CKi in NSCLC pts. Final data will be presented at the ELCC conference.

D44

DETECTION OF CLINICAL AND SUB-CLINICAL MALNUTRITION IN ADVANCED NON-SMALL-CELL LUNG CANCER PATIENTS AND ASSOCIATION WITH OUTCOME

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Background: Weight loss and lean body mass wasting are highly prevalent in non-small-cell lung cancer (NSCLC) patients (pts). Nevertheless, nutritional problems are often misdiagnosed. This study aimed to assess the prevalence of malnutrition and its correlation with outcome in advanced (A)-NSCLC pts.

Patients and Methods: A-NSCLC pts treated at AOUI of Verona (2016-2018) received nutritional counseling by a qualified dietitian. Nutritional Risk Screening (NRS) 2002 was used to estimate the nutritional risk. Bilateral psoas major muscles were measured at L3 vertebrae level with routine staging-computed tomography (CT). Changes in psoas muscles were evaluated using Wilcoxon signed-rank test. Data were correlated to progression-free/overall survival (PFS/OS) and response rate (ORR) using a Cox and logistic regression model. Kaplan-Meier curves were compared with Log-Rank.

Results: Data from 38 pts (20 males [52.6%], 18 females [47.4%]) were gathered, with a median follow-up of 21 months (range 1-197). At baseline, 18.4% were underweight, 18.4% normal weight, 34.2% overweight and 31.6% obese. The majority (65.8%) were at risk of malnutrition (NRS$\geqslant$3). At multivariate analysis, stage (HR 4.99, 95% CI 1.05-27.74, $p = 0.04$), performance status (HR 4.99, 95% CI 1.55-16.03, $p = 0.007$) and NRS (HR 7.61, 95% CI 1.52-38.11, $p = 0.01$), were significant independent predictors for PFS. Pts with baseline NRS$\leqslant$3 had significantly longer 1-year PFS (58.6% vs 16.7%, $p = 0.04$) and 2-year OS (90.6% vs 68.3%, $p = 0.03$) and a better ORR than those with NRS $>$ 3 (66.7% vs 21.4%). A significant loss in psoas muscle mass was detected in pts treated with both immunotherapy and other therapies ($p = 0.01$ and $p = 0.002$, respectively). Of interest, in immunotherapy-treated pts (n = 16) loss in psoas muscle mass correlated with worse ORR, PFS and OS, although differences did not reach a statistical significance.

Conclusions: Malnutrition was common and related to poor ORR, PFS and OS in A-NSCLC pts. Notably, in pts treated with immunotherapy, muscle mass wasting seems to impact on efficacy outcome, suggesting a potential interaction between immunological and nutritional parameters. The introduction in the clinical routine of comprehensive nutritional profiling and monitoring is highly recommended in A-NSCLC. A comparison between NSCLC pts who underwent a tailored nutritional intervention during therapy and who did not is ongoing, together with a series of biomolecular analysis.

D45

REAL WORD MULTI-INSTITUTIONAL EXPERIENCE: USE OF LIQUID BIOPSY IN NON-SMALL-CELL-LUNG CANCER

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Background: Circulating tumor DNA (ctDNA) is a recognized valid option for EGFR testing when resistance to I-II generations TKI-therapies occurs or if tumor is not easily amenable to sample. Multidisciplinary approach and patient context are crucial for accurately interpreting molecular findings and guarantee an optimal management of non-small cell lung cancer (NSCLC) patients.

Material and Methods: Aim of the study was describing the use of EGFR testing by liquid biopsy in clinical practice of seven major lung-cancer centers in North Eastern Italy. A multi-regional survey about clinical practice of EGFR ctDNA testing in the period January-December 2018 was conducted.

Results: Overall 360 samples (316 patients) have been tested for EGFR on ctDNA, with a medium number of 1.1

samples/patient. All institutions used commercially available real time CE-IVD tests on two different diagnostic platforms. NGS or droplet digital PCR were used by one center each, as second level confirmation methods.
Among all patients tested, 108 (34%) were upfront analysis at the time of diagnosis with an EGFR mutation rate of 15%. At progression to TKI treatment 208 (66%) patients were tested with a T790M+ rate of 45%. Cases negative for both T790M and known actionable mutation were 86 (41%) and were considered inconclusive with indication to histological/cytological re-biopsy given by all centers. In all centers blood drawing was performed in the same hospital of EGFR testing and collected in EDTA tubes. Plasma separation was performed within 30 minutes (43%), 1 hour (43%) and 2 hours (14%) by the same laboratory who did EGFR testing. Molecular analysis was done in Surgical Pathology Department in 6/7 (86%) institutions and in 1/7 (14%) in Oncologic Molecular Pathology Laboratory. Reports were drawn up within 24 hours in 3/7 (43%) centers and within 3-5 working days in 4/7 (57%) centers by biologist 6/7 (86%) or oncologist 1/7 (14%).
Conclusions: The multi-institutional survey about EGFR testing in ctDNA showed a technical approach substantially coherent with national guidelines and literatures data among interviewed centers. We noticed a significant proportion of liquid biopsies at the time of diagnosis mainly related to a reference center collecting specimens from several institutions. However overall, our experience induces to reconsider sampling workflows aimed to obtaining specimens suitable both for cito-histological diagnosis and multitargeted molecular profiling.

D46

ASSOCIATION BETWEEN OPIOIDS AND OUTCOME OF 1ST LINE IMMUNOTHERAPY IN ADVANCED NON-SMALL-CELL LUNG CANCER(aNSCLC) PATIENTS(pts): A RETROSPECTIVE EVALUATION

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Background: Opioids represent a backbone of cancer-related pain treatment. Preclinical studies suggest that opioids can cause immunosuppression. We aimed at retrospectively evaluate the impact of chronic opioid treatment on the outcome of aNSCLC pts treated with 1st line ICIs.
Materials and Methods: We reviewed the records of aNSCLC pts treated with anti-programmed-death-1 (PD-1) or its ligand (PD-L1) single-agent ICIs in 2 Italian institutions. We included all pts with enough follow-up to have at least one radiological evaluation during treatment. Pts with rapid clinical progression were included in the analysis. We analyzed response rate (RR), progression-free survival (PFS), and overall survival (OS). Response was evaluated using RECIST v1.1 criteria.
Results: 75 pts were found, 64 included in the analysis. Mean age at diagnosis 66.5 years (range 37-84), 65% male. Histological type: 76.5% adenocarcinoma, 14% squamous, 9.5% others, most with high PD-L1 expression (90.5% with = 50% TPS). 58 pts (90.6%) were stage IV at ICIs start, with mean number of metastatic sites 1.8. Most pts were current/former smokers (87.5%); ECOG performance status (PS) at ICI start: 0 in 34 pts (53.1%), 1 in 25 (39%), 2 in 5 (7.9%). 20 pts were receiving opioids at ICIs start (31.3%), with a mean daily dose equal to 59 mg of oral controlled-release morphine. Median follow-up was 10.9 months. Median number of ICIs cycles was 7.5 (range 1-26). RR, mPFS and mOS were 40.6%, 9.4 months and 17.1 months, respectively. Compared to the others, pts receiving opioids had numerically lower RR (45.5% vs 30.0%, $p = 0.24$), a shorter PFS (median 12.7 vs 1.7 months, Hazard Ratio [HR] 4.16, 95%CI 2.15-8.05, $p < 0.001$) and OS (median not reached vs 3.2 months, HR 4.68, 95%CI 2.09-10.52, $p < 0.001$). At the multivariate analysis, opioid use continued to be significantly associated with worst PFS (HR 3.19, 95%CI 1.45-7.01, $p = 0.004$) and OS (HR 4.16, 95%CI 1.61-10.76, $p = 0.003$), even when accounting for PS, disease stage and number of metastatic sites.
Conclusions: Our results suggest a possible detrimental effect of opioids in aNSCLC pts treated with 1st line single-agent ICIs, even when correcting for other prognostic factors. Due to the short follow-up, the small number of pts, and the lack of a control group, our results should be considered exploratory.

D47

PEMBROLIZUMAB FOR THE FIRST LINE TREATMENT OF ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC): A "REAL LIFE" EFFECTIVENESS STUDY

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Background: Pembrolizumab is considered the gold standard in the first line treatment of advanced NSCLC with a PD-L1 tumor proportion score of 50% or greater.

Patients and Methods: Since September 2017, we have been prospectively recording all patients treated in ATNO with Pembrolizumab at the dose of 200 mg every 3 weeks in the first line setting. Patients had to have, accorging to AIFA indications, an ECOG-PS of 1 or less, a measurable disease and an adequate organ function. Key exclusion criteria included an history of systemic immunosuppressive therapy or active autoimmune disease. The PD-L1 expression was assessed at a central laboratory with the use of the commercially available PD-L1 SP263 antibody (Ventana platform). Responses and toxicities were evaluated by using RECIST criteria version 1.1 and the National Cancer Institute common terminology criteria (NCI-CTC 4.0 version), respectively. All patients were recorded and analyzed according to the intention-to-treat principle. The Kaplan method was used to plot progression-free survival (PFS) and overall survival (OS).

Results: Fifty-five patients were enrolled, 16 (29%) females and 39 (71%) males; histology was adenocarcinoma in 47 cases (85%), squamous carcinoma in 7 cases (13%) and unspecified NSCLC in 1 case (2%). Median age was 70 years (range 41-84); The median value of PD-L1 was 70% (50-95%). Thirty patients had a performance status (PS) = 0, 23 patients a PS = 1, and 2 patients a PS = 2. At the time of this analysis, the median number of administered courses was 5 (range 1-30) and 41/55 patients were evaluable for response: 18 PRs (44%), 13 SDs (31.7%) and 10 PDs (24.4%); 29 patients (53%) were on treatment. We observed G3-4 toxicity in 5 patients (9%) that led to treatment discontinuation in 4 patients.

Conclusions: Our preliminary results suggest that the activity of Pembrolizumab administered in a "real life" contest was comparable to that of literature although the median age of our population was higher (70 years); An update of the results will be presented at the meeting

D48

CLINICAL-PATHOLOGICAL CHARACTERISTICS AND OUTCOME ANALYSIS OF PATIENTS WITH ORAL METASTASES FROM LUNG CANCER: A MULTICENTER RETROSPECTIVE STUDY

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Background: Oral metastases are a rare event, accounting to less than 1% of all oral malignancies, sometimes being the first manifestation of a wide-spread disease. Irrespective of the site of the primary tumor, patients with oral metastases have a poor prognosis, with a reported median overall survival (mOS) of 6 months. Lung cancer, particularly adenocarcinoma, represents the main source of oral metastases, even if large datasets still lack. We conducted a multicenter retrospective study investigating incidence, clinic-pathological features and outcome of patients with oral metastases from lung cancer.

Methods: Between January 2014 and April 2019 we collected data from all consecutive patients diagnosed with lung cancer in four oncological Italian centers. Clinical-pathological features of those patients with oral metastases involving jaw or/and soft tissues were described.

Results: Among 4,846 consecutive lung cancer patients, the incidence of oral cavity metastases was 0.17% (8 out of 4,846 patients,). Patients were more frequently male (7 out of 8, 87.5%), current or former smokers (6 out of 8, 75%), with a median age at diagnosis of 61 years (range 53-69) [table 1].

Four different histotypes of lung cancer were detected. Seven patients (87.5%) were stage IV *ab initio*, with synchronous histologically confirmed oral metastases in 6 cases (75%). All these patients had distant metastases other than in the oral cavity (median of 5 different metastatic sites). The mOS since the diagnosis of oral metastases was 57 days (95% CI 17.8-96.2).

Conclusions: To our knowledge, this is the largest study assessing the incidence of oral metastases in lung cancer patients. Oral involvement, usually diagnosed at an advanced

Table 1. Patients characteristics.

Gender	Age (years)	Smoke	Histotype	N° metastatic sites	Site of oral lesion	Time between stage IV diagnosis and oral lesion occurrence	Local RT	OS from oral lesion occurrence (days)
M	69	Current	Poorly differentiated	4	Jaw	Syncronous	Yes	57
M	61	Current	Sarcomatoid	5	Jaw	Syncronous	Yes	107
M	61	Former	Adenocarcinoma	3	Gingiva	11 months	Yes	77
M	53	Former	Poorly differentiated	4	Gingiva	Syncronous	No	44
M	59	Current	SCLC	5	Gingiva	Syncronous	No	36
F	66	Unknown	Squamous EGFR+	5	Gingiva	Syncronous	No	Alive
M	69	Former	Adenocarcinoma EGFR+	6	Jaw	7 months	No	21
M	55	Unknown	Sarcomatoid	7	Submandibular gland	Syncronous	No	Alive

stage, seems to be associated with a very poor prognosis, with a mOS of about 2 months. Further confirmatory datasets are warranted.

D49

ONE-YEAR EXPERIENCE OF A "CHOOSING WISELY" APPROACH IN THE DECISION MAKING OF ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) IN AZIENDA USL TOSCANA NORD-OVEST (ATNO)

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Background: the treatment scenario of advanced NSCLC has dramatically changed in last few years with the availability of new compounds. Unfortunately, no real predictive factor could help clinicians in patients selection.
Materials and Methods: all ATNO clinicians involved in the treatment of NSCLC met at the end of 2017 and defined some common treatment criteria based on a "choosing wisely" approach. They highlighted top level value treatment options not to be missed and some clinical settings in which the benefit of new drugs was unclear. We set up a treatment form to be filled for each new patient independently of the selected drug. The form included some mandatory items to be checked before treatment decision with the aim to exclude from treatment patients who will probably not benefit from therapy (low-predictive-benefit LPB group) and to show alternative treatment possibilities including best supportive care. Filling the form was voluntary and all forms were centrally reviewed. Primary objective of the approach was to make treatment algorithm homogeneous among hospitals of ATNO and to assure the appropriateness. Secondary objective was data collection based on forms.
Results: in 2018 a total of 169 treatment forms were filled by all ATNO hospitals grossly representing 70% of new treatments thus indicating a good adherence to the just released voluntary procedure. All top level value therapy were delivered to appropriate subjects and all new treatments included a careful evaluation of LPB characteristics. We observed an overall 20% reduction in treatment delivered to low PS patients in both first and second-line respect to historical local series and 90% of proposals for treatment were included into the baseline list.
Conclusions: a "choosing wisely" approach based on local clinicians agreement, identification of LPB subgroups of patients, form compilation with central reviewing met its end-points assuring treatment consistency across different ATNO oncology services and reducing unnecessary therapies to LPB subgroups so sparing patients from toxicities. Overall patients outcome by treatment will be presented.

D50

PLATINUM-BASED CHEMOTHERAPY (P-CT) FOR ADVANCED NON-SMALL-CELL LUNG CANCER (A-NSCLC) PATIENTS (pts) WITH PLEURAL OR PERICARDIAL METASTASES EXPERIENCING SYMPTOMATIC MESOTHELIAL PROGRESSION (DSP) DURING UPFRONT PEMBROLIZUMAB (PEMBRO): A SINGLE-INSTITUTION PTS SERIES

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Background: PEMBRO had significantly demonstrated to improve outcomes in comparison with upfront chemotherapy for A-NSCLC with high PD-L1 expression on tumor cells. Although according to these data PEMBRO has become the standard first-line option for these pts, those pts with pleural or pericardial metastases receiving immunotherapy appear to have a higher risk of DSP, leading to treatment discontinuation and overall poor prognosis.
Patients and Methods: The medical records of pts affected by A-NSCLC with PD-L1 (TPS ⩾50%) and pleural or pericardial metastases who experienced rapidly mesothelial DSP on PEMBRO requiring intervention, such as chest catheter insertion, pericardiocentesis or antalgic therapy, referring to our Institution (FPUG-UCSC), were retrospectively gathered and analyzed. The primary and secondary end-points were Overall Response Rate (ORR) according to RECIST criteria and Disease Control Rate (responses plus stable disease, DCR); 95% Confidence Intervals (CIs) were derived.
Results: Fourteen patients referring FPUG-UCSC to discontinued PEMBRO because of mesothelial DSP (pleural and/or pericardial drainage and/or pain therapy: 13/4/6) requiring intervention. Median patient age was 65, and a median number of 6 cycles (range 1-26) was delivered. The majority of pts (12/14, 85%,) had a high disease burden (more than 2 metastatic sites) and brain metastases (6/14). Due to worsening clinical condition, 6 patients were not eligible for further active treatment, while 9 patients received standard P-CT (mainly platinum plus pemetrexed). ORR was obtained in 5 out of 9 pts receiving P-CT (55%, 95% CIs 23.1-88.0%) and it was associated with significant symptoms improvement in all these pts. The overall DCR was achieved in 8/9 pts (88%, 95% CIs 68.6-100%). With a median follow-up of 6.03 months (Data-Lock: May 19th, 2019), median PFS and OS were not reached.
Conclusions: P-CT represent an active rescue treatment for treatment for A-NSCLC pts with mesothelial metastases who progressed to first-line immunotherapy. These data support that the forthcoming combinations of chemo-immunotherapy have the potential for optimizing the clinical outcomes and management of mesothelial metastases

D51

THORACIC RADIOTHERAPY AND IMMUNE CHECKPOINT INHIBITITORS: SAFETY OF COMBINATION IN CANCER PATIENTS

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Background: To evaluate the onset of toxicity in cancer patients receiving both immune checkpoint inhibititors (ICIs) and thoracic radiation therapy (RT).
Material and Methods: In this study, we conducted a retrospective study of patients receiving ICIs and who underwent RT to the lungs. Patients with concurrent (within 1 month) and sequential treatments (up to 6 months) were included. All medical records of patients were reviewed for adverse events (AEs, CTCAE v4.0) reported after the beginning of the second treatment (RT or immunotherapy) in order to highlight the toxicity related to the combination.
Results: We have analyzed 15 treated patients, from January 2016 to December 2018, with ICIs and thoracic radiotherapy. Median total dose and fraction number was 3000 cGy (range: 600-5400 cGy) in 10 fractions. The most frequently reported toxicity was pneumonia in 10 cases (3 x Grade 1, 6x G2, 1x G3) and esophagitis in 9 cases (5 x G1and 4x G2); other toxicities found were mucositis (8%), fatigue (30%), dermatitis/rash (66%), thyroid (23%) and gastrointestinal toxicities (13%).
Conclusions: In conclusion, Despite the low number of cases, it can be stated that the toxicity correlated with thoracic radiotherapy is not increased by the association with immunotherapy. Prospective studies are needed to analyze the toxicity profile of the combination of immunotherapy and thoracic radiotherapy.

D52

NIVOLUMAB AT FLAT DOSE FOR SECOND-LINE TREATMENT OF METASTATIC NON-SMALL CELL LUNG CANCER: ECONOMIC SUSTAINABILITY

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Background: The 240 mg and 480 mg flat dose of nivolumab every two (Q2W) and four weeks (Q4W) showed comparable efficay and safety towards nivolumab at 3 mg/kg Q2W schedule. The aim of this study is to compare pharmacological costs of real-life treatment with nivolumab at flat dose versus (vs.) nivolumab at 3 mg pro Kg in metastatic non-small cell lung cancer (NSCLC).
Materials and Methods: A retrospective analysis of all consecutives patients with metastatic NSCLC treated with nivolumab in second-line and followed at our Medical Oncology Unit between December 2016 and December 2017 was performed. The costs are at the Pharmacy of our Hospital and are expressed in euros (€). Overall survival

(OS) was estimated starting from the first day of the first cycle of nivolumab to the last visit or patient's death date, censoring surviving patients at the time of last follow-up (FUT).

Results: We evaluated 9 patients with metastatic NSCLC treated with nivolumab in second-line, 5 patients (55.6%) with squamous NSCLC and 4 patients (44.4) with non-squamous histology (adenocarcinoma in all cases), without EGFR-activating mutations or ALK or ROS1-translocations; PDL1 was not tested. One patient (11.1%) was female. Median age was 66 years (range: 49-76). Nivolumab was used in second-line treatment in all cases (100.0%). Median follow-up time (FUT) was 12.04 months (range: 8.19-22.57 months). At the last FUT, 3 patients (33.3%) were deceased and 6 patients (66.7%) were alive with metastases. Median OS was 4.74 months (range: 2.0-10.95 months), with a mean of 9 cycles of nivolumab for patient (range: 5-19). No serious (>=3) adverse events were reported. The mean pharmacological cost for patient treated with nivolumab at 240 mg flat dose Q2W was 29 025 € (range: 16 125-61 275 €). The mean pharmacological cost for patient treated with nivolumab at 480 mg flat dose Q4W was 26 875 € (range: 16 125-53 750 €). The mean pharmacological cost for patient treated with nivolumab at 3 mg pro Kg was 20 305 € (range: 11 280-42 864 €).

Conclusions: Comparing pharmacological costs of real-life treatment in metastatic NSCLC, it is evident that nivolumab flat dose, even in presence of comparable efficacy and safety data, is less economic sustainable than nivolumab per-kilo dose regimen. In particular, nivolumab at 240 mg flat dose Q2W is less economically sustainable than nivolumab at 480 mg flat dose Q4W.

D53

EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS AND CT FINDINGS IN LUNG ADENOCARCINOMA PATIENTS

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Background: Determination of the EGFR mutation status is crucial for a molecular targeted therapy in patients with lung cancer. Analysis of EGFR mutation is usually performed on tissue biopsies, but in the absence of tissue DNA a noninvasive and cost-effective modality is preferred. Aim of the study was to correlate the EGFR mutation status with CT image features at the diagnosis in patients with lung adenocarcinoma.

Table 1. EGFR mutation and CT findings.

	Wild type	Mutation	P
	N (%)	N (%)	
Maximal nodules diameter (mm), median (range)	45.0 (13-110)	30.5 (15-74)	0.01
Nodule pattern			0.01
Solid	50 (69.4)	22 (30.6)	
Mixt	15 (100)	-	
Margin			0.14
Regular	32 (68.1)	15 (31.9)	
speckled	33 (82.5)	7 (17.5)	
Incisures			0.06
No	49 (70.0)	21 (30.0)	
Yes	16 (94.1)	1 (5.9)	
Shape			0.45
Round	41 (71.9)	16 (28.1)	
Other irregular	24 (80.0)	6 (20.0)	
Cavitation			0.67
No	59 (73.8)	21 (26.3)	
Yes	6 (85.7)	1 (14.3)	
Calcification			0.67
No	59 (73.7)	21 (26.3)	
Yes	6 (85.7)	1 (14.3)	
Air bronchogram			0.73
No	56 (75.7)	18 (24.3)	
Yes	9 (69.2)	4 (30.8)	
Pleural connection			0.57
No	17 (81.0)	4 (19.0)	
Yes	48 (72.7)	18 (27.3)	
Tumor density, Hounsfield Unit (UH)			
Pre *	35.0 (19-70)	40.0 (10-50)	0.12
Post *	70.0 (30-176)	80.0 (30-125)	0.03

GGO ground-glass opacity; * pre and post intravenous contrast enhancement

Methods: Patients were retrospectively selected from those consecutively referred to the Oncology Department of Villa Scassi Hospital already tested for EGFR expression. The EGFR status was compared with CT chest morphological features of the lesions.

Results: 87 patients (52 males, median age 66 years, 90% stage III-IV, 59% smokers) were identified. EGFR mutations were found in 22 patients (25.3%) and were more frequent among females ($p=0.013$) and never smokers ($p<0.001$). The median maximal diameter of the nodules was smaller in mutated than in wild-type patients ($p=0.010$). All mutated tumors had solid nodule pattern. A higher number of mutations, not statistically significant, were found in tumors with regular margins, no incisions, and with no central necrosis or calcification. Median tumor density was higher ($p=0.03$) in mutated tumors after intravenous contrast (Table 1).

Conclusions: EGFR mutations were associated with shorter maximal nodules diameters, presence of solid patterns,

absence of incisions and with a higher post contrast enhancement. The study is retrospective and has been performed on a low number of patients, but results are consistent with some data in literature.

D54

PEMBROLIZUMAB-INDUCED ENCEPHALOPATHY IN A PATIENT WITH METASTATIC LUNG CANCER

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Background: Immune checkpoint inhibitors (ICIs) are now routinely used in clinical practice and a new class of treatment-related toxicities termed immune-related adverse effects (irAEs) has emerged. We report a case of encephalopathy caused by pembrolizumab.
Materials and Methods: In April 2017 a 50-year-old woman was diagnosed as having a stage IV adenocarcinoma, EGFR and ALK negative, PDL1 more than 50%. She received chemotherapy with cisplatin and pemetrexed with partial response initially, followed subsequently by disease progression. Considering the presence of bone metastasis, a palliative radiation therapy was performed and pembrolizumab was started. She completed a total of five cycles with no laboratory or clinical signs of toxicity and a partial response. However ten days after last dose of pembrolizumab she reported a change in behavior, confusion and a history of uncontrollable movements of the mouth. Her family started to say that she was unable to performe daily activities. A physical neurological examination was unremarkable. A psychiatrist described our patient as depressed.
Results: Brain CT was performed, ruling out obvious cerebral metastases. Magnetic resonance imaging of the brain was suspicious for encephalopathy. An electroencephalogram demonstrated a bilateral slowing in the parieto-occipital area. Results of routine blood count, biochemistry profile, and thyroid function tests were normal. No serum paraneoplastic antibody were detected. Lumbar puncture was performed. Cerebrospinal fluid was acellular and the results of polymerase chain reaction assay for JCV and neurotropi virus were negative. The patient was given high-dose methylprednisolone intravenously at 1 g daily, resulting in a gradual improvement of mental status after two months. Although Pemrolizumab was permanently discontinued in February 2018, the most recent restanging show maintenance of response
Conclusions: The incidence of neurological irAEs is often not well reported in clinical trials. Only 10 cases of encephalitis have been published in the literature and most presentationts seem to occur early, with the majority of them developing within 4 months of the start of immunotherapy. Most encephalitis respond to high dose steroids but severe cases can be fatal. It seems that development of a neurological irAE may be a positive predictor of outcome. Diagnosis is challenging and oncologist should be aware about early recognition and management of these irAEs.

D55

EFFICACY AND SAFETY OF SINGLE AGENT CHEMOTHERAPY (SAC) FOR ADVANCED NON-SMALL-CELL LUNG CANCER (A-NSCLC) PATIENTS (pts) WHO HAD PROGRESSED TO PLATINUM-BASED CHEMOTHERAPY (P-CT) AND IMMUNOTHERAPY (IO): A SINGLE INSTITUTION RETROSPECTIVE ANALYSIS

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Background: IO represents the standard second line treatment option for A-NSCLC pts undergone disease progression to first-line P-CT. Besides, only few pts experience a significant survival and clinical benefit. To date, few and controversial data are available regarding the activity of SAC after failure of the sequence P-CT-IO.
Patients and Methods: The medical records of pts affected by A-NSCLC with PD-L1 (TPS $<$50%) who had progressed on previous P-CT and IO, who received third-line SAC referring to our Institution (FPUG-UCSC), were retrospectively gathered and analyzed. The primary end-points were Overall Response Rate (ORR, according to RECIST criteria) and Disease Control Rate (responses plus stable disease, DCR); secondary end-points were Progression Free Survival (PFS), Overall Survival (OS).
Results: Thirteen A-NSCLC pts were included in the analysis (Adeno/Squamous: 8/5; median age 60 years, range 39-84). Previous treatments details and third line outcomes are shown in table below.
The ORR and DCR were 15% (95% CIs 1.8 - 45.0%) and 30% (95% CIs 8.6 - 60.7%), respectively. Symptomatic pts (PS ECOG 1-2) with unfavorable metastatic spread, i.e. brain and/or liver metastases, did not experience any clinical benefit and showed worst survival outcomes. After a median follow-up of 5.2 mo., the median PFS was 5.09 mo. (95% CIs 2.3 – 6.3 mo.); the median OS was not reached. Treatment-related overall grade 3 toxicity incidence occurred in 38% of pts, mainly fatigue and anemia.

	First-line	Second-line	Third-line
Treatment	PL-Pem (5 pts) CBDCA + TXL (4 pts) CBDCA + GMZ (2 pts) CBDCA + TXL + Beva (2 pts)	Nivolumab (8 pts) Pembrolizumab (3 pts) Atezolizumab (2 pts)	GMZ (7 pts) TXT (5 pts) VNL (1 pt)
ORR	Partial response: 8 pts Stable disease: 4 pts Progressive disease: 1 pt	Partial response: 2 pts Stable disease: 4 pts Progressive disease: 7 pts	Partial response: 2 pts Stable disease: 2 pts Progressive disease: 9 pts

PL =platinum compound, Pem= Pemetrexed, CBDCA: carboplatin, TXL =paclitaxel, GMZ =gemcitabine, TXT= docetaxel, VNL= vinorelbine, Beva =bevacizumab.

Conclusions: Despite a series patients experienced significant response to first-line P-CT, third-line SAC after IO showed modest activity and relevant toxicity. Thus, SAC should be considered with caution, mainly for pts with preserved clinical conditions. Larger multicenter data collection is needed in order to amend treatment strategies for A-NSCLC patients.

D56

SAFETY AND EFFICACY OF IMMUNOTERAPY IN ELDERLY PATIENTS WITH NSCLC: OUR EXPERIENCE

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Background: Although around half of all people newly diagnosed with NSCLC are elderly there is currently limited evidence on the efficacy and safety of immunotherapy in this age group of patients because they are generally under-represented in clinical trials. It is not known whether age-related decline in the immune system of elderly patients can affect on the efficacy and on the toxicity of immunotherapy, especially with regard to immune-related adverse events. The aim of this study is to investigate in elderly patients with NSCLC stage IV, PD-L1–positive, the efficacy and safety of Pembrolizumab as first-line treatment or Nivolumab as second, third or later-line therapy;

Patients and Methods: We have designed a monocentric, prospective phase II study in patients with age≥65; histologically confirmed stage IV NSCLC, previous treated or untreated with systemic therapy for metastatic disease; adequate baseline functional parameters. The efficacy endpoints were ORR, PFS, OS. Only patients that complete at least 3 months of treatment were evaluable for ORR. Tumors were assessed by CT at baseline and every 3 months.

Results: From March 2017 to May 2019 19 patients were enrolled: median age 77 (range 67-87); male/female 16/3. Hystology was 63% adenocarcinoma and 37% squamous. 44,7% had PD-L1 expression >50% and 52,6% < 50%: Pembrolizumab was administered as first-line therapy in 47,4% of patients, Nivolumab as second-line therapy in 42,1% and as third-line therapy in 10,5%. The average number of cycles received by patients was 20 (range 2-15) in the Pembrolizumab group and 31 cycles in the Nivolumab group (range 2-56). No hematological toxicity were observed; immune-related adverse events occurred in 44,4% of the patients in the pembrolizumab group (G3 skin reaction 11,1%, G2 hypotyroidism and skin reaction in 11,1% and G1 hypotyroidism in 11,1%) and in 30% of the patients in the Nivolumab group (G3 pneumonitis and colitis in 10% of patients and G1 hypotyroidism in 10%). At May 2019, 84,2% of patients were alive and only 18,8% of them stopped immunotherapy due to disease progression. The median PFS was 7 months for Pembrolizumab group and 15,8 months for Nivolumab group. No patients discontinued treatment because of treatment-related adverse events. The study is ongoing, the required sample size is 62 patients in 24 months.

Conclusions: The preliminary results of this study encourage the use of immunotherapy in elderly patients with NSCLC.

D57

PROGNOSTIC VALUE OF THE NEUTROPHIL-TO-LYMPHOCYTE RATIO IN PATIENTS WITH NSCLC TREATED WITH NIVOLUMAB

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Background: An elevated NLR (neutrophil-to-lymphocyte ratio) is a known marker of the systemic inflammatory response and is significantly associated with poor outcomes in many types of malignancies, included NSCLC.

In our study, we aimed to explore the association between NLR and outcomes in patients with NSCLC treated with nivolumab.

Material and Methods: In our study we enrolled 38 patients (12 women and 26 men) with metastatic NSCLC

who received nivolumab. Mean age was 70 years (range 48-82). Squamous and non squamous histologies were diagnosed in 12 (31,6%) and 26 (68,4%) patients, respectively. NLR was calculated by dividing neutrophil count by lymphocyte count measured in peripheral blood before start of immunotherapy. We calculated the NLR of 31of the 38 patients enrolled in the study. The patients were divided into two groups based on theNLRvalue (NLR$\geqslant$2.5 andNLR$<$2.5). We compare the results with the response to the treatment, which was assessed by computed tomography.

Results: At the fist instrumental evaluation, 7 of the 14 patients with high NLR had disease progression (50%) while 4 patients (28,6%) showed partial response and 1(7,14%) stable disease. 2 patients were not evaluated. Instead, with regard the 17 patients with a low NLR, 5 of them had RP (29,4 %) 6 patients SD(35,3%) 3 PD (17,6%); 3 patients were not evaluated.

Conclusions: Our results suggest that an elevated pretreatment NLR is associated with a worse outcomes and lower response rate and it could be considered as an effective prognostic marker for patients treated with Nivolumab.

E - Genitourinary Tumours

E01

ASSOCIATION BETWEEN IMMUNO-RELATED ADVERSE EVENTS (irAEs) OCCURRENCE AND CLINICAL FEATURE AND OUTCOME IN METASTATIC RENAL CELL CARCINOMA (mRCC) PATIENTS TREATED WITH NIVOLUMAB: DATA FROM FINAL ANALYSE OF IRAENE

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Background: Data emerging from several trials, revealed a correlation between irAE during treatment with immune checkpoint inhibitors and clinical outcome in different cancers.

Method: We conduct a retrospective analysis of patients (pts), from 16 Italian centres, with mRCC treated with nivolumab between March 2017 and January 2018. IrAEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Event version 4.0 (CTCAE v4.0).

Results: 167 pts met inclusion criteria. Median age was 66.8 years (yr), 124 pts (74.3%) were male, 151 pts (90.4%) had clear cell carcinoma; 43.5% of pts, 46.4% and 20.2% had respectively, favourable, intermediate and poor prognosis sec Heng. 77 patients (46%) showed irAEs of any grade and 15 pts (8.9%) showed grade (G) 3/4 irAEs. Cutaneous toxicity was the most common irAE (33.7%), followed by fatigue/asthenia (25.9%), gastrointestinal (23.3%), pulmonary (14.2%) and endocrine (14.2%) toxicity. Pulmonary toxicity was the most common severe grade irAE (G3/4) reported (5.1%). There was a relation between age $>=$75 yr and the occurrence of irAE ($p=0.015$). There was no correlation between irAE and Heng score ($p=0.221$), the presence of comorbidity ($p=0.093$), number ($p=0.657$) and type of previous systemic treatment. Pts with irAEs showed a more significant OS (HR 0.38, 95% CI, 0.23-0.63) and PFS (HR 0.44, 95% CI, 0.29-0.66) benefit, better ORR (27.3% vs 13.7%, OR 2.36, 95% CI, 1.03-5.44) and better DCR (68.8% vs 48%, OR 2.4, 95% CI, 1.23-4.67) if compared to pts without irAEs. There was not a relation between grade of irAEs and ORR and DCR but patients with G1-G2 irAEs had better OS and PFS than patients with $>=$G3 irAEs or without irAE. Median time to appearance of irAEs was 10 weeks. Patients with median time to irAEs $>=$10 weeks achieved better OS (HR 0.37, 95% CI, 0.16-0.85), PFS (HR 0.33, 95% CI, 0.17-0.63), ORR (OR 3.97, 95% CI, 1.28-12.33) and DCR (OR 5.83, 95% CI, 1.97-17.26). Steroid treatment was necessary in 38.8% of pts for the management of irAEs with a median time of 20 days (5-210 days). There was no a correlation between steroid's use and clinical outcomes.

Conclusions: The development of irAEs may be correlated with better clinical outcomes in a real-life population of mRCC pts treated with nivolumab.

E02

PHASE 3 STUDY OF ANDROGEN DEPRIVATION THERAPY (ADT) WITH ENZALUTAMIDE (ENZA) OR PLACEBO (PBO) IN METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC): THE ARCHES TRIAL

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Background: ENZA, a potent androgen receptor inhibitor, has demonstrated benefit in men with metastatic and nonmetastatic castration-resistant prostate cancer (CRPC).
Patients and Methods: ARCHES is a multinational, double-blind, phase 3 study (NCT02677896). Patients (pts) with mHSPC were randomized 1:1 to ENZA (160 mg/day) + ADT or PBO + ADT, stratified by disease volume (CHAARTED criteria) and prior docetaxel therapy. Primary endpoint was radiographic progression-free survival (rPFS) assessed centrally or death within 24 weeks of treatment discontinuation. Secondary endpoints included time to prostate-specific antigen (PSA) progression, PSA and radiographic responses and overall survival (OS). Treatment continued until disease progression or unacceptable toxicity.
Results: 1150 men were randomized to ENZA (n=574) or PBO (n=576); baseline characteristics were balanced between groups. Overall, 67% had distant metastasis at initial diagnosis; 63% had high volume disease, 18% had prior docetaxel. Median follow-up was 14.4 mo. ENZA + ADT significantly improved rPFS (Table); similar significant improvements in rPFS were reported in prespecified subgroups of disease volume, pattern of spread, region and prior docetaxel (HRs 0.24-0.53). Secondary endpoints improved with ENZA + ADT (Table); OS data are immature. Grade 3-4 adverse events (AEs) were reported in 23.6% of ENZA pts vs 24.7% of PBO pts with no unexpected AEs.
Conclusions: ENZA + ADT significantly improved rPFS and other efficacy endpoints vs PBO + ADT in men with mHSPC, with a preliminary safety analysis that appears consistent with the safety profile of ENZA in previous CRPC clinical trials.

Endpoint	ENZA + ADT (n=574)	PBO + ADT (n=576)
Primary: rPFS, HR (95% CI)	0.39* (0.30, 0.50)	
Median (mo)	NR	19.4
Key secondary		
Time to PSA progression, HR (95% CI)	0.19* (0.13, 0.26)	
Time to initiation of new antineoplastic therapy, HR (95% CI)	0.28* (0.20, 0.40)	
PSA undetectable (<0.2 ng/mL) rate,[a]%	68.1*	17.6
Objective response rate, [a]%	83.1*	63.7

NR=not reached; *p<0.0001; [a]Of those with detectable PSA or measurable disease at baseline, respectively

E03

SAFETY OF NIVOLUMAB (NIVO) IN COMBINATION WITH STEREOTACTIC BODY RADIOTHERAPY (SBRT) IN II AND III LINE OF PATIENTS (pts) WITH METASTATIC RENAL CELL CARCINOMA (MRCC) IN NIVES STUDY

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Background: NIVO is an anti-programmed cell death-1 (PD-1) monoclonal antibody; it might work even better when combined with SBRT improving clinical outcomes with a phenomenon known as abscopal effect. To date there are limited data on safety profile of combined SBRT and NIVO in mRCC. We report for the first time the toxicities occurred in phase II NIVES Study.
Material and Methods: This is a phase II, single arm, multicentre study in pts with mRCC with progression disease after=2 prior anti-angiogenic therapies and with measurable non-brain metastatic sites, at least one of which potentially suitable for SBRT. The pts included received hypofractionated radiation in one lesion at dose of 10 Gy/3 fractions after 7 days from the first infusion of NIVO. NIVO will be given as flat dose of 240 mg on day 1 every 14 days for 6 months, then switch to 480 mg q4-weekly in responding pts until progression disease (PD) or unacceptable toxicity.
Descriptive statistics are reported for patient/tumor/treatment characteristics and observed Adverse Events (AEs) graded by CTCAE v. 4.0.3
Results: Sixty-nine pts were enrolled from July 2017 to March 2019 in 11 Italian centers. 79.7% of pts had clear cell histology, median age was 67 years (range 43-85), 82.6% were male. ECOG PS was
0 in 57 pts (82.6%), only 18.8% pts had received 2 previous lines of therapy. The most frequent sites of SBRT were lung (39.4% of pts), lymphonodes (16.7%) and bone (10.6%). Toxicities of grade (G) 3-4 related to NIVO were experienced in 13 pts (18.8%); all G3-4 toxicities were

outside of the irradiated area. The most frequently observed grades 3-4 treatment-related AEs included diarrhea (5.8%), fatigue (4.3%), anemia (2.9%) and increase of amylase/lipase (2.9%). To date only 5 pts (7.2%) reported G1-2 pneumonitis, but no G3-4 were observed. Six pts (8.7%) were hospitalized due to treatment-related SAEs. Overall, 5 of 69 treated pts (7.2%) discontinued therapy because of G3-4 AEs (3 of 5 pts for SAEs). At the time of this analysis 32/69 pts (46%) are still on treatment. The last patient enrolled started treatment at the end of March 2019.

Conclusions: Concurrent NIVO plus SBRT is generally well tolerated, without increased rates of severe toxicity also in irradiated tumor sites. Definitive data of toxicities and efficacy of immunotherapy and radiotherapy are not yet mature.

E04

IMMUNOHISTOCHEMICAL EVALUATION OF MICROSATELLITE INSTABILITY (MSI) AS A POTENTIAL BIOMARKER OF RESPONSE TO HORMONAL AGENTS IN METASTATIC HORMONE-SENSITIVE (mHSPC) AND CASTRATION-RESISTANT PROSTATE CANCER (mCRPC): PRELIMINARY DATA

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Background: Microsatellite instability (MSI) has been studied as a possible biomarker of response to immunotherapy in several cancers. Data are also available in patients with prostate cancer, where MSI-H tumours represent a small subgroup of cases responsive to anti-PD1 therapy. However, no data on MSI role as a predictive biomarker of response to androgen deprivation (ADT) therapy in metastatic hormone-sensitive prostate cancer (mHSPC) and to new hormonal agents in metastatic castration-resistant prostate cancer (mCRPC) are available. Our study aims at exploring this aspect.

Material (patients) and Methods: We performed an immunohistochemical evaluation of MSI on archival tissue from prostatectomies or prostatic biopsies of patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) who underwent first-line therapy with abiraterone (ABI) or enzalutamide (ENZ). We identified two populations: pts with stable microsatellites or low microsatellite instability (MSS) and pts with high microsatellite instability (MSI-H). We analyzed their clinical characteristics and performed a Kaplan-Meier analysis of time of duration of ADT in the mHSPC phase and of radiographic progression-free survival (rPFS) to first-line treatment in the mCRPC phase.

Results: 30 pts have been included so far. 5 (16.67%) pts patients were classified as MSI-H and 25 (83.33%) as MSS. The two populations were well balanced in terms of Gleason score (GS), stage at diagnosis, and site of metastases: most pts had a GS $\geqslant$ 8 (3 [60%] and 13 [52%] in the MSI-H and MSS groups, respectively), were localized at diagnosis (3 [60%] and 14 [56%], respectively), and had lymph node and/or bone metastases (only 1 [20%] pt in the MSI-H group and 2 [8%] pts in the MSS had visceral metastases). MSI-H pts experienced a median shorter duration of ADT in the mHSPC phase (12.67 [95% CI 0-32.51] vs 25.5 [95% CI 16.52-34.48] months of MSS group, $p=0.013$). Pts in the MSI-H group had a statistically-significant shorter mPFS than pts in the MSS group when treated with ABI or ENZ for mCRPC (9.4 months [95% CI 6.74-12.06] vs 15.3 months (95% CI 12.97-17.63], $p=0.006$).

Conclusions: Even if it has involved a small group of patients so far, our study suggests a possible role of MSI expression as a potential biomarker of response to androgen deprivation therapy in mHSPC and to new hormonal agents in mCRPC and it encourages further larger prospective studies to confirm it.

E05

PROGNOSTIC ROLE OF PLATELETS TO LYMPHOCYTE RATIO (PLR) AND NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) IN PATIENTS WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER (mCRPC) TREATED WITH ABIRATERONE OR ENZALUTAMIDE

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Background: PLR and NLR are recognised markers of systemic inflammation associated with poor outcome in many solid tumors. We retrospectively investigated the role of PRL and NLR as prognostic factors in mCRPC patients (pts) treated with new generation hormone-therapies, both in docetaxel-naïve and post-docetaxel setting.

Materials and Methods: 225 mCRPC pts treated with Abiraterone Acetate (AA) or Enzalutamide (E) between 2010 and 2018 with basal value of platelets, lymphocytes and neutrophils were included. Pts were divided in 3 groups according to PLR (PLR1 if PLR $<$128; PLR2 if PLR 128 - 190; PLR3 if PLR $>$190) and in 2 groups according to NLR (NLR $<$ 3 vs $\geqslant$3). Outcome measures

were progression-free survival (PFS) and overall-survival (OS), measured from the start of AA or E. Univariate and multivariate analyses were performed.

Results: 110 pts (48.9%) were in PLR1 group, 58 (25.8%) in PLR2 and 57 (25.3%) in PLR3. Differences in OS (HR PLR 2 vs 1 0.971, 95%CI 0.621-1.519; HR PLR 3 vs 1 1.369, 95%CI 0.900-2.080; p=0.260) and PFS (HR PLR 2 vs 1 0.869, 95%CI 0.592-1.275; HR PLR 3 vs 1 1.150, 95%CI 0.797-1.660; p=0.441) among the 3 PLR groups were not statistically significant. In docetaxel-naïve pts, median OS was 36.1 months in PLR1, 25.5 months in PLR2 and was not reached in PLR3 (p=0.428). Median PFS was 11.1, 25.1 and 18.9 months in PLR1, PLR2 and PLR3 group respectively (p=0.281). In docetaxel pre-treated pts, median OS was 18.1 months in PLR1, 19.8 months in PLR2 and 13.2 months in PLR3 (p=0.133). Median PFS was 7.6, 11.4 and 5.5 months in PLR1, PLR2 and PLR3 respectively (p=0.084). Median OS for subjects treated with AA was 17.3 months in PLR1, 19.5 months in PLR2 and 16.0 months in PLR3 (p=0.522). Median PFS was 8.4, 10.1 and 8.3 months in PLR1, PLR2 and PLR3 group respectively (p=0.483). For pts treated with E, median OS was 39.5 months in PLR1, 34.7 months in PLR2 and 30.4 months in PLR3 (p=0.431). Median PFS was 9.9, 16.3 and 12.5 months in PLR1, PLR2 and PLR3 group respectively (p=0.766). As for NLR, median OS in pts with NLR <3 was 26.5 months, while in pts with NLR ⩾3 was 17.0 months (HR 1.751, 95%CI 1.222-2.511, p=0.02). Median PFS was 10.1 months in pts with NLR <3 vs 7.6 months in pts with NLR ⩾3 (HR 1.372, 95%CI 1.001-1881; p=0.049).

Conclusions: In this retrospective analysis of mCRPC patients treated with AA or E, we did not identify a prognostic role of baseline PLR, while we found a significant prognostic role of baseline NLR.

E06

SHORT-TERM EFFECT IN TUMOR SHRINKAGE AND SYMPTOMS PALLIATION OF CABOZANTINIB IN METASTATIC RENAL CELL CARCINOMA PATIENTS (pts)

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Background: Cabozantinib (cabo) is a multiple tyrosine kinase inhibitor approved as treatment for metastatic Renal Cell Carcinoma (mRCC) after prior antiangiogenic therapy. The aim of our study was to evaluate the fast therapeutic effect of cabo in palliating symptoms.

Patients and Methods: We retrospectively evaluated pts treated with cabo after at least one line of treatment for mRCC from Sep 2016 to Feb 2019. As part of our clinical practice, a 5 minutes questionnaire, investigating disease related symptoms (DrS), pain and psychological impact of treatment, was administered to all pts before starting cabo and monthly thereafter. We evaluated DrS and pain palliation at 1 and 3 months (mo) after the beginning of cabo. Background (BP) and Breakthrough cancer pain (BtcP) responses were graded as complete response (CR) defined as the discontinuation of pain and analgesics, partial response (PR) as an > 50% decrease in both pain and analgesic dosage, minimal response (MR) as a less decrease in pain and in analgesic dosage. First radiological responses were also evaluated and classified as stability (SD), progression (PD) or PR according to RECIST.

Results: Out of 54 patients included in our analysis, 26 (48%) were symptomatic for pain at baseline and received analgesic therapy to control the BP, 24/26 (92%) experienced also BtcP. 21/26 presented with bone metastases. Furthermore, 37/54 (68%) pts reported DrS. After 1 mo all pts remained symptomatic for pain but 16/26 (62%) experienced a significant pain palliation: 7 pts presented a CR on BtcP and 9 a MR on BP. At mo 3, all pts experienced a pain benefit. In particular, 7/26 experienced a CR, 3/26 a PR, 14/26 a MR and in 2/19 no change was observed concerning BP. Of 24/26 cases presenting with BtcP, 14/24 patients experienced a CR, 2/24 a PR, 8/24 a MR. At mo 3 a DrS palliation was observed in 29/37 patients, 9 of whom were asymptomatic for pain. At first radiological evaluation, between 26 pts presenting benefit at mo 3, 10 presented PR, 10 SD, 3 presented PD, and for 3 patients information was not available (NA). Of 9 patients experienced a DrS with no pain, 7 presented PR, 1 SD, for 1 NA.

Conclusions: Cabo is effective in obtaining a fast palliation of pain and DrS in mRCC.

E07

A LARGE SEER-BASED STUDY OF SURVIVAL TRENDS IN PATIENTS WITH DE NOVO METASTATIC PROSTATE CANCER

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Background: The treatment landscape of metastatic prostate cancer (mPCa) has completely changed during the last two decades. Chemotherapy and new androgen-receptor signalling inhibitors (ARSi) significantly improved the survival of patients (pts) with both hormone-sensitive and castration-resistant mPCa in randomized trials. Here, we explored the clinical outcomes of *de novo* mPCa in three large cohorts of pts diagnosed in 3 treatment eras: pre-docetaxel 2000-2003 (T1), docetaxel 2004-2010 (T2) and ARSi + cabazitaxel 2011-2016 (T3).

Methods: The US Surveillance Epidemiology and End Results (SEER) 18 Regs Research Data (Nov 2018 Sub) were

Table 1. OS and CSS, expressed as % of survivors, in T1 T2 and T3 treatment eras.

	1-year	2-year	3-year	4-year	5-year
T1 OS	77.0	55.5	41.8	32.7	26.1
T2 OS	77.5	55.8	42.0	32.7	26.9
T3 OS	79.8	59.9	45.1	34.9	28.0
T1 CSS	81.0	61.3	48.8	40.0	33.5
T2 CSS	81.1	61.4	48.5	39.4	33.6
T3 CSS	83.1	65.1	51.4	41.7	35.1

investigated using the SEER*Stat software. We used the Kaplan – Meier method, log-rank test, Cox regression, hazard ratio (HR) and confidence intervals (CI) to analyse age-standardized overall survival (OS) and cancer-specific survival (CSS). Given the expected discrepancy among the cohorts, the maximum follow-up time point was fixed to 5 years.

Results: A total 34.034 pts with *de novo* mPCa were analysed for OS, of these 6.621 T1, 12.711 T2 and 14.702 T3. Median OS was 29 months (mo) [95% CI: 28.5-29.5], 28 mo [27.0-28.9], 28 mo [27.3-28.7] and 31 mo [30.2-31.8] in whole, T1, T2 and T3 cohorts, respectively. T3 pts showed better OS compared to T1 and T2 pts (HR: 0,89 [95% CI: 0,86-0,93] and 0,92 [0,89 to 0,95], respectively, $p<0.00$). A total of 33.641 pts were analysed for CSS, of these 6.514 T1, 12.540 T2 and 14.587 T3. Median CSS was 36 mo [35.3-36.7], 34 mo [32.6-35.3], 34 mo [33.0-35.0] and 38 mo [36.9-39.1] in whole, T1, T2, T3 cohorts, respectively. T3 pts had better CSS compared to T1 and T2 pts (HR: 0,91 [0,88-0,95] and 0,92 [0,89 to 0,95], respectively, $p<0.00$). No difference in OS or CSS was found between T1 and T2 cohorts.

Conclusions: The prognosis of pts with *de novo* mPCa remains poor, with a median CSS of 3 years and a 5-year CSS of 35%. Approximately 10% decrease in the risk of death was found in the era of ARSi and cabazitaxel. Despite possible inferential errors due to the intrinsic limits of this large retrospective analysis, our data suggest that intensification of therapy might be warranted for *de novo* mPCa to improve the survival outcomes.

E08

IS THE EPIGENETIC REPROGRAMMING THE KEY OF THE IMMUNOTHERAPY RESPONSE? A "LYMPHOCYTE MICRORNA SIGNATURE" AS NOVEL PREDICTIVE BIOMARKER IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (mRCC)

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Background: Many elements represent a barrier to the use of PD-(L)1 expression as potential biomarker for nivolumab activity in patients with metastatic renal cell carcinoma (mRCC). Thus, more dynamic biomarkers are required for patient selection. Emerging evidences reveal that microRNAs (miRNAs) represent key regulatory elements of tumor immune evasion by changing the expression of immune checkpoints (ICPs). A different strategy to predict if a patient will respond to ICP-inhibitors could be the identification of miRNA network that controls the level of ICPs. The aims of this study were: i) to analyze the peripheral lymphocyte miRNA expression profile in long-responders patients (RP/RC/SD to nivolumab>12 months) to identify a signature of miRNA predictive of immunotherapy response; ii) to find the miRNAs that correlate with ICPs expression through the determination of soluble PD-1/PD-L1 concentrations in plasma.

Material and Methods: The blood samples of 21 mRCC patients treated with nivolumab as second line were collected before starting treatment (T0) and after 4 weeks (T1). In these sample we analyzed: i) the expression profile of 377 miRNAs isolated from peripheral lymphocytes; ii) the plasma PD-1/PD-L1 levels measured by specific ELISA assays not yet commercially available, and their dynamic change after treatment.

Results: Microarray analysis showed a "lymphocyte signature" of 8 miRNAs, part of miR-20 family, silenced at T0, before the nivolumab treatment. These miRNA are surprisingly restored at T1, and only in peripheral lymphocytes of long-responder patients, with an exceptional up-regulation. Furthermore, we showed that the miR-22 and miR-24 levels are statistically inversely correlated with PD-1 plasma levels: PD-1 is high and miR-22-24 are silenced at baseline; PD-1 is strongly reduced and miR-22-24 restored after 4 weeks, only in patients with RP/RC/SD to nivolumab>12 months, suggesting that a miRNA network inhibits PD-1 mainly via miR-20 family.

Conclusions: Our study, for the first time, analyzed the miRNA expression profile in the peripheral lymphocytes and showed the exceptional up-regulation of a specific subset of miRNA only in RCC patients with durable response to nivolumab treatment. We provide also the evidence that miRNAs represent an additional level of regulation of ICP expression. These findings could help to identify novel dynamic biomarkers, urgently needed to predict the potential response of RCC patients to immunotherapy.

E09

IMPROVING IMDC PROGNOSTIC PREDICTION THROUGH EVALUATION OF PRIMARY SITE OF METASTASES

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Background: Several models are adopted in clinical practice to estimate prognosis of patients with metastatic renal cell carcinoma (mRCC) however none of these models have been validated in ''new immunotherapy era'' and heterogeneity may exist among risk groups recognized.
Objective: Our aim was to investigate if primary sites of metastases could be a parameter able to stratified prognosis among patients with mRCC stratified in different groups according to International Metastatic Renal Cell Database Consortium (IMDC) model.
Design: 134 patients treated between January 2010 and December 2018 in our institution, were retrospectively evaluated. All patients received at least one line of treatment. Primary sites of metastases and number of metastatic sites were collected from each patients analysed.
Statistical Design: The primary outcome was Overall Survival (OS) defined as the time from initiation of First line therapy to death from any cause. Univariable analysis was performed through log-rank test to estimate the effect of number of metastatic sites and primary site of metastases on OS. Subsequently Cox-Regression proportional hazards model was employed in multivariable analysis.
Results: Of the 12 variables analysed, 4 were statistically associated to worst OS in univariable analysis (number of metastases, liver, bone or central nervous system metastases). Multivariate analysis confirmed and bone (HR = 1.92; 95%CI 1.17-3.13), liver (HR = 2.65; 95%CI 1,59-4,42), and SNC (HR = 3.3; 95%CI 1.62 – 6.74) metastases as independent parameters related to worst OS (Table 1). The presence of one of the selected site recognized a population associated to worst prognosis in both good risk (p = 0.003) and intermediate (p = 0.047) risk groups.
Conclusions: Primary sites of metastases recognized specific population of patients associated to worst prognosis in good and intermediate IMDC groups. Independent studies to validate this finding are warranted.

E10

ROLE OF NOVEL HORMONAL THERAPIES IN THE MANAGEMENT OF NON-METASTATIC CASTRATION RESISTANT PROSTATE CANCER: A LITERATURE BASED META-ANALYSIS OF RANDOMIZED TRIALS

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Background: Novel hormonal therapies have been recently investigated in non metastatic castration-resistant prostate cancer (CRPC). We performed a meta-analysis to assess the efficacy and safety of novel hormonal therapies in non metastatic CRPC.
Methods: The primary outcome was metastases free survival (MFS). We planned a subgroup analysis according PSA doubling time (>6 vs <6 months), ECOG (1 vs 0) and concomitant use of bone-targeting agent (yes vs no)
Results: Three studies were ultimately included in the analysis for a total of 4117 cases (2694 cases were in the experimental group and 1423 cases in the control group). The pooled analysis of novel hormonal therapies revealed significantly increased MFS compared with placebo (hazard ratio (HR): HR = 0.32, 95%CI: 0.25-0.41; p<0.00001). The subgroup analysis showed a statistically significant MFS advantage in favour of men with the lower ECOG performance status (HR = 0.30 versus HR = 0.45). No consistent differences have been observed in term of MFS regardless the PSA doubling time and the use of concomitant bone-targeting agents.
Conclusions: This study confirmed the efficacy and safety of the novel hormonal therapies in non metastatic CRPC especially for ECOG 0 patients.

E11

AUTOIMMUNE DISEASES AND RESPONSE TO THERAPY WITH ABIRATERONE AND ENZALUTAMIDE IN CASTRATION-RESISTANT PROSTATE CANCER (CRPC) PATIENTS

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Background: Androgens and androgen deprivation therapy (ADT) have been profound effects on the immune system, but limited studies have been performed to investigate the association between ADT and immune disorders. We first aimed to analyze the incidence and the impact of a concurrent autoimmune disease on outcome of CRPC patients (pts) treated with abiraterone (abi) or enzalutamide (enza)

Methods: We retrospectively assessed CRPC pts underwent treatment with abi or enza in 12 Italian Institutes between July 2011 and December 2018. In particular, we evaluated the risk of systemic or single-organ autoimmune diseases [according to the International Classification of Diseases 10th Revision (ICD-10)] before starting abi or enza, by performing a logistic regression analysis and clinical outcome by the Kaplan-Meier method.

Results: We included 844 pts treated with abi or enza [477 (56.5%) and 367 (43.5%) were treated with abi and enza, respectively, and 359 (42.5%) were chemotherapy naive]. We identified 36 (4.3%) pts with a concurrent diagnosis of autoimmune diseases at baseline [13 (1.5%) arthritis (rheumatoid or psoriatic), 12 (1.4%) autoimmune thyroiditis, 4 (0.5%) gastrointestinal autoimmune disease, 4 (0.5%) psoriasis, and 3 (0.4%) vasculitis]. Median age was 70 years [interquartile range (IQR) 63-75)]; 788 (93.4%) pts had ECOG performance status 0-1, and visceral metastases were in 92 (10.9%) cases. All patients did prior ADT for hormone-sensitive prostate cancer (HSPC) with a median HSPC duration of 29 months (IQR 14-59). In CRPC, 764 (90.5%) patients did $\leqslant$ 2 therapeutic lines while a median CRPC time of 22 months (IQR 13-39). In abi/enza treated pts, we showed a median progression-free/overall survival (PFS/OS) of 10.0 months, 95% confidence interval (CI) 9.1-11.1, and 24.8 months, 95% CI 22.7-27.4, respectively. We observed no significant impact of the presence of concurrent autoimmune disease on PFS, OS and PSA response. However, a shorter global OS from diagnosis of prostate cancer to the death or last follow-up was observed in cases with autoimmune diseases compared to CRPC pts without immune alterations (HR 1.69, 95% CI 1.10-2.61, p = 0.016).

Conclusions: Autoimmunity would not seem to impact the response to abi or enza, but the presence of autoimmune diseases should be considered when deciding on therapeutic strategies in the overall course of prostate disease for its negative prognostic role. Further prospective trials are warranted.

E12

CIRCULATING TUMOR CELLS COUNT IN PROSTATE CANCER PATIENTS TREATED WITH ENZALUTAMIDE: THE LANZA STUDY

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Background: The prognostic value of circulating tumor cells (CTCs) count in patients on abiraterone is supported by multiple studies, including two prospective phase 3 trials enrolling patients treated with abiraterone (COU-AA-301) and docetaxel (Southwest Oncology Group; SWOG S0421). Although studies conducted with the CellSearch platform have shown that the presence of $\geqslant$ 5 CTCs is associated with poor survival in patients with mCRPC, CTCs cells can also be enumerated by using flow cytometry and fluorescent antibodies for negative and positive selection. In this prospective trial, we aimed to collect evidence confirming the role of CTCs count measured with flow cytometry as done by Hu et al (Citometry, 2010) in castration-resistant prostate cancer patients receiving enzalutamide.

Patients and Methods: Patients with metastatic castration-resistant prostate cancer who are started on enzalutamide as part of standard clinical practice are eligible for the LANZA trial. CTCs count is measured at baseline and after 12 weeks. Overall survival is the primary end point of the study. Radiographic progression-free survival (rPFS), >30% PSA and >50% decline at 12 weeks are secondary end points.

Results: A total of 53 patients have been enrolled in this study. In the sub-group of 45 patients in which CTC count was successfully performed, median CTC count was 5 and 6, at baseline and after 12 weeks. Median rPFS and OS were 6 and 9,5 months. A baseline CTCs count of >=5 vs. <5 was associated with a statistically significant worse rPFS (p=0,0455; HR=2,2870; 95% CI=1,0165 to 5,1454) and OS (p=0,0271; HR=3,0575; 95% CI=1,1351 to 8,2358). A stable or decreasing CTCs count at 12 weeks was associated with numerically improved rPFS (p=0,0668; HR=0,4615; 95% CI=0,2019 to 1,0551) and OS (p=0,1148; HR=0,4855; 95% CI=0,1978 to 1,1918). A CTCs count at baseline >=5 was also associated with reduced odds of having >50% and >30% declines at 12 weeks (OR=0,22; 95% CI=0,06 to 0,83; p=0,02 and OR=0,16; 95% CI=0,04 to 0,60; p=0,006, respectively).

Conclusions: Our study adds evidence that flow cytometry can be successfully used to enumerate CTCs in peripheral blood in patients with castration-resistant prostate cancer treated with enzalutamide. Further research is

required to improve outcomes in patients on enzalutamide with a baseline CTCs count >=5 and those with increasing CTCs count at 12 weeks.

E13

PROGNOSTIC ROLE OF BASELINE HEMOCHROME PARAMETERS AND THE DEVELOPMENT OF MACROCYTOSIS IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (mRCC) TREATED WITH SUNITINIB

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Background: Several data are available regarding baseline hemochrome parameters in metastatic renal carcinoma (mRCC) patients receiving TKI. Erythrocyte's mean corpuscular volume (MCV) increase is often observed during Sunitinib treatment and it is associated with better outcome.

Patients and methods: We retrospectively collected and analyzed data of 100 patients (pts) affected by mRCC treated with Sunitinib as first-line therapy between January 2006 until December 2018 in six Italian Oncology Unit (Como, Varese, Busto Arsizio, Gallarate, Vigevano and Pisa). We evaluated cellular blood count at the diagnosis of metastatic disease and during Sunitinib treatment. We evaluated NLR (neutrophil lymphocyte ratio), PLR (platelet-lymphocyte ratio) LMR (lymphocyte–monocyte ratio) and macrocytosis to establish the prognostic role of these factors. According to the available literature,we used the following cut off: NLR >3, PLR >150, LMR< 3 and for macrocytosis MCV >100 fl. Data regarding age, sex, performance status (PS), histology, BMI, previous nephrectomy, Furhman's grading, MSKCC score, Heng score and number of metastatic sites were collected. Overall survival (OS) and progression free survival (PFS) were calculated. Univariate and multivariate analysis using Cox's regression model with time-dependent (macrocytosis) covariate were applied to study factors influencing progression and survival, hazard ratios (HR) together with 95% confidence intervals were calculated.

Results: Of the100 patients enrolled,41 presented high NLR,41 presented high PLR, 37resented low LMR. Twenty-six patients developed macrocytosis;more frequently our patients developed macrocytosis during the third cycle of Sunitinib (range: 2-10). Low LMR was associated with worse outcome: median PFS was 10 months vs 14 months (p=0.02) and median OS was 23 vs 29 months (p=0.06). High PLR was associated with worse outcome in terms of PFS: median PFS was 8 month s vs 14 months (p=0.005); median OS was 23 vs 28 months (p=0.13). No significant differences in PFS and OS were observed between patients with high NLR and patients who developed macrocytosis. At the multivariate analysis, poor risk (Heng score), and high PLR and low LMR were significantly associated to lower PFS (HR 7.1, 2.0 and 1.9 respectively); poor PS and poor risk (Heng score) were related to worst OS.

Conclusions: In our cohort of patients affected with mRCC receiving Sunitinib in first-line treatment, high PLR and low LMR resulted associated with shorter PFS. Further prospective studies are required.

E14

PROGNOSTIC ROLE OF THE DURATION OF RESPONSE TO ANDROGEN DEPRIVATION THERAPY (ADT) IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER (mCRPC) PATIENTS (pts) TREATED WITH ENZALUTAMIDE (E) OR ABIRATERONE ACETATE (AA)

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Background: The introduction of new drugs for mCRPC brought the need of prognostic factors to guide treatment. Our retrospective study aims to evaluate the prognostic role of ADT duration in pts treated with E or AA.

Materials and Methods: 255 mCRPC treated with AA or E were included. Pts were divided in 3 groups according to ADT response (group 1 [G1]:<12 months [m]; group 2 [G2]: 12-36 m; group 3 [G3]: >36 m). Outcome measures were progression-free survival (PFS) and overall survival (OS).

Results: Pts with longer ADT response had better OS (median 17.3 m G1, 19.9 m G2, 31.6 m G3; HR G2 vs G1 0.64, 95%CI 0.40-1.02; HR G3 vs G1 0.41, 95%CI 0.25-0.64; p=0.001) and better PFS (median 5.9 m G1, 8.8 m G2, 11.7 m G3; HR G2 vs G1 0.56, 95%CI 0.37-0.85; HR G3 vs G1 0.41, 95%CI 0.41-0.27; p<0,001). In docetaxel-naïve pts, median OS was 18.8 in G1, 35.2 in G2 and not reached in G3, while median PFS was 7 m in G1, 9.3 m in G2 and 20 m in G3. The difference among 3 groups was significant for both OS (HR G2 vs G1 0.57, 95%CI 0.26-1.28; HR G3 vs G1 0.33, 95%CI 0.14-0.78; p=0.038) and PFS (HR G2 vs G1 0.57, 95%CI 0.30-1.11; HR G3 vs G1 0.31, 95%CI 0.15-0.62; p=0.003). In post-docetaxel pts

median OS was 13.1 m in G1, 17.2 m in G2 and 21.4 m in G3 (HR G2 vs G1 0.72, 95%CI 0.41-1.28; HR G3 vs G1 0.52, 95%CI 0.29-0.94; p=0.082), while median PFS was 5.2 m in G1, 6.8 m in G2 and 8.3 m in G3 (HR G2 vs G1 0.60, 95%CI 0.35-1.02; HR G3 vs G1 0.54, 95%CI 0.32-0.91; p=0.067). In pts treated with AA median OS was 17.3 m in G1, 16.3 m in G2 and 25.5 m in G3, while median PFS was 5.9 m in G1, 8.2 m in G2 and 11.4 m in G3. The difference among 3 groups was significant for both OS (HR G2 vs G1 0.71, 95%CI 0.41-1.25; HR G3 vs G1 0.38, 95%CI 0.22-0.67; p=0.001) and PFS (HR G2 vs G1 0.50, 95%CI 0.29-0.859; HR G3 vs G1 0.35, 95%CI 0.21-0.60; p=0.001). In pts treated with E median OS was 20.7 m in G1, 34.6 m in G2 and 41.1 m in G3 (HR G2 vs G1 0.56, 95%CI 0.24-1.30; HR G3 vs G1 0.37, 95%CI 0.14-0.96; p=0.121), while median PFS was 6 m in G1, 9.6 m in G2 and 17.6 m in G3 (HR G2 vs G1 0.65, 95%CI 0.34-1.25; HR G3 vs G1 0.40, 95%CI 0.19-0.82; p=0.041).
Conclusions: This retrospective study shows that ADT duration is an independent prognostic factor of outcome with AA or E.

E15

PROSPECTIVE TRANSLATIONAL STUDY INVESTIGATING MOLECULAR PREDICTORS OF RESISTANCE TO FIRST-LINE PAZOPANIB IN METASTATIC RENAL CELL CARCINOMA (PIPELINE STUDY)

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Background: Pazopanib is one of the standard of care in metastatic renal cell carcinoma patients The present study investigated plasma levels of circulating angiogenic factors (CAFs) in pts with mRCC treated with pazopanib to assess predictive biomarkers of resistance.
Patients and Methods: mRCC pts treated with first line pazopanib in a single Institution between July 2015 and February 2017 were prospectively enrolled. Levels of 7 CAFs of interest including IL-6, IL-8, SDF-1, VEGF-A, HGF, Osteopontin and E-selectin, quantified by Luminex® technology, were measured before treatment and every 4 weeks until disease progression (PD) defined by RECIST 1.1 criteria. Wilcoxon test for paired samples was used to compare CAFs levels at baseline (B) and PD.
Results: 25 pts were evaluated according to the statistical plan. Median follow-up was 29,2 months (m) (range [r] 3,4-41,8 m) and median progression free survival was 14,6 m (r 2,5-41,8 m). 6 pts (24%) are still in therapy, while 15 (60%) had PD and 4 (16%) stopped pazopanib due to toxicity. CAFs' levels in the samples of the 15 pts at PD were compared to correspondent B samples. Overall, median plasma levels of SDF-1 and VEGF-A were significantly higher at PD compared to B [SDF-1: B 574,67 pg/mL (r 200,8-2018,39) vs PD 1328,03 pg/mL (r 472,55-2126,96) p=0,011; VEGF-A: B 45,10 pg/mL (r 6,16-256,14) vs PD 62,4 pg/mL (r 39,42-186,74) p=0,011]. Conversely, median levels of E-selectin were significantly lower at PD compared to B [B 23882,51 pg/mL (r 11016,44-56948,61) vs PD 20588,30 pg/mL (r 10991,75-38415,71) p=0,017]. None of the remaining CAFs evaluated showed a significant variation between B and PD.
Conclusions: PD during first-line pazopanib was associated with significantly higher plasma levels of SDF-1 and VEGF-A. Monitoring of select CAFs levels during treatment may be useful to predict resistance to therapy. These findings warrant further investigation in larger trials.

E16

ANALYSIS OF POTENTIAL CLINICAL AND LABORATORY BIOMARKER OF RESPONSE TO IMMUNOTHERAPY IN ADVANCED, PRE-TREATED UROTHELIAL CARCINOMA

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Background: Immunotherapy is a new standard of care in the treatment of advanced, pre-treated urothelial carcinoma (UC). To date there is no validated biomarker of clinical outcome in this setting.
Patients and Methods: We evaluated clinical characteristics and laboratory biomarkers of 33 patients affected by UC treated at our institution with immunotherapy in second or further line from March 2017 to February 2019. Patients received anti-PD-L1 antibodies (namely, atezolizumab and durvalumab) within clinical trials that were available at our centre in that timeframe. Laboratory data at the beginning of immunotherapy (leukocytes, neutrophils, platelets, lymphocytes, eosinophils, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, haemoglobin, LDH) and clinical characteristics (line of therapy, site of metastases, best response to immunotherapy, development of immune-related adverse events (IRAEs) and their grade) were evaluated as possible predictors of outcome in terms of overall survival (OS) with Cox proportional hazards model (as far as laboratory parameters were concerned) and Kaplan-Meier estimator (when clinical parameters were considered).

Results: Median OS in our population was 5.17 months (range 0.53-22). We did not find a correlation between any of the considered laboratory data at the beginning of immunotherapy and overall survival. Among the explored clinical characteristics, we observed a statistically significant correlation between OS and the development of IRAEs: 15 patients who developed any kind of IRAE showed a significantly longer median overall survival than those who did not (6.53 [95%CI 3.92-9.15] vs 4.13 [95%CI 2.65-5.61] months, log-rank p = 0.043). Furthermore, 10 patients who developed clinically significant IRAEs (grade 2 or higher) had a significantly better median OS than those patients who developed no or lower grade of IRAE (grade 0 or 1) (6.6 [95%CI 3.6-9.6] vs 4.73 [95%CI 3.12-6.36] months, log-rank p = 0.021).
Conclusions: With the limitation of a small case series, our study suggests that the development of IRAE, in particular clinically significant ones, can be associated with a better outcome in patients treated with immunotherapy for advanced, pre-treated UC. However, no other baseline clinical or laboratory parameters were associated with clinical outcome. The research of biomarkers in this setting of patients is then very important and research efforts should be done in order to bridge this gap.

E17

CLINICAL OUTCOME OF METASTATIC RENAL CELL CARCINOMA PATIENTS TREATED WITH SYSTEMIC THERAPY: COMPARATIVE ASSESSMENT BETWEEN YOUNG AND OLD PATIENTS

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Background: Targeted therapy and immunotherapy have become standard of care for mRCC (mRCC). The objective of this study is to evaluate the impact of age on clinical outcomes of mRCC patients receiving targeted therapies and immunotherapy.
Patients and Methods: We conducted a retrospective analysis of 111 patients with mRCC treated at Modena Oncologic Center between 2006 and 2018. The patients were stratified into three groups: young (aged <45 years), middle-aged (aged 45-64 years), and old (aged ≥ 65 years). Overall survival (OS) curves were drawn using the Kaplan-Meier method, and Cox's proportional hazard regression model was used to compare OS within age groups.
Results: Among all the patients, median age was 65 years, 69.3% of patients were male, 86% had a clear cell histology and 76.6% received a previous nephrectomy. In according to Heng risk classification: 36 pts (32.4%) had a poor risk, 48 pts (43.2%) intermediate risk and 27 pts (24.3%) had a good risk. Median OS of all patients was 24 months (CI 95%, 18.21-29.78).
Young group included 14 pts (12.6%), middle-aged group 52 pts (46.8%), and old group 45 pts (40.5%).
There were no significant differences in terms of OS among young, middle-aged, and old group: median OS was 15 months (CI 95%, 12.94-17.05), 24 months (CI 95%, 14.68-39.31) and 27 months (CI 95%, 17.20-30.79) respectively, p = 0.068. All patients received at least one a line of targeted therapy. Patients treated with immunotherapy were 4 (28.6%) in young group, 17 (32.7%) in middle-aged group and 8 (17.8%) in old group.
Conclusions: To our best knowledge, this is the first analysis that takes into consideration the impact of age on the clinical outcome of patients treated both targeted therapy than immunotherapy in a real word setting. Younger patients with mRCC treated with systemic therapy seem to have a worse OS not statistically significant compared with old patients but our data are limited for the small number of patients of this group.

E18

THE ROLE OF 18F-FDG-PET/CT IN ASSESSING THE RESPONSE TO NIVOLUMAB IN METASTATIC RENAL CELL CARCINOMA (mRCC)

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Background: ^{18}F-FDG-PET/CT (PET/CT) showed high sensitivity in predicting response to immunotherapy in melanoma and lung cancer. Its role in metastatic renal cell carcinoma (mRCC) remains debated. We aimed to evaluate the role of PET/CT in assessing disease response in mRCC patients (pts) and to compare metabolic and morphological criteria of response to immunotherapy.
Materials and Methods: We retrospectively evaluated pts with mRCC who performed both PET/CT and CT-scan to stage the disease before and after 6 cycles of nivolumab (N) (3 mg/Kg, two-weekly) at our Institution. We tested the agreement between the two imaging modalities by using RECIST 1.1 criteria for the CT-scan and EORTIC criteria for PET/CT.
Results: Seventeen cases were analyzed. The basal staging showed an agreement between the two exams in 14/17 cases (82%). In 2/3 discordant cases, PET/CT showed the presence of bone metastases (mets), not described at CT-scan. In the third patient, the metabolic imaging resulted negative despite the presence of bone and pancreatic mets at the CT-scan. After 6 cycles of N, in 12/14 cases concordant at the basal evaluation (86%) it was confirmed the inter-modality agreement. In the remaining 2 pts

(14%), the agreement was lost with PET showing a complete metabolic response and CT-scan a partial response. Of the 3 basal discordant cases, the restaging showed an inter-modality agreement in 2 pts, while the 3rd case remained discordant with negative PET/CT and positive CT scan. Thus, the post-treatment agreement was observed in 14/17 cases (82%).

Conclusions: The agreement between CT-scan and PET/CT was high and maintained after N. Although PET/CT was found to be sensitive in staging patients with mRCC, the exam did not add further information with respect to CT-scan.

E19

SAFETY PROFILE OF TIVOZANIB IN FIRST-LINE TREATMENT FOR ADVANCED RENAL CELL CARCINOMA (RCC): A REAL-WORLD RETROSPECTIVE STUDY

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Background: Tivozanib is an oral selective VEGFR1/2/3 inhibitor with limited off-target interaction, that was recently authorized in our country as a first line therapy for metastatic renal cell carcinoma (mRCC) within a nominal patient program (NPP).

Patients and Methods: We retrospectively collected clinical data of patients (pts) diagnosed with clear cell mRCC treated with first-line Tivozanib between November 2018 and May 2019 at a single Italian Institution. Tivozanib was administered at the dose of 1340 mcg once daily for 21 days, followed by a 7-day rest every four weeks. Restaging whole-body CT-scan was performed every 12 weeks. Aims of this study were to evaluate early safety profile and to assess incidence of primary resistance of Tivozanib (defined as the percentage of patients experiencing disease progression [PD] according to RECIST 1.1 at the first radiological evalutation) in the real-world population.

Results: 17 pts received Tivozanib. They were mostly male (13, 76,4%), with median age of 70 years (range, 47-83 years), ECOG performance score 0-1 in 14 pts (82,3%), ⩾2 in 3 pts (17,6%). According to Heng's criteria, 3 pts (17,6%) were classified as low risk, 12 (70,5%) as intermediate (among them 10 pts [83,3%] scoring 1 and 2 [16,6%] scoring 2) and 2 (11,7%) as poor risk.

At a median follow up of 4,4 months, 3 pts (17.6%) experienced adverse events (AEs) grade (G) 3-4 (i.e. 1 patient had an hypertensive crisis, 2 patients experienced fatigue), requiring a dose reductions of Tivozanib to 890 mcg in 2/3 pts (11,7%). Common G1-2 AEs included stomatitis (41%), hypertension (35%), hand-foot syndrome (29,4%), nausea/vomiting (29,4%), fatigue (29,4%) and diarrhea (23,5%). At a lower frequency we also observed hypothyroidism (11,7%), dysphonia (11,7%), xerostomia (5,8%), epistaxis (5,8%), cough (5,8%) and penile mucositis (5,8%). One patient discontinued Tivozanib due to patient's decision without evidence of PD. 12 pts (70,5%) had at least one radiological tumour restaging.

Among the evaluable cases, only 1 pt (8.3%) experienced PD at first radiological evaluation.

Conclusions: Tivozanib was safe and well tolerated as first line in patients with mRCC. Few patients had progressive disease as best response.

E20

EFFECT ON RENAL FUNCTION OF REPEATED ADMINISTRATIONS OF CONTRAST MEDIA IN NEPHRECTOMIZED CANCER PATIENTS AFFECTED BY METASTATIC RENAL CELL CARCINOMA: A RETROSPECTIVE STUDY

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Background: Patients with renal carcinoma (RCC) presents with concomitant chronic kidney disease (CKD) with a frequency which is about twice that of the general population; moreover, being often nephrectomised and therefore with a reduced renal functional reserve (RFR), they also present a higher incidence of acute kidney failure (AKI). Thus, we decided to evaluate the progression of renal impairment in metastatic RCC patients who underwent computed tomography (CT) scans every three months, being enrolled in experimental trials. The presence of risk factors for CKD and the possible correlation with the time elapsed between nephrectomy and the first CT scan showing the presence of metastatic disease was also evaluated.

Patients and Methods: We analyzed a total of 76 patients, 59 males (78%) and 17 females (22%); 68 (89.5%) were nephrectomized for neoplasia (average age: 59.72, standard deviation (SD): 10.51; average Body Mass Index: 26.55, SD: 4.47). The trend of renal function was evaluated on the 40 mRCC patients for which all the data investigated at the following timepoints were available: T0 (i.e. baseline), T3, T6 and T9.

Results: The eGFR trend (calculated by means of the CKD-EPI formula) was substantially stable, a drop of just 2 ml/min in 9 months having been observed. Intriguing, and statistically significant ($p = 0.007$), was the finding of a more marked worsening of eGFR (10 ml/min in 9

months) in hypertensive patients, worsening that is not observed in the other populations of patients considered, and that it could have been caused by the additional effect of the antiangiogenic drugs used. No correlations were found between renal function and the time elapsed between nephrectomy and the first CT scan.

Conclusions: Even in nephrectomized patients, CT contrast medium appears to play a secondary role on the incidence of AKI, or on worsening of CKD. We should therefore be more liberal in the use of contrast medium, even in nephrectomized cancer patients.

E21

ESTABLISHMENT OF A NEAR-PATIENT PRIMARY CULTURE OF BONE METASTASIS FROM UROTHELIAL CARCINOMA

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Background: Bladder cancer is the most common malignant disease of the urinary tract. Among these, urothelial carcinoma (UC) accounts for 90% of cases of bladder cancer. In advanced UC diagnosis, skeletal involvement is frequent. Here we report the establishment of a primary culture of bone metastasis (BM) from High Grade UC derived from a 81 years-old patient with a previous diagnosis of papillary urothelial cancer in 2016. After 2 years, patient relapsed to bone and visceral sites and because of poor clinical condition, she underwent palliative best supportive care.

Material and Methods: Patient-derived bone metastatic cell culture was obtained from a surgical specimen. Tumor cells were isolated by collagenase digestion. Cells were seeded on 2D in vitro plates or into 3D in vitro collagen scaffolds composed of bovine collagen type I. The establishment of tumor cell isolation was confirmed through the evaluation of cytomorphologic features and positive pancitokeratin staining. Then, drugs treatment was performed both in 2D and 3D platforms. Cell survival was evaluated through MTT assay. The study was approved by Ethical Committee and patient signed an informed consent.

Results: Cells cultured on 2D plates were heterogeneous and composed by fibroblast-like and tumor cells. After a long-term culture, we were able to isolate from a 3D scaffold a tumor clone that successfully grow in 2D plates until passage 11. Stabilized cells generated spheroid-like aggregates, similar to acinar-structures typical of the primary papillary urothelial tumor. Next, we treated cells with the following drugs: Gemcitabine (Gem), Carboplatin (Carbo), Docetaxel, Carbo+Gem and Bone targeted drugs (Zoledronic Acid and Denosumab). The most effective treatment was Gem+Carbo, obtaining 24% of survival in 2D plates and 87% on 3D collagen scaffold. For all the treatment, cells cultured on 3D scaffold were more resistant to drugs, mimicking more closely the in-vivo condition.

Conclusions: We were able to isolate and establish a BM primary culture from UC using a 3D in-vitro collagen scaffold. This system can recreate microenvironmental conditions more similar to in-vivo ones and it promoted the isolation of tumor cell clones from the stromal components of the heterogeneous primary culture. This cell line could be useful to investigate the molecular and genetic profile in order to identify promising molecular targets and to better understard the natural history of BM from UC.

E22

TREATMENT DURATION OF UPFRONT ABIRATERONE ACETATE (AA) FOR METASTATIC CASTRATION RESISTANT PROSTATE CANCER (MCRPC) PATIENTS

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Background: AA is a selective androgen synthesis inhibitor that showed efficacy in both mCRPC and metastatic castration sensitive prostate cancer. Treatment duration in first-line may vary, depending on patients' characteristics and disease-related factors, and may affect overall outcome.

Patients and methods: In our monoinstitutional real-world observational study we report retrospective data on 53 patients (pts) treated with AA in first-line setting. Pts were divided in two groups according to treatment duration ($\geqslant$ or $<$ 13.8 months, group 1 and 2, respectively). The cut-off was based on the median treatment duration in the COU-AA-302 trial.

We recorded median duration of AA treatment, objective responses according to RECIST criteria, 50% PSA reduction rate, toxicity, and median overall survival in both groups.

Results: Group 1 included 28 pts, while group 2 included 25 pts. Median age at treatment start, prevalance and types of comorbidities, disease volume and metastatic sites were similar between the groups. Median duration of previous hormonal treatment was 35 months (r. 9-157) in group 1 versus 16 months (r. 4-47) in group 2. In group 1, 25% of the pts presented with metastatic disease at diagnosis, while they were 40% in group 2. Nearly all the pts (96%) in group 1 had PS ECOG 0-1, while there were 32% PS ECOG 2 pts in the second group. The median PSA level was lower in group 1 (4,9 ng/mL), while it was 16,2 ng/mL in group 2. The 50% PSA reduction rate was 86% in group

1 and 40% in group 2. Median AA treatment duration in group 1 was 24 months (r. 16-47) and in group 2 it was 6 months (r. 3-13). Overall response rate was 43% in group 1 with 11% of complete responses and 8% in group 2. Accordingly, median overall survival was doubled in group 1 with 40 months (r.17-56) versus 18 months (r.4-42) in group 2.
Subsequent treatments were given to 56% of pts in group 1 and 48% of pts in group 2.
The most frequent toxicities in both groups were fatigue and anemia, thus not exceeding grade 2 of WHO scale. Cardiac toxicity caused permanent dose reduction in 2 pts in group 1 and treatment withdrawal in 3 pts (1 pt in group 1, 2 pts in group 2).
Conclusions: To have localized disease at diagnosis, longer exposure to hormonal agents in castration sensitive setting, low PSA levels and better PS at AA start seemed to predict longer AA exposure, with higher response rate, increased chances to receive subsequent therapy after AA failure, and longer overall survival.

E23

INTERVAL STEREOTACTIC RADIOTHERAPY FOR THE TREATMENT OF OLIGO-PROGRESSIVE PATIENTS WITH METASTATIC RENAL CARCINOMA RECEIVING VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS

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Background: To date metastatic renal cell carcinoma (mRCC) remains a major cause of cancer-related death for in the western world. Despite considerable progresses achieved in the last decade, nearly 30% of patients with RCC still present with synchronous metastases at diagnosis, and up to one third of surgically excised patients subsequently develop recurrent and/or metastatic disease. This retrospective observational study evaluated the role of hypo-fractionated stereotactic radiotherapy (SRT) in patients with oligoprogressive metastatic renal cell carcinoma (mRCC) treated with first-line oral tyrosine kinase inhibitors (TKI). Local control, delay of further progression and safety data are reported.
Material and Methods: Between January 2010 and December 2016, 28 patients with mRCC who showed oligoprogressive disease while receiving first-line pazopanib were treated with hypo-fractionated SRT on progressive metastatic sites in order to delay change of systemic therapy. First and second progression-free survival (PFS-1 and PFS-2) were recorded, as well as objective response and toxicity.
Results: After pazopanib 9 partial remissions (32%), 12 stable disease (43%) and 7 progressions (25%) were recorded. Median time to progression (PFS-1) to first-line pazopanib before oligoprogression was 9.45 months (range 2-30 months). Seventeen patients (61%) showed progression at pre-existing tumor sites and 11 patients (39%) showed the appearance of new metastases. PFS-2 after radiation therapy was 4.55 months (range 1-11 months). PFS-1 + PFS-1 was 14.0 months (range 3-41 months). SRT is feasible and effective without severe toxicity in most patients.
Conclusions: Oligoprogressive mRCC patients treated with first-line pazopanib may benefit from a hypo-fractionated high-dose SRT at progressing sites achieving a a further increase in median progression-free survival (PFS-2). Further studies and prospective validation are required to establish if this minimally invasive approach may have a positive impact on overall survival and patients' reported outcomes.

E24

THE TREATMENT OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC): INITIAL EXPERIENCE WITHIN THE ONCOLOGY UNITS OF THE DEPARTMENT OF ONCOLOGY (DO) OF THE AZIENDA TOSCANA NORD OVEST (ATNO)

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Background: This work describes the "real life" experience based on retrospective data of a sample of patients (pts) with a diagnosis of mCRPC treated in the DO of the ATNO. The chosen sample includes pts who accessed in our divisions in the last 6 months and analyzed all treatments received in their clinical history.
We analyzed 92 mCRPC pts who received at least one line of treatment for mCRPC. Median age 78 years (range 58-90), with a percentage of GS >=OF 55%. 39 had

metastatic disease *ab initio*; almost all of these (90%) had bone or lymph nodes metastases, while only 10% had at least three sites of disease with visceral organ involved.
Patient and metods: 92 pts received a first-line treatment: 55 (60%) Abiraterone Acetato/prednisone (AA/P): 50 are assessable for response with 23 RP* and 26 SD and a median time to progression (mTTP) of 13 months (mos) (range 6-39); -22 (24%) Enzalutamide (E): 19 are assessable for response with 10 RP* and 8 SD with a mTTP of 9.5 mos (range 7-16); 15 (16%) Docetaxel (TXT): 12 are assessable for response with 8 RP* and 2 SD and a mTTP of 11 mos (range 4-13). In second-line we treated 35 patients: 11 (31%) pts with new hormonal agents (NOA): 10 are assessable for response with 5 RP* and 5 SD and a mTTP di 19.5 mos (range 5-45); 24 (68%) pts with TXT:18 are assessable for response with 9 RP* and 8 SD and a mTTP of 7.5 mos (range 3-19).
If we analyze data of 22 pts who received a sequence of 2 lines of therapy we find that: 16 (73%) pts who received the sequence of NOA (AA/P or E) --> TXT have a mTTP of about 26 mos (range 15-49); 6 (27%) pts treated with the sequence of TXT-->NOA achieve a mTTP of about 22 mos (range 16-56).
**RP: radiologic or biochemical*
Results: Although the analysis includes only a little sample of our pts the experience is consistent with data reported in literature. We are collecting data about the entire populaton and plannig to perform bio-molecular analysis in order to identify possible predictive factors of response to treatments.
Conclusions: In our sample 84% of pts used NOA as first-line treatment; these data suggest that an advantage could derive from the use of NOA, but this is a small and not selected series; our objective is to evaluate in a large series the ideal sequence of treatments and the prognostic impact of further lines of therapy.

F - Gynaecological Tumours

F01

EFFECT OF MAINTENANCE RUCAPARIB ON POSTPROGRESSION OUTCOMES IN PATIENTS WITH PLATINUM-SENSITIVE, RECURRENT OVARIAN CARCINOMA (OC) AND UPDATED SAFETY DATA FROM THE PHASE 3 STUDY ARIEL3

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Background: In ARIEL3 (CO-338-014; NCT01968213), rucaparib maintenance treatment significantly improved progression-free survival (PFS) vs placebo in all predefined cohorts: *BRCA* mutant; *BRCA* mutant + wild-type *BRCA*/high loss of heterozygosity (LOH high); and intent-to-treat (ITT) population. Here we report prespecified exploratory, investigator-assessed postprogression endpoints, including time to start of first subsequent therapy (TFST), time to second PFS or death (PFS2), and time to start of second subsequent therapy (TSST). We also report updated safety data using a later cutoff (31 December 2017) than previously published (15 April 2017; Coleman et al. *Lancet*. 2017;390:1949-61).
Material and Methods: Patients were randomised 2:1 to receive oral rucaparib 600 mg twice daily or placebo. Exploratory endpoints were analysed in all 3 predefined cohorts.
Results: Exploratory efficacy endpoint data are given in the Table. As of 31 December 2017, the most common treatment-emergent adverse events of any grade (rucaparib vs placebo) were nausea (75.8% vs 36.5%), asthenia/fatigue (70.7% vs 44.4%), dysgeusia (39.8% vs 6.9%), and anaemia/decreased haemoglobin (39.0% vs 5.3%). The most common grade ⩾3 treatment-emergent adverse events were anaemia/decreased haemoglobin (21.5% vs 0.5%) and increased alanine/aspartate aminotransferase (10.2% vs 0.0%).
Conclusions: Prior treatment with rucaparib significantly improved the clinically meaningful postprogression endpoints TFST, PFS2, and TSST vs placebo in all predefined cohorts of patients with platinum-sensitive, recurrent OC. The updated safety profile was consistent with prior reports.

F02

BEVACIZUMAB OR PARP-INHIBITORS MAINTENANCE THERAPY FOR PLATINUM-SENSITIVE (PS) RECURRENT OVARIAN CANCER (ROC)? A NETWORK META-ANALYSIS (NMA)

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	BRCA mutant		*BRCA* mutant or wild-type *BRCA*/LOH high		ITT	
	Rucaparib (n = 130)	Placebo (n = 66)	Rucaparib (n = 236)	Placebo (n = 118)	Rucaparib (n = 375)	Placebo (n = 189)
TFST						
Median, mo	19.0	7.2	16.4	7.6	12.5	7.4
HR (95% CI); *P* value	0.29 (0.20–0.42); *P*<0.0001		0.40 (0.30–0.52); *P*<0.0001		0.43 (0.35–0.53); *P*<0.0001	
PFS2						
Median, mo	26.1	17.9	24.7	17.9	21.1	16.5
HR (95% CI); *P* value	0.44 (0.29–0.69); *P* = 0.0003		0.57 (0.41–0.79); *P* = 0.0006		0.62 (0.48–0.79); *P* = 0.0001	
TSST						
Median, mo	NR	19.4	26.5	19.4	22.2	18.6
HR (95% CI); *P* value	0.49 (0.31–0.78); *P* = 0.0024		0.58 (0.41–0.82); *P* = 0.0018		0.70 (0.54–0.91); *P* = 0.0064	

Visit cutoff 15 April 2017 (date of unblinding for primary efficacy analyses).
HRs estimated with a Cox proportional hazards model.
CI, confidence interval; HR, hazard ratio; NR, not reached.

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Background: Patients (pts) experiencing a PS rOC are generally re-exposed to a platinum based-chemotherapy (CT). In this setting, the addition of a concomitant and/or maintenance targeted agent as bevacizumab (BEV) or as PARP inhibitors (PARPi) has shown to improve progression free survival (PFS). In the absence of direct comparison in randomized trials (RCTs), we have performed a NMA to evaluate differences in efficacy between BEV and PARPi in pts with PS rOC, according to BRCA status.

Material and methods: We searched PubMed, Embase and Medline for RCTs involving pts with PS rOC treated with BEV (n=3, 1563 pts) or PARPi (n=5, 1839 pts). Only trials with PFS as primary endpoint were included. Trials in first line setting were excluded. Analyses have been done pooling pts who had received PARPi in three groups, according to the available data on BRCA genes status: all comers (AC), BRCA mutated pts (BRCAm) and BRCA wild-type pts (BRCAwt). A frequentist approach has been used with R statistical software. To rank the effect size of treatments, surface under the cumulative ranking value (SUCRA) has been applied.

Results: In AC pts, PARPi improved PFS compared to BEV (hazard ratio [HR]=0.70, 95% CI 0.54-0.91). In BRCAm pts the gain in PFS for PARPi was even higher compared to BEV (HR=0.46, 95% CI 0.36-0.59). In BRCAwt pts the benefit of PARPi over BEV was not statistically significant (HR=0.87, 95% CI 0.63-1.20) but PARPi had the highest likelihood of being ranked as the best treatment in terms of efficacy according to SUCRA (90% and 60%, respectively for PARPi and BEV).

Treatments	AC	BRCAm	BRCAwt
PARPi vs BEV	0.70 (0.54-0.91)	0.46 (0.36-0.59)	0.87 (0.63-1.20)
PARPi vs CT	0.38 (0.31-0.47)	0.25 (0.21-0.31)	0.48 (0.36-0.63)
BEV vs CT	0.55 (0.31-0.47)	0.55 (0.48-0.63)	0.55 (0.47-0.64)

Conclusions: According to indirect comparisons, PARPi performed the best for the treatment of PS rOC, especially in BRCAm pts who had not previously received PARPi. BEV could be still an option in BRCAwt pts.

Hazard ratio for PFS between PARPi, BEV and CT in the three cohorts.

F03

EFFECT OF PRIOR BEVACIZUMAB THERAPY IN PATIENTS WITH PLATINUM-SENSITIVE RECURRENT OVARIAN CARCINOMA IN THE PHASE 3 STUDY ARIEL3 OF RUCAPARIB MAINTENANCE TREATMENT

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Cohort	Rucaparib, n	Placebo, n	PFS (investigator review)		PFS (BICR)	
			HR[a] (95% CI)	Median PFS, mo; *P* value[b]	HR[a] (95% CI)	Median PFS, mo; *P* value[b]
			Rucaparib vs placebo		Rucaparib vs placebo	
BRCA mutant						
Prior bevacizumab	28	11	0.31 (0.11–0.89)	15.9 vs 2.8; *P* = 0.0213	0.20 (0.06–0.68)	22.9 vs 3.0; *P* = 0.0053
No prior bevacizumab	102	55	0.20 (0.13–0.31)	17.1 vs 5.4; *P*<0.0001	0.19 (0.11–0.32)	26.8 vs 5.5; *P*<0.0001
BRCA mutant or *BRCA* wild type/LOH high						
Prior bevacizumab	52	26	0.34 (0.17–0.70)	11.1 vs 3.0; *P* = 0.0021	0.38 (0.17–0.88)	22.9 vs 4.1; *P* = 0.0191
No prior bevacizumab	184	92	0.30 (0.22–0.41)	13.6 vs 5.4; *P*<0.0001	0.32 (0.22–0.47)	24.7 vs 5.5; *P*<0.0001
ITT						
Prior bevacizumab	83	43	0.42 (0.26–0.68)	10.3 vs 5.4; *P* = 0.0002	0.39 (0.23–0.68)	13.7 vs 5.4; *P* = 0.0005
No prior bevacizumab	292	146	0.35 (0.28–0.45)	10.9 vs 5.4; *P*<0.0001	0.35 (0.27–0.46)	13.7 vs 5.4; *P*<0.0001

[a]Stratified Cox proportional hazards model; *P* values for treatment-by-prior bevacizumab subgroup interactions were nonsignificant for all analyses.
[b]Stratified log-rank *P* value.
CI, confidence interval; HR, hazard ratio.

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Background: In ARIEL3, rucaparib significantly improved progression-free survival (PFS) vs placebo in all predefined nested cohorts: *BRCA* mutant; *BRCA* mutant or *BRCA* wild type/high loss of heterozygosity (LOH high); and intent-to-treat (ITT) population. This exploratory subgroup analysis investigated the effect of prior bevacizumab therapy on the primary and secondary endpoints of investigator-assessed and blinded independent central review (BICR)-assessed PFS.
Material and Methods: Patients were randomised 2:1 to receive oral rucaparib (600 mg BID) or placebo as maintenance after response to platinum-based chemotherapy. PFS was assessed in the predefined cohorts of subgroups based on prior bevacizumab use (allowed as part of penultimate or earlier treatment [not a stratification factor]).
Results: The visit cutoff dates for efficacy and safety were 15 April 2017 and 31 December 2017. In the rucaparib and placebo arms, 22.1% (83/375) and 22.8% (43/189) of patients had received prior bevacizumab. PFS data are shown in the Table. The most frequent any-grade treatment-emergent adverse events (TEAEs; rucaparib vs placebo) were asthenia/fatigue (prior bevacizumab, 78.3% vs 37.2%; no prior bevacizumab, 68.5% vs 46.6%) and nausea (77.1% vs 27.9%; 75.4% vs 39.0%); the most frequent grade ⩾3 TEAE was anaemia (28.9% vs 0%; 19.4% vs 0.7%).
Conclusions: In ARIEL3, rucaparib significantly improved PFS in all predefined cohorts regardless of whether patients received prior bevacizumab therapy.

F04

ATHENA (GOG-3020/ENGOT-OV45): A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 STUDY OF THE POLY(ADP-RIBOSE) POLYMERASE (PARP) INHIBITOR RUCAPARIB + THE PD-1 INHIBITOR NIVOLUMAB FOLLOWING FRONTLINE PLATINUM-BASED CHEMOTHERAPY IN OVARIAN CANCER

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Background: Rucaparib has clinical activity in patients with recurrent ovarian cancer with or without homologous recombination (HR) deficiency (HRD; eg, a *BRCA* mutation or high genomic loss of heterozygosity [LOH high]) and is hypothesised to provide clinical benefit to patients following frontline treatment. ATHENA (EudraCT 2017-004557-17; NCT03522246) is evaluating rucaparib + nivolumab as maintenance treatment following frontline platinum-based chemotherapy in patients with newly diagnosed, high-grade ovarian, fallopian tube, or primary peritoneal cancer. The rationale for this combination includes: tumours with *BRCA* mutations express tumour-specific proteins (neoantigens), which attract PD-L1-expressing, tumour-infiltrating lymphocytes; ovarian tumours with HRD have more neoantigens relative to HR-proficient tumours and may respond to immune checkpoint inhibitors; rucaparib combined with anti-PD-1/PD-L1 demonstrated improved antitumour activity in an ovarian cancer model; it is hypothesised that PARP inhibitor–induced DNA damage may increase neoantigens, regardless of HRD status.

Material and Methods: Eligible patients must have completed frontline platinum-doublet chemotherapy and surgery and achieved an investigator-assessed response without disease progression or rising CA-125 at any time during frontline treatment. Cytoreductive surgery (R0 permitted) could have been completed prior to chemotherapy or following neoadjuvant chemotherapy. Patients will be randomised 4:4:1:1 to receive maintenance treatment in Arm A (oral rucaparib 600 mg BID + intravenous [IV] nivolumab 480 mg Q4W), Arm B (oral rucaparib + IV placebo), Arm C (oral placebo + IV nivolumab), or Arm D (oral placebo + IV placebo). Stratification factors include centrally determined tumour HRD status (*BRCA* mutant, non-*BRCA* mutant/LOH high, non-*BRCA* mutant/LOH low, or non-*BRCA* mutant/LOH indeterminate), posttreatment disease status (residual vs no residual disease), and timing of surgery (primary vs interval debulking). Investigator-assessed progression-free survival (RECIST v1.1, primary endpoint) will be compared between arms. Secondary endpoints include blinded independent central review of progression-free survival, overall survival, objective response rate, and safety.

Results: Patients (n≈1000) will be enrolled at >270 sites worldwide, including in Italy.

Conclusions: ATHENA is evaluating rucaparib + nivolumab as frontline maintenance treatment in patients with ovarian cancer.

F05

FIRST-LINE TREATMENT IN A REAL LIFE COHORT OF ELDERLY PATIENTS WITH OVARIAN CANCER: DETERMINANTS OF CHOICE AND OUTCOME

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Background: Women aged=70 represent nearly 25% of ovarian cancer (OC) patients (pts). However, elderly OC pts are significantly under-represented in clinical trials and they are less likely to receive the optimal treatment. Furthermore, multidimensional geriatric assessment is still underused. The present study aims to provide an overview of real-life treatment strategies for elderly advanced-OC pts and to investigate clinico-pathological features that could potentially drive choice of first-line treatment.

Materials and methods: A retrospective analysis was conducted on a consecutive series of 45 OC pts aged=69, FIGO stage IIb-IV, treated with first-line chemotherapy (1L_CT) from 2011 to 2018 at CRO Aviano National Cancer Institute (Italy). Factors associated with treatment choice and rate of adverse events were analyzed through Fisher-exact test; differences in progression free survival (PFS) and overall survival (OS) were tested by log-rank test.

Results: Overall, 67% of pts received 1L_CT with a standard carboplatin-paclitaxel combination (CPC). Conversely, 33% received single-agent treatment (SAT) (31% with carboplatin and 2% with paclitaxel). ECOG PS=1 was the only factor significantly associated with choice of SAT (P=0.021); conversely, comorbidities and polypharmacy were not associated with treatment decision. No differences were observed between CPC and CPC with dose reductions (CPCdr), neither in PFS (HR=1.29 P=0.59) nor in OS (HR=1.40 P=0.56). On the other hand, SAT was associated with shorter PFS (HR=4.35 P=0.001) and OS (HR=4.48 P=0.005). Rates of neutropenia, thrombocytopenia, neuropathy,

constipation, diarrhoea, asthenia, and treatment discontinuation were not statistically different among different subgroups (CPC, CPCdr and SAT).
Conclusions: CPC represents the first-line standard therapy for advanced OC pts. The present study suggests that, in elderly patients, a dose reduction could be preferable to single agent regimen. Of note, clinical decision-making was mainly driven by PS ECOG, emphasizing the value of multidimensional geriatric assessment. Notwithstanding the limitations due to the small sample size, the evaluated regimens showed a comparable toxicity profile.

F06

ARTHRALGIA IN PATIENTS WITH OVARIAN CARCINOMA TREATED IN FIRST LINE WITH BEVACIZUMAB AND CHEMOTHERAPY

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Background: Chemotherapy with carboplatin, paclitaxel and bevacizumab is the standard therapy in patients with advanced stage ovarian cancer after primary surgery. Most frequent side effects of bevacizumab in this setting are hypertension, thrombosis, haemorrhage, proteinuria, while arthralgia has been poorly described.
Patients and Methods: A retrospective analysis was performed to describe the occurrence and outcome of arthralgia in 114 patients with advanced ovarian cancer, treated in first line with combination of carboplatin, paclitaxel and bevacizumab. Statistical analyses was performed to investigate a possible prognostic role of arthralgia with progression-free survival (PFS) as endpoint.
Results: Forty-seven out of 114 patients (41%) developed arthralgia during therapy. All patients had grade 1 and grade 2 arthralgia. The toxicity persisted after the end of bevacizumab in 17 patients (36%). Median PFS for patients without arthralgia was 18 months (95% CI: 14-24) compared to median PFS of 29 months (95% CI: 21-not reached) for patients experiencing arthralgia. This difference was statistically significant. In order to avoid possible biases related to treatment duration, a multivariable Cox proportional hazards model including the toxicity as a time dependent variable and age, stage and residual disease after primary surgery was performed. In this model no variable showed a statistically significant association with PFS.
Conclusions: Our retrospective analysis showed a high incidence of arthralgia (30%), with several patients with residual symptoms after the end of therapy. The prognostic role of arthralgia is not demonstrated in this study probably due to the limited sample size; further wide investigation focused on occurrence of arthralgia, evaluating also the mechanisms involved in the pathogenesis, particularly the relationship with the immune system response, are needed. Also guidelines for treatment are needed.

F07

INCIDENCE AND PREVALENCE OF SEXUAL DYSFUNTIONS AMONG WOMEN TREATED FOR OVARIAN CANCER. OBSERVATIONAL STUDY

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Background: Some cancers such as breast, ovarian and uterine have a direct effect on woman sex organ moreover the treatments delivered have the potential to alter sexual function. Literature data about the prevalence of sexual dysfunctions among cancer women are scarce, but nevertheless emerges that sexual consultancy and psychological support are insufficient.
Patients and Methods: From January 2014 to December 2017, we asked 31 consecutive women with surgical treated ovarian cancer to participate at observational study focused on sexual dysfunction. 24 women accepted to participate by filling out " the Female Sexual Function Index (FSFI" after 3, 6 and 12 months from the end of treatment (surgery + chemotherapy). Mean age was 53 years (44-61), all pts were sexual active before ovarian cancer diagnosis and all pts completed the study.
Results: Based on the total function score 23 out of 24 women had sexual dysfunction after 3 months from end treatment. At 6 and 12 months, 21 and 19 women continued to suffer of sexual dysfunctions based on FSFI.Sexual dysfunctions were irrespective of age, marital status, educational level, stage of disease and chemotherapy period. At 12 months, 5 women reported improvement of FSFI but with residual degree of sexual dysfunctions. These shared some characteristics: younger age (41-46 years), healthy life style and gynecological support. No women received sexual consultancy or psychological support as care plan before or after treatment.
Conclusions: Our observational study underlines the highest incidence and the prevalence in time of sexual dysfunctions among women with treated ovarian cancer. Healthy lifestyle and sexual consultancy could improve sexual dysfunctions.

F08

LONG SURVIVAL IN PATIENTS WITH OVARIAN CANCER TREATED WITH TRABECTEDIN AND PLD: EXPERIENCE OF A SINGLE CENTER

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Background: In the natural history of ovarian cancer (OC), the majority of patients experience disease recurrence; when it falls between 6 and 12 months after the end of the first platinum-containing chemotherapy (CT) line, OC is defined as partially sensitive to platinum. In this patient setting a therapeutic alternative is represented by the association of Trabectedin and Pegylated Lipisomal Doxorubicin (PLD). We report our experience that brings together 4 cases treated with this CT scheme who had a complete response that remained so for a particularly long period of time.
Patients and Methods: Patients, aged between 62 and 68 years at diagnosis, are affected by OC with histology of serous carcinoma, grade 3 of malignancy, stage IIIC. Three of these patients were negative for mutations in the BRCA 1 and 2 genes, while one patient was positive for the BRCA 1 gene mutation. All have performed surgery of total laparoisterectomy, bilateral annessiectomy, pelvic peritonectomy, omentectomy and appendectomy (Litaboa). Two of these patients underwent adjuvant CT with carboplatin and paclitaxel for 6 cycles and went into lymph node recurrence of disease after 10 and 11 months respectively, after the end of adjuvant CT. The third patient presented, after 8 months from the end of CT, a pelvic recurrence to the PET for which she was subjected to surgery which confirmed the presence of disease at the level of the vagina, bumper and intestinal wall. The fourth patient performed Carboplatin and Paclitaxel for 4 cycles with a neoadjuvant purpose, interval surgery and a further 5 cycles of the same scheme for adjuvant purposes. After an 8-month disease-free interval, she performed a second surgery for relapse at the lymph nodes and intestinal wall.
Results: All four patients underwent CT with Trabectedin and PLD for a number of cycles between 6 and 9. All patients are free of disease for at least 60 months after the end of that CT. Regarding treatment-related gastro-enteric and cutaneous toxicities, the CT scheme with Trabectedin and PLD was well tolerated. With regard to haematological toxicity, we report only in a patient grade 3 neutropenia that did not, however, cause a delay in drug administration. We do not report grade 1 and 2 toxicities.
Conclusions: The patients examined confirm the efficacy of Trabectedin and PLD in relapsed OC in partially platinum-sensitive patients, in agreement with the results observed in the randomized phase III trial OVA-301.

G - Sarcomas

G01

CAN THE PLASMA PD-1, PD-L1, PAN-BTN3AS AND BTN3A1 LEVELS HAVE A PROGNOSTIC ROLE IN PATIENTS WITH METASTATIC GASTROINTESTINAL STROMAL TUMORS?

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Background: Gastrointestinal stromal tumours (GISTs) account for 1% of all primary gastrointestinal cancers and represent the most common mesenchymal malignancy of gastrointestinal tract. In cancer, suppressive immune checkpoints, including butyrophilin sub-family 3A/CD277 receptors (BTN3A), programmed death protein (PD-1) and its ligand PD-L1, are often hyper-activated to ensure an effective evasion of tumor cells from immune surveillance. Since recent studies showed that PD-1 and PD-L1 expression in cancer may be an important prognostic factor, the aim of our study was to investigate if soluble forms of inhibitory immune checkpoints can help predict survival in GIST patients.
Patients and Methods: Using specific homemade ELISA assays not yet commercially available, the plasma PD-1, PD-L1, BTN3A1 and pan-BTN3As levels were analyzed in 20 metastatic GIST patients harbouring *c-KIT* exon 11 mutations, before starting treatment with 400 mg Imatinib. Survival curves were estimated by using the Kaplan-Meier method and log-rank test to evaluate significant differences among them. Data was generated using the MedCalc software for Windows, version 18.2.1.
Results: Kaplan-Meier survival analysis was used to characterize prognostic relevance of soluble PD-1, PD-L1, BTN3A1 and pan-BTN3As in metastatic GIST patients, suggesting that their plasma levels could serve as survival predictor. For each analyzed biomarker, statistically significant differences in progression free-survival (PFS) between patients with plasma concentrations above and

under median values were detected. Plasma level thresholds correlated with shorter survival and poor prognosis were established for sPD-1 (>6.89 ng/ml), sPD-L1 (>0.74 ng/ml), BTN3A1 (>7.19 ng/ml) and pan-BTN3As (>4.38 ng/ml). Conversely, patients with plasma levels under thresholds showed a median PFS that was approximately 58 months longer than to the previous.
Conclusions: Our study, for the first time, reveals that monitoring the concentration of soluble forms of inhibitory immune checkpoints in plasma can help predict survival in metastatic GIST patients and therefore improve their treatments. We showed that high plasma levels of these immune checkpoints correlate with poor clinical outcome and could be used in future as prognostic factors.

G02

RELATIONSHIP OF PEAK SERUM METHOTREXATE CONCENTRATION AND DRUG TOXICITIES IN EXTREMITY OSTEOSARCOMAS

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Background: High-dose methotrexate (HD-MTX) with leucovorin rescue is widely used to treat osteosarcoma. Our study aimed to explore whether peak serum methotrexate concentration (C max) correlated with drug toxicities in patients with primary extremity osteosarcoma.
Methods: Patients with extremity osteosarcoma who were treated at our medical oncology department between 2018 and 2019 were evaluated. All the patients were Enneking stage II and had received standard chemotherapy based on high-dose methotrexate, doxorubicin and cisplatin. Methotrexate (MTX) serum levels measured at 4 h after the beginning of the infusion (C max) and treatment-associated adverse events of each administration were recorded. Hepato- and nephrotoxicity parameters were categorized according to Common Terminology Criteria for Adverse Events v 4.02. Incidences of adverse events were comparated using Chi square test.
Results: In total, 5 patients were followed for an average of 6 months (2-10 months). C max ranged from 795 to 2280 mmol/L with a mean value of 1375 mmol/L. No significant differences in increased rates of grade 2-5 toxicity were observed among patients with a C max > 1500, > 1200 and > 1000 mmol/L ($p=0.696$; $p=0.350$; $p=0.719$, respectively). No significant association was found between adverse events and age ($p=0.361$).
Conclusions: Our results suggest that C max did not correlated significantly with toxicities and complications. However we believe that our data should be confirmed by further study with greater number of patients.

G03

SAFETY AND EFFICACY OF GEMCITABINE PLUS PREDNISONE FOR METASTATIC NON ASSOCIATED HIV KAPOSI SARCOMA

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Background: To evaluate outcomes in the use of single-agent Gemcitabine plus prednisone for the treatment of progressive Kaposi Sarcoma (KS) in first line setting. KS is an indolent pigmented mucocutaneous malignancy with several variant presentations and clinical courses. A wide variety of systemic chemotherapeutic agents have been efficacious in KS, both as single agents and as combination chemotherapy. In metastaticsetting liposome-encapsulated doxorubicin is the standard chemotherapy, with response rate up to 60-80% and durable remission of disease. However a gold standard for therapy remains unclear. Progressive disease remains a challenge for the oncologist, but results are poor. Gemcitanine is an S-phase nucleoside anti-metabolite that has demonstrated activity in a variety of solid tumors, including sarcomas. The most common dose e schedule of this agent is 1.000 mg/m², given on day 1,8,15 of a 28 day cicle. The toxicity profile of gemcitabine is acceptable, with a dose-limiting toxicity of thrombocytopenia, hepatic dysfuntion and fatigue.
Material and Methods: We collected and analysed data from five patients (pts) with non-associated HIV KS who had no previously treated with first-line chemotherapy including liposome-encapsulated doxorubicin due of previous cardiac pathology The pts have been treated until disease progression or appearance of non-tolerable toxicity with Gemcitabine 1.000 mg/m², given on day 1,8,15 of a 28 day cicle and prednisone 25 mg orally twice daily starting on day 1, to reduce the related symptoms of disease and toxicity of chemotherapy.
Results: Baseline data, activity and toxicity are available in five patients. Patients with median age 82 years (range 71-92) were treated for a median of six cycles (range 4-10). All pts had skin metastases and one pz skin and left cervical adenopathies. Out of five pts with measurable disease, 2 had complete response, 3 partial response, with clinical benefit (improvement in performance status, pain, pruritus). All pts are on treatment. The haematological toxicity was moderate with anemia G 2 in one pz and elevation of the transaminases G1 in two pts. Additional toxicities experienced include mild fatigue.
Conclusions: This experience show that gemcitabime plus prednisone has promising activity and is safe in pz. with metastatic non-associated HIV Kaposi Sarcoma. Both

objective responses and clinical benefit observed in this care setting are encouraging.

H - Melanoma and Skin Cancers

H01

PROGNOSTIC FACTORS FOR EFFICACY OF IPILIMUMAB USED AFTER ANTIPD1 AND/OR BRAF+MEK INHIBITORS IN MELANOMA PATIENTS: AN ITALIAN MELANOMA INTERGROUP STUDY

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Background: Ipilimumab (Ip) is an option in Metastatic Melanoma (MM) patients (pt) in case of disease progression after antiPD1 (AP) treatment and BRAF+MEK inhibitors (BMi) administration (for BRAF mutated melanoma). Clinical trial are evaluating potential Ip-based combinations in 2nd/3rd line setting. Many studies underline the role of some parameters (as LDH, ECOG PS, Neutrophile/Leucocyte ratio) as progostic factors for immunotherapy used in first line. We evaluate the prognostic role of some relevant clinical or laboratoristic parameters for Ip used in late line after AP, Bmi, in order to define pt that benefit most from Ip monotherapy in this setting.

Methods: A retrospective multicenter study was conducted in 8 Italian Oncology Centers, evaluating MM pt treated with Ip after AP and/or BMi. Endpoints were OS and PFS, Kaplan Mayer and Cox regression were applied for survival analysis.

Results: Among 200 pt that received AP or Bmi, 48 were eligible for Ip administration in 2nd/3rd line. Before Ip treatment, ECOG PS was 0 in 21 pt, number of metastatic sites was less then 3 in 14 pt, LDH was within normal range in 19 pt, NLR ratio (= baseline neutrophils/total leukocytes) was less then 0.7 in 28 pt: in univariate analysis, only ECOG PS and NLR resulted significantly associated with better PFS and OS. For pt with ECOG PS 0 or 1 medianPFS was 3.2, 2.3 month respectively (p value 0.0066; HR 0.377 IC95% 0.186-0.762), median OS was 12.1, 4.0 respectively (p value 0.0016 HR 0.287 IC95% 0.132-0.622). For pt with NLR <0,7 or >0,7 medianPFS was 3.2, 2.0 month respectively (p value 0.002 HR 0.241 IC95% 0.0978-0.593), median OS was 7.63, 2.67 respectively (p value 0.0037 HR 0.251 IC95% 0.0986-0.0637) A score was counted for each pt considering the number of favorable basal factors present (ECOG PS 0, NLR<0.7), from 0 to 2. For pt with SCORE 0,1,2 medianPFS was 4.8, 2.4, 1.4 month respectively (p value 0.0009), median OS was 25.6, 5.8, 1.9 respectively (p value <0.0001).

Conclusions: ECOG PS 0, NLR <0.7, resulted prognostic factors associated with favorable PFS and OS of MM pt treated with Ip after AP or BMi progression. Subgroup with all these factors has a better prognosis. These data can help treatment choice and should be evaluated prospectively.

H02

ASSOCIATION BETWEEN IMMUNE-RELATED ADVERSE EVENTS WITH CLINICAL BENEFIT IN PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS FOR METASTATIC MELANOMA IN MODENA CANCER CENTER

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Background: Immune checkpoint inhibitors (ICIs) changed the landscape of advanced melanoma, but immune-related adverse events (irAE) are common and the most typical manifestations are cutaneous, gastrointestinal (GI) tract, hepatic and endocrine. This study aims to evaluate the real-life experience of toxicities (tox) in our patients (pts).

Patients and Methods: We retrospectively analysed a total of 94 pts who received >=1 dose of ICIs at Our Cancer Center from July 2013 to December 2018 (M/F 61/33; median age 61 y, range 20-88). 73 pts received one line of ICIs and 21 had two lines, for a total of 115 different patient's therapies. Among these, 36% received nivolumab (N), 35% pembrolizumab (P), 27% ipilimumab (I) and 2% atezolizumab (A). irAE were classified according to CTCAE v 5.0.

Results: 80% of pts were ECOG PS 0, mBMI at baseline was 26,45 (range 17-46), 9,5% had history of autoimmune disease. 31% received concurrent ICI and radiotherapy. 4% had complete response (CR), 23% partial response (PR), 14% stable disease (SD) and 52% progression disease (PD). 11,3% experienced tox Grade (G)3-4, 47%

G1-2. Toxicity rate of G3-4 was 12,9% and G1-2 48,8% with I, 14,3% and 40,5% with N, 5% and 52,% with P, 50% and 50% for A, respectively. Patients characteristics (age <65y/=65y; BMI <25/>=25; sex M/F; ECOG 0-1/2; baseline use of steroids Yes/No) do not seem related with the development of tox (Fisher's exact test, p=n.s.), but duration of therapy (=1y/<1y) and best response (non PD/PD) yes (p=0,045 and 0,001 respectively). The most frequent tox reported were cutaneous (25,2%, of them 7,8% of vitiligo), endocrine (19,1%), GI (13,9%), pancreatic (6,1%), hepatic (5,2%), fatigue (5,2%), pulmonary (4,3%), neurologic (2,6%) and muscular (2,6%). Duration of therapy correlates with the development of endocrine (p=0,022) and cutaneous tox (p=0,008). mOS for pts with tox was 29 mo (95% IC 15-43) vs 6 (4-41) in pts without tox (p=0,0001) (HR 0,35 (0,20-0,59)). mOS for pts with endocrine tox was 34 (10-43) vs 9 (6-19) (p=0,0116) (HR 0,49 (0,28-0,85)). mOS for pts with cutaneous tox was 43 (22-43) vs 7 (5-10) (p<0,0001) (HR 0,32 (0,19-0,54)). mOS for pts with GI tox was 22 (15-43) vs 9 (7-29) (p=0,1738).

Conclusions: The association between experience of tox and clinical benefit from ICIs was already reported. Our pts confirmed these evidences and underline the positive role especially of cutaneous and endocrine toxicities.

H03

THERAPEUTIC STRATEGIES FOR OLIGO-PROGRESSION MANAGEMENT IN METASTATIC MELANOMA (MM)

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Background: In MM patients treated with target or immune therapy, oligo-progression (OP) is defined as a very limited degree of progression after a good response to treatment. The limited progressive metastases could benefit from local treatment which could delay the change of systemic therapy leading to a prolonged PFS and OS. However, despite a huge trend toward local therapies to treat metastatic disease, there are currently very limited available data on this therapeutic strategy.

Methods: To identify the subset of patient in whom local therapy should play a role in OP management, to examine the sequence and timing of treatment and to discuss the clinical and biological features which could predict better outcomes, we retrospectively revised the clinical record of MM patients treated in our oncology centre.

Results: Among 240 patients, 21 (9%) (13 [62%] man; median age 56 [41-74]) developed OP during systemic treatment. BRAF v600 mutation was present in 15 (71%) patients. Target therapy (as first line in 8 cases) and check-point inhibitors (as first line in 2 cases) were the ongoing treatments in 11 and 10 patients respectively. The site of oligo-progression was soft tissue in 4 patients, lymph nodes in 7, brain in 8, bowel as gallbladder in 1 case. As local treatment was utilized surgery, radiotherapy and a combination of surgery and radiotherapy in 12, 7 and 2 cases and were performed after a median time of 13 months (2-30). After a median follow-up of 40 months, 10 patients were died, median PFS was 21 months (6 to ongoing 43) with a median PFS beyond oligo-progression of 9 months (2 to ongoing 35) while median OS from OP treatment and from metastatic disease was not reached. In Cox univariate analysis skin OP, surgery and a neutrophil to lymphocyte ratio under 2 is associated to prolonged PFS and OS.

Conclusions: OP is a rare event arising during systemic treatments in MM. Increasing biological knowledge and clinical experiences are improving the accuracy in identifying patients to apply for local ablative therapies. In our experience local treatments have been able to control disease OP. Nevertheless, in decision making, an optimal patient selection and management are required by clinicians to propose the right treatment to the right patient at the right time.

H04

IDENTIFICATION AND DIRECT COSTS OF UNRESECTABLE AND ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA: RESULTS FROM A LARGE ITALIAN HEALTHCARE ADMINISTRATIVE DATABASE

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Background: The epidemiology of non-melanoma skin cancers, in particular of cutaneous squamous-cell carcinoma (cSCC), is uncertain at national level. The aim of this study was to identify patients affected by unresectable and advanced cSCC through Italian administrative databases, and to provide prevalence and costs in the perspective of the National Health System (NHS).

Methods: A real-world analysis was performed by using healthcare administrative data (ReS database) of more than 7 million of Italian inhabitants. Patients affected by unresectable and advanced cSCC in 2015 were identified by a step-by-step strategy: patients hospitalised with a diagnosis of non-melanoma malignant skin cancer were selected (1st step); the advanced cancers were ascertained

by the presence of metastasis diagnoses, or chemotherapy/radiotherapy supplies, or prescription of antineoplastic or immunostimulant drugs (2nd step); subjects receiving vismodegib were excluded, to select only cSCC (3rd step): patients experienced surgical excision were excluded to identify unresectable cases (4th step). The prevalence (per 1 million of inhabitants) was estimated. Demographic and clinical characteristics of the cohort were described. The cohort was followed-up for 1 year to describe healthcare utilisation and integrated costs (hospitalisations, pharmaceuticals and outpatients services) paid by the NHS.

Results: Out of 7,365,954 subjects, 43 cases of unresectable and advanced cSCC were selected (prevalence: 5.8 per 1 million). Twenty-nine subjects were males (67.4%) and the mean age of the cohort was 75±11. The 88.4% was affected by at least one comorbidity, especially hypertension (81.4%), dyslipidaemia (39.5%), and diabetes (27.9%). A patient affected by unresectable and advanced cSCC generated an yearly average cost of €10,281 for the IHS. Hospitalizations accounted for the 42.0% of total cost, followed by drug consumption (33.7%) and outpatient services (24.3%). The annual cost per patient for chemotherapy or radiotherapy was €2,028.

Conclusions: The study, based on real-world data from healthcare administrative databases, identified and characterised patients affected by unresectable and advanced cSCC. Findings on the actual healthcare resources utilization and direct costs of these patients could be considered the starting point for appropriate supply allocation in view of incoming therapeutic strategies for this specific target population.

H05

DOES MELANOMA BRAIN METASTASES DETECTION PATTERN IMPACT ON CLINICAL OUTCOME?

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Table 1

Covariates	HR	95% CI	P
BRAF wild type	1.95	1.22-3.12	< 0.01
BM > 1	2.20	1.35-3.59	< 0.01
LDH ⩾ 2 x upper normal limit	1.83	1.07-3.11	0.026
ECOG PS > 0	2.68	1.62-4.43	0.0001
Extracranial metastatic sites ⩾ 3	1.91	1.17-3.10	< 0.01
Age ⩾ 65	1.86	1.15-3.02	0.012
Asymptomatic vs Symptomatic BM progression	0.82	0.51-1-32	0.41

Background: Among patients (pts) with stage IV melanoma, the presence of brain metastases (BM) is associated with poor prognosis. Namely, median overall survival (OS) is about 4-6 months. Aim of the present study is to evaluate whether BM detection pattern (symptomatic vs radiological) may affect clinical outcome.

Patients and Methods: The retrospective series included 150 consecutive pts with melanoma BM treated at two Italian cancer centers from 2008 to 2018. Baseline clinicopathological factors and systemic/loco-regional treatments were evaluated. Prognostic impact in terms of OS was analyzed with Kaplan-Meier method and Cox model; associations were explored by Chi-squared test.

Results: At BM diagnosis, 39.3% of pts were ⩾ 65 year-old, 42% had a single BM, 40% high LDH levels, 51.3% ⩾3 extracranial metastatic sites, 38% an ECOG performance status (PS) of 0, and 50.7% had BRAF mutation. Neurologic symptoms occurrence led to BM detection in 44% of cases. Motor function impairments were the most frequent clinical presentation (44%) followed by language disorders (30%), cognitive dysfunctions (27%), epilepsy (16.7%), headache, nausea/vomiting (15% each). BM at stage IV diagnosis, <3 extracranial metastatic sites and neurosurgery approach were significantly associated with symptomatic BM detection (p=0.01, p=0.02, p=0.003 respectively). Overall, median OS after BM diagnosis was 5.78 months (95% CI 4.80-6.67), and median intracranial progression-free survival (iPFS) was 4.63 months (95% CI 3.81-5.12). No significant prognostic differences were observed between symptomatic vs radiological groups. According to treatment modality, stereotactic radiosurgery/neurosurgery plus systemic therapy showed the best outcome (12.32 months 95% CI 7.39-25.30). Baseline factors independently associated with OS at multivariate analysis are listed in Table 1. Noteworthy, no differences in OS were noticed between symptomatic vs asymptomatic BM progression.

Conclusions: No impact on clinical outcomes was observed for symptomatic versus asymptomatic BM progression in patients with advanced melanoma. Further prospective studies are needed in order to identify the best management strategy.

H06

EARLY LOSS OF MUSCLE MASS AS PROGNOSTIC FACTOR IN PATIENTS WITH METASTATIC MELANOMA TREATED WITH IMMUNOTHERAPY

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Background: High BMI is associated with better survival in metastatic melanoma patients (MM pts), while the prognostic value of sarcopenia is unknown in these pts.
The aim of this study was to examine the prognostic impact of body-mass index (BMI), baseline sarcopenia and loss of skeletal muscle mass (LSMM) on overall survival (OS) in MM pts who received immunotherapy (IT).
Material and Methods: The retrospective series included 42 consecutive MM pts (Jan 2011-Dec 2018) treated with IT in a single referral center. Sarcopenia was defined according to Prado's criteria. Skeletal muscle index (SMI) was calculated as cross-sectional-area of muscle (cm^2), using CT-scan, at the L3 level divided by the square of the height (m^2). Early LSMM, during IT, was defined as a decrease in SMI>=10% from baseline at first evaluation. BMI was calculated as weight (kg) divided by the square of height (m^2) and categorized according to standard WHO definitions. Weight loss was analyzed as continuous variable.
Results: At baseline, 27 pts (64,3%) were male, 26 pts (61.9%) were < 70 years and 31 pts (73.8%) had ECOG PS=0. Overall, 26 pts (61.9%) had LDH <ULN, 24 pts (57.1%) had ³3 metastatic sites,10 pts (23%) had CNS metastases, BRAF was mutated in 17 pts (40.4%), 22 pts (52%) had received at least one previous line of systemic therapy. As a first line IT treatment, 16 pts (38.1%) received an antiCTLA-4 agent and 26 pts (61.9%) a PD1 inhibitor. Of note, 23 pts (54.8%) had a sarcopenic state, and 23 pts (54,8%) had a BMI >=25. Out of 42 pts, 30 (71.4%) had a CT-scan at first evaluation, and 30% of them had an early LSMM. Median OS was 11.38 months and 9.37 months in pts with early LSMM >=10%. Both in univariate and multivariate analysis, ECOG PS>=1, and early LSMM >=10% were significantly associated with worse OS. Conversely, pts with weight loss had better outcome (Table 1).
Conclusions: Early LSMM >=10% and ECOG PS>=1 may negatively influence the outcome of MM pts treated with IT. Further prospective investigations are needed to confirm these preliminary data.

Table 1. OS multivariate and univariate analysis.

Factors	OS univariate analysis			OS multivariate analysis		
	HR	p	95% Confidence Interval	HR	p	95% Confidence Interval
PS ECOG>=1	3.02	0.01	(1.29-7.08)	3.99	0.043	(1.04-15.31)
Weight loss	0.88	0.03	(0.78-0.98)	0.85	0.02	(0.74-0.97)
Early LSMM >=10%	4.24	0.006	(1.50-11.97)	3.09	0.04	(1.04-9.22)

H07

SURVEY IMI: EXPERIENCE ABOUT MANAGEMENT OF IMMUNOTHERAPY TOXICITIES

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Background: Checkpoint inhibitors, immunomodulatory antibodies that are used to enhance the immune system, have substantially improved the prognosis for patients with advanced malignancy. The management of toxicities due to mmunotherapy is an emergent topic. We explored individual medical experience and practice.
Methods: Italian medical doctor members of the Italian Melanoma Intergroup were invited to participate in an online survey addressing management of toxicities due to immunotherapy.
Results: A 18-item questionnaire was delivered to 31 medical doctor: 74% aged 30-40 years, 80% oncologist, 16% dermatologist, 35% still in training, 67% works in Universities or Research Institutes. A 32% has prescribed immunotherapy for at least 6 years, 93% has participated in Clinical Trials or Expanded Access Program, 51% has enrolled patients in study with combo-immunotherapy (median 10 patients, range 2-50). 50% of doctors cure more than one cancer, 87% treat melanoma, 32% lung cancer. To manage immunotherapy toxicity, doctors use guidelines, the most common is ASCO guide lines (45%).

In most Centre (71%) there are more specialists, at least 2 or 3, dedicated to manage collateral effects or radiological response of therapy (endocrinologist 51%, dermatologist 51%, radiologist 45%, gastroenterologist 35% etc). The most frequent toxicities due to anti-CTLA4 are gastrointestinal 48%, dermatological 29%, 52% of physician treated at least 5 or more patients who experienced ⩾G3 toxicity. The most frequent toxicities due to anti-PD1 are thyroiditis 67%, dermatological 25%, 41% of physician treated at least 5 or more patients who experienced ⩾G3 toxicity. The most frequent toxicities due to Combo-immunotherapy are gastrointestinal 26%, Hepatitis 13%, 41% of physician treated at least 5 or more patients who experienced ⩾G3 toxicity. An average of 3 patients per centre for each treatment had a need for hospitalization. A 61% of physicians used Infliximab or Mycofenolato Mophetile to manage immunotherapy toxicities at least one time.

Conclusions: This is a preliminary evaluation, the doctors who took part have a high experience on the treatment, so we need to extend the analysis to a more general sample to have an assessment of the national experience on the management of immunotherapy toxicities.

The Italian Melanoma Intergroup (IMI) includes the following additional members who participated as investigators to this study and should be considered as co-authors: Paola Queirolo, Ignazio Stanganelli, Pietro Quaglino, Gerardo Botti, Corrado Caracò, Mario Mandalà, Anna Maria Di Giacomo, Vanna Chairon Sileni, Carlo Riccardo Rossi, Giuseppe Palmieri

H08

IPILIMUMAB COMBINED WITH RADIATION IN METASTATIC MELANOMA PATIENTS

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Background: Despite recent advances in treatment, at present malignant melanoma remains a devastating disease. Preclinical data suggest that immunotherapy may synergize the "abscopal" effect of radiotherapy and to generate "abscopal" responses outside the radiation field. The "abscopal" phenomenon remains relatively unexplored and shows that radiation may induce a regression of tumor cells outside the field of irradiation. In this study we reviewed our experience in the treatment of 12 consecutive metastatic melanoma patients treated with CTLA-4 inhibitor ipilimumab and Radiotherapy.

Material and Methods: All consecutive patients who received ipilimumab from November 2015 to December 2017 were retrospectively reviewed. Responses of lesions outside the radiation field were compared before and after radiotherapy, and parameters associated with response were assessed.

Results: Median survival was 18 months. In 7% of cases the lesions were already reduced before radiotherapy and in 18% of cases after radiotherapy. In 55% of cases radiotherapy is associated with an increase in favorable response of the treated lesions. Only the 3 Gy fraction dose is associated with a favorable response.

Conclusions: Our study shows that in patients with melanoma treated with radiotherapy and ipilimumab it is possible to highlight a subgroup of patients that could have more favorable off-field responses following radiation treatment. These results are encouraging regarding synergism between radiation and immunotherapy, but prospective studies are needed to analyze and highlight the radiotherapeutic parameters related to the abscopal effect in the treatment of cancer patients.

L - Head and Neck Tumours

L01

EVALUATING HYPERPROGRESSIVE DISEASE (HPD) IN HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC) PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS (ICI)

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Background: HPD was reported in 9% of cancer patients (pts) treated in phase I trials, in 13.8% of advanced non-small cell lung cancer and 29% of 34 HNSCC pts upon ICI. A better definition of HPD in a larger cohort of HNSCC is still lacking.

Methods: We retrospectively analyzed all advanced HNSCC pts treated with ICI between October 2014 and December 2018. Three scans (before ICI, at baseline and at first evaluation during ICI) were assessed according to RECIST 1.1. Tumor Growth Kinetics (TGK) pre- (TGK_{pre}) and post-baseline (TGK_{post}) were measured as previously reported (Saâda-Bouzid E, Ann Oncol 2017). Pts were defined HPD if they had progression at first radiological evaluation and $TGK_{post}/TGK_{pre} \geqslant 2$. Correlation between HPD and clinical characteristics was performed by Fisher or t-student test. Median overall survival (mOS) and progression free survival (mPFS) were estimated using the

Kaplan-Meier method and compared between HPD and non-HPD using the log-rank test.

Results: Ninety pts were eligible: 18% were female, 4% had ECOG PS ⩾ 2, 73% smoking history, 37% oropharyngeal cancer (61% HPV+), 65% locoregional disease (89% previously irradiated), 54% received combined immunotherapy, 75% in ⩾ 2nd line. Two out of 90 pts had $TGK_{pre} = 0$ and were not evaluable for TGK ratio. HPD was observed in 7.9% (7/88) of pts. HPD pts were significantly younger compared to non-HPD pts (median age 53 ± 3.7 vs 63.3 ± 0.9 years, p = 0.002) and had a significantly higher median neutrophil-lymphocyte ratio (NLR) (11.5 ± 3.5 vs 6.4 ± 0.4, p = 0.004). Overall, mOS and mPFS were 7.5 (95% CI: 4.2-10.8) and 2.2 months (95% CI: 0.9-3.4), respectively.

At a median follow-up of 20.9 months (95% CI: 19-22.8), HPD pts had a significantly worse mPFS compared to non-HPD pts [1.8 (95% CI: 1.5-2.2) vs 3.5 (95% CI: 2.2-4.8) months; p = 0.001]. HPD correlated with a not significant trend in lower mOS compared to non-HPD group [3.7 (95% CI: 2.4-5.1) vs 8.3 (95% CI: 4.1-12.5) months; p = 0.348]. Three (43%) out of 7 HPD pts early switched to chemotherapy after PD to ICI having a mOS of 8.1 months (range 3.7-25.3). Excluding these 3 pts, HPD correlated with a significantly worse mOS compared to non-HPD [2.6 (95% CI: 1.9-3.3) vs 8.3 (95% CI: 4.1-12.5) months; p = 0.006].

Conclusions: HPD was identified in 7.9% of HNSCC and correlated with younger age and higher NLR. To better assess the existence of HPD in HNSCC, a formal comparison with a control cohort of advanced HNSCC upon chemotherapy is mandatory and still ongoing.

L02

BIG DATA AND MODELS FOR PERSONALIZED HEAD AND NECK CANCER DECISION SUPPORT (BD2DECIDE)

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Background: Loco-regionally advanced HNSCC (stages III-IV according to TNM 7th edition) can be cured with multimodal treatments. Approximately half of cases relapse in the first years and mortality remains high. There is an unmet need to improve the ability of TNM to forecast patient (pt) prognosis. We hypothesize to achieve this aim by an approach based on the analyses of multisource big data through innovative models, including artificial intelligence such as machine learning.

Methods: BD2Decide is a multicenter project funded by the European Union under Horizon2020 (H2020-PHC30-689715, http://www.bd2decide.eu). The international consortium consists of 11 organizations encompassing 3 research institutes, 3 small/medium-sized enterprises, 5 cancer clinics. In the project data of 2 cohorts are collected and mined (1086 retrospective 2008-2014; 457 prospective 2015-2017) of stage III-IV HNSCC pts treated with curative intent (NCT02832102). Clinical, pathological data were recorded. Population data from cancer registries and socio-economic datasets were also added to contextualize patients' risk factors and social status. Gene expression profile and radiomics analyses and signature testing, and their integration with clinicopathological and population based data are currently ongoing. Here, the results of the retrospective study are reported.

Results: A total of 1086 pts were enrolled in the retrospective study:

Site	n.	%
Oral cavity	273	25%
Oropharynx	444	41%
Hypopharynx	130	12%
Larynx	239	22%
cTNM (7th edition)		
III	296	27%
IVa	679	63%
IVb	111	10%
Median follow-up	63.8 months	

Survival rates are reported in the following tables:

Disease-free survival	Median	1-year	2-year	5-year	p value
Overall	Not reached (NR)	82%	72%	61%	–
III	NR	90%	79%	68%	0.0008
IV	100.9 months	79%	69%	59%	

Overall survival	Median	1-year	2-year	5-year	p value
Overall	NR	87%	74%	57%	–
III	91.4 months	94%	82%	63%	0.0026
IV	68.1 months	85%	71%	55%	

Conclusions and future directions: In this project a population of 1543 stage III-IV HNSCC pts treated with

curative intent will be considered. It constitutes the largest and clinically homogeneous dataset available in select locally advanced HNSCC, being almost 3-fold wider than the TCGA (The Cancer Genome Atlas). For future analyses, retrospective and prospective study will be combined and used for generating the testing, training and validation sets; the final dataset will be compared to population data. Statistical analyses will include both classical prognostic models and machine learning techniques.

L03

TREM-1 EXPRESSION HAS A NEGATIVE IMPACT ON RELAPSE INCIDENCE OF HPV-RELATED OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

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Background: Immunotherapy in head and neck squamous cell carcinoma (SCC) is a hot topic and PD1/PDL-1 checkpoint blockade is a promising approach even if there is a lack of robust progno-stic/predictive biomarkers and treatment benefits in overall survival are variable. Triggering Receptor Expressed on Myeloid cell 1 (TREM-1) reverses the M2-polarizing effect of hypoxia imparting a M1-skewed pro-inflammatory phenotype to macrophages that controls tumour growth. Aim of this study is to evaluate the prognostic role of TREM-1 in oropharyngeal (OP) SCC.
Methods: In 25 patients with stage III-IV HPV+ OPSCC we evaluated, with immunohistochemistry, in surgical specimens the following immunologic parameters in intratumoral (IT) and peritumoral (PT) environment: PD1-PDL-1 (1+ =<20% positive cells (pc); 2+ =21-50% pc; 3+ =>50% pc) CD4, CD8, FOXP3 (1+ =<10% pc; 2+ =10-20% pc; 3+ => 20% pc) IL22 (1+ =1-33% pc, 2+ =34-67% pc, 3+ =>67% pc) and TREM (1+ =1-50% pc, 2+ =>50% pc). The McNemar test was used to assess differences between IT and PT environment.
Results:

Markers	IT	0/1+	2+/3+	PT	0/1+	2+/3+	
CD4		12%	88%		6%	94%	
CD8		12%	88%		48%	52%	
FOXP3		88%	12%		65%	35%	
PD1		100%	0%		100%	0%	
PDL1		53%	47%		6%	94%	
TREM-1		94%	6%		82%*	18%	*1+ = 64%
IL22		59%	41%		29%	71%	

Statistical analysis showed a concordant expression of CD4, CD8 and PDL-1 both in IT and PT while TREM-1 was more expressed in PT (p=.001) and PD-1 in IT (p=0.12).There was no correlation between TREM-1 pc and CD68 and CD35 pc. Tumours with low PT TREM-1 positivity have a lowest risk of relapse (p=.01).
Conclusions: HPV+ OPSCC is promoted by inflammatory infiltrate anergy. TREM-1 PT positivity has unfavourable impact on relapse.

L04

DRUG RESISTANCE INDUCTION BY 3D COLLAGEN-BASED SCAFFOLD MODEL OF HEAD AND NECK CANCERS

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Background: Head and Neck cancers (HNCs) represent the sixth most common non-skin cancers worldwide, with an incidence of about 400,000 new cases and 50% of mortality rate. As other cancers, HNCs are dynamic masses that remodels the 3D extracellular matrix and interacts constantly with stroma components. In order to partially reproduce these features, 3D cultures have been developed to mimic the architecture of tumor niche structures. We have used a collagen-based scaffold to characterize cancer cell phenotype and the drug response of two HNC cell lines on an innovative 3D in vitro model.
Meterial and Methods: We have synthesized 3D scaffolds composed of bovine collagen type I with a diameter of 9mm. The growth curves of two oropharyngeal squamous cell carcinomas cell lines, UPCI:SCC090 and UM-SCC6 were performed; cells were seeded on scaffolds at different concentrations (1,0 x 10^6 and 0,5 x 10^6 cells per scaffold). The cell proliferation was performed through MTT tests at: 24h, 72h and 7 days. The drug sensitivity to Cisplatin, Fluorouracil, Cetuximab and Gemcitabine were performed treating at plasma peak concentrations on 2D and 3D cultures.
Results: UM-SCC6 grew rapidly and reached a plateau at 7 days post seeding at both concentrations. Differently, UPCI:SCC090 showed a lower proliferation rate. Both cell lines have displayed the capability to penetrate inside the whole scaffold area. UM-SCC6 acquired a mesenchymal-like phenotype with homogeneous distribution along the collagen fibers. Conversely, UPCI:SCC090 developed a dense clustered organization. UM-SCC6 displayed high resistance to each treatments when seeded on scaffolds. This behavior was reproduced by UPCI:SCC090 except for cetuximab that displayed an high cytotoxicity effect on 3D culture.

Conclusions: We have validated our 3D-collagen scaffold device that might have an high impact to in vitro preclinical research, improving the existing standard culturing techniques. This system provides an innovative technology for the evaluation of HNCs drug efficacy.

L05

BLEEDING EVENTS (BE) IN PATIENTS (pts) WITH RECURRENT OR METASTATIC (R/M) HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC): RETROSPECTIVE REVIEW OF ISTITUTO NAZIONALE TUMORI OF MILAN

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Background: BE is a complication of R/M HNSCC. However, data regarding the incidence of BE are limited. The majority of HNSCC pts die from progression (PD), including BE. PATIENTS AND METHODS We reviewed 259 consecutive HNSCC pts treated between 1984 and 2016 with systemic palliative treatments at our Institution. We divided the population in 2 groups: pts with and without at least one BE.

Results: Bleeding was minor (69%) or major (31%). Median life expectancy (LE) at first minor BE was of 66 days (0 – 771) and 34 days (0 - 680) at first major BE. Thirty-three pts experienced fatal bleeding within 15 days from last treatment.

Conclusions: Fourty-three percent of pts treated by palliative treatment presented BE. Among these, the majority has a minor BE, and global survival probability were not different from the non-BE pts. However LE of any type of BE pt seems to be reduced.

L06

A POSSIBILE PREDICTIVE FACTOR OF MUCOSAL REACTION INDUCED BY RADIOTHERAPY: ANALYSIS OF A SMALL SERIES

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Background: Aim of this paper is to investigate if Lymphocyte blood count (LBC) can be a predictve factor of mucosal oral reaction (MOR) induced by radiotherapy in head and neck squamous cell carcinoma (HNSCC).

Methods: We retrospectively analyzed a series of 13 patients (10 males and 3 females; median age 53 years) who underwent concurrent radiotherapy and chemotherapy for HNSCC in Ivrea Hospital from January 2017 to March 2019.

Diagnosis of HNSCC included nasopharyngeal (1), oropharyngeal (5), laryngeal (3), oral (4). Nine patients receveid chemoradiation for locally advanced HNSCC; 4 patient underwent radiotherapy in adjuvant setting after radical surgery. Conformal intensity modulation

CHARACTERISTICS OF PTS	Pts non-BE	Pts BE	Total pts
N (%)	149 (57)	110 (43)	259 (100)
Male/Female	117 (78)/ 32 (22)	81 (73)/29 (26)	198 (76)/ 61 (24)
Age, median *(range, r), years*	66 (33 - 93)	50 (67 - 83)	62 (24 - 93)
ECOG PS *median (r)*	1 (0 - 3)	1 (0 – 2)	1 (0 – 3)
Site			
- Oral cavity	49 (33)	48 (44)	97 (38)
- Larynx-Hypopharynx	47(31)	25 (22)	72(27)
- Oropharynx and Tx	53 (35)	37 (33)	90 (35)
Type of R/M			
Local/nodal/soft tissue/trachea	97 (65)	91 (84)	188 (72)
Lung	48 (32)	13 (12)	61 (23)
Survival from relapse *median (r), months (m)*	13 (0 – 293)	13 (0 – 148)	13 (0 - 293)
Overall survival median *(r), m*	23 (1 – 303)	24 (1 – 207)	24 (1 – 303)
Type of treatment			
Chemotherapy (CT)	119	76	195 (75)
AntiEGFR + CT (E-CT)	97	86	183 (70)
Immunotherapy (IT)	27	20	47 (18)

radiation therapy was delivered to the patients with a range of dose beetween 60 and 70 Gy. All patients receveid concurrent chemotherapy either single platinum regimen (12) or platinum plus fluorouracil (1). Ananlysis of LBC was performed before starting chemoradiation (Lympho-t0), weekly during the treatment and after the end of the therapy for four weeks. Value of LBC observed the week before the onset of oral mucosal reaction of any grade is described as Lympho-t1. Based on the Radiation Therapy Oncology Group (RTOG) grading of acute radiation mucosal injury, patients were assigned into acute reaction (grades 2-4) and minimum reaction (grades 0-1) groups.

Results: Twelve patients completed radiotherapy during the study period. At the beginnig of radiotherapy, Lympho-t0 was lower than 1000/mcL in two patients. MOR were recorded as 8 in acute group (61%) and 5 as minimun (39%) group respectively. One patient stopped treatment because of grade 4 MOR. Only 2 patients developed oral injury after the end of radiotherapy, 10 patients during the treatment. Median duration of MOR was 30 days from diagnosis to complete resolution. In the week before clinical development of mucosal oral reaction of any grade we observed reduction of Lymphocyte blood count (Lympho-t1) lower than 1000/mcL in twelve patients ((92,3%). In the acute group MOR we observed a Lympho-t1 lower than 500/mcL in 37,5% of cases in the week before the onset of injuries; in the minimun MOR we observed a Lymphot1 lower than 500/mcL in 20% of cases.

Conclusions: LBC lower than 1000/mcL and even than 500/mcL could be a predictive factor of MOR and could be used as a signal to anticipate prophilactic care to reduce intensity and duration of mucositis. This survey is our pivotal analysis for a larger prospective trial.

M - Brain Tumours

M01

HEALTH-RELATED QUALITY OF LIFE (HRQOL) EVALUATION IN THE REGOMA TRIAL: A RANDOMIZED, PHASE II CLINICAL TRIAL ANALYZING REGORAFENIB ACTIVITY IN RELAPSED GLIOBLASTOMA PATIENTS

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	T0	T1	T2	p- value
Global Health Status	63.0 (21.3)	60.7 (20.2)	54.2 (23.3)	0.2
Role Functioning	73.2 (30.3)	71.3 (29.1)	63.1 (34.1)	0.07
Cognitive Functioning	78.0 (26.2)	81.3 (25.6)	75 (21.4)	0.8
Emotional Functioning	74.0 (23.3)	72 (24.6)	76.8 (16.4)	0.4
Social Functioning	78.9 (26.5)	76 (25)	76.2 (29)	0.8
Appetite Lose	8.9 (19.6)	18.7 (32)	31 (44.3)	0.002
Motor Dysfunction	17.1 (21.3)	17.8 (24.4)	19.8 (29.3)	0.3

Some HRQoL items during REG treatment.

Background: REGOMA trial showed that regorafenib (REG) significantly improved OS and PFS in patients (pts) with relapsed GBM with respect to lomustine (LOM). REG showed a different toxicity profile compared to LOM. Here, we report final results of the HRQoL assessment, a secondary end point.

Material and Methods: HRQoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and brain module (QLQ-BN20) administered before any MRI assessments, every 8 weeks (+/- 2 weeks) until disease progression. To evaluate treatment impact on HRQoL, questionnaires at progression were excluded. Mixed-effect linear models were fitted for each of the HRQoL domain to examine the change over progression-free time within and between arms. The models included the time of questionnaire assessment, the treatment group and their interaction, as fixed effects, and a compound symmetry covariance structure for the random effects. Differences of at least 10 points were classified as a clinically meaningful change. To correct for multiple comparisons and to avoid type I error, the level of significance was set at P=0.01 (2-sided).

Results: Of 119 randomized pts, 117 participated in the HRQoL evaluation, and 114 had a baseline assessment (n=56 REG; n=58 LOM). No statistically significant differences were observed in any generic or cancer specific domain during treatment in the REG and LOM arms, or between the two arms, except for the appetite loss scale which was significantly worse in PTS treated with REG (Global mean 14.7 (SD=28.6) vs 7.6 (SD=16.0); p=0.0081). The rate of pts with a clinically meaningful worsening for appetite loss was not statistically different

between the two arms (9 out of 24 and 0 out of 13 in the REG and LOM arm, respectively;p=0.02).
Conclusions: In the REGOMA trial, HRQoL did not change during regorafenib treatment. Pts treated with regorafenib and lomustine reported no significant difference in HRQoL.

M02

THE ROLE OF GRADE IN IDH MUTANT GRADE II AND III GLIOMAS

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Background: The 2016 WHO classification dramatically changed the diagnosis of gliomas. Diffuse gliomas are classified according to the presence of IDH-mutation (IDH-mut) and the deletion of both 1p and 19q chromosome arms (1p/19q codel). Now debate is whether grade still has an independent prognostic value. The aim of this study was to find out if grade is a prognostic factor independently of molecular status.
Methods: We analyzed our institutional data warehouse for all consecutive patients (pts) with newly diagnosed, histologically proven Grade II or Grade III IDH-mut gliomas. IDH 1/2 assessment by polymerase chain reaction (PCR) or immunohistochemistry (IHC) was accepted. Next Generation Sequencing (NGS) for IDH1 (exon 4) and IDH2 (exon 4) was performed on all specimens wild-type for the IDH.
Results: The analysis included all the 399 pts who had a Grade II (n=250, 62.7%) or Grade III (n=149, 37.3%). Median follow-up time was 105.3 months. After surgery, 72 pts (18.0%) received RT alone, 44 (11.0%) received CT alone, 135 (33.8%) received both RT and CT, and 142 (35.6%) follow-up without any treatment. Median survival was 148.1 months. In multivariate analysis Grade (HR=0.342, 95% CI: 0.221 – 0.531; P<0.001) and 1p/19q codeletion (HR=0.440, 95% CI: 0.290 – 0.668; P<0.001) were independently associated with a lower risk for death. The difference in survival remained when adjusted for histological subtype. Residual disease after surgery or biopsy negatively affected survival (HR 2.151, 95% CI 1.375 –3.367, P=0.001). Post-surgical treatment with RT + adjuvant CT improves survival in respect to follow-up and other treatments (HR: 0.316, 95% CI 0.156 –0.641, P=0.001).
Discussion: Grade still affects survival in IDH mutant Grade II and III gliomas. This effect was independent on molecular features, surgical extension and post-surgical treatments. Clinical management of gliomas should continue to take into account grade as well as molecular characteristics.

M03

THE ROLE OF ADJUVANT CHEMOTHERAPY IN AVERAGE-RISK ADULT MEDULLOBLASTOMA PATIENTS: LONG TERM RESULTS

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Background: Medulloblastoma is extremely rare in adults and, therefore, it is difficult to accrual patients in clinical trials. Radical surgery and radiotherapy (RT) provide a significant control of disease. Nevertheless, about 25% of average-risk patients have a relapse and die because of disease progression. The role of chemotherapy (CT) after standard RT for average-risk adult patients remains controversial.
Methods: We analyzed 48 average-risk patients according to Chang classification diagnosed from 1988 to 2016. Median age was 29 years (range 16-61), M/F ratio was 26 (54.2%)/22 (45.8%). Fifteen patients had classic medulloblastoma (31.3%), 15 patients had desmoplastic medulloblastoma (31.3%), 5 patients had extensive nodularity (10.4%) and 2 patients had large cells/anaplastic histology (4.2%). The patients were homogeneously distributed in the two groups: 24 (50%) received adjuvant RT alone and 24 (50%) received RT + CT that consisted in a platinum-etoposide based combination.
Results: After a median follow-up of 12.5 years, CT increases PFS (PFS-15 82.3 ± 8.0% in RT-CT group vs. 38.5% ± 13.0% in RT group p=0.05) and OS (OS-15 89.3% 7.2% vs. 52.0% 13.1%, p=0.02). Among patients receiving CT, the reported grade ⩾ 3 adverse events were: 9 cases of neutropenia; 6 cases of G3 neutropenia (25%) and 3 cases of G4 neutropenia (13%), 1 case of G3 thrombocytopenia (4%) and 2 cases of G3 nausea (8%).
Conclusions: Our study with a long follow up period suggests that adding adjuvant chemotherapy to RT might improve PFS and OS in average-risk adult medulloblastoma patients.

M04

PEMBROLIZUMAB (PEM) IN RECURRENT HIGH-GRADE GLIOMA (HGG) PATIENTS WITH MISMATCH REPAIR DEFICIENCY (MMRD): AN OBSERVATIONAL STUDY

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Background: Pem, an immune checkpoint inhibitor, demonstrated to be active in various neoplasms with MMRd. No data exists about its efficacy in MMRd glioma patients.
Materials and Methods: MMRd HGG relapsed after receiving RT and CT were treated with Pem. MMR status was analyzed by immunohistochemistry, including the MLH1, MSH2, MSH6, and PMS2 markers. MMR deficiency was defined as presence of a weak (wMMRd) or absent (aMMRd) signal at immunohistochemistry for at least one MMR protein. Other inclusion criteria were: ECOG PS 0-2, histologically confirmed gliomas, dexamethasone ⩽4 mg.
Pem was administrated at 200 mg every 3 weeks until progression disease or unacceptable toxicity. Tumor response was evaluated by brain MRI every 10 weeks according to the RANO criteria. OS and PFS were evaluated by Kaplan-Meier curves. CTCAE v4.0 was used for toxicity.
Results: Among 167 glioma patients, we found 22 MMRd gliomas. 12 PTS were treated with Pem: 8 wMMRd and 4 aMMRd. According to Bethesda criteria, all PTS had microsatellite stability. Tumor histologies included 5 anaplastic astrocytoma, 1 anaplastic oligodendroglioma, 6 glioblastoma (GBM). MSH2 deficiency was found in 6 cases, MSH6 deficiency in 9 cases, PMS2 and MLH1 deficiency in 2 cases. Median number of prior line of chemotherapy was 1 (range 1-5). Stable disease (SD) was reported in 4 PTS (33%); 8 PTS showed progressive disease (PD). PTS with anaplastic gliomas showed a statistically significant association with SD ($p=0.03$, OR=3); all GBM PTS reported PD; status of MMRd (weak/absent), IDH (mutated/wild-type), MSH2 and MLH6 (deficient/proficient) were not associated with SD. Median follow up was 14.7 ms. OS was 5.6 ms (95% CI 0.1-13.8), PFS 2.4 ms (95% CI 1.8-2.9). OS was 2.8 ms and 5.6 ms ($p=0.9$), PFS was 1.8 ms and 3.1 ms ($p=0.5$) in PTS with wMMRd and aMMRd. PTS reporting SD and PD had PFS of 7.4 ms (95% CI 4.6-10.2) and 1.8 ms (95% CI 0.2-3.4), $p=0.002$; OS was "not reached" and 2.8 ms in PTS having SD vs PD ($p=0.04$). Grade ⩾3 adverse events were reported in 8% of PTS.
Conclusions: A subgroup of recurrent MMRd HGG might benefit from Pem, especially anaplastic gliomas. There was a trend for a longer PFS and OS in PTS with aMMRd. Analyses for identifying additional molecular predictive factors is ongoing.

M05

COMPREHENSIVE GERIATRIC ASSESSMENT (CGA) CAN CATEGORIZE ELDERLY GLIOBLASTOMA (GBM) PATIENTS INTO THREE GROUPS PREDICTING SURVIVAL: A MONOINSTITUTIONAL STUDY

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Background: Treatment for GBM elderly patients (pts) is a challenge in neuro-oncology. The CGA is currently used for assessing elderly pts and its score correlate with outcome in many type of tumors. We have yet reported some general outcome of CGA in GBM pts. Here we performed a large retrospective analysis for identifing specific CGA categories correlations with PFS and OS.
Methods: Pts aged=65 years, with histologically diagnosis of GBM and availability of CGA result were enrolled. The CGA was administered before starting radio/chemotherapy(RT/CH) or palliative care.
Results: We enrolled 113 pts; median age was 71.7. Radical surgery was performed in 33% of cases; 80% of pts were treated with RT/CH combination; median number of maintenance temozolomide(TMZ)cycles was 3.9. Most pts had a high KPS (80%). According to CGA score, 35% of pts were categorized as "fit", 30% as "vulnerable" and 35% were "frail" and median overall survival was 16.5 vs 12.1 vs 10.3($p=0.1$). On multivariate analysis, CGA score resulted an independent predictor of survival: vulnerable and frail pts reported an HR of 1.5 and 2.2, respectively, compared to fit pts($p=0.04$). Moreover, we demonstrated a statistically association between CGA and type of treatment, being fit pts more frequently treated with RT/CT (98% vs 90% and 52% of vulnerable and frail pts, $p<0.001$); yet, frail pts received less cycles of maintenance TMZ than vulnerable and fit(2.8 vs 5 and 5.2, respectively; $p<0.001$). No association between CGA and PFS was demonstrated.
Conclusions: CGA score showed to be a significant predictor of mortality in elderly GBM pts. The score can classify pts into three categories statistically correlating with survival. It could be a useful treatment decision-tool suggesting the more appropriate treatment. However, a prospective study is warrant.

M06

EVALUATION OF PROGNOSTIC ROLE OF INFLAMMATORY INDEX IN GLIOBLASTOMA MULTIFORME PATIENTS UNDERGOING TO CONCOMITANT RADIO-CHEMOTHERAPY (STUPP)

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Table 1. Multivariate Cox analysis.

Overall Survival			Progression-free Survival		
	HR (95%CI)	p-value		HR (95%CI)	p-value
Age, years			Age, years		
<60	1.00 (referent)	0.006	<60	1.00 (referent)	0.010
⩾60	2.22 (1.26-3.91)		⩾60	2.17 (1.20-3.91)	
Pre treatment SII			Pre treatment SII		
<480	1.00 (referent)	0.022	<480	1.00 (referent)	0.015
⩾480	1.98 (1.10-3.56)		⩾480	2.11 (1.15-3.86)	

Background: Hematologic markers of inflammation have been shown to be prognostic in several malignancies including glioblastoma multiforme (GBM). The purpose of this study is to retrospectively evaluate the prognostic role of these markers in patients (pts) affected by GBM receiving a concomitant radio-chemotherapy (STUPP scheme) after surgery.

Methods: Adult pts (> 18 years old) with GBM diagnosed between 2008 and 2017 were selected for this study. All patients have been treated with STUPP scheme after surgery. Information on blood counts were carried out the day before starting therapy and after the last cycle of chemotherapy. Neutrophil/lymphocyte ratio (NLR) and Platelet/lymphocyte ratio (PLR) were computed as the ratio of the absolute neutrophil count and absolute platelet count by the absolute lymphocyte count respectively. Systemic Inflammatory Index (SII) was calculated as platelet count × neutrophil count/lymphocyte count. The optimal cut-point was obtained using X-tile software version 3.6.1.

Results: Sixty-five GBM pts were identified. Mean age was 59 (range 36-77); 92.3% of pts had an ECOG performance status of 0-1. Twenty-four pts had a gross tumor resection, 2 pts received just a diagnostic excision and 39 pts received surgery with radiological evidence of residual disease. MGMT methylation was ⩽10% in 35 pts, 12 ps had MGMT methylation between 10 and 30%; 13 pts had a methylation ⩾ 30%. NLR and PLR baseline value didn't show a statistic a statistically significant prognostic role in PFS or OS. Patients with baseline SII <480 showed both better PFS and OS (OS: 22.1 VS 11.8 mo p-values 0.0516; PFS: 10.6 VS 5.7 mo p-values 0.0351). Patients aged <60 years showed better PFS and OS. (PFS 10.3 VS 5.5 p-values 0.0501; OS: 20.6 VS 11.2 mo p-values 0.0124). Statistical significance for SII and age was maintained for both PFS and OS in multivariate analysis as shown in Table 1.

Conclusions: This retrospective study confirms the prognostic value of inflammatory indices in patients with GBM. An analysis of correlation between MGMT methylation and SII is ongoing.

M07

OUTCOME AND MGMT METHYLATION IN RECURRENCE GLIOBLASTOMA PATIENTS, TREATED WITH FOTEMUSTINE: EXPERIENCE OF THE NEURONCOLOGY MULTIDISCIPLINARY GROUP, CCCN OF ROMAGNA

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Background: Patients affected by glioblastoma multiforme (GBM) receive adjuvant Stupp regimen as first-line therapy, but there are no standard therapies for recurrent GBM. Fotemustine (FTM) is a treatment option for patients not suitable for clinical trials. The aim of the study is to observe the effect of FTM on progression free survival (PFS) and overall survival (OS) and its correlation with different O6-methylguanine-methyltransferase (MGMT) gene promoter methylation status.

Patients and Methods: This retrospective multicentric study analyzed 80 pre-treated patients with histological diagnosis of GBM referred to the Osteoncology and Rare Tumors Center (IRST-Meldola) and Oncology Unit of Rimini between January 2008 and January 2019. Clinical and molecular data were recorded at diagnosis (Table 1). We identify 2 classes: methylated (⩾10%) and unmethylated (⩽9%). OS was calculated as the time interval between the start of FTM treatment and death for any cause, while PFS was the time between start of FTM treatment and first evidence of progression of disease, or death

Table 1. Patients characteristics.

	N pts	%
Overall	80	100
Age		
Median (range)	56 (27-78)	–
Gender		
Male	54	67.5
Female	26	32.5
Metylation %		
0%-9%	44	76.7
⩾10%	16	23.3
Unknown	*20*	
Line of therapy		
Second line	66	82.5
Third line	14	17.5
FMT cycles		
One	48	60.0
>One	32	40.0
Stupp therapy	62	78.5
Re-Radiotherapy	4	5.2
Other Chemio	23	30.3

for any cause, whichever came first. Survival curves were estimated using the Kaplan–Meier product-limit method. The role of potential independent factor was analyzed with the log-rank test.

Results: The follow up interval was 41.6 months (range 0.3-52.4). We observed a PFS at 6 months (PFS-6) of 16.3% (95% CI:9.2-25.1) and a median PFS of 1.8 months (95% CI:1.5-2.3). OS at 6 months (OS-6) was 41.1% 95%CI:30.4-51.7) while median OS was 5 months (95% CI:3.9-6.2). Considering MGMT gene promoter methylation status, PFS-6 was 13.6% (96%CI:5.5-25.4) versus 18.7%(95%CI:4.6-40.3) and OS-6 was 34.1%(95%CI:20.7-47.9) versus 62.5% 95%CI:34.8-81.1) in unmethylated and methylated respectively ($p=0.31$, $p=0.34$). Chemotherapies after FTM had a impact on OS (p 0.0016) and efficacy of FTM is independent of its use in II or III line (p 0.30).

Conclusions: Despite a limited cases and 60% of patients could not receive more than 1 cycle, our study reflected literature data for PFS-6 and OS-6. MGMT methylation status is not predictive of response to FTM however better trend in methylated patients.

M08

MULTIDISCIPLINARY APPROACH TO PATIENTS WITH DIAGNOSIS OF GLIOBLASTOMA: A THREE YEARS REAL –LIFE EXPERIENCE AT THE LIVORNO HOSPITAL

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Background: Glioblastoma (GBM) is the most frequent malignant primary tumor of the CNS; all patients (pts) relapse with a median survival (mOS) of about 15 months from diagnosis; the optimal management of GBM represents a challenge and the best changes of care are obtained wthi a high quality multidisciplinary approach. We performed a retrospective analysis to evaluate the real-life experience in the Neuro-Oncology center at Livorno Hospital.

Patients and Methods: Retrospectively, we reviewed the medical records of pts referred to our center from January 2016 to April 2019 with a diagnosis of GBM. We analyzed clinical outcome. Each patient was evaluated into a multidisciplinary team (MTD), composed by oncologist, radiotherapist, neuroradiologist and neurosurgeon, from the initial diagnosis and every periodic assessment.

Results: We analyzed 90 pts with a diagnosis of GBM. At diagnosis, median age was 67 (range 84-44); about 51% were male. Among pts who underwent surgery, 58% had a radical surgery and underwent postoperative MRI scan within 48 h of surgery, demonstrating the absence of residual pathologic enhancing. 71% of pts were treated with standard treatment (temozolomide concomitant with radiotherapy), and 20% with only radiotherapy. Median progression free survival was 6,7 months. At progression, each case was evaluated by the MTD, 60% of pts was candidate to further treatment. About 35% of pts underwent to a relapse surgery.Analyzing overall survival (OS) only for the pts with a proper follow up (more than 1 year from surgery), we observed a median OS (mOS) of 17+ mos (range 14-24+). The best probability of cure was represented from a second surgical approach to the brain relapse.

Conclusions: In 3 years, about 90 pts with GBM have been evaluated, which represents a wide groups for a single center. In terms of OS, the results seem to confirm those reported in literature.Further analysis, about treatment, biomolecular characterization (MGMT metilation, IDH1/ IDH2 mutations and 1p-19q codeletion) are currently underway and will be presented soon.Moreover, taking into account that many other patients are expected to be treated in a short time, we have planned a Next Generation Sequencing (NGS) analysis with a gene panel

to investigate news possible molecular prognostic-predictive factors.

N - Neuroendocrine Tumours

N01

TREATMENT WITH SUNITINIB IN ADVANCED MALIGNANT PHEOCHROMOCYTOMA/ PARAGANGLIOMA

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Background: Pheochromocytoma and Paraganglioma (PCs/PGLs) are rare neural crested-derived neuroendocrine tumors arising from the adrenal medulla and extra-adrenal ganglia, respectively. Around 30-40% of these neoplasms are genetically determined. PCs/PGLs are malignant in 15% of cases. Metastatic spread is the principal criterion for malignancy. There is no standard of care for advanced disease. Chemotherapy based on cyclophosphamide, vincristine and dacarbazine and metabolic therapy with I^{131}MIBG are often used in clinical practice, despite the low number of prospective studies available and the limited solidity of the evidence.
Methods: SUTNET is a prospective phase II study active at our center, aimed at evaluating the activity of sunitinib in patients affected by advanced or unresectable PCs/PGLs.Forty-six patients with confirmed histological diagnosis of advanced or unresectable PCs/PGLs, pretreated or naïve, were planned to be enrolled. Sunitinib is administered orally at the standard dose of 50 mg/day for 4 weeks followed by a two-week break, until disease progression or unacceptable toxicity. The primary end point of the study is the 1year progression-free progression (PFS) rate.
Results: From January 2012 to November 2017, 46 patients were enrolled. Seven patients were excluded by this analysis due to the lack of minimum follow-up time (12 months) or due to the not-compliance with the study inclusion criteria. The 39 patients analyzed had a median age of 43 years (range 19-75 years) and 61.5% were male. In 38.4% cases the primary tumor was in the adrenal glands and in 28.2% in extra-adrenal abdominal sites. Head and neck district was the site of tumor origin in 28.2%. 94.9% patients received surgery on the primary tumor and 17 patients (43.6%) received one or more than one lines of therapy (70.6% with PRRT/I^{131}MIBG). The median dosage and number of cycles administered were 37.5 mg/day and 7 respectively. The 1 year PFS rate was 53.8%. Overall, 30% patients had an adverse event (AE) greater than grade 2. Hypertension (17.9%), fatigue (17.9%) and mucositis (15.4%) were the most commonly reported AEs.
Conclusions: The treatment options in advanced or unresectable PCs/PGLs are limited. Our preliminary results suggest that sunitinib could be an effective and safe therapeutic strategy in these rare neoplasms.

N02

PROGNOSTIC SIGNIFICANCE OF SYSTEMIC INFLAMMATORY INDICATORS IN NEUROENDOCRINE CARCINOMAS OF THE LUNG: A SINGLE INSTITUTION EXPERIENCE

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Background: Neuroendocrine carcinomas (NEC) of the lung encompass two high grade neuroendocrine neoplasms: small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC), both characterized by dismal prognosis. The incoming of immune checkpoint inhibitors (ICIs) in the SCLC scenario raises the need for new prognostic indicators to guide treatment strategies. This study aimed at evaluating the prognostic impact of systemic inflammatory indicators, including neutrophil-lymphocyte ratios (NLR), lLymphocyte-to-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR) and aAdvanced luLung cCancer iInflammation iIndex (ALI), in patients affected by NEC of the lung.
Patients and Methods: A retrospective analysis of lung NEC patients treated in our Institution was performed. Clinical characteristics, hematologic tests and outcome data were collected from January 2002 to December 2018. We included patients who received at least two cycles of chemotherapy as first line treatment. The value of ALI was calculated as body mass index x serum albumin/NLR. Median value was used to determine the cut-off levels. Kaplan-Meier analysis and log-rank test were used to evaluate survival differences.
Results: Eighty-eight patients were included: 79 (90%) were SCLC and 9 (10%) LCNEC, with a median follow up of 10 months. Median OS was 11 months in the whole patients' population, 10 months in SCLC and 11 months in LCNEC.A trend towards a favourable OS was found in patients with pre-treatment NLR <3, LMR $\geqslant 3$, PLR <139 and ALI $\geqslant 38$ although only this latter reached significance ($p=0.0010$). Moreover other parameters such as age ($p=0.0017$), performance status ($p=0.0005$), Charlson

Score (p=0.0245), number of metastatic sites, (p=0.0050), response to first line treatment (p=0.0004), first line sensitivity (p=0.0013) were all factors significantly associated with a more favourable OS.
Conclusions: This study, consistently with previous reports, shows that systemic inflammatory markers can predict prognosis in lung NECs, even if, given the small sample size, these results cannot be generalized. However, our findings could facilitate the understanding of survival differences in lung NEC patients in clinical practice, and could help to identify responders to ICIs in further prospective studies.

N03

A SINGLE-CENTRE RETROSPECTIVE ANALYSIS OF EPIDEMIOLOGICAL CHARACTERISTICS OF NEUROENDOCRINE TUMORS

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Background: Neuroendocrine tumors (NETs) are a small heterogeneous group of cancers, developing from the neuroendocrine system. NETs may occur with a wide variety of either functional or non-functional endocrine syndromes; moreover, they may be familial and have further associated tumors. In 1973, the annual age-adjusted incidence of NETs was 1.09 over 100.000 people, raising to 6.98 over 100.000 people by 2012. Dasari et al proved an incidence and survival increase of people affected by NETs; these data reflect an increased diagnosis of early- stage tumors, while extension of the survival of patients (pts) with metastatic tumors relates to therapies improvements.
Patients and Methods: We identified all NET cases evaluated between 2004 and 2019 at a single Sicilian oncological centre in order to compare the frequency we detected to the one reported in literature. We determined different subgroups layered according to sex, age at diagnosis, staging and grading.
Results: We identified 329 pts with NET diagnosis; the 52,3% were females. The average age at diagnosis was 57. The most common organ involved was lung (19,4%), followed by pancreas (16,7%) and small bowel (10,9%). Other organs involved was thyroid (9,7%), stomach (4,6%), skin (4,3%), colon (4,3%), appendix (4,3%). Other or unknow primary site was 25,8%. As to lung NETs, average age at diagnosis was 55,4 in males and 72,3 in females. Histological subgroup revealed 46 pts with poorly differentiated cancers (LCNEC and SCLC) and 18 bronchial carcinoid. Pancreatic NETs did not show any difference in terms of sex; the average age at diagnosis was 58,9. A 54,5% of pts was metastatic at diagnosis and metastases mainly concerned liver. 36 pts were affected by small bowel NETs; among them, 29, interested by ileum NETs, were averagely aged 59,17, whilst 7, affected by duodenum NETs, were averagely aged 65,5. Synaptophysin and chromogranin were the most frequently employed immunohistochemical markers. Ki67 was used to mark either a higher or lower histological malignancy degree. Pts with distant disease at diagnosis presented mainly pancreas, SCLC and LCNEC metastases.
Conclusions: This analysis represents a large number of cases at a single center in Sicily. It could serve as a basis for an epidemiological and histopathological features and for the subsequent prognostic and therapeutic evaluation within the same region.

N04

NATURAL HISTORY, CLINICAL MANAGEMENT AND OUTCOMES OF PATIENTS WITH LIMITED OR ADVANCED THORACIC AND GASTRO-ENTERO-PANCREATIC TUMORS. REPORT FROM A LARGE RETROSPECTIVE REGIONAL DATABASE

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Background: Neuroendocrine neoplasms (NENs) are rare tumors that arise from cells of the endocrine system distributed throughout the body. These tumors most commonly occur in the gastro-entero-pancreatic tract or in the chest, showing relevant heterogeneity with varying natural history, biological behavior and malignant potential. Therefore, their management is complex and involves the discussion of different options. For the same reason, conducting epidemiological researches can be very difficult, and cooperative efforts to collect data are essential.
Materials and Methods: A multicenter retrospective study was performed. We collected data about primary tumor characteristics, histotype, therapeutic approach, clinical course and outcome of patients treated between January 2000 and December 2016 in 6 different hospitals within the department of "Rete Oncologica Piemonte e Valle d'Aosta". The aim of this study was to analyze

epidemiology, clinical features and treatment options for patients with NENs.

Results: Overall, 405 patients were included in the study. Median age was 62.1 years (range 12.7 – 96.5); 221 (54.6%) were males and 184 (45.4%) females. The primary tumor site was pancreas in 112 (29.1%), followed by small bowel (n=?86, 22.3%) and lungs (n?=?60, 15.6%). Only 21 patients (5.5%) had a gastric NET, whereas 35 patients (9.1%) had occult tumors. 54 patients (16.2%) presented carcinoid syndrome, and 14 patients (4%) had hereditary syndromes, including Multiple Endocrine Neoplasia type 1 (n=10) and von Hippel-Lindau syndrome (n=3). The histologic tumor grade was G1 in 120 patients (45,9%), G2 in 95 patients (36,4%) and 46 (17,6%) were neuroendocrine carcinomas. A first- line systemic treatment (including somatostatin analogs, cytotoxic chemotherapy and targeted therapy) was administered in 311 patients (76.8%) while 143 patients (35.3%) started a second line regimen. The survival rate at 5 years was 91% for pancreatic NENs, 82% for gastro-intestinal NENs, 95% for lung NENs and 95% for occult primary NENs.

Conclusions: With all the limitations of a retrospective study, this population-based study describes epidemiology, pathological features and clinical course of NENs in the Piedmont-Valle d'Aosta Regions, not available from other regional Register. These data reproduce the expected heterogeneity of the disease. A prospective database is necessary to optimize resources and costs for a rare disease.

N05

OUR EXPERIENCE ON SECOND MALIGNANCIES IN PATIENTS WITH NEUROENDOCRINE NEOPLASIA

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Background: Neuroendocrine tumors (NETs) are a heterogeneous group of tumors originated from neuroendocrine cells located at various sites. They have various clinical presentations and growth rates. Typically, patients experience long delays before diagnosis because these tumors do not have specific symptoms and there is a lack of sensitive and specific methods for early detection. The majority of patients are diagnosed with advanced disease, for which a limited number of specific antineoplastic therapies exist. They are frequently associated with synchronous or metachronous secondary primary malignancies (SPM).

Materials and Methods: From 2009 to 2019 a total of 262 NET cases were diagnosed at Oncology Unit Sapienza, Roma. We examined 30 patients with NET associated with synchronous or metachronous SPM. NET and SPM were regarded as synchronous when they were diagnosed at the same time or within 6 months before or after diagnosis of the NET and as metachronous lesions were defined as cancers that were discovered more than six months after diagnosis of NET.

Results: We retrospectively reviewed our institutional database of NET patients. The most common site of NET origin was lung (52.3%); 58 patients (22,1%) had a gastrointestinal origin. Regarding the 30 patients with SPM there were no significant differences in sex, age, NET site, disease stage between those patients who developed a SPM and those who did not. Ten patients had a synchronous cancers, five cases were observed in the GI tract. We can note the association of two cases of thymoma with mammary neoplasia, two cases of pancreatic NET with colon neoplasia and two cases of colon adenocarcinoma plus NET. Twenty patients revealed metachronous lesions. In 2 there was an association of prostate neoplasia with a NET of the pancreas.

Conclusions: NETs are frequently associated with synchronous or metachronous SPM, of whom the most common site is the gastrointestinal tract. The occurrence of second cancers could be attributed to the late effect of cancer treatment, genetic susceptibility, such as hereditary cancer-predisposing syndromes (MEN-1, MEN-2), and etiologic factors (smoking, alcohol) while some NETs are sporadic. The etiology of this malignant predisposition may be due to the various neuroendocrine peptides elaborated and secreted by neuroendocrine cells that have properties of tumorigenesis like secretin, gastrin, bombesin, cholecystokinin (CCK) and vasoactive intestinal peptide (VIP).

N06

HIGH DOSES OF SOMATOSTATIN ANALOGS IN WELL DIFFERENTIATED NENs: SAFETY AND EFFICACY IN ELDERLY

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Background: Neuroendocrine neoplasms (NENs) are a heterogeneous group of neoplasms, which can be treated with different therapies; for example analogs of somatostatin (SSA) can be used due to their proved antineoplastic and antisecretory effects in well differentiated (WD) NENs. This multicentre analysis studies the safety of high doses

Tab 1.

Age at the diagnosis (years)	% side effects
<60	10,00%
61-70	13,73%
71-80	20,41%
>81	20,00%

(HDD) analogs of somatostatin (SSA) in WD NENs with particular attention for patients (pts) over 70 years of age.
Material and Methods: Clinical data from 13 Italian NENs dedicated Units were collected: the analysis considered patients with WD NENs, in progression on previous treatments, included SSA, and subsequently treated with HDD-SSA.
Results: 170 pts were included: 61.76% male, 38.24% female. At the diagnosis, the median age was 58.83. The most frequent sites were the gastro-intestinal system (54.71%), pancreas (27.06%) and lung (8.24%). Typical lung carcinoids were 2.95%, G1 NENs 54.11% and G2 42.94%. Carcinoid syndrome or other clinical conditions like gastrinoma, insulinoma, Zollinger-Ellison, were observed in 31.76% patients. 25 patients (14.71%) were affected by side effects (SEs) and the most frequent were: cholecystitis (4%), G1 asthenia (12%), G1 hyperglycemia (8%), G1 steatorrhea (76%). We divided patients in 4 groups considering the age at the diagnosis: lower than 60 years, 61-70, 71-80 and more than 81 years. The treatment was well tolerated without important side effects also in the group of patients > 70 years although there was a higher percentage of SEs (Tab.1) with the increase of age with a maximum percentage of 20.41% in the group with an age of 71-80 years. The median PFS was 20.18 months.
Conclusions: In patients with an age >70 and a WD NEN in progression to standard doses of SSA, HD-SSA can represent a safe and effective second line therapy.

N07

DIAGNOSTIC ACCURACY OF PRO-GASTRIN-RELEASING-PEPTIDE (PROGRP) IN NON-SMALL CELL NEUROENDOCRINE CARCINOMA (NEC): A PROSPECTIVE SINGLE CENTRE CASE-SERIES

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Background: Pro-gastrin-releasing-peptide (PROGRP) is a multi-functional bombesin-like peptide that has been tested in patients (pts) with small cell lung cancer (SCLC) demonstrating high diagnostic accuracy both in limited and diffuse disease. It has been proposed as independent prognostic factor in SCLC. This observation has also been confirmed in a recent retrospective analysis conducted in our Institute on pts with SCLC: in our study we noticed that PROGRP is sensitive for SCLC and that high levels are related to high disease burden and may have a negative prognostic significance. Basing on these data we decided to test PROGRP in order to explore its diagnostic accuracy and its potential role in non-small cell neuroendocrine carcinomas (NECs) and in Merkel carcinomas.
Methods: We have tested PROGRP values in pts hospitalized in our Institute from May 2018 until May 2019 who received a diagnosis of advanced large cell, highly undifferentiated/mixed small-large cell NECs, mixed adenocarcinoma/neuroendocrine carcinomas (MANECs) and Merkel cell carcinomas (MCCs), before starting any antineoplastic treatment. Serum pro-GRP levels have been measured with electrochemiluminescence at our laboratory (cutoff 77.8 pg/mL).
Results: A total of 12 pts were studied (10 men and 2 women, median age 68 years, range 44 – 87): 4 pts had lung large cell NECs, 3 MANECs (1 rectal, 1 pancreatic and 1 lung), 2 mixed large/small cells NECs, 2 highly undifferentiated-NECs (1 gallbladder, 1 lung), 1 MCC. Four pts had a higher value of PROGRP (cutoff 77.8 pg/mL), 2 of them had large cell NECs (452,10 pg/mL and 139,40 pg/mL), 1 had mixed small/large NEC (28883 pg/mL) and 1 had Merkel cell carcinoma (164.2 pg/mL).
Conclusions: In 4 pts with diagnosis of NEC PROGRP was significantly high at baseline: this limited preliminary observation supports the rationale of an ongoing study in our Institute in which we are collecting PROGRP at diagnosis, after 3 and 6 months from the start of first line chemotherapy, in order to confirm diagnostic accuracy of this marker also in non-small cell NEC and explore its clinical role as prognostic factor.

N08

SAFETY AND EFFICACY OF CAPECITABINE AND TEMOZOLOMIDE (CAPTEM) IN PATIENTS WITH PROGRESSIVE METASTATIC NEUROENDOCRINE TUMORS (NETs): OUR EXPERIENCE

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Background: Treatment with Temozolomide and Capecitabine is a valid regimen for advanced NETs with a high and durable response rate especially in pancreatic NETs.

Materials and Methods: A total of 19 patients (pts) with metastatic NETs were treated at our hospital with temozolomide (200 mg/m2 once daily, days 10-14) and capecitabine (750 mg/m2 twice daily, days 1-14) every 28 days between 2010 and 2019. Patients included 11 males and 8 females with performance status ecog 0-1. Median age was 58,3 years (range 32-80). Primary tumour was pancreatic in 3 pts, lung in 11 pts, midgut in 2 patient, others in 3 pts. Six pts had moderately differentiated NET, 13 pts had NET with ki 67> 20%. Three pts received CAPTEM as first line treatment, 8 pts as second line treatment and 8 pts as > third line treatment. Pretreated patients with a poorly differentiated NET received a platinum etoposide regimen while patients with moderately differentiated NET were pretreated with Somatostatin Analogs. Safety and efficacy were retrospectively evaluated.
Results: The regimen was well tolerated and grade 3 toxicity was observed in 1 case resulting in neutropenia and thrombocytopenia. The median Progression free survival (mPFS) was 6,2 months irrespective of origin tumour. Patients receiving CAPTEM as first line treatment (3 pts) had a higher mPFS (12,7 months). Patients (6) with a ki 67<20% had a 12 months mPFS. Only 30% of patients experienced a rapid disease progression after three cycles of treatment.
Conclusions: CAPTEM is well tolerated and prolongs survival in patients with metastatic NET irrespective of treatment's line. Neverthless, in our experience, the better mPFS was observed in patients with moderately differentiated NET and in first line treatment.

P - Management of Cancer Pain

P01

OBSERVATORY ON BREAKTHROGH CANCER PAIN (BTCP): SUB-ANALYSIS OF THE PROSPECTIVE OBSERVATIONAL STUDY ITALIAN ONCOLOGIC PAIN MULTISETTING MULTICENTIRC SURVEY (IOPS-MS)

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Background: Despite adequate pain control for most hours of the day, cancer patients may develop transient flares of pain through the day (BTcP).
Based on the data already existing in the literature the IOPS-MS expert group planned a survey to provide further information regarding the characteristics of this phenomenon. 32 centres were involved for 24 months. A standard algorithm was used to diadnose BTcP. It was obtained a database of 4016 patients with more than 1000 variables.
Based on this background, 3 questions arise: Can we define different BTcP intrinsic subtypes? What are the determinants of satisfaction for BTcP therapies? Can we imagine a tailored BTcP treatment according to pre-defined parameters?
Primary end point: to investigate whether "subtypes" of BTcP exist using a clustering method.
Secondary end point: to determine variables that define satisfaction to BTcP therapy.
Methods: In order to performe a statistical analysis, a preprocessing flow of the original database was carried out.
Given the high dimensionality of our database, we used some *machine learning* algorithms. Particularly, we used *unsupervised learning* to see whether BTcP features were clustered according to similar groups.
Results: In order to investigate whether "subtypes" of BTcP exist, we used BTcP features to build an unsupervised clustering model. The number of BTcP episodes, the duration of BTcP peaks, the BTcP type, the BTcP intensity, the number of days since the begun of BTcP episodes, the eventual benefit from pharmacotherapy, the eventual benefit from rest and whether the BTcP was enhanced by movements were the variables selected for the final model, which was built with k-medoids algorithm obtaining 12 clusters.
We analysed the features of each BTcP cluster in order to identify different BTcP subtypes, obtaining significantly different characteristics for each variable.
Next we found that all the cluster retained some peculiar clinical features significantly different from other clusters.
Next, we tried to assess what factors are associated with BTcP therapy satisfaction, elaborating a description cluster by cluster.
Conclusions: These results will allow in the future to target BTcP therapy based on patient characteristics and to define a "precision medicine strategy" also for supportive care.

P02

IMPACT OF BREAKTHROUGH PAIN ON QUALITY OF LIFE IN END OF LIFE CANCER PATIENTS

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Background: Symptoms management, including pain, in cancer patients with poor prognosis is crucial to improve quality of life (QoL). Between 40 and 80% of cancer

patients are affected by breakthrough pain (BTP), and at the end of life, BTP becomes a disruptive issue. The heterogeneous nature of BTP among different patients and even in the same patient, makes treatment tailoring difficult. Thus, patients' involvement is required to understand this multifaceted phenomenon. The Alberta Breakthrough Pain Assessment Tool (ABPAT) was designed to manage this limitation.

The innovative approach of ABPAT is that it considers a list of pain descriptors to help patients in describing BTP in addition to its frequency and severity. Understanding the specific characteristics of pain can help healthcare professionals to better manage pain. This study aimed to characterize BTP and investigate its impact on QoL in end of life cancer patients.

Methods: BTP was assessed with a short form of the Italian version of the ABPAT in 92 patients from two Italian palliative care services. QoL was assessed with the Palliative Outcome Scale (POS) (range 0-40). Patients were stratified by self-reported predictability or unpredictable of BTP.

Results: 665 BTP episodes were recorded (median of 0.86 episodes per day). A median duration of 30 minutes and a median peak intensity score of 7/10 were reported. The BTP peak was reached in <10 minutes in 267 (41.1%), 10 to 30 minutes in 259 (39.9%), and $\geqslant 30$ minutes in 30 (4.6%) of the episodes. Onset of relief occurred after a median of 30 minutes. Time to peak ($p<0.001$) and duration ($p=0.046$) of BTP was shorter in patients with predictable pain ($n=31$) that usually were younger than those with unpredictable pain ($p=0.03$). Most common triggers were 'movement in bed' ($n=36$, 39.1%) and 'coughing' ($n=13$, 14.1%); the most common relieving factor was 'as needed BTP medications' ($n=73$, 79.4%), followed by scheduled pain medications ($n=62$, 67.4%). Mean QoL scores was low (POS = 14.6, ± 4.6). No difference in QoL between patients with predictable and unpredictable BTP was found ($p=0.49$).

Conclusions: In end of life cancer patients BTP is a frequent and high intensity symptom with a negative impact on the QoL and has different characteristics according to its predictability. BTP therapy should be tailored on the patient's clinical conditions and BTP triggers to optimize pain management and thereby QoL.

P03

TERRITORIAL CARE OF THE PATIENT WITH CANCER PAIN IN THE NETWORK OF RETE ONCOLOGICA CAMPANA (ROC)

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Background: Most of the clinical activities for the care of cancer patients are given by the National Health System in an outpatient setting. The concept of simultaneous care, consider the importance of taking concurrently in consideration the need of a specific anti neoplastic therapy and the treatment of all the remaining patient need. In particular pain management is not only related to the phase of the end of life, but must be followed all over the clinical history of the disease through adaptation of therapy according to a dynamic assessment. The link among cancer specialized hospitals and the clinical services that manage cancer patient in their local area of residence is not fully developed in Regione Campania. One of the main goal of the ROC is to take care of the oncological needs both before the access to the hospital, in the diagnostic phase of the disease, and after the therapy is started giving the opportunity to the patients and families to satisfy all the needs that do not require directly management in the hospital in the services available in the local territorial system.

Methods: To this aim an electronic platform of ROC has been developed to manage both phases of the disease. The specific goal of the project is related to the activation of the local assistance when the patient after being treated in the hospital go back home and local services for the continuation of the care. Electronically, all the information regarding the needs of the patient that is going to be sent home again after therapy are reported to the central portal of the local health system close to its residence. Baseline assessment of pain is done in the cancer center and this report is transmitted to the residence regional services in order to prepare the following actions required.

Results. The pilot experience started in December 2018, involving the National Cancer Institute of Naples, AORN "A. Cardarelli" and the services available for the simultaneous care in the ASLNA1. 900 patients have been screened and 100 patients have received simultaneous care in the setting of this web based procedures.

Conclusions: Focus on cancer pain and breakthrough cancer pain will be give, in accordance to what is defined by the national low 38/2010 in the intent to move from the hospital without pain to the concept of the territory without pain.

R - Miscellanea

R01

FAMILY HISTORY OF CANCER AS SURROGATE PREDICTOR FOR IMMUNOTHERAPY WITH ANTI-PD-1/PD-L1 IMMUNE CHECKPOINT INHIBITORS: THE FAMI-L1 STUDY

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Background: Tumors related to inherited cancer susceptibility seem to have an "immune sensitive phenotype". In the preliminary analysis of the FAMI-L1 study, we found a significant association between family history of cancer (FHC) and better clinical outcomes with anti-PD1/PD-L1 inhibitors.

Methods: To investigate if FHC and diagnosis of metachronous and/or synchronous multiple neoplasms (MN), could be used as surrogate predictors, we conducted a multicenter retrospective study of advanced cancer patients treated with anti-PD-1/PD-L1 immunotherapy. Family history was collected in straight and collateral lines and patients were categorized as follow: FHC-high (in case of cancer diagnoses in both the lines), FHC-low (in case of cancer diagnoses in only one line) and FHC-negative. Patients were also categorized according the diagnosis of MN as follow: MN-high (> 2 malignancies), MN-low (2 malignancies) and MN-negative. ORR, PFS, OS and incidence of irAEs of any grade were evaluated. Univariate and multivariate analyses were performed.

Results: Between September 2013 and May 2018, 822 consecutive patients were enrolled. Primary tumors were: NSCLC (57.8%), melanoma (23.1%), renal cell carcinoma (16.2%) and others (2.9%). 133 patients (16.2%) had ECOG-PS ⩾ 2. 458 patients (55.7%) were FHC-negative, 289 (35.2%) were FHC-low and 75 (9.1%) FHC-high, respectively. 29 (3.5%) had diagnosis of synchronous MN and 94 (11.4%) of metachronous MN. 108 (13.2%) and 15 (1.8%) patients were MN-low and MN-high, respectively. The median follow-up was 15.6 months. No significant differences was found regarding ORR among subgroups. Among FHC-negative, FHC-low and FHC-high patients median PFS was 9.3, 8.4, and 20.5 months, respectively, while median OS was 18.2, 20.8, and 31.6 months, respectively. FHC-high patients had a significantly longer PFS (HR=0.69 [95%CI: 0.48-0.97], p=0.0379) and OS (HR=0.61 [95%CI: 0.39-0.93], p=0.0210), when compared to FHC-negative patients. FHC-high was confirmed an independent predictor for PFS and OS at the multivariate analysis. No significant differences were found according to MN categories. FHC-high patients had a significantly higher incidence of irAEs of any grade, compared to FHC-negative patients (p=0.0012), while FHC-low did not (p=0.1240).

Conclusions: FHC-high seems to be an independent predictor for longer PFS and OS in cancer patients treated with anti-PD-1/PD-L1. DDR genes alterations may underlie these results.

R02

IMPORTANCE OF HEALTHCARE WORKERS' PERFORMANCE IN DETERMINING FINANCIAL TOXICITY OF CANCER IN THE ITALIAN HEALTH CARE SYSTEM: A FOCUS FROM THE "PATIENT REPORTED OUTCOME FOR FIGHTING FINANCIAL TOXICITY OF CANCER" (PROFFIT) PROJECT

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Background: Financial toxicity in cancer patients has been initially reported in the United States and subsequently in other countries, including Italy, despite its health care system is based on universal coverage. Considering that the characteristics of healthcare and welfare systems of the country do influence financial problems faced by cancer patients, we are developing an instrument for evaluating occurrence, gravity, and consequences of financial toxicity in Italy, and hopefully for fighting it.

Methods: Concept elicitation, item generation and qualitative analyses represented the initial tasks of the project. Literature review, focus groups with patients and caregivers, and semi-structured interviews with AIOM and CIPOMO oncologists were conducted for concept elicitation. Importance analysis with a 4-point scale (1=not important at all to 4=extremely important) was done in 3 centers from North, Centre and South Italy to rank items produced during concept elicitation. A committee including oncologists, psychologists, statisticians, patient association's representatives, nurses, social science researchers and economists oversights the project.

Results: 55 candidate items, distributed among 10 themes (bureaucracy, medical care, domestic economy, emotion,

family, job, health workers, welfare state, free time, transportation) were proposed to 45 patients (15 each in Naples, Rome, and Turin) for ranking their importance (one excluded because missing more than half of the responses). Median age was 62, 47.7% were females. Median importance score was 111 (range 77 to 161) out of a potential range 44 to 176. Four items, related to performance of healthcare workers, ranked in the first seven positions, with scores 161 (first position of the rank, performance of doctors and nurses), 146 (communication among health workers), 141 (administrative personnel) and 140 (family doctors). Importance analysis led to the selection of 30 items for further development of the project, which is ongoing.

Conclusions: Items dealing with performance of health workers ranked among the first positions in the importance analysis of the proFFiT project. Such performance is among the most significant factors affecting cancer patients' journey and, possibly, financial toxicity. Supported by Fondazione AIRC IG grant 2017-20402.

R03

POSSIBLE PROGNOSTIC ROLE OF HYPERCHOLESTEROLEMIA IN ADVANCED CANCER PATIENTS TREATED WITH IMMUNE-CHECKPOINT INHIBITORS

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Background: During the last years immune-checkpoints inhibitors (ICI) have been approved in numerous types of solid cancer. However, a great number of unselected patients still do not respond to ICI. Moreover, there is a need to identify biomarkers that could predict the prognosis of immunotherapy treated patients.

The aim of our study is to evaluate the prognostic value of baseline plasmatic cholesterol level in metastatic cancer patients treated with immunotherapy.

Methods: We retrospectively enrolled advanced cancer patients consecutively treated with ICI at our center between October 2013 and October 2018, in order to correlate the blood cholesterol level before treatment with overall survival (OS primary endpoint). The secondary endpoints were the correlation between baseline cholesterolemia and progression-free-survival (PFS), response rate, time-to-treatment failure (TTF) and toxicity.

Results: Among 117 patients evaluated, the blood cholesterol level was available for 83 patients. The median age was 70 years. Primary tumors were: non-small cell lung cancer (59.8%), melanoma (19.7%), renal cell carcinoma (11.1%), urothelial cancer (7.7%), head-neck carcinoma (1.7%). 187 mg/dl was the mean and median cholesterol level and we used this cut-off to distinguish patients with "high-cholesterol" and "low-cholesterol". The median follow-up was 17.9 months. Both OS and PFS were better in patients with high plasmatic cholesterol level: median OS was 22.2 *vs* 7.9 months ($p=0.018$) and median PFS was 6.6 *vs* 2.0 months ($p=0.020$). In this preliminary analysis, data about the other secondary endpoints are not yet available.

Conclusions: Baseline hypercholesterolemia was associated with better PFS and OS in ICI treated cancer patients. Hypercholesterolemia is characterized by a state of low-grade inflammation and it represents a trigger to tumor micro-environment enrichment by myeloid-derived suppressor cells and tumor-associated macrophages [Porta, *Carcinogenesis* 2018]. We hypothesized that hypercholesterolemia could characterize patients which tumors are subtended by an immunosuppressive status, thus more likely to be responsive to immunotherapy, similarly to what happens in patients with high body mass index [Cortellini, *J Immunother Cancer* 2019]. Cholesterolemia could become a simple tool potentially useful to better predict the outcome of patients receiving ICI, although further prospective studies are needed.

R04

JOB LOSS AND RETURN TO WORK OF PATIENTS WITH CANCER. A PROSPECTIVE OBSERVATIONAL STUDY ON 416 CANCER PATIENTS

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Background: Early detection and progression in the treatment of cancer patient have improved the prognosis of many patients. In view of this improvement, cancer should be considered less as a terminal illness, but as a chronic disease. Work could be very important for cancer patients and for society and in the last decades a growing number of studies from North Europe and USA, about work and cancer patients, were published. Conversely, studies on this topic from Italy are fragmentary and very poor.

Material and methods: A prospective observational study started at the medical oncology unit, hospital of Piacenza (North Italy). All the patients between 18 and 65 years of age, diagnosed with early or metastatic cancer, admitted to the outpatient clinic, were analyzed for employment and work-related issues (job interruption, returning to work, job loss). A questionnaire with socio-demographic and job related informations was submitted to each patient.

Results: From January 2015 to June 2017, 2,187 patients with a new diagnosis of cancer were admitted to the outpatient clinic, 551 patients (25.19%) were between 18 and 65 years old, and 416 patients (75.5%) participated to the study. 278 (66.83%) women and 138 (33.17%) men,

median age 50.32 years (range 18-65), 39.18% were employees, 29.81% workers, the majority of patients had an high school degree (53.37%). 196 (47.12%) patients had breast cancer, 85 (20.43%) gastrointestinal cancer, 41 (9.86%) lung cancer, and 94 patients (22.59%) had other cancer; 105 patients (25.24%) showed metastatic cancer and 134 (32.21%) had comorbidity. After 6 months 178 patients (42.79%) interrupted their work, of these the majority were men (57.25%) and worker (58.23%), with low level of education (72.15%). The majority of patients (86.67%) with metastatic cancer left their work after 6 months from diagnosis. Only 22 of 178 patients (12.36%) in our series returned to work, of these, 20 (90.90%) were women, 16 with breast cancer (80%).

Conclusions: Our findings suggest that there is a significant association between job loss and gender (male), type of job (heavy work), low level of education, advanced stage of cancer and comorbidity. It is important that clinicians and nurses recognize patients who are at risk for job loss. They may organize the outpatient clinic considering work related issues. Rehabilitation program for return to work and normative interventions are also needed to improve employment and return to work of cancer patients.

R05

MEASURING FINANCIAL TOXICITY OF CANCER IN THE ITALIAN HEALTH CARE SYSTEM: INITIAL RESULTS OF THE PATIENT REPORTED OUTCOME FOR FIGHTING FINANCIAL TOXICITY OF CANCER PROJECT (PROFFIT)

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Background: Financial toxicity in cancer patients has been initially reported in the United States and subsequently in other countries, including Italy, despite its health care system is grounded on universal coverage. Considering that the way healthcare and welfare systems are shaped does impact on financial problems faced by cancer patients, we are developing an instrument for evaluating occurrence, gravity, and consequences of financial toxicity in Italy, and hopefully for fighting it.

Methods: Concept elicitation, item generation and qualitative analyses represented the initial tasks of the project. Literature review, focus groups with 34 cancer patients or caregivers in three regions located in North, Centre, and South Italy, and semi-structured interviews with 97 oncologists were conducted for concept elicitation. A recursive process was used to identify themes in the data to inform instrument until saturation was reached. Importance analysis questionnaires were administered to further 44 cancer patients to evaluate and revise the draft item pool. A multi-disciplinary committee (including oncologists, psychologists, statisticians, patient association's representatives, nurses, social science researchers and economists) oversights the project.

Results: Overall, 156 concepts were distributed among 10 themes (bureaucracy, medical care, domestic economy, emotion, family, job, health workers, welfare state, free time, transportation). After controlling for redundancy, 55 candidate items were generated and 30 items, with at least one per each theme, remained after importance analysis. Out of the 30 items, 23 (77%) refer to material conditions, 4 (13%) to psychological response and 3 (10%) to coping behaviors.

Conclusions: The first results of the proFFiT project show that most of the items selected by patients are related to material conditions that cause, or derive from, financial hardship. The final questionnaire will be ready by the end of 2019. Supported by Fondazione AIRC IG grant 2017-20402. clinicaltrials.gov NCT03473379.

R06

CLINICAL BENEFIT FROM LATE LINES OF THERAPY OFFERED TO PATIENTS TREATED IN A TERTIARY REFERRAL CENTRE

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Background: Late lines of therapy (LLs) offered to cancer patients (pts) are often characterized by scarce or doubtful clinical benefit and literature evidences about their use and their real impact on survival and quality of life are very few. ESMO-MCBS (ESMO Magnitude of Benefit Scale) is a tool that gives an evaluation of the magnitude of clinically meaningful benefit that can be expected from antitumour therapies. The aim of our study was to evaluate ESMO-MCBS of the treatments that were offered as a LL to pts in our centre and to perform an evaluation of the clinical assistance they received.

Patients and Methods: We calculated ESMO-MCBS of the therapies that were offered as LL to patients that were treated at our centre and whose death happened in the period 1 January 2017 – 31 December 2018. We also evaluated these pts'rate of unplanned access to emergency room or hospitalizations and their access to supportive care and palliative care service in the last 90 days of their lives.
Results: 238 patients were included in the analysis. 12 (5.04%) received a LL with a high ESMO-MCBS (4 or 5), 16 (6.72%) a LL with an intermediate ESMO-MCBS, 77 pts (32.35%) a LL with a low ESMO-MCBS (1 or 2), and 133 (55.88%) a LL whose ESMO-MCBS cannot be calculated because of lack of data from strong literature evidences (e.g. ph3 trials) that are required for the scale. 79 pts (33.19%) had at least an unplanned access to emergency room or hospitalization during the last 90 days before death. 117 pts (49.16%) accessed at least once to our supportive and palliative care service.
Conclusions: Our study confirmed that patients are often offered a LL whose clinical benefit is little, absent or unevaluable. On the other hand, these pts are still not often addressed to supportive/palliative care service whose clinical impact is high in this setting. We strongly suggest integrating ESMO-MCBS as a clinical tool for the evaluation of possible LL offered to advanced-stage pts in order to prevent them from receiving therapies of poor clinical impact and, especially when therapies with a high ESMO-MCBS cannot be offered, to offer them a timely access to valuable, more precocious palliative care.

R07

PROSPECTIVE TRIAL EXPLORING THE ADHERENCE TO DIETARY GUIDELINES (DG) AND BODY WEIGHT CHANGE (BWC) IN EARLY-STAGE BREAST CANCER (EBC) PATIENTS SUBMITTED TO A NUTRITIONAL EVIDENCE-BASED INTERVENTION

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Background: Overweight and obesity are highly prevalent in patients affected by EBC, both prior to diagnosis and after therapy. These conditions have been associated with an increased risk of therapy-related morbidity, recurrence and mortality. However, the adherence of patients affected by EBC to nutritional intervention is not entirely explored. The aims of this prospective study are to evaluate the adherence to DG and the effectiveness of nutritional intervention in terms of BWC in patients with EBC.
Methods: This study included EBC patients addressed to receive neoadjuvant or adjuvant treatment; eligible patients received a nutrition evidence-based educational intervention by a skilled dietitian. Adherence to DG was estimated through the validated Med-Diet 14-item questionnaire. Health-Related Quality of Life was analyzed with the EORTC QLQ-C30. Anthropometric and dietary assessments were performed. Associations between variables and groups according to nutritional variables were analysed (Chi-square test).
Results: From February 2016 to December 2018, 204 patients were enrolled (median age 49 years): 27.5% of patients were underwent to neoadjuvant treatment and 72.5% to adjuvant treatment. Overall, 80.4% of participants were underwent endocrine therapy. At baseline, 2.5% of patients were underweight, 41.7% were normal weight, 33.3% were overweight and 22.5% were obese. Moreover, 47.5% of patients gained $\geqslant$5% of their usual weight and 25.5% performed routine physical activity. During treatment, most patients reported significant nutritional impact symptoms, such as dyspepsia (51.5%), constipation (62.3%) and dysgeusia (34.8%). Six months after the nutritional evidence-based intervention by a skilled dietitian, the median adherence to DG was high (median Med-Diet score was 12). A high adherence to nutrition guidelines (defines as a Med-Diet score $\geqslant$10, 112 patients) significantly correlated with a weight loss $\geqslant$5% from the baseline weight ($p = 0.005$). Furthermore, the weight loss $\geqslant$5% was correlated with a lower rate of depression ($p = 0.05$).
Conclusions: These results suggest that a tailored nutritional intervention for EBC patients undergoing treatment may help to improve their adherence to the DG and finally to weight loss. Thus, a high adherence to DG represents a tool to control the body weight and, consequently, to potentially improve the disease outcome.

R09

BREAST CANCER FOLLOW-UP: A NATIONAL SURVEY OF CURRENT CLINICAL PRACTICE BY THE CENTERS OF ITALIAN ONCOLOGICAL GROUP OF CLINICAL RESEARCH (GOIRC)

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Background: The number of breast cancer (BC) survivors is increasing due to the aging of the population and the improvement of survival rates. Survivors have health care needs including detection of early recurrences, treatment of therapy-related complications and psychological support. No randomized data exist to support any individual follow-up (FU) sequence or protocol. Physicians' adherence to international guidelines is unknown. The aim of this study is to investigate the survivorship care plan in Cancer Centers affiliated to Italian Oncological Group of Clinical Research (GOIRC).

Methods: A questionnaire survey with 12 questions was e-mailed to the members of GOIRC in March 2019. Respondents were asked how they follow-up BC survivors. We have collected the survey data and compared them to national/international guidelines.

Results: 20 out of 30 GOIRC centers completed the survey. The majority of the oncologists (75%) reported to follow AIOM guideline in FU management. Although, 14 respondents (70%) are used to perform routinely tumor markers and imaging tests (chest X-ray and liver ultrasound) as screening tools for early detection of recurrence. Advanced imaging studies (bone scan, CT scan, PET/FDG CT) are routinely recommended in high-risk patients by 4 interviewed. Considering patients on aromatase inhibitors, all the respondents recommend lipid profile and bone density evaluation every two years. Moreover, nutritional counselling is offered in 7 centers (35%). Frequency of checkup is scheduled according with BC risk of relapse in 11 centers (55%), while visits are conducted six-monthly in the other 9 cases. Duration of FU is variable: 60% of interviewed monitor the patients until the end of the adjuvant endocrine therapy while in the other cases checkup is carried on over 10 years. At the end of oncology FU, all the interviewed recommended yearly mammography, in four cases annual tumor markers check is suggested too.

Conclusions: A majority of respondents in Italian Cancer Centers perform more intensive FU compared to guidelines recommendations. FU of BC survivors is still an unmet clinical need. Randomized national trial on survivorship care plan should be considered.

R10

HOW DO SKELETAL MORBIDITY RATE AND SPECIAL TOXICITIES AFFECT 12-WEEKS VERSUS 4-WEEKS SCHEDULE ZOLEDRONIC ACID EFFICACY? A SYSTEMATIC REVIEW AND A META-ANALYSIS OF RANDOMIZED TRIALS

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Background: The bone health of patients with cancer is deeply influenced by the treatments received. The endocrine therapy and the chemotherapy can cause an impairment of the bone strength and a consequent enhanced risk of fractures.The use of zoledronic acid (ZA), a nitrogen containing bisphosphonate, has been demonstrated to provide benefits in the delay of bone metastases occurrence, the prevention of endocrine treatment-induced bone loss and the delay and the reduction of skeletal related events in patients with bone metastatic cancer. ZA is used in a 4-week schedule for the treatment of bone metastases. Some randomized trials supported its role also when administered every 12 weeks.
Material and Methods: We performed a systematic review using electonic databases and a meta-analysis in order to evaluate the two different schedules (4-weeks vs 12 weeks) in terms of skeletal morbidity rate (SMR), skeletal related events (SRE), time to first skeletal-related event (tSRE), time to multiple skeletal-related events (tmSRE), discontinuation rate and adverse events (AEs). For dichotomous outcomes (SRE, AE and SMR) we used relative risk (RR) as measure of association. For time-dependent variable (tSRE and tmSRE) we used hazard ratio (HR) with a 95% of confidence interval (CI). Heterogeneity was evaluated using Chi-square or I-square tests. We also evaluated the publication bias risk performing the Egger's test and the Funnel plot. All results were considered as statistically significant if p values were = 0.05.
Results: Our results showed a clinical difference favouring the 12-week schedule in terms of AEs (RR 1.17, 95% CI 1.06 – 1.29). In particular, we reported a significant lower renal impairment with the 12-week schedule, while a trend was registered for ostonecrosis of the jaw and hypocalcaemia. No signifcant differences were found for SMR (RR 0.97, 95% CI 0.84 – 1.13) and SRE (RR 1.02, 95% CI 0.89 – 1.16).
Conclusions: At our knowledge, our findings support for the first time in clinical practice the 12-week schedule as a valid alternative to the standard 4-week schedule in breast and prostate cancer, above all in terms of special toxicities and skeletal morbidity rate and when the clinical comorbidities of the patients suggest a higher risk of renal failure or hypocalcaemia.

R11

HEDGEHOG PATHWAY IS INVOLVED IN CANCER IMMUNE SURVEILLANCE THROUGH PDL1 MODULATION

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Background: Recently, the immunotherapy has shown efficacy in triple-negative breast cancer (TNBC). Since the Hedgehog (Hh) signaling mediates crosstalk between breast cancer cells and tumor-infiltrating immune cells, we investigated the connection between Hh activation, PDL1 expression and tumor-immune microenvironment in TNBC.
Methods: TNBC tumors from untreated patients were subject to PDL1 and Gli1 expression analysis by IHC. Correlation of Hh pathway activation and PDL1 expression was assessed in TNBC human cells treated with Gli1 siRNA or the SMO-inhibitor NVP-LDE225. Study aims were to evaluate PDL1/Gli1 cross-talk by knockdown and overexpression assays, Gli1 genomic activity by ChIP-PCR and gene expression by RT-PCR.
Results: To assess the correlation of Hh pathway activation and PDL1 expression a tissue microarray of TNBC samples from 237 untreated patients was prepared; 203/237 evaluable cases were analyzed for the expression of PDL1 and Gli1, the major indicator for the canonical Hh signaling activation. We found a significant correlation between PDL1 and Gli1 expression: indeed, of 77/203 PDL1 positive tumors 42/77 expressed Gli1. Interrogating the open-access database cBioPortal for Cancer Genomics, PDL1 positive TNBCs showed high levels of SMO and PTCH1, Hh pathway receptors. We studied the linkage between the two pathways in a panel of TNBC cell lines: 1) The pharmacological inhibition or genomic knockdown of Hh led to a reduction of PDL1 expression; 2) Engineering cells harbouring Gli1 overexpression showed higher levels of PDL1. Therefore, we hypothesized that Hh pathway could modulate the transcription of PDL1. We performed a ChIP analysis followed by PCR amplification and we found that Gli1 binds to the PDL1 gene promoter. Translating our hypothesis in 4T1 cells, a highly aggressive TNBC murine model when injected into Balb/C mice, we observed that cell viability and PDL1 protein expression were inhibited by NVP-LDE225. I*n vivo* experiment will be performed in Balb/C mice orthotopically xenografted with 4T1 cells to confirm the crucial role of Hh

pathway to modulate the PDL1 expression and to identify new therapeutic strategies in TNBC.

Conclusions: Our results suggest that Hh pathway has a specific role in cancer immune evasion trough PDL-1 modulation. Due to their ability to target both tumor cells and the pro-tumor microenvironment, Hh inhibitors represent promising therapeutics to be clinically investigated in Gli1 overexpressing TNBC patients.

R12

THE ROLE OF PRO-CTCAE IN THE MANAGEMENT OF PATIENTS UNDERGOING ANTICANCER TREATMENT

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Background: Toxicities are common during cancer treatment and can affect functional status,quality of life,health care resource utilization,treatment adherence and cancer survivorship. Patient-reported outcomes (PROs) has been demonstrated to be a valid approach to tabulating toxicities and to capture a unique perspective of oncology therapy. The aim of our analysis was to compare patient-reported symptom severity and practitioner-reported adverse events (AE) among patients (pts) receiving anticancer treatments

Patients and Methods: We prospectively collected data on pts undergoing anticancer treatments(all cancer types,stage I-IV) in Ferrara Oncology Unit. AE were assessed by physicians using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.Patient-reported symptom severity was measured using the NCI PRO-CTCAE ITEMS-ITALIAN, Item Library Version 1.0. Descriptive statistics were used to characterize the agreement between CTCAE grades and PRO-CTCAE severity ratings.

Results: We conducted an analysis on 167pts (63% women; 37% men) treated from February to July 2018. The median age was 65 years (35-84). 7% of pts were treated in neoadjuvant setting, 23% in adjuvant setting and 72% in advanced setting.54% of pts receveid chemotherapy (CT),18% a combination of CT and target therapy (TT), 12% immunotherapy, 8% TT,4% hormonotherapy, 4% a combination of hormonotherapy and TT. The most frequent practitioner-reported CTCAE AE was gastrointestinal toxicity(28% of pts). The most frequent PRO-CTCAE AE reported was cutaneous toxicity(54% of pts). The highest practitioner/patient agreement was seen for low grade AE. An overall decrease in practitioner/patient agreement was seen for high grade AE. Practitioner-reported CTCAE grades were generally lower than PRO-CTCAE scores, especially for symptom domains not easily evaluable by physical examination,like psychosocial disorder (1.67% vs 40%). For each symptom domain, we analysed the agreement between CTCAE grade and PRO-CTCAE symptom severity by Pearson correlation coefficient:we demonstraded a statistically significant correlation ($r>0,4$) for nausea, vomiting, disuria and anorexia. PROs led to a modification of supportive therapy in 50% of the cases.

Conclusions: The inclusion of PRO-CTCAE, taking into account patients' treatment experiences,provides informations that can potentially enhance clinical management of anticancer treatment AE,enabling more informed decisions by pts and clinicians facing treatment choices.

R13

CHEMOTHERAPY DRUGS RESIDUES MONITORING: THE EXPERIENCE OF NATIONAL CANCER INSTITUTE "G. PASCALE" OF NAPLES

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Background: The Centralized Unit for Handling Antineoplastic of National Cancer Institute "G. Pascale" of Naples set up many chemotherapies. Chemotherapy drugs have a different chemical stability related to drug reconstitution and/or dilution. A study was performed to evaluate in a month: the drug residues daily produced, the amount of drug used in the following days and those wasted due to instability or not use.

Materials and methods: From 05.02.2018 to 08.03.2018 were analyzed 28 high-cost oncology drugs subject to central monitoring through AIFA registers. The drug day was established for nivolumab, pembrolizumab and ipilimumab. Drug stability was found in the technical data sheet. In primis a diary was daily compiled with the number of patients treated and drug residues at the end of all therapies. After the residues wasted and those reused for the following day were separated. At the end drug waste in mg and total expenditure were evaluated.

Results: In a month there were 2,828mg residues corresponding to €24,863.

There were no residues for 11 drugs.

Azacitidine had the largest residue 406mg and €1,295 waste, because the reconstituted drug stability is 8h between 2-8 °C; in fact only 3 patients were treated equal to 19 preparations.

Eribulin had the highest cost/mg € 308/mg and 24h stability at 2-8 °C, however had the lowest residue (2.19mg) and only €673 wasted; moreover 7 patients were treated and 24 therapies prepared.

Cabazitaxel (24h stability at 2-8 °C) had the greatest impact on total costs 95mg residue and €5,030 wasted indeed only 5 patients treated and 11 preparations.

The drug day was established on Tuesday and Wednesday every week considering that nivolumab, pembrolizumab and ipilimumab stability was 24h at 2-8 ° C. Despite 105 patients treated with nivolumab and 210 preparations, there was a residue of 100mg and €1.075, therefore only a single vial of drug was lost. Instead, 32 patients were treated with pembrolizumab, 51 preparations were made and there was a residue of 105mg and €2,699. Finally 7 patients received ipilimumab unfortunately due to the high cost of the drug (53,7 €/mg), although only 9 preparations made, there were 56mg residues and €3.007 unused.

Conclusions: One month of residues monitoring showed that the unused drug affect the total pharmaceutical expenditure for 0,93%. Waste production is linked not only to the poor stability of the drug but also to the limited availability of different dosages of drug packaged and marketed.

R14

ENROLLMENT OF ELDERLY PATIENTS IN PHASE I CLINICAL TRIALS: A RETROSPECTIVE ANALYSIS OF A SINGLE CENTER EXPERIENCE

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Introduction: In the last decades, increasing life expectancy of western countries has led to expansion of the elderly cancer population, defined as individuals aged 65 ⩾ years. Elderly are commonly considered as a frail subgroup. For this reason, they are less likely to receive adequate cancer treatment and are often under-represented in clinical trials. The main goal of our study is to analyze clinical features and outcomes of elderly patients (pts) in early phase studies.

Methods: Data of consecutive pts screened for phase I trials in our Institution between Dec 2014 and Nov 2018 were retrieved from clinical reports.Elderly pts (age ⩾65 years) were selected as study population. The primary aim was to compare the eligibility to phase I trials of elderly to the control group(age < 65 years). Overall response rate (ORR), clinical benefit rate (CBR) and adverse events (AE) have been evaluated.The impact of different variables was analyzed using logistic regression.

Results: We identified 174(24%) elderly pts out of 723 screened pts. The most frequently primary tumors included breast (26.2%), lung (9.2%), mesothelioma (9.2%), H&N (7.7%), pancreas (7.7%), and urinary tract (7.7%). Regarding comorbidities, 72/174 (41%) had cardiovascular diseases and the median Charlson score was 9 (8-14). The median number of concomitant medications was 4 (0-10). Among elderly population, 64/174 patients (37%) were eligible for the investigational treatment: 26/64 pts (40%) pts received target therapy and 38/64 (60%) immunotherapy as single agents or in combination. Conversely, 110 pts (63%) resulted screening failure; the main reasons included the absence of druggable molecular alteration(s) for biomarker-driven studies (57.3%), abnormal results in screening procedures (9.1%) and poor performance status (11.4%). No statistically significant differences between elderly patients and control group were observed in terms of eligibility ($p=0.31$) and causes of screening failure. ORR and CBR were 9.2% and 52.3%, respectively. Most of toxicities were grade 1. Only 4% of pts experienced grade 3-4 AE. At univariate and multivariate analyses, no statistically differences were found per sex, drug class, Charlson score, presence of brain mets, >2 metastatic sites and >2 lines of previous treatment.

Conclusions: In our cohort, elderly population enrolled in early phase studies had comparable outcomes results in terms of safety and response to experimental treatments when compared to the younger.

R15

FOOD HABITS AND WEIGHT CHANGES DURING ADJUVANT CHEMOTHERAPY IN EARLY BREAST CANCER PATIENTS IN THE MODERN ERA: PRELIMINARY RESULTS OF A SINGLE-CENTER PROSPECTIVE TRIAL

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Background: Adjuvant chemotherapy has been shown to be associated to weight gain in early breast cancer (EBC) patients (pts). The aim of this single-centre cohort study is to investigate prospectively in EBC pts on adjuvant chemotherapy food habits change and their possible impact on weight gain.

Patients and Methods: From April 2014 to June 2018 205 consecutive EBC pts treated at the Medical Oncology Unit of ASST Spedali Civili of Brescia entered the study. A dietary assessment analyzing quantity and frequency of intake of the following foods: fruit, vegetables, pasta, rice, bread, breadsticks, white and meat, fish, fat and lean salami, eggs, fresh and aged cheese, legumes, milk, yogurt, sugar, biscuits, snacks, cakes, ice cream, soft drinks, fruit juices, wine, beer, spirits was done at baseline by a dietitian and repeated every 2-3 months. Information regarding job activites and lifestyle attitudes was also collected.

Results: Median age was 54 years (range 25–80 years). At baseline condition mean body weight was 64.82 kg (95% CI, 63-66,5 Kg) and mean BMI was 24.8 kg/m^2 (95% CI, 24-25,4 kg/m^2). Anthracycline and taxane were the regimens most frequently used. A statistically significant decrease in consumption of pasta, bread, breadsticks, read meat, fat and lean salami, fresh and age cheese, milk, yogurt, sugar, soft drinks, wine, beer, oil and butter was reported whereas the consumption of fruit statistically increased over treatment. During treatment up to 57.6% of women abandoned their job and the physical activity decreased progressively. Mean body weight and BMI did not significant change during chemotherapy (+0.41 kg and +0.14 Kg / m2 respectively). In details: 31% and 26% of pts reported weight gain and loss respectively while the weight did not change in 43%. Patients who gained weight did not reduce sugar, salami and alcohol intake than the other groups.
Conclusions: Contrary to the literature, our data show that mean weight did not change significantly among EBC pts on adjuvant chemotherapy despite reduction of physical activity. The possible reason is that EBC pts are more sensitized to the aspects of nutrition and tend to follow more correct and healthy diets with reduction of foods and beverages with a high calorie content, red meat, snacks, and increase the consumption of fruit.

R16

WHEY PROTEIN ISOLATE SUPPLEMENTATION IMPROVES BODY COMPOSITION, MUSCLE STRENGTH AND TREATMENT TOLERANCE IN MALNOURISHED ADVANCED CANCER PATIENTS UNDERGOING CHEMOTHERAPY

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Background: Malnutrition is a frequent comorbidity in cancer patients, particularly in advanced disease requiring multidisciplinary interventions. We evaluate the benefit of whey protein isolate (WPI) supplementation in addition to nutritional counseling in malnourished advanced cancer patients undergoing chemotherapy (CT).
Patients and Methods: In a single-center, randomized, pragmatic, parallel-group controlled trial (ClinicalTrials.gov: NCT02065726; February 2014 - June 2018), 166 malnourished advanced cancer patients with mixed tumor entities candidate to or undergoing CT, were randomly assigned to receive nutritional counseling with (N=82) or without (N=84) WPI supplementation (20 grams/daily) for 3 months. Primary endpoint was the change in phase angle (PhA). Secondary endpoints included changes in standardized PhA (SPA), fat-free mass index (FFMI), body weight, muscle strength, quality of life and CT toxicity (CTCAE 4.0 events).
Results: In patients with the primary endpoint assessed (modified intention-to-treat population), counseling plus WPI (N=66) resulted in improved PhA compared to nutritional counseling alone (N=69): mean difference, 0.48° [95%CI, 0.05 to 0.90] (P=0.027). Imputation of missing outcomes yielded consistent findings. WPI supplementation resulted also in improved SPA (P=0.021), FFMI (P=0.041), body weight (P=0.023), muscle strength (P<0.001) and in a reduced risk of CT toxicity (risk difference, -9.8% [95%CI, -16.9 to -2.6]; P=0.009), particularly of severe (grade ⩾3) events (risk difference, -30.4% [95%CI, -44.4 to -16.5]; P=0.001).
Conclusions: In malnourished advanced cancer patients undergoing CT and receiving nutritional counseling, a 3-month supplementation with WPI resulted in improved body composition, muscle strength, body weight and reduced CT toxicity. Further trials, aimed at verifying the efficacy of this nutritional intervention on mid and long-term primary clinical endpoints in newly diagnosed specific cancer types, are warranted.

R17

DECISIONS AND OPINIONS ABOUT END-OF-LIFE IN CANCER CARE: SURVEY IN PATIENTS, CAREGIVERS AND PROFESSIONALS

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Background: Biotechnological evolution of the means of life support are leading to a progressive medicalization of the dying process, full of bioethical implications. There are few studies investigating decisions and opinions of the health care providers, respect to patients and caregivers sensitivity about end-of-life issues.
Aims of the study: We investigate: 1) features of Decisions to End Life (DEL) take by the health care providers 2) comparison between professionals' and users' attitudes about the main end-of-life issues and the compilation of Advance Health Directives (AHD) 3) quality of communication among health care providers, patients and caregivers 4) pregress level of education and request for training in bioethics and palliative care.
Materials and Methods: Three questionnaires for professionals (physicians, nurses, and other health providers), patients and caregivers were administered in Istituto Oncologico Veneto in june-september 2018. The questionnaire for professionals questioned the respondent on the end of life decisions and opinions on bioethical issues. The

questionnaires for patients and relatives questioned the respondent on opinions about end-of-life decisions and related to communication with the practitioner.
Results: 488 questionnaires were distributed to professionals, 582 to patients and 546 to caregivers with a response rate of 28,5%, 29,6% and 21,6%. DEL were 19% of all 63 deaths followed in the last year (100% non-treatment decisions). AHD have been stated by 6,5% of patients. Professionals stated that the patients were incompetent or partially competent in AHD (36,4% and 27,3%). Professionals and users agree on the importance of family involvement in end-of-life decisions. There is a consensus that MDs communicate mainly to patients, but only to relatives about DEL. Finally most of the respondents declared that he had not received specific training in bioethics (66.8%) and in palliative care (77.5%).
Conclusions: Comparison with previous Italian and European studies reveals a progression towards a greater diffusion of end-of-life practices in Italy, a greater role recognized to the patient's will and a greater direct health-user/patient communication. About AHD the prevalence remains low and there is important difference declared by caregivers and patients respect to health care providers. Lastly there is still a lack of competence in bioethics and palliative care, but there is a great demand of training.

R18

SIMULTANEOUS CARE CLINIC: DIVERSITY BETWEEN ADULT AND ELDERLY PATIENTS. THE 2014-2018 IOV SERIES

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Background: Early Palliative Care has been shown to improve the quality of life and of life-end care in advanced cancer patients (pts). In accordance with the ESMO and AIOM recommendations, in 2014 a simultaneous care clinic (SCC) was set up in our institute by a multidisciplinary team (medical oncologist, palliative care physician, nutritionist, psychologist and case manager).
Methods: From March 2014 to December 2018, 1008 metastatic cancer pts were evaluated at the SCC. The pts were divided into two groups (adults $\geqslant$ 18 years; elderly $\geqslant$ 70 years) evaluated retrospectively.
The need for access to SCC was defined on the basis of the request form filled out by the medical oncologist; the score obtained fined the priority of taking charge by the SCC team.
Results: 463 (45.9%) adult pts and 545 (54%) elderly pts evaluated, of 1008 total pts were taken in at the SCC. Nutritional, physical (pain) and psychological needs were the main showed at the first visit for both groups.
256 (55.29%) adult pts presented nutritional problems with weight loss in 103 (40.23%) pts and lack of appetite found in 91 (35.55%) pts, while among the 259 (47.7%) elderly pts had nutritional problems with weight loss in 123 (22.5%) pts. Pain was present in 155 (33.48%) adult pts and in 243 (44.59%) elderly pts. Psychological distress was found in 197 (42.55%) adult pts and in 184 (33.8%) elderly pts. In both groups the grade was moderate to severe (respectively 57.36% and 56,52%). After the first access to the SSC, a formal request for the activation of home assistance services was sent to the Health Territorial Unit for 112 (24.19%) adult pts and for 146 (27.8%) elderly pts. After the first visit to SSC, 106 (22.89%) adult pts and 113 (20.7%) elderly pts went to the emergency room (PS). 336 (72.57%) adult pts and 384 (70.5%) elderly pts died: the average time elapsed from the date of the last cancer treatment was 15 weeks and 17.6 weeks respectively.
Conclusions: No differences were observed between the two groups for the needs found. The two groups differ in nutritional problems (higher in the adult pts) and for pain (higher in the elderly pts). SCC's experience over the years seems to have reduced the PS access for both groups. This analysis has shown that an early integrated activation of the SSC can intercept pts' problems in advance, allowing a better taking care.

R19

CAN CANCER SITE HELP TO ATTENTION PARTICULAR TOXICITIES WITH IMMUNOTHERAPY IN DIFFERENT CANCERS?

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Background: The landscape of melanoma (M), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), urothelial cancer (UC) and head and neck cancer (H&N) has changed with the use of immunotherapy (IT). Adverse events, although rare, may occur and should not be underestimated. This study aims to evaluate the incidence of different toxicities (tox) with IT in different tumours.
Patients and Methods: We retrospectively analysed a total of 403 pts who received >=1 dose of IT at our institution from July 2013 to December 2018: 222 NSCLC (151 nivolumab (N), 67 pembrolizumab (P), 4 atezolizumab (A), 116 M (42 N, 40 P, 32 ipilimumab, 2 A), 34 mRCC (33 N, 1 P), 19 UC (6 durvalumab, 13 A) and 12 H&N (all N). 88,8% pts were ECOG PS 0-1, mBMI at baseline was 25,1 (15,7-50,4), male/female 274/129,

median age 68 y(20-88). 118 pts received IT in I line. 34 pts had history of autoimmune disease (AD).
Results: At data cut off, median duration of IT was 84 days. Overall disease control rate was 45,2%. Toxicity rate of Grade (G)3-4 was 10,4% and G1-2 48,9% (9,9% and 47,7% in NSCLC; 11,2% and 47,4% in M; 11,8% and 67,6% in RCC; 10,5% and 42,1% in UC; 8,3% and 41,7% in H&N). No toxic death occurred. Overall, the most frequent tox were skin (17,9%), gastro-intestinal (GI) (16,9%), fatigue (14,1%), endocrine (9,2%), lung (6%), hepatic (5%). Comparing different tox according to different cancers (Fisher's exact test) we found in NSCLC a higher frequency of arthralgia (p=0,004) and a higher trend of lung tox (0,0558), lower endocrine (p=0,005) and skin tox (p=0,006); in M higher endocrine (p=0,0001) and skin tox (p=0,0041), lower fatigue (p=0,0008) and a lower trend of arthralgia (p=0,0770); in RCC a higher frequency of fatigue (p=0,0010); in UC a higher trend of hepatic (p=0,0608) and neurologic (p=0,0622) and lower GI tox (p=0,0539); in H&N no significant different tox comparing with other cancers. 231 pts received steroids, 55 of them for tox (42 at dose > 15 mg/die prednisone or equivalent). Among pts with history of AD 27 had tox (5 G3-G4). Pts in I line had 43,2% G1-2 and 11,9% G3-4 tox; overall, female 53,1% and 11,7%; male 47,4% and 9,6%; BMI >=25 49,1% and 11,3%; BMI <25 48,7% and 8,9%, respectively.
Conclusions: Toxicities with IT may be influenced by patients' characteristics, agents, prior therapies and also by tumours' types. Cancer site may help to attention particular toxicities and their timely identification. Further investigations on this topic might be of interest.

R20

COOPERATIVE GROUPS. WHAT BENEFITS FOR PARTICIPATING CENTERS?

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Background: The increased complexity of clinical trials (CT) is worrying especially for academic research, which has very low funds, often without the possibility of entrusting the study management to specialized organizations. For this reason, centers specialized in a specific pathology decide to join forces, creating dedicated cooperative groups. The MITO cooperativeGroup, specialized in gynecological tumors, decided to investigate on how this collaboration was decisive in the growth of the individual centers involved.
Methods: In April 2019 the MITO working group "Clinical Research Coordinator" (CRC) released an anonymous survey composed by 14 questions, covering the following topics: centers' characteristics, number and types of professional figures dedicated to CT, number and typesof ongoing CT, subjective perception of how participation in the group has influenced the performance of the respondent center. Only 1 response of each center was considered.
Results: The survey was completed by 56 centers, for a total of 14 represented regions; most of them (71.5%) are members of the MITO group for over 5 years. Few Centers (14.3%, n=8) participate to more than 10 MITO studies and 10 (17.9%) play also the role of Coordinating. Moreover, 34 also participate in studies promoted by the European equivalent of MITO, the ENGOT group. Over two-thirds of centers (n=40) have a dedicated research team. There are almost always (97.5%, n=39) clinicians and CRC (95%, n=38) while other figures are much less represented, such as study nurses (42.9%, n=24), administrative staff (41.1%, n=23), contract specialists (48.2%, n=27) and biologists (3.3%, n=22).
30 centers (56.6%) felt the need to change their organization after becoming a MITO member, hiring additional support staff, alone (n=14) or with new clinicians (n=11) and in 6 cases expanding the building. When asked about the possibility that having joined the cooperative group could have improved internal performance, centers replied positively, with a median point equal to 7.1 on a score 1-10.
Conclusions: Joining a cooperative group means putting together one's forces for a common goal. This benefits not only the group itself, but leads to an evolution of the individual centers that compose it. Probably this is due to a sort of chain reaction: the less experienced centers learn from those leading in the field and are led to evolve to reach higher standards, with positive implications for them and for the group.

R21

EXERCISE IN CANCER PATIENTS: A CROSS SECTIONAL STUDY

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Backgroud: Physical exercise (EX) provides benefits for cancer survivors, such as improvement of quality of life,

cancer-related fatigue, health-related skills. Despite the evidences, most cancer survivors are sedentary or insufficiently active. The purpose of this study is to provide an assessment of EX preferences in cancer patients.

Materials and Methods: A questionnaire to assess EX preferences, EX, demographic and health information, was developed for use in cancer patients. A representative sample of patients from the Medical Oncology Unit of the Verona Hospital were asked to anonymously complete the questionnaire in April 2018-March 2019. EX behavior was assessed by leisure score index (LSI) from the validated Godin's Leisure Time Exercise Questionnaire (GLTEQ). (3) EX preferences questions were drawn from previous studies.

Results: With a 57% of response rate, a total of 405 survey were completed and analyzed. Breast (26%) and upper gastrointestinal (42%) were the most frequent diagnosis. Only 10% of patients resulted to be sufficiently active, with LSI>23. A large majority (80%) indicated that they are willing to participate in an EX program designed for cancer patients. Regarding the preferred source of PA information, "the oncologist" was the preferred category (57%) followed by physiotherapist (29%). The preferred way of information delivery was "face-to-face" (71%) followed by no particular preferences (20%). The preferred composition of EX group was with "other cancer patients" (27%). The patients chose outdoors (27%) and a fitness center for adapted physical activity (21%) as favorite places to perform EX. Training in group was preferred (39%), followed by an individual program to perform at home (27%) and an individual program with a personal trainer (25%). The majority preferred a supervised Ex program (57%). The favorite EX frequencies were two times/week (37%) and three times/week (30%), whereas "mild" intensity was chosen by 44% of patients followed by "moderate" (36%).

Conclusions: Despite the demonstrated benefits of EX in oncological patients, we found 90% of them insufficiently active, but 80% willing to start an EX program. This preliminary results encourages intervention studies to improve EX in cancer patients offering multiple options based on patient's EX preferences.According to these data, we designed a prospective clinical trial including dedicated EX programs based on patient's preferences, currently recruiting.

R22

HOW CAN DENOSUMAB SAVE BONE HEALTH FROM ENDOCRINE THERAPIES SIDE EFFECTS IN PROSTATE AND BREAST CANCER? A SYSTEMATIC REVIEW AND A META-ANALYSIS OF RANDOMIZED TRIALS

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Background: Endocrine therapies for hormone receptor positive-breast and prostate cancer patients have shown clinical efficacy but also several side effects including osteoporosis, loss of bone mass and increased fractures risk. Denosumab represents an anti RANKL (receptor activator of nuclear factor-kB ligand) monoclonal anti-body acting as inhibitor of osteoclasts activity, then increasing bone mass. We performed a systematic review and meta-analysis to evaluate the role of Denosumab in saving bone health in prostate and breast cancer patients.

Material and Methods: We used electronic database to select randomized controlled trials (RCTs) including prostate and breast cancer patients receiving respectively androgen deprivation and adjuvant endocrine therapy. Moreover, all the patients have to be treated with Denosumab at the dose of 60 mg every six month versus placebo. Outcomes studied included the bone mass density (BMD) increase at 24 and 36 months, BMD loss, reduction of fractures risk and safety (serious adverse events – SAEs and discontinuation rate). Outcomes were analyzed using risk ratio (RR) and mean difference (MD), with a 95% of confidence interval (CI). For each study we collected the number of patients with an event and the total number of patients to perform meta-analysis. Heterogeneity was explored using I-square and Chi-square tests. As regards the risk of bias, we performed a publication bias analysis using Egger's test and a Funnel Plot. All the p-values were considered as statistically significant if $p<0,05$.

Results: Our results showed a reduction of the BMD loss up to 36 months (RR 0.21, 95% CI 0.19 – 0.23), a BMD increase both at 24 and 36 months at any site (lumbar spine, total hip, femoral neck and distal third radius). Interestingly, it was also found a reduction in the number of new fractures at the above mentioned sites (RR 0.52, 95% CI 0.42 – 0.65). Importantly, it was shown that Denosumab did not affect both the SAEs (RR 1.06, 95% CI 0.98 – 1.15) and therapy discontinuation risk (RR 0.90, 95% CI 0.69 -1.18).

Conclusions: Our meta-analysis prompted us to conclude that Denosumab administration can be considered effective and safe in the prevention and management of the

skeletal issues and side effects related to hormonal therapies designed for early breast and prostate tumors.

R23

REAL-WORLD INSIGHTS ON THE USE AND ADVANTAGES OF CLINICAL NUTRITION IN METASTATIC CANCER PATIENTS IN ITALY

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Background: Reports suggests that approximately 20%-30% of cancer patients (pts) may die as a consequence of malnutrition. Although recommendations on the optimal management of nutritional support for pts with malignancies have been provided, malnutrition often stays undiagnosed and a large proportion of malnourished pts does not receive adequate clinical nutrition (CN) interventions. An European multi-country study has been conducted using administrative databases investigating malnutrition diagnosis, healthcare resource use, and CN utilization in cancer pts. Here we present the results of an in-depth analysis of the Italian data with the aim to provide further real-world insights on the use of CN and outcomes.

Patients and Methods: In this retrospective observational cohort study, data source comes from electronic medical records captured by the administrative databases from 10 Italian Local Health Units, geographically distributed throughout the national territory. All pts with at least one diagnosis of metastasis (ICD-9-CM codes 196-199) from 2010 to December 2015 were included. Metastatic pts were also grouped depending on cancer site: head&neck (HN), gastrointestinal (GI), respiratory tract, genitourinary (GU), hematological. Two different survival analyses were set: the first one included pts receiving CN, the second pts diagnosed with malnutrition in which outcome of CN treated vs no CN administration was evaluated.

Results: A total of 53,042 metastatic pts were included in the study. Our results suggest that assessment of malnutrition and the administration of CN in cancer pts is not a common practice in Italy as the proportions of metastatic pts who received CN were small for all the considered cancer types, ranging from 5% of hematologic to 13% of HN pts. Data on outcome suggest that cancer pts, particularly those with GI tumors, might benefit from the administration of CN. In particular, our findings show that 1) administration of CN is associated with survival benefit in pts with GI, respiratory, and GU cancer, while no benefit was observed for concomitant CT: 2) CN in malnourished pts with GI and GU cancer was associated with significant improvement in survival, and this effect was comparable to that of concomitant CT.

Discussion: Our study, other than highlighting the urgent need for an improvement in the assessment nutritional status in oncologic pts, suggest a potential survival benefit by CN treatment in metastatic disease.

R24

SMOKING PREVALENCE AND PERCEPTIONS AMONG HEALTHCARE PROFESSIONALS: A SURVEY IN AN ITALIAN CLINICAL CANCER CENTRE

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Background: A survey has been conducted on employees of our Clinical Cancer Centre about the smoking prevalence and knowledge of the smoking-related harms. The results have been compared to those emerged from a previous survey when the current smoke-free-hospital policies (national and internal) were not yet active.

Methods: In June 2017, during two weeks, 400 subjects received an anonymous questionnaire (36items) investigating demographics, smoking-habits, second-hand-smoke exposure, knowledge of Italian smoke-free legislation.

Results: 104 subjects (26%) returned the self-completed form (M=45.34 years, SD=10.5; 67.3% women). 17,8% of responders were smokers, 26,2%former smokers, 56% no smokers, while in 23,8% the data were missing. Among the former smokers, the mean age of smoking cessation was 33,3 years (sd=10,2), without drugs in 77,3% of cases, for the following reasons: preventive health purposes (29,6%), a child birth (26%), suggestions from family members (3,%); no one stopped on medical advice. The ex-or never smokers share the working room with one (23,2%) or more (8,5%) smokers, pointing out the smoke exposure in hospital (30%), and feeling intense uneasiness (46,8%). The smoke-free-hospitals policy is not fully accepted, indeed only 40% declared that the smoking ban is observed and 63,2% said to smoke during the working-time.

Regarding the policies that prohibit smoking inside and outside the hospital, the responders perceived it as a good way to protect the health (65,4%), to reduce the prevalence of smokers in hospital (20%), to protect non-smokers (46,1%) and to decrease tobacco-related disorders (37,5%) ($p<0,001$). The implementation of Italian smoke-free policies has favoured the reduction of the number of smoked cigarettes (55%), but did not increase the desire of a complete cessation (63%).

Conclusions: The adopted strategies are partially efficient; among personnel there is a large prevalence of smokers and interventions aimed at the development of a culture of health promotion are strongly warranted.

R25

Comparison of outcomes of central venous catheters in adult patients with solid and hematological malignancies receiving oncological treatments: a real world analysis

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Background: Safe intravascular accesses are essential for oncological patients, allowing prolonged administration of anticancer agents and supportive care. Although many reports analyzed the outcomes of central venous catheters (CVCs) in oncological and hematological patients, current guidelines do not routinely recommend a specific type of CVC over the other.
Material and Methods: We retrospectively evaluated the outcomes of 195 consecutive CVCs referred to the Medical Oncology Department of the National Cancer Institute of Milan between January 2016 and December 2018.The analyzed devices included peripherally inserted central venous catheters (PICCs) and tunneled catheters (tCVCs) with central insertion (Port-à-caths and Groshongs).
Results: A total of 146 PICCs (74.9%) and 49 tCVCs were analyzed. The mean duration in situ was 110 days (range 6-310) for PICCs and 332 (25-1030) days for tCVCs ($p<0.0001$). The overall complication rate was significantly increased in the PICC cohort compared to the tCVCs cohort (43.2% vs 24.5% respectively, $p=0.027$), leading to precocious device removal in 30.1% of PICCs vs 12.2% of tCVCs ($p=0.014$). No significant differences in terms of catheter-related thromboses (4.1% of PICCs and 2% of tCVCs, $p=0.682$) and catheter related infections (6.8% of PICCs vs 14.3% of tCVCs, $p=0.142$) were detected. Non-thrombotic obstructions were significantly higher in the PICC group compared to the tCVC cohort (20.5% vs 4.1%, $p=0.007$). CVC displacements were numerically superior in the PICC cohort (10/146, 6.8%) when compared to tCVCs (1/49, 2%), although the difference did not reach statistical significance ($p=0.297$). Complication-free survival was significantly longer for tCVCs compared to PICCs (log-rank $p=<0.0001$; HR 0.253; 95% CI:0.124-0.514), as well as obstruction-free survival (logrank $p<0.0001$; HR 0.087; 95% CI:0.020-0.389). In multivariable analysis, the type of CVC was the only parameter that independently correlated with the occurrence of any complication (OR tCVCs vs PICCs: 0.415 [95% CI 0.192-0.900], $p=0.026$).
Conclusions: Our real world experience suggests that PICCs are associated with a higher risk of overall complications compared to tCVCs, leading to CVC removal in a relevant percentage of patients. Catheter choice in oncological patients should be guided by treatment type and duration, risk-benefit assessment, patient's preferences and compliance.

R26

THE MANAGEMENT OF CANCER-RELATED MALNUTRITION AND THE ATTITUDE TOWARDS NUTRITIONAL CARE: A NATIONAL SURVEY AMONG ITALIAN ONCOLOGY UNITS AND PATIENTS ASSOCIATIONS

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Background: Recent data showed that the attitude towards cancer-related malnutrition varies considerably among oncologists and that nutritional support is often not handled according to the available guidelines.
Methods: Between September 2017 and December 2018, the joint Working Group between the Italian Society of Medical Oncology (AIOM), the Italian Society of Artificial Nutrition and Metabolism (SINPE) and the Italian Federation of Volunteer-based Cancer Organizations (FAVO) conducted a national web-based survey addressed to all the Italian Oncology Units referees and to Cancer Patients Associations. The aim was to investigate the management of malnutrition and the perception of nutritional care among oncologists and patients.
Results: One hundred seventy-one (51.6%) of the 331 registered Italian Oncology Units and 75 (38,5%) of the FAVO Associations participated in the survey. Nutritional assessment is routinely integrated into patient care since diagnosis for 27% of Oncology Units referees and 14% of FAVO associates. According to 42% of Oncologists, nutritional assessment is carried out merely upon patients' request, while it is not performed at all for 45% of FAVO associates. Nutritional assesment, performed using validated multi-dimensional tools (MUST, NRS2002, MNA, NRI, SGA), is carried out by 16% and 8% of cases according to oncologsts and patients, respectively. While almost 60% of oncologists declare that home artificial nutrition (HAN) is prescibed and monitored by clinical nutrition specialists, more than 60% of patients report that they do not know who is in charge of HAN management For 98% of Oncologists and 100% of FAVO associates, nutritional status is decisive or often crucial in predicting whether anti-cancer treatment is practicable or would be tolerated.

Conclusions: Although malnutrition was confirmed to be perceived as a relevant factor for the efficacy of oncologic treatments by both oncologists and patients, nutritional care practices appear still largely inappropriate, and its perception differs between oncologists and patients, the latter reporting a more inadequate situation. Improving nutritional care in Italy is still a challenging task.

R27

INVESTIGATING THE ROLE OF MALNUTRITION UNIVERSAL SCREENING TOOL (MUST) IN ONCOLOGY ROUTINE CLINICAL PRACTICE: THE EXPERIENCE OF NATIONAL CANCER INSTITUTE OF MILAN

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Background: Malnutrition is a major complication in advanced cancer patients with well known impact on outcome in terms of survival and quality of life. An accurate nutritional screening at the time of diagnosis and throughout the patients treatment is a clinical need. This must be efficient, brief, inexpensive, with high sensitivity and good specificity. In our Institute we use MUST (Malnutrition Universal Screening Tool), a validated nutritional screening tool. It evaluates weight loss, BMI and/or fasting risk for over 5 days. Our aim was to investigate the performance of this tool in a routine oncological clinical setting with patients admitted to the Medical Oncology Department of National Cancer Institute of Milan.
Matherial and Methods: Between January and December 2018, the medical chart relative to MUST of all admitted pts was analyzed focusing on the high risk of malnutrition (MUST⩾2). Then we evaluated the reason behind this score, the clinical features linked with a high risk of malnutrition and the following nutritional intervention.
Results: Out of 924 consecutive pts screened, for 147 (16%) a MUST⩾2 was recorded. The pts characteristics were as follow. M/F: 1,01. Median age 62 yrs (range 26-88 yrs). Primitive origins were gastric (n=29, 20%), lung (n=27, 18%), colon-rectal (n=20, 14%), pancreatic (n=16, 11%), breast (n=10, 7%), esophageal (n=10, 7%) and others (n=35, 23%). At admission Stage was metastatic in 85% of cases and locally advanced in 15% of cases. In terms of frequency PS 0-1 was observed in more than half of cases (64%). The reason behind the high risk was weight loss/low BMI (median BMI 21) in 71% of pts, whereas for 29% it was fasting over 5 days. A nutritional intervention was planned in 63% of cases (N=93); of whom, 50 (54%) received a nutritional counseling. Artificial nutrition was started in 43 pts (46%): parenteral nutrition in 34 pts; enteral nutrition in 9 pts. Home artificial nutrition was activated for 26 pts. Reasons for not receiving nutritional intervention were terminal pts, not compliant ones or the beginning of a therapy that is able to reduce the risk of malnutrition.
Conclusions: In our experience MUST has been introduced routinely to identify patients at risk for malnutrition and approximately two-third of pts benefit of a nutritional intervention during oncological treatement. Then, interestingly, we noticed a high correlation with good performance status and MUST⩾2 empathizing the preventive role of the tool.

R28

BURNOUT RISK IN CANCER CARE STAFF: IS LAUGHTER YOGA A POSSIBLE TOOL FOR PREVENTION?

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Background: Burnout syndrome is present among cancer care providers, with severe involvement ranging from 8% to 51% in a systematic review (Trufelli, EJCC 2008). "Laughter Yoga" (Yoga della Risata) was codified on 1995 by an Indian doctor, Madan Kataria. It is based on psychological and physiological positive effects of voluntary laughter. Routine group exercises include clapping, eye contact, body movement, breathing exercises, acting and visualization techniques, characterized by children-like playfulness. The final aim is to share consecutive minutes of laughing without any humorous reason. Laughter Yoga showed to be very useful for body and mind health, and it might be a candidate for burnout syndrome prevention.
Materials and Methods: Two different experiences were organized. a) Cancer care professionals and other healthcare staff of Alessandria Hospital were invited to bimonthly meetings, of one hour at least, to have well-being time and to learn Laughter Yoga exercises. Furthermore, aid organization volunteers, cancer patients (on active treatment or survivors) and caregivers were invited to join, after the first year experience. b) One-day educational meetings with Italian Healthsystem Education Accreditation (ECM) were organized for cancer care staff of a regional Cancer Network (Rete Oncologica del Piemonte e della Valle d'Aosta), for wellbeing of professionals.
Results: a) 72 meetings were organized in 4 years, with increasing number of attendees (range between 8 and 70; median increasing between 8 in 2015 and 30 in 2019, including patients and caregivers). A satisfaction questionnaire among 40 care professionals revealed high positive

evaluation in 90% and positive evaluation in 7.5%. b) 11 one-day meetings were organized for cancer network professionals, with a median of 23 attendees. A burnout screening brief test (Potter test) was administered to more than 250 professionals and is under evaluation.
Conclusions: Preliminary data show high level of satisfaction among cancer care professionals, as well as among cancer patients and survivors, and their caregivers. Strongest points of the experience are: well-being time sets for professionals (and potentially shared by patients, caregivers and cancer care staff); easy process of acquiring knowledge of the techniques; emotional bonding.

R29

TREATMENT-FREE SURVIVAL (TFS) AFTER IMMUNOTHERAPY DISCONTINUATION: A MULTICENTER REAL-LIFE EXPERIENCE

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Background: Unlike chemotherapy, the optimum treatment duration with Immune checkpoint inhibitors (ICIs) is not clearly established. The aim of this study was to assess the outcome of patients (pts) who discontinued immune-based therapies for any reason except progressive disease.
Material and Method: We conducted an observational, retrospective analysis of 46 consecutive pts with advanced cancer who received ICIs as clinically indicated, at eight Italian institutions. Tumor response to treatment was defined according to RECIST criteria. TFS was defined as the time from discontinuation of immunotherapy for any reason except progressive disease to start of subsequent anticancer therapy or best supportive care or death. Median overall survival (OS) and the 95% confidence interval (CI) were estimated with the Kaplan -Meier method.
Results: 46 pts (median age 68 years [range 41-86]; male: 65.2%) with advanced cancer (n.39 non-small-cell lung cancer, n.15 renal cell carcinoma and n.2 melanoma) were treated with ICIs: 44 pts received programmed death 1 (PD-1) inhibitors (n.31 nivolumab, n.13 pembrolizumab) and 2 pts programmed death ligand 1 (PD-L1) (n.1 durvalumab, n.1 atezolizumab). A median of 8 cycles were administered [range 1 to 52]. 36 pts discontinued ICIs due to toxicities (diarrhoea, pneumonitis, hepatotoxicity)and 10 pts for reasons non immune-related. The median progression free survival (PFS) from the beginning of ICIs was 12.4 months (mo) [95% CI: 8.2-16.6] and the median OS was 20.0 mo (95% CI: 11.8-28.2). Median PFS from discontinuation of therapy was 5.0 mo [95% CI: 2.7-7.3] and median OS was 16.1 mo (95% CI: 5.4-26.8). Median TFS was 7.4 mo (95% CI: 5.8-8.9). Best response achieved according RECIST criteria were: 1 complete response, 18 partial response, 21 stable disease, 2 progressive disease and 3 non evaluable. During interruption of ICIs 1 pts achieved a PR.
Conclusions: This study shows the antitumour activity of ICIs, in terms of outcome and durable immune-response, in pts with advanced cancer even after treatment discontinuation.

R30

RAPID DRUG DESENSITIZATION (RDD) APPLIED TO PATIENTS WITH MODERATE TO SEVERE HYPERSENSITIVITY REACTION (HR) TO ANTICANCER DRUGS

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Background: Anticancer drugs administered intravenously expose patients to HR. Once a HR has occurred, in the majority of the cases a rechallenge induce a similar or more severe reaction. Thus HR restricts the availability of potentially useful drugs. RDD is a novel approach to the management of HR aiming at inducing a temporary tolerance and at giving the full dose of the medications that have induced the HR. We prospectively applied a protocol of RDD in any case of moderate to severe HR to anticancer drug. We hereby describe the results of the protocol in the population included.
Methods: Any occurrence of grade 2-4 HR was described and referred to the allergologist. After thorough evaluation and skin prick/intradermal testing a protocol of premedication and of RDD was prescribed. A 12-step RDD protocol was used, consisting in dilution of the drug and administration in repeated steps with increasing flow.
Results: From January 2017 to December 2018, 47 consecutive patients were treated according to the RDD protocol and are evaluable for the analysis. Males 9 (19%); females 38 (81%); median age 61 (range 25-77). Patients had ovarian (13/27.7%), breast (8/17%), colorectal (11/23.4%), head&neck (3/6.4%) and other cancers (12/25.5%). Patients experienced HRs to the following drugs: Paclitaxel (19/40,0%), Oxaliplatin (12/25,5%), carboplatin (6/12,7%), Docetaxel (5/10,6%), other drugs (Cetuximab, lyposomal doxorubicin, Nivolumab 5/10,6%). A total of 257 RDDs were performed. In 240 cases (93,4%) no reactions occurred during RDD. Breakthrough reactions developed in 17 cases (6,6%) although in one case treatment was carried on with a further dilution.

Conclusions: RDD makes feasible the large majority of drug administrations. In our experience the procedure is safe and should be attempted in any case of moderate to severe HR.

R31

AN OBSERVATIONAL MONO-CENTRIC STUDY INVESTIGATING THE EFFICACY OF CANCER PREHABILITATION ON REDUCING COMPLICATIONS OF CHEMOTHERAPY IN METASTATIC CANCER PATIENTS

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Background: Cancer prehabilitation is a multimodal process that occurs between the time of cancer diagnosis and the beginning of acute treatment. It includes physical and psychological assessments that establish a baseline functional level, identify impairments and provide interventions that promote physical and psychological health to reduce the incidence or severity of future complications. The aim of this study was to evaluate the efficacy of prehabilitation to prevent the severity of anticipated chemotherapy-related physical impairments and psychological distress in metastatic cancer patients.
Materials and Methods: This observational study was conducted on 40 metastatic cancer patients, admitted to the Oncology Department of INI Grottaferrata. Patients received exercise programs, nutritional interventions, and psychological coping for 60 days, before the start of chemotherapy. Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales were utilized to evaluate the Health-related Quality of Life and functional ability, before prehabilitation and after one months of chemotherapy. Percentage of completely independent, partially independent and dependent patients was measured pre- and post-treatment. Wilcoxon rank-signed test was used to statistically compare the percentage of positive replies of cancer patients pre- and post-treatment.
Results: The study showed that the percentage of completely independent cancer patients in washing, feeding and moving themselves from the bed, increased from the start of prehabilitation to the end of the first month of chemotherapy (respectively, 80% vs 90%; 60% vs 75%; 70% vs 82.5%). In addition, 62.5%, 63% and 70% of patients were respectively independent in doing housework, cooking and assuming drugs after treatment, compared with 45%, 50% and 60% before prehabiltation, The overall results of ADL scale showed an increased number of patients obtaining 100% of positive replies from the start of prehabilitation to the end of treatment (18/40 vs 26/40). Interestingly, the overall results of IADL scale demonstrated a nearly statistically significant increase of the number of independent patients after chemotherapy (32/40 vs 20/40) ($p=0.05155$).
Conclusions: We demonstrated a nearly statistically significant improvement in quality of life of metastatic cancer patients after the program. *Further prospective and larger studies* will be *needed to clarify* these very important observations.

R32

ADVANCE TREATMENT DIRECTIVES/ LIVING WILL: WHAT IS THE COMMON FEELING AFTER 219/2017 ITALIAN LAW?

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Background: On December 2017 Italian Parliament has enacted the 219 law about anticipate disposals and in January 2018 the law has been published in Italian Gazzetta Ufficiale and has become operational. This study aimed to verify the level of information about the rights established by law among people attending Hospital for any reason, not only oncological disease. The study was preliminary to a large informative campaign planned in the month of April in our department.
Methods: In March 2019, 159 persons (18-89 years, median age 60 years, 64% women, 36% men) accepted to fill a questionnaire consisting of 7 general items. The questionnaire was administered by our young voluntaries of the National Civil Service. 49% of the persons of the sample had a secondary school degree, 24% middle school degree, 20% University degree, 7% primary school degree.
Results: 41 out of 159 din't ever heard news about the 219 law and they didn't know what the law establishes but 92% of the people of the sample said that it was very important to decide for him/herself in adavance about end of life, expecially in case of unconsciousness. 84% said he/she would like to leave written disposals but only 10 (6 for religious reasons) out of 159 had already done it. 77% knew in some way that it possible to identify a trustee and 32 had already decided who he could be. The trustee according to the sample coudl be a relative (46%) but also a phisician (9%) or any person >18 years. Notwithstanding a large and sometimes conflicting debate in medical community according to 57% of our sample the anticipate disposals can be disregarded.
Conclusions: Our study demonstrates that people do not have enough information about 219/2017 law but most of them could be interested in expressing their living will.

The role of the trustee is considered important but it is not said that he has to be a family member. An interesting observation is that most of our interviewed don't think that anticipate disposals should be binding for doctors. Only people who have religious reasons have laid down their anticipate disposals. We need to give more information about 219/2017 law and even about 38/2010 law: people don't know many important aspects about their rights. Voluntary Associations could help Health services to provide more public information to help persons to decide about crucial aspects as their end of life.

R33

THE ROLE OF CLINICAL RESEARCH COORDINATOR IN CLINICAL TRIALS: BETWEEN REQUIREMENTS AND UNMET NEEDS

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Background: Clinical trials have become increasingly complex due to change in study procedures, work intensity, and design complexity. Moreover, the regulatory requirement about quality assurance and risk management have increased the work burden for experimental sites. The presence of dedicated supportive figure, as the Clinical Research Coordinator (CRC), has become essential to manage clinical trials in compliance with standard requested by Sponsors and Regulatory Agencies. At the same time this figure was not yet recognized by Healthcare Authorities and there is not a well defined job description.

Methods: The Italian Group of Data Manager (GIDMcrc) spread an online anonymous survey open to all figures involved in clinical research to investigate the Italian CRC's situation and underline the unmet needs about this professional profile.

Results: The survey was completed by 80 subjects (66.3% CRC, 18.8% MD, 14.9% other). Oncology was the more represented area (53.5%) followed by haematology (22.6%). All the experimental sites surveyed have CRC in their staff, but 35% of these declare that are insufficient to cope the workload. CRC were $<=2$ in 54.6% of clinical units, in 37.7% were between 3 and 5, and only in 7.8% of cases were >5. The major quote of CRC (86.5%) has short-term and precarious contracts while only few (9.0%) have an undetermined one. Trainings on GCP and clinical research for new staff are self-made by each clinical unit in 81,3% of cases, while the 13.5% are not able to train new CRC. The choice of outsourced CRC could be a theoretical option in 78.8% of interviewed, but 76.2% consider this solution only as a future hypothesis, not yet applicable.

Conclusions: CRC is confirmed as an essential figure to manage and conduct clinical trials with high quality standard. However, the number of CRC is often not sufficient for the current workload. A high staff turnover in experimental site, especially due to precarious contracts, leads to an increase of workload and to difficulties to find the resources to train the new CRC. This data suggests that contract stabilization and adoption of an official job description for this figure is now an increasing necessity, although bureaucratic barriers still represent a major obstacle. Outsourced CRC could be an option to keep in consideration for the future.

R34

EFFICACY AND SAFETY OF CONTROLLED OVARIAN STIMULATION WITH OR WITHOUT LETROZOLE CO- ADMINISTRATION FOR FERTILITY PRESERVATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Mature oocyte vitrification and storage is currently used to help patients preserving their ability to have offspring either for fertility preservation (FP) before gonadotoxic treatment such as chemotherapy or for elective purposes. Our meta-analysis investigated whether letrozole co-administration during controlled ovarian stimulation (COS) for FP is effective and safe.

Materials and Methods: A literature search using PubMed was conducted up to March 8th, 2019 to retrieve information from studies that compared the performance of COS with or without letrozole co-administration for FP. Mean or median values and 95% confidence intervals (CIs) or standard deviations (SDs) were collected for efficacy (number of collected oocytes, number of mature oocytes, maturation rate) and safety (peak estradiol levels [E2], total gonadotropin dose, number of stimulation days) endpoints. Statistical analysis was conducted with random-effects model.

Results: A total of 10 articles were eligible including 1930 patients undergoing COS with or without letrozole. Studies compared COS with and without letrozole in cancer or

	MR (letrozole vs no letrozole)	95% CI	P-value
Collected oocytes	1.02	0.90-1.16	0.748
Mature oocytes	0.98	0.83-1.16	0.830
Maturation rate	0.94	0.86-1.03	0.181
Peak E2	0.27	0.22-0.32	<0.001
Total gonadotropin	0.97	0.86-1.10	0.676
Length of stimulation	1.00	0.95-1.04	0.849

infertile cohorts (N=9) and infertile cohort only (N=1). The total number of oocytes and mature oocytes collected were similar between letrozole and no letrozole groups while the peak estradiol was significantly higher in the standard COS without letrozole (Table).

Conclusions: Letrozole co-administration during COS resulted to be as effective as standard COS but with significantly decreased peak estradiol levels, suggesting its increased safety especially for hormone-sensitive cancer patients.

R35

CLINICAL RESEARCH AND INSPECTIONS – WHAT HAVE WE LEARNED?

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Background: Clinical trials' recent legislation demands for extremely high-quality requirements, to the point that the competent Authority has decided to publish for the first time outcomes from inspections conducted so far.

We have analyzed the published document in order to single out the points of greater concern where action needs to be taken by clinical trial centers.

Materials and Methods: The Report from Good Clinical Trail (GCP) Inspections between 2015 and 2017, published in March, was examined, with a focus on those deviations directly affecting the trial centers.

Results: During the analyzed period 231 inspections were performed, 197 to verify compliance with GCP and current legislation and 34 focused on the mandatory requirements to conduct phase 1 studies. Most were conducted in Northern Italy (57%), followed by Center (30.3%) and South (12.7%), and on phase III (86.6%) and profit (53.7%) studies. Clinical Trial Centers were especially targeted by inspections (33%), followed by Ethics Committees (27,4%) and Pharmacies (25,4%). Deviations concerning the centers, in the two-year period considered, amount to 592 (66.9%/total), mostly minor (53.9%), but with a significant number of critical (45, 7.6%). Deviations relating to Informed Consent add up to 40, most of which minor (n=23, 57.5%), although 4 were critical (10%). 13 anomalies regarding subject safety were also reported, for a total of 7 minor deviations (53.9%), 5 major (34.5%) and 1 critical (11.6%). Many findings related to regulatory deficiencies (16), 37.5% of which were critical, with 4 cases of study initiation without prior authorizations.

Focusing on the phase 1 studies certified structures, 103 deviations were found (16 critical, 39 major and 48 minor). Most (89.3%) were found at the experimental centers, which represent the 47% of the performed inspections.

The critical deviations represent the 15.5% of the total found deviations and the main categories concern the lack of the quality system, compliance with self-certification and emergency training.

Conclusions: The wide number of deviations recorded calls for serious pondering, especially considering the majority apply to subject safeguard. Unfortunately, this Report doesn't allow for specific investigations based on the therapeutic areas of interest and the populations involved in order to carry out an even more targeted action on the most critical areas.

R36

PATIENT ASSOCIATIONS INVOLVEMENT IN CLINICAL ONCOLOGY RESEARCH: AN ITALIAN SURVEY

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Introduction: Despite the significant improvement in clinical oncology research, worldwide less than 5% of cancer patients benefit of this exciting approach. Recently the new legislation, as the Regulation (EU) No. 536/2014 and the Italian la n.3/2018, have proposed an expanding role of patient associations in clinical research, promoting their relevant contribution in this setting and defining new approaches to evaluate and authorize clinical trials.

Materials and Methods: A dedicated survey, made by 16 open-ended and multiple-choice questions about the active involvement of patient associations in clinical research was created by AIOM Working Group Clinical Research Coordinators (CRC) in collaboration with AIOM Foundation. The survey was submitted to Italian oncological associations from January to March 2019. Questions regarded characteristics and aims of associations, their current normative Knowledge and expectations. The aim of the survey was to evaluate the current approach of

oncological associations for clinical research and the impact of new legislations in this setting.
Results: A total of 46 associations participated in survey providing complete data. Most of them (67.4%) offer support and services for people with specific types of cancer and all were not predominantly involved in any specific clinical research (71.7%) and participated in clinical research working group (78.3%). Moreover, a large share did not carry out training and education activities for trials (78.3%), not play an active role in definition and conduction of clinical studies (95.7%) and never cooperated with other associations to better define patient's role in this setting (84.8%).
The 71.7% of surveyed associations were aware of the new legislation and the 82.6% consider their application as a turning point, mainly to centralize patients' needs (78.3%) and to improve their support during trial participation (52.2%).
Conclusions: Survey results highlight the current limited involvement of Italian patient associations in clinical oncology research activities and the need to improve information, training and communication activities in this setting.

R37

DETECTION OF RAS MUTATIONS IN CIRCULATING TUMOR DNA: A NEW WEAPON IN AN OLD WAR AGAINST COLORECTAL CANCER. A SYSTEMATIC REVIEW OF LITERATURE AND META-ANALYSIS

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Background: Colorectal cancer (CRC) represents the third neoplasm worldwide by incidence. Although many screening efforts are being made to diagnose CRC at early stage, at least 50% of patients will have local or distant disease recurrence or present with advanced disease. Tissue evaluation for RAS (KRAS or NRAS) gene status in metastatic colorectal cancer (mCRC) patients represents the standard of care to establish the optimal therapeutic strategy. Unfortunately, tissue biopsy is burdened by several critical limitations due to its invasiveness, difficulty to access to disease site, patient's compliance and, more recently, neoplastic tissue spatial and temporal heterogeneity.
Material and Methods: We performed a systematic literature review to identify available trials with paired matched tissue and ctDNA RAS gene status evaluation. We searched Embase, MEDLINE, Cochrane, online site www.ClinicalTrials.gov and relevant abstracts from international meetings. In total, 19 trials comparing standard tissue RAS mutational status evaluation matched with paired ctDNA were included in outr analysis. A subgroup analysis according to different techniques (polymerase-chain reaction - PCR, next-generation-sequencing - NGS or beads, emulsions, amplification and magnetics - BEAMing) was performed.
Results: The pooled sensitivity and specificity of ctDNA were 0,83 (95% CI: 0,80 to 0,85) and 0,91 (95% CI: 0,89 to 0,93) respectively. The pooled PPV and NPV of the ctDNA were 0,87 (95% CI: 0,81 to 0,92) and 0,87 (95% CI: 0,82 to 0,92), respectively. PLR was 8,20 (95% CI: 5,16 to 13,02) and NLR was 0,22 (95% CI: 0,16 to 0,30). The pooled DOR was 50,86 (95% CI: 26,15 to 98,76) and the AUC of the sROC curve was 0,94. These results showed a good performance of ctDNA in detecting RAS mutational status.
Conclusions: Our meta-analysis produces a complete and updated overview on ctDNA diagnostic accuracy to test RAS mutation in mCRC. Results provides a strong rationale to include RAS ctDNA test into randomised clinical trials to validate it prospectively.

R38

A NARRATIVE DIGITAL DIARY APPLIED TO CHEMO/RADIOTHERAPY TREATMENT TO PERSONALIZE PATIENT CARE (PILOT STUDY)

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Background: Patients (P) narration applied to the path of cure embodies the P-centered care model. Objective: Evaluating feasibility (F) and utility (U) of a model integrating P theme-oriented narratives with clinical data during chemo (CT)/radiotherapy (RT) treatment.
Patients and Methods: From May 2017, 46 breast or colorectal cancer P, undergoing CT or RT at "Regina Elena" National Cancer Institute, Rome, were asked to participate. Eligible criteria were: age >18 years, availability of an

electronical device and an e-mail address. P told about him/herself in a digital diary (DNM), a platform for the application of narration in clinical practice, using a guided narrative path. Eight health care providers (HCP), 2 physicians (Ph) and 6 nurses (N), read the stories, shared and used them to personalize the cure. P access was gained by invitation from HCP in accordance with health data confidentiality criteria. Ethics Committee approved the study. A written informed consent was required. A semi-structured questionnaire investigating F and U items was administered at the end of the study period (12 months) to P and HCP. PF items were: friendliness and easiness to diary (to be handle), its adequacy in reflexive writing, compliance with diary; HCPF items were: diary friendliness and easiness, time saving, length of visit. PU items concerned: communication, cure relationship, awareness, self-confidence, empowerment; HCPU concerned: P communication and relationship, therapeutic alliance, illness/disease knowledge. A mixed qualitative and quantitative analysis methodology was used: basic content methods (i.e. theme category, word cloud) and Likert scale (level of agreement/disagreement ranging from 1to 5).

Results: 31(67%) P used DNM; they were mostly female (83%.) and aged 53 yrs (range 31-79) on average. F medium scores were high (4,5). PU score was related to Ph feed-back to narration: from 3,6 (scarce) to 4.7 (regular). N are considered the guarantors of the continuity of care. HCP strongest reported advantage were: the opportunity to disclose relevant data otherwise not detectable (Ph) and to strengthen communication and care relationship (N). Both P and HCP strongly suggested the introduction of DNM in clinical practice.

Conclusions: The study confirms the advantage of integrating P narratives with clinical data, in medical and nursing practice. HCP narrative competence, the involvement of the whole care team and an appropriate health organization are required.

R39

ASSESSING AWARENESS AND KNOWLEDGE OF HUMAN PAPILLOMA VIRUS INFECTION IN HIGH SCHOOL STUDENTS

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Background: Among the cancers that affect women, cervical cancer is the most common worldwide after breast cancer. According to data reported in the volume "The numbers of cancer - 2018" (AIRTUM - AIOM) in 2018 about 2,400 new cases are estimated in Italy. This cancer is more frequent in young subjects (4% of the cases, fifth most common cancer). The most important risk factor related to the disease is the Human Papilloma Virus (HPV) infection, that is sexually transmitted (STI). Moreover, HPV infection transmitted by oral sex may be a risk factor for oropharyngeal tumors and may also affect men. Other HPV-related cancers are: anus, penis, vagina and vulva.

Aim: To investigate the levels of knowledge on HPV, its prevention and the risks related to STI.

Material and Methods: April 2019- A sample of students (S) from a secondary school in Catania, completed an anonymous survey during a meeting on cancer prevention. Participants self-reported demographics, sexual behaviors, vaccination and behaviors related to the use of substances (alcohol, drugs, etc.)

Results: 109 S aged between 18 and 21 years (males/females:26/83) were enrolled on April 2019.The analysis of the study showed that 77 S (70.6%) do not know that HPV is a STI; 25 (23%) incorrectly believe that HPV infection increases the risk of developing HIV. Only 11 S (10%) know that HPV can cause penile, anus and oropharyngeal cancers in humans, while the majority (66 cases, 60,5%)considerit associated to increased risk of developing cervical cancer. As for the sexual behaviors 72 S (66%) have had complete sexual intercourses and less than half of them (30 - 27.5%) always uses precautions. Majority of sexually active high school students reported having had more than one sexual partner. 72 S (66%) have oral sex and only 9 of 109 (8%) know that HPV can be transmitted through oral sex. 68 S (62.3%)assert to have received the HPV vaccine. From the analysis of other risk behaviors, alcoholis the most consumed substance in 66 cases (60.5%) while 32 (29%) are smokers. Finally, most of the S (47) request more information about HPV.

Conclusions: This study has the limitation of including a sample unbalanced by gender (with more females than males) and does not allow comparison between males and females. Even among the S who know how HPV is transmitted, a relevant number of incorrect sexual behaviors has come out. Further works are needed about prevention programs for HPV risk factors related to young people.

R40

BRCA1/2 TESTING: FOUR YEARS EXPERIENCE IN MULTIDISCIPLINARY TEAM AT NON ACADEMIC CANCER CENTER

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Background: The evaluation of germline mutations in BRCA1/2 genes for individuals at high risk for breast/ovarian hereditary cancer has become a standard in medical care as an important tool for the risk assessment, prevention, early diagnosis and, more recently, for determining patient susceptibility to targeted therapy. Here we report and discuss our clinical experience regarding germline BRCA1/2 testing from 2015 to 2019 in our institution
Methods: Genetic testing, according to AIOM-SIGU, ESMO and NCCN guidelines, was performed after genetic counseling on subjects referred to our institution by breast surgeons and radiologist, oncologist and/or for familiar risk. DNAs, extracted from peripheral blood, were amplified by Ion AmpliSeq BRCA1/2 Panel and sequenced on an Ion Torrent PGM sequencer. Every pathogenic mutation detected was confirmed by Sanger sequencing. Testing results and clinical implications were discussed at genetic-oncology multidisciplinary groups (GOM), including oncologist, genetist and psychologist. BRCA mutated patients were managed by multidisciplinary team within their specific treatment or follow up program. High-risk subjects were referred to surveillance or risk- reduction program for breast and ovarian cancer, at our institution.
Results: Since January 2015 577 subjects were tested at our center: 444 patients affected by a cancer and 133 healthy subjects. 37 of healthy subject were referred for suspected familiarity and 96 were relatives of patients bearing BRCA1/2 mutation. 358 (62%) were breast cancer patients, 75 (13%) ovarian cancer, 8 prostate cancer and 3 pancreatic cancer. 31 (8.7%) breast cancer and 14 (18,7%) ovarian cancer patients carried BRCA1/2 mutation. BRCA1 and BRCA2 mutation was detected in 17 and 14 patients with breast cancer and 8 and 6 patients with ovarian cancer respectively. 23 (17.3%) of the healthy subjects resulted BRCA mutation carrier: 17 BRCA1 and 6 BRCA2. A VUS was detected in 38 patients (8.6%). All 45 patients mutated as well as the 23 healthy subjects were followed within the surveillance/risk-reduction program
Conclusions: Our data show a percentage of breast cancer and ovarian cancer bearing BRCA1/2 mutations according to the literature. Moreover, a genetic oncology multidisciplinary team can allow the more appropriate management of high-risk subjects with BRCA1/2 mutation in line with the most important national and international recommendations

R41

TOXICITY FROM COMBINED RADIATION AND NIVOLUMAB

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Background: In the last few years, indications for Nivolumab, in treating a variety of metastatic cancers has markedly increased, while Radiation therapy (RT), is also commonly used in this patient population, at the same time we have little data on the toxicity profile of the combination of nivolumab and radiotherapy.
Material and Methods: In this study, we retrospectively evaluated 27 patients treated, with radiotherapy (sequential or concomitant) and nivolumab, in metastatic cancers, from January 2016 to December 2018 in order to evaluate the toxicity profile of the association.
Results: The median foll ow-up was 5.3 (3-12) months and 7 (26%) were still alive at last analysis. Among 27 patients who received nivolumab, 12 (44%) received concurrent RT to different sites and 15 (56%) sequential RT. In 3 patients were experienced grade 4 toxicities, but all grade 4 toxicities were outside of the irradiated area and nivolumab related, while we found in 10 (37%) patients grade 3 toxicities related to the combined treatment of RT and nivolumab.
Conclusions: In conclusion, concurrent and sequential combination of RT and nivolumab is generally well tolerated, although we recommend close monitoring when radiating lung, abdomen and brain.

R42

PROFESSIONAL BURN OUT IN HEALTHCARE. DOES IT AFFECT PHYSICIAN AND NURSES ONLY?

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Background: The Maslach Burnout Inventory (MBI) is a psychological test widely used to calculate the occupational stress levels typical of health professionals in close contact with patients, as physician and study nurses. However, previous research has shown that other health professionals involved in clinical trials management, may suffer from burnout. Previous research about was conducted using a not

validated test, so we to investigate how the BMI test could be applicable in this professional category.

Methods: The Italian Group of Clinical Research Coordinator (GIDMcrc) spread an online anonymous survey among its members. The survey consisted of the MBI test, together with 11 additional items on workload and perceived stress levels. Kolmogorov-Smirnov test was employed as normality test; Student's t test was used to assess the statistical significance of observed differences.

Results: The survey was completed by 113 subjects. The majority of respondents (85.8%) feel stressed; 68% of them is convinced that such stress adversely affects work performance and 74.2% is thinking of changing jobs. The main cause of perceived stress is contract type (31%), followed by workload (20.4%) and lack of skillsrecognition (17.7%). Results from MBI confirmed the interviewees' subjective perception. If the risk of depersonalization was low (average: 4.3), an intermediate level of emotional exhaustion (19.1) and a very high sense of reduced professional achievement (26.8) were observed. Emotional exhaustion numerically correlated with job duration (mean value 19.5 $<$5 years worked, 21.5 5-10 years, 26.1 $>$10 years), with a statistically significant difference between $<$5 years and $>$10 years ($p=0.013$). Depersonalization and sense of reduced professional achievement did not differ according to job duration. 16 professionals (14.2%) reported that at least one MBI test question was not applicable; all the answers considered not applicable concerned the relationship between the subject and the patient.

Conclusions: Although some test questions are not fully applicable to research support professionals, the BMI test represents a promising indicator of the levels of professional burnout. An adapted version could improve its performance in this category. A moderate degree of professional stress affects the interviewed professionals, mainly related to contractual instability and lack of a well define professional profile and job description.

R43

THE HOSPITALIZED CANCER PATIENT: A SINGLE-INSTITUTION PROSPECTIVE PICTURE

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Background: About 3% of all the subjects referring to hospital-based Emergency Departments (ED) are cancer patients. These patients have a higher hospitalization rate compared to the non-cancer population.

Material and Methods: Along 6 months, we collected data from consecutive patients admitted to the Oncology Department of San Luigi Hospital, following an access to the ED. At the admission, the nurses filled in the Blaylock Risk Assessment Screening (BRASS) in order to identify the risk of a difficult discharge and the Edmonton Symptom Assessment System (ESAS) was administered to each patient to pinpoint the most disabling symptoms. The objective of the study was to obtain a picture of the hospitalized cancer patients' characteristics.

Results: From September 2018 to March 2019, 94 patients were admitted to our ward from the ED. Fifty-seven (60%) were males and the median age was 66 (range: 31-83). The most frequent cancer was lung cancer (55%). Eighty patients (88%) had a metastatic tumor, with over 3 organs involved in 34% of the cases. The Eastern Cooperative Oncology Group performance status was 1-2 in 54% of patients and 3-4 in 24%. The most frequent causes of hospitalization were: worsening of performance status with fatigue and organic deterioration (24%), dyspnea (17%), infection-related fever (17%) and uncontrolled pain (12%). At admission, 31 patients (33%) reported an ESAS score $\geqslant$8 in at least 2 items; the most disabling symptoms were: fatigue (19%), pain (16%), hyporessia (13%), depression (13%), anxiety (10%), insomnia (10%), dyspnea (10%) and nausea with general malaise (6%). Only 16% of patients had a BRASS score $\geqslant$20. The median hospitalization time was 15.2 days (range 3-65). Fifty-five (58%) patients needed at least one line of antibiotic therapy, 41% of which for a hospital-acquired infection. Pneumonia was observed in 28 patients (51%) and urinary tract infections in 7 (13%). Blood cultures-confirmed sepsis was detected in 12 (22%) patients and in 4 the sepsis originated from the central venous catheter. Of the 94 inpatients, 17 (18%) died during the hospitalization.

Conclusions: Lung cancer patients have more frequent admissions to ED with subsequent hospitalization when compared to other tumor patients. The most debilitating symptoms are performance status worsening, dyspnea and fever. In these patients the increases risk of hospital-acquired infection and mortality represents a worrisome issue.

R44

HBV AND HCV SCREENING SEROLOGICAL TEST IN PATIENTS CANDIDATED TO ADIUVANT OR NEO-ADIUVANT TREATMENT IN SOLID TUMORS

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Background: HBV and HCV reactivation during chemotherapy is widley reported, in particular with hematological tumor or lymphomas and less for solid tumor. Above all HBV reactivation may develope hepatitis, liver failure and death, during cancer treatment and during at least 6 months after the end of chemotherapy.
A preventive antiviral therapy in patients (pts) with high risk of HBV reactivation showed a benefit. There is not yet consensus about screening with serological tests in pts with solid tumours candidated to cancer tretament, because there are no data about cost-efficacy.
We analyzed the incidence of HCV and HBV positivity in pts evaluated for adjuvant or neoadjuvant treatment in solid tumors, to consider if screening is favorable in this setting of pts.
Patients and Methods: From october 2016 to march 2019 in a single center all consecutive patients cadidated to adjuvant or neoadiuvant chemotherapy or Radiochemotherapy for solid cancer were analyzed. We tested at basal evaluation Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) and Hepatitis C antibody (HCVAb). If they were positive HBV DNA and/or HCV RNA were tested.
Results: We analyzed 148 patients, 56 male and 92 female. The porpose of treatment was adjuvant in 125 pts and neoadjuvant in 21 pts, esclusive radiochemotherapy strategy was 2 pts with anal cancer.
28 pts were positive to screening tests (18%). 3 pts resulted exposed to hepatitis C virus (2%), 24 pts to hepatitis B virus (16%), only 1 pts showed both positive tests. Of the 142 HBsAg negative blood samples, 19 samples were positive for HBcAb (13%), 3 pts had HBV DNA overexpression.
Conclusions: According to our results, screening with serological tests of HBsAg, and HBcAb may be considered in pts with solid tumour. Above all in pts candidated to adjuvant and neoadjuvant treatment this strategy may be important to reduce the long term side effects of treatment, as the viral reactivation

R45

CAREGIVER AND PATIENT AS A CARE SUBJECT

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Background: Many studies investigated the importance of caregiving activities carried out by caregivers and the effects on the quality of life and psychophysical well-being generated by being constantly in contact with the invalidating disease of one's own family member. When a family member becomes ill, the whole family feels it is falling into a tunnel from which there is no possibility of return (fear, loss, worry, uncertainty, anxiety, fragility). Cancer becomes a real *family pathology*, in which the distress is mutual and interdependent. To verify this claim, based on our clinical experience, we compared the stress reports of caregivers (objective, psychological, heavy, social, emotional burden) with those of distress, anxiety and depression of their sick family members.
Material (patients) and Methods: 93 cancer patients completed self-assessment questionnaires about their distress (Ditress Thermometer), and their levels of anxiety and depression (Hospital Anxiety and Depression Scale, HADS). At the same time 93 caregivers completed a self-assessment questionnaire of the family burden (Caregiver Burden Inventory, CBI). We then correlated the scores of each caregiver with those of their family member.
Results: We found two statistically significant positive correlations between the psycho-physical burden of caregivers and levels of distress ($r=0.54$, $p<0.01$) and anxiety ($r=0.45$, $p<0.01$) of the patients, while the correlation between CBI scores and Hads depression scale was not significant ($r=0.33$, $p<0.01$).
Conclusions: We can observe a significant positive interrelationship between the caregivers' psycho-physical burden and patients'distress and anxiety, that is, when the scores of the ones increase or decrease, the scores of the others increase or decrease too. The strength of the correlations is strong for the relationship between caregivers' burden and patients' distress, medium-strong for CBI scores and HADS anxiety scores. This leads to an important implication about the care and the psychological support interventions to the cancer patient and to his family: by reducing levels of distress of the caregiver we can reduce anxiety and distress of the patient, with remarkable relapses on the well-being and the quality of life of the patient and his family. That is, the family becomes an integral part of the healing process, so much so that we could talk about taking charge of the "family with cancer" system.

R46

CHARACTERIZING DEMORALIZATION IN TERMINALLY ILL CANCER PATIENTS

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Background: Cancer patients can be affected by existential distress, deriving from feelings of loss and changes due to their serious health status. It can manifest through demoralization, that is a syndrome characterized by subjective incompetence, sense of failure, hopelessness, loss of purpose/meaning and low self-esteem. The study aimed to investigate demoralization in a sample of terminally ill cancer patients, i.e. its prevalence, subdimensions and associated variables.

Patients and Methods: Cross-sectional methodology was adopted. Validated rating scales were used to explore patients' demoralization, anxiety, depression, physical symptoms, pain, spiritual well-being, and dignity. Final sample was of 235 end-of-life cancer patients with a Karnofsky Performance Status (KPS) lower than 50 and a life expectancy of few weeks.
Results: Fifty-three patients (22.6%) were highly demoralized, while sixty-four participants (27.2%) had low demoralization and 118 (50.2%) had moderate demoralization. Factor analysis evidenced the following demoralization subdimensions: emotional distress and inability to cope, loss of purpose and meaning, worthlessness, sense of failure and dysphoria. Demoralization significantly correlated with depression, anxiety, dignity, spiritual well-being and all the analyzed physical symptoms, with the exception for nausea and breathing problems.
Conclusions: Results seems to show that demoralization levels in end-of-life cancer patients are higher than those characterizing advanced cancer patients. It could be possible that they depend on person's clinical condition and nearness to death. Demoralization subdimensions could be typical forms of expression of the existential distress of the end-stage. The considerable number of patients suffering from demoralization strengthen the need for psychological interventions to reduce the existential distress at the end of life, focusing on finding meaning and detecting spiritual concerns.

R47

IMMUNO-RELATED TOXICITIES: A SINGLE CENTER EXPERIENCE

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Background: Immunotherapy has completely revolutionized the treatment of different neoplasms but its use is associated with a spectrum of adverse effects that can affect different organs. We evaluated the incidence of immune-related toxicity in our Oncology Unit.
Patients and Methods: We retrospectively collected and analysed data from 111 patients (pts) treated with immunotherapy in label use focusing on toxicities between April 2014 until April 2019. Data regarding age, sex, performance status, histology, patient's history for autoimmune disease, number of metastatic sites, treatment lines, smoking habitude, PD-L1 status, type of toxicities, grading according to CTCAE, treatment and outcomes were collected.
Results: Of the 111 patients enrolled, 74 were treated with Nivolumab, 25 with Pembrolizumab, and 11 with Ipilimumab; 70pts (63%) were affected by lung cancer, 29 (26%) were affected by melanoma, 7 (6,5%)by renal cancer and 5 pts (4,5%) by head and neck cancer. Twenty-nine pts(26%) presented some form of toxicities.The most common toxicity observed was skin toxicity (27,5%), and gastrointestinal toxicity (24%,GI and liver), followed by thyroid (20,5%) and kidney (20,5%) toxicities. One patients experienced immune-mediated pneumonitis, one patient developed arthritis and one patient experienced hypoadrenalism. Two pts experienced more than one toxicity. Considering pts treated with Nivolumab 26/74pts (35%) experienced toxicity; median time of development of toxicity was after the 7th administration. Considering Pembrolizumab, we recorded 3/25 (12%)toxicity; median time after 2nd admistration. No toxicity with Ipilimumab was recorded. In our cohort 21 pts (19%)experienced G1,G2 toxicity, while 8 pts (7%) experienced G3-G4 toxicity. Nine pts (8%) were treated with oral steroids, and 8 pts (7%) required intravenous steroids and hospital admission. Immunosuppressive therapy was never necessary, but two patients needed intensive care due to the immune-related adverse event (GI and pulmonary adverse event treated with Nivolumab and Pembrolizumab, respectively). Immune related toxicity was not predictive of better outcome in our cohort.
Conclusions: We recorded 26% of immune related toxicity.The most common toxicity observed in our centre was skin toxicity. Severe toxicities that required hospitalization affected 7% of pts.

R48

IMPACT OF COGNITIVE-BEHAVIORAL-THERAPY (CBT) ON LEVELS OF ANXIETY, DEPRESSION AND DISTRESS IN CANCER PATIENTS (pts)

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Background: Cancer patients usually experience symptoms that include anxiety, depression and distress. The aim of this preliminary study was to explore the effect of brief Cognitive-Behavioral-Therapy (CBT) intervention on distress and BMI in breast and lung cancer patients referring to a clinical psychology health service specialized in psycho-oncology, to reduce distress symptoms.
Methods: Before and after CBT intervention, BMI index, Hospital Anxiety and Depression Scale (HADS) the

Distress Thermometer (DT), were collected in all patients attending the service between February and December 2018. Wilcoxon-Mann-Whitney and Spearman rank tests were adopted to evaluate CBT treatment effect on BMI and distress variables.

Results: 43 patients (88% breast and 12% lung cancer, median age: 49 years) were included in the study. At baseline, 34.9% and 30.2% of patients reported clinically significant symptoms of anxiety and depression (HADS score $\geqslant$ 11), while 62.8% and 44.2% were borderline (HADS score = 8-10). All patients had high levels of distress (DT score $\geqslant$ 4). Depression HADS score significantly correlated with anxiety (r_s =0.55; $p < 0.01$), distress (r_s =0.70; $p < 0.01$), BMI (r_s =0.41; $p < 0.01$), age (r_s =0.30; $p = 0.05$) and time from diagnosis (r_s =0.30; $p = 0.04$).

Focusing on breast cancer patients, baseline BMI was correlated with anxiety (r_s =0.49; $p = 0.002$) and distress (r_s =0.37, $p = 0.02$). Physical activity level was inversely associated with anxiety (r_s =-0.41; $p = 0.01$), depression (r_s =-0.49; $p = 0.002$) and distress (r_s =-0.40; $p = 0.01$).

After 6 months of CTB treatment, 7% and 5% of patients had still high HADS scores for anxiety and depression, while 58% and 40% showed borderline HADS scores. Comparisons between baseline and 6 months follow-up, showed an improvement in anxiety ($p < 0.001$), depression ($p < 0.001$) and distress ($p < 0.001$) levels.

Conclusions: The study showed that CBT treatment could be effective on anxiety, depression and distress management, but specific interventions need to be implemented to change physical activity attitudes and therefore BMI index.

R49

IDENTIFICATION OF THE FOUNDER BRCA1 MUTATION C.4117G>T (P.GLU1373*) RECURRING IN ABRUZZO AND LAZIO REGIONS OF CENTRAL ITALY AND PREDISPOSING TO BREAST/OVARIAN AND BRCA1-RELATED CANCERS

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Background: Founder *BRCA1/2* cancer predisposing mutations have been reported in Italian population. We reported the founder *BRCA1* mutation, c.4117G>T - p.Glu1373*, recurring in unrelated families of Abruzzo and Lazio regions of Central Italy.

Methods: Preliminary analysis of 17 unrelated families carrying *BRCA1* c.4117G>T nonsense mutation reported in the Hereditary Breast/Ovarian Cancer Registry of the Oncology Territorial Care Unit, University of L'Aquila and Genetic Unit, Catholic University of Rome was performed by genetic counselling and peripheral blood collection after written informed consent from affected and unaffected probands. *BRCA1/2* genetic analysis were performed by direct sequencing; haplotype analysis was carried out using microsatellite markers in the 17q21 region: *D17S846, D17S1328, D17S855* (intragenic), *D17S902, D17S806*. Post-test genetic counselling was performed to address Therapeutic and/or Preventive Clinical strategies. Geographic area of origin, cancer family trees, cancers affecting the probands were collected. To date, overall 23 unrelated families were enrolled.

Results: In the preliminary analysis, *BRCA1* c.4117G>T mutation was identified in 17 unrelated families with familial origin in a territory of Central Italy including Abruzzo and Lazio regions: this mutation was always and significantly associated with the Allelic Variant (AV) *BRCA1*, c.3119G>A (p.Ser1040Asn), in 52 tested carriers, 20 affected and 32 unaffected. Microsatellite markers confirmed a common haplotype shared by the 52 probands, comprising the region between D17S1328 and D17S902 markers. In overall 23 unrelated families, the association of *BRCA1* founder mutation and the AV were identified in 66 tested carriers, 28 affected and 38 unaffected.

Conclusions: The *BRCA1* c.4117G>T is a founder mutation prevalent in the territory of Central Italy in Abruzzo and southern Lazio regions, cosegregating with AV *BRCA1* c.3119G>A, providing faster identification of affected and unaffected carriers to specifically address therapeutic and preventive clinical pathways for breast, ovarian and BRCA1-related cancers.

R50

PROPHYLAXIS WITH INTRATHECAL CHEMOTHERAPY AND HIGH DOSE METHOTREXATE IN PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA AT HIGH RISK FOR CENTRAL NERVOUS SYSTEM RELAPSE: A SINGLE CENTRE EXPERIENCE

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Central nervous system (CNS) relapse is a serious and mostly fatal complication of diffuse large B cell lymphoma (DLBCL) and. there are not randomised prospective trial which specifically address a decision-making process for

CNS prophylaxis. Several site-specific risks are described in literature such as testicular, breast, paranasal sinuses, epidural spaces. Recently a modified IPI score (CNS IPI) was described to predict risk of CNS relapse.
In order to evaluate the efficacy and feasibility of intrathecal methotrexate (MTX) administration and high dose MTX after first line chemotherapy, we retrospectively reviewed 31 patients at high risk for CNS relapse, among 265 newly diagnosed DLBCL, treated from January 2012 to November 2018 at Veneto Institute of Oncology IOV-IRCCS.
CNS-IPI was intermediate or high in 20 patients. In the other, disease localization was considered at risk for CNS relapse (breast, paravertebral, orbit, paranasal sinus, testis). All patients performed brain MRI and lumbar puncture at diagnosis (all negative at flow cytometry analysis).
Almost all patients received R-CHOP as first line treatments, two patients with paravertebral localization were treated with HyperCVAD, other two received DA-EPOCH-R (triple-hit lymphoma and high CNS-IPI score) as front line approach. Nineteen patients (61%) received at least 2 lumbar punctures with MTX and 20 (64%) two courses of high dose intravenous MTX 3,5 g/mq after first line therapy with R CHOP.
At the end of first line treatment, 26 (84%) patients obtained a complete remission at PET scan and 5 patients (16%) presented progressive disease, with CNS involvement in two cases. Furthermore, 2 patients experienced CNS relapse after obtaining complete remission with R-CHOP chemotherapy. Among the four patients treated with more intensive schedules, 2 are in complete remission, one developed an early CNS relapse and died and one patient presented progression of disease at the end of treatment.
So, at a median follow up of 24 months (4-118 months) all patients who received the planned treatment including CNS prophylaxis did not experience central nervous system relapse. In conclusion, CNS prophylaxis including intrathecal MTX administration and high dose MTX infusion after first line chemotherapy is feasible and effective with no CNS relapse.
Prospective trials are needed to evaluate the most effective strategy and the correct timing of intravenous MTX infusion for CNS relapse prophylaxis.

R51

INCIDENCE OF HEART INVOLVEMENT FROM SOLID TUMORS: A SINGLE-CENTER, REAL-WORLD EXPERIENCE FROM NATIONAL CANCER INSTITUTE OF MILAN

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Background: Heart is an unusual site of metastatic involvement in cancer patients. This could be the consequence of thromboembolic dissemination, direct organ infiltration or solid metastases throughout haematic and lymphatic spread. Most data derive from post-mortem studies and clinical information is lacking.
Patient and Methods: Herein we present a monocentric, retrospective analysis to investigate the rates and clinical characteristics of patients affected by advanced disease and heart involvement. The presence of endoluminal vegetations and intracardiac masses was investigated by transthoracic echocardiography (TTE), computed tomography (CT) scan, positron emission tomography (PET) scan, or thoracic magnetic resonance (MRI). Primary cardiac tumors and pediatric sarcomas were excluded from the analysis. Medical records were reviewed to determine which tumor and treatment-related factors were involved.
Results: Among 832 Caucasian patients screened from December 2017 to March 2019 at Medical Oncology Department, 10 cases with heart dissemination were collected. Eight patients were male, two patients were female, with a median age of 56 (range 35-75) years. The primary tumor sites were: lung (5), melanoma (2), renal cell carcinoma (1), thymoma (1) and vertebral cordoma(1). Cardiac lesions were first diagnosed with thoracic CT scan in half of cases, while TTE (2), thoracic MRI (2) and PET scan (1) were used in the remaining. In all cases, diagnostic tools were effective at discriminating thrombus (3) from solid metastasis (7), suggesting a different medical approach: therapeutic anticoagulation with LMWH in case of thrombosis, prophylactic anticoagulation with LMWH for metastases. All patients received antineoplastic therapy. Three patients developed acute complications requiring intensive care: one symptomatic pulmonary embolism, one cardiac failure with cardiogenic shock and one ventricular tachycardia.
Conclusions: In our experience less than 1% of patients with advanced solid tumors spread to the heart. Nevertheless, anticoagulation therapy associated to antineoplastic active treatment was only partially effective at avoiding serious adverse events. Better understanding about this eventuality is warranted.

R52

EARLY NUTRITIONAL INTERVENTION IN CANCER PATIENTS UNDERGOING CHEMOTHERAPY: IMPACT ON NUTRITIONAL STATUS

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Background: Malnutrition and sarcopenia are independent negative predictors of clinical outcomes in cancer patients. In some cases, oncological therapies may further negatively affect nutritional status suggesting the need of specialistic intervention. Aim of our study was to prospectively evaluate the impact of nutrition intervention on body weight and skeletal muscle (SM) in patients undergoing chemotherapy (CT).
Material and Methods: In our pilot study, malnourished patients (reporting involuntary weight loss (WL) in the previous 6 months >10%) with a new diagnosis of advanced solid tumour and candidate to first-line chemotherapy, were referred to the nutrition unit for nutrition intervention. Patients were prospectively assessed before starting CT (T0) and after 4-6 months of treatment (T1). Anthropometric measurements were collected and SM was measured by analysis of computed tomography images taken for diagnostic purposes. Cut-off points used to define sarcopenia were skeletal muscle index (SMI) <38.5-52.4 cm^2/m^2 (for female and male respectively). Nutritional interventions included: dietetic counselling, oral nutrition supplements, enteral or parenteral nutrition. Descriptive statistic was presented and t test was performed.
Results: From January to November 2018, 20 patients were evaluated: 16M/4F, average age 60±11years, 10 upper gastrointestinal (esophagus, gatro-esophageal junction, stomach and pancreas), 6 lung and 4 colorectal cancer. At baseline patients reported an average WL of 15% and BMI 22±3, SMI was 44.4±3.3 for male and 29.7±6.7 for female. At T1 mean BMI was 22±3, SMI 43.4±6.1 for male and 30.4±6.6 for female. No statistical differences were recorded in body weight and skeletal muscle between T0 and T1.
Conclusions: Our preliminary results suggest that an early nutrition intervention allowed to maintain not only body weight but also SM in patients with a new diagnosis of advanced solid tumour undergoing chemotherapy. Nutritional assessment is fundamental in monitoring cancer patients during treatments and the role of computed tomography for the evaluation of SM should be further explored.

R53

CONTROL AND IMPROVEMENT OF THE QUALITY OF CONSULTATION REPORTING (CR) AND DISCHARGE LETTERS (DL) IN AN ONCOLOGY UNIT

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Background: CR and DL are important means in communicating pt history, clinical findings and future program to multiple users. They are also tools to hold the thread of clinical history. In Oncology, this function is of the utmost importance: oncologists need to have an updated description of clinical details together with a complete summary of the actual condition. Unfortunately, the quality of these documents is frequently disregarded. This translates into information gaps, mistakes, adjunctive efforts in retrieving lacking details. We designed a systematic quality control of CR and DL and an improvement project.
Methods: Within our group of 11 oncologists, we used the audit instrument to share the entire process through the following steps: 1) we randomly selected 2 CR and 2 DL and revised their content in two plenary meetings; 2) using opinion iteration we selected the desired main structure of the documents and identified the 4 (CR) and 3 (DL) mandatory issues; 3) we checked these issues in randomly selected documents at baseline; 4) after a written advice on the filling rules, we repeated the selection at 3-months intervals and reported the audit results to the group. An improvement action was planned in case the issue was not present in at least 80% of the documents.
Results: The items of the CR selected for control were: 1) length of the document less than 3 word-formatted pages; 2) list of the currently taken drugs; 3) description of the year of diagnosis and the TNM staging; 4) absence of acronyms and abbreviations. The fulfillment of the items in the 3 audit rounds was respectively: 1) 8/10 (80%); 17/20 (85%); 25/27 (92%); 2) 4/10 (40%); 16/20 (80%); 22/27 (81%); 3) 4/9 (44%); 5/20 (25%); 16/27 (59%); 4) 5/10 (50%); 15/20 (75%); 21/27 (77%). The items of the DL were: 1) summary description of the cancer history; 2) description of the reason of admission (acute event, symptoms, diagnostic process or other); 3) details about in-hospital clinical course. The fulfillment of the items in the 3 audit rounds was respectively: 1) 9/10 (90%); 8/10 (80%); 8/10 (80%); 2) 8/10 (80%); 7/10 (70%); 8/10 (80%); 3) 8/10 (80%); 9/10% (90%); 10/10 (100%).
Conclusions: The observed quality of the clinical documents was not satisfactory. The project highlighted the desired requirements of CR and DL. A trend toward improvement was found in near all items in repeated audits. Quality control and improvement should be a continuous effort.

R54

TRENDS AND CHARACTERISTICS OF CLINICAL TRIALS IN THE REGGIO EMILIA CLINICAL CANCER CENTRE

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Background: The Oncology Unit of AUSL-IRCCS of Reggio Emilia has a long history of clinical trials. The

characteristics and complexity of clinical trials has changed in the years, becoming more challenging.

Methods: We analyzed the clinical phase I-IV studies active in the Oncology Unit of Reggio Emilia between January 2013 and December 2018. The data collected for each study were: phase, sponsor, setting, endpoints, cancer site, drug class, number of patients (pts) enrolled and request for biological samples and CT scan central review. The data collected for each pt were: gender, age, ECOG Performance Status (PS), employment and residence. Descriptive statistics were used to summarize the data.

Results: In this period 471 pts were enrolled in 92 studies (mean 79 pts/year; 92 pts in 2013, 64 in 2014, 47 in 2015, 73 in 2016, 102 in 2017, 93 in 2018); 31.5% in phase II and 57.6% in phase III studies, 56.5% nonprofit and 43.5% profit. The study drugs were target therapy in 55.4%, immunotherapy in 15.2%, chemotherapy in 16.3%. Breast cancer studies had the highest number of pts enrolled (46.1%), followed by ovarian (9.8%), colon (8.3%), pancreas (6.6%), and urological tract (5.5%) cancer. The overall treatment setting was 27.2% neo/adjuvant, 42.4% 1st line therapy, 30.4% 2nd and subsequent lines. In 60.9% and 63% of the studies, tumor blocks and blood samples, respectively, were collected and shipped; the central review of CT scans was requested in 26.1% of trials. Primary endpoints were progression-free survival (43.5%), overall survival (16.3%) and safety (12%). Median age of pts was 64 years (17.4% <49y, 55% between 50-69y and 27.6% > 70y), 69% were female and 31% were male, all pts were PS 0-1. 41% of pts were employed, 34.8% were retired, 12.1% unemployed. Our pts mostly resided in Reggio Emilia and its Province (85.3%), followed by Emilia Romagna Region (9.1%) and all other regions/countries (5.3%).

Conclusions: This analysis shows the need to enhance the research infrastructure in relation to the continuous increasing trend of number and complexity of clinical trials, and to encourage the enrollment of elderly and PS 2 pts.

R55

FAIREST-RT: A PRE-EMPTIVE SKIN TREATMENT OF SKIN TOXICITY CAUSED BY CETUXIMAB

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Introduction: Treatment with anti-EGFR agents has been associated with a number of dermatologic toxicities; papulopustular skin rash is the most common skin toxicity followed by xerosis, fissures, pruritus, paronychia, and blepahritis.

Fairest-RT is a cream composed by jaluronic acid (0.2%), calendula officinalis (2%) and beta-glucagon (0.05%).

In this paper we report preliminary results of pre-emptive use of Fairest-RT in patients with colorectal cancer (CRC) and head and neck cancer (HNC) treated with cetuximab (CET).

Material and Methods: All patients had at least one unidimensional measurable lesion. Other eligibility criteria included patients aged > 18 years,a Eastern Cooperative Oncology Group performance status of 0-2, adequate hematologic, renal metabolic, and hepatic function, a life expectancy > 3 months.

CET was administered on a weekly schedule, with a 400 mg/m2 initial loading dose, followed by 250 mg/m2 weekly infusions until disease progression. Chemotherapy was given according to the standard clinical practice in CRC and HNC: FOLOFOX 4 + CET was the regimen for CRC while cisplatin + fluorouracil + CET was HNC regimen.

The primary objective of the study was to evaluation of the impact of preemptive use of FAIREST-RT on the incidence of CET-induced dermatologic toxicity.

FAIREST-RT was administered beginning day -3 (three day before CET administration) and continued through weeks 1 to 6, and consisted of 2 applications to face, neck, hands, feet, back and chest. All patients were given an instructional paper that provided suggestions to reduce skin irritation

Results:

Grade 1-2 Grade 3 Grade 4
Rash 6 (50%) 2 (6%) 0
Dermatitis Acneiform 3 (25%) 1 (3%) 0
Dry Skin 2 (12%) 0 0
Pruritus 2 (12%) 1 (3%) 0
Acne 2 (12%) 1 (3%) 0
Skin Fissures 1 (6%) 0 0

Conclusions: Our preliminary experience with pre-emptive use of Fairest-RT is very effective in reducing severe cutaneous toxicity. The low incidence of G3 toxicity is very similar to that observed in pre-emptive trials and this has induced a low number of CET withdrowal with a maintenance of a good quality of life.

R56

THE SELECTIVE INHIBITOR OF THE SODIUM GLUCOSE CO-TRANSPORTER 2 (EMPAGLIFLOZIN) EXERTS CARDIOPROTECTIVE AND ANTI-INFLAMMATORY EFFECTS IN PRECLINICAL MODELS: A PATHOPHYSIOLOGICAL STUDY

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Background: Sodium-glucose co-transporter 2 (SGLT2) inhibition reduces heart failure hospitalizations in patients with diabetes. Empagliflozin (EMPA), an SGLT2 inhibitor, exerts anti-oxidant and cardioprotective effects in clinical studies. We hypothesize that EMPA could have cardioprotective and anti-inflammatory effects in Doxorubicin (DOXO)-Induced cardiotoxicity.
Materials and Methods: We tested the effects of EMPA alone or in combination with DOXO in HL-1 adult cardiomyocytes evaluating: cell viability, Leukotriene-B4 and p65-NF-κB expression, Interleukin 1ß, 8 and 6 secretion and lipid peroxidation (quantifying Malondialdehyde [MDA] and 4-hydroxynonenal [4-HNA]). The same parameters were studied also in cardiac lysates of C57BL6 mice pretreated or not with EMPA (10 mg/kg/day per os) and DOXO (2.25 mg/kg/day ip) for 7 days. To evaluate cardiac function in vivo, Global Longitudinal Strain (GLS) was measured using 2D speckle tracking echocardiography.
Results: EMPA, co-incubated with DOXO, increases the cardiomyocyte viability of 33 and 82% at 100 and 500 nM, respectively (compared to only DOXO treated cells). Moreover, EMPA reduces the Leukotriene B4 expression and p65-NFkb activation of 38% and 32% at 100 nM and of 58 and 64% at 500 nM, respectively (all compared to only DOXO treated cells). Notably, EMPA also decreases significantly the expression of Interleukin 1β, Interleukin-8 and Interleukin, compared to only DOXO exposed cells. EMPA exerts anti-oxidant properties by by halving the lipid peroxidation processes under DOXO exposure. Interestingly, in mice treated with EMPA+DOXO, EMPA prevents the GLS's reduction, indicating cardioprotective properties. In DOXO-EMPA groups heart IL-1β, IL-6 and IL-8 tissue extract were reduced of around 45-58% compared to only DOXO group ($p<0,001$ for all).
Conclusions: EMPA has strong anti-inflammatory and cardioprotective effects in DOXO-Induced cardiotoxicity and these effects are mainly mediated by a reduction of the lipid peroxidation, Leukotriene-B4 and NF-κB activation. Preclinical studies demonstrate cardioprotective effects of EMPA with anti-inflammatory effects in heart lysates proposing as possible cardioprotective tool during treatments with anthracyclines.

R57

TABAGISM AND CESSATION PROGRAMS IN PRIMARY CARE

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Background: According to WHO, the percentage of smoking deaths is between 25% and 50%.Phyisicians give poor attention to prevention. Italian smokers are a quarter of the population, including health workers. Almost 50% of patients relapse smoking after an acute cardiovascular event.
Aim: To evaluate the prevalence of Tobacco smoking among General Practitioners (GPs) of ASL Bari (Italy), their level of knowledge and awareness about smoking harms and their attention in prevention, treatment and implementation of cessation programs.
Materials and Methods: An anonymous questionnaire (29 items)was administered by web with Google account, in collaboration with Thoracic Oncology Unit - IRCSS Istituto Tumori "Giovanni Paolo II" Bari, to 680 GPs, members of FIMMG (Federazione Italiana Medici di Medicina Generale) from October 2018. The survey is ongoing, and the results, updated to January 8th, are presented.
Results: 110 questionnaires (16.17%) have been completed. The characteristics of responders are: Male/Female 70/30%, age 30-50y: 4.14%, 51-65y: 78.2%, >66y: 16.4%). 24.5% of GPs have in care <1000 patients,75.5%>1000 patients. 86.4% don't smoke,13.6% smoke (cigarettes 56,3%, cigar 18.8%, pipe 12.5%, electronic cigarette 18.8%, IQOS 12.5%). 4.84% started smoking at 15-30. 55.6% stopped smoking (100% of these by non-pharmacological method) and 18.18% tried to quit. 81.8% consider smoking as an addiction,14.5% an habit, 3.6% both. 67.3% of GPs said that smoking abstinence-syndrome generally lasts a long time, 23.6% a few days, whereas according to 9.1% it doesn't exist. 63.63% recommend cessation to motivated patients, 55.5% consider that counseling could be an useful tool only in high risk patients and 80% only in presence of previous cardiovascular event. 81.81% of GPs are going to participate to cessation programs, but 77.27% consider themselves inadequate. 66.4%never sent patients to anti-tobacco-centers and only 33.4% did it, whereas 12.72% would prescribe a pharmacologycal cessation treatment.
Conclusions: The ASL/Bari GPs recognize smoking as an addiction. Althoughthey feel themselves inadequate, they are available to implement their knowledges toward smoking cessation programs. This Survey could be useful to learn more about GPs'skills to plan training meetings and to share educational programs with anti-tobacco centers.

R58

INTERIM ANALYSIS OF THE FABREGA STUDY - FAMILIAL AGGREGATION OF BREAst and GAstric CANCER

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Background: A biological and epidemiological relation between gastric cancer (GC) and invasive lobular carcinoma of the breast (ILC) was hypothesized, on the basis of the excess risk of both entities observed in the hereditary diffuse GC (DGC) syndrome, and on the larger incidence of family history of GC observed in ILC patients (pts) than in pts with ductal histology.

Patients and Methods: FABREGA is a retrospective study aimed to explore the epidemiological connection between early-onset GC (diagnosis <50 years of age) and family incidence (parents, siblings) of ILC, breast cancer (BC), GC and any cancer. Primary endpoint is the difference of family incidence of ILC between intestinal GC [IGC] and DGC pts. Family members' identities were extracted from population administrative files and occurring cancers were identified in the Piedmont Cancer Registry (RTP). Standardized Incidence Ratios (SIRs) were calculated through the comparison with the number of expected cases from the cumulative probability of developing a cancer at the age of each linked family member up to 2012.

Results: 374 diagnoses of early-onset GC were retrieved (1985-2012), of which 168 (45%) could be definitely attributed to either histology type [IGC 23 pts (13.7%), DGC 145 pts (86.3%)]. 293 family members of the first 123 pts were considered apt to be sought for in the RTP, where 61 distinct tumor occurrences (20.8%) emerged.

DGC pts had a larger number of family occurrences of BC (4 vs 0 in IGC) and signet-ring cells GC (5 vs 0), however such small figures discourage statistical analysis (both Fisher's exact test p=0.55). The odds ratios (DGC pts vs IGC) of family occurrence of any cancer, gastrointestinal cancers, and GC were 1.04 [$CI_{95\%}$ 0.53-2.04], 0.75 [$CI_{95\%}$ 0.28-2.02], and 0.71 [$CI_{95\%}$ 0.18-2.82], respectively. Overall, family incidence of any-type GC was higher than the expected (SIR 6.0; $CI_{95\%}$ 2.89-11.08); no increase of BC incidence was observed.

Conclusions: A registry study implying the retrieval of family members across two generations is feasible; however, the loss of information was conspicuous and reduced the sample size. Despite the focus on early-onset cases, DGC seems not to correlate to higher family incidence of ILC when compared to IGC. However, the study also showed: a numerical increase of occurrences of both BC and GC in family members of DGC pts; a marked imbalance towards DGC in diagnoses at young ages; the role of any-type GC as a strong risk factor for family incidence of GC.

R59

GENETIC TESTING FOR HEREDITARY BREAST AND OVARIAN CANCER: UPDATE OF MULTICENTER ITALIAN EXPERIENCE

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Background: More than 90% of hereditary breast and ovarian cancer are the risult of a mutation in BRCA1/BRCA2. Genetic mutations in BRCA1/BRCA2 are associated with a life time risk of breast cancer from 60 to 80% and an ovarian cancer risk from 10 to 40%. Genetic susceptibility to breast and ovarian cancer might also be associated with known hereditary cancer syndromes, such as PALB2, p53, PTEN, STK11, BRIP1,ATM. We would like to offer genetic testing to patients with breast and/or ovarian cancer, selected for risk of hereditary cancer, based on oncologic familial and personal history.

Patients and method: In the Genetic Work Group of Oncology Department of Azienda Toscana Nord Ovest (estabilished in October 2017), 353 families were selected for risk of hereditary breast and/or ovarian cancer. We did genetic testing to these patients for BRCA1 and BRCA2 mutations. BRCA carriers families were submitted to genetic counseling outlining options for screening for early detection and risk-reducing measures (prophylactic surgery). In BRCA-negative high risk families it was considered to proceed with second-level testing (multigene panel).

Results: From October 2017 to May 2019 we have selected 353 index cases (age from 27 to 84 years) eligible for genetic testing: 303 (85.8%) with breast cancer, 50 (14.2%) with ovarian cancer. Of these, 336 (95.2%) genetic testing have been completed. BRCA mutations was detected in 96 (28.6%) patients: 34 (10.11%) had a deleterious mutation and 62 (18.4%) a Variant of Uncertain Significance (VUS).

Conclusions: In our small population, with a careful selection of patients at genetic risk, we observed a prevalence of BRCA1 and BRCA2 mutations according to the rates

found in the main guidelines on genetic and familial high-risk assessment. Genetic counseling based on accurate information should be provided to BRCA mutation carriers. In our Work Group we are starting to provide optimal genetic counseling and testing for healty family members.

R60

HOW MANY PATIENTS ARE ELIGIBLE FOR A CLINICAL TRIAL? USE OF INSITE, A FEDERATED EHR TECHNOLOGY TO SUPPORT RESEARCHERS AND ACCELERATE ENROLMENT

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Background: Patient recruitment is a key success factor for clinical trials. Computerized recruitment support re-using routine care data for clinical research is a very promising approach. InSite, a federated electronic health record (EHR) research platform, provides a near real-time method of querying hospital records to optimize clinical study protocols and accelerating recruitment. We present the use of InSite for the prospective monitoring of potentially eligible patients for a clinical study in oncology.
Material and methods: InSite enables the re-use of EHR data for research compliant with GDPR regulation. This facilitates the collaboration between clinicians and researchers and increases the performance of clinical research. InSite manages a network of clinical research sites across Europe and ensures that no patient data ever leaves the participating hospitals.
Screening and enrollment tools were validated in a clinical trial (STRONG study) conducted at IRST, one of the participating investigational sites. The search was for patients with advanced urothelial or non-urothelial carcinoma treated in 2nd or subsequent line with Durvalumab given 3 inclusion and 15 exclusion criteria.
Results: Queries executed monthly over 14 months (Dec 2017-Feb 2018) on InSite found 89 potentially eligible patients: 16 were enrolled, 22 are still in evaluation stage, 51 were not eligible after deeper chart review (18 for lack of metastatic disease, bad clinical condition or 2nd tumor development, 17 treated with anti-PD1/PDL1, 12 dead, 3 lost to follow up, 1 subject refused).
Conclusions: InSite suggested 89 potential candidates from a cohort of 80,000 patients. 38 verified and confirmed as eligible, matching exactly the population found using our traditional approach. This confirms InSite's accuracy and completeness. 57% of patients were excluded due to lack of coded data in the EHR or data concepts not yet made available in InSite.
These results suggest that the InSite recruitment tool facilitates the identification of eligible patients at the research center and it promises to be a valid support for the investigator. Trial patients can be identified on a daily or weekly schedule instead of monthly as it is usually. Moreover, InSite constantly monitors the quality of the data in EHR, pointing to issues at data entry and suggesting changes to the EHR itself to enhance completeness and use while adhering to international standards, interoperability infrastructures and common data models.

R61

DRUG-DRUG INTERACTIONS EXPOSITION: AN OBSERVATIONAL RETROSPECTIVE ANALYSIS

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Background: During chemotherapy oncological patients frequently suffer from severe drug reactions with strong impact on their quality of life. Clinicians have to manage chemo-toxicity and cancer symptoms, furthermore they have to consider various comorbidity, which often affect oncological patients. The management of such a complexity require contemporary administration of high number of drugs, exposing the patients to risk for drug-drug interactions (DDIs). This work wants to evaluate the exposition risk to DDIs and the correlated increasing in Emergency Room (ER) access for patients treated in the Ambulatory Day Service (DSA) of Hospital Guglielmo da Saliceto.
Material and Methods: We extracted registry, pathology and treatment data of patients treated in DSA since 01 Oct 2017 to 30 Sep 2018 from the hospital prescription software; the data on the accesses and discharge from ER have been extracted from the hospital management software. All data have been organized in a database using the patients' fiscal code as primary key. From literature we defined the principal DDIs to examinate, classifying them by their scientific evidence using GRADE method and by their gravity: severe, moderate and minor. Finally we identify the DDIs and we crossed DDI data with the accesses to the ER.
Results: On 41118 drug administration we identified 1441 (3.5%) possible DDI which affected 256 (29.77%) of 850 patients. The possible DDIs were both pharmacokinetics and pharmacodynamics (51.56% vs 48.44%); the most of possible DDIs occurred between ancillary drugs (83.84%) and have a moderate risk of severity (85.57%) and a grade of evidence 2 (62.46%). Of all the population 436 patients (51.29%) had at least one access in ER, of the population exposed to possible DDIs, 151 patients (35%) had at least one access in ER; the accesses which results in a hospitalization were 97 (34% of all hospitalizations).

Conclusions: We didn't observe a correlation between the presence of possible DDIs and an increasing in access in ER, at the same time we didn't observe a correlation between the access in emergency room and the effects of the possible DDIs. Nevertheless we think the precautionary principle should prevail, and it's advisable to have a professional figure dedicated to check the oncological patients polipharmacy, identify risk of possible DDIs and to register data on their clinical effects with the purpose to increase safety, efficacy and quality of life of our patients.

R62

SAFETY AND TOLERABILITY OF PD-1 INHIBITORS NIVOLUMAB AND PEMBROLIZUMAB: OUR EXPERIENCE

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Background: PD-1 inhibitors Pembrolizumab and Nivolumab are programmed death receptor-1 (PD-1) inhibitors immunotherapies approved for treatment, in first and second line, of several human tumors. A clear knowledge of their toxicity is important for their management and use in clinical practice.
Material and methods: We retrospectively analyzed safety and tolerability of PD-1 Inhibitors in 145 patients (pts), (90 male and 53 female, median age 63 years) with a diagnosis of metastatic cancer, since April 2017 to April 2019. 115 (79,30%) had Lung Cancer, 9 (6,20%) Melanoma and 21(14,50%) other type of cancer. 130 (89,65%) and 15 (10,35%) received Nivolumab and Pembrolizumab respectively. Toxicities were analyzed.
Results: Of 145 pts analyzed, toxicities G1-G2 and G3-G4 were respectively in 88 pts (60,68%) and 20 pts (13,79%) G1-G2 toxicities of any types were found in 83 (63,84%) cases in Nivolumab group vs 5 (33,33%) in Pembrolizumab group, while G3 and G4 were 16 (12,30 %) vs 4 (26,66 %) respectively. In Pembrolizumab group one patient died of myocarditis. Toxicities in Nivolumab vs Pembrolizumab group were respectively: Fever G1-2: 20% vs 20%; Fatigue G1-2: 51,5% vs 40%, G3-4: 4,6% vs 0; Diarrhea/Colitis G1-2: 16,1 % vs 13,3%; G3-4: 2,3% vs 0; C. Difficile infection G1-2: 0,77% vs 0; Endocrine toxicities G1-2: 25,38% vs 20%; G3-4: 0 vs 6,67%; Pneumonitis G1-2:7,6% vs 6,67%; G3-4: 0,77% vs 6,67%; Dyspnea G1-2: 36,9% vs 26,6% ;G3-4: 4,62% vs 0; Hepatic toxicities G1-2: 16,9% vs 0; G3-4: 0,77% vs 6,67%; Pancreatic toxicity G1-2: 8,46% vs 0; Hematological toxicity G1-2: 14,6% vs 0; G3-4: 1,54% vs 0; Hypereosinophilia G1-2:7,6 % vs 0; Dermatologic toxicities G1-2: 26,1% vs 6,67%; G3-4: 0,77% vs 0; Nausea and vomit G1-2:11,5% vs 13,33%; G3-4: 0 vs 6,67% ; Myalgia G1-2: 16,92% vs 0; Cardiovascular toxicity and hypertension G1-2: 3,84% vs 0; G3-4: 2,31% vs 6,67%; G5: 0 vs 6,6%; Thrombophlebitis G1-2: 3,08% vs 0; Hypomagnesemia G1-2: 6,92% vs 0; OedemaG1-2:18,46% vs 6,67%.
Conclusions: In our experience, G3-G4 toxicities were uncommon with PD-1 inhibitors Pembrolizumab and Nivolumab immunotherapies. Although they are both PD-1 inhibitors with satisfying safety, our analysis showed a better tolerability of Nivolumab, as demonstrated by less G3 and G4 toxicities.

R63

HODGKIN LYMPHOMA IN HIV-POSITIVE PATIENTS: A SINGLE INSTITUTION RETROSPECTIVE STUDY

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Background: The introduction of highly active antiretroviral therapy (HAART) since 1997 has completely changed the prognosis of HIV-positive patients (pts), decreasing the risk of developing myeloproliferative disorders. Unexpectedly incidence of HIV related Hodgkin lymphoma (HL) has not been declining. Recent clinical studies show that HIV-positive HL pts treated with concomitant HAART achieve encouraging results, as those seen in the general population. Our aim was to compare the characteristics, the response to treatment and the survival of the HL treated with first line chemoteraphy between HIV-positive (HIV+) on HAART and HIV-negative (HIV-) pts.
Methods: This is a single institution retrospective cohort study conducted in Ospedale Luigi Sacco Milan, Italy. We selected pts aged >18 years with histopatologic diagnosis of HL from April 2008 to January 2018. We included HIV+ on HAART and HIV- pts both treated with ABVD. Differences between HIV+ and HIV- pts were assessed using Chi-square, Fisher's exact or Wilcoxon Rank-sum test. Overall survival (OS), progression-free survival (PFS) and response rate (RR) were compared across groups defined by HIV-status, HAART treatment prior to HL diagnosis (yes vs no), IPS (0-2 vs ⩾3) and stage (early vs advanced) using the log-rank test.
Results: We included 45 pts, 20 HIV+ and 25 HIV-. The HIV+ pts were on average older (49 vs 39ys p=0.18), they were more likely to be male (95% vs 60% p=0.01), at an advanced stage at diagnosis (90% vs 72% p=0.26), they had ⩾1 extranodal site involved (80% vs 40% p=0.01), EBV infection (78.6% vs 36.8% p=0.03), a worst performance status (PS ECOG ⩾2 35% vs 8% p=0,06), a higher prognostic index score (IPS ⩾3 75% vs 13% p<0.001). During ABVD chemotherapy, HIV+ pts developed more frequently myelotoxicity (anemia G3-4

23.6% vs 0% p=0.02). During a median (IQR) follow-up of 33 months in HIV+ and 43 months in HIV- pts no difference was observed in RR (88.2% vs 95.6% p=0.56), OS (89.4% vs 100% p=0.3) and PFS (75.8% vs 86.7% p=0.7) at 2 years. Stratifying pts based on HAART prior to HL diagnosis, stage and IPS, no difference was observed in RR, OS and PFS at 2 years.

Conclusions: Although HIV+ pts had more aggressive baseline features in this series, there were no differences in response rate or survival. Probably exposure to HAART tends to balance outcomes overtime.

R64

NEED FOR HOSPICE: MONOINSTITUTIONAL EXPERIENCE

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Background: Hospices are care-designed residences for pts with advanced cancer, when there's no further possibility of specific cancer treatment and home-based care is no longer possible. Notwithstanding the increased availability of hospice-beds., the number of hospitalized pts who require hospice admitance is still high.

Methods: Clinical records of all in pts of the Homogeneous Medical Area and Cancer Surgery of our Institute were retrospectively analyzed from Jan 1st to Dec 31st 2018, in order to evaluate the number of home care and hospice-care activation requests. With regards to each hospice requests, the period of time from the submission to the territorial hub (COT) to the convocation of UVMD was evaluated. Our data were cross-linked with the data from COT: we evaluated the number of reported pts for which an UVMD took place, with availability of a report. We also assessed the number of pts transferred to Hospices, over the total number of requests.

Results: During 2018, a total of 517 territorial care services/hospice care activation requests were sent from the wards of our institute. 71 (13,7%) concerned Hospice-admittance. The UVMD report was available for only 48 pts out of 71 (67,6%). The average time was 3.6 days (range 0-36 days) from COT activation to the UVMD convocation. Concerning the remaining 23 pts (32,4%) for whom no UVMD report was available: for 1 f them the UVMD hadn't actually been summoned; 7 of these patients were transferred to hospices of their own districts (provinces outside Padova's jurisdiction); 1 patient was taken care of by the territorial Palliative Care service; 14 patients died hospitalized (before transfer). Considering all 71 hospice activation requests, 43 patients (60.5%) were transferred to a hospice, 27 (38%) died during hospitalization, one patient died at home. Average hospitalization length in our wards for the patients reported for hospice transfer was 18 days.

Conclusions: Compared to, in 2018 we registered a 12,4% increase in the total number of territorial services/hospice care activation requests sent from our wards (517 vs 460). Furthermore, we registered a parallel increase in the number of hospices' admittances requests: 71 requests out of 517 (13,7%) sent during year 2018 vs 52 requests out of 460 (11,3%) sent during year 2017. The territorial response to our requests was rapid: 3.6 days on average. The number of deaths during hospitalization is still high: 38% of the pts with bed-occupation rate of 8.6% /beds/year.

R65

NUTRITIONAL SCREENING ASSESSMENT AND IMPROVING QUALITY OF LIFE THROUGH THE EFFECTIVE COLLABORATION BETWEEN ONCOLOGIST AND NUTRITIONAL TEAM

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Background: Treatments for cancer have been expanded, for clinical and translational research. Chronicization in cancer can affects nutritional status, and cachexia syndrome. Undernutrition prevention and care, are useful to improve nutritional aspects and quality of life. We decrease undernutrition risck in patients using screening tools, such as MUST, MNA and PG-SGA. We stratified patients by cancer's type, therapy and treatment. Nutritional counseling has been implemented along with oral or parenteral supplementation or both.

Patients and Methods: 200 patients,60 male (age 32 - 78), and 140 female (age 34 – 82): 27% breast, 13% colon, 5% non small cell lung cancer, 55% other sides. Therefore we stratified patients by Karnofky P. S. and oncological treatment (chemotherapy, target-therapy or immune-checkpoint inhibitors). Patients were studied with full history, examination and laboratory tests. We did not include patients with severe clinical features or whose cancer is heavely affecting general status.

Results: 60% of patients with BMI $<$ 22 kg/m2, Karnofskiy P.S. $>$ 60%, MNA $<$ 11, MUST $>$ 1 and PG-SGA, and with anorexia (5% cases), diarrhea (7%), vomit (10%), nausea (7%), stomatitis (7%) we treated. Furthermore we treated symptoms associated with specific cancer treatment. In addition to antiemetic and antidiarrhoeic drugs, megestrole acetate to improve appetite and

body weight. For Nutritional advices we gave according to guide lines, Cachexia has been detected in 20% of patients, and patients who undergo target-therapies such as anti EGFR antibodies, anti HER-2 antibodies or immunotherapy didn't show gastroenteric symptoms. Personalized dietary counseling,nutritional plan including oral supplents and parentaral nutrition, improved weight and quality of life in 15% of cases.

Conclusions: MUST system shows undernutrition, MNA shows risk of developing undernutrition among the elderly at an early stage. PG-SGA is an assessment tool with screening components. In our ward professional partnership between oncologist and nutritional team has been critical and we hope that the optimal nutritional benefits may improve not only quality of life but also survival rates.

R66

VALIDATION OF VARIANT FILTERING PIPELINE USING A CE-IVD SOFTWARE FOR NGS ANALYSIS IN BREAST AND OVARIAN CANCER PREDISPOSITION

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Background: Next Generation Sequencing has made more comprehensive genetic testing increasingly accessible. In breast and ovarian cancer predisposition, sequencing more than just BRCA1/2 genes may offer the advantage of more clinically valuable information. However, NGS generates massive amounts of data that require multiple computationally intensive steps for appropriate data analysis. Processing raw NGS data to detect genomic alterations has significant impact on disease management and patient care. It is extremely important to develop, validate and monitor pipelines that may generate inaccurate results. Some companies provide CE-IVD software for alignment and variant calling, and the variant filtering workflow can be customized based on biomolecular characteristics. The filtering process becomes crucial when analyzing a multiple-gene panel, in which hundreds of variants may be found.

Materials and Methods: Our bioinformatic pipeline was validated analyzing NGS data from 58 patients applying different variant filtering methods. 34 patients were tested for breast and ovarian cancer predisposition using a target panel including BRCA1, BRCA2, ATM, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11 and TP53 genes. Alignment, variant calling, prioritization and interpretation were performed by a CE IVD software applying our customized bioinformatic pipeline. Pathogenic results were confirmed by Sanger Sequencing.

Results: In the pipeline validation phase, we set the molecular parameters to filter significant variants. We then evaluated the discarded variants to check the pipeline workflow, to be sure that only benign variants were discarded. Once the pipeline was set and tested, we analyzed the results from patients requiring BRCA extended panel. 30 patients showed no pathogenetic mutations, 15 of them showed variants of uncertain significance outside of BRCA genes. 4 patients presented pathogenetic BRCA2 mutations and 2 of them also had pathogenetic ATM mutation.

Conclusions: Validating a variant filtering pipeline is extremely important to ensure a good quality of NGS analysis. The combination of the BRCA extended panel, the CE-IVD Software and a validated variant filtering bioinformatic pipeline allows to detect pathogenic variants in genes associated with breast and ovarian cancer that would not have been detected with BRCA1/2 test only. This aspect could be an advantage for patient care and management.

R67

A MULTIDISCIPLINARY ONCOLOGICAL SETTING DEDICATED TO THE APPROACH TO CANCER PATHOLOGY IN THE ELDERLY PATIENTS: TWO YEARS OF EXPERIENCE IN S. PIETRO FATEBENEFRATELLI HOSPITAL

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Background: The elderly cancer patient is in a state of fragility whose lack of classification can invalidate the success of oncological therapies. In oncology being able to have a forecast of both acute and chronic toxicity is essential because the first is a potential cause of interruption of treatment with consequences on quality of life (QoL) and survival.

Materials and Methods: From June 2017 to January 2019 in a multidisciplinary geriatric setting (oncologist, geriatrician and radiotherapist), 57 patients (36 M; 21 F) were evaluated. 75.4% were affected by non-metastatic while 12% by metastatic disease. All were subjected to VGM on first visit. The evaluation of acute and chronic toxicity was performed using the CTCAE scale v 4.02. The QoL was evaluated at the end of the treatment and at each follow-up.

Results: Following the VGM, for 87.7%. more studies were requested 78.9% patients were assessed with a second (88.8%), or third (11.1%) subsequent visit. 5.26% were not started a treatment. 98.2% concluded the treatment. 89.4% required temporary suspension; 96.4% had acute toxicity GRADE=1; 23.5% acute toxicity GRADE=2; 0% acute toxicity GRADE=3. 1.75% patients required medical

management for chronic toxicity. No one needed hospitalization.
Conclusions: The VGM on first visit allowed a clinical risk classification essential for the confirmation of the indication to the oncology treatment but above is necessary for the prevention and management of the acute and chronic side effects of the oncology treatment.

R68

HEPATIC ARTERIAL OR CELIAC TRUNK INFUSION OF CHEMOTHERAPY AS RESCUE THERAPY IN PRETREATED WIDESPREAD LIVER METASTASES

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Background: Liver is one of the most common sites of metastases from solid tumors. If it is the mainly metastatic site with widespread lesions unsuitable for local treatment, patients are at risk to develop liver failure as the result of loss of a critical mass of hepatocytes due to replacement with malignant cells, and also from ischemia and hepatic venous obstruction produced by tumor emboli or compression. Hepatic arterial or celiac trunk infusion of chemotherapy (HATI) may enhance the activity on tumor cells of some drugs that have a very high vascular extraction ratio on first pass removal.
Patients and methods: This is an observational, single-center, retrospective analysis of HATI in pretreated patients with liver metastases from biliary tract (BTC), breast (BC), and pancreatic cancer (PC) in which liver is the mainly life-threatening site of disease. Combination chemotherapy for HATI was 5-fluorouracil, epirubicin, and mitomycin-C in BC metastases, or cisplatin and epirubicin in BTC and PC metastases. HATI was associated to systemic low dose/dense chemotherapy in BTC and PC. Celiac trunk infusion was only for PC.
Results: From 2000 to 2018, 72 patients were treated. The median age was 62 (range 34-71). Liver metastases were from BTC, BC, and PC in 26 (36%), 23 (32%), and 23 (32%) cases respectively. Median lines of previous treatments for metastatic disease were 1, 4, and 1 in BTC, BC, and PC respectively.
Overall, the HATI approach achieved a disease control rate (DCR) of 50% (with overall response rate, ORR, for BTC: 19%; BC: 26%; PC: 4%), and a clinical benefit rate (CBR) of 40% (BTC: 38.5%; BC: 47.8%; PC: 34.7%). An immediate disease progression occurred in 50% (BTC: 50%; BC: 43%; PC: 57%) of patients. The median progression-free survival (PFS) was 3.8, 6.4, 3.9 months in BTC, BC, and PC respectively.
Conclusions: In this series, patients with liver metastases from BTC, BC, and PC who failed standard previous treatments for metastatic disease, achieved with HATI a disease control in about one out of two cases, with a durable (equal or more than 6 months) benefit in 40% of treated patients (CBR).
The activity of HATI on liver metastases from different cancers encourage the prospective evaluation of this treatment inside clinical trials like rescue therapy to preserve liver from visceral crisis/organ dysfunction.

R69

WHO ARE THE PATIENTS REFERRED TO THE ONCOLOGICAL SERVICE FOR A SUSPECTED CANCER OR WITHOUT AN OBVIOUS PRIMARY? AN ANALYSIS OF CLINICAL FEATURES

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Background: The "Piemonte e Valle d'Aosta Oncological Network" established a model of care of all the patients entering a clinical pathway for cancer. Patients referred for a cancer diagnosis or a suspected cancer are admitted through a reception center ("Centro Accoglienza e Servizi" - CAS) that has the mission of caring for medical, nursing and administrative needs. While disease-specific pathways are quite predictable and patients' needs are well known, in case of suspected cancer or difficult diagnosis, clinical pathways are not well defined. We were interested in studying this population with the aim of improving the diagnostic pathway.
Patients and Methods: At their first consultation patients are required to fill a form that summarizes medical history, current drugs, actual symptoms and social issues. The form is used for completing the medical health record and for guiding all the services that need to be activated. Each completed form was then entered into a electronical database. Symptoms are through the validated Edmonton System A Scale (ESAS). We included all the patients encountered from October 2018 to April 2019 (6 months) with the aim of highlighting their characteristics and of shaping health care services.
Results: Data on 117 consecutive patients were available. Males/Females: 58/59; mean age 67,2 (18-65: 42%; 65-75: 24%; >75: 34%). 70% of the pts were married and 88% had a stable caregiver. A NRS > 3 pain score was present

in 37% of the patients and a > 5% weight loss in 32%. 47% had 2 or more concomitant clinical conditions; 64% were taking 1 to 5 drugs per day and 22% more than 5 (median number of drugs: 3,5). The reason for referral was: symptoms only 21%; symptoms + some imaging 58%; completed cancer diagnosis 21%. After exclusion of patients with confirmed cancer diagnosis the mean time for completing the diagnostic process was 19,6 days (range 1-70). In 4% the diagnosis of cancer was excluded and 7% had an unknown primary.

Conclusions: Patients referred for cancer diagnosis to the oncological services belong to a frail population. They are frequently old, have more than 2 associated clinical conditions and take multiple drugs.

R70

A PRELIMINARY EXPLORATORY STUDY OF PATIENTS REPORTED OUTCOMES (PROSEXPLOR) IN MESOTHELIOMA AND OTHER RARE TUMORS

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Background: "Patient Reported Outcomes" (PROs) are now-a-days considered an important mean to assess the results of a medical interventions from the patients' perspectives and can help clinicians to evaluate the toxicities of cancer treatments. We tested a simplified PROs tool in clinical practice to assess toxicities of systemic therapies within an exploratory study run at the rare cancer unit of our Hospital.

Patients and Methods: we prepared a simplified PROs questionnaire (PQs) including 16 items related to the main toxicities of chemotherapy and immunotherapy. PQs were administered to consecutive patients suffering from advanced mesothelioma, melanoma and sarcoma receiving systemic treatments to monitor adverse events. A baseline PQ was completed by patients during the oncological visit performed before starting treatment and then again at home in the interval time between two subsequent courses for a total of 4 PQs for each patient. Patients were asked to communicate the results of the PQs by phone, email or fax. A data manager checked the replies timely and alerted the general practitioner or the referral oncologist, accordingly to the severity of symptoms and signs, in case they were different from the replies recorded in the baseline PQ. At the end of the study patients were also asked to fill in a satisfaction survey.

Results: Between May and August 2018, 10 mesothelioma patients and 17 melanoma and sarcoma patients were enrolled. All pts completed the 4 PQs and the satisfaction survey. Pain and fatigue were the most frequent symptoms reported as different from the baseline. The oncologist was involved in the management of adverse events in 46% of mesothelioma and 57% of melanoma and sarcoma patients, home therapy variations were recommended by the oncologist in 18% of mesothelioma and 29% of melanoma and sarcoma patients, additional visits were performed in 27% of mesothelioma and 14% of melanoma and sarcoma pts. None of the patients acceded to emergency room or had unplanned accesses to the oncological department during the study. All patients judged the questionnaire simple, useful and satisfactory and recommended to persue its use in the routine practice.

Conclusions: PQ allowed us to timely recognize and promptly manage AEs after systemic therapy in this study including advanced advanced mesothelioma, melanoma and sarcoma patients reducing to zero unplanned accesses to the oncology department and emergency room.

R71

PERSONALITY FACTORS, FAMILY DYNAMICS AND RISK OF PSYCHOLOGICAL DISTRESS IN THE BRCA 1-2 ONCOLOGICAL GENETIC COUNSELING

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Background: The cancer genetic counseling (CGC, NSGC, Resta et al. 2006), defined in Italy from 2013 Oncological Genetic Counseling (CGO, AIOM, SIGU), identified genetic mutantions for hereditary neoplastic disease, but little is known on psychological factors and social issues that characterize patients who follow this path. A deeper understanding of these factors would allow an early identification of the patients most at risk of negative effects following (or previous to) the test and would prove useful for the implementation of genetic counseling protocols that minimize these effects and can support those individuals who need personalized psychological support (Lerman et al. 2008). In this context, the present observational study is inserted, with the aim of identifying the psychological profile, the traits that distinguish patients with breast and / or ovarian cancer with a history of individual and / or family illness that justify access to the genetic counseling service. SAMPLE: 45 SS (average age = 48.2; range 22-64; sex F) with diagnosis of mammary K (N = 35) and/or ovary (N = 10) with indication to perform CGO c / o AOU oncogenic clinic Polyclinic Vittorio Emanuele of Catania.

Material and method: Each patient underwent a semi-structured interview during the pre-test consultation and subsequently, in the form of a self-report, completed the following questionnaires: the SCL-90-R clinical scale (Derogatis, 1994); the BFQ personality inventory (Caprara

et al. 1997), the FACES IV (Olson, 2007) for the assessment of cohesion and flexibility in family functioning.
Results: The research is still ongoing. The preliminary results show a tendency to psychosocial vulnerability related to young age, to parental planning, to low family cohesion and high values of anxiety and depression.
Conclusions: From the comparison with the general population (T-Test sample for socio-demographic homogeneity), there emerges a greater tendency to develop a condition of distress that appears in line with the most recent psycho-physiological literature, which could interfere with the entire CGO pathway under different aspects: such as the process of understanding information; in communicating the results within the family context; in the choice between a clinical surveillance pathway vs a surgical prophylaxis. Personalized and integrated psychological paths could therefore represent a protective factor for the well-being of patients who access the CGO.

R72

NON-HODGKIN LYMPHOMA IN HIV-POSITIVE PATIENTS TREATED WITH ANTIRETROVIRAL THERAPY AND CHEMOTHERAPY: A SINGLE INSTITUTION RETROSPECTIVE STUDY

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Background: HIV+ pts have a 25-fold higher risk of developing NHL. Two independent prognostic factors influence the incidence and prognosis of HIV+ pts: highly active antiretroviral therapy (HAART) and the CD4+ lymphocyte count. The diagnosis of NHL can occur simultaneously (naïve-patients) or after the diagnosis of HIV infection and during HAART (experience-patients). The aim of the study is to evaluate the two cohorts of naïve- and exp-pts.
Methods: Single institution retrospective cohort study conducted in ASST FBF-Sacco Polo Luigi Sacco (Milan), from Jan 2007 to Jan 2017. Pts aged >=18 ys, diagnosis of HIV infection and NHL, on HAART, treated with first line R-CHOP-like chemotherapy regimens. Differences between naïve and experience-pts assessed using Chi-square, Fisher's exact or Wilcoxon Rank-sum test; OS, PFS and RR using the log-rank test or Cox regression model.
Results: 46 HIV+ pts: 11 naive-pts and 35 exp-pts. No difference in median age at diagnosis (49 vs 48 ys p=0.40), sex (male 72.7% vs 85.7 p=0.37), histological types: DLBCL (2 vs 24), BL (3 vs 3), PEL (1 vs 0), PCNSL (1 vs 0), PBL (2 vs 2) low-grade B-cell (2 vs 4) T-cell lymphoma (0 vs 2) (p=0.13).
Naïve-pts higher stage at diagnosis (stage IV 90.9% vs 41.2% p=0.05). No difference in frequency of B symptoms (40% vs 41%), bulky masses (18.2% vs 20.6%), ⩾ 2 extranodal sites (45.5% vs 40%), CNS involvement (44.4% vs 38.2%), AIDS-defining diseases (44.4% vs 28.6%) HCV/HBV infection (p>0.05). Naive-pts more likely in advanced aaIPI (intermediate-high risk: 90.0% vs 58.1% p=0.11), lower median CD4+ at NHL diagnosis (102 vs 222/mcl p=0.05).
During R-CHOP-like cht naïve-pts more frequently infectious toxicity (50% vs 10.7% p=0.02).
During a median (IQR 2-44) follow-up of 12 months no difference in RR (CR 60% vs 62.5%), median OS (67 mts vs 69.4 mts) and PFS (p>0.05).
Conclusions: The compromised immune status in naïve-pts may explain their worst NHL conditions at diagnosis (advanced stage and aaIPI) and toxicity during chemotherapy. The immediate start of HAART in combination with chemotherapy probably reduce the impact of these factors in term of response to treatment and survival (RR, PFS and OS). CD4+ count together with HAART remain the independent prognostic factor with the greatest influence on OS [exp vs naïve-pts: OS HR 0.83 (95% CI); OS/CD4+ HR 1.80 (95% CI)]. Naive-pts should be treated with standard chemotherapy regimens, without modification of dose or schedule.

R73

CHOOSING FOOD AFTER A TOTAL GASTRECTOMY FOR GASTRIC CANCER: A GROUNDED THEORY STUDY

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Background: Scarce is the qualitative research exploring what is patients' experience of food and eating following total gastrointestinal cancer surgery, despite its importance for patients' quality of life. This qualitative study aimed to conceptualize the process of food choice after surgery,from the perspective of patients,healthcare professionals and family members.
Material and Methods: We followed the Grounded Theory Method,according to Charmaz's constructivist perspective. We performed initial and theoretical sampling and conducted semi-structured, face-to-face interviews were. We interviewed 11 patients who underwent to total gastrectomy for gastric cancer at the Clinical Cancer Centre in Reggio Emilia from 2012 and 2016, 5 doctors (2 oncologists, 2 surgeons and 1 general practitioner) and 2 family members. Interviews were recorded, transcribed verbatim and qualitatively analyzed through initial, focused and theoretical coding.

Results: The data analysis identified the core category of the food-related process we named: "finding a new balance". The patients gain a state of balance well-being toward food choice and nutrition after traversing four main phases: 1) relying on the healthcare professionals' suggestions; 2) perceptual restructuring; 3) food reorganizing and 4) regulating sociality. Within these phases,patients constantly struggle with fear while the role of healthcare professionals is critical.
Conclusions: The results of this study provide new insights into the experiences of gastric cancer patients dealing with food choice, the role of family members and physicians and its impact on the decision-making process. The results are relevant for healthcare professionals: the importance of a nutritional evaluation to support food choices emerged, which was not routinary for our participants. Thank this study, involving a nutritionist has become a clinical practice in the context of a post-operative surgical protocol. Answering to health professionals' training needs about food intake after a gastrectomy appears not postponable. Besides, it would be advisable to include in the follow-up care pathway a constant reference to the nutritionist to reassure the patients and help them for better management of both food choices and weight monitoring. We also recommend the figure of the clinical nutritionist within the multidisciplinary groups dealing with gastric pathology, in such a way as to have early and lasting management, during the surgical path and subsequent follow-up.

R74

RETURN TO WORK: A NEW STEP OF INTEGRATED ONCOLOGICAL REHABILITATION

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Background: Cancer diagnoses in individuals who are still at the working age are becoming more common, with almost half of the adult cancer survivors being younger than 65 years (Short et al, 2005). An increasing number of survivors of cancer return-to work following treatment (Hoffman, 2005). The recovery time of work ability change a lot according to sociodemographic and disease-related factors, with breast cancer survivors showing in main studes the worst outcomes.
Objectives: To identify predictors of perceived reduced work ability following return to work among women treated for breast cancer.
Methods: One of our recent study/research about women in the workforce age who had undergone a breast cancer surgery at AUSL Bologna has revealed that, while 6% do not return to work after treatments, 42% have difficulties returning to work, due to post surgery treatment symptoms and psychological complaints (distress), and they develop a kind of disability that, in 12 month period tend to become chronic. The main risk factors for a difficult return to work are linked to age, psychological-social conditions, aggressive treatments, state of health before sickness. In order to reduce the symptoms burden of cancer survivors and the related risk of work disability, the Onconauti Association has drawn up a comprehensive program for women at risk, including both innovation education courses and programs to follow a better life style to be promoted within companies including self-assessment of work ability, counselling of the Occupational Phisician to guarantee proper and reasonable workplace accommodation and also provide a three month period of rehabilitative intervention in people at risk. Hence, it is important to identify those patients with a higher risk of sick leave from work and provide them with an appropriate rehabilitative support and counselling in returning to work (Musti M. et al., MDL [Internet]. 20Dec.2018 cited 19May2019];109(6):407-19.
Conclusions: We concluded that a multimodal and interdisciplinary approach in the workplace combined with an integrated rehabilitation intervention could play an important role in the returning to work process of more sensitive cancer survivors (Onconauti), that must be considered an essential outcome of the rehabilitation process, most of all in patients under 65. In addition to this patients should be informed, when choosing their medical treatments, of the working disability risks connected to them.

R75

THE CENTRAL ROLE OF PATIENT IN SAFETY EVALUATION OF CHEMOTHERAPY: A SPECIFIC PATIENT PATHWAY FOR THE EVALUATION OF ADVERSE EVENT WITH PRO-CTCAE AS PART OF ROUTINE CARE

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Background: Adverse events (AEs) reporting is critical to understand the effectiveness and toxicity profiles of cancer treatments and is vital as part of clinical trials and drug labeling to ensure patient safety. Therefore,methods for collecting this information must be accurate and reliable. The standard approach for documenting AEs in cancer trials involves investigator reporting using the NCI-CTCAE. Empirical evidence demonstrates that a comprehensive and accurate symptom assessment instrument should involve patients in AEs reporting. We plan to evaluate the implementation of PRO-CTCAE as part of oncological

patient routine care,considering a specific pathway for the patient referred to IRST.

Materials and Methods: In order to evaluate if the implementation of PRO-CTCAE in our Institute ensures a better reporting of AEs,we conducted a preliminary analysis. A total of 18 patients with gastrointestinal cancer referred to IRST completed the paper final version of Italian PRO-CTCAE. All these patients,as per Institute routine practice, performed both the routinary triage visit with the nurse and the oncologist visit (that reported AEs using the NCI-CTCAE).

Results: The preliminary analysis confirms that PRO-CTCAE allows to collect additional and more specific information,compared to oncologist and nurse reports. In particular oncologist and nurse evaluations are: always confirmed by patient self-reporting (all AEs reported during visits are confirmed by patient), sometimes underestimate the severity of AEs (for example fatigue and neurotoxicity), some symptoms are not always reported (for example dry mouth,difficulty in swallowing,decrease of appetite, insomnia and decrease of sexual interest). Usually the severity of symptoms not reported by oncologist and nurse are evaluated by the patient as "mild".

Conclusions: The use of PRO-CTCAE into routine clinical practice could be considered feasible.

In order to create a correct patient pathway we need to perform more evaluations,as frequency and better time of PRO-CTCAE assessment, personal to be involved in the presentation and the review of the PRO-CTCAE,type of questionnaire (general or the tumor specific version), method of administration (electronic or paper format).

The implementation of PRO-CTCAE in routine clinical practice could result in a better quality of patient condition,a better patient compliance to treatment,a better risk-benefit analysis and a more reliable and complete safety data collection.

R76

PSYCHOLOGICAL FACTORS THAT AFFECT ADJUSTMENT IN CANCER PATIENTS WITH CHRONIC PAIN: ACCEPTANCE OF CHRONIC PAIN (CPA) AND COMMITTED ACTION (CA)

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Background: Psychological flexibility is considered a basic quality of behaviour and a fundamental aspect of healthy functioning. Committed Action in patients with chronic pain is associated with lower levels of depression and with better social functioning, mental health, vitality and general health. Acceptance of chronic pain (CPA) and Committed Action (CA) are two processes of Psychological Flexibility according to the Contextualist Functionalism approach uses in the ACT (Acceptance and Commitment Therapy). Present study aims to investigate committed action and acceptance of pain in cancer patients with chronic pain compared with other types of diseases (headache, ibd and low back pain) to observe any intergroup differences.

Methods: 110 consecutive outpatients (80 female) with pain were recruited. Patients were assessed with following standardized self-report measures: CAQ-8 (Committed Action Questionnaire), CPAQ-8(Chronic Pain Acceptance Questionnaire), BPI (Brief Pain Inventory), AAQ-II (Acceptance and Action Questionnaire), HADS (Hospital Anxiety and Depression Scale), PHQ-9 (Patient Health Questionnaire), SF-36 (The Short Form Health Survey), PCS (Pain Catastrophizing Scale).

Results: Preliminary data show a significant correlation between CAQ-8 and CPAQ-8 ($r = .499$; $p < 0.001$) and a negative correlation between CAQ-8 and PHQ-9 ($r = -0.501$; $p < 0.001$), CPAQ-8 and PHQ-9 ($r = -0.491$; $p < 0.001$), CAQ-8 and HADS ($r = -0.536$; $p < 0.001$), and CPAQ and HADS ($r = -0.482$; $p < 0.001$).

Conclusions: Preliminary data showed a non-significant difference between the different groups of patients with chronic pain. The data showed that the committed action and the acceptance of pain have a significant effect in the process of adjustment to chronic pain and in the patient's psychological well-being.

R77

SPONTANEOUS ADRS OF NIVOLUMAB AND IPILIMUMAB

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Background: In Italy Nivolumab is reimbursed by the National Health Service (SSN) for various indications including the treatment of melanoma, non-small cell lung cancer (NSCL) and renal cell carcinoma (RCC). Ipilimumab is instead borne by the SSN for melanoma. The aim of this work is to provide a description of the spontaneous adverse reactions (ADRs) related to Nivolumab and Ipilimumab, collected in the real clinical practice of the IRCCS Pascale of Naples.

Material and Methods: The ADRs included in the Italian National Pharmacovigilance Network from November 2018 to May 2019 were extracted for each active substance considered. Subsequently they were processed based on the severity, the indication, the treatment line and by Meddra (SOC and PT).

Results: There were 39 ADRs for nivolumab and 13 ADRs for ipilimumab, respectively. For nivolumab the largest number of ADRs was found when used for melanoma

(79.9%) while the toxicity was lower in the NSCL both overall (5.1%) and because not serious ADRs occurred. Regarding not serious ADRs, when nivolumab is used in first-line melanoma, haematological toxicity (15.4%) and the musculoskeletal and connective tissue (15.4%) were greater than those found in renal carcinoma (2.6% and 5.1%). Finally, first-line use in melanoma resulted in increased skin and subcutaneous tissue disorders (12.8%) compared to when used as a second line in RCC (5.1%) and NSCL (5.1%). Also for ipilimumab the largest number of ADRs involved skin toxicity (itchy, rash and vitiligo).
Conclusions: Nivolumab and Ipilimumab, due to their use, showed greater skin toxicity, which instead was lower in the RCC and NSCL. Finally, an analysis of the cost of managing adverse events would be useful.

R78

BEST SUPPORTIVE CARE TO OPTIMIZE QUALITY OF LIFE IN EARLY MANAGEMENT OF CANCER PATIENTS

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Background: Cachexia pain and fatigue has sometimes forced to stop cancer treatments. Severe pain and symptoms of adverse trials were the worst elements for the patient's QOL. Early management with Supportive Care improves Bmi, controls Pain and reduces OIC. Current therapies also focus on palliation. Cancer cachexia is seen in several disease states, the loss of muscle mass has been shown to occur most rapidly in cancer patients. Multiple mechanisms are involved in the development of cachexia, including anorexia, physical activity,altered host metabolic response with abnormalities in protein, lipid, and carbohydrate metabolism and for seizure of Iron by the tumor.
Material and Methods: We treated 96 cancer's patients in ECOG 2-3 measuring significant parameters at first visit and in the following 4 months: cachexia, pain, nausea, vomiting, constipation, diarrhea, P.S.Karnofsky. Furthermore, we measured the quality of life through the EORTC QLQ questionnaire every month, elvaluating cachexia with the Nutrition Risk Screening. We used the model proposed by the group of Gustave Roussy for the management of adverse events by anticancer's treatments: early supportive care treats cachexia using oral nutrition supplements for dysphagic patients, or parenteral nutrition with sacs in the setting without chance of swallowing. We treated anorexia with megestrol acetate to improve appetite. Pain has been measured using Numeric Rates Scale and treated with analgesic opioids at a stable dose equivalent to 60 mg oral morphine to control background pain, and BTCP measured with algorithm to use oral/ transmucosal ROO, we also used pregabalin 50 mg BID in neuropathic pain, also improving quality of sleep. We used transdermal fentanyl dose equivalent to 60 mg oral morphine, and intranasal fentanyl 400 mcg on BTCP in dysphagic / odynophagic patients and in settings with severe mucositis. To improve evacuation we early treated OIC with Naloxegol 25 mg per die.
Results: The early management in supportive palliative care involves an improvement of symptoms in cancer patients and optimizes the quality of life measured with validated scales.
Conclusions: An early and correct management with supportive care is desirable in order to optimize the quality of life in cancer's patients, for a better both familiar and social life, and in order to be able to resume useful treatments for prolonging survival.

R79

DIGNITY PROJECT: MANAGING PATIENTS' EMOTIONS IN SIMULTANEOUS CARE

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Background: The management of the psychological and emotional aspects of patients who have to manage a serious health condition, becomes of fundamental importance in an Oncology Department. The patient's sense of dignity is influenced by the relationship that develops with the healthcare team. In recent years, greater attention has been devoted to safeguarding one of the most important dimensions of man, dignity, on which personal identity is based. Listening to the patient's psychological pain means supporting the person at the most important moment of his existence.
Methods: The concept behind the Dignity Project is that of the generativity described in E. Erikson's model of the stages of psychosocial development. Generativity refers to the interest in guiding the next generation with productive or creative companies, while its opposite, stagnation, indicates self-absorption and the lack of psychological growth. Taking advantage of generativity, therefore, it is proposed to the patient to fill in and leave a document for posterity in which important aspects or values of his life are treated. The document, as hypothesized by H. M. Chochinov in his studies, brings dignity back to a subjective dimension of the patient, through the analysis of factors linked to the disease, a catalog of indicators of conservation of dignity and the inventory of social dignity. Upon arrival of the patient in the Oncology Department, he is informed of the possibility of participating in the dignity project performed by a psychologist. The meetings take place in a setting where you feel free to talk about your most intimate aspects or the issues that have remained unresolved in your life and that you would now like to concretize or redefine.
Results: The patients who participated in the dignity project report an improvement in the general psycho-emotional

state, a higher compliance to the treatments and a better acceptance of the aspects related to the end of life.
Psychological benefits are observed in family members who received the generative document compared to those who did not receive it because the patient decided to destroy it.
Conclusions: The management of the psycho-emotional aspects in the patient's end-of-life phases has a double consequence: a) a substantial improvement in the patient's compliance and his psychological state; b) an improvement in relations with family members and important persons who, through the generative document, go beyond the patient's death.

S - Oncology Nursing

S01*

TAKE CARE OF WHO CARES QUALITATIVE AND QUANTITATIVE ANALYSIS OF THE "CAREGIVER BURDEN" IN THE ONCOLOGY WARD IN PIACENZA HOSPITAL

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Background: The CareGiver (CG) can be subjected to "caregiver burden". This term is used to describe the negative effects resulting from the experience of caring for a sick relative. Literature data provide several studies showing that the "CG burden" has direct consequences on the quality of life of the family member and has an impact on the patient's good treatment. The detection and measurement of the caregiver overload are fundamental activities in the care process. The aim of the study is to analyze the role of the CG and the emotional overload of a group of CG of cancer patients managed at the Oncology of Piacenza.
Methods: The research design used, is based on a qualitative and quantitative research approaches. First, a qualitative research was carried out, involving in a focus group the health professionals. Later, a semi-structured interview was conducted on a sample of 5 caregivers, to understand their emotional states and their experiences in relation to the role of caregiver. As regards quantitative research, a monocentric prospective observational study was performed. The research involved a sample of 150 caregivers. The CBI Questionnaire (CG Burden Inventory), validated for Italy and specific in the multidimensional overload detection, was submitted to all the caregivers. The data emerging from the various survey techniques were interpreted jointly and a training project was elaborated.
Results: The research shows that the prevalent profile of the caregiver is represented by women retired aged between 50 and 65. The most representative data is that 86% of subjects have a medium to high overload in all the dimensions investigated by the CBI. The analysis of the collected data, integrating the research methods, shows that the problems most frequently manifested by the caregivers are: the daily management of the basic needs, the need for timely and comprehensive information from the health services, the relationship with the sick person, the psychological discomfort.
Conclusions: The study shows some limits, such as the exclusive enrollment of CG of outpatients and the use of a multidimensional assessment tool but not specific to the cancer patient. However, research can be a starting point to create a specific tool for the detection of CG burden in oncology. The study, in accordance with literature data, identified the areas in which the CG presents the greatest difficulties and the skills for which a dedicated training must be designed.

S02*

UNMET NEEDS IN PATIENTS UNDERGOING CANCER TREATMENTS

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Background: Cancer patients experience problems in different areas of life during their disease and supportive care represents an umbrella of services designed to deal with such issues. Unmet needs refer to needs that patients feel are dealt with inadequately or not at al. Despite previous studies correlating health status and unmet needs for supportive care, it is still not clear how the latter relate to symptom intensity. Early assessment of patient perceived needs is crucial for planning and prioritizing supportive care services to tailor need-based interventions and improve patient outcomes. Our aim was to measure unmet needs and to assess their relation to symptom intensity.
Methods: A cross-sectional study of cancer patients undergoing active treatments in ambulatory and day hospital settings was conducted in an Italian cancer center (IRST IRCCS). The validated versions of the Italian Supportive Care Needs Survey Short Form 34 (SCNS-SF34It) and Edmonton Symptom Assessment Scale (ESAS) were used to evaluate supportive care needs and symptom intensity, respectively.

Results: 232 adult patients with different cancers were included in the study. The highest prevalence of supportive care needs specified by patients were in psychological (28%), information (19%) and physical (18%) domains. Only 8% of patients reported uncontrolled symptoms measured by ESAS compared to 18% of those reporting a moderate-to-high level of supportive needs in the physical domain of the SCNS. Although 28% of patients reported the need for psychological support, no patients reported uncontrolled psychological symptoms measured with the ESAS scale. However, those who described physical symptom intensity >0 with ESAS reported higher supportive care needs in the physical domain than the other patients (odds ratio [OR] 4.20 (1.21-14.53), p<0.023 for pain and OR 1.88 (1.06-3.33), p<0.032 for fatigue).
Conclusions: Measuring unmet needs in clinical practice would help to complete clinical evaluations with patients' perception of problems so that supportive care can be provided on the basis of the importance that patients ascribe to their problems. Unmet needs in our study were highest in the psychological, information and physical domains, highlighting the importance of improving supportive care services in these specific areas.

S03*

QUALITY OF INFORMED CONSENT IN CANCER CLINICAL TRIALS SUBJECTS: A LINGUISTIC AND PSYCHOMETRIC VALIDATION STUDY

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Background: The informed consent process is vital in clinical trials as an ethical and legal prerequisite for subjects' participation. The Quality of Informed Consent (QuIC) questionnaire is a valid tool developed to assess the objective (subjects' actual comprehension) and subjective (subjects' perceived comprehension) understanding of patients enrolled in clinical trials. This study was conducted to validate the psychometric properties of the Italian version of the questionnaire (QuIC-I).
Methods: An observational cross-sectional multicenter study was conducted with Italian cancer patients. The original QuIC questionnaire consists of two sections: part A (20 items) assessing objective understanding and part B (14 items) assessing subjective understanding of cancer clinical trials' participants. Demographic and clinical data were collected. The original questionnaire was translated and cross-cultural validated according to the EORTC guideline including forward and backward translation, and comparison of the two versions. For content validity, a panel of experts reviewed the QuIC-I before face validity. Ten cancer patients reviewed the clarity of the items (face validity). Internal consistency and reliability test-retest (two weeks apart) were determined by the Cronbach α and the Intraclass Correlation Coefficient (ICC), respectively. Exploratory Factor Analysis (EFA) was used to explore the construct validity. The α error was set at 5%. The study was approved by the Ethics Committees of the Ligurian Region and participants who accepted to participate signed the informed consent form.
Results: We included 292 cancer patients; most of them were male, n=155 (53,1%), mean age was 60,21 years (±12,54). The Italian version of the QuIC-I included 21 items for part A and 16 items for part B. The content validity index was 0.84 (part A), and 0,95 (part B) and all the items were described as clear requiring minor revisions. The internal consistency showed a Cronbach α of 0,661 (part A) and 0,842 (part B). The test-retest showed an ICC of 0,535 (±0,28) IC95% 0,452-0,617 for part A and 0,64 (±0,12) IC95% 0,604-0,675 for part B. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0,638 and Bartlett's test was significant; the principal component analysis in the EFA revealed an 8-factor structure.
Conclusions: Our findings indicate that the QuIC-I is a valid and reliable questionnaire for assessing quality of informed consent in cancer clinical trials subjects.

S04

FACTORS INFLUENCING THE LEVEL OF FATIGUE IN PATIENTS UNDERGOING HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN PROTECTIVE ISOLATION

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Background: Patients undergoing haematopoietic stem cell transplantation (HSCT) receive myelosuppressive chemotherapy and become pancytopenic. Post-transplant fatigue is one of the most common symptoms patients

Table 1. Regression model predicting post-transplant fatigue (n = 178).

	Fatigue		
	β	95% CI	P
Sex (female)	.095	(−.040;.227)	.169
Age	−.147	(−.305;.014)	.073
Education level	.138	(.003;.273)	.045
N children	.131	(−.017;.274)	.082
Comorbidity	.128	(−.012;.263)	.074
Pain level	.439	(.295;.583)	<.001
R^2	0.32		
F	11.64		
P	<.001		

experience while they are hospitalised in protective isolation. The aim of this study was to identify which factors can influence the level of post-transplant fatigue in adult patients with haematological malignancies undergoing HSCT.

Methods: This is a secondary analysis of a prospective study conducted in 10 haematology centres of the Italian Group of stem cell transplant (GITMO). The level of fatigue was measured between day +7 and +9 post-transplant using a single item ranging from 0 (no fatigue) to 10 (worst possible fatigue). Multiple linear regression analysis was employed to predict fatigue level.

Results: Study participants were 178 patients receiving autologous (51%) or allogeneic (49%) HSCT in protective isolation. Their mean age was 50.9 (SD = 13.3; range = 19-71) and 63% were male. The average level of post-transplant fatigue was 5.9 (SD = 2.5), with 48% reporting severe fatigue (⩾7). The regression model explained 32% of the total variance (p<.001) (Table 1). Education and pain level were independently associated with post-transplant fatigue. In turn, higher fatigue significantly predicted longer hospital stay, over and beyond day of engraftment and type of HSCT.

Conclusions: A large proportion of patients suffer from severe fatigue following HSCT. In particular, patients with higher education and those reporting pain are at risk for experiencing more severe post-transplant fatigue. Oncology nurses could mitigate fatigue by reducing pain, for example implementing strategies to prevent oral mucositis. This will result in increased patients' quality of life and shorter hospital stay.

S05

NEW STANDARD MANAGEMENT OF PORT CATHETERS: ANALYSIS OF ECONOMIC AND ORGANIZATIONAL IMPACTS

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Background: In cancer patients stable venous access is often necessary to allow adequate administration of chemotherapy. Currently, fully implantable Port-type systems must be periodically washed during follow up. A retrospective observational study conducted at the SC Oncology of AOU – Novara, involved 381 adult patients with cancer diagnosis and to whom a Port device with Groshong valved catheter was implanted in the period from January 2007 to August 2014. This study showed that dressing and washing with saline solution the PORT type catheter every three months, compared to the monthly dressing and washing (current standard), does not increase the risk of occlusion and catheter related infections.

Material and methods: In light of the equivalence results between the two catheter management methods a cost analysis was performed comparing the two scenarios (1 month vs 3 months Port management). Through this comparison we evaluated the economic and organizational impacts of replacing the current Port catheter washing standard with the new procedure carried out every three months. This study analyzed the prices of the materials used for medication and washing, the cost of the nurse employed and evaluated the variations in costs for the management of a single patient during a year.

Results: The cost of a single wash is € 6.87.

Total cost per individual patient in the two scenarios.

	Scenario 1	Scenario 2	Saving
Single wash cost	€ 6,87	€ 6,87	
Number of washings per year	12	4	
TOTAL YEAR COST	€ 82,44	€ 27,48	€ 54,96

Nurse time.

	Scenario 1	Scenario 2	Saving
Time nurse for washing	8 min	8 min	
Annual nurse time per patient	96 min	32 min	64 min
Time nurse for observed patients	36.576 min = 609,6 h	12.192 min = 203,2 h	24.384 min = 406,4 h

Conclusions: Benefits of introducing the new quarterly management standard for PORT catheters: the reduction of washing numbers allows to save money in terms of direct cost and time of the nursing staff dedicatedto this activity; a longer time interval between one dressing and another significantly reduces the time and resources dedicated by patients and their family members in terms of hours taken from other activities and cost of transport and cost of

assistance; the patients' reduced commitment in terms of time allows for greater compliance with the PORT catheter management methods; the lower number of accesses to the device guarantees a significant reduction in the risk of infections.

S06

NURSING DIAGNOSES: IMPORTANCE, RELEVANCE AND MOTIVATION. AN OBSERVATIONAL STUDY AT "EMATOLOGIA E CTMO DELL'AZIENDA ASL DI PIACENZA"

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Background: Nursing diagnoses is a clinical judgment concerning answers to healthy problems in place or potential regarding the patients, family or community. Nursing diagnoses is the basis on which to choose adequate nursing interventions to get results of which the nurse is responsible. The relevance of diagnostic reasoning within care planning, justifies its presence inside a specific place on computerized documentations. This study aim is to involve the nursing staff of UO Ematologia e CTMO dell'Azienda ASL di Piacenza in choosing the type of nursing diagnoses to put in the computerized documentations. They will be use them in the future during nursing practise.
Material and Methods: The study is composed of two different step. In the first step the Head Nurse gave an interview to some nurses working in four different Unit inside "Ospedale G. da Saliceto" selelcted by specific criteria. They were asked to respond if it was useful to have nursing diagnoses inside computerized documentations. It has also been verified if nurses were using this specific documentation in daily practice. The second step was done at UO Ematologia e CTMO involving fourteen nurses working at Inpatient Unit and four nurses working at the Outpatient Unit. The Head Nurse gave a questionnaire in which there were 64 possible nursing diagnoses, relevant in oncohematological patient, based on a dutch study (2011). The nursing diagnoses have been grouped into eleven different functional models following the directions of Gordon. The nurses were asked to respond based on their hematological expertise, about the relevance of those nursing diagnoses.
Results and Conclusions: Through statistical analysis it emerged that in that four Unit of "Ospedale G. da Saliceto" five diagnoses obtained a high consensus (100%), seventeen obtained a quite high consensudu (75-95%), five a not so high consensus ($\leqslant$50%). By the way only 13 of the 35 nursing diagnoses were filled in the clinical charts in $\leqslant$30% of cases.

S07

EVALUATING THE ROLE OF THE CLINICAL NURSE SPECIALIST (CNS) A YEAR AFTER ITS IMPLEMENTATION IN A CANCER RESEARCH CENTER IN ITALY

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Background: In 2018 the role of clinical nurse specialist (CNS) was implemented in our cancer research center in northern Italy, specifically in an ambulatory setting for 6 of the most representative tumors treated. The CNSs received specific training before taking on their new role. Although measuring the impact of CNSs is vital to support decision-making on the development and implementation of advanced nursing roles, the identification of indicators reflecting their impact on clinical practice remains one of the most challenging nursing research issues, mainly because of the complexity of the contributors who determine patient and organizational outcomes.
Methods: The study evaluated indicators measuring the implementation process and the impact of the CNS role one year after its introduction. Indicators for the former were: CNS interface mapping in disease pathways, participation rate of CNS in multidisciplinary team (MDT) meetings, and number of training hours/CNS on specific cancers. Indicators for the latter were: patient satisfaction with CNS (survey), compliance with priority criteria for waiting times for the first visit, total number of documented CNS-patient communications (i.e. first nursing interviews with new patients, phone interviews); and number of improvement projects to which CNSs contributed.
Results: One year after CNS introduction, pathway mapping was 100%; MDT meeting participation 95%; training hours 40.5/CNS vs. defined standard of 30 hours. 83.2% of interviewed patients were very satisfied with CNSs. An average of 27 patient interviews and 126 phone interviews per month were performed. Improvements to the instruments used for patient agenda management were made, positively impacting compliance (+13%) with waiting time criteria.
Conclusions: CNSs were successfully introduced into all identified disease pathways and played an active role within the MDTs. Although there are data in literature indicating optimal CNS staffing for specific cancers, there are no previous Italian experiences that can be used for comparative purposes. We need to better clarify how disease characteristics and the number of new patients influence CNS staffing in our specific organizational care context, which obviously differs from that of other countries. Measuring CNS activities and outcomes would also help to optimize CNS core activities.

S08

ROLE OF NURSE-DISCHARGE MANAGER IN AN ONCOLOGY WARD: A SINGLE CENTRE EXPERIENCE

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Background: Progressive hospital overcrowding and gradual reduction of beds profoundly affects the whole health system, reducing productivity and efficiency. Aging population and increasing of chronic-degenerative diseases, susceptible to acute exacerbations, make frail patients (pts) as frequent users of the emergency room. There is a general agreement that the current disease-oriented and episodic model of care does not adequately cope with the complex needs of frail pts. Hospital discharge planning requires individualistic, holistic assessment of a patient's needs so that links with primary care and community resources, and reduces the risk of long term hospitalization or re-admission. Cancer pts represent a good model for re-engenirig this process although no data are reported in this setting.
Material and Methods: We planned, in the context of OMFT program, a pilot project of a nurse-directed discharge planning starting at the moment of the ward admission. As no scales has been developed for cancer pts, we adopted the BRASS modified scale, administered to all pts within the first day. Communication between the various team members was scheduled daily. Interaction with pts and care-givers was supported by a psychologist and their possible education was performed by nurses during recovery. End point included: median hospital stay, number of 30-days re-admission and effectiveness of BRASS scale to orient discharge program pts.
Results: 358 pts (median age 65.3 yrs) prospective analyzed in a 6 month period was compared with an historical series. BRASS scale was administered to all pts with a median time consuming of 3 min. Median all stay decreased from 13.1 to 9.7 days. Readmission at 30-days presented a 50% reduction. BRASS index was straightforward and swift and can prove a valuable tool in directing nurses' attention to those pts at a high risk of prolonged hospitalization and oriented the discharge program. Moreover BRASS sale performed as well as Karnowsky index. Interesting data emerged from the analysis of the single items of the BRASS index.
Conclusions: Our data show as nurse-led early discharge planning program represents a new effective strategy. Early assessment, early planning and co-ordination the team involved in the patient's care are essential and impact on several aspects of care for cancer inpatients including reducing readmission and length of stay. These finding may be taken into account in other units and in future health policy development.

S09

CARE MANAGER DEDICATED TO THORACIC MALIGNANCIES

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Background: With the growth of malignancies prevalence and the advent of payment reform, care managers are expected to serve an increasing role in managing high risk patients. They are responsible to initiate, facilitate, and monitor specific patient activities, interventions and chronic care protocols that will become the patient's care plan. Moreover, they assist the movement of their patients to or from different care settings and also improve the adherence to the home therapy by a dedicated telephone number. Despite the role of care manager is expanding, nowadays only few evidences have been reported about care manager dedicated to a specific type of tumor. As regard, we reported the experience of our Medical Thoracic Oncology Unit.
Methods: From 1 st February 2018, a care manager dedicated to chest neoplasms began its activity in the thoracic medical oncology unit, IRCCS "Giovanni Paolo II" Institute of Tumors of Bari. The major activities of this nurse are: 1) the initial assessment of the patient, starting all basic diagnostic procedures (i.e. chest radiography, electrocardiogram, blood tests, and oxygen saturation measurement) and identifying patients who need to a pulmonologist evaluation; 2) improve the diagnostic performance through a better timing of radiological procedures and specialist evaluations, resulting in an earlier cancer staging; 3) Follow the state of histological and molecular examinations related to the biopsy procedures occurred during hospitalization, for a prompt communication to the patient.
Results: Comparing the first year of the care manager activity with the previous year, the duration of hospitalizations is significantly reduced. In particular, a low number of hospitalizations comprising 8 to 12 days (28 vs 33), 12 to 20 days (19 vs 26) and hospitalizations of more than 20 days (5 vs 9) have been reported. On the other hand, the analysis of hospitalization time demonstrated an increase of the short hospitalizations comprising 4 to 7 days (35 vs 23) and 1 to 3 days (13 vs 9).
Conclusions: The introduction of a care manager resulted in a significantly reduction of the duration of hospitalization, improving the quality of life of the patients and reducing the costs of care.

Table

Duration of hospitalization.	More than 20 days	From 12 to 20 days	From 8 to 12 days	From 4 to 7 days	From 1 to 3 days
Hospital admissions from 1 st February 2018 to 31 st January 2019.	5	19	28	35	13
Hospital admissions from 1 st February 2017 to 31 st January 2018.	9	26	33	23	9

S10

EVALUATION OF THERAPEUTIC ADHERENCE AND ASSOCIATED SYMPTOMATOLOGY, IN CANCER PATIENTS TREATED WITH ORAL CHEMOTHERAPY AT HOME: SURVEY CONDUCTED AT L'U.O. ONCOLOGIA DAY HOSPITA OF THE AUSL OF PIACENZA

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Background: O.M.S. defines therapeutic adherence as the extent to which a person's behavior - in taking drugs, following a diet and / or implementing lifestyle changes - corresponds to the recommendations of healthcare professionals shared by the patient. The value that describes therapeutic adherence is expressed as a percentage of the number of people who scrupulously follow all medical prescriptions compared to the total number of people who should follow those same therapies.
Methods: In order to evaluate the adherence to prescribed oral chemotherapy and the symptoms associated with the intake in cancer patients, we examined the recruitment diaries, issued by the Company Information System in Direct Distribution Pharmacy, at the time of dispensing the prescribed oral chemotherapy. In the diary, the patient must indicate in the spaces provided, date, time, possible appearance of side effects on the days of employment and return it to the U.O. Oncology dh of the Ausl of Piacenza. The sample consists of 105 patients who were prescribed and delivered the oral chemotherapy and recruitment diary, in the period between March 2018 and August 2018.
Results: Data analysis shows that as many as 97 patients equal to 92.4% were adherent results, while only 8, equal to 7.6%, were non-members. It should also be noted that of the 105 patients examined, during treatment, 83 (79%) experienced one or more symptoms, 22 (21%) did not show any. The most commonly expressed symptoms are gastrointestinal disorders, itching, tingling, rash, alopecia, dysgeusia. However we are not able to determine the intensity due to the lack of this data in the recruitment diary.
Conclusions: The study showed the good adherence of the examined sample, however, could be improved by implementing targeted therapeutic education programs, stimulating the active participation not only of the patient, but also of its support network. To do this it might be useful to introduce information tools such as medication cards and symptom assessment scales, such as the Edmonton Symptom Assessment System (ESAS) or other specifications, as well as the introduction of computerized surveillance systems. With the aim of improving patient empowerment, thus promoting therapeutic adherence, symptom assessment and intensity over the treatment period.

S11

REP-ARTE: BRINGING ART IN ONCOLOGY

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Background: This project aims at investigating the impact that visual art might have on cancer patients' well-being. This proposal is based on a series of studies highlighting the importance of the physical features of an hospital: visual art seems to affect patients on a biological, social and emotional level (Alfonsi et al., 2014; Nielsen et al., 2017). A possible reason accounting for this outcome is that artworks help people to socialize, trigger personal memories, distract from pain and anxiety and remind them of their identity. To this purpose, the Oncology Department of Giovanni Bosco Hospital asked the students of the Primo Liceo Artistico (Turin) to make some paintings to decorate some free spaces in the Oncology Unit. Another goal of the project is to raise the students' awareness on Oncology diseases and their psychological and social implications.
Methods: The students were taught about the mission of the project by some professionals of the Oncology Department. The students realised different sketches; 27 patients answered to a semi-structured interview while watching at 8 selected paintings. 30 images representing colourful abstract patterns and subjective interpretations of natural elements were commissioned to the students and posted on the walls of the Day Hospital.

Results: During the semi-structured interview, two main categories emerged: the idea of a "reassuring" nature and, on the other hand, a sense of "disturbing" nature. For 5 patients the paintings triggered memories related to their private life. Furthermore, patients often started a conversation with their caregivers to confront each other about the sketches. Furthermore, the students showed to be sensitive about the discussed themes.
Conclusions: The results suggest that physical environment might impact on patients' well-being in terms of socialization, reference to their memories (and therefore their identity) and distraction from their condition. The ambivalence of the emotions aroused by the paintings does not diminish their potential benefit: in other studies visual stimuli managed to modulate the pain of the patients (de Tommaso et al., 2013) and their coping resources (Nielsen et al., 2017; Gelo et al., 2014) regardless of the positive valence of the stimulus. In addition, the intervention successfully managed to involve the students in a wide reflection about the impact that art might have on psychological distress of cancer patients.

S12

PATIENT REPORTED OUTCOMES AND LOW DOSE TAMOXIFEN (BABYTAM) IN BREAST INTRAEPITHELIAL NEOPLASIA. PATIENT REALITY, CLINICIAN PERCEPTION AND ROLE OF THE RESEARCH NURSE

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Background: We recently conducted a de-escalation phase III trial of low dose tamoxifen ("babytam") in women with breast in situ disease (DeCensi et al. JCO 37; 2019). A total of 500 women treated with tamoxifen 5 mg/day for 3 years had a 52% reduction of ipsilateral or contralateral recurrence vs placebo. Since menopausal symptoms, including hot flashes (HF), joint pain, weight gain, sexual dysfunction, anxiety and depression are a major reason for treatment withdrawal during hormone therapy, we compared patient reported outcome measures (PROMs) with the physician reported outcome measures to detect subtle changes in menopausal symptoms.
Methods: Menopausal symptoms associated with the use of babytam were detected using a self-reported questionnaire described by Stanton et al (JNCI 2005) before each visit. Visits were performed at baseline and every 6 months up to 36 months. The answers obtained from the Stanton questionnaire were categorized by the BCPT Symptom Scale into 8 items, including HF, nausea, bladder control, vaginal problems, musculoskeletal pain, cognitive problems, weight change and arm problems. Moreover, HF were detected through a self-report 7-day diary (Sloan et al JCO 2001) for frequency and intensity over 24 hours.
The events reported by the patients using PROM and the events reported by the clinicians with the CTCAEs were compared. HF frequency was the main outcome measure.
Results: The comparison between PROs and CTCAEs showed that there were 246 vs 12 HF events, 238 vs 8 and 210 vs 4 at 12, 24 and 36 months, respectively. The majority were grade 1. A similar difference was noted for the other PROMs. There was no difference in PROMs between babytam and placebo except for the frequency of HF, which consisted in an increase in the mean number of daily HF from 1.5 (IC 95% 1.1-1.8) on placebo to 2.1 on babytam (IC 95% 1.7-2.5, $p = 0.05$). Interestingly, the presence of HF was a favorable prognostic factor for recurrence and a predictive factor for response to babytam (p-trend = 0.002, HR = 0.11, IC 95%, 0.02-0.84 for women on babytam and HF vs no babytam and no HF).
Conclusions: The use of PROMs is effective for identifying symptoms even of minor entity. Apparently, clinicians report only clinically relevant events and tend to underestimate minor events. The presence of HF represents a favorable prognostic and predictive factor. This translates into a strong tool that can be used by the Research Nurse to reassure patients and increase adherence.

S13

FUNCTIONAL STATUS IN PATIENT RECEIVING ORAL THERAPY AT ONCOLOGY NURSE CLINIC: A PROSPECTIVE STUDY IN AZIENDA OSPEDALI RIUNITI MARCHE NORD (AORMN)

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Background: Maintenance of functional status and ability to complete activities of daily living (ADLs) are a key issue in cancer patients. Katz ADLs Index is used to assess independence in self-care activities. Oral oncology drugs are perceived to offer better quality of life compared with intravenous. Nurse-led clinics, embedded in clinical pathways, can improve taking on the patient, monitoring, continuity and quality of care.
Material and Methods: A prospective, descriptive study conducted at oncology nurse clinic in AORMN aims to describe the evolution of functional status (FS) during oral oncology therapy with reference to type of medication. All patients underwent a nursing basic assessment including

ADLs scale with a score for each item (bathing, dressing, eating, toileting, continence and transferring) ranging from 1 (able to perform the activity) to 0 (unable). FS of patients was followed by repeating score during the treatment.

Results: From June 2017 to March 2019, data of 57 patients receiving therapy with Temodal® (57.9%), Xtandi® (19.3%), Zytiga® (10.5%), Sutent® (7%), Giotrif® (3.5%), Xalkori® (1.8%) were available and Katz Index score were collected; 7 patients (12%) with only basic ADLs available were excluded. Outpatient nurse clinic visits, according protocols, was 340 (Mean 6.4, range 2.5 to 10.5); ADLs were evaluated at the start and every 2/3 months. Autonomy increased for all drugs in the activity "bathing" (from + 9,1 to +25 pp *[percentage point], p*>.05 *["N-1" χ2 test]*) except for Zytiga® (-14.2% pp, *p*>.05); for Temodal® (+19.6% pp, *p*=.01) and Xtandi® (+9.1 pp, *p*=.007) data were statistically significant; in"dressing" increased for all, (from +17,6 to +18,1 pp) except for Zytiga® (-14.2 pp, *p*>.05), significant only for Temodal® (+17.6 pp, *p*=.03) and Xtandi® (+18.1 pp, *p*=.0002). Also in "toileting" increased for all (from +9,1 to +18,4 pp), significant for Temodal® (+18,4 pp, *p*=.02) and Xtandi® (+9.1 pp, *p*=.007). In "transferring", autonomy increased for all (+17.6 pp) except for Zytiga® (-14.9 pp, *p*>.05); result significant only for Temodal® (+17.6 pp, *p*=.03); "continence" increased for all (from +2.2 to +2.8 pp) except for Xtandi® (-15.8 pp, *p*>.05); "eating" increased for all (+10.9 pp), statistically significant only for Temodal®(+10,9 pp, *p*=.002).

Conclusions: During oral oncology therapy patients maintain or considerably improve the level of autonomy in most basic activities, while improving the quality of life.

S14

INNOVATIVE APPROACH FOR THE PREVENTION OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY (CIPN) IN CANCER PATIENTS. A PILOT STUDY WITH THE HILOTHERM® DEVICE. THE POLIAMBULANZA EXPERIENCE

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Background: Chemotherapy Induced peripheral neuropathy (CIPN) is an adverse event of many commonly used cancer treatments, in particular taxanes, with no effective prevention or treatment available and with a highly negative impact on patients' Quality of Life. We hypothesize that the constant application of cooling with hands and feet cuffs might reduce the amount of drug in the capillaries of extremities, in order to prevent or mitigate CIPN.

Patients and methods: A prospective trial is ongoing to investigate the neuroprotective effect of regional cooling of hands and feet in cancer patients receiving regimens contain taxanes. Patients with breast and gynecologic cancer who received chemotherapy including weekly taxol and taxol/carboplatin, for any indication, at the therapeutic schedule dosage, are included in this study. Hilotherapy, a regional hands and feet cooling, works with the Hilotherm® Chemo care device, which forms a closed-loop system with cuffs and piping, through which the coolant flows at a temperature of 10°C. The cooling start from 30 minutes before to 60 minutes after chemotherapy delivery. The CIPN is monitored using a symptom questionnaire (EORTC QLQ-C30; edition 3.0) before the start of chemotherapy and at the end of the treatment. The tolerability and side effects are scored by using Common Terminology Criteria for Adverse Events (CTCAE; table 4.03 2017) at each chemotherapy infusion and at three months after the end of treatment.

Results: Up to now, we have enrolled twenty-eight patients. Preliminary data show that continuous cooling is well tolerated. From the nineteen patients treated with taxol weekly three stopped Hilotherapy: one for paronychia of fingernails grade 2 and CIPN grade 1, one due to excessive coldness and one for toxicity related to taxol administration. Among the eight patients treated with the combination of taxol/carboplatin, two stopped Hilotherapy: one for toxicity to taxol and one for disease progression. Twenty-seven patients had no grade ⩾ 2 CIPN, five of them actually have completed the treatment. Patients recruitment is still ongoing.

Conclusions: Regional cooling of hands and feet might have good effectiveness and tolerability, and seems able to prevent or reduce symptoms of CIPN. Other German hospitals are experimenting this device with encouraging results. Recently, we have open the accrual to patients with pancreatic cancer treated with nab-paclitaxel/gemcitabine. Updated results will be presented at the meeting.

S15

SAFETY AND EFFECTIVENESS OF INCREASING TIVADS FLUSHING INTERVAL

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Background: The producers indicate in 4 weeks the TIVADs (Totally Implantable Vascular Access Devices) flushing interval in non-use condition. Several studies have shown that monthly access may not be necessary to maintain proper and safe operation of the device. Furthermore increasing the flushing interval is particularly appreciated by patients and reduces costs for families and for the health system. In the last few years several studies

have been carried out about safety and effectiveness of this procedure. The aim of this study is verify through a literature review safety and effectiveness of increasing over 4 weeks tivads flushing interval.
Matherials and Methods: It was conduced a literature review on databases Medline (Pubmed), Embase and Cinahl.
Results: Literature review included seven retrospective studies and a perspective ones. 1841 patients with TIVADs have been included. Studies were published between 2005 and 2018. Each studies shows that increasing over 4 weeks TIVADs flushing interval is not associated with increasing of CRBSI (Catheter Related BloodStream Infection) and device occlusion.
Conclusions: Increasing TIVADs flushing interval in non-use condition seems to be safe and effective. Patients appreciate it because this procedure increase their quality of life and reduce costs for families and health systems. Seven out of eight analyzed studies were retrospective and uncontrolled. Further studies are needed.

S16

FROM EFFICACY TESTS TO CLINICAL PRACTICE: NANDA-I NURSING DIAGNOSIS: "SPIRITUAL SUFFERING" (00066)

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Background: Holistic Nursing is centered in all the person's dimensions including the emotional, perceptive and spiritual ambit. It can be applied also in breast cancer diagnosis in the three main moments of the journey:at the time of diagnosis; during radio and chemotherapy treatment; post-treatment.
Materials and methods: The purpose of the study was to identify the care needs present in women diagnosed with breast cancer. It is a descriptive phenomenological study. The data collection was carried out using the Gordon Model, bringing out the unexpressed needs. A proactive sampling was carried out where 10 women diagnosed with breast cancer, where chosen. The study was conducted in the clinics of the Complex Oncology Structure of the Maggiore Hospital of Trieste in July and August 2017.
Results: Only 9 Diagnoses were found to be present in all 10 case studies; two Diagnoses in particular stood out: Spiritual Suffering (NANDA-I, 00066) and Risk of Spiritual Suffering (NANDA-I, 00067). The NOCs emerged were: Hope (1201) and Spiritual Health (2001). The NICs emerged were: Spiritual Support (5420) and Emotional Support (5270). For the risk diagnosis NOC and NIC were comparable to the first diagnosis.
Conclusions: The study highlighted how the use of the Gordon Model, allows to identify the needs also in the psychological, emotional, social and spiritual needs, usually not identified. Furthermore, standardized nursing terminologies are fundamental communication tools for nurses in supporting the planning, delivery and evaluation of nursing care as well as in the measurement of patients' health outcomes and in the definition of resource management, productivity and costs.
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S17

INTRACAVITARY ECG AND PICC POSITIONING: A SINGLE INSTITUTION EXPERIENCE

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Background: Implantation of Peripherally Inserted Central Catheter (PICC) is a well recognized method to safely deliver intravenous drugs. The tip of PICC must reach the junction between the superior vena cava and the right atrium. Usually, standard chest x-ray is performed to verify the correct PICC positioning. However, this approach provides undue patient ionizing radiation exposure and can be not appropriate in case of severe kyphosis, scoliosis or obesity. Intracavitary electrocardiogram (ECG) could properly monitor the PICC tip position and replace thorax radiography for this purpose.
Material and methods: The PICC, usually inserted through the basilic or brachial vein, can work throughout its tip as an intracavitary electrode. Accordingly, the tip may capture ECG "P" waves, that tend to be higher as the tip advances toward the superior vena cava. The maximum level of P wave is registered at the junction between superior vena cava and right atrium, that also represents the ideal site for tip positioning. In contrast, when the tip reaches the right atrium, the P wave initially becomes

biphasic, negative and positive, then only negative. The PICC is filled with sodium chloride solution before registering intracavitary ECG for favoring signal transmission. A standard red electrode is attached to the external extremity of PICC. The ECG evaluation was followed by a chest x-ray.

Results: Since January 2018 to May 2019 we conducted an observational study on 140 selected patients with diagnosis of oncohematological cancers and without cardiac diseases, such as atrial fibrillation. Median age was 57 (range 20-86). Most of PICCs were implanted trough the right arm, but reliability of study results were not influenced by the arm side. All patients received PICC implantation by an expert operator and without notable complications. Baseline standard ECG with normal P wave represented a restrictive criterion for accrual. An intracavitary ECG was performed when the PICC reached the planned insertion deep and the level of P wave was used for predicting the tip positioning. Post-procedural chest x-ray was prescribed and matched with data of intracavitary ECG, confirming the proper PICC insertion in all patients.

Conclusions: Intracavitary ECG is a reliable, easily interpretable, safe and cost-effective method for monitoring in real time the correct PICC positioning. If validated in other patient cohorts this procedure could replace traditional thorax radiography.

S18

CHEMOTHERAPY INDUCED ALOPECIA: PATIENTS AND NURSES POINT OF VIEW

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Background: Chemotherapy induced alopecia is a frequent side effect of cancer treatment with an important psychological impact. The alteration of the body image influences the quality of life and the adherence to the therapeutic plan. The scalp cooling system may be a solution for a better quality of life. Our literature review underlined the efficacy of scalp cooling in chemotherapy induced alopecia prevention until 90%. The patients enrolled don't show side effect related to the cooling system. No evidence associate scalp cooling device to scalp metastasis. Our literature review underlined no compliance about scalp cooling systems by nursing staff. The patients don't obtain enough informations and support. The effect is a lesser request of the scalp cooling device.

Patients and Methods: The aim of this study is to identify distress level alopecia related, investigating the impact of alopecia on the patient quality of life and identify the level of awareness of stress related to chemotherapy induced alopecia from oncological nurse staff. The data collection was conducted, in the period of September – October 2018, in an Italian oncological ward where scalp cooling system isn't use. This study enrolled 60 women cancer affect in chemotherapy treatment interviewed by the I-CADS and 10 nurses interviewed by an adaptation of "Alopecia management scale".

Results: The results indicate that the 65% of the patients refer to wear a wig or a foulard to hide alopecia. The 40% of the women felt very sick in relation with alopecia. The 78% didn't know scalp cooling system and only 22% had some informations about scalp cooling device. The 81% would used scalp cooling system if it was possible. Only 19% was no interested. The 50% of nursing staff interviewed underlined that alopecia is a priority for the patient; the 80% of nurses support that prevention is essential, but they don't apply none prevention and they demonstrated lacking sensibility and interest. Finally, in our study setting, the nurses use only two refrigerates cap, pioneer of modern scalp cooling systems. Only 2 nurses already knew scalp cooling systems but they believe the device isn't efficient and related of cooling metastasis.

Conclusions: One of the most evident chemotherapy side effect may be faced by the use of scalp cooling device and by therapeutic education of the patient.

S19

MODEL OF EXPERIMENTATION OF A CLOSED CIRCUIT DEVICE FOR BATTLING OF THE RISK OF CONTAMINATION DURING PREPARATION OF ANTIBLASTIC CHEMOTHERAPIES

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Background: Many drugs used in onco-hematology need to be prepared in their form of administration by specialized nursing staff. These procedures may require numerous types of individual and collective protection devices in order to prevent product contamination on the one hand and operator safety on the other. In order to facilitate the manipulation of these drugs, an innovative circuit has been designed that allows the preparation and therapy without ever disconnecting any of the components and consequently ensuring the sterility of the preparation and the safety of the operator even without the use of laminar flow hoods. This innovative device uses a complex series of valves and connectors and is disposable. For this device an Italian invention patent was requested.

Materials and methods: The trial is conducted in the IME Foundation at the Tor Vergata General Hospital. Each center will carry out at least 20 simulated preparations using 50 ml bottles, fitted with a rubber stopper, and pockets of 5% glucose solution. The simulations will be

carried out by the same operator, in two distinct areas according to the level of environmental protection: 1) Experimentation Arm: Work plan of the medical establishment using the device; 2) Control Arm: Inside the vertical laminar flow hood without using the device. The objective is to verify the effectiveness of the device by testing whether the preparations prepared outside the hood using the device ensure a level of sterility on the product and safety for the operator compared to a standard preparation under the hood. The bags derived from the simulated preparations they will be stored at room temperature for 24 hours and will be subjected to a withdrawal of liquid from the bag that will be sown in an appropriate culture medium.

Results: The results of this study will be of considerable value in daily practice, as they will allow to test an instrument capable of guaranteeing, in emergency and uncomfortable situations, the microbiological stability of the infusion preparation even without the use of vertical laminar flow hoods. The trial will be considered passed if the difference in contamination between the testing arm and the control will not be statistically significant.

Conclusions: The trial model of a closed-circuit device capable of preparing and administering infusion drug therapies in onco-hematology could determine the massive introduction of this device into clinical practice.

S20

FROM CARING TO TAKING CARE

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Background: The "chronic" patient lives in the condition of having to live over the time with one or more pathologies that, if well controlled, allow a good quality of life.

In Lombardy, people suffering from chronic diseases are 3.5 million, equal to about 30% of the population. In Bergamo it is estimated that these pathologies constitute the 29,4% of the population and consume the 79% of health resources, trend destined to increase in the next years.

From January 2018, in Humanitas Gavazzeni, a new path of taking charge of citizens affected by chronic diseases and in conditions of fragility has started: this model suggests a series of changes in the health systems in order to help improving the condition of chronically ill patients and suggests a "proactive" approach between health staff and the patients themselves, so that the latter may become an integral part of the welfare process.

Materials and Methods: The proposed welfare model for the management of patients suffering from chronic pathologies in our structure consists in the following points: mapping and identification of areas of interes, analysis of collected data, definition of objectives through interviews and questionnaires proposed to the patients, definition of the strategy of action.

Results: In chronic diseases patient becomes an active protagonist of the care processes because the management of these diseases can be taught in the majority of the patients.

The structure of the assistance team must be changed by introducing a clear division of the work and by separating acute patient care from programmed management to chronic patients. Non-medical staff is trained to support self-care of patients, to carry out specific care and to ensure the scheduling and conduct of patient follow-up. Scheduled visits are one of the most significant aspects of the new organizational design of the team. The adoption of evidence-based guidelines provide the team with the standards to supply an optimal care to chronic patients.

Conclusions: In taking care of the chronic patient the hospital becomes a reference point. The creation of a dedicated nursing clinic could finally meet the lack of follow-up and the deficiencies found. The nursing Case Manager represents the reference for the patient and the caregiver as well as for the other health and social workers, with the responsibility to show the process of taking care of the patient and by ensuring the continuity of care and the best quality of life for the patient.

S21

FREQUENCY, SEVERITY, AND IMPACT ON DAILY LIVING OF DELAYED CHEMOTHERAPY-INDUCED NAUSEA, VOMITING AND RETCHING (CINVR)

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Background: Management of Chemotherapy(CT)-Induced Nausea, Vomiting and Retching (CINVR) has improved with the new antiemetic regimes[1,2]. However, delayed nausea remains a critical issue[3] and retching is still largely understudied[4]. This study aimed to describe (i) the incidence and impact on daily living of CINVR; (ii) strategies to relief symptoms and severity of CT-related toxicities.

Methods: Single center cross-sectional study on 60 consecutive outpatients with solid or hematological cancer who received CT between August-December 2016. Patients self-reported on a diary, 4-times/day from the day of CT to 120h later the frequency, severity and impact on daily living (Numerical Rating Scale 0-10) of nausea, vomiting and retching, as well as strategies to control symptoms and nausea and vomiting occurring beyond 120h. The severity of n*ausea and vomiting was assessed*

Table 1. Efficacy measures.

Outcome	Overall N (%)	Acute N (%)	Delayed N (%)
No nausea (NRS = 0)/vomiting/ retching	35 (58.3)	47 (78.3)	37 (61.7)
No nausea	43 (71.7)	53 (88.3)	45 (75.0)
No significant nausea (NRS⩽3)	49 (81.7)	56 (93.3)	50 (83.3)
No vomiting	53 (88.3)	57 (95.0)	56 (93.3)
No retching	56 (93.3)	59 (98.3)	56 (93.3)
No rescue anti-emetics	43 (71.7)	52 (86.7)	44 (73.3)
CR	40 (66.7)	51 (85.0)	42 (70.0)
CP	39 (65.0)	51 (85.0)	40 (66.7)
TC	35 (58.3)	49 (81.7)	37 (61.7)

CP, complete protection (no vomiting/retching/significant nausea, and no rescue antiemetics-RA); CR, complete response (no vomiting/retching and no RA); TC, total control (no vomiting/retching/nausea, and no RA)

with the CTCAE v4.0. Acute, delayed, and overall periods were defined as up to 24h, >24-120h, and 0-120h following CT.

Results: Overall, 39 (61.7%) patients had nausea and 49 (81.7%) had vomiting beyond 120h with a median impact on daily living of 1/10 (IQR: 0.75-5.00).

Metoclopramide (n = 57 administrations), dexamethasone (n = 28), paracetamol (n = 9) and ondansetron (n = 3) were the most common pharmacological rescue therapies; also eating small servings of food (n = 13), aloe (n = 11), sour food/drink (n = 8), ginger (n = 7), arsenicum, artemisia annua, and curcuma (n = 6 each) were reported.

According to the CTCAE v4.0, 45 patients had no nausea and 55 no vomiting; nausea scored grade 1 in 11 and 2 in four patients; five patients reported grade 1 in vomiting.

Conclusions: One-fourth of patients had delayed nausea and only 60% showed no symptoms in the delayed period. Nausea and vomiting persisted beyond 120h following CT with a low to moderate impact on daily living.

S22

NURSING GENETIC COUNSELING: PILOT STUDY

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Oncogenetics is a new branch of Oncology dedicated to the hereditary component of tumor diseases whose main purpose is to develop diagnostic, therapeutic and preventive measures for those at risk. 3-10% of cancer cases are attributable to an eredo-family form. Most of the studies concern the mutations of the BRCA 1 and BRCA 2 genes that are associated with the "Hereditary Breast / Ovarian Cancer Sindrom (HBOC)" and those of the colorectal and endometrium, which constitute the so-called Lynch syndrome or "Hereditary Non-Polyposis Colorectal Cancer (HNPCC) Sindrom". With this work we want to evaluate the effectiveness of the intervention of the nursing staff in sending genetic counseling to patients not selected from a cancer day hospital. The study was conducted in the Oncology ward of Fano (AORMN), during the period August-September 2018. Inclusion criteria: all patients diagnosed with cancer under chemotherapy or with biological drugs. Exclusion criteria: non certain diagnosis, lack of knowledge of written Italian, presence of cognitive. A questionnaire was subdivided into 3 sheets: Form A, Form B and Form C. Form A presents sections V, in which personal data, familiarity for neoplasia, interest in consulting are collected. Schedule B identifies the criteria for sending advice to the HBOC Syndrome, while Schedule C identifies the criteria for the HNPCC Syndrome. The questionnaire was submitted to 120 patients, of which 90 (75%) agreed to complete it, while 30 (25%) refused. Almost half of the entire sample contacted (49.2%) was interested in genetic counseling, while 16% had already consulted. 16.9% of those interested would have to be reassessed during the consultation with the geneticist doctor, since although they do not meet the inclusion criteria, there are some features highlighted in Form A to be examined in more detail through a more detailed analysis of family history and characteristics of the tumor. The latter, without the nursing assessment, would have escaped sending advice. The figure of the Genetic Nurse would favor the improvement of the management of the cancer patient.

S23

THE STOMIZED PATIENT CHEMIO AND RADIOTEATED VS. THE NOT TREATY: COMPLICATIONS AND COMPARISON WITH DATA LITERATURE

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Background: The patient with a stoma develops many problems in itself: skin changes, early and / or late complications, acceptance of the new body image. The ostomy is packaged due to oncological diseases. Chemotherapy and / or radiotherapy is often associated with the presence of the ostomy. The objective of this study is twofold: to verify if complications increase and to see what the ET. he did to improve his quality of life.

The side effects induced by chemo-radiotherapy represent an important problem for these patients, who during radiochemotherapy represent an example of how the QV (quality of life) can be heavily influenced by chemotherapy. In this regard, we have little data in the literature, since the care and assistance surgeries for ostomy patients are almost always in the surgery and urology departments and

very few, like ours, linked to the Medical Oncology departments.

Materials and Methods: Stomal complications have a varying incidence of between 25 and 35%. There are no specific data on chemo and/or radiotreated patients. Even in the limit of the methodology and the sample taken into consideration, in our center we have ventured to evaluate this problem, because the clinic for the treatment and the reabilation of the patient carrying ostomy was born in our S.C. of oncology.

Results: Of The 60 cancer patients carrying stomia, 29 were treated with chemotherapy, 2 chemo and radiotherapy, the remaining have not done chemotherapy. The 29 patients treated with chemotherapy, 15 showed complications: in particular skin alterations classified L1. According to the Study SACS (redness without loss of substance), 1 lesion type L2 with loss of substance. In particular: 8 manifest are the cutaneous alteration L1, the remaining are associated complications such as plaque detachment, diarrhea and a patient stenosis. The results obtained in the study showed an increase in stomal complications.

S24

MULTIDISCIPLINARY MANAGEMENT OF SKIN METASTATIC ONCOLOGICAL INJURIES

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Background: Some authors estimate that 5-10% of patients with cancer have cutaneous involvement;breast cancer is the one most frequently associated with the development of skin localizations(62%). The venues are multiple. Knowledge of the techniques for treating this type of injury (*CT,surgery,RT,ECT,topical local treatments*) together with multidisciplinary collaboration are fundamental in this challenge. The purpose of the treatment is to alleviate the burden of the disease, improve the quality of life. In the injury assessment process,we have been using digital photography for an additional 10 years, supporting the multiprofessional team after acquiring the patient's informed consent.

Methods: Retrospective analysis of patients under the care of the U.O. Oncology day Hospital from 2006 to November 2018 with metastatic oncological skin lesions (monitoring data). After inserting the data in an Excel spreadsheet we have developed a descriptive statistical analysis of the described phenomenon.

Results: The patients taken in charge are 43,of which 31 (72%) females and 12 (28%) males. The average age is 67 years with a range of 36 to 98 years.9 patients are still in care and 34 have died, of which we have calculated the treatment time in months,from taking charge to death. They have been treated for an average time of 30.7 months with a minimum of 1 and a maximum of 95 months. *Graph 1* shows the distribution of patients over the years;the average number of patients/year is 11 with an increasing trend from 2006 to the present. The primary tumor sites are shown in *graph 2* and the distribution of the sites of the vegetative oncological lesion in *graph 3*. The breast is the most frequent site of both primary.

Conclusions: The evolution of oncological care have led,nowadays,to rely on increasingly targeted and precise therapies: *chemotherapy, radiotherapy, electrochemotherapy*, in addition to *surgery*, and these can be used alone or in association between them and at different times. The management of these treatments becomes fundamental as they are delivered in different places and by professionals and for this reason multiprofessionalism comes into play, aimed at sharing all the information regarding the person with this problem in order to plan all those interventions necessary for the care of the person in charge. Precisely for this reason we have thought of the multidisciplinary discussion of cases of people with this pathology, as shown in the flow chart from taking charge to follow up.

S25

A COMPARISON OF BLOOD SAMPLES COLLECTED VIA PERIPHERAL AND PERIPHERALLY INSERTED CENTRAL CATHETER (PICC) IN ADULTS WITH HEMATOLOGICAL MALIGNANCIES

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Background: People with hematological malignancies often require frequent blood sampling. Samples drawn by Central Venous Catheters (CVC) reduce the risk of complications due to venipuncture such as irritation, anxiety, and superficial bleeding. There is evidence that samples collected via CVC are as reliable as that drawn by venipuncture. Despite this, to our knowledge, no studies have evaluated the equivalence of blood samples collected via peripheral phlebotomy (PP) compared to Peripherally Inserted Central Catheter (PICC). Thus, this study aimed to assess the reliability of blood samples obtained from PICCs as an alternative to venipuncture.

Material and Methods: A cross-sectional design was used to recruit adult hematological patients. Blood samples collected via PICC were performed following the most up to date guidelines. For the peripheral blood

sampling, a 21G butterfly needle was used. The blood samples were collected within 5 minutes by a specialist nurse. Hemoglobin (Hb), Haematocrit (HCT), and Platelet count (PLTS) blood tests were evaluated. Wilcoxon test for non-normal distribution was used to compare test results. P-values < 0.05 was considered significant.

Results: 28 individuals (18 male) with a mean age of 66.5 years (sd=14.0) were included. No significant difference for PLTS were found (p=0.512). No clinically meaningful differences were found (Hb mean PP=8.94, sd=1.18 vs. PICC=8.82, sd=1.24; HCT mean PP=26.90, sd=30.80 vs. PICC=26.51, sd=3.91) despite Hb and HCT levels differed significantly (p=0.002 and p=0.001 respectively).

Conclusions: The results of our study are in line with those reported in literature where blood samples drawn by CVC are as reliable as those collected via peripheral phlebotomy. Thus, sampling through PICC could be beneficial for people with cancer as it reduces patients' discomfort and possible complication. Moreover, vessel stiffness due to previous anticancer treatments could increase the risk of multiple venipuncture and related consequences. Blood sampling via PICC should be recommended in people with hematological malignancies in needs of frequent blood tests.

S26

STEP BY STEP: DESIGN AND IMPLEMENTATION OF A INFORMATION BOOKLET, TO FACILITATE THE PATH OF THE PATIENT IN THE ONCOLOGY SERVICE

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Back Ground: "Step by step" design and implementation of an informative brochure, to facilitate the patient's path in the oncology service. In the face of a diagnosis the patient asks questions like what will happen to me? Or what should I do? Or even where should I go? The aim of this project is to give some information, a computer support that could be useful to the patient and to the relatives to facilitate their path in the oncology service before, during and after the chemotherapy and radiotherapy treatment.

Methods: 3 articles were taken into consideration concerning the dissemination of information through leaflets and leaflets, researched on PubMed and Google scholar published between 2014 and 2016.

Results: In the first article, informative texts consisting of 748 and 2075 words were analysed, two main themes, emotional responses and cognitive responses emerged. The 14 patients' representatives read the illustrative leaflets and provided suggestions for improvement, which have largely included the development of simplified and more attractive informed consent forms and have identified multiple deficiencies in Written information used in clinical cancer studies. The second article examines the reactions of 35 patients and the consequent behaviour towards information on the risk transmitted in (PILs, patient leaflets) of drugs commonly prescribed by general practitioners. The study found that PILs should transmit information on potential risks in a less frightening language, while retaining the informative content needed to make informed decisions about the prescribed drug. The third article showed that the 12 patients in question were generally enthusiastic about the brochure and everyone found the information clear and easy to understand. All the patients believed that the information was relevant and answered all their questions.

Conclusions: The information leaflet must be a reinforcement and a resource to improve operator and patient communication, provide the right answers to certain questions that each patient poses and who are often not satisfied and cause anxiety and agitation. The information must therefore be placed in a clear, simple way and with a correct setting in such a way as to reassure at least in part the patient and the family.

Late Breaking Abstracts

*LBA3538 - Plenary Session

FINAL RESULTS OF A STEPPED-WEDGE, CLUSTER RANDOMIZED CLINICAL TRIAL (RCT) TO EVALUATE EFFECTIVENESS OF THE HUCARE QUALITY IMPROVEMENT STRATEGY (HQIS) AIMED AT INTEGRATING PSYCHOSOCIAL CARE INTO ROUTINE CANCER CARE IN 15 ONCOLOGY CENTERS IN ITALY

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Background: Psychosocial needs of cancer patients, defined as psychological, emotional, social and spiritual aspects of health, frequently are not detected and adequately addressed. We evaluate the effects of an implementation strategy we previously demonstrated feasible, which includes communication skills training for all physicians and nurses; four support visits at the centers by an improvement team to assist staff in identifying obstacles, finding solutions, and strengthening motivation; screening for distress and social needs; individualized pts' education with a referring nurse; use of a question prompt list

Material and Methods: Multicenter, stepped-wedge cluster RCT (3 clusters of 5 centers each). The intervention is applied at a cluster level and assessed at an individual level with a cross-sectional model. Consecutive outpatients requiring medical treatment and diagnosed in the previous 2 months were eligible. Primary endpoint: a difference of at least one of the 2 HRQoL functions, emotional (EF) or social (SF), at 3 months from baseline, in pts of the centers that implemented the HQIS vs standard of care (SoC). Analyses used a beta-binomial regression model. Secondary endpoints include the effect in the long-term, on global and specific subscales of HRQoL, and on mood.

Results: 762 pts were enrolled, and 647 included in the analysis. At baseline, 41% showed high anxiety and 88% had at least one psychosocial need. 299 health professionals attended 3-day courses (84% of clinical staff). For the primary endpoint, the 315 pts who received HQIS exhibited better quality of life for the emotional domain than those assigned to SOC (OR=1.115, p=0.016); EF was also influenced by needs met (OR=1.182, p<0.001), anxiety at baseline (OR=1.172, p<0.001) and age (OR=1.003, p=0.035). The difference was not significant for the social domain (OR=0.955, p=0.353). Effect on EF was confirmed at 12 months (OR=1.118, p=0.013). No effect on mood, on HRQoL global or other subscales, was observed.

Conclusions: To our knowledge, this is the first RCT demonstrating the effectiveness, even in the long term, of a psychosocial care implementation strategy on cancer patients' emotional well-being.

Clinical trial identification ClinicalTrials.gov Identifier: NCT03008993

*LBA3646 - Plenary Session

RANDOMIZED PHASE II STUDY OF CAPTEM VERSUS FOLFIRI IN RAS MUTATED, MGMT METHYLATED METASTATIC COLORECTAL CANCER (MCRC): FINAL ANALYSIS, TUMOR BIOMARKERS AND METHYLATED CTDNA

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Background: Temozolomide (TMZ) has shown activity in about 10% of pts with pretreated mCRC bearing MGMT methylation.

Methods: This multicenter, randomized phase 2 trial investigated PFS superiority of second-line CAPTEM (Arm A) vs FOLFIRI (arm B) in RAS mutated mCRC pts with MGMT methylation centrally confirmed by MSP. Eligible pts had ECOG PS 0-1, measurable disease and failed prior oxaliplatin-based therapy. Randomization to arm A (capecitabine 750 mg/sqm b.i.d. days 1-14 plus TMZ 75 mg/sqm b.i.d. days 10-14 q28) or B was stratified according to time elapsed from the start of oxaliplatin-based therapy and PD (</≥9 months (mos)); prior bevacizumab. A one-sided log-rank test with an overall sample size of 82 pts (41 per arm) achieved 90% power at 5% significance level to detect PFS increase from 2 to 4 mos. Secondary endpoints: safety, QoL (quality of life), OS, ORR. Exploratory biomarkers: MGMT IHC; methylBEAMing (MB) in tumor and ctDNA. Qol was investigated through EORTC QLQ-C30 V3.0 and FACT-C V4.0 tests at baseline and every 8 weeks (wks).

Results: A total of 86 pts were randomized (43 per arm). After a median follow-up of 30.5 mos (IQR 12.2-36.3), 79 disease PFS events occurred. PFS and OS were 3.5 (2.0-5.0) and 9.5 (8.2-25.8) mos in arm A vs 3.5 (2.3-6.1) and 10.6 (8.5-20.8) in arm B (HR=1.86 [0.82-1.72] and HR=0.97 [0.58-1.61]), respectively. ORR and DCR were 11.6% and 53.5% in both arms. Grade ≥3 treatment-related adverse events had higher incidence in arm B (47.6% vs 16.3%). Analysis of QoL changes from baseline were better in arm A for QLQ-C30, both after 8 wks (+5.42vs.-17.19, p<0.001) and 16 wks (+3.57vs.-11.67, p=0.02), and for FACT-C, both after 8 wks (+0.19vs.-7.06, p=0.016) and 24 wks (-2.07vs.-9.74, p=0.003). In the subgroup with negative MGMT IHC expression, there were no significant differences between the two arms in activity and efficacy, whereas positive MGMT IHC expression in arm A was associated with significantly inferior outcomes in terms of PFS (2.0 vs 3.5 mos; HR=2.08 [1.02-4.21]), OS (5.7 vs 10.6 mos; OR=1.07 [0.39-2.93]) and DCR (15.4 vs 56.5%; OR=0.23 [0.04-0.99]), interaction test p=0.125, 0.732, 0.028.

Conclusions: TMZ-based treatment should be investigated by a phase III trial, ideally conducted in patients with MGMT methylated/MGMT IHC negative tumors.

BLBA3722 - Session B: Gastrointestinal (non-Colorectal) Cancers

ADJUVANT CHEMOTHERAPY IN RESECTED GASTRIC CANCER: DEGRAMONT VERSUS XELOX IN A REAL-LIFE MONOCENTRIC EXPERIENCE (THE ASTER STUDY)

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Background: The benefit of adjuvant chemotherapy (aCT) in gastric cancer (GC) has been demonstrated in some clinical phase III trials. However, the clinical benefit is still controversial, there is no consensus on which is the optimal adjuvant regimen and efficacy of oxaliplatin-containing regimen is obtained only from a randomized prospective study on Asian population. The aim of this study is to evaluate our single European center experience and to compare Degramont versus XELOX regimen on clinical outcomes.

Material and Method: One-hundred and six-four patients (pts) with GC (pathological stage II or III) treated with aCT at our Institution from Jan-2001 to Jan-2018 were included in our analysis. The primary endpoints were disease-free survival (DFS) and overall survival (OS). The secondary endpoint the safety. The Kaplan–Meier method was used to estimate outcome and the use of log-rank was used to compare the differences, considering statistically significant a p value < 0.05.

Results: 95 pts and 69 pts received Degramont and XELOX regimen respectively. Median DFS and OS were not reached in Degramont regimen and 78 and 96.5 m in XELOX cohort respectively (p=0.68 HR 1.12 CI 0.6-2.11 and p=0.31 HR 1.36 CI 0.68-2.69). No differences in DFS or OS were found. Grading 3-4 adverse events (AEs) were more common in oxaliplatin-cohort than fluoropyrimidines group (18.6% vs 12,6%) with higher interruption rates (10.1% vs 4.8%).

Conclusions: Our study, although underpowered and retrospective analysis, shows a similar efficacy between Degramont and XELOX regimen in resected Gastric Cancer adjuvant setting in our European population, though suggesting a better toxicity profile in Degramont than XELOX cohort.

Future and prospective trials are needed to confirm and investigate our data discerning the pts who real need an adjuvant treatment from whom require only surgery.

BLBA3775 - Session B: Gastrointestinal (non-Colorectal) Cancers

MOLECULAR CHARACTERIZATION OF ADVANCED GASTRIC CANCERS (GC) AND ITS CORRELATION TO CLINICAL OUTCOMES: FROM THE CANCER GENOME ATLAS (TCGA) PROJECT TO CLINICAL PRACTICE

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Background: As part of The Cancer Genome Atlas (TCGA), an integrative analysis of genomic and proteomic data revealed 4 molecular subtypes of GC: Epstein Bar Virus (EBV), microsatellite instability (MSI), chromosomal instability (CIN) and genomically stable (GS). Data on primary tumor series correlated TGCA subgroups and prognosis. However, this classification has poor clinical utility, particularly in the metastatic setting, given its complex reproducibility in clinical practice (except for MSI test). Our study aims to evaluate the prognostic impact of GC molecular profile using reproducible genomic methods.

Methods: Formalin fixed paraffin embedded (FFPE) tumor samples from 265 metastatic GC patients (pts) treated at Istituto Nazionale dei Tumori,Milan, between July 2011 and February 2019, were evaluated. Next generation sequencing (NGS) was used to find hot-spot mutations (ION-Torrent platform); bright-field ISH was performed to detect HER2/EGFR/FGFR2/MET amplification and EBV infection and PCR to determine MSI status. Tumors were assigned to 4 molecular subtypes: EBV and MSI, if EBV infection or MSI-high status was detected; CIN-like if any amplification was found; GS-like for the other cases.

Results: One-hundred-eleven tumor samples were excluded from the final analysis due to insufficient tumor or a low DNA available to undergo a complete molecular analysis. Among the 154 evaluable cases, EBV infection was found in 4 cases (2.6%), 14 cases (9.1%) were classified as MSI-high, 91 cases (59.1%) as GS-like and 45 (29.2%) as CIN-like. HER-2, EGFR, FGFR2 and MET amplifications were found in 30 (19.7%), 8 (5.3%), 7 (4.6%) and 2 (1.3%) cases, respectively. Two cases had a co-amplification (FGFR2/EGFRand FGFR2/MET). TP53 was the most frequently mutated gene (41.4%), followed by PIK3CA (5.9%), KRAS(5.3%), ERBB2(4.6%) and APC(3.9%). At a median follow-up of 29.8 months (mos), EBV pts showed the best prognosis. Median overall survival was not reached for EBV pts.It was 31.8 mos for MSI pts,23.2 mos for CIN-like and 19.7 mos for GS-like pts.

Conclusions: Selected molecular alterations might be used to characterize mGC pts, defining specific molecular subgroups with a different prognosis and identifying potentially targetable alterations. EBV mGC pts showed an impressive survival.

CLBA3553 - Session C: Breast Cancer

EFFICACY AND SAFETY OF NEOADJUVANT CHEMOTHERAPY PLUS TRASTUZUMAB AND PERTUZUMAB IN NON-METASTATIC HER2-POSITIVE BREAST CANCER IN REAL LIFE: NEOPEARL STUDY

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Background: In HER2+ breast cancer (BC) patients (pts) the pathological complete response (pCR) is associated with improved survival. Trastuzumab (T), Pertuzumab (P) and chemotherapy (CT) association, increases the pCR rates slightly over 48%. We conducted a retrospective analysis on HER2+ BC pts to describe the outcomes of neoadjuvant combination of P+T+ CT in real-life setting.

Methods: Our cohort included 64 pts treated, between Sept 2015 and Mar 2018, in 15 Italian Cancer Centers in the neoadjuvant setting. Treatment outcomes were analysed in terms of pCR (defined as ypT0/Tis, ypN0i-) and toxicities, recorded according to CTC-NCI v.4 criteria. Statistical analysis was performed according to T- Student test and χ^2 test.

Results: 55 out of 64 pts were evaluable: median age was 50 yrs (range 28-77), 29 pts (53%) were pre-menopausal. 24 pts (45%) were ER-/PgR-, 12 (21%) ER+/PgR-, 16 (29%) ER+/PgR+, median ki67 was 40%. 9% of pts were cT1, 73% cT2, 13% cT3 and 5% cT4; 42 pts (76%) were cN+. All pts received 4 cycles of T (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) and P (loading dose 840 mg, followed by 420 mg every 3 weeks). 42 pts T+P received docetaxel (75 mg/sm every 3 weeks), 8 pts weekly paclitaxel (80 mg/sm), 5 pts docetaxel/carboplatin (AUC5). 13 pts also received 3 cycles of anthracyclines, according to the FEC regimen. A pCR was achieved in 29 pts (53%), pPR in 26 (47%). No significant associations were found between pCR and baseline characteristics or treatments schedule. Seven out of 55 (13%) pts reported G3-G4 toxicities (5 pts G3-G4 neutropenia, 1 G3 vomiting, 1 G3 diarrhoea, 1 G3 anemia). A significant association was found between CT schedule and toxicities (p= 0,004). Three out of 4 pts treated with docetaxel/carboplatin and P+T reported G3/G4 toxicities.

Conclusion: The association of P+T+CT confirm to improve the rate of pathologic responses in the real-life setting of HER2+ BC pts Our results showed that the selection of CT regimen, to be associated with the dual blockade of HER2, is of paramount importance in order to avoid severe toxicities and increase the compliance to treatment.

DLBA3685 - Session D: Thoracic Cancers

IMMUNE CHECKPOINT INHIBITORS (ICIS)-RELATED HEPATIC ADVERSE EVENTS IN PATIENTS WITH NSCLC: A SINGLE-CENTER EXPERIENCE

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Background: ICIs have showed improvement in OS in advanced or metastatic NSCLC, being often linked with a better toxicity profile, but a broad and unique spectrum of side effects (immune-related events, irAEs) is frequent and difficult to predict. In literature, liver irAEs incidence in patients treated with ICIs is around 5%, with 1-2% of G3-G4 toxicity; cholangitis are even rarer. As hepatic irAEs are mostly asymptomatic, they can be discovered only by laboratory tests.

Methods: A retrospective analysis of all consecutive NSCLC pts treated with ICIs in our Oncology Department between Aug 2015 and Aug 2018, with last follow-up in Feb 2019 has been conducted, collecting all data (demographic, clinical, radiological, laboratoristic and therapeutic) with the aim of finding out possible predictive criteria of developing liver irAEs.

Results: Among the 73 pts collected, liver toxicity was developed in 5 (6.8%) pts, all treated with Nivolumab, with a severe adverse event (SAE) incidence of 1.4%. Median time to onset was 6 weeks (1-67). Most pts who developed liver toxicity were asymptomatic (4 out of 5); 2 pts temporarily discontinued ICI treatment and one permanently (pt with G4 cholangitis); 4 out of 5 pts (80%) were affected by liver metastasis before treatment beginning compared to 17 out of 73 (23%) in total population. The incidence rate of irAEs was approximately 30% (5.5% pneumonia, 5.5% skin irAEs, 5.5% thyroid disorders, 4.1% colitis, 1.4% nephritis and 6.8% liver toxicity). Response rate was higher in the 17 pts who developed at least one irAE (17.6%) compared to 7% in pts with no irAE occurrence. 2 of the 5 pts with liver toxicity had a clinical benefit from ICI treatment.

Conclusion: In our clinical records, irAEs incidence is similar to literature. Due to the low number of pts analyzed, we could not identify a predictive risk factor for the development of hepatic irAEs, although they appear more frequent in pts affected by hepatic metastases before the beginning of ICIs treatment. Although rare, hepatic irAE turns out to be serious enough to lead to suspension or permanent discontinuation of treatments, with possible fallout on the OS.
It would be useful to carry out further evaluations to identify predictors of such toxicity; a prospective observational study has just begun in our institute, based on the data obtained from this retrospective phase.

HLBA3330 - Session H: Melanoma and Skin Cancers

A RETROSPECTIVE CHART REVIEW STUDY OF DABRAFENIB (D) AND TRAMETINIB (T) COMBINATION THERAPY IN PATIENTS (PTS) WITH ADVANCED OR METASTATIC BRAF V600 MUTATED MELANOMA TREATED IN ITALY WITHIN THE INDIVIDUAL PATIENT PROGRAM: THE DESCRIBE ITALY STUDY

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Background: D+T demonstrated long-term benefit in pts with unresectable or metastatic(M) BRAF V600–mutated melanoma in two global, randomized phase 3 trials (COMBI –d and COMBI-v). There is limited real-world data with extended follow-up for this population. The purpose of DESCRIBE Italy(CDRB436BIT03), an observational retrospective chart review study,is to characterize the use of D+T combination tx for pts with BRAF V600 mutation-positive unresectable or metastatic melanoma who received this tx as part of the Novartis Individual patient Programin Italy.
Materials and Methods: We collected data of 499 pts in 34 Italian Centers. Pts received the D+T tx, starting from the first dose until treatment discontinuation, death, last clinical encounter or until 31 October 2017, whichever came first. The trial was approved by all Independent Ethics Committees. The objective of the study was to describe and evaluate baseline characteristics, treatment patterns, efficacy and safety of this setting of pts. Analysis was based on baseline LDH level, number of M sites, and Performance Status ECOG (PS).
Results: All patients were evaluated for the safety analysis; 395 were evaluable also for efficacy. The remaining pts were not evaluable for efficacy mainly for study protocol deviations or for lack of any post-baseline tumor evaluation. Treatment was ongoing in 28% of pts at the data cutoff. The median age was 59 years; 57% of pts had ECOG PS 0, 16% PS 1, 5% PS 2 (data missing in 22% pts). Baseline LDH levels were elevated in 29% pts (data missing in 26% pts) and 42% pts had more than 3 M sites and/or BM at baseline. Objective Response Rate was 61% in the evaluated pts. In this population the median Progression Free Survival (mPFS) was 9.2 months (mo). In the subgroup with elevated LDH mPFS was 5,6 mo and 6,8 mo in pts with more than 3 M sites and/or BM. In pts with normal LDH level mPFS was 12.8 and 13 mo in pts with less than 3 M sites. Median Duration of Response was 9.8 mo for the evaluable pts, 7.3 and 13.1 mo respectively for pts with more than 3 M sites and/or BM and less than 3 M sites and 5.7 and 13.1 mo respectively for pts with high LDH level and normal LDH level. The safety profile observed is consistent with what was reported in the global phase 3 studies. No new safety signal was observed.
Conclusions: Treatment with D+T in MM in real world setting is effective and safe, also in a non selected population with a large number of pts with high tumor burden.

SLBA3381 - Session S: Oncology Nursing

VADLOGIC: WEB-BASED APPLICATION FOR THE REASONED CHOICE OF THE DEVICE FOR VENOUS ACCESS IN THE CANCER PATIENT

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Many of the cancer patients who refer to a hospital need venous access for intravenous therapy. This requirement combined with the wide availability of devices for this indication and their diffusion makes it necessary to apply a logical scheme to the choice of the most suitable device and, both for peripheral and central catheters, must be based on different considerations such as: the therapeutic plan with the prescribed drugs, the expected duration of the therapy, the present comorbidities and also the characteristics of the patient's veins, his age, the positive

anamnesis for previous infusion therapies, possible preferences for the type or location of the device, as well as the abilities and the resources available for its maintenance. All this is to protect the peripheral heritage of patients and to administer infusion therapy appropriately. In our centers we implant around 1200 devices for venous access per year. We therefore identified 22 factors that must be analyzed and in many cases correlated with each other to formulate, case by case, the most logical suggestion with respect to the device for venous access among those available. The different elements are based on the evidence of the most recent literature and the latest guidelines and on personal experience in the few cases where evidence was not available or did not have the necessary strength. The elements have been grouped into 3 groups of factors:

1 Patient-related factors;
2 Laboratory data;
3. Factors related to therapy.

VADlogic, this is the name of the tool, is realized in the form of a web-based application based on an algorithm that analyzes the inputs provided by the user to reach the set target. The instrument has been designed to be used by less experienced health professionals in devices for vascular access to give them the right address and is to be used only in elective patients in whom the choice of the device can and must be reasoned; in any case it is always synergistic with the judgment of health professionals.

SLBA3443 - Session S: Oncology Nursing

AWARENESS IN ONCOLOGY PATIENTS IN TREATMENT WITH ORAL THERAPIES AND COMPLIANCE ASSESMENT

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Backgraund: In recent years, a growing number of oral oncological therapies have been introduced in Europe and the USA. Currently, more than a quarter of antineoplastic agents are for oral use, and over the upcoming years a further increase in the prescription of oral treatments is foreseen. A recent meta-analysis on the awareness of prognosis in cancer patients has concluded that more than 75% of patients are unaware of their prognosis and more than 95% of their diagnosis. The purpose of investigating the awareness of cancer treatment could increase knowledge about the rate of aware cancer patients and the level of comprehension among patients undergone the two different ways of administration. This study is aimed at evaluating quantitative and qualitative aspects of cancer diagnosis and oral antineoplastic therapy awareness in cancer patients.

Materials: A hundred consecutive patients diagnosed at the Oncology Department of IRCCS San Martino of Genoa were selected for analysis. In order to investigate the level of compliance, all patients were interviewed by the same trained psychologist using a semi-structured questionnaire composed of 31 items which were able to pointed out four distinct behavioral areas: 1) general information about therapy; 2) specific information about therapy; 3) therapeutic management; 4) compliance assessment.

Methods: For each area a compliance score was computed and analyzed through the logistic regression model. Odds ratio, along with 95% confidence interval, was estimated as an index of association between the proportion of compliant patients and individual characteristics with particular reference to the awareness degree (unaware, partially aware, fully aware). Likelihood ratio test was used to evaluate statistical significance.

Results: Thirty percent patients received an oral chemotherapy or biological therapy. Descriptive analyses highlighted that patients were mostly unaware of their real state of health (55%), a smaller part partially aware (19%) and the rest of them completely unaware (26%). In addition, 21% had an acceptable compliance (> 80%) while 79% resulted to be poorly compliant (< 50%).

Conclusions: This study shows that oncological patients are not always fully aware of their pathology. Further and more in-depth investigation should be focused on the gap between the knowledge due to a correct clinical information received from nurse and medical staff and the individual unreliable perception acquired prior to diagnosis.

SLBA3715 - Session S: Oncology Nursing

PREVENTION OF SKIN ERYTHEMATOUS REACTIONS FROM STANDARD DRESSINGS IN PATIENTS WITH CVC AND PICC

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The improvement of clinical-technical-assistance practice in the nursing field also requires a research-based approach. Observing phenomena, collecting data, analysing them, understanding them and processing them all contribute to a significant improvement in the clinical and nursing practice from which everything starts and to developing an approach based increasingly on the critical analysis of reality, always bringing the right corrective actions with a view to placing the person assisted at the centre of each action.

In AORMN's UOC of Oncology since November 2018, it was observed that several patients with Picc had redness

of the skin in the area below the fastening dressing in standard polyurethane. Subsequent application of an alcohol-free, transparent, liquid barrier film to protect the skin reduced redness and kept the skin intact. It was therefore decided to apply this dressing to all new patients with Picc. The purpose of this work is to collect specific data to evaluate the elimination of cases of redness and / or infection.

All patients who from 01/02/2019 have positioned a Picc until 30/07/2019 have been enrolled; these have been subjected to weekly dressings.

Patients who developed redness and/or injury despite the positioning of the barrier film left the study.

In the period considered 46 patients were enrolled, of whom 38 (82%) showed no signs of redness and/or itching. The remaining 8 patients (18%) suspended treatment with the barrier film because they had itching in 5 cases (62.5%), in 3 cases redness (25%), 1 case showed redness and itching, and finally only one person showed a small lesion on the skin (12.5%).

There were 3 (6.5%) patients lost to the FU (deceased, hospitalised).

The work, even within the limits of small numbers, shows us that the application of a barrier film reduces the development of skin events related to the placement of standard dressings in patients with PICC.