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Printed by Henry Ling

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Dear Colleagues,

On behalf of the Scientific Board, it is a great pleasure for me to introduce the proceedings of the XX 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, many young oncologists are co-authors of the abstracts and several of them are first-time authors. It should be an encouragement for all of us that there is a present and also a future for AIOM, which celebrates the 45th anniversary of its founding this year.

As you will understand 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 would like to thank the Scientific Committee and all the reviewers for their invaluable work and I hope that the meeting will be an occasion to share 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.

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 https://www.aiom.it/ from November 20th, 2018

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20th National Congress of Italian Association of Medical Oncology (AIOM)
16-18 November, 2018 - Rome, Italy

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Plenary Session

01*

COMPREHENSIVE BIOMARKER ANALYSES AND UPDATED RESULTS OF PURE-01 STUDY: NEOADJUVANT PEMBROLIZUMAB (PEMBRO) IN MUSCLE-INVASIVE UROTHELIAL BLADDER CARCINOMA (MIBC)

Raggi D.[1], Briganti A.[2], Luciano' R.[2], Colecchia M.[1], Massa S.[1], Giannatempo P.[1], Colombo R.[2], Gallina A.[2], Mortarini R.[1], Montorsi F.[2], Madison R.[3], Ali S.[3], Ross J.[3], Chung J.[3], Anichini A.[1] and Necchi A.[1]

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Background: PURE-01 (NCT02736266) is a single-arm, phase 2 study of Pembro preceding radical cystectomy in MIBC. Updated results and exploratory biomarker analyses are presented.
Methods: 71 patients (pts) will be enrolled, with cT⩽3bN0 MIBC, regardless of cisplatin eligibility. Pembro is given 200mg q3w x3 cycles. Pathologic complete response (pT0) in ITT population is the primary endpoint (EP). The H_1 is pT0 ⩾25%, H_0 pT0⩽15%. 15/71 pT0 are required. Biomarker analyses include: IHC PD-L1 combined positive score (CPS, Dako 22C3), hybrid-capture based comprehensive genomic profiling (CGP, FoundationONE), and expression of a 22-gene "T-cell inflamed" signature via quantitative PCR (qPCR).
Results: As of 05/2018, 65 pts have been enrolled and all underwent CGP from TURB samples: 42% showed DDR genomic alterations (GA). Median CPS was 21%. CPS and qPCR showed a significant correlation (r=0.71, p<0.0001), whereas CPS did not correlate with neither tumor mutational burden (TMB) nor DDR-GA (R=-0.16). 37 pts are evaluable for the primary endpoint. With 15 (40.5%) pT0 responses, the study has already achieved its PE.

RB1 and *PBRM1* GA were significantly associated with pT0 (p=0.014 and p=0.007). pT0 responses were obtained in 10 (52.6%) pts with CPS⩾21% and, most noteworthy, in 13 (61.9%) with DDR or *RB1* GA. 8/8 pts (100%) with DDR/*RB1* GA and CPS⩾21% achieved pT0. The 22 gene T-cell inflamed signature also significantly discriminated pT0 from non-pT0 pts (p=0.0032).

17 pts had matched pre-post Pembro tumor samples analyzed, showing a mean of 51.9% shared GA. Concordant increases in gene expression by qPCR, observed in post- vs pre-Pembro lesions, from at least 5/7 non responding patients, were consistent with promotion of adaptive immunity (*IFN-g, CXCL9, CXCR6, CD27, GZMB*), being counteracted by strong adaptive resistance mechanisms (*CD274, PDCD1, CD276, PDCD1LG2, IDO1*).
Conclusion: Pembro has already exceeded the pT0 responses required in this study. Many new observations and the immune-genomic features interplay may contribute identifying those pts who might deserve a bladder-sparing approach. Full results on the entire dataset will be presented.

02*

CHEMOTHERAPY PLUS OR MINUS BEVACIZUMAB FOR PLATINUM-SENSITIVE OVARIAN CANCER PATIENTS RECURRING AFTER A BEVACIZUMAB CONTAINING FIRST LINE. THE RANDOMIZED PHASE 3 TRIAL MITO16B -MANGO OV2B - ENGOT OV17

Daniele G.[1], Lorusso D.[2], Joly F.[3], Gallo C.[4], Colombo N.[5], Sessa C.[6], Bamias A.[7], Pisano C.[8], Selle F.[9], Zaccarelli E.[5], Scambia G.[10], Pautier P.[11], Nicoletto M.O.[12], De Giorgi U.[13], Dubot C.[14], Bologna A.[15], Orditura M.[4], Ray-Coquard I.[16], Perrone F.[1] and Pignata S.[17]

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Background: Bevacizumab (BEV) is approved in recurrent ovarian cancer (rOC) for patients not previously

treated with the drug. Our study aimed at evaluating whether the addition of BEV to a platinum-based chemotherapy prolongs progression-free survival (PFS) for rOC patients who had already received it during first line.
Methods: FIGO stage IIIB-IV rOC patients relapsing at least 6 months after last dose of platinum, who had received BEV during first-line treatment, ECOG PS≤2, were randomized to 6 cycles of platinum-based doublets (carboplatin/paclitaxel or carboplatin/gemcitabine or carboplatin/PLD) with or without BEV administered concomitant with chemotherapy and as maintenance until disease progression. The primary endpoint is PFS. With 90% power in detecting a 0.67 HR, with 2-sided α error 0.05, 265 events were needed. All efficacy analyses are done on an intention-to-treat basis. PFS and OS curves are estimated by Kaplan-Meier method, and compared with a two-sided log-rank test. Toxicity is graded according to NCI-CTCAE v 4.0.
Results: 405 pts were enrolled. Median age was 61; 64% of patients had progressed ⩾12 months after last dose of platinum and 72% of patients after completion of first-line BEV maintenance. With a median follow-up of 20.3 months, 304 PFS events and 147 deaths were recorded. Median PFS was 8.8 months and 11.8 months without and with BEV, respectively (HR 0.51, 95%CI: 0.41-0.64, p<0.001). Median OS was 27.1 months and 26.7 months without and with BEV, respectively (HR 1.00, 95%CI: 0.73-1.39, p=0.98). Severe (⩾G3) hypertension (27.5% vs 9.7%, p<0.001) and proteinuria (4% vs 0, p=0.007) were more frequent with BEV.
Conclusion: This study shows that for rOC patients previously treated with BEV in first line relapsing ⩾6 months after last platinum, rechallenge with BEV in combination with platinum-based doublets is associated with a significantly prolonged PFS, with no unexpected toxicity.

Supported by Roche. NCT01802749

03*

POTENTIAL IMPACT OF THE INTRODUCTION OF NONAVALENT HUMAN PAPILLOMAVIRUS VACCINATION: ANALYSIS OF 13.665 WOMEN OVER A 18-YEAR STUDY PERIOD

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Background: Recently, the FDA licensed the nonavalent vaccination against human papillomavirus (HPV). Several trials showed the befecifial effects of nonvalent vaccine in a selcted cohort of patients. Here, we aimed to test the theoretical utility of incorporation of nonavalent vaccination against HPV into a real wolrd clinical setting.
Patients and methods: Data of consecutive 13,665 patients undergoing HPV-DNA testing from 1998 to 2015 were retrospectively searched to identify changes in HPV prevalence during three study periods (T1, 1998-2003; T2, 2004-2009; and T3, 2010-2015).
Results: Overall, 1361, 5130, 7174 patients were included in T1, T2 and T3. Potentially, the quadrivalent vaccine protected against HPV in 71.5%, 46.5% and 26.5% of patients in T1, T2 and T3 (p-for-trend<.001). Nonavalent vaccine protected against HPV in 92.5%, 72.3% and 58.1% of patients in T1, T2 and T3, (p-for-trend<.001). The proportion of patients with genital dysplasia grade2+, not related to HPV genotypes covered by quadrivalent vaccine (13% in T1, 21% in T2 and 34% in T3) and nonavalent (3% in T1, 12% in T2 and 19% in T3) increased over the time (p-for-trend<.001). For all study period the protection of nonavalent vaccine was superior to quadrivalent (p<.001, Chi-square test).
Conclusions: The introduction of nonavalent vaccine would improve protection against HPV infections and HPV-related genital dysplasia2+. Cross-protection of nonavalent vaccine should be related to a highest coverage against other HPV types.

A - Breast Cancer

A01*

THE 41-GENE CLASSIFIER TRAR PREDICTS RESPONSE OF HER2 POSITIVE BREAST CANCER PATIENTS IN THE NEOALTTO STUDY

Di Cosimo S.[1], Triulzi T.[1], Pizzamiglio S.[1], De Cecco L.[1], De Azambuja E.[2], Fumagalli D.[3], Putzai L.[4], Harbeck N.[5], Izquierdo M.[6], De La Pena L.[7], Daidone M.G.[1], Huober J.[8], Gori S.[9], Cinieri S.[10], Baselga J.[11], Piccart M.[2], Verderio P.[1] and Tagliabue E.[1]

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Background: NeoALTTO showed significantly higher pathologic complete response (pCR) with neoadjuvant Lapatinib (L) + Trastuzumab (T) + Paclitaxel (P) as compared with either L or T + P. We previously reported that the 41-gene classifier TRAR is an accurate predictor of clinical outcome, with low scores being predictive of response to T and favourable prognosis (Triulzi et al., 2015). Here, we present the analysis of the association of TRAR with pCR in NeoALTTO pts.

Methods: Gene expression profiling was performed using RNA from baseline core biopsies. Logistic regression analysis was used to assess the predictive role of TRAR with respect to pCR and the discriminatory capability was evaluated in terms of Area Under the Receiver Operating characteristic (ROC) Curve (AUC) with the corresponding 95% confidence interval (CI).
Results: The TRAR score was estimated in 226 of the 455 (50%) pts. Specifically, baseline TRAR score was available for 79, 69, and 78 pts randomized to L, T, and L+T, respectively. TRAR was significantly associated with pCR in both univariate (Odds Ratio (OR): 0.25, 95%CI: 0.15;0.42) and multivariate analysis (OR: 0.26, 95%CI: 0.14;0.47) by considering ER status and treatment arm as covariates. The predictive capability of TRAR with respect to pCR was statistically significant in the overall population (AUC: 0.73; 95% CI: 0.67;0.80) and confirmed in ER negative (AUC: 0.71, 95% CI: 0.62-0.80) and ER positive cases (AUC= 0.70, 95% CI: 0.59-0.81) and within each treatment arm (L: AUC= 0.76, 95% CI: 0.65-0.87; T: AUC= 0.74, 95% CI: 0.60-0.88; L+T: AUC= 0.71, 95% CI: 0.59-0.83). As compared with the established molecular classifier PAM50, TRAR score provided significantly higher discriminatory capability in both univariate ($p<0.01$) and multivariate models including ER status and treatment arms (p= 0.02). A class comparison analysis in discordant cases (i.e., within TRAR high and low pts with and without pCR) revealed that the expression levels of LBP, a gene encoding for a well known inflammatory protein, are directly associated with pCR in TRAR high and inversely associated in TRAR low pts (interaction test $p<0.01$).
Conclusion: TRAR can classify HER2 positive breast cancer patients, including ER positive cases, with respect to their likehood of attaining pCR beyond what can be achieved with already established clinico-pathological factors. The value of inflammatory proteins in differential response to anti-HER2 agents deserves further investigation.

A02*

CDK4 AS A PROGNOSTIC DRIVER IN PURE INVASIVE LOBULAR BREAST CARCINOMA (ILC): TARGETED NEXT-GENERATION SEQUENCING (NGS) ANALYSIS IN EARLY-STAGE PATIENTS (PTS) STRATIFIED ACCORDING TO A VALIDATED CLINICO-PATHOLOGICAL MODEL.

Carbognin L.[1], Sperduti I.[2], Simbolo M.[3], Vicentini C.[3], Caliò A.[4], Manfrin E.[4], Schettini F.[5], Dieci M.V.[6], Griguolo G.[6], Pilotto S.[7], Fassan M.[8], Arpino G.[5], Guarneri V.[6], De Placido S.[5], Brunelli M.[4], Conte P.[6], Scarpa A.[9], Scambia G.[10], Tortora G.[7] and Bria E.[11]

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Background: The aims of this analysis were to develop and validate a prognostic model for early-stage ILC and to investigate the distribution of molecular abnormalities (with particular regard to CDK4/6 alterations) in ILC pts, grouped according to prognosis.
Methods: Clinico-pathological data of early-stage pure ILC pts from 4 Italian institutions were correlated to disease-free survival (DFS) and overall survival. A continuous score was derived according to multivariate Hazard Ratios, to develop a 3-class model. The model was validated in an external patients' cohort. Gene mutation and Copy Number Variation (CNV) analyses by targeted NGS, including 26 genes, were performed for pts with poor and good prognosis. Quantitative-PCR analysis was applied for CNV validation; immunohistochemistry for CDK4 and 6 was accomplished. Fisher's exact test and *Peto* Odds Ratio (OR) were adopted for comparison.
Results: Data from 773 patients (Training/Validation Set [TS/VS]: 491/282) were gathered. At multivariate analysis, T-category and N-status were independent predictors for DFS. A significant difference between patients at low/intermediate/high risk was found (10-years DFS: 76.3%/67.6%/39.8%, respectively, $p<0.0001$) in the TS. The model discriminated DFS in the VS ($p<0.0001$). The molecular analysis was applied to 20 patients from the high-risk group, compared with 14 patients from the low-risk group. In the poor prognosis group, *CDH1* was the most mutated gene (50.0%) followed by *PIK3CA* (35.0%). *MAP3K1* (10.0%), *ERBB2* and *PTEN* were mutated with low frequency (6.1%), only in the poor prognosis group. With regard to CNV, *CDH1* loss (55.0%) were the most frequent event, followed by gain in *ESR1, FGFR1*. In the goos prognosis group, *TP53* was the most mutated gene (35.7%) and *ARID1A* loss (57.1%) was the most frequent CNV event. *CDK4* gain was present exclusively in the poor prognosis group (35.0%, $p=0.03$; OR 7.98, 95%CI 1.51-42.1, $p=0.014$). Moreover, CDK4 and 6 overexpression showed a trend toward an association with poor prognosis (OR 2.7, 95%CI 0.4-18.1, $p=0.3$; OR 3.29, 95%CI 0.56-19.25, $p=0.18$).

Conclusions: A risk stratification model based on clinicopathological variables allowed to investigate with targeted NGS potential biomarkers of prognosis in pts affected by early-stage ILC. *CDK4* gain is suggested for future validation as a prognostic biomarker and a potential therapeutic opportunity.

A03*

IMPACT OF 21-GENE RECURRENCE SCORE® ON TREATMENT DECISION FOR T1-3 N0-1 ER+/HER2- BREAST CANCER PATIENTS: FINAL RESULTS OF THE PROSPECTIVE MULTICENTRIC ROXANE STUDY

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Background: We previously published and reported at this meeting the results of the multicentric prospective Breast-DX study, showing that using the 21-gene Recurrence Score® (RS) on all consecutive intermediate-risk (according to clinicopathologic factors) early ER+/HER2- breast cancer (BC) pts led to a low rate (16%) of change in adjuvant treatment decision. Here we present for the first time the results of the no-profit decision impact ROXANE study, where the decision to use the RS was left at physician's discretion.

Methods: Nine centers participated. Pts with ER+/HER2-, T1-T3, N0-N1 early BC were eligible. Physicians used the RS test whenever unsure about their adjuvant treatment recommendation. Pre-RS and post-RS physicians' treatment recommendations were collected.

Results: A total of n=251 pts underwent the RS-assay. Median age was 55 yrs (range 25-85). The majority of pts had ductal (85%), T<2cm (68%), N0 (61%) and G1-2 tumors (63%). Median Ki67 was 25% (range 2-75%). The N0 group was enriched with pts with more aggressive biology as compared to N1: G3 49% in N0 vs 17% in N1 ($p<0.0001$), Ki67 median 25%, range 2-75% in N0 vs median 20%, range 2-57% in N1 ($p=0.0006$).

The distribution of RS result was: <18 (58%), 18-30 (32%) and >30 (10%). Higher RS was found in N0 vs N1 pts ($p<0.0001$) and in case of G3 ($p<0.0001$) and higher Ki67 ($p=0.0049$).

Pre-RS indication was chemotherapy (CT) + hormonal therapy (HT) in 51% of cases (49% of N0 and 55% of N1). The overall rate of change in treatment decision was 31% (n=77), mostly from CT+HT to HT (n=58, of whom 52 with a RS<18). According to nodal status, rate of change in treatment decision was 28% for the N0 cohort and 34% for the N1 cohort.

The proportion of patients recommended to CT-HT was significantly reduced from pre-RS to post-RS (51% to 35% $p<0.0001$). CT use reduction was more evident for N1 pts cohort (55% to 26%, $p<0.0001$) than in N0 pts (49% to 41%, $p=0.042$).

Conclusions: Physicians predominantly identified for RS use pts with ER+/HER2- N0 disease with an aggressive biology or N1 pts showing a less aggressive biology. In this selected pts population, the use of RS led to a 31% rate of change in treatment decision. In the group of N1 pts, the use of RS contributed to reduce by more than a half the use of CT.

A04

ONCOTYPE DX® IMPACT ON TREATMENT CHANGE BETWEEN NODE NEGATIVE N0 AND NODE POSITIVE N1 PATIENTS IN ITALY

Masetti R.[1], Barni S.[2], Fabi A.[3], Bianchi G.[4], Colleoni M.[5], Scavina P.[6], Zampa G.[7], Gottardi O.[8], Rognone A.[9], Vigna L.[10], Naso G.[11], Santini D.[12], Pizzuti L.[3], Generalli D.[13], Giuliano M.[14], Cianniello D.[15], Burattini M.[16], Angelucci D.[17], Scognamiglio G.[18] and Cognetti F.[3]

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Aims: OncotypeDX® (ODX) is a multigene assay allowing physicians to tailor treatment in HR+, HER2- early-stage breast cancer patients. Clinical validation and utility of ODX have been demonstrated across multiple studies worldwide. It provides level 1A evidence and has been incorporated in major international clinical guidelines. An Italian market access program was initiated in 2016 in order to collect real-life data regarding the test utilization and its impact in current clinical practice.

Methods : Patients information is prospectively collected through an online database including traditional clinical and pathological features (histology, tumor grade, size, ER, PR, HER2 status and % of Ki67), patient age as well as the Recurrence Score (RS) Result and treatment recommendations before and after testing. This analysis

compared N0 and N1 (1-3 positive nodes) patients from the PONDx cohort.

Results: Data are available in 1752 patients: 1197 (68%) were N0 and 438 (25%) were N1. In the N0 cohort, patients were mainly aged 51-70 (50%), post-menopause (57%), most tumors were 1-2cm (63%), 60% were G2, with a widely distributed KI67: 10-20% (29%), 21-30% (37%) and >30% (25%). In the N1 cohort, most patients were aged 35-50 (44%) to 51-70 (44%), post-menopause (51%), and most tumors were 1-2cm (55%) to 2.1-5cm (34%), 69% were G2 tumors, and KI67 ranged from 10-20% (45%) to 21-30% (30%). 54% and 65% patients had RS<18, 35% and 30% RS18-30 and 11% and 5% RS>30 in the N0 and N1 cohorts respectively. 517 (43%) and 263 (60%) patients, in the N0 and N1 cohorts respectively had pre-ODX treatment recommendations for chemo-hormonotherapy (CT-HT). Post-ODX testing recommendations for CT-HT decrease to 386 (32%) and 127 (29%) for N0 and N1 cohorts respectively. Highlighting that testing results in sparing unnecessary CT to a significant number of patients, for both N0 and N1 cohorts. Among the latter, post-testing, physicians change treatment decision in 37% cases leading to a 34% net reduction in CT.

Conclusions: This real-life survey confirms that the assay changes treatment decisions, sparing CT (up to 57%) and the benefit of the test is seen for both N0 and N1 patients, which result in potential savings to the healthcare system.

A05

PREDICTIVE ROLE OF BASAL FLUORODEOXYGLUCOSE (FDG) UPTAKE IN STAGE II-III BREAST CANCER (BC) TREATED WITH NEOADJUVANT CHEMOTHERAPY (NACT)

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Background: Accumulating evidence suggests that early metabolic response assessed by FDG Positron Emission Tomography – Computed Tomography (PET-CT) is predictive of clinical and pathological response to NACT for BC. Only few studies investigated the predictive role of basal tumor metabolism assessed by FDG PET-CT in BC patients treated with NACT.

Methods: Patients (pts) who underwent FDG PET-CT before NACT for stage II-III BC at our institution from 2010 to 2017 were enrolled in this study, and the following data were retrospectively collected: tumor hormone receptor (HR) status, HER2 status, grading and ki67 before NACT; tumor standard uptake volume (SUV) max assessed by FDG PET-CT before NACT; pathologic response after NACT.

NACT consisted of 4 cycles of epirubicin plus cyclophosphamide followed by 12 cycles of weekly paclitaxel for all pts, with the addition of trastuzumab for pts with HER2+ BC. Pathologic complete response (pCR) was defined as the absence of invasive carcinoma both in the primary tumor and in axillary nodes.

Results: 119 pts with stage II-III BC were enrolled in the study, 50 (42%) with HR+/HER2-, 24 (20%) with HR+/HER2+, 22 (18%) with HR-/HER2+, 23 (19%) with triple-negative BC (TNBC). pCR rates were significantly different across subtypes: 0% (0/50) for HR+/HER2-, 29% (7/24) for HR+/HER2+, 64% (14/22) for HR-/HER2+, 26% (6/23) for TNBC ($p<0.001$). In the overall population mean SUVmax of primary tumor was 11, and this was considered as cut-off value to discriminate between pts with high (SUVmax $\geq$ 11) and low (SUVmax <11) FDG uptake. Pts with high FDG uptake achieved significantly higher pCR rate compared with pts with low FDG uptake (37% vs 13%, p=0.002). High tumor grade (G3) and high ki67 (≥35%) correlated with higher pCR rates (G3 vs G2: 54% vs 18%, $p<0.001$; ki67 $\geq$ 35% vs <35%: 40% vs 13%, p=0.001). At multivariate analysis, HR status (negative vs positive, OR 7.73, 2.27-26.35; p=0.001), HER2 status (positive vs negative, OR 12.30, 3.40-44.49; $p<0.001$) and FDG uptake (SUVmax $\geq$ 11 vs < 11, OR 3.96, 1.23-12.71, p=0.021) were significantly associated with pCR.

Conclusion: Our data suggest that basal FDG uptake is predictive of pCR in patients treated with NACT for BC.

A06

LYMPHOCYTES RATIOS AND LACTATE DEHYDROGENASE LEVELS: A NOVEL PROGNOSTIC SCORE FOR METASTATIC BREAST CANCER PATIENTS.

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Background: Lymphocytes ratios (LRs), in particular monocyte-to-lymphocyte ratio (MLR) and neutrophil-to-lymphocyte ratio (NLR), as well as lactate dehydrogenase

(LDH) levels have been associated with worse prognosis in several malignancies, including metastatic breast cancer (MBC). Aim of the present study was to explore the prognostic role of a novel risk score, comprising LRs and LDH levels at first-line therapy start in MBC patients (pts).

Patients and methods: Baseline parameters, tumor features and treatment data of 396 consecutive MBC pts treated between 2007 and 2017 at the Oncology Department of Udine (Italy) were retrospectively collected and anonymously analyzed. LRs and LDH levels were derived from a blood sampling performed before first-line therapy start. MLR and NLR cut-offs were previously defined through ROC analysis using propensity score-matched healthy controls (Gerratana et al 2018). The LDH cut-off value (480 U/L) corresponds to the local laboratory upper reference limit. Based on these data, an integrated LRs-LDH score (LLS) was built, ranging from 0 (both LRs and LDH low) through 1 (LRs or LDH high) to 2 (both LRs and LDH high). The prognostic impact of baseline LLS was investigated through Cox regression and differences in survival were tested by log-rank test.

Results After a median follow-up of 52.8 months, median progression-free survival was 9.2 months and median overall survival (OS) was 30.9 months. Baseline elevated MLR, NLR or LDH levels were observed in 64.2% (251/391), 70.8% (277/391), and 31.5% (70/222) pts, respectively. Overall, 78.8% (308/391) pts had elevated LRs (MLR, NLR or both). Considering subgroup analysis, no interaction was found between LDH levels and LRs. By multivariate analysis, after adjustment for performance status, biological subgroup, number of metastatic sites, central nervous system and liver involvement, a worse OS was seen for pts with elevated levels of both LRs and LDH levels compared to pts with normal ones (HR 2.41, 95%CI 1.31-4.37, p=0.003). Notably, significant differences in terms of OS were observed according to the LLS (LLS 2: median OS 19.2 months, LLS 1: median OS 43.9 months, LLS 0: median OS 54.9 months; $p<0.0001$).

Conclusions: LLS is an easy-to-obtain score that provides independent prognostic information in pts with MBC. Prospective studies are warranted to validate this score and to explore its possible role in guiding treatment strategies.

A07

MONARCH 3: ABEMACICLIB AS INITIAL THERAPY FOR PATIENTS WITH HORMONE RECEPTOR POSITIVE (HR+), HER2- ADVANCED BREAST CANCER – RESULTS FROM THE PREPLANNED FINAL PFS ANALYSIS

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Background: Abemaciclib is a CDK4 & 6 inhibitor dosed on a continuous schedule. At MONARCH 3 interim analysis, abemaciclib plus a nonsteroidal aromatase inhibitor (NSAI) significantly improved progression-free survival (PFS) (hazard ratio [HR], 0.543; 95% confidence interval [CI], 0.409, 0.723; p=.000021) and objective response rate (ORR) (measurable disease: abemaciclib arm, 59.2%; placebo arm, 43.8%; p=.004) with a generally tolerable safety profile. Here we present MONARCH 3 results from preplanned final PFS analysis.

Methods: MONARCH 3 is a double-blind, Phase 3 study of abemaciclib/placebo (150 mg, twice daily continuous schedule) + NSAI (1 mg anastrozole or 2.5 mg letrozole, daily) in postmenopausal women with HR+, HER2- advanced breast cancer (ABC) and no prior systemic therapy for advanced disease. Endocrine therapy (ET) naïve patients (pts) or pts with disease relapse >12 months after (neo)adjuvant ET were randomized 2:1 and stratified by metastatic site (visceral, bone-only, or other) and prior ET (AI, no ET, or other). Primary objective was investigator-assessed PFS. Additional objectives included ORR, clinical benefit rate (CBR), duration of response (DoR), overall survival (OS), safety and tolerability. Study was powered to 80% at 1-sided α=.025 assuming a HR of 0.67 in favor of abemaciclib + NSAI, (final analysis at 240 PFS events).

Results: Pts were randomized to abemaciclib + NSAI (n=328) or placebo + NSAI (n=165). At the final PFS analysis, 246 PFS events had occurred. Abemaciclib + NSAI significantly extended PFS (HR, 0.540; 95% CI, 0.418, 0.698; p=.000002; median: abemaciclib arm, 28.18 vs placeboarm, 14.76 months). PFS was improved across all subgroups. For pts with measurable disease, ORR was 61.0% (abemaciclib arm) and 45.5% (placebo arm) (p=.003), and CBR was 79.0% (abemaciclib arm) and 69.7% (placebo arm) (p=.037). Median DoR was 27.39 months (abemaciclib arm) compared to 17.46 months (placebo arm). An exploratory analysis of initiation to chemotherapy showed a significant increase when adding abemaciclib to NSAI (HR 0.539; 95% CI 0.381, 0.763; p=.0004; median: abemaciclib arm, not reached vs placebo arm, 32.52 months). OS was immature at the time of analysis. Adverse events were consistent with previous reports.

Conclusions: Abemaciclib + NSAI demonstrated a generally tolerable safety profile and was an effective initial treatment for pts with HR+, HER2- ABC, significantly improving PFS and ORR.

A08

REAL-LIFE USE OF THE ONCOTYPE DX BREAST RECURRENCE SCORE® TEST IN ITALY: IMPACT ON TREATMENT RECOMMENDATION AMONG CLINICALLY HIGH-RISK PATIENTS

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Objective: Oncotype DX® (ODX) is a genomic test allowing to personalize treatment decision among HR+, HER2- breast cancer patients. ODX has been extensively validated for both its prognostic and chemotherapy predictive value and the test is now included in all major clinical guidelines. A market access program collecting real-world clinical use of the test in Italy was initiated in 2016. This analysis presents results of ODX impact on clinically high-risk patients, defined according to traditional clinical & pathological criteria, locally evaluated: G3 or KI67>20%.

Method: The PONDx market access program collected real-life use of the ODX test in current clinical practice. Collected data describe clinical and pathological parameters currently used for tumor assessment (histologic type, Grade, size, ER, PR, HER2 and Ki67), patients' age, as well as ODX Recurrence Score (RS) results and treatment recommendation pre- and post-test.

Results: Data are available in 1752 patients, 1488 are selected for this analysis of which 491 have high-grade (G3) tumors, 997 patients have a high KI67 (>20%) and 384 have both G3 and high KI67. In this cohort 357 (73%) and 615 (62%) of patients with G3 and high KI67 features respectively, had pre-ODX treatment recommendations for chemo-hormonotherapy (CT-HT). Post-ODX testing recommendations for CT-HT decreases to 260 (53%) and 398 (40%) for patients with G3 and high KI67 respectively. This finding highlights that testing results in sparing a significant number of patients, unnecessary CT. Indeed, post-testing physicians change treatment decision in 36% and 36% of patients with G3 and high KI67 disease leading to a 20% and 23% net reduction in CT respectively.

Conclusion: In this Italian real-life setting, the Oncotype DX test provides critical information that changes and supports final treatment decisions in breast cancer patients clinically identified as high-risk according to traditional tumor grade and high Ki67 levels.

A09

EXPRESSION AND PROGNOSTIC ROLE OF ANDROGEN RECEPTOR IN TRIPLE-NEGATIVE BREAST CANCER: A MONO-INSTITUTIONAL RETROSPECTIVE STUDY

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Background: Triple-negative breast cancer (TNBC) is a heterogeneous disease that includes distinct molecular subtypes, including the Luminal Androgen Receptor (AR). We aimed to evaluate prevalence, correlation with clinico-pathological features and prognostic role of AR expression in a large series of patients diagnosed with primary TNBC.

Material and methods: This is a single-institution retrospective study including patients diagnosed with primary TNBC between 2000 and 2014 at Istituto Oncologico Veneto. Archived FFPE tumor tissue slides were stained for AR. AR expression on tumor cells was assessed on digitally scanned slides by Visiopharm® software. The level (%) of expression was combined with intensity to generate a score from 0 to 12; cases with AR score > 3 were considered positive, as previously described (Loibl S, BCRT 2011). Disease-free survival (DFS) was calculated from diagnosis to relapse or death.

Results: We included 214 primary TNBC patients. Mean and median AR expression on tumor cells was 14% and 0%, respectively (range 0-100%). A total of 37 patients (17%) showed a positive AR score > 3. AR-positive vs AR-negative cases presented more frequently older age at diagnosis (median yrs 68 vs 53, $p < 0.001$), stage I disease (57% vs 36%, p=0.021), lobular or apocrine histology (40% vs 2%, $p < 0.001$), G1-G2 (38% vs 10%, $p < 0.001$), lower Ki67 (median 30% vs 60%, $p < 0.001$) and lower TILs (median 5% vs 10%, p=0.006). With regards to treatment, patients with AR-positive TNBC received less frequently (neo)adjuvant chemotherapy: 65% vs 89% of AR- negative patients, $p < 0.001$. As of march 2018, with a median follow up of 6.7 years, 31% of patients experienced relapse or death: 25% of AR-positive and 32% of AR-negative patients (p=0.430). 3-yrs DFS rates were 86% vs 73% for AR-positive and AR-negative patients (HR 0.75 95%CI 0.37-1.52, p=0.430). No difference in DFS was observed according to AR-status when excluding

patients not treated with chemotherapy (HR 1.11 95%CI 0.52-2.35, p=0.792). Among patients receiving neoadjuvant chemotherapy (n=66) pathological complete response rate was 0% in AR-positive vs 25% in AR-negative patients (p=0.142) .

Conclusions: Higher AR expression is significantly associated with more favorable clinicopathologic characteristics of primary TNBC patients. However, we did not detect any significant prognostic role of AR status in this cohort. Tools to accurately define the Luminal-AR TNBC subtype are needed.

A10

EFFICACY OF SINGLE ADMINISTRATION OF ORAL NEPA (NETUPITANT PLUS PALONOSETRON) AND DEXAMETHASONE TO PREVENT CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV) IN BREAST CANCER PATIENTS RECEIVING ADJUVANT AC-BASED CHEMOTHERAPY – RESULTS FROM GIM15-NEPA STUDY

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In women with breast cancer receiving AC-based chemotherapy, antiemetic guidelines recommend a 3-drug regimen consisting in a $5HT_3RA$, a NK_1RA and Dex to prevent chemotherapy-induced nausea and vomiting (CINV).

NEPA is a fixed antiemetic combination of netupitant, a highly-selective NK_1RA and the $5HT_3RA$ palonosetron, indicated in the prevention of acute and delayed CINV.

This study was open-label, multicentre and multicycle. Antiemetic prophylaxis was administered on day 1 before each AC administration, for a maximum of 4 cycles.

The main objective of the study was to evaluate the rate of patients achieving and maintaining the efficacy on CINV of a single dose NEPA plus Dex on day 1 only, analysing the complete response (CR: no emetic episode and no use of rescue medication) during the overall phase (0-120h) after chemotherapy administration.

The following secondary endpoints were evaluated between 2 consecutive cycles: Emesis-Free, No Significant Nausea (NSN – no more than mild nausea), Regular Caloric Intake.

The AC regimen reflects the real clinical practice.

The statistical hypothesis was based on one stage Fleming design for the determination of responder percentage. The maximum value for which the treatment was considered ineffective was 0.64, while 0.74 was the minimum value for which the treatment was considered effective.

146 patients were administered 1 oral capsule of NEPA and Dex 12 mg.

The primary endpoint was reached during all 4 cycles. During all the intercycle intervals, secondary endpoint rates were high and rates were maintained supporting the hypothesis of a treatment efficacy persistence over time (Table 1).

NEPA was well tolerated. Most adverse events were mild and moderate grade and consistent with the safety profile of NEPA as reported in SmPC.

This study confirmed the results of the pivotal study in a real clinical setting practice showing a clinically relevant efficacy of one day NEPA plus Dex in preventing CINV

Table 1. Primary and secondary endpoints.

Overall Phase (days 1-5)				
Cycle	**1**(n=139)	**2**(n=139)	**3**(n=138)	**4**(n=136)
% CR	70.5	70.5	72.5	70.6
% Emesis-free	94.2	94.2	95.7	91.2
% Regular Caloric Intake	68.3	61.9	66.7	67.6
Intercycle intervals (days 6-21) - Patients average percentage				
Cycle	**1**(n=138)	**2**(n=138)	**3**(n=135)	**4**(n=135)
% Emesis-free	99.7	99.1	99.8	99.3
% NSN	99.7	99.1	99.8	99.3
% Regular Caloric Intake	99.7	99.1	99.8	99.3

and shows an extended effectiveness beyond the risk period in breast cancer patients undergoing AC-based chemotherapy.

A11

WHOLE EXOME SEQUENCING SIGNATURES CORRELATED WITH PREDISPOSITION TO LUNG CANCER IN WOMEN PREVIOUSLY TREATED FOR BREAST CANCER

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Background: During their life, women treated for primary breast cancer (BC) are at risk to develop a subsequent lung cancer (LC; relative risk ranging from 1.38 to 5.05); this risk is further increased in case of smoking history and if adjuvant radiation (aRT) was administered for BC. We hypothesized that genetic variants might predispose patients (Pts) to develop LC after BC. Our aim was to perform whole exome sequencing (WES) to identify genes associated with such predisposition.

Patients and methods: 28 women with diagnosis of LC after BC were enrolled as study population (SP), while 32 women treated for BC and with no secondary cancer after a follow-up ⩾10 years were enrolled as control population (CP). DNA was extracted from tumors and normal tissue samples from both SP and CP. Libraries were prepared with Agilent SureSelect All Exon kit and sequenced on Illumina HiSeq2500. Variant calling was performed with FreeBayes software.

Results: The median age of SP at BC diagnosis was 63.5 years (range: 47-76); the median interval between diagnosis of BC and occurrence of LC was 4.5 years (range: 0-11). 13 Pts (46%) were never-smokers and, among the 21 Pts who had received aRT, 13 (62%) developed ipsilateral LC. At somatic analysis, no common mutation among known driver genes was shared between each BC and LC pair in SP Pts. WES performed on BC and LC samples identified two mutational signatures (S1 and S2). S1 (C>T substitutions) was observed in all BC samples and 16/28 (57%) LC samples and was more frequent in never-smokers (11 vs. 5 Pts) and among Pts who developed ipsilateral LC after aRT (10 vs. 6 Pts). S2 (C>A transversions) was observed in 12/28 LC samples (43%) and was strongly associated with smoking habit (10 vs. 2 Pts). When compared to COSMIC libraries, S2 resulted similar to COSMIC 4, common in LC samples collected from smokers. Since S1 was largely shared between paired BC and LC samples, we explored the eventuality of a genetic predisposition to S1-related malignancies with a gene-based burden test over rare germline variants in normal tissue of S1-LC Pts compared to CP Pts; 249 candidate genes were identified (FDR<0.05).

Conclusions: Our data identified two mutational signatures underlying the LC development. Germline analysis suggests that genetic variants may contribute to increase the risk of LC after BC. Validation is ongoing in an independent patient cohort.

A12

EXPRESSION OF CDK4, CDK6, TK1 AND CDK9 MAY IDENTIFY EARLY RESPONDERS TO CDK4/6 INHIBITORS IN ADVANCED BREAST CANCER

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Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) improve PFS in patients (pts) with hormone receptor-positive (HR+) advanced breast cancer. In order to better characterize the response to these agents and increase our knowledge on the pharmacogenetic profile of CDK4/6i, the aim of this study was to analyze the expression of targets relevant to the activity of CDK4/6i in plasma-derived exosomes.

Methods: Blood samples were collected from pts affected by HR+, HER2- advanced breast cancer receiving palbociclib/ribociclib in association with hormonal therapy. Three ml of plasma were taken at the beginning of treatment (baseline) and at the first clinical evaluation (after 3 months). Objective responses were defined following the RECIST criteria v.1.1. RNA from plasma-derived exosomes was extracted by the ExoRNeasy kit (Qiagen) and analysed for the expression of thymidine kinase 1 (TK1), CDK 4, 6 and 9 by digital droplet PCR (BioRad). Mann-Whitney test was applied.

Results: Thirty-four metastatic breast cancer pts were prospectively enrolled in this study. 18 (53%) pts had newly diagnosed advanced breast cancer. 27 out of 34 (79%) had visceral disease, 7 (21%) non visceral disease. Most pts (n=21; 62%) had two or more metastatic sites. 22 pts

received aromatase inhibitor + CDK4/6 inhibitor (20 palbociclib, 2 ribociclib) and 12 fulvestrant + palbociclib. 17 pts received a CK4/6 inhibitor as intial treatment for advanced disease, while 17 pts had already received =1 line of treatment (range 2-9, medium number 4,7). Objective responses were: 1 (2,9%) CR, 4 (11,8%) PR, 16 (47,1%) SD and 13 (38,2%) PD. The comparison of changes in the expression between TK1, CDK 4, 6 and 9 at baseline compared to first evaluation was statistically significant for TK1 (PR+SD vs. PD p=0.009), CDK4 (PR+SD vs. PD p=0.020), CDK6 (PR+SD vs. PD p=0.047) and CDK9 (PR+SD vs. PD p=0.008). The univariate analysis didn't find any significant correlation between pts clinical variable and PFS (i.e. type of hormonal treatment, the line of treatment, performance and menopausal status, visceral metastasis, bone only metastasis, number of metastasis, previous hormonal or lines of chemotherapy received).

Conclusions: Althought with a limited sample size, our single-institution prospective study showed a strong association between expression of CDK4, CDK6 and in particular TK1 and CDK9 and clinical benefit from a treatment with CDK4/6 inhibitors, suggesting a possible role as predictive biomarkers.

A13

EFFECTIVENESS OF TRASTUZUMAB EMTANSINE (TDM1) IN PATIENTS WITH HER2-POSITIVE ADVANCED BREAST CANCER (ABC) PROGRESSING AFTER TAXANE PLUS PERTUZUMAB PLUS TRASTUZUMAB

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Background: In patients with HER2-positive ABC who were previously treated with taxane and trastuzumab without pertuzumab, TDM1 showed a progression free survival (PFS) of 9.6 months and an overall survival (OS) of 29.9 months. Paucity of data is available on the efficacy of TDM1 in patients progressing after the current standard first-line therapy in this setting, based on the association of a taxane plus trastuzumab and pertuzumab (i.e. the TPH regimen).

The present study aims to evaluate the effectiveness of TDM1 after first-line TPH.

Methods: The Gruppo Italiano Mammella (GIM) 14/BIOMETA is a retrospective/prospective multicenter study on treatment patterns and outcomes of patients with ABC. The present analysis was performed on patients who received second-line TDM1 after previous TPH between January 2012 and March 2017. Median PFS, 1-year OS (i.e. percentage of patients alive 1 year after the starting of TDM1) and clinical benefit rate (CB) were calculated. Descriptive statistics are reported with point estimated and 95% CIs. PFS was estimated with the Kaplan-Meier method.

Results: Out of 1858 patients included in the GIM14/BIOMETA study, 70 were eligible for the present analysis. Median age was 54 years; 36 patients (51%) had hormone receptor-positive/HER2-positive disease, and 27 (39%) had visceral involvement. All patients received TPH in the first-line setting, and 35 (50%) received taxane and trastuzumab in the adjuvant setting.

At the time of data cutoff (April 30, 2018; median duration of follow-up 17.8 months), 30 patients (43%) were still receiving TDM1. Disease progression was the reason for treatment discontinuation in the remaining cases. Median PFS was 8.5 months (95% confidence intervals [CI] 5.3-12 months), and CB rate was 73%. One-year survival rate was 91%.

Conclusions: Our findings suggest that TDM1 is effective in patients progressing after TPH. A better performance was observed as compared to data previously published on TDM1 effectiveness after first-line TPH.

A14

METASTATIC TNBC BREAST CANCER REAL LIFE TREATMENT AND OUTCOMES: A MULTICENTRIC ITALIAN OBSERVATIONAL STUDY

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Background: Triple negative breast cancer (TNBC) is defined by the lack of expression of estrogen, progesterone and Her2 receptors. Nearly 10-17% of new diagnosed breast cancer are TNBC. TNBC is characterized by high rate of recurrences and worse outcomes.

Material and methods: From 2000 to 2018, 13 GIM (Gruppo Italiano Mammella) centers registered 1911 metastatic breast cancer patients (pts) in GIM14 Biometa

study. Among these patients we selected 123 triple negative metastatic breast cancer (TNmBC) pts (ER <1 %, PgR <1%, Her2 negative). Progression free survival (PFS) and overall survival (OS) rates were calculated by Kaplan-Meier method.

Results: The median age of pts was 54 years (range: 26-94) and 33 pts (26.8%) were premenopausal. 22 (18%) pts were M1 ab initio. Neoadjuvant chemotherapy was administered in 30 pts (24.4%) and adjuvant chemotherapy in 76 pts (62%), 12 pts underwent both treatments. Median DFS was 23 months (range:4-139). Both visceral (VM) and non-visceral metastases (NVM) were observed in 42 pts (34%), NVM alone in 53 pts (43%), VM alone in 27 (22%). Data from 1 pt were not available. 7 pts (6%) had brain metastasis. Among 117 pts with available data, taxane-based first line chemotherapy was administered in 55 (47%), other CTs in 62 (53%). First line CT responses were RC in 6 pts (5%), RP in 21 pts (18%), SD in 22 pts (19%) and PD in 19 pts (16%), with a response rate of 23% and a clinical benefit rate of 42%. The median PFS was 5.7 months (range:5-6.5; available data among 93 pts) and the median OS was 21 months (range:16- 26).

Conclusions: The "real life" results of GIM14 study confirmed poor prognosis and aggressive behaviour of TNmBC pts and showed a PFS and OS similar to those observed in the recently published TNT trial (Tutt A. et al. Nature Medicine, Apr. 2018; PFS: 5.7 vs. about 4 months. OS: 21 vs. about 12 months).

A15

LYMPHOCYTE RATIOS (LRS) AND CIRCULATING TUMOR CELLS (CTCS) IN METASTATIC BREAST CANCER (MBC): A NEW POTENTIAL LINK BETWEEN IMMUNITY AND TUMOR BIOLOGY

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Background: Circulating tumor cells (CTCs) in MBC are a promising prognostic factor and a candidate for the dynamic assessment of tumor biology, including metastasizing potential. Aim of this study was to investigate the integration of adaptive immunity biomarkers such as monocytes', neutrophils' and platelets' LRs (MLR, NLR and PLR) with CTCs phenotypic data as an indicator of the interplay between MBC, immunity and inflammation.

Methods: DEPArray microfluidic system was employed to detect and sort $CD45^{neg}$circulating cells (CC) from the peripheral blood of 44 MBC patients (pts) enrolled at the University Hospital of Udine, Italy, between 2013 and 2015, regardless of the line of treatment. The $CD45^{neg}$ CC phenotypes were determined using a multiparametric fluorescence analysis and categorized in epithelial (E CTC), mesenchymal (MES) and transitional (EM CTC). MLR, NLR and PLR cut-offs were previously obtained through ROC analysis using propensity score-matched healthy controls (Gerratana et al 2018). Kruskal Wallis test was employed to explore the association between LRs and $CD45^{neg}$CC subsets. CC counts were considered both as a percentage of total $CD45^{neg}$CCs and as absolute numbers.

Results: In pts with HER2 positive MBC, PLR was significantly associated with E CTC (P=0.042), while in luminal-like MBC pts, both NLR and PLR were significantly associated with EM CTC (P=0.016). Notably, only MLR was associated with EM CTC in the total population (P=0.02) and a trend was observed with respect to luminal-like MBC. MLR^{high}pts with 2 or more sites of distant involvement, had higher EM CTC and lower MES (P=0.015 and P<0.001, respectively). Furthermore, pts with visceral involvement had higher EM CTC and E CTC when MLR^{high} (P=0.036 and P=0.031, respectively) and E CTC when PLR^{high} (P=0.025), while MES was significantly lower when MLR^{high}(P=0.001). Interestingly, in case of liver localizations, the MLR^{high}subgroup showed higher E CTC (P=0.022) and lower MES (P<0.001). Pts with bone localizations had lower MES when MLR^{high}(P=0.004).

Conclusions: We demonstrated that MLR is associated with $CD45^{neg}$CC subtypes proportions and, indirectly, predicts metastatic spread. The direct association with EM CTCs suggested an interesting interlink between CTCs and immunity in MBC pathogenesis and progression. Further studies should be conducted to explore more granular classifications for $CD45^{neg}$CC.

A16

PONDX: A PROSPECTIVE MULTICENTER ITALIAN SURVEY OF THE 21-GENE ASSAY: IMPACT ON TREATMENT SELECTION IN LOBULAR BREAST CANCER PATIENTS

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Aims: The 21-gene Onco*type* DX Recurrence Score test has been extensively validated to predict the risk of distant recurrence and the magnitude of response to hormone and chemotherapy in patients with ER+ N0 and N1-3+ HER2- early stage breast cancer. Outcomes data from multiple large studies further confirm the assays clinical validity and utility. In 2016, a market access program has been initiated to address lack of data in current clinical practice in Italy. It collects data assessing the real-life use of the test in Italy and its impact on treatment decision. This analysis focuses on patients with lobular tumors.

Method: Participating centers collected patients' information, prospectively, through an online database including traditional clinical and pathological features (histology, tumor grade, size, ER, PR, HER2 status and % of Ki67), patient age as well as the 21-gene Recurrence Score Result and treatment recommendations before testing and final therapy prescribed after Recurrence Score result is known in each participating center.

Results: Data are available in 1752 patients, 214 are selected for this analysis of patients with lobular tumors. In this cohort patients' characteristics were distributed as follow: age 35-50 (34%), 51-70 (44%), >70 (21%); pre-, peri- and post-menopause were 30%, 8% and 60% respectively, and there was 64% N0, 8% Nmic and 29% N1. Most tumors were 1-2cm (54%) and 2.1-5cm (34%), G2 and G3 in 64% and 27% patients, and KI67 was widely distributed: <10% (14%), 10-20% (41%), 21-30% (31%) and >30% (14%). Sixty-seven percent patients had RS<18, 29% RS18-30 and 4% RS>30. In this cohort 100 patients (49%) had pre-ODX treatment recommendations for chemo-hormonotherapy (CT-HT). Post-ODX testing recommendations for CT-HT decrease to 47 patients (23%). This finding highlights that testing results in sparing a significant number of patients, unnecessary CT. Indeed, post-testing physicians change treatment decision in 32% leading to a 26% net reduction in CT.

Conclusions: The 21-gene test provides critical information that changes and supports final treatment decisions in lobular breast cancer patients leading to important CT net reduction and thus potential cost-saving.

A17

PLATINUM-BASED NEOADJUVANT CHEMOTHERAPY IN TRIPLE-NEGATIVE BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The role of platinum-based neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) patients is highly controversial and is not endorsed by current guidelines. The present meta-analysis aimed to better elucidate its activity, efficacy and safety.

Methods: A systematic search of MEDLINE, Web of Knowledge and conferences proceedings up to October 30, 2017 was performed to identify randomized controlled trials (RCTs) investigating platinum-based vs. platinum-free neoadjuvant chemotherapy in TNBC patients. Summary risk estimates (odds ratio [OR] and hazard ratio [HR] with 95% confidence intervals [CI]) were calculated for the effect of platinum-based vs. platinum-free NACT in terms of pathological complete response (pCR: ypT0/is pN0), event-free survival (EFS), overall survival (OS), and grade 3-4 adverse events (AEs: neutropenia, anemia, thrombocytopenia and neuropathy). Pooled analyses were performed using the fixed- and random-effect models. This study is registered in the PROSPERO website (CRD42018080042).

Results: Nine RCTs (N=2,109) were included. Overall, platinum-based neoadjuvant chemotherapy significantly increased pCR rate from 37.0% to 52.1% (OR 1.96, 95% CI 1.46-2.62, P<0.001). Platinum-based neoadjuvant chemotherapy remained significantly associated with increased pCR rate also when including only the three RCTs (N=611) that used the same standard regimen in both groups of weekly paclitaxel (with or without carboplatin) followed by anthracycline and cyclophosphamide (OR 2.53, 95% CI 1.37-4.66, P=0.003). Conversely, among the 96 *BRCA*-mutated patients included in two RCTs, the addition of carboplatin was not associated with significantly increased pCR rate (OR 1.17, 95% CI 0.51-2.67, P=0.711). In the two RCTs (N=748) reporting survival outcomes, no significant difference in EFS (HR 0.72, 95% CI 0.49-1.06, P=0.094) and OS (HR 0.86, 95% CI 0.46-1.63, P=0.651) was observed.

Platinum-based neoadjuvant chemotherapy was associated with a significantly higher risk of grade 3-4

hematological AEs and no increased risk of grade 3-4 neuropathy.
Conclusion: In unselected TNBC patients, platinum-based neoadjuvant chemotherapy significantly increased pCR rates at the cost of worse hematological toxicities. The addition of platinum to neoadjuvant chemotherapy may be considered an option in these patients.

A18

IMPACT OF ADJUVANT TREATMENT WITH AROMATASE INHIBITOR ON RESTLESS LEGS SYNDROME IN POSTMENOPAUSAL WOMEN WITH ENDOCRINE RESPONSIVE EARLY BREAST CANCER (NCT02166281)

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Background: Restless legs syndrome (RLS) is a sensorimotor disorder characterized by uncomfortable and unpleasant sensations in the legs that are relieved by movement that may cause considerable sleep disruption and insomnia. One of the aim of NCT02166281 was to evaluate prospectively the prevalence of RLS in EBC pts before starting AI and the change in RLS frequency during therapy and its correlation with insomnia, depression, anxiety and quality of life (QoL).
Patients and method: Between March 2014 and November 2017 154 EBC patients (pts) candidate to AI therapy referred to Breast Unit and Oncology department of Spedali Civili Hospital were enrolled. The following questionnaire were administered at baseline and after 3, 6 and 12 months from starting AI therapy: International RLS Study Group scale, Pittsburgh Sleep Quality Index, Insomnia Severity Index, Hospital Anxiety and Depression Scale and Functional Assessment of Cancer Therapy?Breast. Moreover, in a subgroup of 41 pts sleep disturbances were studied using actigraphy for 7 consecutive nights according to the same timeline.
Results: The prevalence of RLS at baseline was 23,4% (36/154 pts), and had a statistically significant increase at the third month during AI therapy (37%; $p = 0.02$). Sixty % of pts reported sleep abnormalities at baseline, 28% anxiety and 14% depressive disorder. The prevalence and severity of psychologic distresses and quality of life did not change during the first 12 months of treatment. Noteworthy pts with RLS had lower quality of sleep ($p = 0.001$), higher levels of anxiety ($p = 0.001$) and depression ($p = 0.001$) and worse QoL ($p = 0.004$) either at baseline and during the 12 month treatment. A significant relationship was found between RLS assessed by questionnaires and the evaluation of the actigraphic report done by a sleep specialist: pts with moderate or severe RLS according to IRLSSG scale had a lower actigraphic score compared to their counterparts ($p = 0.034$).
Conclusions: RLS is a relevant disorder in EBC affecting nearly 24% of pts. AI therapy led to an increase in both frequency and intensity of RLS while did not have any impact on the other psychologic distresses and QoL. However the highly correlation between RLS and greater anxiety, depression, sleep disorders and worse QoL suggest that IRLS could be potentially a simple effective tool to identify frail patients who need additional medical or psychological support during adjuvant hormone therapy.

A19

TIME TO TREATMENT CHANGE (TTC) AS A SURROGATE END POINT OF PROGRESSION FREE SURVIVAL (PFS) FOR REAL WORLD STUDIES (RWS) IN METASTATIC BREAST CANCER (MBC) PATIENTS (PTS). RESULTS FROM THE GIM 13-AMBRA STUDY

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Background: RWS are a useful method to evaluate clinical outcome of cancer pts, however their results are difficult to compare to randomized trials, mainly regarding time parameters, such as PSF, due to the absence of preplanned time-line evaluations. AMBRA is an observational study, aiming to describe the choice of first and subsequent lines of treatment in HER2-ve MBC pts receiving chemotherapy (CHT). One of the aims is the validation of TTC as a surrogate parameter of PFS. The present analysis is focused on the comparison between TTC and PFS of 1st-line Paclitaxel + Bevacizumab (P+B) as an example of TTC performance in RWS.
Patients and methods: PFS was calculated using the progression dates declared by physiscians. TTC was defined

as the time between 1st line CHT start and the beginning of the subsequent therapy, if any, or the last observation or death. Since some pts could have changed therapy due to side effects rather than progressive disease, we considered acceptable a difference of ± 8 weeks.

Results: Pts treated with P+B were 173/607 CHT (28.5%). Median age at relapse was 52 years with median DFS of 49 months. Median TTC was 9.36 months (40,67 wks) and median PSF 10.8 (46.92 wks). The difference of 6.2 weeks is not significant (Wilcoxon rank-sum Test, a0.050, p=0.089) and within the pre-planned boundary limit. Median Overall Survival was 5.9 years. Median Survival from declared first progression was 18.1 months and from start of 1stline P+B of 16.1 mos (#8 wks).

Discussion: A tentative comparison with P+B arm of the 1st-line E2100 trial (Miller et al, NEJM 2007) and our results is shown in table 1.

PFS in our study is 1 months shorter vs E2100, and seems reliable for the clinical setting because of a different population mainly for the higher nr of adjuvant taxanes and Luminal tumors. The 6 wks difference in 1st line and 8 wks in metastatic survival of TTC vs PFS confirm the reliability of TTC because of the increase of treatment delays as compared to the declared 2nd or further progression.

	E2100	GIM-13 AMBRA
Median PFS (months)	11.8	10.7
Median age (ys)	56 (29-84)	52 (32-83)
Luminal subtypes	65.5%	76.8%
Visceral disease	79.5%	72.8%
DFS > 24 months	58.5%	78.6
Taxane adjuvant	17.3%	37%

Conclusions: TTC is a valid surrogate end point of PFS in RWS and should be considered the most reliable choice for new observational trials.

A20

RANK EXPRESSION IN CIRCULATING TUMOR CELLS (CTCS): CLINICAL UTILITY IN MONITORING METASTATIC BREAST CANCER PATIENTS (MBC) UNDER DENOSUMAB TREATMENT

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Introduction: The direct pro-metastatic effects of RANKL, independent of osteoclasts, via activity on RANK-expressing cancer cells suggest an anticancer effect of Denosumab, a human monoclonal antibody (mAb) against RANKL. Hence, we consider the RANK expression on the surface of circulating tumor cells (CTCs) in metastatic breast cancer (MBC), under Denosumab therapy as predictor of treatment response in MBC and as prognosticator of skeletal outcome.

Methods: CellSearch System was integrated with a specific mAb for detecting RANK-positive CTCs. CTCs from blood were analyzed at baseline and at day 2, 7, 14, 28 after the first Denosumab administration. A companion algorithm (?AUC) was developed to express the difference between RANK-positive and RANK-negative CTC concentration-Time Area (AUC):

$$\Delta AUC = \text{RANK-positive CTC AUC} - \text{RANK-negative CTC AUC}$$

Time-to-first-SRE, Time-to-Bone-Metastasis-Progression (TBMP) and Time-to-Visceral-Metastasis-Progression (TVMP) were estimated by COX Regression analysis, evaluating ?AUC as continuous variable and as a categorical variable (cut-off value: <0 vs. >0). Moreover, to evaluate changes of CTCs' levels during treatment, we determined the Slope of the straight line connecting the pair T0-T1 of RANK-positive and RANK-negative CTCs, respectively, in individual patient. Time-to-first-SRE, TBMP and TVMP were estimated by Kaplan-Meier analysis and the p-value calculated by log-rank test according to RANK-positive and RANK-negative CTC slope.

Results: We enrolled 43 MBC: 65% patients were CTC-positive; 75% out of them showed at least 1 RANK-positive CTC. We found significant association between longer Time-to-first-SRE, TBMP and TVMP, respectively, and positive ΔAUC, expression of persistence of RANK-positive CTCs during Denosumab treatment. Furthermore, the analysis of the Slope demonstrated a significant association between positive Slope value of RANK-positive CTCs and longer Time-to-first-SRE, TBMP and TVMP, respectively.

Conclusions: The persistence of RANK-positive CTCs in MBC treated with Denosumab predicts therapy efficacy. Furthermore, more rapid is the increase of RANK-positive CTCs at the 2° day of treatment, more efficacious will be the therapy suggesting that the effective abrogation of RANKL/RANK axis by Denosumab could mobilize RANK-positive CTCs from metastatic site to pheripheral blood. Overall, we demonstrate the clinical utility of the RANK-integrated CTC test to evaluate SRE risk and bone metastasis in MBC under Denosumab therapy.

A21

BMI IS AN INDEPENDENT PROGNOSTIC FACTOR FOR LATE OUTCOME IN PATIENTS DIAGNOSED WITH EARLY BREAST CANCER: A LANDMARK SURVIVAL ANALYSIS

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Background: Obesity has been shown to negatively affect survival after early breast cancer (BC) diagnosis. The aim of this analysis is to evaluate the association between BMI and prognosis, focusing on late outcome, in a large cohort of early BC with long-term follow up.

Materials and methods: All pts diagnosed with early BC between 2000 and 2007 at our Institution with available BMI were identified.

Invasive-DFS (iDFS) event was defined as any relapse, second primary BC, second primary non-BC tumor, death from any cause. Late-iDFS was calculated from the landmark of 10 years after diagnosis and included pts free from iDFS event at that time. OS was calculates from diagnosis to death from any cause.

Results: 918 subjects were included: 51% underweight or normal weight, 32% were overweight and 16% obese.

The majority had hormone receptor-positive BC (88.3%) and was postmenopausal (64%). Higher BMI classes were associated with older age (>50 yrs, $p<0.0001$), postmenopausal status ($p<0.0001$), more advanced stage ($p<0.0001$) and nodal involvement ($p<0.0001$).

Late-iDFS rates at 5 years after the landmark of 10 years post-diagnosis were: 86%, 74% and 51% for underweight/normal, overweight and obese pts, respectively (log-rank $p<0.0001$), with significantly poorer outcome for obese and overweight vs underweight/normal pts (HR 3.69, 95% CI 2.18-6.24, $p<0.0001$ and HR 1.81, 95% CI 1.07-3.06, $p=0.027$ respectively). Total late-iDFS events rates were 10%, 15% and 31% for underweight/normal, overweight and obese patients ($p<0.0001$). The type of late-iDFS events was significantly different across BMI categories, with distant relapse, second non-BC primary tumors and death from any cause showing the highest rates in obese pts ($p<0.0001$).

In multivariate cox proportional models including other significant prognostic variables BMI maintained an independent prognostic value for late-iDFS (obese vs underweight/normal HR 2.70 95% CI 1.50-4.84, $p=0.001$).

15-yrs OS rates were 78%, 71% and 62% for underweight/normal, overweight and obese pts, respectively (log-rank $p=0.097$). Cox model showed significantly poorer OS for obese as compared to underweight/normal patients (HR=1.50, 95%CI 1.03-2.18; $p=0.033$)

Conclusions: BMI was an independent prognostic factor for late iDFS after early BC diagnosis. Obese pts showed significantly increased rates of distant relapse, second non-BC primary tumor and death from any cause as late iDFS events, compared to non-obese pts.

A22

THE HERBA STUDY: A MULTI-INSTITUTIONAL ITALIAN STUDY ON PATIENTS WITH BRAIN METASTASES (BM) FROM HER-POSITIVE (HER2+) BREAST CANCER (BC)

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Background: Currently, there is no sufficient high-level evidence to establish a standard of care for patients with BM from HER2-positive BC. The aim of this study was to assess the impact of local and systemic treatments on the outcome of patients diagnosed with BM from HER2+ BC and BM over a period of 10 years, between 2005 and 2014.

Methods: Data of 154 patients were retrospectively collected at 14 Italian institutions through a specifically designed database. Patients were divided in 2 cohorts according to the period of BM diagnosis: period A (2005-2009) and period B (2010-2014), when lapatinib and stereotactic radiosurgery (SRS) became widely available in routine clinical practice in Italy, to explore whether there was any survival difference between the 2 periods.

Results: The distribution of local and systemic treatments was not significantly different between the 2 periods. Median OS was 24.5 months in the overall population, with no significant difference between the 2 periods. Significantly longer OS was achieved by surgery/SRS compared with whole brain radiotherapy (WBRT) or no treatment (33.5 vs 11.4 months; HR 0.34, 95% CI 0.22-0.52, $p<0.001$). HER2 targeted therapy was associated with better OS when compared with systemic therapy without HER targeted therapy (27.5 vs 13.8 months, HR 2.26, 95% CI 1.29-3.96, $p=0.004$) or no systemic therapy (27.5 vs 2.2 months, HR 11.53, 95% CI 6.32-21.01, $p<0.001$), with no difference between trastuzumab-based and lapatinib-based therapy. At multivariate analysis stratified by type of local treatments, systemic therapy, Karnofsky PS and neurological symptoms significantly affected the OS.

Conclusion: Based on these result, SRS/surgery and HER2 targeted therapy represent the most effective therapeutic approach, when feasible. An ongoing observational prospective study is collecting data to assess the impact of novel HER2 targeted therapy in the management of BM.

A23

PROGNOSTIC FACTORS FOR TRIPLE NEGATIVE BREAST CANCER: WHEN SAYING TIL IS NOT ENOUGH!

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Background: Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype with lack of specific targets and therapies. Presence of TIL (tumor infiltrating lymphocytes) has a well-known favorable prognostic value in TNBC. It is not clearly established which kind of TILs (peritumoral vs intratumoral) has the predominant role in recurrence and survival and if lymphoid follicles have prognostic significance in TNBC.
Materials and Methods: We enrolled 134 consecutive patients with TNBC treated in our Istitution between 2009 and 2016. The pathologist evaluated stromal intratumoral TIL percentage (area of stroma occupied by infiltrating lymphocytes), stromal peritumoral TIL percentage (percentage of stroma lymphocytes encountered in entire circumferential invasive tumor front) and primary or secondary follicles (presence of germinative component inside peritumoral stroma). Expression of AR was considered with a cut off of 10%.
Results: At the Chi-square analyses intratumoral TIL correlates with peritumoral TIL (P<0,0001) and peritumoral primary and secondary follicles (P=0,0007; P=0,0009). Peritumoral TIL relates with tumoral dimension (P=0,01), high KI67 (P=0,0025), intratumoral TIL (P<0,0001), peritumoral primary and secondary follicles (P<0,0001; P=0,0027), less progressions (P=0,0007) and deaths (P=0,0001). Peritumoral and intratumoral TIL were not statistically related with AR status (p=0,80; p=0,55).

Age (p=0,03), tumor dimension (p=0,01), limphovascular invasion (p=0,02), peritumoral TIL (p<0,0001) and peritumoral follicles (p=0,02) relates with DFS at the univariate analyses. Limphovascular invasion (p<0,0001), age (p=0,01), tumor dimension (p=0,0005), peritumoral TIL (p<0,0001) and peritumoral follicles (p=0,0067) were prognostic factors at the univariate analyses for OS. At the multivariate analysis limphovascular invasion and tumor dimension show a significant correlation with OS (p=0,007 and p=0,0008, respectively).
Conclusions: Our study suggests that lymphoid follicles and peritumoral TIL may have prognostic value in recurrence and survival of TNBC; thus, they should be specified in the histopathological report in order to modulate adjuvant treatment and identify prognostic classes and possible therapeutic targets.

A24

THE NEO-ACT STUDY: A RESTROSPECTIVE EVALUATION OF NEOADIUVANT ANTHRACYCLINE-FREE CHEMOTHERAPY (CT) WITH TRASTUZUMAB (H) IN HER2-POSITIVE BREAST CANCER (BC)

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Background: Sequential regimens with anthracyclines, taxanes and anti-HER2 agents are commonly used as neoadjuvant treatment for HER2+ BC. Few trials evaluate the efficacy of neoadjuvant anthracycline-free strategies in this setting. The Neo-ACT is a retrospective monocentric study on neoadjuvant anthracycline-free CT with H in HER2+ BC pts.
Methods: The study analyzed 83 consecutive patients (pts) with HER2+ BC, treated with neoadjuvant weekly paclitaxel (T) (80 mg/m^2 IV) and H (loading dose 4 mg/kg IV, then 2 mg/kg weekly) before surgery, followed by 1 year of adjuvant H, between 2006 and 2017 at CRO National Cancer Institute, Aviano (Italy). The primary endpoint was the pCR rate. The pCR was defined as no evidence of invasive BC, both in breast and axilla, or residual carcinoma in situ in the absence of invasive BC. The prognostic impact of baseline clinico-pathological features and pCR was investigated through Cox regression, and differences in distant disease-free survival (DDFS) according to pCR were tested by log-rank test.
Results: Of 83 patients, 41.2% were stage III and 57.5% were stage II. The 93.9% of pts had cT≥2, and 75.3% were node-positive (58% cN1, 14.8% cN2, 2.5% cN3). Of note, the 53.7% of pts were hormone-receptor positive.

Median number of TH administrations was 24. Overall, 34 pCR (41%) were achieved, with residual carcinoma in situ in 7 pts. No baseline characteristics were associated with pCR. Anthracycline-based adjuvant CT was administered to 22/83 pts (21/49 without pCR), while 49/83 pts received additional adjuvant T. With a median follow-up of 5.2 years, the 5-year disease-free survival (DFS) rate was 68.8% (95% CI 58.0-81.6%), the 5-year DDFS rate was 76.8% (95% CI 67.0-88.1%), and the 5-year overall survival (OS) rate was 89.7% (95% CI 81.5-98.8%). A significant difference in DDFS was observed according to pCR (HR 0.18 for pCR, 95% 0.04-0.80, p=.01), with a 5-year DDFS rate of 93.0% (95% CI 84.0-100%) among pts achieving pCR, and of 66.1% (95% CI 52.4-83.3%) for those without pCR. By multivariate analysis, a worse prognosis in terms of DDFS was seen for pts with stage III disease (HR 3.39, 95% CI: 1.17-9.8, p=.02) or without pCR (HR 5.03, 95% CI: 1.12-22.2, p=.03).

Conclusions: These data indicate that neoadjuvant TH do not compromise outcomes in HER2+ BC pts. Prognostic value of pCR was confirmed. A prospective validation is warranted, but escalating strategies should be pursued for pts with stage III disease or without pCR.

A25

TIME TO TREATMENT CHANGE (TTC) AS A VALID SURROGATE OF TTP IN REAL-WORLD STUDIES (RWS): THE PARADIGM OF NAB-PACLITAXEL (NAB-P) ANALYSIS IN THE CONTEXT OF GIM-13 AMBRA STUDY

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Background: One of the main limits of the RWS is the impossibility to compare time-dependent outcomes with those obtained in randomized clinical trials (RCTs), such as Time To Progression (TTP), due to the non-predefined times of disease evaluation. AMBRA is an observational study, aiming to describe the choice of first and subsequent lines of treatment in HER2-ve Metastatic Breast Cancer (MBC) pts receiving chemotherapy (CHT). In order to define a reliable time-dependent parameter for RWS, we previously compared TTC of the 1st-line combination Paclitaxel+Bevacizumab in the AMBRA study with TTP of the same line RCT (Cazzaniga et al, ASCO '18 #13081), demonstrating that TTC is a valid surrogate end point of PFS in RWS. Here, we present TTC data of Nab-Paclitaxel according to the line of treatment and BC subtype.

Patients and Methods: TTC was defined as the time between 1st line treatment start and the beginning of the subsequent therapy, if any, or the last observation or death. Since some pts could have changed therapy due to side effects rather than progressive disease, we considered acceptable a difference of ±8 weeks. Pts who received Nab-P as any line treatment were selected from the AMBRA data base.

Results: Pts treated with Nab-P were 80/878 (9.1%) independently of the line of treatment. Median age at relapse was 54.9 (range 31-80) years with median DFS of 43.5 months (95%CI49.3-71.2). Median TTC (95%CI) was 9.2 months (6.2-12.2) for 1st-line treatment (N=15), 10.7 (7.5-13.8, N=39) and 13.5 (9.5-17.5, N=26) for second- and third-line, respectively. Median TTC (95%CI) for Nab-P according to the molecular subtypes were 12.2 (1-33.8), 9.36 (5.7-14) and 4.9 (1-13.2) for Luminal A, Luminal B and TNBC, respectively. RCTs results are available for indirect comparison only for 1st-line setting (Gradishar, 2009) where median PFS was 12.9 months.

Conclusions: TTC is a reliable and useful surrogate of TTP for RWS. Nab-P provides a significant benefit in terms of disease control along the time across the lines of treatment and this result is observed especially in Luminal A breast cancers.

A26

REAL-LIFE DATA ON THE CARDIAC TOXICITY OF ADJUVANT FIXED-DOSE SUBCUTANEOUS TRASTUZUMAB IN HER2-POSITIVE BREAST CANCER

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Background: Fixed-dose adjuvant subcutaneous (s.c.) trastuzumab (T) has been approved in the treatment of early HER2-positive breast cancer (BC), based on the evidence of its non-inferiority to standard intravenous (i.v.) infusion. Few data from real-life are available regarding cardiac toxicities associated with fixed-dose subcutaneous T administration. We conducted a retrospective study in order to compare cardiac toxicity profile of adjuvant fixed-dose s.c.-T and weight-based i.v.-T, according to anthropometric data which takes into account more than simply weight.

Methods: Patients treated with adjuvant T for HER2-positive breast cancer at Humanitas Research Hospital from December 2013 to October 2017 were evaluated. T was administered at a either fixed dose of 600 mg s.c. or 6 mg/kg i.v, respectively. Data regarding previous chemotherapy, Body Mass Index (BMI), and development of cardiotoxicity (decrease in LVEF >10% points, to a value < 50%) were extracted from medical records. Four BMI classes were considered: underweight (BMI < 18 kg/sqm), normal weight (18-24.9 kg/sqm), overweight (25-29.99), and obesity (⩾30). All variables were compared with categorical tests (Pearson Chi-squared with Yates correction or Fisher exact test).
Results: A total of 260 HER2-positive BC patients receiving adjuvant T were analyzed. Median age was 56 (range, 32-88), median BMI 23.5 (range, 15.8-50.2 kg/sqm). 196 (75.38%) patients received s.c.-T and 64 (24.62%) i.v.-T. 156 had a normal weight, while 11 were underweight, 54 overweight and 39 obese. The incidence of cardiotoxicity was not different among the BMI classes according to the route of administration of T (p=0.28). In the subset of the patients who had developed cardiac toxicity, BMI did not result as a risk factor, as well as a previous treatment with anthracyclines (p= 0.89).
Conclusions: Cardiac toxicity profile of fixed-dose s.c.-T is consistent with that of weight-based i.v.-T in the real-world setting regardless differences in anthropometric data as BMI. Our study confirms safety of subcutaneous T administration, which still represents a valid and more convenient alternative to intravenous administration.

A27

SEQUERPLUS: A MULTICENTER REAL PRACTICE OBSERVATIONAL STUDY INVESTIGATING THE ENDOCRINE-BASED THERAPIES SEQUENTIAL APPROACH IN HORMONAL RECEPTOR POSITIVE (HR+) HER2 NEGATIVE (-) METASTATIC BREAST CANCER (MBC)

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Background: Despite the sequential endocrine-based therapy is recognized as the preferred approach for HR+/HER2- MBC, no data from clinical trials support the choice between the different sequential strategies.
Methods: Descriptive statistics are reported using the median (range) or frequency. Progression Free Survival (PFS) curves were estimated with the Kaplan-Meier method. Analysis were performed by SPSS version 21.0 (SPSS Inc., Chicago, IL).
Results: From 2006 to 2017, 233 patients (pts) with HR+/HER2- MBC, receiving at least two consecutive endocrine-based therapies as first therapeutic approach, were selected from 12 cancer Institutions. The median age at the time of metastasis onset was 63 (37-86) years; 76 (33%) pts were in premenopausal status; 36 (15%) had de novo stage IV disease and the remaining 197 (85%) had recurrent BC with a median Distant Free Survival of 96 months (2-396 months) from the initial diagnosis. At the beginning of MBC diagnosis 139 out of 233 (60%) pts had a single site of distant disease, 103 (44%) of which with bone only disease and 70 out of 233 (30%) pts presented visceral involvement too. The preferred first-line choice was a non-steroidal aromatase inhibitor (AIs) for 145 (62 %) pts, followed by Fulvestrant (F) used in 60 (26%) pts; the alternative options were tamoxifene (T), everolimus-exemestane (Eve-Exe) and F+AIs in 13 (5.6%), 14 (6%) and 1 (0.4%) pts, respectively. F resulted the most favourite second-line option for 108 (46%) pts; the Eve-Exe combination was choosen in 66 (28%) pts, AIs in 30 (13%) pts; T, AIs+F and Palbociclib (P)+F were administered in 8 (3.6%), 20 (9%) and 1 (0.4%) pts, respectively. For first and second-line the most common sequential therapeutic approaches resulted Ais followed by F (40%) and F followed by Eve-Exe (18%); the several alternative options were scanty used (in less than 10% of pts). The median Progression-Free Survival (PFS) from first and second-line endocrine-based therapies resulted 15.4 months (95% CI 13.2-17.6) and 10.9 (95% CI 9.4-12.4), respectively.
Conclusions: The sequential use in first and second-line setting of endocrine-based therapies for HR+/HER2- MBC improves median PFS up to 26.3 months. According to real practice experience the optimal sequences could be AIs followed by F and F followed by Eve-Exe. A role for these compounds should be redefined in the light of recently introduction of CDK 4/6 inhibitors in combination with AIs or F for the first or later lines.

A28

ARE CA15-3 LEVELS DEPENDENT ON BREAST CANCER SUBTYPE? SOME INSIGHTS TO

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Background: To date serum tumor markers (TM) Ca15-3 and CEA measurement are only indicated to support monitoring of treatment response in patients (pts) with metastatic breast cancer (BC). In fact, because of lack of sensitivity and specificity, their use to intercept BC recurrences is not recommended. Our study aimed to investigate whether TM levels at diagnosis of metastatic disease were associated to BC biological subtypes and pts' characteristics.
Material and methods: We retrospectively analyzed a consecutive cohort of 396 women with metastatic BC, treated between 2010 and 2016 at the Department of Oncology, Academic Hospital of Udine, Italy. Demographic and clinico-pathological data were collected. The association of TM levels at diagnosis of metastatic disease with biological and clinical factors was explored through multivariate logistic regression.
Results: The series included the different subtypes of BC as follows: luminal A-like (14%), luminal B-like (49%), luminal HER2 (14%), HER2 enriched (11%), triple negative (12%). Median follow up was 53 months, median progression free survival was 9 months, and median overall survival was 31 months. Of note, 51% of pts presented bone involvement and 26% had liver involvement at diagnosis of MBC; furthermore, 20% had ⩾3 sites involved. An increase of Ca15-3 and CEA baseline serum levels was present in 61% and 29% of pts, respectively. At multivariate analysis, HER2+ and TN subtypes were associated with a lower probability of high baseline Ca15-3 levels (OR = 0.24, 95%CI = 0.08-0.76, p = 0.015 and OR = 0.14, 95%CI = 0.04-0.44, p = 0.001 respectively) while the involvement of ⩾3 sites was related with higher Ca15-3 serum levels (OR = 2.56, 95%CI = 1.11-5.87, p = 0.027). Regarding CEA, only liver (OR = 1.93, 95%CI = 1.06-3.52, p = 0.030) and bone (OR = 2.03, 95%CI = 1.17-3.52, p = 0.011) involvement were associated with high baseline levels.
Conclusions: Among breast cancer subtypes, the luminal-like is the one associated with high levels of serum Ca 15-3 at diagnosis of metastatic disease. The study provides suggestions in redefining the use of TM for the surveillance of patients with BCin the perspective of their potential integration with emerging liquid biopsy assays (i.e. CTC and ctDNA).

A29

TEN-YEARS ELECTRONIC PHENOTYPING ARCHIVE AND AUTOMATED RECONSTRUCTION OF HER2+ BREAST CANCER PATIENTS CAREFLOW, THROUGH THE EXPORTABLE, OPEN-SOURCE I2B2 DATA WARE-HOUSING PLATFORM

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Background: The appropriateness of cancer-care plays a central role in modern oncology and the implementation of optimal patterns of care can improve quality metrics while achieving financial benefits and savings. Cancer careflows should address the full spectrum of the cancer journey, including diagnostic studies, cancer treatments and any other interventions of care. Unfortunately, the reconstruction of the cancer careflow is limited by the absence of integrated information in the hospital informatics system (HIS). In this project, the exportable, open-source, I2B2 data ware-housing platform was implemented to obtain an automated electronic phenotyping and accurate reconstruction of cancer careflows in HER2+ breast cancer (BC).
Material and methods: I2B2 allows to build an integrated patients data ware-house, using a taxonomy of terms, international standards and personalized concepts. Inside the i2b2's database, all available different patients data-sources, already stored in the HIS, are fully integrated and freely queryable. Moreover, the system is able to automatically reconstruct the entire cancer careflows, by temporally-based data extraction algorithms. Through I2B2, we identified the consecutive HER2+ BCs treated at Papa Giovanni XXIII Hospital in the last decade, recording all clinical relevant data (demographics, pathology reports, drugs, clinical outcomes). In a consistent sample size of patients, we validated the I2B2-automatically extracted information through a manual review of the medical records.
Results: From 2007 to 2017 we automatically identified and described 4,239 BC patients. 561 out of 4,239 (13.2%) were HER2+ BCs. Among the HER2+ BCs, 531 (95%) had early-BC: 109 (20.5%) were HR-/N-, 72 (13.6%) were HR-/N+, 202 (38.0%) were HR+/N- while 113 (21.3%) were HR+/N+. Through freely interrogation of the I2B2, we obtained all specific information about diagnosis, cancer treatments and survival outcomes. Moreover, we were able to automatically reconstruct the full breast cancer patients' careflows, from diagnosis to the last follow up/exitus.
Conclusions: I2B2 is an exportable, open-source platform able to automatically and retrospectively retrieve and integrate information from different electronic databases, already stored in HIS. In this 10 years HER2+BC analysis, we demonstrated the ability of I2B2 to use the electronic phenotyping archive for an automated reconstruction of all BC patterns of care.

A30

ABERRANT FGFR PATHWAY SIGNALING MEDIATES RESISTANCE TO CDK4/6 INHIBITORS THERAPY IN ER+ BREAST CANCER

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Background: CDK4/6 inhibitors have been approved in combination with endocrine therapy for treatment of ER+ metastatic breast cancer. The goal of this study was to discover mechanisms of resistance to ER antagonists alone and in combination with CDK4/6 inhibitors.

Results: We expressed 559 kinase open reading frames (ORFs) in ER+ MCF-7 cells treated with fulvestrant ± the CDK4/6 inhibitor ribociclib. Eleven kinases induced a >30% increase in viability in cells treated with this combination and five of these (FGFR1, FRK, HCK, FGR, CRKL) also induced resistance in secondary screens. FGFR1-amplified ER+ breast cancer cells as well as MCF-7 and T47D cells transduced with FGFR1 were resistant to fulvestrant ± ribociclib or palbociclib. This resistance was abrogated by the adding the FGFR tyrosine kinase inhibitor (TKI) lucitanib. Treatment with fulvestrant, palbociclib or both delayed growth of FGFR1-amplified ER+ patient-derived xenografts (PDXs). However, an addition of the FGFR TKI erdafitinib to fulvestrant/palbociclib resulted in complete responses without associated toxicity. Treatment of FGFR1-amplified cells with FGF2 strongly induced a CCND1 (cyclin D1) gene expression signature. Downregulation of CCND1 with siRNA restored sensitivity of FGFR1-amplified cells to fulvestrant/palbociclib, thus phenocopying the effect of FGFR TKIs. Next generation sequencing of circulating tumor DNA (ctDNA) in 34 patients pre- and post-progression on CDK4/6 inhibitors identified FGFR1/2 amplification or activating mutations in 14/34 (41%) post-progression specimens. Finally, ctDNA analysis in MONALEESA-2, the registration trial of ribociclib, showed that patients with FGFR1 amplification exhibit a progression free survival of 10.61 months vs. 24.84 months in patients with wild type FGFR1.

Conclusions: In sum, aberrant FGFR signaling is associated with resistance to the combination of CDK4/6 inhibitors and antiestrogens. Breast cancers with FGFR pathway alterations should be considered for trials using combinations of ER, CDK4/6 and FGFR antagonists.

A31

ERBB2 MUTATIONS IN HORMONE RECEPTOR POSITIVE PRIMARY BREAST CANCERS SAMPLES AND IN THEIR MATCHED ENDOCRINE-RESISTANT RECURRENCES

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Previous preclinical studies showed that mutations in *ERBB2* might represent an alternative mechanism for HER2 activation and the rate of mutations in BC is around 2%. They occur more frequently in HER2-negative (HER2-) BC and are associated with poor survival. On these bases, HER2- pts with mutation are potentially candidates for HER2-targeted therapy, as already showed by Neratinib. We evaluated the incidence of *ERBB2* mutations in 14 hormone receptor (HR) positive BC and in their matched endocrine-resistant recurrences.

Using an NGS technology, we evaluated a panel of genes including *ERBB2*, in FFPE tissues. We analysed 14 HR positive BCs and their matched recurrences. All the relapses have been developed during an endocrine treatment.

29% of pts were diagnosed with HER2+ BC, while 71% of pts developed HER2- BC. 3 pts were diagnosed at stage I, 6 pts at stage II, 5 pts at stage III. We found 8 different mutations in 9 samples: A356D, Q1206X, Q396X, Q393X, P523L, I654V, G1220C, 135+3G>T. Only I654V was previously described in literature. All but one (135+3G>T) of these mutations are exonic variants. 5 mutations were in the extracellular domain, 1 in the tyrosine kinase domain and 2 in the carboxy tail. 28.6% of pts had *ERBB2* mutations in the primary BCs and 35.7% in the relapsed site. 66.6% of HER2+ primary BCs showed an *ERBB2* mutation, while only 21% of HER2- samples brought a mutation. 2 patients acquired a new mutation in the relapsed site, while 1 patient lost the mutation in the relapsed tissue. The mDFS was 35.3 months. mDFS in HER2+ and/or mutated pts was 46.4 months, while mDFS in HER2- wild type pts was 28.5. The mOS was 104 months (6 pts still alive). mOS in HER2+ and/or mutated pts was 115.6 months while mOS in HER2- wild type pts was 97.5.

We found an overall detection rate of mutations higher than that described in literature (*ERBB2* mutations were present in 32.1% of our samples), meaning that our pts have been highly selected. In fact, only tumors relapsing

under an endocrine treatment, and thus with proved endocrine resistance, have been included in our analyses. The identification of an *ERBB2* mutation in primary BCs might justify a more targeted neo/adjuvant approach and, might guide the subsequent treatment choices when the mutation is identified in the relapsed tissue. Contrary to previous literature, in our study the majority of mutations occurred in HER2+ samples and HER2+ and/or mutated samples did not show worse outcomes.

A32

BALD IS BEAUTIFUL: NO MORE. THE STIGMA OF ALOPECIA DURING CHEMOTHERAPY: BRINDISI ONCOLOGY DEPARTMENT EXPERIENCE

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Background: The cancer treatments bring with it body image challenges, causing low self-esteem and contributing to worsen the quality of life. Chemotherapy (CT)-induced hair loss (HL) is one of the most emotionally distressing side effects of several breast cancer (BC) treatments. The DigniCap system (DCS), using the scalp cooling system, has been shown to reduce CT-induced alopecia (A) in a multicenter prospective trial. The purpose of this prospective observational study was to describe our experience

Methods: Two DCS device are available at the Brindisi Oncology Dpt. From February 2016 and May 2018, 86 consecutive early stage BC pts who received anthracycline and/or taxane-based treatment were enrolled, post local Ethics Committees approval. A nurse and a psychologist were dedicated for these pts. Success of scalp cooling was defined according to the Dean's scale: G0= no HL; G1 < 25% HL; G2=25–50% HL; G3=50–75% HL; G4 >75% HL.

Results: A total of 86 women were included in the following treatment cohorts: n= 37 (43%) received 4 courses of EC (epirubicin at 90 mg/m2 and cyclophosphamide at 600 mg/m2 intravenously (IV) on day 1, with 21 days between cycles) followed by 12 courses of Paclitaxel (P) 80 mg/m2 IV once a week); n=39 (45%) received only 4 courses of EC and n=10 pts (12%) P (80 mg/m2 IV once a week) and concurrent Trastuzumab (2 mg/Kg IV; loading dose 4 mg/kg) for 12 consecutive doses. Median age was 48 years (range 31-74). Overall success was observed in 61 pts (71%) (tab2). Full preservation of the hair (G0) was observed in 16 pts (19%), G1 in 31 pts (36%) and G2 in 14 pts (16%)(tab 1). Most frequent scalp cooling-related symptoms were: coldness (n=70, 81%), neck pain (n=50, 58%) and headache (n=60, 70%). Overall, 11% (n=9) of pts discontinued DCS because of unsatisfactory hair preservation (n=5, 6%) and cold discomfort (n=2; 2.5%). Furthermore we observed a hair growth when DCS was continued for pts with A G3 – G4.

Tab 1. A/HL according to the Dean's scale.

ALOPECIA H/L	G0	G1	G2	G3	G4
N (%)	16 (19%)	31 (36%)	14 (16%)	20 (23%)	5 (6%)

Tab 2. Overall Success/Unsuccess according to the Dean's scale.

Overall Success (G0 – G2)	N= 61 (71%)
Overall Unsuccess (G3 – G4)	N= 25 (29%)

Conclusions: Our results confirmed and reinforced previous evidences, showing that DCS is a good chance to prevent A during CT with anthracycline and/or taxane-based regimen and supported the wider use to all women with early stage BC.

A33

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: Structural alterations of *BRCA1/2* genes predispose to 3-5% ovarian and breast cancers, mostly early onset, bilateral/multiple, with positive cancer family history. Multidisciplinary Therapeutic and Preventive Clinical Pathways have been developed for affected and unaffected carriers, respectively. Some founder mutations have been

reported in Italian population. We reported a new founder *BRCA1* mutation, c.4117G>T - p.Glu1373*, predisposing to Breast/Ovarian Cancers, recurring in unrelated families of Abruzzo and Lazio regions of Central Italy.

Material and methods: Preliminary analysis of unrelated families carrying *BRCA1* c.4117G>T nonsense mutation reported in the Hereditary Breast/Ovarian Cancer Registry of the Oncology Territorial Care Unit, Oncology Network ASL1 Abruzzo, University of L'Aquila and Genetic Unit, Policlinico Gemelli, Catholic University of Rome, identified 17 unrelated families. Genetic counselling was performed in affected and unaffected probands, peripheral blood was collected after written informed consent, from 52 affected and unaffected probands. *BRCA1/2* genetic analysis were performed by direct sequencing. Post-test genetic counselling was performed properly addressing Therapeutic and/or Preventive Clinical strategies. Geographic area of origin, cancer family trees, cancers affecting the probands were collected. Haplotype analysis was carried out using microsatellite markers in the 17q21 region: *D17S846, D17S1328, D17S855* (intragenic), *D17S902, D17S806*.

Results: *BRCA1* c.4117G>T mutation was identified in 17 unrelated families with familial origin in a territory along the Liri river between Tagliacozzo (L'Aquila, Abruzzo) and Sora (Frosinone, Lazio). The c.4117G>T variant was always and significantly associated with the Allelic Variant (AV) *BRCA1*, c.3119G>A (p.Ser1040Asn), (allele frequency 1.3% according to data ExAC), 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.

Conclusions: The *BRCA1* c.4117G>T is a founder mutation common in the territory of Central Italy in Abruzzo and southern Lazio regions, cosegregating with AV *BRCA1* c.3119G>A. It provides faster identification of affected and unaffected carriers, to specifically address therapeutic and preventive clinical pathways for breast, ovarian and BRCA1-related cancers, to reduce their incidence in this territory of Central Italy.

A34

PROGNOSTIC IMPACT OF KI-67 CHANGE IN LOCALLY ADVANCED BREAST CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY: A SINGLE INSTITUTION EXPERIENCE

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Background: Systemic neoadjuvant chemotherapy (NCT) is the current standard treatment option for locally advanced breast cancer (LABC). Detection of prognostic and predictive clinicopathological features in NCT treated patients is required for a correct decision-making after surgical resection. In this setting the prognostic and predictive role of ki-67 proliferation index before and after NCT is yet a subject of debate and few data regarding ki-67 change due to NCT are available. The aim of our study was to investigate the prognostic role of the change in ki-67 before and after NCT in a subset of LABC patients which did not achieved pathological clinical response (pCR).

Patients and Methods: We retrospectively analyzed data of consecutive patients who received an anthracycline and taxane-based NCT for LABC (stage II-III) between August 2005 and April 2017 and did not achieved pCR. Expression of ki-67 was assessed in pre- and post-NCT tissue samples. Based on the change of Ki-67 we stratified three groups of patients: high reduction (>20%), low reduction (1-20%) and no reduction or increase in ki-67 index. These groups were then correlated with clinicopathological data by chi-square test. We estimated Relapse-free survival (RFS) and overall survival (OS) using Kaplan-Meier method and we adopted univariate and multivariate Cox proportional hazard models.

Results: We selected 82 patients from a database of 143 patients, excluding those who achieved pCR: median age at diagnosis was 54 years (range 30-75); 35 patients (42,7%) were ER+ HER-2-, 16 (19,5%) ER+ HER-2 +, 10 (12,2%) ER- HER-2 + and 21 (25,6%) ER- HER-2 negative. A significant correlation between high reduction in ki-67 and luminal B HER-2-negative molecular subtype was observed (p= 0,0035). Change in ki-67 was significantly associated with RFS (p=0,0596) and OS (p=0,0120) and this correlation was confirmed at multivariate analysis (p=0,0256 95% CI 0,3589-0,9333 for RFS; p= 0,0093 95% CI 0,2962-0,8406 for OS). In particular, as compared to patient with low/no reduction of Ki-67, those with high Ki-67 reduction (≥20%) after NCT showed the better survival (90% vs. 70% vs. 55% after 5 years from diagnosis, respectively; p=0.01).

Conclusions: In our study ki-67 change showed a significant prognostic role in LABC patients treated with NCT who did not achieved pCR. Crucially, Ki-67<20% identifies a high-risk population that may be eligible to clinical trials with novel therapeutic interventions in the adjuvant setting.

A35

PHARMACOGENETIC INTERACTION ANALYSIS IN ADVANCED BREAST CANCER PATIENTS TREATED WITH PACLITAXEL AND BEVACIZUMAB

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Background: In our previous study (Pharmacogenomics, 2014) we described a possible pharmacogenetic interaction between VEGFR-2 rs11133360 and IL-8 rs4073 genotypes that could predict a better outcome in terms of Progression Free Survival (PFS) when pts are treated with Paclitaxel plus Bevacizumab. In 113 patients (pts) the median PFS was 14.1 months (95% CI: 11.4–16.8) and 10.2 months (95% CI: 8.8–11.5) for the favorable and the unfavorable genetic profile, respectively (HR: 0.44, 95% CI: 0.29–0.66, $p < 0.0001$). Based on this results we planned a prospective trial including a control arm cohort with the aim to confirm previous data.

Material (patients) and methods: Prospectively, we included pts treated with Bevacizumab (10 mg/Kg on days 1 and 15) and Paclitaxel (90 mg/m2, on days 1, 8 and 15) as first-line treatment for HER2-negative metastatic breast cancer in 11 Italian Oncology Units between January 2009 and May 2017, and pts treated only with only chemotherapy (CT). Analyses performed on germline DNA obtained from blood samples collected are still ongoing and will be presented to the meeting.

Results: 215 patients (Pacliaxel + Bevacizumab cohort) were included in the final analysis. 20,5% of pts were =65 years old. 81.4% and 18,6% of patients had luminal and triple negative breast cancer, respectively. 65% of pts received adjuvant CT and 26% received adjuvant taxane-based CT. 60% received adjuvant ormonotherapy. About 26,5% of pts had a disease free interval < 12 months. 67.9% of patients had both visceral disease and = 3 sites involvement. 74,4 % of pts received Bevacizumab as maintenance. Overall response rate was 67% . After a median follow-up of 35 months, median PFS and overall survival (OS) were 11,8 months (95% CI: 15.1-20.7) and 30,7 months (95%CI: 25.9-35.4), respectively. As a note about 28% of pts were alive at 4 years.

Conclusions: Our data can be overlapped with those of the literature with a better performance in terms of overall survival (30,7 vs 26,7 months - Miller 2007, NEJM). Patients included had triple negative breast cancer, progressed during ormonotherapy or with a rapidly evolving disease. Of note, about one third of population are long survivors. However, pharmacogenetic evaluation is actually pending and it will intriguing investigate if a prognostic favorable genetic profile can identify the population of pts with the highest probability of responding to Paclitaxel + Bevacizumab in terms of overall survival.

A36

ROLE OF BMI AND HORMONAL RECEPTORS IN HER-2 POSITIVE EARLY BREAST CANCER PATIENTS: DO THEY MAKE THE DIFFERENCE?

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Background: No strong evidences support the standard 12-month duration of adjuvant Trastuzumab (T) for early breast cancer (eBC) and researchers are trying to modify the treatment by either de-escalation or escalation strategies or even combining T with other HER2-inhibitors. A reliable risk stratification based on tumor biology and host factors of patients (pts) is then needed. Aim of our study was to assess the role of the interaction between BMI index and hormonal receptor (HR) expression in this setting.

Patients and methods: We retrospectively evaluated 238 women with stage I to III HER-2 positive BC treated in two Hospital (Ospedali Riuniti-UNIVPM, Ancona and AOUP, Pisa) between 2006 and 2016. Only pts who completed adjuvant chemotherapy (CHT) and 1 year of T were included. The endpoint was 3 years distant disease-free survival (3yDDFS). Survival analysis was calculated by Kaplan-Meier method and strata were taken into account by log-rank test. Multivariate analysis was performed by Cox-Model adjusting for HR status, BMI index, tumor staging, size, nodal status, grade, hospital and type of adjuvant CHT. Association among categorical variables was assessed by Chi-square test. P value was set at 0.05.

Results: HR+/HER2+ tumors were 69% (n = 165) and HR-/HER2+ 31% (n = 74). Obese pts (according to WHO categorization) were 14% while 69 of them (29%) were overweight. The distribution of BMI categories at time of

diagnosis was different (p=0.03) among HR+/HER2+ and HR-/HER2+ pts (36% of overweight/obese pts in the HR+ groups and 54% in the HR- groups). Looking at early recurrence after 3 years, only 10 events were reported (4.2% of whom 40% HR+ and 60% HR-). Neither subtype alone nor BMI alone showed association with 3yDDFS at multivariate analysis. However, the hazards for pts with HR- tumors who have also BMI⩾25 (3yDDFS 86.9%, 95% CI: 75.0-97.7%) were amplified when compared to pts with HR+ tumors and with BMI<25 (3yDDFS 98%, 95% CI: 94.8-100.0%) and other subgroups (p=0.03). This observation was confirmed at multivariate analysis (adjusted HR: 1.75, 95% CI: 1.05-2.93, p=0.03) taking the HR-/BMI⩾25 group as the reference one.

Conclusions: Our real-life data, obtained from pts whose adjuvant treatment was strongly homogeneous across subgroups, highlight a different risk of eBC distance recurrence after grouping pts by HR status and BMI index. These results, apart from potentially influencing pts' follow-up, might help future trials design at a stratification level.

A37

EVALUATION OF SAFETY AND ACTIVITY OF PALBOCICLIB PLUS HORMONAL THERAPY IN ADVANCED BREAST CANCER (ABC): A SINGLE INSTITUTION EXPERIENCE-

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Background: Palbociclib in an oral inhibitor of cyclin-dependent kinase 4/6 (CDK 4/6), approved for the treatment of ER-positive, HER-2 negative aBC in combination with endocrine therapy (ET).

Methods: We retrospectively collected all consecutive ER-positive, HER-2 negative, aBC patients (pts) treated at our institution with Palbociclib plus ET. We reported pts characteristics, outcomes and adverse events (AEs).

Results: Between April 2016 to date we identified 89 pts. 21 (23%) pts had newly diagnosed aBC. 50 out of 89 (56%) had visceral disease and most pts (n=53; 59%) had two or more metastatic sites. 50 pts (56%) were previously exposed to chemotherapy (CT) in neo/adjuvant setting. 60 pts (67%) received adjuvant ET, among them 29 pts completed five years of therapy, while 31 pts progressed during adjuvant treatment. Palbociclib was administered as first line treatment for aBC in 40 (45%) pts. 49 (55%) pts were already pretreated with ⩾1 line (range 1-9, medium number 3,2), among them 32 pts received CT for aBC before CDK 4/6 inhibitors. Pts outcome data were available for 79 pts out of 89: 3 (3,7%) CR, 14 (17,7%) PR, 42 (53,3%) SD and 20 (25,3%) PD, with a DCR of 75%. Hematological AEs were the most common toxicities reported: any grade neutropenia was observed in 87 (98%) pts, G3/G4 neutropenia in 63 (71%) pts, G3/G4 neutropenia at first cycle in 44 (49%) pts, any grade anemia in 30 (34%) pts, any grade piastrinopenia in 27 (30%) pts. The most common non haematological AEs were fatigue (72 pts; 81%), nausea (28 pts, 31%), and mucositis (21 pts, 23%). The dose of Palbociclib was reduced in 28 (31%) pts: in 25 pts for recurrent G3/G4 neutropenia, in the remaining 3 cases for G3 anemia, G3 mucositis and G3 diarrhea respectively. Nevertheless the dose reduction we observed a DCR of 85% in this subgroup. Interestingly 24 out of 25 pts (96%), who needed a dose reduction for recurrent neutropenia, showed a grade 3/4 neutropenia since first cycle; 15 out of 25 (60%) pts were previously exposed to CT in any setting.

Conclusions: In our real life experience the activity and safety of Palbociclib in combination with hormonal therapy was comparable to Paloma studies. We observed a higher risk of dose reduction of Palbociclib in pts that developed early neutropenia G3/G4 since first cycle and in pts already exposed to CT in any setting. A careful patient's proactive monitoring is strictly necessary in order to minimize the toxicity and obtain the best results of combination.

A38

A NOMOGRAMS' VALIDATION TO PREDICT NON SENTINEL NODE STATUS IN BREAST CANCER PATIENTS WITH POSITIVE SENTINEL NODE, INTRA-OPERATIVELY ASSESSED WITH ONE STEP NUCLEIC ACID AMPLIFICATION (OSNA) METHOD

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Background: In breast cancer (BC), tumor-positive sentinel node (SLN) biopsy results in a risk of nonsentinel node metastases in case of micro and macro metastases ranging from 20 to 50%, respectively. Therefore, most patients underwent unnecessary axillary lymph node dissections (ALND). Thus, the development of a mathematical model for predicting patient-specific risk of non sentinel node (NSLN) metastases is strongly warranted.

Material and methods: We identified 2 nomograms (Di Filippo et al. and Rubio et al.) for the prediction of NSLN metastasis after OSNA assessment of SLN. We applied these 2 nomograms in the BC population referred to the Breast Unit at Papa Giovanni XXIII Hospital in Bergamo in the last 5 years. Accordingly, we selected 235 consecutive patients who underwent sentinel lymph node biopsy (SLNB) and subsequent ALND for SLN (OSNA-assessed) involvement. In this cohort of patients we recorded the parameters of interest of the 2 nomograms (i.e. number of a CK19 mRNA copies, T size, Nuclear Grading and LV invasion) and we measured the prediction of the risk of NSLN metastases according to the results of the models. Thus, we compared the models' risk-prediction with the actual evidence of NSLN metastases observed at ALND.

Results: In our population both nomograms (Di Filippo and Rubio) are able to predict the risk of NSLN metastasis with an acceptable accuracy. The discriminations of the models, quantified with the area under the receiver operating characteristics (ROC) curves, were 0.66 (95% CI 0.63-0.69) and 0.63 (95% CI 0.60-0.66) respectively, confirming a good level of reliability of the nomograms, without any statistical differences between the 2 models. The best cut-off values identified through ROC curves were 45.3% (Di Filippo nomogram) and 28.0% (Rubio nomogram), representing the best compromises between false negative and positive rates i.e. when ALND is unnecessary (<45.3% or 28.0% respectively) or recommended.

Conclusions: The application of these nomograms in our population is effective and may be employed by the surgeon as a decision making tool on whether to perform an intraoperative axillary lymph node dissection on breast cancer patients with SLN positive assessed by OSNA.

A39

ERIBULIN MESYLATE(EM) ADJUSTED SCHEDULE IN METASTATIC BREAST CANCER OCTUAGENARY PATIENTS (MBC-OP): FIRST EVALUATION OF TOXICITY

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Background:. The new age in new drug development has shifted from cytotoxic chemotherapy to molecularly targeted agents. Nevertheless, Eribulin Mesylate (EM), a microtubule-destabilizing agent, is the only classical cytotoxic agent approved for the treatment of breast cancer in these last five years.

This synthetic analog of "halichondrin B," was defined also to prolong overall survival of heavily pretreated metastatic breast cancer (MBC) patients. Furthermore, main adverse events: limited neutropenia, fatigue and peripheral neuropathy are especially appreciate in the treatment of elderly population.

Aim: We lead to design new clinical trials to evaluate if EM is more effective than conventional treatments also in MBC octuagenary patients (MBC-OP).

Methods: Treatment plan: E 0.96-1.1 mg/sqm IV on d1 every 21 (Dose depend on evaluation of Creatinine Clearance according to Kintzel-Dorr's method), schedule administration continued until progression or intolerable toxicity.

Eligibility criteria: acquired written consensus; confirmed diagnosis of MBC, one or two measurable lesion, bone or visceral no brain, age: eighty years or more, progression after conventional treatments; 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.

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 2015 Jan to 2016 dec, 32 metastatic MCB-OP, mean age 83.5 were treated . 30 of these are still under maintenance therapy (2 pts discontinued treatment for personal reasons). A total of 759 cycles were delivered to pts: 6 % of these develop G4 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%.

Conclusions: EM in the treatment of MBC-OP shows non-inferiority outcomes vs. conventional treatments. Further, It appears more safety in presence of comorbidity or frailty than other chemotherapy regimens for MBC. These data shows that this regimen is more comfortable for MBC- OP. An enlarged polycentric study is ongoing to confirm these first results.

A40

CDK INHIBITORS IN HORMONE SENSITIVE AND HORMONE RESISTANT ADVANCED BREAST CANCER: A META-ANALYSIS OF RANDOMIZED TRIALS

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Background: Combining abemaciclib/palbociclib/ribociclib and aromatase inhibitors (AIs) or fulvestrant improved

outcomes for the treatment of metastatic HR+ Her 2- breast cancers. We performed a meta-analysis of randomized clinical trials (RCTs) to better define the benefit and the risk of abemaciclib/palbociclib/ribociclib plus AIs (hormone sensitive setting) or fulvestrant (hormone resistant setting) and the impact of all CDK inhibitors plus endocrinal therapy (ET) in HR+ HER 2- breast cancer.

Material and Methods: A systematic literature search of Pubmed, Embase, and the Cochrane Library was carried out up to 30 January 2018. Hazard ratios (HRs) and 95% confidence intervals (CIs) for progression free survival (PFS), as well as Odds Ratios (ORs) for objective response rates and ⩾ G3-G4 adverse events (AEs) were calculated for each trial. A pooled analysis was carried out using the random effects model.

Results: six RCTs were eligible including 3164 breast cancer patients. Adding CDKi in hormone sensitive (HR: 0.55, 95% CI 0.48-0.64) or hormone resistant setting (HR: 0.49, 95% CI 0.37-0.63) improved significantly the PFS of metastatic HR+ Her 2- breast cancers regardless menopausal status and site of metastasis. CDK inhibitors plus ET meaningfully improved PFS (HR: 0.53, 95% CI 0.47-0.59) and objective response rate (OR: 0.52, 95% CI 0.40-0.67). The use of these drugs was characterised by a significant increase of G3-G4 AEs (OR: 7.61, 95% CI 5.54-10.45) mostly due to neutropenia (OR: 83.48, 95% CI 33.88-205.69).

Conclusion: Emerging data provide a new potential standard treatment for advanced HR+/Her2- breast cancer, regardless of menopausal status, prior hormonal/chemotherapy treatments delivered, sites of metastasis. However, benefits should be balanced with longer treatment duration, toxicities and costs.

A41

CANCER TREATMENT INDUCED BONE LOSS (CTIBL) IN BREAST CANCER WOMEN: A MULTIDISCIPLINARY APPROACH AT THE MODENA CANCER CENTER SCREENING OVER 600 PATIENTS

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Background: CTIBL in breast cancer (BC) women is well know. It is commonly, but not exclusively, related to aromatase inhibitors. The "Nota 79" by AIFA contemplates the primary prevention of fracture risk in BC women in adjuvant hormonal treatment with bisphosphonates or denosumab, at osteoporosis dosage. At the Modena Cancer Center we started a collaboration with oncologists hematologists and bone specialists in order to offer the best tailored treatment in high risk fracture patients.

Patients and Methods: patients newly diagnosed with BC in hormonal treatment fill-out a form, in order to evaluate the risk factors for osteoporosis, and based on the results and the bone density they are referred to the osteoncology unit along with serological and urinary markers of bone turn-over.

Results: in over 18 months of activity, more than 600 patients have been screened by self-completed questionnaire. From the analysis of the first 400 questionnaires emerged that 61% had one or more risk factors, 20% received supplement of vitamin D, and approximately 5% were on bisphosphonates. At baseline, the measurement of the height, the evaluation of the spine at the chest X ray or by morphometry highlighted asymptomatic vertebral fractures in few patients. Several patients presented with secondary hyperparathyroidism, that required correction before to start any treatment with antiresorptive agents. Cases with hypercalciuria were also corrected along with antiresorptive therapy. Few cases demonstrated high bone turn-over with CTX levels above the limits. The treatment has been individualized based on the medical history and comorbidities, oncological treatment and the bone turnover. All the patients have been informed of the possible risk of osteonecrosis of the jaw; dental medical history was collected for each patient, but orthopanthomography and odontoiatric evaluation was prescribed in selected patients. Vitamin D level was corrected before any therapy and improvement of the dietary habits and physical activity was highly recommended. Data analysis is still ongoing.

Conclusions: all the patients receiving AIs require the prevention of CTIBL, but the limited resources pushed us to select, at this time, the patients with special needs to be evaluated in multidisciplinary group. The complexity of the bone health requires attentive evaluation by bone specialists in selected cases before to start antiresorptive agents. Supplemental data will be presented at the meeting.

A42

GENETIC TESTING FOR HEREDITARY BREAST AND OVARIAN CANCER: A 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 or 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 Methods: In the Genetic Work Group of Oncology Departments of Azienda Toscana Nord Ovest (estabilished in October 2017),144 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 (PALB2) and subsequently third-level testing (multigene panel).

Results: From October 2017 to May 2018 we have selected 144 index cases (age from 27 to 83 years) eligible for genetic testing: 107 (74.3%) with unilateral breast cancer, 17 (11.8%) with bilateral breast cancer, 15 (10.4%) with ovarian cancer. Of these, 104 (72.2%) genetic testing have been completed. BRCA mutations was detected in 38 (36.5%) patients: 17 (16.3%) had a deleterious mutation and 21 (20.2%) 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 BRCA 1 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. There is a need for providing optimal genetic counseling and testing for healthy family members.

A43

A REAL LIFE MULTICENTER TRIAL OF PALBOCICLIB PLUS FULVESTRANT IN HORMONE RECEPTOR-POSITIVE (HR+)/ HER2 RECEPTOR-NEGATIVE (HER2-) METASTATIC BREAST CANCER (MBC): ACTIVITY AND SAFETY BEYOND CLINICAL TRIALS

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Background: Palbociclib (P), a CDK4/6 inhibitor, combined with endocrine therapy (ET) represents a new standard of treatment for women with HR+/HER2- MBC. The drug has proven its activity in patients whose disease progressed after prior ET, in association with fulvestrant (F). Few data are available regarding the performance of such a regimen outside a clinical trial, especially in heavily pretreated disease.

Patients and Methods: We report a multicenter real-life experience aimed to verify the patterns of treatment and outcome of P+F in an unselected population of MBC patients. The primary aim was to verify the activity (objective response rate-ORR, clinical benefit rate-CBR, median progression-free survival-mPFS) and safety of the combination. Statistical analysis was performed to identify variables potentially predictive of treatment response and outcome. Patients received P (125 mg/day orally, 3 weeks on, 1 week off) plus F 500 mg q4wks with loading dose, until disease progression, unacceptable toxicity or patient's refusal. Dose reduction of P to 100 mg (then 75 mg) was applied in case of febrile grade 3 or 4 neutropenia or any grade ⩾3 non-haematological toxicity.

Results: The study enrolled 85 postmenopausal patients treated from December 2016 to April 2018 at 4 Italian Institutions. Median age was 63 years (range 47-77); 23 patients (27%) had *de novo* metastatic disease; 47 (55%) had visceral involvement, while 17 (20%) had bone-only disease. The median number of prior lines was 3 (range 2-5), including ET (median 3) and chemotherapy (median 2); 37 (43%) had previously received F and 13 (15%) everolimus. A partial response as best response was observed in 21 patients (25%), stable disease in 41 (48%), lasting ⩾ 24 weeks in 35% with a CBR of 60%; 23 patients (20%) had progressive disease. The most common adverse events were neutropenia (grade 1-2 in 65%, grade 3-4 in 35%), grade 1 anemia (48%) and thrombocytopenia (34%), requiring dose reduction in 25% of cases. At a median follow-up of 12 months (range 1-16), mPFS was 5.5 months in the whole cohort, 8.8 and 4.1 months in treated as ⩽ 3rd or > 3rd line, respectively (p= 0.002). No significant outcome differences were observed according to prior ET with F or everolimus, patient's age (<65 years versus ⩾65) or dominant metastatic site (visceral versus bone-only disease).

Conclusions: Our real life data confirm that P+F is an active strategy in MBC with a tolerable safety profile, including ET-pretreated disease.

A44

ENDOCRINE SENSITIVE METASTATIC BREAST CANCER AND BONE ONLY DISEASE: ARE THE NEW TREATMENTS ALWAYS BETTER?

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The standard first-line for endocrine sensitive metastatic breast cancer (BC) is represented by endocrine therapy. Several phase III clinical trials searched for more effective strategies. The SWOG, FACT and FALCON trials analyzed the role of Fulvestrant (Fv), producing contradictory results. The Monaleesa2, Monaleesa7, Monarch3 and Paloma2 trials showed that the addition of a CDK4/6 inhibitor to an aromatase inhibitor (AI) increases the PFS. The use of the combination for the first-line treatment of bone-only disease (BoD) is widely discussed. Our meta-analysis aims to explore the role of the new endocrine strategies in BoD.

The Prisma statement was used. A systematic review of electronic databases identified the phase III clinical trials comparing the standard AI to a novel experimental strategy. The hazard ratios (HR) for PFS for the subgroup of BoD were pooled in a meta-analysis. The heterogeneity of the data was evaluated by Chi-square Q test and I^2 statistic.

7 studies were included in the analyses. 4 trials explored the role of CDK4/6 inhibitors (Monaleesa2 and 7, Monarch3 and Paloma2), 2 trials analyzed Fv + AI (SWOG and FACT), while one trial studied Fv monotherapy (FALCON). 5 trials reported data regarding the BoD, while 2 trials included the BoD in the non-visceral disease. Overall, the meta-analyses showed a PFS advantage for the experimental arms [HR 0.67 p 0.01], with a significant moderate/high heterogeneity [I^2 69.88% p 0.003]. Only the FALCON and Paloma2 showed a significant improvement in PFS, respectively for Fv and Palbociclib + Letrozole. Considering only trials reporting data for BoD, the experimental arms significantly improved the PFS [HR 0.60 p 0.001], with a low/moderate non-significant heterogeneity [I^2 37.73% p 0.17].

The meta-analyses of trials reporting data for BoD, showed that the novel strategies are able to improve the PFS. Nonetheless, only Palbociclib + Letrozole provided statistically significant data of advantage in this setting. In clinical trials, BoD is often included in the non-visceral disease subgroup. Future clinical trials should take into account the differences in natural history and better prognosis of BoD, in order to define the best approach to these patients.

A45

EFFICACY AND SAFETY OF PLATINUM AND METRONOMIC CYCLOPHOSPHAMIDE IN TRIPLE NEGATIVE BREAST CANCER

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Background: Triple negative breast cancer (TNBC) accounts for approximately 15-20% of breast carcinomas and is associated with poor prognosis. Platinum-based regimens, showed efficacy in this tumor subtype, particularly in cases with defective BRCA DNA repair pathways. Cyclophosphamide administered at low metronomic doses has the potential of downregulating regulatory T cells.
Methods: Our aim was to evaluate the efficacy and safety of a combination of cisplatin and metronomic cyclophosphamide in patients with advanced TNBC. Cisplatin was administered at the dose of 60 mg/mq every 3 weeks up to 6-8 cycles; cyclophosphamide was given orally (50 mg daily) in a continuous regimen both concomitant and as maintenance therapy after cisplatin. Data on toxicity were reported according to Common Terminology Criteria for Adverse Events Version 4.0.
Results: A total of 47 patients with advanced TNBC were enrolled and treated in our Institute from October 2011 to September 2015. More than 40% of the patients received the combination therapy as second line treatment, but 36% of the cohort was largely pretreated, with ⩾3 lines of chemotherapy received in the metastatic setting. The most common adverse event (AE) was G1-G2 hematologic toxicity, but the incidence of G3 anemia and leukopenia was 2% and 9.4% respectively. Other observed AEs were nausea, vomiting, neurotoxicity and fatigue, commonly of grade 1-2. Severe adverse events occurred in 3 patients (2 thromboembolic events and 1 case of pulmonary edema). Hematologic toxicity was managed with cisplatin dose delay (23% of patients) or dose reduction (28% of patients) in the majority of cases, but 3 patients definitively interrupted treatment. An additional 10 % of cisplatin dose reduction was due to other causes. Although no dose reductions were made for cyclophosphamide, 4 patients temporary suspended treatment due to persistent neutropenia. Data on efficacy were available for 43 patients: objective response rate was 23.3 % and clinical benefit – defined as partial/complete response or stable disease at 6 months after treatment- was 57.9%. No significant correlation between response to treatment and age, extent and site of disease, or time after surgery has been observed.
Conclusion: The combination of cisplatin and metronomic cyclophosphamide showed efficacy with a favorable toxicity profile in patients with advanced TNBC. This regimen could represent a potential therapeutic option with a biologic rationale in TNBC.

A46

PROGRESSION FREE SURVIVAL (PFS) BENEFIT FROM FIRST LINE ENDOCRINE BASED THERAPIES IN POSTMENOPAUSAL WOMEN WITH HR+ HER2- METASTATIC BREAST CANCER (MBC) ACCORDING TO DIFFERENT PROGNOSTIC SUBGROUPS: A COMBINED

ANALYSIS OF DATA FROM PALOMA 2, MONALEESA 2, MONARCH 3, FALCON, SWOG AND FACT TRIALS

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Background: This analysis combines data from six phase III trials investigating the role of endocrine-based therapies in the first-line setting of MBC to identify which factors may guide the clinical choice among available drugs.
Methods: For PFS, Hazard Ratio (HR) and 95% CI were reported. Subgroup meta-analysis was conducted stratifying by age, ECOG, ethnicity, prior chemotherapy or endocrine therapy exposure, measurable disease at the time of metastasis occurrence, visceral or bone only disease, time from the initial diagnosis of breast cancer to the metastasis onset. Random-effect model was used and heterogeneity was quantified by I^2 statistics. Test of interaction was performed to compare treatment effect in subgroups. Data analysis was performed using R Statistical Software version 3.4.3.
Results: In absence of indirect comparison between cycline dependend kinase (CDK) 4/6 inhibitors (Palbociclib, Ribociclib, Abemaciclib) combined to nonsteroidal aromatase inhibitors (AIs) and Fulvestrant endocrine-based therapies, all these therapeutic options resulted in significant PFS benefit compared to AIs endocrinemonotherapy (HR: 0.74; 95% CI 0.67-0.80). Test of interaction showed similar treatment effects among subgroups with the exception of Ethnicity and ECOG. Specifically, a longer PFS from CDK 4/6 inhibitors plus AIs strategies was observed in Asian (Asian HR: 0.38; 95% CI 0.20-0.72 versus non-Asian population HR: 0.61; 95% CI 0.50-0.75, $p<0.001$) and ECOG$\geqslant$1 patients (ECOG$\geqslant$1 HR: 0.53; 95% CI 0.51-0.56 versus ECOG=0 HR: 0.60; 95% CI 0.49-0.74, $p<0.02$).
Conclusions: CDK 4/6 inhibitors or Fulvestrant endocrine-based therapies as first-line treatment for postmenopausal women with HR+/HER2- MBC showed significant PFS improvement in comparison with AIs endocrinemonotherapy. Further indirect comparison by a network meta-analysis is needed to explore which patients may derive the greatest benefit from the different therapeutics options.

A47

MIRNAS AS PROMISING BIOMARKERS IN BREAST CANCER PATIENTS

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Background: The prognostic value of pathological complete response (pCR) is still a matter of debate. Previous studies have revealed that breast cancer intrinsic subtypes show different molecular profiles and several miRNAs have important roles to regulate such subtypes. The aim of the present exploratory study was to identify potential molecular biomarkers able to predict prognosis of patients underwent to NAC (neoadjuvant chemotherapy).
Methods: We retrospectively analyzed 24 patients who received NAC not achieving pCR. Purification of miRNA from paraffin-embedded tissue sections was performed by miRNeasy FFPE kit; miRNA sequencing libraries, prepared with the QIAseq miRNA Library Kit, was sequenced using an Illumina NGS system. Identification of miRNAs in the samples was performed using the software QIAseq miRNA-NGS data analysis. The miRNA targets were predicted by the MiRDB tool.
Results: The median follow-up was 61 months. We have identified 27 miRNAs: all these miRNAs were differently ipo- or iper-expressed, when we compared the miRNAs expression in pre- and post-NAC specimens. When we correlated each of 27 miRNAs with outcome, only some of them were significantly correlated with survival. Outcome was significantly improved in patients with iper-expression of *let-7a-5p* (EFS 58 vs 28 months p 0.006 HR 0.38 (0.08-0.66) and OS 65 vs 35 months p 0.0001 HR 0.27 (0.03-0.33)), *mirR-100-5p* (EFS 56 vs 17 months, p 0.01 HR 0.39 (0.11-0.75) and OS 56 vs 39 months, p 0.03 HR 0.45 (0.15-0.94)), *miR-101-3p* (EFS 56 vs 20 months p 0.05 HR 0.48 (0.16-1.03) and OS 58 vs 35 months p 0.01 HR 0.38 (0.10-0.75)) and *miR-199a-3p* (EFS 61 vs 20 months p 0.02 HR 0.41 (0.14-0.85) and OS 69 vs 46 months p 0.01 HR 0.39 (0.13-0.80)) in post-NAC samples compared to their counterpart, independent from breast cancer subtypes. Likewise, when we analyzed *miRNA signature* (let-7a-5p, mirR-100-5p, miR-101-3p, miR-199a-3p), EFS (64 vs 20 months, p 0.004 HR 0.31 (0.4-0.66)) and OS (71 vs 46 months, p 0.005 HR 0.31 (0.11-0.68)) were significantly improved compared to their counterpart. At multivariate analysis, up-regulation of let-7a-5p only was significantly correlated with EFS (p 0.009) and OS (p 0.0008) in our cohort of 24 patients.
Conclusion: Taking into consideration all findings, our hypothesis is that overexpression of above mentioned miRNAs in post-NAC specimens may represent a signature able to identify a population at good prognosis in the group of patients not achieving pCR.

A48

CLINICAL AND PSYCHOMETRIC VALIDATION OF THE BRESAS QUESTIONNAIRE FOR SYMPTOM ASSESSMENT AMONG BREAST CANCER SURVIVORS

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Background: With improved early detection and treatment, large numbers of breast cancer (BC) patients are now surviving many years post diagnosis. The large number of women surviving many years post BC diagnosis has heightened interest in studying long-term effects of cancer on quality of life. A number of cancer-specific health-related quality of life (QoL) measures have been developed but these measures may not be appropriate for use with long-term survivors.

With this study we want to evaluate the reliability, clinical and psychometric validity of the BreSAS Questionnaire (BQ) among BC survivors.

Patients and Methods: BQ is a quick, simple 10 items module for the assessment of long-term physical, psychological, sexual and cognitive effects that may influence quality of life (pain, anxiety, depression, fatigue, irritability, quality of sleep, impaired concentration, hot flashes, vaginal itching, other). The total BreSAS score ranks from 0-100, with a low score indicating a better QoL.

Patients were not stratified into predetermined clinically distinct groups. QoL data were collected alongside standard outcomes in patients undergoing treatment for BC. Patients complete the BQ, the FACT-ES questionnaire, case report forms for clinical and socio-demographic data at different time points during follow up visits. Reliability, and clinical and psychometric validity of the questionnaires are assessed by correlation analyses, exploration of known group comparisons, and responsiveness to clinical changes.

Results: From September 2015 to February 2016, 149 patients from three Italian oncology units were enrolled. Baseline questionnaires were returned from all and the majority of patients (n=134 - 89%) completed the BQ and FACT-ES in less than 15 min. For reliability, Cronbach's alpha coefficients for each scale were greater than 0.70 in all analyzed symptoms. Convergent validity of BQ showed by Pearson's *r* demonstrated a high correlation between intensity of symptoms and QoL, especially for pain and depression. No data were provided about reproducibility with test-retest study.

Conclusions: The BQ demonstrates sufficient validity and reliability to support its use to assess patient-reported outcomes and symptom assessment during planned follow-up clinical visits among BC survivors.

A49

LEFT ATRIAL FUNCTION IN PATIENTS WHIT BREAST CANCER UNDERGOING CHEMOTHERAPY WITH ANTHRACYCLINES

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Background: Breast cancer is the most common cancer in women, usually treated with chemotherapeutic drugs, as anthracyclines, that can induce cardiotoxicity. It is well known that Left Ventricular (LV) systolic function could be impaired in patients treated by anthracyclines, but the effects on left atrial function have not been fully elucidated. The aim of this study is to evaluate the effect of this class of chemotherapeutic agents on atrial function, assessed by 2D speckle tracking imaging (STI) longitudinal strain.

Patients and methods: A total of 40 women (age 55,17±10,75 years) with localized or metastatic breast cancer were enrolled. All patients received chemotherapy with anthracyclines (Epirubicin 75 mg/mq or Doxorubicin 60 mg/mq) and underwent trans-thoracic echocardiography before chemotheraphy (baseline) and after 3-, 6- and 12-months. LV systolic function was estimated by Ejection Fraction (EF) whereas LV diastolic function was evaluated by mitral inflow E/A ratio, E/e' ratio and left atrial volume indexed for body surface area (LAVi). Left atrial function was evaluated by 2D STI longitudinal strain.

Results: LV EF was reduced after 3- and 6-months of treatment and improved at 12-months echocardiogram, after six months of discontinuation of the therapy (baseline 61,1±5,6%; 3-months 58,4±5%; 6-months 57,6±5,7%; 12-months 59,1±4%; p= 0,025). Similarly, LV diastolic function was impaired after 3- and 6-months and improved after 12-months (baseline E/A 1,07±0,26; 3-months E/A 1; 6-months E/A 1; 12-months E/A 1,07±0,26; p= 0,33). Left atrial function, estimated by 2D STI longitudinal strain, significantly decreased during chemotherapy and improved after discontinuation (baseline 34,25±9,9%; 3-months 29,55±7,11%; 6-months 31,25±8,7% and 12-months 32,75±6,73%; $p < 0,005$), whereas left atrial volume did not show significant changes.

Conclusions. Left atrial function estimated by 2D STI longitudinal strain is significantly reduced in patients whit breast cancer undergoing chemotherapy with anthracyclines, but improves after discontinuation of therapy, suggesting it can be a reversible side-effect.

A50

PREDICTIVE FACTORS OF RESPONSE TO NEAODJUVANT CHEMOTHERAPY IN TRIPLE-NEGATIVE BREAST CANCER

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Aim: Nowadays, neoadjuvant chemotherapy is a standard treatment for triple-negative breast cancer (TNBC) at early stage of disease. Pathological complete response (pCR) to neoadjuvant chemotherapy is a strong predictor for long-term outcome. We aimed to evaluate possible predictive factors of response to neaoadjuvant chemotherapy in TNBC.

Methods: We retrospectively analyzed all pts with TNBC who received neoadjuvant chemotherapy and underwent breast surgery at Humanitas Research Hospital between May 2009 and March 2018. Data regarding age at diagnosis, body mass index (BMI), stage at diagnosis and before surgery, nodal status, tumor proliferation index (ki67) at diagnosis, treatment received and pathological response were extracted from medical records. Pearson chi-squared or Fisher exact test were used to evaluate possible association of the above mentioned factors with pCR (achieved or not) and down-staging (from stage 3 to 2 or from 2 to 1). Predictive factors were identified by regression analysis. Significance of p value was set at 0.05.

Results: 44 TNBC pts treated with neaoadjuvant chemotherapy were analyzed. Median age was 50.5 years old (range 32-74), median proliferation index (ki67) was 47.5% (range, 14-90). 10 pts (22,22%) received carboplatin in the chemotherapy regimen. Globally, 13 (29,5%) pts achieved a pCR and 19 (43,18%) a down-staging. At univariable analysis, an age younger than 50 years old, the use of carboplatin in the chemotherapy regimen and a proliferation index (ki67) higher than 30% were associated with a higher rate of pCR (p=0.021, p=0.019 and p=0.029, respectively). An age $\leqslant$ 50 years old was also associated with down-staging after treatment (p=0.006). Multivariate regression analysis did not confirm the independent role of the analyzed variables, but a predictive model including age, use of carboplatin and baseline ki67 could explain the variation in the achievement of a pCR by 20% (p= 0.03).

Conclusions: Our preliminary results show that younger age (<50 years old), use of carboplatin in the neoadjuvant chemotherapy regimen and high proliferation index (Ki67>30%) seem to be predictive factors associated with a higher pCR rate. Multivariate analysis suggests a non-independent role of such variables, indicating a possible role of other predictive factors which should be evaluated in further studies (gene signature analysis, for instance). The larger sample size of our final data analysis would provide more accurate data.

A51

SPARING ADJUVANT CHEMOTHERAPY THROUGH ONCOTYPEDX: PATTERNS OF USE AND IMPACT ON CLINICAL DECISION MAKING

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Background: Precision medicine tools are making their way into the clinic and being utilized to diagnose, prognose and individualized therapy. OncotypeDX is a genomic tumor profiling tool that determin the expression of 21 tumor-associated genes; it helps to know the risk for distant recurrence and whether chemotherapy is an appropriate treatment in patients with early estrogen receptor positive (ER+) Her-2 negative (luminal-like) breast cancer (BC) and limited nodal involvement (0-3 positive nodes). The aim of our study was to identify through OncotypeDx the right therapy for patients with luminal B HER2 negative BC (based on St. Gallen 2017).

Materials and methods: Since April 2017,450 surgically resected invasive BC patients were referred to our institution. 36 patients (8%) with ER+/HER2, N0/N1 BC were selected for Oncotype. For each patient we proposed a treatment option (hormonotherapy vs chemotherapy+ hormonotherapy) and then applied OncotypeDx assay to confirm or change our decision. The results were stratified in low (RS <18), intermediate (RS 18-30) and high risk (RS>30). All data were analyzed by Chi square test to compare clinico-pathological features of each patient with their OncotypeDx result and differences between pre and post-RS therapeutic decisions.

Results: Median age was 52 years (range 41-72 years) and all patients were affected by Luminal B Her2- BC with

median ER expression of 95% (range 80 – 100%), PgR of 70% (range 7- 20%), Mib-1 28%(range 20-40%).10 (27,7%) patients had node-positive disease; 72,2% had G2 disease and 27,8% G3. According to OncotypeDx 23 patients (63,8%) had low,12 (33,3%) intermediate and 1 (2,7%) high risk score. OncotypeDx results were significantly related with the histological subtype (p=0,0431) and with grading (p=0,0305). The majority of G2 BC (73%) got a low risk result; the majority of G3 BC (70%) got an intermediate risk. The addition of chemotherapy to hormonal therapy was initially recommended for 77,7% of the patients. The post RS recommendation change from the pre-RS recommendation for 55,6% patients, mostly from chemotherapy+hormonal therapy to hormonal therapy alone (p= 0,0015);no changes were observed in patients initially candidated to adjuvant endocrine therapy alone.

Conclusions: In our experience, the utilization of OncotypeDx was limited; however this genomic signature showed a crucial role on clinical decision making in more than one half of ER+ Her-2 negative BC patients with uncertain endocrine sensitivity.

A52

ONE YEAR FOLLOW-UP ASSESSMENT OF CHEMOTHERAPY-RELATED VASCULAR TOXICITY

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Background: Therapies used for breast cancer (chemotherapy, targeted therapies and hormone therapies) are known to be responsible of possible cardiac dysfunction, however less is known about their effect on blood vessel function. The aim of the study was to evaluate arterial function after anthracyclines administration, with a 1 year follow-up from the start of chemotherapy.

Patients and methods: 36 women and one man (mean age 49±12 years) with localized or metastatic breast cancer and without history of heart disease were enrolled. All patients received anthracyclines (Epirubicin, 75 mg/mq 75% or Doxorubicin 60 mg/mq 25%) and, in different percentages, further antiblastic therapy: 5-fluorouracil (500 mg/mq, 35.1%), Docetaxel (75 mg/mq, 45.9%), Paclitaxel (175 mg/mq, 5.4%), Cyclophosphamide (500 mg/mq 32.4% and 600 mg/mq 59.4%) and Trastuzumab (loading dose of 8 mg/kg followed by 6 mg/kg 10.8% or 600 mg/5 ml subcutaneously 5.4%). Patients were evaluated at time 0-, 3-, 6- and 12-months after the start of the therapy. We used pulse wave velocity (PWV), augmentation index (AI), and β-stiffness, derived by echotracking software (Aloka, Japan) as markers of arterial stiffness, measured on the carotid arteries. Furthermore, the intimal medial thickness (IMT) was measured and the presence of atherosclerotic plaques was investigated. Repeated measures ANOVA analysis was used for comparing the data at each step during the follow-up.

Results: IMT values were normal in the majority of patients at time 0 and during follow-up. No patient showed atherosclerotic plaques at carotid level. Instead, both carotid PWV (p=0,03) and ß-stiffness index (p=0,04) increased at 3 months, while no significant difference was found at 6 and 12 months (Table 1). No differences were found with respects to the type of anticancer drugs associated with anthracyclines.

Conclusions: Chemotherapy-related arterial toxicity is an early event during treatment with anthracyclines-based chemotherapy regimens, with a partial recovery later in the follow-up. A combined evaluation of cardiac and vascular function should be early started in breast cancer patients receiving these chemotherapeutic agents.

A53

LIQUID BIOPSY: TRACKING MUTATIONAL TRAJECTORIES IN ERBB2 BREAST CANCER PATIENTS UNDERGOING T-DM1 TREATMENT

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Background: The antibody-drug conjugate Ado-Trastuzumab emtansine (T-DM1) is standard of care in ERBB2 breast cancer progressing upon Pertuzumab and or

Table 1. Beta index, PWV and AI values at time 0-, 3-, 6- and 12-months after chemotherapy.

	Basal	FU-3 months	FU-6 months	FU-12 months	p
Beta index	6.7±2.8	8±2.5*	7.3±2.1	7.1±2.6	0.04
PWV	5.4±1.4	6.3±0.9*	5.9±0.9	6±2.5	0.03
AI	21.4±11.8	20.3±10.1	22.3±7.4	22.7±10.9	ns

- ns: not significant.

Trastuzumab plus taxanes. Despite considerable clinical benefit, some patients rapidly develop progressive disease, but the molecular mechanisms remain largely unknown. Analysis of mutational trajectories by liquid biopsy (LB) may help to uncover molecular patterns linked to T-DM1 resistance/responsiveness.

Materials and methods: Tumor tissues (n=11) and plasma samples (n=80) were collected, following informed consent, from 6 breast cancer patients undergoing T-DM1 administration. Tissue (tDNA) and circulating tumor DNAs (ctDNA) were extracted by the QIAmp DNA FFPE and CNA kits (Qiagen), and analyzed by ultra-deep sequencing and dPCR (IonTorrent S5 and QuantStudio 3D, LifeTechnologies). Genomic data were correlated with conventional clinical imaging (TC/PET).

Results: Four out 6 (67%) patients experienced progression on T-DM1 within 1 year of treatment (mean 221±105 days). In 3/4 of these patients, LB revealed both blood increases in pre-existing mutations (TP53 p.R273H) and *de novo*appearance of aberrations (PIK3CA p.H1047R, ESR1 p.Y537C plus CCDN1 amplification) not seen in tDNA from archival tumor tissue. LB anticipated clinical progression (as routinely assessed by imaging), by an average lead time of 1.9 months (range 0.7-2.8). Surprisingly, the fourth patient underwent rapid progression (3 months) in spite of decreased PIK3CA p.E545K in blood, suggesting heterogeneous response to T-DM1 across multiple cancer cell populations. Finally, we observed a progressive accumulation of ERBB2 p.L755S (a known tissue marker of Lapatinib resistance) in multiple serial metastatic foci from a single patient over several years of multimodal ERBB2 blockade. However, a single administration of T-DM1 resulted in ultra-fast (within days) ctDNA clearance, two distinct 'bystander' TP53 ctDNAs (p.R273H and p.S241T) remaining stable throughout.

Conclusions: Non-invasive LB monitoring of a small cohort of T-DM1-treated patients provides proof of principle of intersecting mutational trajectories, anticipation of resistance, and *de novo*onset/clearance of resistance mutations. Thus, LB may provide clues about disease evolution and successive lines of medical treatment.

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A54

THE TRANSERI STUDY: IMPACT OF ERIBULIN (E) ON CIRCULATING TGFß AND TNFA IN METASTATIC BREAST CANCER (MBC) PATIENTS (PTS). RELATIONSHIP WITH OUTCOME

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Background: E is approved for the treatment of mBC pts after previous exposure to antracyclines and taxanes. Besides its role as inhibitor of microtubule dynamics, leading to apoptosis and cell cycle arrest in G2/M, E reverses epithelial mesenchimal transition (EMT) in human cancer cell lines and in mice and reduces metastatization in mice. E modifies the tumor microenvironment. TGFβ is an immunosuppressive cytokine, is a growth factor for cancer-associated fibroblasts (CAFs) and promotes EMT. TNFα synergizes with TGFβ to promote EMT. EMT permits cancer cells trafficking thus driving metastatization. Our study investigates the interference among E and TGFβ and TNFα levels in pts and the correlation with the outcome and the metastatic spread.

Methods: Serum levels of TGFβ and TNFα were determined 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 d.

Results: We report data on 24 pts who completed 5 C or progressed before C 5. We did not observe changes of TNFα during treatment. The median (M) basal TGFβ value was higher in pts than in 4 healthy volunteers (M concentrations: 232 pg/ml vs 114 pg/ml respectively). The population was divided according to basal TGFβ levels, upper or lower the M value. M PFS was similar in the two groups (112 vs 100 d). TGFβ increased in 9 pts from basal to C 5, and decreased in 14 pts. We observed a numerical difference in M PFS between the pts with decreased and increased values (107 vs 82 d respectively). In 8 pts TGFβ decreased at each subsequent point. In these pts M PFS was 167 vs 84 d in the remaining. Notwithstanding the continuous decline of TGFβ, 2 of these pts progressed at C 5 (both at CNS). In pts with continuous TGFβ decline the M value approaches healthy controls (160 pg/ml [range 303-90] vs 114 pg/ml [range 120-85] respectively). At C 5 9 pts did not progress: 3 PR and 6 SD (M PFS 175 d). TGFβ decreased in all but 2 pts (1PR+1SD). Of note, PD occurred as early as 21 and 30 d respectively from C 5 in these 2 pts. The behaviour of pts with SD suggests that there is no correlation between tumor burden and TGFβ level.

Conclusions: Basal TGFβ does not predict outcome. TGFβ changes during treatment with E regardless of tumor load. In our series TGFβ changes correlate with outcome.

A55

LEVERAGING BIG DATA TO EXPLORE THE INTEREST OF BREAST CANCER SCREENING IN ITALY AT THE LEVEL OF HEALTH SURVEILLANCE SYSTEMS AND NOVEL DATA STREAMS

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Background: Cancer screening is a milestone in public health aimed to promote early diagnosis and cancer prevention. In Italy, the "Progress of healthcare agencies in Italy" (Passi) surveillance system is able to detect the proportion of adult population that undergoes screening tests for early diagnosis of breast cancer (BC), both as part of screening programs organized by the Local Health Agency (ASL) and/or by spontaneous or doctor-driven initiative. Recent technological advances in data acquisition, such as Google Trends (GT), may allow for more accurate data collection to track trends in various health-related topics, including cancer screening. GT is a keyword search tool that provides near real-time trend data about user interests, providing them as a volume of Internet searches (RSV).
Material and methods: Prevalence data about breast cancer screening coverage from 2008 to 2017 were obtained from Passi with a monthly frequency, splitted by overall coverage (OC), organized (OS) and spontaneous screening (SS). On GT we have selected the search term "mammografia" a priori based on its relationship with the BC screening test. Monthly RSV data were obtained for the same period. We used Pearson's correlation coefficient to examine the associations between the Italian screening prevalence of GT RSV and PASSI, for each of the three available time series. Statistical analysis was performed using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria.)
Results: In the period 2008-2017, Passi reports that an average of 7 out of 10 women aged between 50 and 69 undergo preventive mammography at the recommended time. The proportion of women taking part in organized screening programs is much higher: 5 out of 10 while 2 on their own initiative. The correlation coefficient between GT RSV and OC was 0,69 (IC: 0,59 - 0,78; $p<0,0001$). Correlation analysis between GT RSV, OS and SS showed values of 0.68 (IC: 0.58 - 0.77; $p<0.0001$) and 0.23 (IC: 0.05 - 0.39; $p=0.0124$) respectively.
Conclusions: According to our findings, there seems to be a strong correlation between the interest in mammography screening and organized screening programs, but much less for spontaneous ones. GT RSV data allowed us to measure public awareness and interest in breast cancer screening. A certain usefulness of such evidence could be functional to existing monitoring systems to track cancer screening.

A56

CDK4/6 INHIBITORS AND AROMATASE INHIBITORS COMBINATION AS FIRST-LINE THERAPY FOR HORMONAL RECEPTOR POSITIVE HER2 NEGATIVE ADVANCED BREAST CANCER IN ANCONA INSTITUTE: LEARNING FROM PRELIMINARY EXPERIENCE ABOUT ADVERSE EVENTS

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Loss of cell cycle control is a hallmark of cancer. Aberrations in cyclin-dependent kinase-retinoblastoma (CDK) pathway are common in advanced breast cancer (aBC). The modern CDK4/6 inhibitors are attractive treatments changing strategy for metastatic hormone receptor (HR) positive BC, but they are also a new challenge in oncologies practice due to management of new Adverse Events (AEs). From April to November, 2017, HR positive Her 2 negative MBC patients were treated with Ribociclib in Combination With Letrozole for HR+ HER2- aBC patients at our Institution. Overall 17 patients (pts) were included. At time of MBC diagnosis, median age was 59 years (range 36-85). All pts, except an Asian one (5.9%), were white race. At study entry, 13 pts (76.5%) were postmenopausal and 4 pts (23.5%) pre/perimenopausal. Histotypes were ductal, lobular and mixed respectively in 76.5%, 11.7% and 2% of enrolled pts. Visceral involvement was present in 13 pts 76.5%). 58.8% (10 pts) had de novo metastatic disease. The remnant received a neo-adjuvant therapy: 29.4% (5 pts) chemo and endocrine, 11.8 % (2 pts) only endocrine and 11.8% (2 pts) only chemo. In all pts any grade neutropenia occurred. Other common AEs were urinary tract infections (29.4%), nausea (17.6%) and fatigue (23.4%), these were of grade 1 and 2. No QTc prolongation was diagnosed. There were also rare AEs requiring special clinical management: palmar xerosis of grade 1 and 2 (29.4%), grade 2 AST and ALT increase (17.7%), grade 2 urticarial rash (5.9%) and grade 3 pacreatitis (5.9%). The first one was resolved using local creams. The second AE was managed witholding ribociclib taking careful laboratory monitoring. The third was treated with steroids and antihistamines since the suspicion of anaphylactic reaction with progressive resolution. Pancreatitis needed patient hospitalization and no risk factor was present in medical history. Five pts (29.4%) needed a first level reduction and 1 patient (5.9%) discontinued treatment due to AEs. The most frequent toxicity was neutropenia, all AEs were reversible by dose interruption and eventually reduction, these allowed most patients to remain on treatment. From our preliminary experience, new rare AEs as palmar xerosis and pancreatitis occurred. Anyway, high suspected relation with ribociclib letrozole combination has to be confirmed from large data. Overall, the combination showed an acceptable toxicities profile since only 5.9% of patients required discontinuation.

A57

ANDROGEN RECEPTOR IN ER POSITIVE BREAST CANCER: A SINGLE CENTER EXPERIENCE

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Background: Endocrine resistance represents a challenge in clinical management of metastatic breast cancer (mBC).

Androgen receptor (AR) is expressed in over 60% of BC, mostly in Er-positive group and several data demonstrate a cross-talk between these two hormonal pathways. The prognostic and predictive role of AR in BC remain controversy although the recent introduction in clinical practice of new anti-androgens drugs, has increased the interest on AR as a potential biomarker to select patients who could benefit from an AR-target treatment overcoming resistance.

Methods: We retrospectively collected data from 40 patients (pts), treated at our Institution between 2007 and 2017, diagnosed with ER+, PR+/−, HER-2 +/− MBC, whose tissue samples were available from primary (N=33) and metastatic tumor (N=38). ER, PR, AR and HER2 were assessed by immunohistochemistry. ddPCR and TaqMan assays were used to detect AR-V7 variants in mBC (AR-V7/AR tot ratio >10% was considered positive). Difference between means were analyzed using Student's t test. Survival analysis were performed using Kaplan-Meier method.

Results: Overall AR expression in primary tumors was 91% (30 pts) and in metastatic tissue 82% (31 pts). The highest expression was observed in luminal A subtype, both in early (90,4%±10,8 range:70-99%) and advanced disease (60,5±42,1 range: 0-98%). Almost half of the patients (47%), showed a lower expression of AR in metastatic tissue rather than primary, although an increase in the mean value of AR in metastatic samples was seen after at least 1 line of HT. However the difference in the AR expression from primary to metastatic tissue among pts treated with HT, was not significant. AR expression (AR ⩾1%) improved OS in primary (92 vs 52 months, 0=0.031) and metastatic setting (104 vs 29 months, p<0.0001), especially for those with AR> 50% regardless of BC phenotypes.

Patients with stable expression of AR from primary to metastatic tissue, showed a trend toward better OS compared to those with positive or negative variations (121 vs 50 vs 68 months p=0,41).

No prognostic value was found for the variation of AR/ER ratio.

55% of patients presented AR-V7 but only 3 pts had AR-V7/AR tot ratio> 10% showing no-significant better OS compared to those with ratio <10%.

Conclusions: This study demonstrates a higher expression of AR in primary tumors and in luminal A subtype, and its positive prognostic value. The limited number of AR-V7 variants does not allow to define their predictive value.

A58

PREDICTIVE FACTORS DETERMINING NEOADJUVANT CHEMOTHERAPY OUTCOMES IN BREAST CANCER - A SINGLE CENTER EXPERIENCE

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Background: Neoadjuvant systemic chemotherapy is the accepted approach for women with locally advanced breast cancer. Anthracycline- and taxane-based regimens have been extensively studied in clinical trials andconsequently are widely used. Approximately 20 to 30 % of breast cancers over express human epidermal growth factor receptor 2 (HER2) and effective HER2-targeting agents such as trastuzumabhave recently been added to NAC regimensconsequently are widely used.

Patients and methods: This study included 117 patients diagnosed with breast carcinoma that had been treated with neoadjuvantchemotherapy with or without Trastuzumab between 2010 and 2015. TNM staging system was used for staging. The histologic response to neoadjuvant chemotherapy was characterized as a pCR when there was no evidence of residual invasive tumor in the breast or axillary lymph nodes. Relapse Free survival was estimated by the Kaplan–Meier method and compared using the log rank analysis. P values was considered statistically significant when<0.05. The statistical analyses were conducted using SPSS software (version 17.0)

Results: The median age of the 117 patients enrolled in this study was 52 years (age range, 29–73 years). The overall objective clinical and radiological response rates (CR and PR) to preoperative chemotherapy were 80 and 74%, respectively. In all, 40% of patients attained a clinical CR. However, pCR was obtained in 30 out of 102 patients and the pCR rate was 29 %. Six patients (5%) developed progressive disease during chemotherapy by clinical (four) and/ or radiological (one) criteria. The Relapse-free survival mean for all group was 85 months (SE=3; 95% CI 79-91). The median was not reached; the mean follow-up time was 55 months (median 52 months;

range 11-100 months). In this time, twenty patients (17%) experienced tumor recurrence. The 1-7 year RFS rates were 99.1, 95.7, 89.4, 83.5, 81.7, 81.7, and 68.6% respectively. The statistical analysis showed no differences between pathological response and Ki67 labeling index. On the other side, the pathological response was significantly associated with receptor-based subtype, menopausal status, T-stage, and age ($p<0.10$).

Conclusions: Based on our findings, we propose that menopausal status, age and estrogen-receptor expression may represent clinical predictive biomarkers of pathological response for patients with inoperable breast cancer treated with primary chemotherapy.

A59

ANDROGEN RECEPTOR PATHWAY IN TRIPLE-NEGATIVE BREAST CANCER

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Background: Triple negative breast cancers (TNBC) are a heterogeneous group of tumors characterized by poor patient survival and lack of targeted therapeutics. Androgen signaling is necessary for normal breast development, and its dysregulation has been implicated in breast tumorigenesis. Androgen receptor (AR) pathway is emerging as a potential therapeutic target in breast cancer and interference with androgen signaling in TNBC is promising. Furthermore, association of AR with clinical and pathological features and prognosis in TNBC is not completely understood.

Patients and methods: We examined androgen receptor protein expression by immunohistochemical (IHC) analysis in 30 women with TNBC and we tested association of AR expression with clinical-pathological variables and we evaluated disease-free survival (DFS) in the AR-negative and AR-positive cases.

Results: In observed triple negative cancers, the percentage of androgen receptor positive cases was 57% (n=17). No statistically significant association was observed between AR-expression and clinical (age, menopausal status, survival) and pathological (tumor size, nodal involvement, Grading and Ki67) features. An exception is the age at diagnosis which is higher for patients with AR-negative (median age was 72 years in AR-negative, range 61-83, median age was 58 years in AR-positive, range 46-70, $p=0.004$). Regarding DFS, the AR-negative subjects present a trend of a greater risk of disease relapse during the initial follow-up period ($p=0.211$).

Conclusions. In the examined cohort, we observed an association between the expression of androgen receptors and a younger age. Regarding the survival data, the small sample size does not allow to reach conclusive considerations. We are collecting more data for future updates.

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A60

REAL LIFE EXPERIENCE WITH ERIBULIN IN PRETREATED BREAST CANCER: DATA COLLECTION IN ARNAS CIVICO HOSPITAL PALERMO

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Background: Eribulin is indicated for the treatment of patients with locally advanced or metastatic breast cancer, who have progressed after at least one chemotherapy regimen for advanced disease. In the Embrace phase 3 study, women with locally recurrent or metastatic breast cancer received eribulin as four -line median therapy . In our experience in real life, patients treated with eribulin had already been pretreated with other therapeutic regimens for MBC. Our aim was to evaluate the efficacy and safety of eribulin.

Material and methods: 39 Patients, Median age 58 years (41-78), ECOG status 0-1, 92 % was HER2 negative - ER/pgR positive, 89 % patients have 2 o more site of metastases, received eribulin (1,23 mg/m2 on days 1 and 8 of every 21 day cycles) therapy until progression, unacceptable toxicity or withdrawal . In our experience we analysed data from 39 patients treated with eribulin monotherapy to evaluate safety profile, PFS and ORR, the median lines of therapy was 5 (3-13).

Results: At time of initiation of eribulin all patients had received treatment with an anthracycline and with taxane in either the adjuvant or metastatic setting . Treatment with eribulin was shown to be quite active in all lines of therapy ; 11 partial response (28 %), 10 stabile disease (26 %), 1 completed response, and 17 tumour progressions (44 %) were recorded . A median PFS of 5,0 months was observed . The ORR was 31 %, the clinical benefit rate was 56%. Overall, eribulin was associated with mild toxicity, most toxicity being grade 1 or 2; neutropenia was the most common grade 2 haematological adverse event (30%), followed by anaemia (10%); among the non.haematological toxicities, fatigue was the most common (15%), followed transaminases increase (5%).

Conclusions: Treatment with eribulin in advenced lines setting for advanced or metastatic breast cancer is effective and minimally toxic, presenting a high clinical benefite rate.

A61

THE PALBOCICLIB ERA IN A REAL LIFE SETTING: A SINGLE CENTRE EXPERIENCE

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Background: Palbociclib is a first-in-class, selective, small-molecule inhibitor of cyclin-dependent kinases 4/6, which represent attractive targets in many human cancers, including breast cancer. On February 2017 palbociclib has been approved in Italy as a treatment for hormone-receptor positive (HR+) HER-2 negative metastatic breast cancer (MBC), showing improvement in PFS. The aim of our analysis was to evaluate usage pattern of palbociclib in a real life setting.

Patients and Methods: We retrospectively collected data on women treated with palbociclib plus endocrine therapy (HT) for HR+ HER-2 negative MBC in Ferrara Oncology Unit. All patients (pts) treated with ⩾ 1 dose of palbociclib were included in the analysis. Adverse events were graded for severity according to CTCAE version 4.0.

Results: From April 2017 to May 2018, 21 pts were treated with palbociclib in our department. The median age was 62 years (range 50-76). 48% of pts had ECOG PS ⩾ 1. Documented visceral metastases were present in 57% of pts and bone only metastases in 19%. 62% of pts had received at least 1 previous therapy in the metastatic setting, with a median number of 2 (range 1-6). HT associated with palbociclib was fulvestrant in 81% of pts and letrozole in 19%. Median number of cycles was 4 (range 2-11). Among the 13 pts already evaluated for response, PR has been observed in 38% of pts, SD in 31% and PD in 31%. In patients with bone only disease no partial response has been obtained. One pt died during treatment due to disease progression. The most common toxicity was neutropenia in 82% of pts (53% grade ⩾ 3). Thrombocytopenia and anemia were less common (10% and 19%, respectively) but grade ⩾ 3 was not observed. 19% of pts reported fatigue and 14% reported gastrointestinal toxicity (none of grade⩾ 3). 100% of pts started at the full dose of 125mg and only 10% of pts required first dose level reduction due to hematologic toxicity. No drug cessation was required owing to toxicity.

Conclusions: Apart from myelosuppressive side effects, palbociclib was well tolerated. Data collected about hematologic toxicity was consistent with the results of clinical trials, even if our study population was more pretreated. Treatment with palbociclib is still ongoing in most of the pts, so additional follow-up time is necessary to provide further insight into the real world outcomes.

A62

PALBOCICLIB IN ER-POSITIVE HER-2 NEGATIVE METASTATIC BREAST CANCER: A SINGLE CENTER REAL-LIFE EXPERIENCE

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Background: Palbociclib is a cyclin-dependent kinase 4 and 6 inhibitor recently approved in combination with Letrozole (as first-line endocrine therapy) or Fulvestrant (in patients previously treated with endocrine therapy) in post-menopausal estrogen receptor positive (ER+) metastatic breast cancer (mBC) patients. We reported a monocentric experience with Palbociclib in mBC, focusing on different outcome and tolerability in low- and heavily pretreated patients.

Material and methods: We retrospectively collected pathological and clinical data about patients with ER+ HER-2 negative mBC treated with Palbociclib and Fulvestrant or Letrozole, referred to our Institution from May 2017 to May 2018. Response to treatment was evaluated according to RECIST 1.1. criteria. Toxicities were evaluated according to CTCAE v4.03.

Results: 36 patients were included in our study; median age was 66 years (range 36-84); 78% of BC were ductal histotype; 25% were luminal A and 65% luminal B. In 16% of cases patients had metastatic disease at the diagnosis. 72% of patients were treated for metastatic visceral disease while 28% had only bone involvement. Median PFS was 9.7 months (range 0.3-12). 47% of cases referred low grade hematological toxicity (grade 1 or 2), 50% high grade (3 or 4) and 8% low grade gastrointestinal toxicity. In one only case a dose reduction was performed and one patient discontinued Palbociclib. At present, 64% of patients are still on treatment.

In 50% of cases, Palbociclib was administered within second-line treatment with 11% of partial response (PR), 23% of stable disease (SD), 22% of progressive disease (PD) and 44% not assessed yet. Median PFS was not evaluable. In this setting 89% of patients reported low grade hematologic toxicity, 66% high grade. For patients with at least two previous lines of anticancer therapy we collected PR=22%, SD=12%, PD=44%, whilst 22% of patients were not assessed, yet. Median PFS was 4.5 months (range

0.9-10.6). Similarly for patients previously treated with Fulvestrant median PFS was 4.5 months (range 0.9-11). All patients of this subgroup experienced low grade hematologic toxicity and 55% high grade.
Conclusions: This monocentric experience investigated Palbociclib in a real-life setting, evaluating its safety and feasibility in pre-treated patients. Our results suggest that Palbociclib is well tolerated also in advanced lines of treatment. Further analysis will reveal the best treatment sequence in term of clinical outcome.

A63

PREDICTIVE FACTORS OF ERIBULIN ACTIVITY IN METASTATIC BREAST CANCER PATIENTS

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Background: Predictive factors of response to eribulin are lacking. We aimed to investigate the activity and safety of eribulin in a real-world population of metastatic breast cancer (mBC) patients and to identify possible predictive factors of progression-free survival (PFS) and objective response.
Methods: We retrospectively analyzed 71 eribulin-treated mBC patients. Best response rate, PFS and adverse events (AEs) were evaluated. The impact of different clinic-pathological factors on PFS was evaluated using Cox proportional-hazard model. Predictive factors of response were identified by Discriminant Function Analysis (DFA).
Results: Median PFS was 3.75 months (95%CI, 2.39-4.48); 12 patients (16.90%) achieved partial response (PR), 27 (38.03%) stable disease. The most common AEs were fatigue (25.83%), neutropenia (16.56%) and peripheral neuropathy (13.91%). A worse performance status (p=0.025) and a higher number of metastatic organ sites (p=0.011) were associated with a worse PFS under eribulin. A DFA-based model showed that neutrophil-to-lymphocyte ratio at baseline, estrogen receptor, ki67, histology and age were predictive of PR with 100% accuracy.
Conclusions: Activity and safety profile of eribulin were consistent with literature data. Performance status and number of metastatic sites were predictive factors of PFS. DFA could be a promising tool to discriminate responses to eribulin among mBC patients.

A64

PROMOTION AND PRESCRIPTION OF EXERCISE IN BREAST CANCER SURVIVORS TO INCREASE OUTCOME EXPECTATIONS AND PHYSICAL ACTIVITY LEVEL

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Background: Healthy lifestyle habits have been associated with improved health outcomes and quality of life for breast cancer survivors (BCS). Physical activity (PA) during and following treatment has been shown to improve both physical and emotional health, and overall quality of life. It can help to improve body weight, muscle strength and physical side effects of BC treatment, such as fatigue, pain and lowered bone density. The aim of this study was to evaluate the effect of a structured physical activity intervention on measures of physical performance and outcome expectations among BCS attending at the Breast Unit of Ospedali Riuniti-Ancona.
Material and methods: Ten BC women (age 58.3 ± 14.4 years) who underwent primary surgery were enrolled from Department of Medical Oncology, University Hospital of Ancona between February and May 2018. After the oncological visit, were assigned to a "Lifestyle Programme" consisting of lifestyle counseling and structured exercise programs. PA levels (International Physical Activity Questionnaire-IPAQ) and functional exercise capacity (6-Minutes Walking Test-6MWT, Hand Grip test and Sit and Reach test) were assessed before and after the 4-week intervention. The planned PA intervention was determined individually considering the FITT-VP principle (American College of Sports Medicine-ACSM) the intensity was prescribed in terms of heart rate considering the 6MWT results. Resistance- and flexibility exercise were also included in the PA program, according to the ACSM physical activity recommendations.
Results: After the 4-week PA intervention the distance covered during the 6MWT increased by 25 ($p<.05$) overcoming the minimal clinically importance difference in 60% of subjects, while the Seat and Reach test improved by 17% ($p<.05$). We did not register any significant differences in upper limb strength between a surgical arm and healthy arm. All subjects reported appreciation for the training with benefits regarding personal well-being and showed an increase in spontaneous activity levels.
Conclusions: The "Lifestyle Programme", including exercise counselling and supervised training improve functional exercise capacity and could motivate subjects suffering from BC to adopt a healthier lifestyle based on regular PA.

A65

THE IMPACT OF "WOMEN SPECIFIC" RISK FACTORS IN BREAST CANCER PATIENTS CARDIOLOGICAL MONITORING, AN OBSERVATIONAL STUDY

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Background: Cardiovascular diseases (CVD) are the leading cause of death in women in every major developed country; with improved cancer survival CVD is also the predominant cause of mortality in breast cancer patients. We are debunking the myth that CVD is a man's disease, but the uniqueness of the female gender in cancer has not been fully addressed, yet. Obstetric (pre-eclampsia (PE), pregnancy-induced hypertension, gestational diabetes and non obstetric (polycystic ovary syndrome, age at menopause) female specific conditions increase the risk of CVD as stated in the 2016 Guidelines for CVD prevention. In the circulation of PE women an upregulated sFLt-1 binds to Vascular Endothelial Growth Factor (VEGF) mimicking an antiangiogenic effect that does not end with the delivery of the placenta.
Methods: Since 2012 we screened, in our institution, female cancer patients with a history of PE for subclinical signs of coronary artery disease by performing a stress/rest myocardial scintigraphy to evaluate myocardial perfusion imaging (MPI) and coronary flow reserve (CFR).
Results: In 10/70 PE patients with early left breast cancer we found abnormalities of MPI and reduction of computed measures of CFR **at baseline**, and **increased abnormalities** of MPI and CFR early **after Radiotherapy** for left breast cancer. With preliminary data we can state that women with a complicated pregnancy are more sensitive to vasculotoxic drugs. With antiangiogenic drug, the enhanced cardiotoxicity can be easily explained by the impressive similarities between antiangiogenic side effects and complications of pregnancy, both including hypertension, proteinuria, thrombosis and cardiomyopathy. But the antiangiogenic-like status of these women will interact with vasculotoxic cancer therapies like thoracic Radiotherapy, Fluoropyrimidines, and Platinum compounds, it will be challenged by antiangiogenic-induced hypertension and by vascular toxicities of new targeted therapies.
Conclusions: Not only CVD but also cardiotoxicity is a different matter in males and females. Gynecologic history is important, gynecardioloncology will become, in a near future, an extremely valuable sex&gender- based tool in precision medicine and will increase the awareness of sex&gender peculiarities of CVD in women and of the neglected impact of "female specific" risk factors,. All these issues will hopefully contribute in reducing the impressive burden of CVD in female cancer patients.

B - Gastrointestinal (Colorectal) Cancers

B01*

PATIENTS TREATED WITH FOLFOX-4 OR XELOX CHEMOTHERAPY WITH HIGH-RISK STAGE II AND III COLON CANCER (TOSCA TRIAL): A DIFFERENT IMPACT OF PHARMACOGENETIC PROFILE ON TOXICITY IN WOMEN AND MEN

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Background: A pharmacogenetic ancillary study to the TOSCA trial (Ruzzo et al. 2015) investigated the association with toxicity of 17 selected polymorphisms (TYMS: rs34743033, rs2853542, rs11280056; MTHFR: rs1801133, rs1801131; ERCC1: rs11615; XRCC1: rs25487; XRCC3: rs861539; XPD: rs1799793, rs13181; GSTP1: rs1695; GSTT1/GSTM1: delection+/−; ABCC1: rs2074087; ABCC2: rs3740066, rs1885301, rs4148386). This analysis was aimed to assess the interaction between these polymorphisms and sex on time to grade (G)>3 haematological (TTH, except anemia), G>3 gastrointestinal (TTG) and G>2 neurological (TTN) toxicity.
Method: TOSCA is a non-profit, Italian, multicentre, randomized, non-inferiority phase III study conducted in high-risk stage II and stage III colorectal cancer patients treated with 6/3 months of FOLFOX-4 or XELOX adjuvant chemotherapy. Patients were prospectively accrued in the ancillary study. In case of significant interaction subgroup analysis by sex were performed using multivariate Cox regression models.

Model	Genetic variantion	HR(95%CI); p-value	Events	Events ref
		TTG	% (n/total)	% (n/total)
	XPD rs13181 T>G			
Dominant Ref.TT		0.043*		
	Female, TG+GG	0.47(0.23-0.96); 0.040	10%(14/136)	21%(16/78)
	Male, TG+GG	1.54(0.64-3.72); 0.336	9%(17/181)	6% (7/113)
		TTN		
	ERCC1 rs11615 T>C			
Recessive Ref. TT+TC		0.021*		
	Female, CC	2.35(1.28-4.29); 0.006	44% (14/32)	25%(47/186)
	Male, CC	0.83(0.45-1.54); 0.552	22% (12/55)	25%(60/239)
		TTH		
	XPD rs1799793 G>A			
Co-dominant Ref. GG		0.022*		
	Female, GA	0.74(0.46-1.19); 0.215	34% (30/89)	46% (39/85)
	Male, GA	2.10(1.20-3.65); 0.009	28%(36/127)	15%(19/125)
	Female, AA	0.88(0.48-1.60); 0.674	42%(15/36)	46%(39/85)
	Male, AA	1.64(0.69-3.93); 0.267	21%(7/33)	15%(19/125)
Dominant		0.009*		
Ref. GG	Female, GA+AA	0.78(0.51-1.20); 0.259	36%(45/125)	46%(39/85)
	Male, GA+AA	2.01(1.17-3.44); 0.012	27%(43/160)	15%(19/125)
	MTHFR rs1801133 C>T			
Dominant		0.035*		
Ref. CC	Female CT+TT	1.37(0.85-2.22); 0.192	44%(64/146)	32%(23/71)
	Male CT+TT	0.66(0.40-1.09); 0.103	20%(40/203)	28% (25/90)
*Interaction test p-value				

Results: 218 women and 294 men were enrolled. The interaction between sex and polymorphisms was detected on TTG for rs13181, on TTN for rs11615, on TTH for rs1799793 and rs1801133. Subgroup analyses by sex is reported in table.

Conclusions: this study highlights that functional polymorphisms can be differently associated to toxicity in men and women, then used as sex-specific biomarkers.

B02

FOLFOXIRI PLUS BEVACIZUMAB (BEV) FOLLOWED BY MAINTENANCE WITH BEV ALONE OR BEV PLUS METRONOMIC CHEMOTHERAPY (METROCT) IN MCRC: FINAL RESULTS OF THE PHASE II RANDOMIZED MOMA TRIAL BY GONO

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Background: MOMA study investigated whether the addition of metroCT to bev as maintenance treatment following 4 months (mos) of upfront therapy with FOLFOXIRI plus bev could improve PFS of mCRC patients (pts). 232 pts, mostly RAS (65%) or BRAF (9%) mutant, were randomized in 16 Italian centers. The primary endpoint was not met. We provide final results of the trial: OS, subgroup analyses and treatments after disease progression (PD).

Methods: Pts with unresectable mCRC were randomized 1:1 to receive up to 8 cycles of FOLFOXIRI plus bev, followed by bev, arm A, or the same induction followed by bev plus metroCT (capecitabine 500 mg/tid and cyclophosphamide 50 mg/die per os, arm B) until PD. According to the comparative Rubinstein and Korn's design, estimating a first-line PFS of 11 months, to detect a HR of 0.75

favoring arm B, with 1 sided-alpha and beta errors of 15% and 80%, 173 events were required. In the case of PD during maintenance, the re-introduction of FOLFOXIRI plus bev or of a modified FOLFOXIRI plus bev regimen (i.e. FOLFOXIRI/FOLFOX or FOLFIRI plus bev) was recommended up to 4 cycles, followed by maintenance.

Results: At a median follow up of 43.9 mos, 210 and 164 progression and death events were registered. No significant differences between arms were reported in terms of PFS (mPFS arm A/B: 9.4 / 10.3 mos; HR: 0.94 [70%CI: 0.82-1.09], p=0.680) and OS (mOS arm A/B: 28 / 22.5 mos; HR: 1.16 [70%CI: 0.99-1.37], p=0.336). Response rate with FOLFOXIRI plus bev was 63% (arm A/B: 68%/58%). No interaction effect between treatment arm and *RAS/BRAF* status or tumour sidedness was reported in PFS or OS. In the overall population mPFS among *RAS/BRAF* wt (N=36), *RAS* mutant (N=150) and *BRAF* mutant (N=20) pts were 10.2, 10.1 and 9.4 mos (log-rank test, p=0.759) and mOS were 31.3, 24.9 and 19.2 mos, respectively (log-rank test, p=0.457). 152 (72%) out of 210 pts with PD event received a treatment after PD. In 87 (57%) and 44 (29%) pts FOLFOXIRI plus bev or modified FOLFOXIRI plus bev were re-introduced, respectively.

Conclusions: The addition of metroCT to maintenance with bev does not significantly improve PFS or OS of mCRC pts irrespective of *RAS/BRAF* mutational status and tumour sidedness. Activity results of FOLFOXIRI plus bev are confirmed with a shorter treatment duration (4 mos). Outcome results in *BRAF* mutant pts are consistent with previous findings with the triplet plus bev. Re-introduction of FOLFOXIRI plus bev was feasible with a favourable safety profile.

B03

CIRCULATING METHYLATED DNA (CMDNA) PREDICTS LONG-TERM SURVIVAL UPON REGORAFENIB TREATMENT

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Background: Regorafenib, a tyrosine-multikinase inhibitor, demonstrated a survival improvement in patients with chemo-refractory metastatic colorectal cancer (mCRC), with durable (>4 months) progression free survival (PFS) confined to 19% of patients. Up to date no circulating biomarkers of regorafenib benefit have been identified. Cancer specific circulating methylated DNA (cmDNA) is a promising diagnostic cancer specific tool in CRC. We previously reported a panel of 5 methylated genes (*EYA4, GRIA4, ITGA4, MAP3K14-AS1, MSC)* which is associated with outcome during treatment for mCRC (Barault et al. *Gut* 2017).

Patients and methods: Seventy-six patients with mCRC refractory to irinotecan/oxaliplatin/5-FU who received regorafenib from 2012 to 2017 at Niguarda Cancer Center, Milan, Italy and Istituto Oncologico Veneto, Padova, Italy, were included. Regorafenib was administered at 160 mg once daily as *per* drug label for three every four weeks until progression. Liquid biopsies for the analysis of cmDNA were collected prior to regorafenib start and then biweekly or at any subsequent access to the hospital during treatment. Liquid biopsies were analyzed for cmDNA values, in blind as for patients' outcome.

Results: Baseline plasma samples were available in 65 patients. cmDNA was positive in 61 patients out of 65 (94%). A decrease in cmDNA value during treatment from baseline was associated with improved PFS (p=0.024, HR=0.43 [95% CI: 0.21 - 0.9]). Univariate and multivariate Cox-regression showed that cmDNA at baseline correlated with both PFS (HR=1.015 [95% CI: 1.003 – 1.027], p=0.009) and OS (HR=1.019 [95%CI: 1.005 – 1.032], p=0.006). A logistic regression model showed that cmDNA at baseline was associated with an increased risk of progression within 16 weeks (OR=2.6). Values of cmDNA prior treatment >18% of methylation showed a PPV of PFS<16 weeks of 79.3%. Also, cmDNA values during regorafenib treatment were related to PFS<16 weeks, and persistently high cmDNA values pre- and upon regorafenib treatment predict worse PFS at 16 weeks (OR=9.9 [95%CI: 2.61 - 37.6], p=0.001).

Conclusion: In this cohort of mCRC patients we validated the negative prognostic role of a panel of 5 methylated genes (*EYA4, GRIA4, ITGA4, MAP3K14-AS1, MSC)* in cmDNA and that decrease during treatment is a predictive pharmacodynamic biomarker of clinical benefit to regorafenib. cmDNA can be used to identify patients with poorest survival, who may not benefit from regorafenib treatment.

B04

CLINICO-PATHOLOGICAL AND MOLECULAR CHARACTERIZATION OF BRAF MUTANT PATIENTS: ARE ALL BRAF MUTATIONS THE SAME?

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	Overall Survival			Progression Free Survival		
	Median (months)	HR (95% CI)	p-value	Median (months)	HR (95% CI)	p-value
BRAF wild type (N=540)	42.2	–	<0.0001	10.1	–	<0.0001
BRAF mutant class 1 (N=92)	21.0	2.38 (1.61-3.54)		7.3	2.02 (1.39-2.94)	
BRAF mutant class 2 (N=12)	23.4	1.90 (0.85-4.26)		7.0	2.49 (0.92-6.74)	
BRAF mutant class 3 (N=13)	44.5	0.93 (0.51-1.69)		13.8	0.85 (0.47-1.54)	

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Background: Functional studies on preclinical models (Yao et al. Nature 2017) identified 3 classes of *BRAF* mutations: activating *RAS*-independent *BRAF* mutations signaling as monomers (class 1-*BRAF* V600E) or as dimers (class 2-codons 601/597) and *RAS*-dependent *BRAF* mutations with impaired kinase activity (class 3-codons 594/596). While clinico-pathological and molecular features of class 1 mutation are well known, limited data are available with regard to class 2 and 3 mutations, due to their rarity in CRC.

Methods: Clinico-pathological, molecular and outcome data from *BRAF* mutated (codons 594, 596, 597, 600, 601) mCRC patients were collected. A group of *BRAF* wild-type patients was included as control. IHC analyses were performed to determine the consensus molecular subtypes (CMS). Clinical features were compared by chi-square or fisher's exact test. PFS and OS were evaluated by Kaplan-Meier and log-rank test.

Results: Class 1, 2 and 3 included 92, 12 and 13 patients respectively. *BRAF* wild-type patients were 540. No clinico-pathological differences were observed comparing class 1 to class 2 *BRAF* mutated. Conversely, *BRAF* class 3 mutated were more frequently left sided (p=0.0028), well differentiated (p=0.0120), pN0 (p=0.0159), and with no peritoneal metastases (p=0.0176) compared to class 1. With regard to CMS, class 2 and 3 tumors were all assigned to CMS2-3. Class 1 tumors were assigned to CMS1, 2-3 and 4 in 39%, 44% and 17% of cases.

Outcome results are reported in the Table below.

Conclusions: Our data confirm previous findings describing specific features associated with *BRAF* rare mutations. For the first time clinico-pathological characteristics and outcome data are reported according to the 3 classes categorization of *BRAF* mutations. In particular, class 1 and 2 share similar features and worse outcome compared to class 3 and wild type patients.

B05

LIQUID BIOPSY ALLOWS PREDICTING BENEFIT FROM RECHALLENGE WITH CETUXIMAB (CET) + IRINOTECAN (IRI) IN RAS/BRAF WILD-TYPE METASTATIC COLORECTAL CANCER PATIENTS (PTS) WITH ACQUIRED RESISTANCE TO 1ST-LINE CET+IRI: FINAL RESULTS AND TRANSLATIONAL ANALYSES OF THE CRICKET STUDY BY GONO

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Background: CRICKET (NCT02296203) was designed to investigate the activity of the rechallenge with cet and iri as 3rd-line treatment in *RAS/BRAF* wild-type mCRC pts with acquired resistance to 1st-line cet- and iri-based therapy. The role of liquid biopsies as a tool to identify pts more likely to benefit from this strategy was investigated.

Methods: Eligibility criteria included *RAS*/*BRAF* wild-type status on tissue samples; prior 1st-line iri-based, cet-containing regimen with at least RECIST partial response (PR), 1st-line PFS ⩾6 months, and progression within 4

weeks after the last cet; prior 2nd-line oxaliplatin- and bevacizumab-based treatment. Pts received 3rd-line cet + iri until PD. The primary endpoint was response rate (RR) according to RECIST v1.1. With p0 = 5%, and p1 = 20%, 1-sided-α and β errors of 0.05 and 0.20, 27 pts were required. The null hypothesis can be rejected if responses are observed in ⩾ 4 pts. Liquid biopsies were collected at the rechallenge baseline. ctDNA was analyzed with ddPCR for specific *RAS*/*BRAF* mutations (mut), and then by ultra-deep NGS with Ion Torrent S5 XL.

Results: Between Jan 2015 and Jun 2017, 28 pts were enrolled in 9 centres. The primary endpoint was met. Six PRs (two unconfirmed) and 9 disease stabilizations (RR: 21%,95%CI: 10-40%, disease control rate: 54%,95%CI: 36-70%) were reported. *RAS* mut were found in liquid biopsies collected at the rechallenge baseline in 12 (48%) out of 25 evaluable pts (6 KRAS G12D, 5 KRAS G12V with 1 harboring also Q61H and 1 NRAS Q61L). No *RAS* mut were detected in samples from pts who achieved a confirmed PR. Pts with *RAS* wt ctDNA had significantly longer PFS than those with *RAS*mut ctDNA (mPFS: 3.9 vs 1.9 mos; HR: 0.48 [95%CI 0.20-0.98], p = 0.048). No *BRAF* or *PIK3CA* mut were found.

Conclusions: This is the first prospective demonstration of the activity of rechallenge with cet + iri in some mCRC pts initially sensitive and then resistant to first-line iri- and cet-based therapy, with no *RAS*/*BRAF* mut in pre-treatment liquid biopsies. Partially funded by Merck Serono SpA.

B06

THROMBOEMBOLIC RISK AND SURVIVAL WITH KHORANA SCORE IN RESECTED COLORECTAL CANCER PATIENTS. SUBGROUP ANALYSIS FROM THE ADJUVANT TOSCA TRIAL

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Introduction: The risk of venous thromboembolic events (VTE) during adjuvant chemotherapy for colorectal cancer (CRC) is unknown. We aim to evaluate if the Khorana score (KS) can predict this risk of VTEs and overall survival (OS) in a randomised phase III, noninferiority, open-label trial of different durations of adjuvant chemotherapy in resected stage II-III CRC.

Material and methods: Data were obtained using a TOSCA ['Randomised trial investigating the role of FOLFOX-4 or XELOX (three versus six months) regimen duration as adjuvant therapy for patients with stage II/III colon cancer'] study. A logistic regression model was used to test the associations between the risk of VTEs and the KS. The results are expressed as odds ratios (OR) with 95% confidence intervals (95% CI). To assess the effect of the KS on OS, multivariate analyses using Cox regression models was performed. The results are expressed as hazard ratios (HR) with 95% CI.

Results: Among n=1,380 CRC patients with available data, the VTE risk (n=72 events: 5.2%) was similar in the three- and six-month duration arms (5.5% vs. 4.9%) with 0.2% of patients belonging to the high-risk KS group. Rates of VTE were similar in the low- and intermediate-risk groups (4.8% vs. 6.4%). KS did not represent an independent predictive factor for VTE risk, with a low positive predictive value and accuracy (6.4% and 74.1%). Chemotherapy duration was not associated with VTE risk. Also, KS was not associated with OS in multivariate analysis (HR=0.92, 95% CI, 0.63–1.36; P=0.68).

Conclusions: The use of the KS was not a predictor of VTEs in a low–moderate thromboembolic risk population as CRC. These data did not support the use of KS to estimate the occurrence of VTE during adjuvant chemotherapy and suggest that other assessment risk tools must be evaluated.

B07

CLINICAL AND MOLECULAR CHARACTERIZATION OF MISMATCH REPAIR DEFICIENT METASTATIC COLORECTAL CANCER: RESULTS FROM A LARGE MULTICENTER ITALIAN COLLABORATION, THE MISSONI PLATFORM

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Background: DNA mismatch repair deficiency is a rare alteration that leads to high microsatellite instable (MSI-H) phenotype, found in 3-5% of metastatic colorectal cancers (mCRC). Current knowledge of clinical characteristics and prognostic behavior of MSI-H mCRC is poor. In this multicenter retrospective study, we aimed to provide a modern and extensive profiling of MSI-H mCRC.

Patients and methods: We collected clinical and pathological characteristics of patients (pts) affected by MSI-H mCRC and treated at 5 Italian Oncology Units from January 2010 to December 2017 (N=172). A group of non-MSI-H mCRC (N=431) from the same time frame served as control group. Primary endpoint was to describe clinical peculiarities of MSI-H mCRC. Secondary endpoints included survival outcome and differences in benefit from standard treatments. Exploratory subgroup analyses were performed to test the interaction between MSI status and benefit obtained with standard first-line treatments.

Results: Compared to non-MSI-H, MSI-H pts were more frequently female; MSI-H mCRC were more often right sided, mucinous, G3/G4 and BRAF mutated. Lymphovascular invasion (LVI) was more frequent in MSI-H mCRC and NRAS mutations (MT) were more common in non-MSI-H mCRC (both $p<0.001$). MSI-H mCRC had more frequently metachronous distant metastases (mets) ($p=0.002$); typical sites of mets were distant nodes and peritoneum (both $p<0.001$). In MSI-H RAS wild type (WT) pts, bevacizumab (bev)-based treatments (N=24) led to greater PFS than anti-EGFR-based ones (N=26) (mPFS 11.3 months vs 5.0; $p=0.01$), while no differences were found in RAS WT non-MSI-H pts (p for interaction=0.018); results excluding BRAF MT cases were similar. At multivariate analysis, distant lymph nodes and peritoneal mets, BRAF MT, G3-4 and LVI correlated with poorer OS; MSI-H phenotype was related to better OS (HR 0.52, 95%CI 0.34-0.80), even when pts treated with immunotherapy in any line (N=102) were censored at immunotherapy start. Better OS for MSI-H pts was confirmed irrespective of BRAF status (in BRAF WT pts: HR 0.72, 95%CI 0.50 – 1.05; in BRAF MT pts: HR 0.48, 95%CI 0.26 – 0.88; p for interaction 0.20).

Conclusions: Our results confirm previous data; differences in LVI, NRAS MT, presentation of disease and metastatic sites are described for the first time. In our cohort, MSI-H status conferred better OS irrespective of BRAF status; RAS WT MSI-H pts may benefit more from bev-than anti-EGFRs based therapies.

B08

PROGNOSTIC VALUE OF NEUTROPHIL-LYMPHOCITE RATIO IN RESECTED HIGH RISK COLORECTAL CANCER: AN ANALYSIS OF ADJUVANT TOSCA TRIAL

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Introduction: Prognostic factors in resected colon cancer (CC) guide adjuvant therapy and intensity of follow up. Inflammation parameters as C-reactive protein and neutrophil counts in relation to lymphocyte number (neutrophil/lymphocyte ratio: NLR) have been correlated with poor prognosis in advanced tumors. To confirm the prognostic value of a prechemoterapy NLR in adjuvant setting, we performed a retrospective analysis of high risk stage II and stage III resected CC patients randomized into the TOSCA phase 3 trial comparing 3 or 6 months of adjuvant chemotherapy.

Material and Methods: Patients randomized in TOSCA trial with data available for NLR analysis before chemotherapy were included. A recursive partitioning analysis was performed to identify the best cut-off that better discriminates patients in terms of relapse-free survival (RFS). According to this cut-off, RFS and overall survival (OS) hazard ratios (HR) for NLR were calculated and adjusted for age, sex, treatment type (XELOX vs FOLFOX) and duration (3 vs 6 months), grade, stage, performance status (PS), site and CEA level

Results: Out of 3759 subjects randomized in the TOSCA trial, 1590 were included in the efficacy analysis. Mean NLR was 2.1 (median 1.8; range 0.3-24.0). Among patients analysed, 17.4% relapsed and 12.2% died. The best NLR cut off detect in this analysis population is 2.33. However, only age, PS, stage III and CEA levels were associated with RFS and OS in multivariate analysis, but not NLR>2.33 (RFS: HR=1.17, 95%CI 0.90-1.51; P=0.24, OS: HR=1.16 95%CI 0.84-1.61; P=0.38). Site was also correlated with poor OS.

Conclusions: prechemotherapy NLR is not significantly associated with poor prognosis in patients with CC undergoing adjuvant chemotherapy. Resection of primary tumor and the associated reduced inflammatory stimulus may explain the lack of correlation with prognosis of NLR. Baseline evaluation, before surgery, likely represents the better timing to collect this information in cancer patients.

B09

RETROSPECTIVE ANALYSIS OF THE IMPACT OF PRIMARY TUMOR LOCATION ON PATTERNS OF RECURRENCE AND SURVIVAL OF PATIENTS UNDERGOING RESECTION OF LIVER METASTASES FROM COLON CANCER

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Background: In recent years, several studies have described different prevalence of molecular carcinogenic pathways in right-sided (RS) and left-sided (LS) colon cancers. Furthermore, a worse prognosis has been reported for RS colon cancer. However, results are conflicting for different tumor stages. The aim of the study was to compare patterns of recurrence and survival following resection of liver metastases (LM) from RS versus LS colon cancers.
Patients and Methods: We retrospectively analysed prospectively collected data of patients undergoing first resection for colorectal LM between 2000 and 2017. Tumors of the cecum, ascending, and transverse colon were defined as right-sided; tumors of the sigmoid flexure, descending, and sigmoid colon were defined as left-sided. Rectal cancer, multiple primaries and unknown location were excluded from this analysis. Metastatic spread pattern and survival data after curative liver resection were analysed. Survival curves were calculated according to Kaplan-Meier method and compared by log-rank test.
Results: Out of 995 patients, 686 fulfilled inclusion criteria (RS=322, 46.9%; LS=364, 53.1%). RS colon cancer had higher prevalence of metastatic lymph nodes (67.4% vs. 57.5%; P =0.008). Liver metastases from RS were more often mucinous 16.8% vs. 8.4%, P=0.005) and poorly differentiated (66.4% vs. 56%, P=0.009). The rate of response to preoperative chemotherapy was lower in RS patients (45.9% vs. 54.1%), although the difference did not reach statistical significance (P = 0.058). After a median follow-up of 81 months, 451 (65.7%) patients experienced recurrence (RS 68.9% vs. LS 62.9%, P=0.097). In RS patients, recurrence was more often encephalic (2.3% vs. 0%; P= 0.029) and at multiple sites (25.5% vs. 17.3%; P=0.037). The rate of re-resection was significantly lower in RS patients (28.3% vs. 38.4%; P = 0.024). Survival analysis showed that RS had lower rates of 5-year relapse-free survival (20.5% vs. 30.8%; P =0.007) and overall survival (5Y-OS 35.8% vs. 47.3%, 10Y-OS 3.7% vs. 18.3%; P <0.001). There were 345 patients identified with 10-year follow-up. Sixty-nine (20%) of them were disease free with a significant higher proportion in LS group (26.8% vs. 13.8%, P<0.001).
Conclusions: In this large series of patients, surgically resected liver metastases from RS colon cancer were more often mucinous and poorly differentiated compared with LS. RS cancer is associated with aggressive rarely re-resectable recurrences and worse survival

B10

PROGNOSTIC IMPACT OF DIFFERENT MRNA IMMUNE-SIGNATURES IN MISMATCH REPAIR DEFICIENT (DMMR) COLORECTAL CANCERS (CRCS).

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Background: Alterations in mismatch repair system lead to accumulation of gene mutations and microsatellite instability in CRC. The high mutational burden of dMMR CRCs induces an increase of neoantigens and elicits a remarkable endogenous anti-tumor immune response, counterbalanced by the strong expression of immunosuppressive ligands and signals. We aimed at describing the immune-profile of dMMR CRCs and its potential prognostic value through mRNA expression analysis.
Patients and Methods: Treatment-naïve primary tumors of both metastatic and non-metastatic (defined by a minimum follow-up duration of 3 years) dMMR CRC patients were analyzed by means of NanoString nCounter® PanCancer Immune Profiling Panel (Seattle, WA, USA), including 730 immune-related genes. The samples were grouped based on the gene expression by using Pearson's correlation. Subsequently, the uncorrelated shrunken centroid machine-learning algorithm was used to classify the samples.

Table 1. Frequency of KRAS/NRAS/BRAF mutations in plasma samples.

	Baseline	8 weeks	PD	3 months after PD
Cases KRAS/NRAS/BRAF mutant on plasma	6/37 (16.2%)	6/31 (19.3%)	14/37 (37.8%)	2/21 (9.2%)

Results: Eighty-nine patients were included (52 non-metastatic, 15 with metachronous metastases, 22 with synchronous metastases). Several immune-related genes were differently expressed in dMMR CRCs. Two tumor subgroups can be identified according to the antigen presentation immune-profile: 28 "HOT" tumors with over-expression of antigen presentation genes and 61 "COLD" tumors with lower expression of these genes. Patients with "HOT" metastatic CRC showed a statistically significant better prognosis in terms of overall survival calculated from the time of diagnosis of metastatic disease (p=0.029). Similarly, among non metastatic patients, those with "HOT" tumors had numerically longer OS than those with "COLD" tumors (p=0.16).

Conclusions: Our results demonstrate that immune-related genes are heterogeneously expressed in dMMR CRCs. Differences of gene expression implicated in mechanism of antigen presentation show a prognostic value with an advantage in "HOT" tumors compared with "COLD" cases; in addition, a predictive value of different sensitivity to immune checkpoint inhibitors could be suggested. These results require further investigation in clinical trials.

B11

ANALYSIS OF LIQUID BIOPSIES FROM METASTATIC COLORECTAL CARCINOMA (MCRC) PATIENTS (PTS) ENROLLED IN THE ERMES CLINICAL TRIAL

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Background: Liquid biopsy is an alternative to tissue biopsy for biomarker testing. In addition, it can be used to monitor the response to therapy and the molecular evolution of the disease.

Methods: The ERbitux MEtastatic colorectal cancer Strategy (ERMES) Study is a phase III randomized trial with FOLFIRI+Cetuximab (arm A) compared to 8 cycles of FOLFIRI+Cetuximab followed by Cetuximab alone until disease progression (PD) (arm B) in first-line treatment of KRAS/NRAS/BRAF wild type (wt) mCRC pts. Plasma samples at baseline (n = 37), at 8 weeks (w) of treatment (n = 31), at PD (n = 37) and at 3 months (mo) after PD (n = 21) were collected from 37 pts (10 arm A/27 arm B) and analyzed for mutations in exons 2, 3 and 4 of KRAS and NRAS and in BRAF V600 using the Idylla system (Biocartis).

Results: Analysis of basal plasma samples revealed KRAS/NRAS/BRAF mutations in 6/37 cases classified as wt based on tissue mutational analysis (concordance 83.8%). The frequency of KRAS/NRAS/BRAF mutant cases on plasma increased progressively during treatment and decreased 3 months after PD (Table 1). The median progression free survival (mPFS) of pts with KRAS/NRAS/BRAF mutations at PD was 7.3 mo (CI 95% 5.9-8.7) versus 7.1 mo (CI 95% 6.2-8.0) in pts with wt plasma samples (p = 0.407). In 4/5 cases with baseline mutations and paired 8 w samples, we observed a partial response and plasma samples become negative. Four cases that were positive at w 8, became negative for KRAS/NRAS/BRAF mutations at PD.

Conclusions: These data suggest that the Idylla system can detect KRAS/NRAS/BRAF mutations in plasma samples from pts receiving anti-EGFR agents at the same frequency as described with other techniques. Occurrence of plasma mutations seems a transient phenomenon in some pts and does not correlate with a shorter mPFS.

B12

IS OXALIPLATIN-BASED CHEMOTHERAPY THE RIGHT CHOICE AS FIRST-LINE CHEMOTHERAPY IN METASTATIC COLORECTAL CANCER PATIENTS WITH MUCINOUS HISTOLOGY? A MULTICENTER, RETROSPECTIVE, COMBINED ANALYSIS ON 897 PATIENTS

Therapy	Histology	n	Median OS (mos)	HR	95% C.I.	P
OXA-based±B	MC	52	14.9	Ref.		
IRI-based±B	MC	52	31.7	0.473	0.295–0.759	0.002
FOLFOXIRI±B	MC	35	28.2	0.405	0.232–0.707	0.001
OXA-based±B	NMC	294	24.3	0.450	0.310–0.654	<0.0001
IRI-based±B	NMC	319	28.5	0.588	0.405–0.853	0.005
FOLFOXIRI±B	NMC	145	32.7	0.498	0.333–0.744	0.001

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Background: In metastatic colorectal cancer (MCRC), mucinous histology has been associated with poor outcome. Recently, we did not find any difference in prognosis between patients (pts) with non-mucinous adenocarcinomas (NMC) and those with mucinous adenocarcinomas (MC), possibly due to the use of different cytotoxic regimens (Catalano et al, Ann Oncol 2017, 28Suppl.6:#A1). In a preliminary subgroup analysis, oxaliplatin (OXA) seemed to be associated with even unfavorable outcomes. We aimed to assess whether OXA-based chemotherapy regimens may affect survival of MCRC pts with mucinous histology.

Patients and methods: The study population included 897 MCRC pts who were treated with first-line chemotherapy (Catalano 2009, Catalano 2017) as follows: OXA-based (FOLFOX, CAPOX, raltitrexed/OXA), irinotecan(IRI)-based (FOLFIRI, CAPIRI), FOLFOXIRI, or the same regimens plus bevacizumab (B). Pts were classified according to the histology in MC and NMC. The possible prognostic interaction between histology and different chemotherapy regimens was assessed by multivariate Cox proportional hazards analyses.

Results: 139 (15.4%) pts had MC, male/female 528/369, median age 65 years (range, 25-89). More pts in the MC group had right-sided tumours (MC 47.5% vs NMC 30.9%, p=0.0002) and peritoneal disease (MC 31.7% vs NMC 16.5%, p<0.0001), whereas pts in the AC group had more frequently liver metastasis (NMC 74.7% vs MC 58.3%, p=0.0001). All other variables were comparable between the two groups. The analysis of interaction between chemotherapy regimens and histology showed a highly significant result (p<0.0001). In particular, by assuming as reference treatment OXA-based regimens, pts with MC had worse overall survival (OS) than those who were treated with IRI-based or FOLFOXIRI. As expected, patients with non-mucinous histology treated with IRI-based, OXA-based and FOLFOXIRI achieved better survival than MC treated with OXA-based chemotherapy.

Conclusion: OXA-based regimens may not represent the optimal chemotherapy treatment option in MCRC with mucinous histology. Considering the lack of prospective data covering this topic, IRI-based regimens should be considered for patients with MCRC MC.

B13

IMMUNE INFLAMMATION INDICATORS IN ANAL CANCER PATIENTS TREATED WITH CONCURRENT CHEMO-RADIATION

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Background: In anal cancer, there are no markers nor other laboratory indexes that can predict prognosis and guide clinical practice of patients treated with concurrent chemo-radiation. In this study, we retrospectively investigated the influence of immune inflammation indicators on treatment outcome of anal cancer patients undergoing concurrent chemo-radiotherapy.

Methods: All patients had a histologically proven diagnosis of squamous cell carcinoma of the anal canal/margin treated with chemo-radiotherapy according to the Nigro's regimen. Pre-treatment systemic index of inflammation (SII), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were obtained.

Results: A total of 161 consecutive patients with anal cancer were available for the analysis. Considering SII, PLR and NLR as continuous variables, a higher baseline value of these indexes was associated to a higher risk of treatment failure and death. A higher SII level was significantly correlated to lower PFS (HR:2.13; 95%CI:1.69-2.59%; p<0.01) and OS (HR:1.70; 95%CI:1.13-2.27%; p=0.046).

NLR level was significantly correlated to PFS (HR:1.13; 95%CI:1.01-1.26%; p=0.05), but not to OS (HR: 1.15; 95%CI:1.0-1.315; p=0.06). PLR level significantly affected both PFS (HR:1.44; 95%CI:1.20-1.68%; p<0.01) and OS (HR:1.43; 95%CI:1.13-1.73%; p=0.02). On multivariate analysis, response to treatment maintained a significant correlation to PFS (less than PR vs CR; HR:30.03; 95%CI:7.97-113.2%; p<0.0001) (PR vs CR HR:2.44; 95%CI:1.05-5.71%; p=0.0028) and OS (less than PR vs CR; HR:43.82; 95%CI:10.03-191.42%; p<0.0001) (PR vs CR; HR:3.51;95%CI-1.01-12.18%;p=0.0492). Pre-treatment SII level had a significant correlation to PFS (HR:0.50;95%CI:0.31-0.83%; p=0.0079), but not to OS (HR:0.80;95%CI:0.48-1.34%; p=0.15). At the ROC analysis, SII obtained an area under the curve (AUC) of 0.61. Setting the cut-off point at 560,000, patients with higher pre-treatment SII had a 5-year PFS of 62.1%, compared to 80.9% for those with lower values . Five-year OS was 78.9% for patients having SII > 560,000, and 73.5% for those having baseline SII < 560,000. Considering all variables potentially predictive of response, SII (OR: 2.99; 95%CI: 2.04-3.94%) and lymphnode status (OR: 5.88; 95%CI: 3.37-8.40%) were the only predictors of response to CT-RT in multivariate analysis.

Conclusions The low cost and easy profile in terms of determination and reproducibility make SII a promising tool for prognostic assessment in this oncological setting.

B14

PROGNOSTIC ROLE OF MONOCYTE-TO-LYMPHOCYTE RATIO IN METASTATIC COLORECTAL CANCER

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Background: Changes in peripheral blood cells composition may reflect tumor immune microenvironment and its role in cancer growth control. High monocyte-to-lymphocyte ratio (MLR) could be a sign of tumor's recruitment of suppressive cells, showing a prognostic role in many cancer types. Aim of this study was to evaluate the prognostic impact of MLR in metastatic colorectal cancer (mCRC).

Methods: This study retrospectively analyzed a consecutive cohort of 392 mCRC patients (pts) who had been treated between 2004 and 2017 at the National Cancer Institute IRCCS CRO Aviano and at University Hospital of Udine (Italy). The best cut-off threshold capable of predicting survival was defined through ROC analysis. The association between MLR and overall survival (OS) was evaluated with uni- and multivariate Cox regression analyses.

Results: At a median follow-up of 60 months, median OS was 26 months. Before first line therapy, 269 pts (69%) were aged <70. Of note, 105 pts (27%) received metastasectomy and 142 pts had >1 metastasis. Overall, 57% of tumors had a KRAS mutation and 11% had a BRAF one. By univariate analysis, sidedness (left HR 0.65, p=0.003; rectum HR 0.73, p=0.042), metastasectomy (HR 0.36, p<0.001) and adjuvant chemotherapy (HR 0.66, p=0.008) were associated with better OS. On the contrary, older age (HR 1.61, p<0.001), nodal status (pN2 HR 1.48, p=0.036; pN3 HR 2.52, p=0.001), KRAS mutation (HR 1.36, p=0.020) and MLR (HR 3.32, p<0.001) were significantly associated with worse OS. At multivariate analysis, sidedness and metastasectomy confirmed to predict a better OS, while MLR (HR 3.20, p<0.001), nodes (pN2 HR 1.89, p=0.006; pN3 HR 2.25, p=0.014), and KRAS mutation (HR 1.50, p<0.001) were significantly associated with worse OS. The cut-off value obtained for MLR (i.e. 0.44) predicted worse OS both in univariate (HR 2.23, p<0.001) and multivariate (HR 2.41; p<0.001) analyses. Interestingly, MLR was associated with number of metastatic sites (p<0.001), type of sites (p<0.001), sidedness (p=0.001) and LDH levels (p<0.001).

Conclusion: In mCRC pts, MLR has emerged as an independent prognostic factor associated with worse OS. This effect is probably related to its role in immune suppressive cells recruitment. However, further prospective studies are needed to confirm these data.

B15

NEUTROPHIL/LYMPHOCYTE RATIO AS SURROGATE OF CETUXIMAB ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY IN FIRST LINE METASTATIC COLORECTAL CANCER: A PRELIMINARY AND EXPLORATORY ANALYSIS OF THE ERMES PHASE III TRIAL

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Background: The ERMES trial is an ongoing phase III randomized clinical trial comparing standard treatment with FOLFIRI+Cetuximab (Cet) until PD (arm A) to de-escalating Cet monotherapy after 4 months of induction with FOLFIRI+Cet (arm B) in first line RAS/BRAF WT metastastic colorectal cancer (mCRC). Neutrophil/lymphocyte ratio (NLR) has been reported as an independent prognostic factor in mCRC, whereas its predictive impact is still questioned. We hypothesized that NLR could represent a surrogate of lymphocyte activity, acting as a marker of antibody-dependent cell-mediated cytotoxicity (ADCC) Cet-mediated. We performed an exploratory analysis to assess the predictive role of NLR in pts receiving Cet maintenance monotherapy in the ERMES trial (arm B).
Patients and methods: Patients (pts) enrolled at Fondazione Policlinico Universitario "A. Gemelli" – IRCCS were included in this analysis. NLR, defined as absolute neutrophil count/absolute lymphocyte count (ANC/ALC), was calculated at baseline (BL) and 1 month after treatment allocation (C10D1). Median NLR at C10D1 was adopted as cut-off value to classify pts as low and high NLR. The primary endpoint was disease control rate (DCR) assessed after 2 months from treatment allocation (C12) in low *vs* high NLR. Secondary endpoint was PFS. The impact of BL NLR in the whole population and of C10D1 NLR in arm A was also evaluated.
Results: Of 37 enrolled pts, 25 received at least 10 cycles of therapy (17 pts in arm B and 8 pts in arm A) and were included. In arm B 8 pts were classified as low NLR and 9 as high NLR at C10D1. DCR at C12 was 100% (including 2 CR) in low NLR and 66.6% in high NLR (p=0.02). An increase in PFS was detected in low NLR *vs* high NLR group (10.3*vs*9.2 months; p=0.1). BL NLR in the whole population and C10D1 NLR in arm A were not associated to treatment efficacy.
Conclusions: Low NLR seems to predict response to Cet monotherapy. Such evidence might be explained by a postulated role of NLR as predictor of ADCC. This marker might allow an early selection of pts who may benefit most from a de-escalating monotherapy with Cet after induction with combination chemotherapy and pts who would benefit from restoration of chemotherapy. An extended evaluation on the whole ERMES population is planned to confirm these preliminary results.

B16

INTENSIVE FIRST LINE FIR-C/ FOX-C ASSOCIATION OF TRIPLET CHEMOTHERAPY PLUS CETUXIMAB IN RAS WILD-TYPE METASTATIC COLORECTAL CANCER PATIENTS: PRELIMINARY PHASE II DATA AND PREDICTION OF INDIVIDUAL LIMITING TOXICITY SYNDROMES BY PHARMACOGENOMIC BIOMARKERS

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Background: Intensive triplet chemotherapy plus bevacizumab significantly increased metastatic colorectal cancer (MCRC) outcome. Phase II study investigated safety and activity of FIr-C/FOx-C triplet chemotherapy plus cetuximab (CET) in first-line *RAS* wild-type and prediction of individual limiting toxicity syndromes (LTS) by pharmacogenomic biomarkers.
Patients and methods: Simon two-step design: p0 70%, p1 85%, power 80%, a 5%, ß 20%; projected objective response rate (ORR) I step 14/19. FIr-C/FOx-C: 5-fluorouracil (5-FU) 12h-timed-flat-infusion 900 mg/m^2 d1-2, 8-9, 15-16, 22-23; irinotecan (CPT-11) 160 mg/m^2 d1, 15, oxaliplatin 80 mg/m^2 d8, 22; CET 400 then 250 mg/m^2 d1, 8, 15, 22; every 28d. Toxicity, individual LTS evaluated, compared by chi-square test; activity/efficacy by log-rank. 5-FU/CPT-11 pharmacogenomic biomarkers, 5-FU degradation rate (5-FUDR), SNPs ABCB1, CYP3A4, DYPD, UGT1A1 evaluated in patients with LTS and at recommended dose.
Results: Enrolled: 29 patients <75 years, primary/intermediate Cumulative Illness Rating Scale (CIRS); from 04/2014 *KRAS*/*NRAS* wild-type; median age 59; 7 young-elderly (yE) 24%; 7 liver-limited (L-L) 24%. Recommended CPT-11/5-FU doses 120/750 mg/m^2. Primary endpoint met: OR 14/18, 78% as-treated, confirmed in preliminary phase II 17/23, 74% intent-to-treat. Liver metastasectomies 14%, 57% L-L. At median follow-up 18 months, progression free survival (PFS) 12 months, overall survival (OS) 23 months. At recommended doses, received dose intensities (DI) >80%; G3-4 toxicities: diarrhea 23%, asthenia 15%, vomiting 8%, hypertransaminasemy 8%; LTS 19 (65.5%), 83% yE. LTS prevalently multiple (ms) vs single site (59 vs 7% P 0.006). Reduced FUDR 56%, SNPs CYP3A4 22%, UGT1A1 71%, >2 positive pharmacogenomics biomarkers 78%, prevalently in patients with gastrointestinal LTS.
Conclusions: Intensive first-line FIr-C/FOx-C at recommended doses is tolerable, highly effective in *RAS*

wild-type. Reduced FUDR, CYP3A4, UGT1A1 SNPs may predict individual LTS-ms to select fit patients. Prospective studies personalized by toxicity biomarkers will confirm efficacy.

Trial registration: Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali (OsSC) Agenzia Italiana del Farmaco (AIFA) Numero EudraCT 2009-016793-32.

B17

THE ROLE OF PRIMARY TUMOUR LOCATION IN THE RECURRENCE RATE OF METACHRONOUS METASTASIS OF COLON CANCER

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Background: Recent studies suggest that primary tumour location (PTL) has a prognostic value in patients (pts) with metastatic colorectal cancer (CRC), while its role in early stage disease remains unclear. The aim of this analysis is to investigate the relationship between PTL and the development of metachronous metastasis.

Material and Methods: We performed a population-based study from Modena Cancer Registry collecting data of patients (pts) with early stage disease (stage I, II, III) who underwent surgery from 1995 to 2010. We hypothesized a potential impact of PTL on the postoperative recurrence rate. Fisher's exact test, univariate and multivariate Cox regression analysis were performed.

Results: During the study period, 1570 pts with left-sided colon cancer (LCC) and 841 pts with right-sided colon cancer (RCC) were registered. In the entire cohort, 268 of 1576 pts (17%) with LCC and 100 of 841 pts (11.2 %) with RCC developed metachronous metastasis, for a total of 368 of 2411 pts (15%). Comparing LCC and RCC clinical and pathological status we found no statistically difference in lymph-node status (p= 0.737) but an increasing rate of G3 cancers in RCC vs LCC (p= 0.010). Median overall survival (OS) from early stage disease diagnosis for LCC patients was 45 months versus 35 months for RCC patients, with no significant difference in relapse free survival between the two groups (23.8 Vs 23.0 months). When relapsed, time to death resulted to be significantly longer in LCC group than in RCC group (14.7 vs 6.3 months; HR 1.46, 95% C.I. 1,16-1,86; p 0,001). In the multivariate Cox regression analysis adjusted for grading and stage at diagnosis, we confirmed a statistically significant impact of the primary tumour sidedness on OS in the relapsed setting (HR 1.48, 95% C.I: 1.15-1.89, p=0.001).

Conclusion: In accordance to literature, our registry data confirm the prognostic role of PTL in advanced colorectal cancers: in particular, right-sided tumours have low recurrence rate but poor prognosis once relapsed. Other investigations are necessary to better understand the substantial heterogeneity within the molecular biology of RCC and LCC in order to provide a better post-operative surveillance and to select the most effective treatment strategies after relapse.

B18

CLINICAL AND PATHOLOGICAL FEATURES OF COLORECTAL CANCER IN ELDERLY PATIENTS (>75YEARS OLD)

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Background: Few studies have been conducted to describe the epidemiology of colorectal cancer (CRC) in large elderly patients (over 75 years old). Owing to the exclusion of this population from clinical trials, no standard treatments exist for this subgroup of patients. The aim of our study is to examine the epidemiological differences between patients over 75 years old and younger ones (< 75y).

Methods: We collected data from Modena Tumour Registry. We identified patients diagnosed with CRC between 1995 and 2010 and analysed the epidemiological differences between the two groups in terms of gender, primary tumor location, grading and stage of disease.

Results: Overall, 3116 patients were included: 2065 were under 75y and 1051 over 75y.

The analysis of our series confirmed a higher incidence of right-sided CRC in elderly (43% vs 30%), particularly in the female subpopulation (48% vs 38% of males).

There were no significant differences in terms of grading and lymph nodes status between the two groups (10% G3 and 25% N+ vs 13% G3 and 27% N+, respectively). Moreover, the highest incidence of G3 in right-sided CRC was confirmed (17% right-sided vs 8% left-sided), in particular elderly showed a higher percentage of T3-T4 (48% vs 33%).

Conclusions: Our study shows an increased incidence of aggressive tumors in elderly, with larger size of primary tumours and higher number of right-sided CRC. Therefore, according to the overall increase in life expectancy, studies aimed at the specific evaluation of this population are eagerly awaited in order to define the best therapeutic strategy.

B19

THE IMPACT OF MULTIDISCIPLINARY TEAM (MDT) MANAGEMENT ON OUTCOME OF HEPATIC RESECTION IN LIVER-LIMITED COLORECTAL METASTASES

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Background: Hepatic resection is the gold standard treatment for patients (pts) with liver-limited colorectal metastases (mCRC) with five- and ten-years survival rates reaching up to 60% and 20%, respectively. Although multidisciplinary team (MDT) management might ensure a more accurate assessment of pts and a faster referral to surgeons, reports discussing the impact of MDTs on survival are controversial and to date there are no strong evidences supporting routinely MDT discussion. The aim of this study was to evaluate the benefit of MDT management in pts with liver-limited mCRC in our single institution experience.

Patients and methods: Clinical records of pts with liver-limited mCRC who underwent radical surgery at Fondazione Policlinico "A. Gemelli" - IRCCS from Jan-2006 to Dec-2016 were retrospectively analyzed. The objective of the analysis was to compare survivals of pts managed within our MDT (MDT cohort) to those of pts referred to surgery from other hospitals without MDT discussion (non-MDT cohort). Primary endpoints were DFS and OS. Differences in baseline characteristics and in post-operative morbidity were also evaluated.

Results: Of the 619 pts analyzed, 230 were included in the MDT cohort and 389 in the non-MDT cohort. No statistically significant difference between the two groups was found in terms of both DFS (12*vs*11 m; p 0.09) and OS (55*vs*51 m; p 0.68). Concerning baseline characteristics, in the MDT cohort compared to non-MDT cohort there was a statistically significant higher number of median metastases (4.5*vs*2.6; $p< 0.0001$) and a higher rate of synchronous metastases (61.7*vs*39.3%; $p < 0.001$). Despite pre-operative CT rate was higher in the MDT group (75.8vs70.7%), the median duration of CT before surgery was significantly lower in MDT pts (7 vs 8 cycle with a mean difference of 1.7 m; $p < 0.001$). Moreover, post-operative morbidity was significantly lower in the MDT cohort (6.2*vs*19.2%; $p<0.00001$).

Conclusions: Our study does not demonstrate a survival benefit from MDT management of pts with liver-limited mCRC. However, the analysis clearly shows that MDT assessment allows to consider eligible for surgery pts with a more advanced disease (higher number of metastases and synchronous disease). Moreover, MDT discussion seems to reduce the median duration of pre-operative CT with a consequent lower rate of post-operative morbidities Our data warrant prospective validation.

B20

CLINICAL AND MOLECULAR DETERMINANTS OF EXTRAHEPATIC DISEASE PROGRESSION (EPD) IN INITIALLY UNRESECTABLE, LIVER-LIMITED METASTATIC COLORECTAL CANCER (MCRC)

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Background: In the last years, the availability of active upfront systemic regimens, the development of surgical techniques and the diffusion of locoregional treatments increased the therapeutic options for mCRC patients (pts) with liver-limited disease (LLD). Estimating the likelihood to develop extra-hepatic metastases (mts) may affect clinicians' attitudes towards locoregional procedures. No tools to predict the probability of ePD of initially LLD are currently available.

Method: We retrospectively analysed a cohort of 225 pts with initially unresectable LLD, treated with first-line doublets or triplet and a biologic agent at two Italian Institutions. Information about baseline clinical, pathological and molecular features, treatments received and metastatic sites from the diagnosis of mCRC were collected. The impact of baseline characteristics and treatments received on extra-hepatic PFS (ePFS) was assessed in uni- and multivariable models.

Results: Overall, 52 (23%) pts were ePD-free and 173 (77%) experienced ePD which occurred within 1, 2 or 3 years from the diagnosis of mCRC in 20%, 63%, and 86% of pts, respectively. Globally, 164 (73%) pts underwent a secondary liver resection, and 66 (40%) of them underwent a subsequent locoregional treatment. Among 164 resected pts, 118 (72%) experienced ePD, occurring within 1, 2 or 3 years from resection in the 43%, 71%, and 91% of cases, respectively. Age <70 years, ECOG performance status (PS) 0, <4 mts, diameter of lesions <30 mm, involvement of <6 segments and secondary resection were significantly associated with prolonged ePFS. In the multivariable model, PS (p=0.022), number (p=0.011) and diameter (p 0.005) of lesions and secondary liver resection (p=0.006) were still associated with ePFS. In the subgroup of analysed pts (N=35), microsatellite instability was associated with shorter ePFS (p=0.029). In the subgroup of pts who didn't undergo mts resection (N=61), PS (p=0.024), diameter of liver lesions (p=0.011) and left-sidedness (p=0.081) were independently associated with longer ePFS.

Conclusions: In our cohort, the vast majority of mCRC pts with initially unresectable LLD underwent surgical procedures (73%) and further locoregional procedures (40%) in their disease history. PS, number and diameter of mts, and sidedness independently predict ePFS. These factors could help physicians in personalizing the intensity and aggressiveness of liver directed treatments in mCRC pts with initially unresectable LLD.

B21

CIRCULATING TUMOR-DERIVED DNA (CTDNA) AS PREDICTIVE FACTOR IN PATIENTS TREATED WITH NEOADJUVANT CHEMORADIOTHERAPY (CT-RT) FOR LOCALLY ADVANCED RECTAL CANCER (LARC)

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Background: Nor instrumental work-up neither molecular markers are currently available to identify a risk-adapted strategy in patients with LARC treated with neoadjuvant appoach. The aim of this study is to evaluate the predictive role of serum ctDNA in patients with LARC.

Patients and methods: Data on the first consecutive 28 patients with detectable mutations out of the 88 statistically required cases were collected using tumor biopsies at baseline and peripheral blood samples at different time points: before CT-RT, after CT-RT, before and after surgery and +/− after adjuvant CT. All patients received neoadjuvant capecitabine concomitant to pelvic 50,4 Gy RT, followed by curative surgery. The serum ctDNA and CEA ability in predicting the pathological complete response (pCR) clinical end-point was quantified by Area under the ROC curves (AUC). The nonparametric approach of DeLong, DeLong and Clarke-Pearson was used to compare ROC curves. All analyses were performed using SAS software v. 9.4 (SAS Institute, Cary, NC, USA).

Results: Main patients characteristics were: 20/8 M/F, median age 62 (37-79 yrs), 15 distal, 11 medium and 2 proximal tumors; 3 T2, 23 T3, 1 T4, 1 Tx; 1 N0, 16 N1,11 N2; 18 KRAS, 1 BRAF (not V006E), 3 NRAS and 7 PIK3CA mutations were detected. Before and after CT-RT median value of ctDNA was 0.06 ng/2ml (range 0-17.4) and 0 ng/2ml (range 0-0.60), respectively. All patients who achieved pCR (7/28, 25%) showed the lowest pre-treatment ctDNA values, while no clear pattern was seen for CEA. Median basal ctDNA levels were 0.0 ng/2ml in patients who reached pCR and 0.11 ng/2ml in 21/28 (75%) patients without pCR, respectively. However, the difference did not result statistically significant, probably due to the small sample size (p=0.18). Interestingly, ROC Curves of pre-Treatment ctDNA and pre-Treatment CEA resulted different (AUC for pre-Treatment ctDNA: 0.67, AUC for pre-Treatment CEA: 0.51; p=0.45).

Conclusions: Pre-treatment ctDNA showed a promising role in predicting pCR in patients with LARC treated with neoadjuvant CT-RT. An appropriate statistical sample size will likely confirme these results. An update of the study will be done during the meeting.

B22

THE SENECA STUDY: PROGNOSTIC ROLE OF SERUM BIOMARKERS IN ELDERLY METASTATIC COLORECTAL CANCER PATIENTS

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Background: Changes in immune system and inflammatory response, such as an increase in the monocyte- lymphocyte ratio (MLR) and serum lactate dehydrogenase (LDH) levels, frequently occur in the elderly. Moreover, these serum biomarkers have showed a negative prognostic role in many cancer types. The primary objective of this study was to investigate the prognostic role of MLR and

LDH levels in elderly patients (pts) with metastatic colorectal carcinoma (mCRC) before first line therapy.
Material and methods: We conducted a retrospective analysis of 120 consecutive elderly (>70 years) pts treated for mCRC from 2004 to 2017 at the National Cancer Institute, IRCCS CRO Aviano and at University Hospital of Udine (Italy). Uni- and multivariate Cox regression analyses were conducted to investigate the prognostic impact of MLR and LDH levels on overall survival (OS). A ROC analysis was performed to identify the best cut-off in predicting patient survival risk.
Results: Overall, 46 pts (38%) presented a right colon cancer, 43 pts (36%) a left colon cancer and 30 pts (25%) a rectal one. Liver (36%), lymph-nodes (22%), peritoneum (22%) and lung (17%) were the most frequent sites of metastasis; noteworthy, 22 pts (18%) had undergone a metastasectomy. In 8 (8%) and 47 (50%) pts a mutation of BRAF or KRAS was detected, respectively. High levels of LDH (>480 U/L) and MLR (>0.45, as derived from ROC analysis) were recorded in 23 (32%) and 51 (42%) pts, respectively. Median follow-up was 50.83 months and median OS was 19.96 months. By univariate analysis, metastasectomy (HR 0.47, p=0.009), tumor resection (HR 0.50, p=0.010) and left sidedness (HR 0.53, p=0.01) were associated with better OS. On the other hand, high levels of LDH (HR 2.81, p=0.001), MLR (HR 2.26, p<0.001) or both (HR 6.42, p<0.001), and node involvement at diagnosis (pN2 vs. pN0 HR 2.15, p=0.019; pN3 vs. pN0 HR 2.69, p=0.052) were significantly associated with worse OS. By multivariate analysis, high levels of LDH (HR 2.64, p=0.004), MLR (HR 2.21, p=0.009) or both (HR 4.19, p=0.019) were independently associated with worse OS.
Conclusions: In elderly mCRC pts, high levels of LDH, MLR or both, before first line therapy, are unfavorable independent prognostic factors. Our preliminary results emphasize the impelling need of prospective studies to validate these potentially cost-effectiveness biomarkers in this subgroup of pts.

B23

THE SLICE STUDY: THE PROGNOSTIC ROLE OF VISCERAL FAT IN METASTATIC COLORECTAL CANCER

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Background: Overweight has been proposed as a risk factor for colorectal cancer initiation and progression. The present study investigated the prognostic impact of visceral fat (VAT) evaluated through CT scan in metastatic colorectal cancer (mCRC).
Methods: A retrospective analysis was conducted on a consecutive cohort of 71 patients (pts) with mCRC treated from 2013 to 2017 at National Cancer Institute, IRCCS CRO Aviano (Italy). VAT area was measured as the cross-sectional (cm^2) area at the L3 level divided by the square of the height (m^2). To define a threshold capable of identifying different prognostic categories of patients according to VAT, a ROC analysis was performed. To evaluate the prognostic impact of VAT index in terms of overall survival (OS) and progression free survival (PFS), uni- and multivariate Cox regression analyses were performed.
Results: At a median follow-up of 2.5 years, median OS was 30.97 months. Interestingly, 59 pts (83%) underwent primitive tumor resection and 24 pts (33%) received metastasectomy. Overall, 19 pts (27%) were aged >70, 14 pts (20%) had a right tumor, 21 pts (30%) a left tumor and 35 pts (50%) a rectal one. Noteworthy, 40 pts (56%) had a body mass index (BMI) >25 and 42 (59%) had median VAT of 51.94. LDH level >480 UI/L was reported in 12 pts (27%), thus indirectly reflecting the inflammatory response. We obtained a VAT cut-off of 44. By univariate analysis, primary tumor resection (HR 0.40, p=0.029) and metastasectomy (HR 0.22, p=0.005) were significantly associated with better outcomes. Conversely, older age (HR 2.46, p=0.013) and VAT>44 (HR 2.85, p=0.011) were significantly associated with worse OS. By multivariate analysis, only VAT>44 (HR 2.64; p=0.030) remained significantly associated with OS. No prognostic impact of VAT was observed in terms of PFS.
Conclusion: This exploratory study investigated the prognostic role of adiposity evaluation in patients with mCRC. Interestingly, high values of VAT seem to predict worse outcome. However, further prospective investigations are needed.

B24

FLUOROPYRIMIDINE-INDUCED CARDIOTOXICITY AND STUDY OF RISK FACTORS CORRELATION IN PATIENTS WITH COLORECTAL CANCER: PRELIMINARY DATA FROM THE PROSPECTIVE OBSERVATIONAL CHECKPOINT TRIAL (NCT02665312)

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Background: Fluoropyrimidines (FP) are the backbone chemotherapy (CT) for colorectal cancer (CRC), both in adjuvant and in metastatic setting. Although the most common toxicities have been extensively studied, robust data and comprehensive characterization still lack concerning FP-induced cardiotoxicity (FIC), an unfrequent, yet potentially life-threatening toxicity. The correlation between FIC and known cardiovascular (CV) risk factors remains controversial, thus the identification of predictive biomarkers of FIC is needed

Material and methods: CRC patients (pts) treated for the first time with FP at Candiolo Cancer Institute were enrolled since January 2016. All pts were evaluated on screening for potential CV risk factors; preexisting CV comorbidities were evaluated and treated by a cardiologist before starting CT. During the first 3 CT cycles pts were monitored with CV symptoms collection, seriated electrocardiograms, troponine I (TnI) and brain natriuretic peptide (BNP) measurements. Primary endpoint was to assess the incidence of FIC. Secondary endpoints included analyses of the relationship between FIC and known CV risk factors and of the role of TnI and BNP levels

Results: An interim analysis was conducted on 81 pts (67% male, median age 69.7 years). We found high prevalence of CV risk factors (BMI ⩾25 54.2%, smoker 55.4%, heavy drinker 28.9%, sedentary lifestyle 66.3%) and comorbidities (diabetes mellitus 20.5%, dyslipidemia 32.5%, arterial hypertension 53%, stroke 2.4%, coronary artery disease 6%, arrhythmias 4.8%, heart failure 2.4%). 16 pts (19.8%) experienced one or more CV event: 1 acute coronary syndrome (ACS), 1 coronary vasospasm, 1 paroxysmal supraventricular tachycardia (PSVT), 2 syncopes, 3 typical chest pain, 3 sudden dyspnea, 2 sudden palpitations, 4 multiple symptoms. After being treated, only 2 pts discontinued FP (ACS and PSTV), while the other pts completed the scheduled cycles. Among symptomatic pts 7 (43%) had CV comorbidities and/or CV risk factors. BNP exceeded normal value in 81 blood samples (20.8%) and TnI in 35 (8.5%); furthermore BNP levels increased after the first cycle in 79% (CI 99% 0.38-1.04), while no significant increase in TnI levels were found

Conclusions: High incidence of cardiac events, apparently not related to CV comorbidities or CV risk factors, was found. Correlation of cardiac events with symptoms, ECG and enzymatic alteratios will be available at completed recruitment (200 pts)

B25

CLINICO-PATOLOGICAL FACTORS PREDICTING "DRUG HOLIDAY" DURING FIRST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER (MCRC)

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Background: New combinations of chemotherapy and biologic agents significantly improved overall survival of mCRC patients (Pts). The need of limiting toxicity led to introduce "drug holidays" in clinical practice. We aimed to describe clinico-pathological and treatment factors that guide clinicians in offering "drug holidays" during first line treatment.

Materials and Methods: We retrospectively analysed a cohort of consecutive mCRC Pts treated with first-line chemotherapy from 01/01/2005 to 15/03/2017 at University Hospital of Udine and IRCCS CRO of Aviano, Italy. According to literature, we defined "drug holiday" as a period of 56 or more consecutive days without chemotherapy during first line. The analysis did not include patients who had undergone upfront metastasectomy. The logistic regression model was used to perform univariate and multivariate analysis aimed to detect and estimate association between predictor factors and "holiday offer". Odds Ratio (OR) was used as summary statistics.

Results: Overall, the series included 648 consecutive Pts treated in first line. Of these, 215 received a "drug holiday" (33.2%), while 433 (66.8%) received continuous treatment. In univariate analysis, the variables associated with "drug holiday" were: non-upfront metastasectomy (OR 11.8, 95% IC 6.62-22.6, $p<0.001$), thermoablation (OR 6.08, 95% IC 3.19-11.58, $p<0.001$), resection of primary tumor (OR 2.79, 95% IC 1.79-4.34, $p<0.001$), G3-G4 pathological grading (OR 1.49, 95% IC 1.01-2.19, $p=0.046$), adjuvant CT (OR 1.54, 95% IC 1.06-2.33, $p=0.023$). No association was found with KRAS, NRAS and BRAF mutational status. More than one metastatic site at diagnosis (OR 0.59, 95% IC 0.42-0.83, $p=0.003$) and nodal metastasis (OR 0.57, 95% IC, 0.34-0.95, $p=0.032$) were associated with lower chance of "drug holiday". In multivariate analysis, only first line non-upfront metastasectomy (OR 9.89, 95% IC 4.38-22.33, $p<0.001$), thermoablation (OR 4.48, 95% IC 1.97-10.19, $p<0.001$) and primary tumor resection (OR 2.43, 95% IC 1.14-5.19, $p= 0.022$) were independently associated with "drug holiday".

Conclusions: The study showed that Pts who had undergone non-upfront metastasectomy, thermoablation or surgery for their primary tumor were more frequently offered a "drug holiday". Clinicians tended not to offer this strategy to Pts with a high tumor burden. When possible, offering surgery and/or ablative techniques to mCRC Pts in first line makes clinicians more confident with "drug holiday".

B26

ITALIAN SURVEY ON CETUXIMAB-BASED THERAPY OF ELDERLY PATIENTS WITH METASTATIC COLORECTAL CANCER

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Background: A relevant issue in treatment of colorectal cancer (CRC) is the management of elderly patients (pts). Clinical data of the younger pts cannot be automatically applied to the elderly counterpart because of co-morbidities and age-specific deterioration in their organ function, especially kidney and bone marrow. There are no sufficient prospective data from clinical trials about efficacy and safety of the cetuximab-based therapy in this setting.
Patients and methods: To evaluate daily clinical practice of 17 Italian colorectal cancer oncologists, a 29-item web-based survey was performed with focus on management and cetuximab treatment of *RAS* wild-type (wt) elderly pts.
Results: The survey was representative of the whole Italian national territory. Most of the responding (13 specialists) work in National Health Service Hospitals and 4 in University hospitals. Prevalence of elderly pts suffering by CRC in Italy is getting higher and higher. Eighty-two percent of specialists treated between 100 e 200 patients in the last 5 years. Not all of them (80%) assess the molecular status of *RAS* at diagnosis of metastatic disease. Three-quarters of specialists use geriatric assessments in order to classify fit and unfit pts, but only 50% use CGA and prefer using faster scales, although not yet fully validated, like G8. The oncologists frequently use chemotherapy (FOLFIRI and FOLFOX) doublets in the first-line in combination with cetuximab and irinotecan plus cetuximab or FOLFIRI plus cetuximab in the second-line, apparently not afraid of the side effects of chemotherapy, especially diarrhea and neutropenia. In 90% of cases neutrophil growth factor are used or customize therapies like reducing initial dosage or modifying chemotherapy timing. Over 50% of specialists treat correctly elderly pts with more than one treatment line that is the only way for increasing survival time of them. In the management of cutaneous toxicity, all physicians agree that it has improved with the use mainly of antibiotics such as tetracycline administered prophylactically and with the use of creams based on vitamin K1.
Conclusions: This is the first survey aimed to examine daily clinical practice in management of CRC wt elderly patients and treated with cetuximab based-therapy. A substantial adherence between practice in Italy and scientific progresses is described, even with some discordances regarding the most appropriate treatment approach of these pts. The Survey was sponsored by Merck.

B27

CLINICAL OUTCOMES AFTER CURATIVE RESECTION OF COLORECTAL CANCER LIVER METASTASES: A SINGLE INSTITUTION EXPERIENCE

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Background: Curative resection of colorectal cancer liver metastases (CRCLM) can provide long-term survival for patients without extrahepatic disease. The impact of prognostic clinical and pathological features, such as tumor sidedness, RAS status and perioperative chemotherapy regimen, has not been well defined yet. We retrospectively reviewed our experience in order to compare outcomes in patients with synchronous and metachronous CRCLM.
Methods: Patients who underwent liver resection for colorectal cancer metastases from 2002 to 2016 were included. Clinical and pathological features were obtained from clinical records. Survival differences between groups were investigated with Kaplan-Meier method and log-rank test. A cox multivariable regression analysis was performed.
Results: Seventy-nine patients were included. Primary tumor location was colon in 58 patients (73.4%) and rectum in 21 patients (26.6%). Among patients with colon cancer, tumor sidedness was right or left in 21 (38.2%) and 34 (61,8%) of cases, respectively. RAS mutations were

detected in 27 patients (34.2%). Fifty-nine patients (74.7%) were surgically treated for synchronous metastases, while 20 patients (25.3%) for metachronous metastases. Thirteen patients (16.5%) were treated with preoperative chemotherapy, 26 patients (32.9%) with postoperative chemotherapy, 29 patients (36.7%) with perioperative chemotherapy, while 11 patients (13.9%) did not receive any treatment. Patients with metachronous disease showed a significant superior overall survival (OS) than patients with synchronous disease [105.9 vs 46.1 months; hazard ratio (HR) 0.40, 95% CI 0.20-0.83, p=0.014]. At five years 20/20 patients with metachronous metastases were still alive (100%) as compared to 23/59 (38.9%) with synchronous disease ($p<0.001$). Overall 5-year survival was 50.6%. No differences in terms of survival were detected among other groups.

Conclusions: In patients with CRCLM treated with optimal radical surgery OS was significantly higher in patients with metachronous metastases who underwent liver metastasectomy compared to those with synchronous metastases, regardless of RAS status, primary tumor sidedness and perioperative systemic treatment.

B28

CIRCULATING TUMOR DNA (CT-DNA) AND CIRCULATING MICRORNA IN COLORECTAL CANCER (CRC): CORRELATION WITH CLINICAL RESPONSE AND CLONAL EVOLUTION OF THE TUMOR

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Background: Liquid biopsy (LB) is a quick, low cost and a minimally invasive test that allows to easily obtain circulating tumor genetic material. The aim of this study is to evaluate the possibility to predict the clinical course of the disease previously of staging standard techniques and to identify new circulating molecular markers that reflect the clonal evolution of CRC patients (pts) RAS Wild Type (WT) and RAS Mutant (MUT).

Materials and methods: We selected both RAS WT and RAS MUT metastatic CRC patients treated with anti EGFR agents with or without chemotherapy and with FOLFOXIRI + Bevacizumab, respectively. After tumor tissue genotyping with MALDI-TOF (Sequenom®), LBs (plasma, buffy coat, serum and urine) were collected at pre-established time-points: baseline, monthly during therapy, every two months concurrently with tumor response evaluations and after progression. Analysis was carried out at the Royal Marsden laboratory in London and consisted in the use of droplet digital PCR® and Next Generation Sequencing (NGS) for the research of mutations of RAS, genes associated with angiogenesis (VEGFA, VEGFB, PIGF, VEGFR1, VEGFR2, VEGFR3, HIF, PDGFR, FGFR, FLT1 and Tie2) and microRNAs (miRNAs).

Results: Collection started in October 2015 and is currently ongoing. We enrolled 22 RAS WT pts and 11 RAS MUT pts. A mean of 15 time points was collected for each patient. Tissutal and ctDNA mutation levels were compared in RAS MUT and correlated with the clinical outcome. First results show a close correlation between the concentration curves of ctDNA mutations and the clinical history of the disease, demonstrating that "molecular" progression takes place before the clinical progression. In RAS WT pts a correlation was found with expression of particular miRNAs. Up or downregulation of these molecular markers have been previously tested on anti-EGFR sensitive or resistant cell lines with gene expression profiling. Subsequently we verified the presence of these biomarkers also in plasma and urine samples to monitor the oscillations during therapy course.

Conclusions: This preliminary analysis shows that liquid biopsy allows the monitoring of cancer patients treated with biological agents. The availability of a dynamic image of tumors thanks to serial sampling allows us to predict a possible progression before the traditional staging techniques and the discover of new molecular biomarkers.

B29

PREVALENCE AND DISTRIBUTION OF KRAS, NRAS AND BRAF MUTATIONS IN PATIENTS WITH METASTATIC COLORECTAL CANCER: A "MODENA CANCER CENTER" EXPERIENCE

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Background: The role of KRAS, NRAS and BRAF mutations in pathogenesis of colorectal cancer (CRC) has been recently investigated worldwide. These mutations are associated with clinicopathological features and have both prognostic and predictive value. In this study, we retrospectively evaluated the prevalence and the distribution of such somatic mutations, analyzing their correlation with clinicopathological characteristics and the impact on Overall survival (OS).

Methods: We collected 258 patients (pts) with metastatic CRC, treated from 2013 to 2015 at Oncology Department, Modena University and tested for K-RAS (exon 2, 3 and

4), NRAS (exon 2,3 and 4) and BRAF mutations. Univariate and multivariate Cox regression analysis (adjusted for sex, tumour site, number of metastatic sites, time to metastasis and BRAF mutational status) were performed.

Results: During this period, a total of 258 pts were included: 160 male and 98 female. The prevalence rates of KRAS, NRAS and BRAF mutations were 45%, 4% and 13%, respectively. The distribution of KRAS and NRAS mutations was well balanced between males and females, while, as expected, BRAF mutations were more common in females (19%) than in males (10%), and in right-sided CRC (24%) than in left-sided (6%). Patients with BRAF mutations have poor prognosis (mOS 13,6 months, HR 1.74, 95%C.I. 1.21 – 2.50, p 0.003), such as pts with 2 or more metastatic sites at diagnosis (mOS 12.2 months: HR 1,52, 95% C.I. 1,16 - 2,00, p 0,003) and pts with right-sided tumour (mOS 16.4 months: HR 1,38, 95% C.I. 1,07 – 1,78, p 0,011). In multivariate analysis adjusted for sex and time to metastasis, the number of metastatic sites at diagnosis, the primary tumour location (PTL) and the presence of BRAF mutation were confirmed as prognostic factors (2 or more metastatic sites: HR 1.44, 95% C.I. 1.08 – 1.93, p 0.013; PTL: HR 1.32, 95% C.I. 1.01 – 1.71, p 0,042; BRAF mutations: HR 1.58, 95% C.I. 1.07 – 2.33, p 0.021). Instead, sex and time to metastasis had no prognostic implication.

Conclusions: According to literature, the prevalence rates of KRAS, NRAS and BRAF mutations are 32-37%, 6-7% and 10-17%. Our population-based analysis confirms these data highlighting that KRAS and NRAS mutations are well balanced between males and females, while BRAF mutations most frequently affect women and patients with right-sided tumour.

B30

ONCOLOGY DAY HOSPITAL CARE OPTIMIZATION USING 5-FU + NALV IN PATIENTS WITH COLORECTAL CANCER: THE EXPERIENCE OF AORN "A. CARDARELLI", NAPLES

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Background: Colorectal cancer (CRC) is the second tumor diagnosed in Europe. First-choice chemotherapy includes intravenous fluoropyrimidine (5-FU) or oral capecitabine, prescribed in combination with irinotecan or oxaliplatin. 5-FU is an inhibitor of thymydilate synthetase, an enzyme that plays a central role in DNA synthesis and repair. Moreover, biomodulators can increase 5-FU efficacy: of these, folinic acid has shown the greatest efficacy. So far, chemotherapy regimens such as FOLFOX, FOLFIRI, or de Gramont, utilized folinic acid calcium salt (calcium levofolinate, CaLV). CaLV must be administered 2 hours before 5-FU, to prevent the formation of calcium carbonate crystals that would cause catheter obstruction. On the other hand, folinic acid sodium salt (sodium levofolinate, NaLV) simultaneous administration with 5-FU, without risk of crystal formation, is demonstrated. Evidence from literature showed that NaLV is effective and safe in CRC treatment.

In this perspective, for 5-FU-based CRC therapy, the use of a simultaneous combination regimen versus a sequential one would reduce the chemotherapy time, with direct benefits for patients as well as for the health service and oncologic centers. Therefore, we evaluated the benefits of replacing CaLV with NaLV in terms of length of patient stay at the DH, nursing load, infusion chair turnover and cost/benefit.

Materials and methods: CaLV was replaced with NaLV, in standard chemotherapy regimens such as FOLFOX, FOLFIRI and De Gramont, for 5 months. An overall number of 1,202 of 5-FU treatments were administered, with 15 infusion chairs and 50 hours for weekly therapy. Three hundred sixty three treatment was managed using the NaLV alternative regimen.

Results: A 30% reduction in the overall time of therapy administration was observed, as well as one-third time reduction in patients' stay at the DH. Cost reduction for € 15,972, over a period of 5 months, based on a mean cost for nurse assistance of € 22/hour, was also obtained.

Conclusions: The observed benefits support an extension in the use of NaLV-based simultaneous regimens as a new standard of care, in combination therapies with 5-FU, in patients with CRC. Actually, based on the 5-monthexperience in our center, the cost reduction that could be achieved over 1 year, with this therapy optimization, would amount to € 117,330.

B31

PROGNOSTIC FEATURES IN METASTATIC COLORECTAL CANCER (MCRC) PATIENTS: A LARGE AND MODERN SINGLE INSTITUTION EXPERIENCE

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Background: In recent years, results from major clinical trials reported a progressive improvement in outcome of mCRC patients, constantly exceeding 24 months of median overall survival (OS). Scarce data are available on results obtained in unselected patients treated in routinary routine clinical practice. Here we present outcome results and retrospective analyses of major prognostic features from a large and modern single institution database.
Material and methods: We retrospectively collected clinical, pathological and molecular features of mCRC patients referred at Istituto Oncologico Veneto, IRCCS from January 2010 to March 2017. OS was calculated from the date of diagnosis of metastatic disease to death due to any cause. Kaplan Meier and log rank test were adopted to identify clinical features affecting survival in the univariate model. Cox model was used for multivariate analyses.
Results: A total of 1455 pts were included. At a median follow-up of 59.2 months, median OS was 29 mos. Median age was 65.2 years (21.1-94.4), 59.5% of cases were males and 89.3% had an ECOG PS equal to 0 or 1. Primary tumor was resected upfront in 57.7% of cases. Primary tumor was located in right side in 32.4% of cases. Patients with synchronous disease presentation were 67%. *KRAS, NRAS* and *BRAF* mutations occurred in 43.0%, 3.2% and 6.4% of patient respectively. Metastases' resection was performed in 46.1%. Features negatively affecting OS in the multivariate model were: ECOG PS >>1 (p=0.001), grade 3-4 (p<0.0001), synchronous disease presentation (p<0.0001), age>70 years (p<0.0001), *BRAF* mutations (p<0.0001).
Conclusions: Outcome results of patients treated in routinely clinical practice at our institution are in line with those recently reported in the major clinical trials thanks to the integration of modern treatment strategies with a multidisciplinary approach. Clinical features such as age and ECOG PS are fundamental in the assessment of mCRC patients. Further details on administered treatments, enrollment in clinical trials and secondary resections will be presented.

B32

PROGNOSTIC AND PREDICTIVE IMPACT OF PRIMARY TUMOR SIDE ON CLINICAL OUTCOMES IN PATIENTS WITH METASTATIC COLORECTAL CANCER (MCRC): A MONOCENTRIC EXPERIENCE

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Background: Recent data highlighted that location in patients (pts) with metastatic colorectal cancer may have a prognostic impact and also predictive value of the outcomes of first-line therapy with monoclonal antibodies (mAbs) and cytotoxic agents.
Materials and methods: We retrospectively reviewed the records of mCRC patients who underwent first-line therapy from 2011 to april 2018 at our institute. Progression-free survival (PFS), Overall survival (OS) and Objective response rate (ORR) according to the primary tumor location were investigated. Primary tumors located at the rectum, sigma, descending colon and the left flexure were defined as left-sided (L-mCRC), while tumors located from the cecum to the distal part of the transverse colon were categorized as right-sided (R-mCRC).
Results: 130 pts were considered eligible: 93 L-mCRC (49 RAS-wt, 40 RAS-mut, 4 not tested) and 37 R-mCRC (15 RAS-wt, 21 RAS-mt, 1 not tested). M/F=81/49, median age 63 years (40-82). Metastatic sites include: liver 93.6%, lung 55.9%, nodes 46.8%. The median duration of follow-up was 17.9 months. The 2-yr OS for all pts was 80.7% whereas 82.9% in L-mCRC and 67.5% in R-mCRC regardless of the treatment performed (p=0.32). The OS of L-mCRC treated with anti-VEGF (90.3%) was longer than L-mCRC treated with anti-EGFR (68.1%) (p=0.18) while in R-mCRC treated was 74.2% with anti-VEGF and 64.3% with anti-EGFR (p=0.25). The mPFS was longer in pts treated with anti-VEGF vs anti-EGFR in L-mCRC: 14 (95% CI= 10-17) vs 8 months (95% CI=5-11) (p=0.06) and longer than just 2 months in R-mCRC treated with anti-EGFR: 9 (95% CI=1-17) vs 7 months (95% CI=3-12) (p=0.92) However, the 1-yr mPFS was statistically longer in L-mCRC vs R-mCRC (46.8% vs 24.2%, p=0.0005), regardless to the therapy performed. The ORR (complete + partial responses) was 51.1% in left-sided and 25% in right-sided (p=0.008). We found a trend towards a higher ORR in R-mCRC treated with anti-EGFR based therapy compared to anti-VEGF based therapy (50% vs 17.9%, p=0.09). 11 complete responses (CRs) (12.5%) have been observed, all in the left-sided, regardless of the therapy performed (p=0.03).
Conclusions: With the limit of the sample size, our data confirm that tumor side has a prognostic impact and might influence the outcomes of mCRC patients. CRs with a significant better mPFS was reached only by left-sided tumors

regardless of the therapy performed. Anti-VEGF seems to prolong OS and PFS in left-sided.

B33

PROGNOSTIC ROLE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO AND PATHOLOGICAL RESPONSE IN LOCALLY ADVANCED RECTAL CANCER TREATED WITH NEOADJUVANT CHEMORADIOTHERAPY

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IOM,Viagrande

Background: In Italy Colorectal cancer (CRC) is still one of the most common malignancy with 56.000 new cases observed every year

About 15,000 (29%) of these new cases are rectal cancer.

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 carcinoma.

A lot of studies mainly correlates the elevation of NLR with poor survival in patients with rectal cancer (RC).

Today, the greatest number of scientific publications regards the Asian population.

We retrospectively investigated the relationship between NLR and response to neoadjuvant treatment.

Material (patients) and methods: From May 2017 to May 2018 we treated 20 consecutive patients (pts) with LARC with capecitabine (830 mg/mq/bid) and concomitant RT. Subsequently patients received radical surgery.

Baseline radiological staging was T4N0 for one patient (pt); T3 N0-1 for 17 pts and T2N0 for two pts.

We collect at baseline before to start CRT white blood cell count (WBC), absolute neutrophil count (ANC) and absolute lymphocyte count (ALC). NLR was calculated as ANC/ALC. NLR $\geqslant$3 were defined high. NLR was correlated with tumor response.

Results: At baseline NLR was $<$ 3 in 13/20 (65%) of pts. 7/13 (54%) pts showed pCR, 2/13 (15%) pts obtained down staging and 4/13 (31%) had unchanged staging at anatomopathological analysis. 7/20 (35%) pts showed NLR $>$3. For all pts with ratio $>$3 no pCR was recodered. Downstaging of tumor was observed in 2/7 (28%) pts. The percentage of lynphocytes in the total WBC population was higher in pts with pCR than that without CR. One pt with NLR=6 showed disease progression, in this case percentage of lymphocytes was low (13%).

Conclusions: Our preliminary 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.

B34

MODIFIED SCHEDULA OF ANTI-EGFR MONOCLONAL ANTIBODIES PLUS CHEMOTHERAPY AS FIRST LINE TREATMENT IN METASTATIC COLORECTAL CANCER PATIENTS. RESULTS BASED ON TUMOR LOCATION

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Background: For metastatic disease, assessment of RAS gene status (KRAS/NRAS) and BRAF status (if KRAS is WT) determines whether or not the tumor is likely to respond to anti-EGFR monoclonal antibodies such as panitumumab and cetuximab. Commonly experienced, dermatologic side effects of antti EGFR when severe, lead to dose modification or discontinuation of treatment with pooe outcome. In our previous experience the schedule was therefore modified with monoclonal antibody infusion 24 hour before chemotherapy infusion. With this schedule the severe dermatologic toxicities resolved in all pts. In this study we wanted to prove if the modified schedule was equally effective in the right colon cancer and in the left colon cancer.

Patients and methods: We have studied nineteen eligible patients (pts) with wilde-type metastatic colorectal cancer, bidimensional measurable disease, PS$<$ 2 and adeguate haematological, hepatic, renal functional of which six whith rigth colon cancer and thirteen with left colon cancer, treated with EGFR inhibitors panitumumab and chemotherapy with FOLFOX 4, until disease progression or appearance of non tolerable toxicity.

Patients with median age of 60 years (range 46-74) were treated for a median of twelve cycles (range 6-18 cycles). The original schedule provide for the concomitant use of monoclonal antibody with Oxaliplatin in the 1° day. In our study the schedule was therefore modified with monoclonal antibody infusion 24 hour before oxaliplatin infusion.

Results: Out 19 evaluable patients for response, we obtained 1 partial response, 2 stable disease and 3 disease progression in the right colon cancer and 10 partial response, 1 stable

disease and 2 complete response in the left colon cancer. The median DFS was 3 months ans 15 months respectively. The duration of response was 4 months for rigth colon cancer and 20 months for left colon cancer The haematologic toxicity was modeste. Seven pts experienced grade 3-4 neutropenia without fever, 5 pts anemia, three pts experienced thrombocytopenia grade 2 and four pts hypertransaminasemia grade 2 . Additional non-haematologic toxicities experienced include mild nausea/vomiting, alopecia, modest acneiform rash, hair changes, pruritus, mucositis, xerosis, paronychia, regardless of the tumor location.

Conclusion. In our preliminary experience the treatment with Panitumumab and FOLFOX 4 was better in the left wilde-type colon cancer. The toxicity was equal regardless of tumor location

B35

THE RAS INFLUENCE ON SURGICAL STRATEGY IN PATIENTS WITH RECTAL CANCER AFTER NEOADJUVANT TREATMENT

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Background: The response to concomitant chemotherapy and radiotherapy in locally advanced rectal disease is variable; some tumors respond completely, reaching a pathological complete response (pCR). For these tumors which show a clinical complete response (cCR), defined as the absence of residual cancer clinically relevant, the role of a subsequent radical surgery is widely debated. The ability to predict which patients will respond to the treatment can be important to appropriately advise the patient the suitable treatment. The primary objective of the study is to identify how far the biomolecular parameter All-RAS in rectal cancer suitable for chemo-radiotherapy in patients with cCR influences the decision to avoid surgery.

Material (patients) and methods: Retrospective analysis of 39 patients from May 2011 to June 2017 treated at the Guglielmo da Saliceto General Hospital, Piacenza, affected by II or III stage rectal adenocarcinoma undergone neoadjuvant treatment (chemo-radiotherapy) followed by surgery. These patients were subjected to evaluation of the All-RAS parameters and Tumor Regression Grade (TRG).

Results: Of this group of 39 patients, only seven reached a pCR, equal to 18% of the patients. Of these, two (13% of mutated patients) showed a KRAS mutation (in one case G13D, in the other K117N), while five were wild-type, 21% of this subgroup. In particular, the patient percentage with RAS mutation grows at the same rate as the TRG value (55.6% for the TRG patients); however, the value is not statistically significant. The presence of RAS mutations seems to increase the risk of relapse (chi-square value 8.03) and mortality (for a $p < 0.05$ to have a RAS mutation is an unfavorable prognosis). If we evaluate the patients presenting lymph nodes metastasis after surgery (seven patients), three patients were KRAS mutated (two with G13D mutation and one G12D).

Conclusions: If the All RAS mutations seems to represent an unfavourable prognosis, in line with other scientific work, there is no statistically significant evidence of a correlation with a reduced pCR rate with respect to wild-type patient after neoadjuvant therapy, even though the presence of mutations seems to correspond to a higher TRG grade. KRAS mutation has a high lymph node metastasis evidence after neoadjuvant therapy; since it isn't possible to predict the absence of lymph nodes metastasis when the imaging show a cCR, KRAS can play an important role to manage the surgical or wait-and-see decision.

B36

MOLECULAR AND CLINICAL-PATHOLOGICAL FEATURES ASSOCIATED WITH EFFECTIVENESS OF AFLIBERCEPT-FOLFIRI IN ADVANCED COLORECTAL CANCER (MCRC): EXPERIENCE IN A REAL-LIFE POPULATION

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Background: FOLFIRI-Aflibercept, a recombinant human anti-VEGF fusion protein, significantly improves response rate (ORR), progression-free survival (PFS) and overall survival (OS) as second-line therapy in patients with mCRC who progressed after being treated with oxaliplatin despite receiving previously either anti-EGFR or antiangiogenetics. We evaluated the benefit of this combination in the daily clinical practice and tolerance.

Material (patients) and methods: Between May 2015 and October 2017 we recorded 25 patients. They were treated with FOLFIRI plus aflibercept each every 15 days as second-line chemotherapy treatment for mCRC. Efficacy and safety outcomes were analyzed.

Results: Patients median age was 62 (38-81). All were classified as ECOG 0-1. 75 % cases had left colon primary. 14/25 pts had only 1 metastatic site (56%), 12/25 pts had liver-limited disease (48%), 44% with synchronous debut. Each patient received oxaliplatin as a first line treatment (6/8 pts were relapsed < 6 months from adjuvant chemotherapy with oxaliplatin). Also prior use of bevacizumab was reported in 12 patients (48%) and anti-EGFR in 7 patients (28%). 72% of them had mutated RAS status, 28

% wild-type RAS status. The median number of cycles given was 9 (1-32). In all patients, some kind of grade treatment-related adverse events occurred. Most frequently 3-4 grade toxicity observed were: astenia (26%), neutropenia (30%), hypertension (26%), diarrhea (20%), stomatitis (8.4%), palmar-plantar erithrodysestesia (8.4%), and proteinuria (13.2%). In patients evaluable for response, the response rate was 14/25 pts (56%) (10 pts had 1 metastatic site) and the disease control rate of 19/25 pts (76%). The progression-free survival median time was 8 months. Benefits were similar in patients aged < 70 years and $\geqslant 70$ years. Pts with left tumors (6.7 vs 4.7 m), surgery of primary tumor (6.6 vs 5.1 m) and ECOG 0-1 (6.4 vs 3.7 m), 1 metastatic site (6.2 vs 4 m), PR with first line (6.4 vs 4.2 m), RAS WT status (7.1 vs 6.5 m) showed higher PFS. Pts relapsed < 6 months from adjuvant chemotherapy had a worse PFS over other pts (6.5 m vs 5 m).

Conclusions: In our patients series, FOLFIRI and aflibercept combination achieves a high clinical percentage benefit, expecially in pts with left tumors, surgery of primary tumor, ECOG 0, 1 metastatic site (liver), PR with first line, RAS WT status and relapsed > 6 months after adjuvant chemotherapy. Observed side effects were consistent to previous III-phase trial.

C - Gastrointestinal (non-Colorectal) Cancers

C01*

PHASE II STUDY OF NAB-FOLFIRI AND NAB-FOLFOX AS FIRST-LINE TREATMENT FOR METASTATIC PANCREATIC CANCER (ITALIAN MULTICENTER NABUCCO TRIAL BY GOIRC)

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Background: FOLFIRINOX is one of approved first-line treatment for metastatic pancreatic cancer (mPC). It obtained an increase in overall survival (OS), progression free survival (PFS) and response rate (RR), with more toxicities, over to gemcitabine. We modified FOLFIRINOX using nab-paclitaxel (nab-p) replacing either oxaliplatin and irinotecan to have two triplets, Nab-FOLFIRI and Nab-FOLFOX, that could be as effective and less toxic. GOIRC group performed a dose finding trial and determined maximum tolerated dose (MTD) of nab-p at 120 mg/m2 with FOLFIRI and 160 mg/m2 with FOLFOX. Phase II trial explored activity and safety of Nab-FOLFIRI and Nab-FOLFOX in first line setting for mPC in term of ORR, PFS, OS, and toxicities.

Patients and methods: NabucCO trial was an Italian multicenter, randomized, phase II trial in which patients (pts) with untreated mPC and PS ECOG 0-1 were randomized to receive 5-fluorouracil (5-FU) bolus 400 mg/m2, l-folinic acid 200 mg/m2, 5-FU 2400 mg/m2 as a 48-hour ci and irinotecan 180 mg/m2 plus nab-p 120 mg/m2 (arm A), or oxaliplatin 85 mg/m2 plus nab-p 160 mg/m2 (arm B) every 2 weeks until death, progressive disease or unacceptable toxicity, for up to 12 cycles.

Results: From November 2015 to January 2017, 42 pts for each arm were enrolled. The ORR was 31% for arm A and B, with a clinical benefit rate (CBR) of 69% and 71% respectively. At a median follow up of 11.4 months (mos) for arm A and 14.5 mos for arm B, 1-year survival was 41% and 50%. For Nab-FOLFIRI PFS and median OS were 6 mos (95% CI:4.7-8.1) and 13.2 mos (95% CI:8.4-16.2), while for Nab-FOLFOX were 5.6 mos (95% CI:4.2-8.4) and 10.5 mos (95% CI: 7.5-12.9). Grade $\geqslant 3$ toxicities in arm A were neutropenia (19%) and febrile neutropenia (12%). In arm B, main grade $\geqslant 3$ toxicities were neutropenia (29%), fatigue (14%) and peripheral neuropathy (7%).

Conclusion: Nab-FOLFIRI and Nab-FOLFOX demonstrated similar activity to FOLFIRINOX (31%) with lower rate of neutropenia, fatigue and neuropathy. Furthermore, OS for Nab-FOLFIRI is superior respect to FOLFIRINOX (13.2 vs 11.1 mOS) warranting a future phase III trial. NabucCO is the first Italian trial exploring the potential of triplets containing nab-p in first line setting. Currently, pts with mPC and good PS could receive nab-p plus gemcitabine or FOLFIRINOX as first line treatment: NabucCO schedules could increase the benefit enhancing the effect of a triplet with nab-p, giving the possibility to receive both strategies at the beginning of the cure.

C02

ANGPT2 POLYMORPHISMS AND CLINICAL OUTCOME IN ADVANCED HEPATOCELLULAR CARCINOMA PATIENTS RECEIVING SORAFENIB

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Introduction: Sorafenib (S), an oral multi-kinase inhibitor, represents the standard of care for advanced hepatocellular carcinoma (HCC), even if a large number of patients reports limited efficacy with respect to toxic effects. Biomarkers of S efficacy or resistance have yet to be identified. Angiopoietin-2 (Ang-2) is an angiogenic factor that

binds Tie2 receptor and cooperates with the vascular endothelial growth factor (VEGF) pathway to maintain physiological functions. Genetic variants in Ang-2 gene (*ANGPT2)* may lead to altered activities of the gene. Llovet and co-workers have found that baseline plasma Ang2 concentrations predicted survival in patients with advanced HCC. We analyzed the prognostic role of *ANGPT2* polymorphisms in relation to clinical outcome and toxicity in advanced HCC patients receiving S.

Methods: Our retrospective multicenter Italian study included 135 advanced HCC patients all undergoing S treatment from 2012 to 2015. DNA was extracted from blood samples and *ANGPT2* polymorphisms (rs3739390, rs3739391, rs3739391, rs1961222, rs3020221, rs6559167, rs2916747, rs17063434) were analyzed by direct sequencing in relation to progression-free survival (PFS), overall survival (OS) and disease control rate (DCR).

Results: All genotype frequencies followed the Hardy-Weinberg equilibrium. In univariate analysis *ANGPT2* rs55633437 was associated with progression free survival (PFS) and overall survival (OS). rs55633437 GG genotypes were significantly associated with a higher median PFS and OS (6.27 and 15.51 months, respectively) than other genotypes (1.58 and 4.66 months, respectively) ($P < 0.001$). *ANGPT2* rs3020221 and rs1961222 were associated only with OS. Moreover patients carrying a GG genotype for rs55633437 showed a higher percentage of DCR at the first CT re-evaluation than those carrying other genotypes (75.3% vs. 20%, respectively) ($P < 0.0001$). Multivariate analysis confirmed this polymorphism as the only independent prognostic factor.

Conclusion: Our results suggest that rs55633437 in the Ang2 gene may be capable of identifying a subset of HCC patients who are more responsive to Sorafenib in terms of PSF, OS and DCR. These data will be confirmed in an ongoing prospective study (NCT02786342).

C03

SAFETY AND EFFICACY OF RAMUCIRUMAB (R) PLUS PEMBROLIZUMAB (P) IN TREATMENT NAÏVE AND PREVIOUSLY TREATED ADVANCED GASTRIC OR GASTROESOPHAGEAL JUNCTION (G/GEJ) ADENOCARCINOMA: A MULTI-DISEASE PHASE (PH) 1 STUDY

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Background: Preclinical evidence suggests simultaneous blockade of vascular endothelial growth factor receptor 2 (VEGFR-2) and programmed death 1 (PD-1) or programmed death-ligand 1 (PD-L1) enhances antitumor effects. We report safety/efficacy of R+P in patients (pts) with G/GEJ cancer.

Methods: This ongoing, multicohort, Ph 1a/b trial enrolled pts with measurable metastatic or unresectable G/GEJ, ECOG PS 0–1 previously treated (PT;cohorts A & B) for advanced disease or treatment-naïve (TN;cohort A2). Positive (combined positive score [CPS]⩾1%) or negative (CPS<1%) PD-L1 status was assessed by DAKO PD-L1 22C3 IHC pharmDx assay. R was administered at 8mg/kg on Days1+8 (cohorts A&A2) or 10mg/kg on Day1 (cohort B) with P 200mg on Day1 q3W. Data cut-off was 31-July-17(NCT02443324).

Results: 28 TN pts were treated; median age 63y, 75% male, 43% ECOG PS 1, 68% PD-L1+. 41 PT pts were treated; median age 58y, 76% male, 66% ECOG PS 1, 54% PD-L1+; 59% received study treatment as ⩾3rd line. Median therapy duration was 130days (R & P) for TN pts. All-grade treatment-related adverse events (TRAEs) occurred in 27(96%) TN pts. TRAEs in ⩾15% of TN pts were fatigue (10pts), hypertension (7pts), and headache (5pts). 17(61%) TN pts experienced grade 3 TRAEs, most commonly hypertension (4pts), diarrhea (3pts), and elevated alanine (2pts) or aspartate (2pts) aminotransferase. Median therapy duration was 84days (R) and 91days (P) for PT pts. All-grade TRAEs occurred in 33(80%) PT pts; 12(29%) pts experienced grade 3–4 TRAEs, most commonly colitis (3pts) and hypertension (3pts). One TR death occurred (pneumonitis). Responses occurred in 3(7%) PT pts (2 PD-L1+,1 PD-L1-) and 7 (25%) TN pts (6 PD-L1+,1 PD-L1-) [see Table].

Table. Preliminary efficacy of R+P.

	PT (N=41)	TN (N=28)
Objective response rate %	7	25
Median (med) time to response, mo	2.1 (95%CI 1.4-4.1)	2.7 (95%CI 1.3-2.8)
Med duration of response, mo	6.7 (95%CI 4.4-not calculable)	10.0 (95%CI 9.7-10.3)
Disease control rate %	51	68
Progression-free survival rates at 6 mos,%	26.4 (95%CI 13.7-40.9)	38.8 (95%CI 18.8-58.4)
Med progression-free survival, mo	2.6 (95%CI 1.5-4.1)	5.3 (95%CI 3.2-11.0)
Overall survival rates at 6 mos %	51.7 (95%CI 34.6-66.4)	68.2 (95%CI 46.2-82.8)
Med overall survival, mo	6.2 (95%CI 4.4-12.6)	Not reached

Conclusion: Safety findings for R+P are consistent with those of the single agents, with no new safety signals observed. The antitumor activity of the combination is encouraging in pts with TN or PT advanced G/GEJ adenocarcinoma.

C04

A NOVEL IMMUNE-INFLAMMATORY SCORE TO PREDICT SURVIVAL IN PATIENTS (PTS) WITH ADVANCED BILIARY TRACT CANCER (ABTC) RECEIVING FIRST-LINE CHEMOTHERAPY (1-LINE CHT)

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Background: Cht is the mainstay of treatment for ABTC with median overall survival (mOS) < 12 months. Given the palliative intent of treatment, its limited survival gain and not negligible toxicities, it is of paramount importance to properly select pts. Determinants of immune-inflammation are regarded as promising prognostic factors in ABTC.
Material and Methods: Clinical and laboratory data before starting 1-line cht were evaluated in 123 pts with unresectable locally advanced and metastatic ABTC (intrahepatic, perihilar and distal cholangiocarcinoma and gallbladder cancer) treated from 1st January 2010 to 31st July 2017 at Modena Cancer Centre. Potential prognostic factors were assessed by univariate (Cox proportional hazard univariate model) and multivariate analyses (multiple Cox proportional hazard regression with the likelihood ratio test).
Results: At univariate analysis ECOG PS > 0, metastatic disease, gallbladder cancer, no previous surgery, monocht, LDH > upper limit of normal, albumine < 3.5 gr/dl, absolute neutrophil count (ANC) > 8000/µl, lymphocyte/monocyte ratio (LMR) < 2.1, neutrophil/lymphocyte ratio (NLR) > 3, platelet/lymphocyte ratio > 160, AST > 40 IU/L, gamma-glutamyl-transpeptidase > 40 IU/L, CEA > 9.5 ng/ml, CA19-9 > 700 U/L were significantly associate with shorter OS. At multivariate analysis, LMR < 2.1, NLR > 3, ANC > 8000/µl, albumine < 3.5 gr/dl retained statistical significance as poor prognostic factors. By combining these four variables, three different risk groups were identified: low-risk group (0 factors), intermediate-risk group (1-2 factors) and high-risk group (3-4 factors), with mOS of 22, 12, and 5 months respectively (P<0.001). The prognostic value of the score was indipendent from treatment procedures (doublet vs monocht) and primary tumour site (P<0.001).
Conclusions: We developed a cost-effective and easily-available scoring system that discriminates ABTC treated with 1-line cht into three different statistically significant prognostic groups. It could become a useful tool to add to established factors for improving pts' selection in daily practice.

C05

DEVELOPMENT AND VALIDATION OF A NOMOGRAM PREDICTING HER2 STATUS IN ESOPHAGO-GASTRIC CANCER

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Background: HER2 status plays a crucial role in advanced esophago-gastric cancer (EGC) and it is mandatory for HER2 inhibitor prescription. We explored the feasibility of a pre-test screening tool for timely predicting the probability of identifying a HER2-positive EGC.
Material and methods: We analyzed clinical and pathological features of 695 consecutive EGC patients (pts), followed in three different Institutions. A multivariate logistic regression model, able to predict HER2 positivity, was built by using 411 cases from one Institution; backwards and forward methods were used to construct multiple models. Validation and calibration were performed on 284 patients of the other two Institutions. Considering statistical significance of the covariate, clinical plausibility and global fit, a model was selected and used to develop a nomogram. C-index, visual inspection of the calibration plot, Brier score and Spiegelhalter z-test were used to assess the performance of the nomogram.
Results: In the development cohort, 17% of cases (119) were HER2 positive. After univariate analyses and adjustment of collinearity, four variables were retained: tumor grading (G1 vs. G2 vs. G3) (p=0.0018), Lauren's histotype (intestinal vs. diffuse) (p=0.044), type and adequacy of pathological material (surgical specimen vs. ⩾5 biopsy samples vs. <5 biopsy samples) (p=0.19) and site of sampling (primary cancer vs. metastasis) (p=0.034). Tumor grading had the highest score in the nomogram, followed

by site of sampling, Lauren's histotype and type of pathologic material. The calibration plot examined by visual inspection revealed an almost super imposable shape of predicted and observed probability curves, with a Brier score of 0.048 and a statistically significant Spiegelhalter z-test ($p<0.0001$). C-index resulted in 0.84 (95%CI 0.75-0.93).

Conclusions: This nomogram, built on four easy-to-collect variables, allows predicting the HER2 positivity in EGC in a timely and accurate way. This tool could be useful in the daily clinical practice and its predictive ability should be further assessed in prospective trials.

C06

IMMUNE INFLAMMATION INDICATORS AND ALBI SCORE TO PREDICT OCCURRENCE AND RECURRENCE OF HEPATOCELLULAR CARCINOMA IN HCV-RELATED CIRRHOSIS TREATED WITH DIRECT-ACTING ANTIVIRALS

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Introduction: Interferon(IFN)-free regimen using new direct acting antivirals (DAAs) has represented a revolution in the treatment of patients with chronic hepatitis C. The impact of DAAs-based treatment on the development of hepatocellular carcinoma(HCC) in patients with cirrhosis has emerged as a controversial issue with potential clinical implications, particularly on the HCC recurrence after successful curative treatment. The aim of this study was to evaluate the predictive value of ALBI score and immune-inflammation indicators to identify the risk of occurrence or recurrence of HCC in patients treated with DAAs for chronic hepatitis C.

Method: In this retrospective cohort study, we analysed data from all the consecutive HCV-infected cirrhotic patients treated with DAAs in seven centers of Italy.

Results: We performed our analysis on the 514 consecutive patients with HCV-related liver cirrhosis treated with different DAA regimens between January 2015 and August 2016. We split the population into two categories for analysis: patients with history of HCC (98) and without (416). HCC was detected, and confirmed by at least two independent imaging techniques, or biopsy, in 30 out 98 patients (30.6%,)with a history, and in 29 out 416 patients (6.9%) without a history of HCC. Based on univariate analysis, as a continuous variable, the increase of AST ($p=0.036$, HR:1.01, 95%CI:1.00–1.01), bilirubin ($p=0.035$, HR: 1.46, 95% CI: 1.03–2.08), ALRI ($p =0.002$, HR: 1.01, 95% CI: 1.0–1.01), ALBI score ($p = 0.001$, HR: 2.99, 95% CI: 1.45–6.15) and decrease of albumin ($p = 0.004$, HR: 0.34, 95% CI: 0.17–0.71), platelet count ($p = 0.007$, HR: 0.99, 95% CI: 0.98–1.00) were significantly associated with HCC occurrence. At multivariate analysis, two variables resulted independently associated with HCC occurrence: the increase of ALBI score ($p = 0.038$, HR: 2.35, 95% CI: 1.05–5.25) and the decrease of platelet count ($p =0.048$, HR: 0.99, 95% CI: 0.98–1.0). Based on this final multivariate model, a nomogram for predicting the HCC-free probability at 1-year from DAA initial was built. In patients with history of HCC, only increase in ALRI index ($p = 0.037$ HR: 1.00, 95% CI: 1.01–1.20) resulted the only significantly associated with HCC recurrence.

Conclusions: Our results demonstrated that ALBI score, platelet counts and ALRI index are promising tools for identifying patients with higher risk to develop HCC after treatment.

C07

EPIDEMIOLOGICAL, CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF GASTRIC NEOPLASMS. THE EXPERIENCE OF THE FIRST POPULATION-BASED SPECIALIZED GASTRIC CANCER REGISTRY IN CREMONA, ITALY

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Background: Gastric cancer (GC) incidence rate changes widely across geographical areas. In Italy, the province of Cremona is characterized by a high incidence, compared to the national one. For this reason a specialized population-based Registry was set up. Methods. The collection encompasses all GCs diagnosed in the three districts of the province since January the 1st, 2010. The main data sources were represented by the pathological records and patient clinical charts. Only diagnoses of primary GCs were considered. For each case the following variables were registered: personal data, medical history and symptoms at diagnosis; imaging assessments performed, details on surgery and other treatments received, genetic background and biomolecular characteristics, social and environmental factors.

Results: As of November 2017, 1087 cases were collected; of which 876, diagnosed until December 2015, analyzed. Male/female ratio was 1.4. European Age-standardized Incidence Rate was 41.4 (CI95% 35.4-48.5) for male and 28.3 (24.2-33.1) for female as compared to a national average of 33.3 and 17.0, respectively. Median age at diagnosis was 73 for male and 78 for female. Helicobacter Pylori infection was present in less than 20%

of cases. HER-2 gene resulted amplified in about 25% of cases. Primary tumour location was gastroesophageal junction or cardia in 17.5% in male and 8.3% in female. Majority of cases (58.3%) was diagnosed in advanced stage and overall only 41.2% underwent surgery. Median overall survival was 14.8 months for men and 18.5 for women. Age standardized 5-year relative survival was 31.4% for men and 40.5% for female. Neoadjuvant treatment was performed in less than 10% of patients who underwent surgery, and the rate of postoperative therapy adherence was low.

Discussion: This study shows a high GC incidence in the province of Cremona, with a geographical spread across different districts. Moreover, a high percentage of GCs detected in advanced stage and a low rate of 5-year relative survival were registered. Based on these findings, effective preventive interventional health strategies and screening procedures need to be implemented to reduce the impact in this pathology for this geographical area.

C08

OUTCOMES BASED ON AGE IN THE PHASE 3 CELESTIAL TRIAL OF CABOZANTINIB (C) VERSUS PLACEBO (P) IN PATIENTS (PTS) WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC)

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Background: The incidence of HCC generally increases with age, although the age of onset varies depending on disease etiology and geographic region (Yang, Nat Rev Gastroenterol Hepatol 2010). In the phase 3 CELESTIAL trial (NCT01908426), C, an inhibitor of MET, VEGF receptors, and AXL, improved overall survival (OS) and progression-free survival (PFS) compared with P in pts with previously-treated advanced HCC. Overall, median OS was 10.2 mo for C vs 8.0 mo for P (HR 0.76, 95% CI 0.63–0.92; p=0.0049), and median PFS was 5.2 mo for C vs 1.9 mo for P (HR 0.44, 95% CI 0.36–0.52; p<0.0001). Here, we evaluate clinical outcomes based on age in the CELESTIAL trial.

Material and methods: 707 pts were randomized 2:1 to receive C (60 mg qd) or P. Eligible pts had pathologic diagnosis of HCC, Child-Pugh score A, ECOG PS ⩽1, and must have received prior sorafenib. Randomization was stratified by disease etiology, geographic region, and extent of disease. Outcomes were analyzed for subgroups based on age (<65 years and ⩾65 years).

Results: Median age at baseline was 64 years; 51% of pts were <65 years old. Etiology of HBV was more frequent in pts <65 years vs ⩾65 years old (52% vs 22%), while etiology of HCV occurred at a similar frequency in both age groups (24%). Asian race and enrollment in Asia were more frequent in pts <65 years vs ⩾65 years old (46% vs 21% Asian race; 35% vs 14% enrolled in Asia). Median OS was 9.6 mo for C vs 7.7 mo for P (HR 0.81, 95% CI 0.62–1.05) for pts <65 years old and 11.1 mo for C vs 8.3 mo for P (HR 0.74, 95% CI 0.56–0.97) for pts ⩾65 years old. Median PFS was 5.0 mo for C vs 1.9 mo for P (HR 0.45, 95% CI 0.35–0.57) for pts <65 years old and 5.4 mo for C vs 2.0 mo for P (HR 0.46, 95% CI 0.35–0.59) for pts ⩾65 years old. The discontinuation rate due to treatment-related adverse events in the C group was lower in pts <65 years vs ⩾65 years old (11% vs 22%), while the percentage of pts with any dose reduction (61% vs 64%) and the median average daily dose of C (37 mg vs 34 mg) were similar in both age groups. The most common grade 3/4 adverse events in both age groups were consistent with those in the overall population.

Conclusion: C improved OS and PFS vs P in pts with previously-treated advanced HCC irrespective of age category.

C09

CORRELATION BETWEEN CLINIC-PATHOLOGICAL FEATURES, MSI, PD-L1 AND SURVIVAL IN RESECTED GASTRIC CANCER: LOOKING FOR PROGNOSTIC BIOMARKERS

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Background: The identification of prognostic biomarkers (PB) for gastric cancer (GC) patient selection is compelling to improve survival outcomes. Microsatellite instability (MSI) is related with a positive prognostic effect in resected GC, whereas perioperative chemotherapy (CT) is detrimental. In metastatic MSI GC, immunotherapy (IT) with anti-PD1/PDL-1 drugs has shown promising results. Nevertheless, in early stages (ES), data on the relation between MSI, clinic-pathological (CP) features, PDL-1 expression and overall

survival (OS) remain sparse, especially in Western population. In this study, the prognostic role of MSI status, CP features and PDL-1 status in a large cohort of Italian GC patients (pts) was examined.

Methods: CP data of 148 consecutive stage I-III GC pts resected in Cremona Institute between 2010 and 2014 (mostly chemo and/or radio-naive) were collected. MSI analysis was performed on tissue samples for all cases by polymerase chain reaction. PDL-1 expression, evaluated by immunohistochemistry, was assessed in MSI group. Differences between subgroups were evaluated with Chi-square test; Kaplan-Meier method and Long Rank test were used to calculate OS.

Results: Female sex (p=0.012), earlier TNM stages (p=0.011) and lower nodal involvement (p=0.029) significantly correlated with MSI status. MSI is significantly associated with prolonged survival ($p < 0.001$), with an advantage of 28.6 months in OS compared to the microsatellite stable (MSS) group. Most MSI pts (71%) expressed PDL-1. Although not statistically significant, MSI pts without PD-L1 expression showed a better trend in OS compared with MSI GC pts expressing PDL-1 and with MSS group.

Conclusions: MSI is an independent PB in GC and identifies a subset of pts with better OS and specific CP characteristics, including high expression of PDL-1. MSI could be a promising biomarker to select pts for CT vs IT in ES of GC.

C10

REAL-WORLD CLINICO-PATHOLOGICAL FEATURES OF ADVANCED BILIARY TRACT CANCER (ABC) LONG-TERM SURVIVORS (LS).

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Background: Advanced biliary tract cancers (ABC) are relatively rare and heterogeneous tumours with median overall survival (mOS) < 12 months when treated with chemotherapy. Among the overall population, an outlier subset of patients with a mOS ≥ 24 months (11% of the total) has been recently identified in an updated analysis of the ABC-02 trial. However, a clinico-pathological characterization of these LS in a clinical practice setting is lacking.

Materials and Methods: Retrospective analysis of medical records of patients with unresectable locally advanced or metastatic biliary tract cancer treated with chemotherapy from January 2010 to December 2017 at the Modena Cancer Centre was conducted. We defined as LS those patients surviving over 2 years from the diagnosis of advanced disease.

Results: A total of 153 ABC patients fulfilling our criteria were identified. Among them, 22 (13%) patients survived ≥ 2 years. The median age of LS was 67 years (range 29-80) and 82% were female. ECOG PS was 0 in 18 cases (82%) and 1 in 4 cases (18%). 13 (60%) had an intrahepatic, 4 (18%) had a perihilar, 4 (18%) had a gallbladder and 1 (4%) had a distal tumour. Disease status was metastatic in 18 cases (82%) and locally advanced in 4 cases (18%). As first-line treatment: 10 patients received cisplatin/gemcitabine (45%), 7 monochemotherapy (32%) and 5 (23%) other chemotherapy doublets. 18 patients (82%) received a second-line, 14 (64%) a third-line and 5 (22%) a fourth-line treatment. The mPFS and mOS were 12 months and 36 months, respectively. In univariate logistic regression, ECOG PS 0, female gender, locally advanced disease, neutrophils/lymphocytes ratio (NLR) ≤ 3.0, > 1 line of treatment and CEA ≤ 9.5 were associated with a higher likehood of survive ≥ 2 years. Female gender (p=0.020), NLR ≤ 3 (p=0.004) and > 1 line of treatment ($p < 0.001$) retained statistical significance in multiple logistic regression. Female patients with a NLR ≤ 3 display the highest chance of surviving ≥ 2 years (45%).

Conclusions: These results support a treatment strategy based on the delivery of sequential chemotherapy lines in selected ABC patients. Common clinical features do not appear to impact on the likehood of surviving longer than 2 years, while female gender and NLR ≤ 3 do. On these premises, we have launched a translational research project (BILONG study) aimed at molecularly characterized ABC LS, particularly focusing on gender- and immune-related determinants.

C11

ELDERLY VS NON ELDERLY ADVANCED PANCREATIC DUCTAL ADENOCARCINOMA (PDAC) PATIENTS: A RETROSPECTIVE ANALYSIS ON SECOND-LINE TREATMENT OUTCOME

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Background: Pancreatic cancer is predominantly seen in elderly patients, with incidence peaking in those over 70 years. Nevertheless, a very few data are available for the management of this disease in elderly population. In particular, the role of second-line chemotherapy remains

unclear in PDAC in this setting and considering the marginal benefit observed, patients' selection is crucial to identify those more likely to benefit from treatment.

Patients and methods: In this retrospective study we analyzed clinical and laboratoristic features and treatment data of 144 advanced PDAC patients treated with at least two lines of chemotherapy. Characteristics of eldery (age ⩾ 70 years) and non-elderly patients were compared using chi-squared test. The Cox proportional hazards regression model was used to identify prognostic factors. Progression-free survival (PFS) and overall survival (OS) were calculated using Kaplan-Meier estimation and compared by log-rank test.

Results: Median age of the patients was 62 years (range 31-81 years). Ninety patients (63%) were male and fifty-four (37%) female. Median PFS for second-line treatment was 2.76 months while median OS was 5.26 months for the whole population. Twenty-nine patients (20.1 %) were 70 years old or older at the start of second-line treatment. No statistically significant difference was found between age groups in terms of gender (p= 0.50), ECOG Performance Status (PS) (p= 0.76), peritoneal metastases (p= 0.73) or presence of two or more metastatic sites (p= 0.90). Combination chemotherapy was used in 48.3% of elderly patients and in 66.4% of non-elderly patients but the difference was not statistically significant (p= 0.11). Median OS of elderly group was 5.0 months vs 6.6 months in non-elderly group (p= 0.46; HR= 0.82, 95% CI 0.51 – 1-35). Elderly had also similar PFS compared to non elderly patients (p= 0.90; HR= 1,02, 95% CI 0.66 – 1.59). In elderly group, poor ECOG PS (HR= 2.9, 95% CI 2.13-4.20; p= 0.01), first-line PFS ⩽ 4 months (HR= 0.12, 95% CI 0.02-0.72; p= 0.02) and high LDH (HR= 1.6, 95% CI 1.61-17.1; p= 0.02) were negative prognostic factors at multivariate analysis.

Conclusions: Our analysis did not shown significant difference in terms of survival between elderly and non-elderly advanced PDAC suggesting that age should not limit the use of second-line treatment. Conversely, poor ECOG PS, early progression to first-line treatment and high LDH were negative prognostic factor in this setting.

C12

SECOND-LINE CHEMOTHERAPY FOR THE TREATMENT OF METASTATIC PANCREATIC CANCER AFTER FIRST-LINE GEMCITABINE-BASED CHEMOTHERAPY: A NETWORK META-ANALYSIS

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Background: Guidelines for treatment of metastatic pancreatic cancer recommend a second line based on Fluoropyrimidine (FP) alone or in combination with Oxaliplatin (OXA) or Irinotecan (IRI) after a first line treatment based on Gemcitabine (GEM).

Material and methods: We conducted a Bayesian network meta-analysis to compare currently available therapies to treat metastatic pancreatic cancer in the second line, considering as efficacy measures overall survival (OS) and progression free survival (PFS). Published randomized trials were identified using electronic databases (MEDLINE, PubMed, ClinicalTrials.Gov and American Society of clinical oncology).

Results: 8 studies met the inclusion criteria for a total of 1,587 patients and 7 different therapeutic schemes. Bayesian network meta-analysis models were specified separately for the two outcomes, accounting for heterogeneity between study.

Conclusions: The results suggested that the use of IRI-FP-Folinic Acid scheme in the second-line treatment of metastatic pancreatic cancer may offer a benefit in terms of OS and PFS for patients not previously treated with these drugs.

C13

ANALYSIS OF PROGNOSTIC FACTORS IN PATIENTS WITH LOCALLY ADVANCED PANCREATIC CANCER (LAPC) TREATED WITH PRIMARY FOLFOXIRI

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Background: Patients with LAPC are usually treated with primary chemotherapy followed by evaluation for subsequent locoregional treatment such as srgery or radiotherapy. Prognostic factors that could help to select the right therapeutic strategy are still lacking.

Material and methods: Patients with LAPC (cT4, cN0-N1, cM0), ECOG PS 0-1, with age =75 years, were treated in our center with FOLFOXIRI every 2 weeks for 4-6 months. Tumor assessment was performed by computed tomography (CT) every 8 weeks and multidisciplinary team evaluated patients baseline and after every CT in order to evaluate patients for surgery or radiotherapy. The

prognostic role of clinical (age, sex, ECOG PS, tumor site, neutrophil/lymphocyte ratio, response, surgery) and pathological data (histology, grading, pathological stage, regression grade, lympho-vascular or perineual invasion) was retrospectively evaluated in order to derive insight for a better selection of patients for surgical treatment.

Results: From 2010 to 2017, 77 patients with LAPC were FOLFOXIRI. At a median follow up of 31 months, median overall survival (OS) was 11.9 months. According to RECIST criteria, response rate was 35.1%, progressive disease was 9.1%. Surgical resection was carried out in 39 patients (50.6%). Median OS was 23.5 months in resected and 13.9 months in not resected patients. At univariate analysis, both surgery (p=0.0002), Ca19.9 decrease>50% during treatment (p=0.001) and basal ECOG PS (p=0.014) were associated with better OS, but only Ca19.9 decrease (p=0.003; HR: 3.74,95% CI 1.59-8.83) and ECOG PS (p=0.014; HR: 2.5; 95% CI 1.12-5.82) maintained their prognostic value in multivariate analysis. Considering only the group of resected patients, none clinical factor resulted prognostic for OS while some pathological data as tumor histology (p=0.027), tumor grading (p=0.004) and regression grade according to Dworak score (p=0.016) were associated with OS at univariate analysis, but did not confirm their prognostic role at multivariate analysis.

Conclusions: ECOG PS and Ca19.9 decrease identify patients with better outcome and could help to select LAPC patients that could benefit from surgical resection after primary FOLFOXIRI.

C14

POTENTIAL PROGNOSTIC MARKERS IN UNRESECTABLE OR RELAPSED PSEUDOMYXOMA PERITONEI (PMP) TREATED WITH METRONOMIC CAPECITABINE PLUS CYCLOPHOSPHAMIDE REGIMEN

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Background: The standard treatment of PMP is cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). No consensus was reached on treatment of unresectable/recurrent disease and prognostic/predictive markers are lacking. PMP has been considered chemoresistant for its low mitotic index but uncontrolled series showed promising results with modern regimens used for gastrointestinal tumors. Metronomic schedules may be preferred for their antiangiogenic and immunomodulatory activity.

Patients and Methods: We conducted a single center prospective single arm trial. Inclusion criteria were histologically confirmed PMP, unresectable or relapsed after CRS/HIPEC, in progression to surgery or previous treatments. Patients received continuous metronomic capecitabine (625 mg/sqm b.i.d.) plus cyclophosphamide (50 mg/day) until progressive disease/unacceptable toxicity/consent withdrawal. The primary endpoint was progression free survival (PFS); secondary endpoints were disease control rate (DCR), overall survival (OS) and safety profile. The correlation of tumor markers (CEA, CA19.9, CA125) level and neutrophil/lymphocyte ratio (NLR) with PFS was studied.

Results: 23 consecutive patients were enrolled from April 2015 to October 2017. At a median follow up of 13.5 months (mo), median PFS was 9.5 mo and 1-year OS rate 73.7% (95%CI 47.3-88.3%). No partial or complete responses were observed but DCR was 74% and 22% patients achieved a prolonged disease stability (>13 mo). The safety profile was manageable: 17% G3 drug related adverse events and none G4/5. 43% patients had a >20% reduction of CA19.9, 22% of CA125 and 39% of CEA. CA19.9 decrease >20% vs <20% was not associated with PFS (9.5 vs 9.5 mo, p=0.7861). CEA and CA125 reduction >20% vs <20% showed a trend to better PFS, respectively 12.6 vs 6.9 mo, p=0.2217 and not reached vs 8.3 mo, p=0.6195. Median NLR baseline value was 1.65. NLR maintained <3 had a non-significant higher PFS than NLR baseline <3 switched to >3 during treatment and NLR baseline >3, respectively 9.54 vs 7.99 vs 4.69 mo, p=0.1436.

Conclusions: Metronomic capecitabine plus cyclophosphamide is an active regimen in unresectable/recurrent PMP, with a safety profile comparing favorably with historical data. CEA and CA125 decrease >20% and NLR maintained <3 showed a trend to better PFS, not statistically significant due to small sample size. Further studies are needed to confirm the potential prognostic value of tumor markers in this setting.

C15

CHANGES OF IMMUNOLOGICAL PARAMETERS AFTER ADMINISTRATION OF NAB-PACLITAXEL + GEMCITABINE IN PATIENTS WITH ADVANCED PANCREATIC CANCER

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Background: The prognosis of pancreatic cancer (PC) is extremely poor. The only curative approach is surgical

resection that is not an option for the large majority of pts diagnosed in advanced stage. Cytotoxic chemotherapy (CT), that remains the mainstay of treatment, traditionally has been regarded as immunosuppressive while increasing evidences suggest that it may actually increase tumor immunogenicity. This role of CT has been studied in different solid tumors leading to the hypothesis that, also in PC, immunomodulation via CT may sensitize cancer cells to immune therapy.

Patients and Methods: To explore the role of the immune system response after combination CT in PC we studied the effect of Nab-paclitaxel + Gemcitabine on different T-cell populations. Using high-resolution multicolor flow cytometry, Foxp3+ T*reg* populations, sub-populations of cytotoxic CD8+ T-cells and CD57+ NK cells were analyzed in 21 pts (11M/10F, median age 58, range 43 - 72 yrs,) with unresectable PC undergoing a first-line medical treatment. A group of 10 healthy subjects matched for sex and age was utilized as control.

Results: There was a progressive decrease in absolute numbers of leukocytes, lymphocytes and CD8+ T-cells during CT. Starting from the second CT 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 CD28-CD57+ cells.

Conclusion: In advanced PC pts, Nab-paclitaxel + Gemcitabine elicit several changes of some immune-related parameters including the composition and phenotype of immune cells. In particular, regulatory activities in T cells were increased through decreasing Foxp3+*Treg* cell populations. These features might help to tailor novel combination therapies based on immune cell response in this disease.

C16

CLINICAL SIGNIFICANCE OF MISMATCH REPAIR PROTEIN STATUS AND PD-L1 EXPRESSION IN RESECTED GASTRIC CANCER PATIENTS

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Background: Multimodality treatment represents the standard of care for non-metastatic gastric cancer (GC) patients (pts), but still today there are no validated prognostic and predictive biomarkers for these pts at the diagnosis. Unlike colon cancer, the prognostic and predictive role of microsatellites and mismatch repair proteins (MMR) remains unclear in GC. A microsatellite instability state (MSI) could be a potential predictive factor for response to immunotherapy, because MSI tumors frequently express different immunological checkpoint proteins, including PD-1 and PD-L1. However, the relationship between PD-L1 expression and MMR status remains poorly understood. The aim of this study was to define a potential correlation between PD-L1 expression and MMR status and their prognostic role in resected GC.

Materials and methods: We performed the immunohistochemistry (IHC) analysis to evaluate MMR proteins (MLH1, PMS2, MSH2 and MSH6) and PD-L1 expression in a series of 49 resected GC FFPE specimens of pts treated in our institution between July 2009 and October 2016. Statistical analysis was performed by SPSS 21.0 software.

Results: Pts characteristics were the following: median age: 63 years old (range 30-83 yo), male/female ratio: 32/17, PS ECOG 0/1: 46/3; primary tumor location: junction: 18.3%, stomach: 82.7%; adenocarcinoma with signet ring cells: 18.3%; stage at diagnosis: IB: 4.2%, IIA: 14.2%, IIB: 30.6%, III: 51%. 20.4% of pts received a neoadjuvant treatment. MMR status was stable (MSS) in 18.4% and MSI in 51% of cases. PD-L1 status was evaluated in 63.2% specimens and its expression was observed in 12.9% of cases. Only in 49% of cases was able to evaluate both MMR status and PD-L1 expression. All PD-L1 positive tumors showed a concomitant loss of expression of MMR proteins. With a median follow-up of 77 months (95% CI: 43.5-70.5), median OS was higher in pts with PD-L1 expression (NR vs 47 months in PD-L1 negative) as well as in pts with MSI (NR vs 47 months for MSS).

Conclusions: Our preliminary results showed that MSI could have a relationship with PD-L1 expression, influencing the outcomes of pts. Further prospective studies involving a larger number of specimens are needed to define their predictive and prognostic role in GC.

C17

HER2-POSITIVE ADVANCED GASTRIC CANCER: CLINICAL AND PATHOLOGICAL DATA COLLECTION IN REGGIO EMILIA CLINICAL CANCER CENTRE

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Background: HER2 is an important target in advanced gastric cancer (GC). Toga study demonstrated an improved survival with addition of trastuzumab to chemotherapy

(CHT) in patients (pts) with metastatic GC harboring overexpression of HER2.

In the first step of the study we intend to analyse main clinical characteristics and outcome of the pts with HER2 positive GC.

Methods: From 2009 to 2017 we selected pts with HER2 positive GC in Reggio Emilia Clinical Cancer Centre. Pathological and clinical data of them were collected.

Immuno-Histo-Chemistry (IHC) for HER2 overexpression and fluorescence in-situ hybridization (FISH) for gene amplification were used.

Results: HER2 analysis were conducted in 443 pts with GC and 135 (30%) pts resulted HER2 positive, 93 men (69%) and 42 women (31%), with a mean age of 67 years (range 37-86).

There was a concordance of 87% in 94 pts evaluated with both IHC and FISH. We found IHC 3+ in 63 pts (47%), IHC 2+ and FISH+ in 51 pts (38%), IHC- and FISH+ in 10 pts (7%) and only FISH+ (IHC not evaluated) in 10 pts (7%).

Ten pts not presented a metastatic disease and were excluded from analysis. Primary tumour site was gastric in 76 pts (62%), gastroesophageal junction in 45 pts (35%) and unknown in 4 pts (3%).

We observed synchronous metastasis in 95 (76%) of 125 pts and metacronus metastasis in 30 (24%) pts; 34% of pts have multiple site of metastasis and 66% have 1 site of metastasis.

Ninety-nine pts (79%) were treated with a first line and platinum/fluopirymidines/trastuzumab regimen was administered in 95 pts with a mean duration of treatment of 8 cycles (range 1-50).

Forty eight pts (38%) received a second line of CHT and 16 (12%) a third line. Twenty one pts were not treated: 14 pts early died due to poor clinical condition and for 7 pts we have no data. Survival analysis are reported in the table.

OS	HER2 positive 125 pts	Treated with Trastuzumab 95 pts	Trastuzumab <6 cycles 44 pts	Trastuzumab ⩾6 cycles 42 pts
	%	%	%	%
1 yr	38.5	47.7	25	76.2
2 yrs	12	14.7	2.3	28.6
3 yrs	6.5	7.4	0	16.7

Conclusions: In our Cancer Centre we observed a incidence of 30% of HER2 positive GC. Almost all pts (96%) received first line trastuzumab based CHT regimen with a longer survival in a subgroup of subjects that completed more than 6 cycle of therapy. The research of predictive biomarkers is ongoing in responsive pts.

C18

CHEMOTHERAPY IN ELDERLY PANCREATIC CANCER PATIENTS: THE SAN RAFFAELE HOSPITAL EXPERIENCE

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Background: Median age of pancreatic adenocarcinoma (PDAC) newly diagnosed patients (pts) is about seventy years old. Despite that, PDAC pts enrolled in registration phase III trials are usually⩽ 65, and specific age-focused studies for the treatment of the older PDAC sub-population are missing. We aimed to assess the efficacy of chemotherapy in elderly PDAC pts in our Institution.

Patients and Methods: We retrospectively analyzed 90 pts affected by stage IV PDAC and enrolled for chemotherapy from 2008 to 2017. Minimum age was 70 years old and ECOG PS 0-2. According to the chemotherapy treatment we identified 3 groups: A) 37 pts (41%) underwent to monotherapy (gemcitabine/capecitabine); B) 30 pts (33%) underwent to doublets (gemcitabine and nab-paclitaxel) and C) 23 pts (26%) were treated with 4-drugs combination therapy (cisplatin-capecitabine and gemcitabine plus epirubicin or nab-paclitaxel or doxorubicin).

Results: In group A median age was 77.5 (70-87), ECOG PS was 0-1 in 86.5% of pts (32/37), liver metastasis were found in the 70.3% (26/37) and CA19.9 median value was 1019 U/mL (101-11316). In group B median age was 76.5 (71-84), ECOG PS was 0-1 in 86.7% of pts (26/30), liver metastasis were found in the 46.7% (14/30) and CA19.9 median value was 434 U/mL (37-739108). In group C median age was 73 (70-77), ECOG PS was 0-1 in 91.3% of pts (21/23), liver metastasis were found in the 56.5% (13/23) and CA19.9 median value was 2862 U/mL (3749-36645). Median OS was 7.5 months, 9.6 months and 13.7 months respectively for group A, B and C. 1years OS and 2years OS were 24.3% and 8.1% in group A; 33.3% and 3.3% in group B; 56.5% and 26.1% in group C. There were no statistical differences among the three groups. The pts aged ⩾75 were 70.3% in group A (26/37), 66.7% in group B (20/30) and 30.4% in group C (7/23). Median OS was 6.7; 9.6 and 19 months each group respectively, according to the ⩾ 70 whole population (p:n.s)

Conclusions: In our Institution older pts receiving chemotherapy showed similar benefit compared to data from literature. In particular, especially for the very-old subgroup of pts (⩾75) we showed a numerical increase of median OS between mono and multi-drugs regimen, even if no statistical significance was reported, most probably due to the limited sample size. Moreover we proved that elderly pts may benefit from chemotherapy independently by age.

C19

LONGITUDINAL ASSESSMENT OF NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) FROM DIAGNOSIS UNTIL DEATH REVEALS A BIFASIC TREND IN METASTATIC PANCREATIC ADENOCARCINOMA PATIENTS

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Background: Baseline NLR has been found to have a significant prognostic value in metastatic pancreatic adenocarcinoma (mPA) patients but no data are yet available aboutNLR assessment during the entire course of mPA disease.

Material and methods: We analyzed 1025 cell blood counts (CBCs) saved to PTV-BIO.CA.RE. (Biospecimen Cancer Repository) in 44 mPA patients (23.3 CBCs/patient) who had reached the overall survival endpoint (death ascertained) and NLR was calculated as per standard. Trend of NLR over the remaining weeks to death was analyzed, and where a clear correlation was observed a standard regression analysis was performed. Potential association between NLR trends and short survival was analyzed.

Results: NLR values over the time had a clear bifasic trend, remaining roughly constant (median NLR 2.5, 95% CI 2.2-2.7) up to 24 weeks prior to death (correlation coefficient R 0.03, p 0.603) and then displaying a marked rectilinear increase from week -24 to death (time 0) (R 0.48, $p < 0.001$). The equation that expressed the rectilinear increase of NLR during the last 24 weeks of life was NLR=9.663 – 0.325* (weeks-to-death), indicating an increase of about +0.3 in NLR for every week passing from -24 to 0 (death). A NLR above 3.0 with a confirmed increase of $> +0.3$ points/week in two subsequent CBCs was able to predict an imminent death (within 24 weeks) in 97.8% of cases (Relative Risk as compared with NLR < 3 and/or increase rate < 0.3points/week: 2.75, $p < 0.0001$).

Conclusions: Longitudinal assessment of NLR in mPA patients is able to predict with great precision death occurring within 24 weeks. Treatments able to lessen the unfavourable NLR increase rate of +0.3 points/week are likely to change the natural history of this disease

C20

RETROSPECTIVE EVALUATION OF ROS1 REARRANGEMENTS IN BILIARY TRACT CANCERS (BTCS). AN ITALIAN MULTICENTRIC OBSERVATIONAL STUDY BY GOIRC

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Background: Biliary Tract Cancers (BTCs) still remain a pool of diseases with poor prognosis and orphan drug. Cisplatin and gemcitabine is the standard chemotherapic regimen for first line in fit patients, while no there are no established regimens for the second line and beyond. Furthermore, currently no molecular target has been discovered as oncogenic driver in BTCs. Reactive Oxygen Species 1 (ROS1) rearrangements have been described in a variety of tumors, including some preclinical observations in BTCs. In lung cancer ROS 1 rearrangements represent a target for which we have a clinically active targeted therapy (crizotinib). Actually informations about the incidence and the biological significance on BTCs are lacking.

Methods: The aim of this retrospective epidemiological multi-center study was to assess the incidence of ROS1 rearrangements in BTCs. We collected archival surgical specimens or core liver biopsies from patients (pts) affected by BTCs diagnosed since January 2012 to December 2015 in 7 italian centers. ROS1 determination was centrally performed by a dedicated pathologist with Immunohistochemistry (IHC) and, when positive, a confirmatory Fluorescent In Situ Hybridization (FISH) analysis . Pts' clinical informations derived from medical records were also collected.

Results: Overall100 samples were collected (67 surgical specimens, 33 biopsies) from 69 male and 31 female pts, with a median age of 70 (35-84) and a known ECOG performance status of 0 in 59 pts, of 1 in 27 pts and 2 in 11 pts. Primary tumour origin was: intra-hepatic bile ducts (55 pts), hilar (4 pts), extra-hepatic (32 pts) and unknown (2 pts). Clinical stage distribution at diagnosis was: 48 cases were localized, 24 cases were locally advanced and 26 cases were metastatic; in 2 cases it was unknown. Surgery was performed in 67 pts, 58 of whom was radical R0. At the time of data collection (April 2018) 20 pts were still alive whereas 78 were dead, 72 of whom due to disease relapse or progression. Any of the paraffin material analysed resulted positive for the ROS1 rearrangements with the IHC analysis. No confirmatory FISH analysis was then performed.

Conclusions: We conclude that despite pre-clinical data, ROS1 does not seem an oncogenic driver to be evaluate in BTCs. BTCs still remain a pool of diseases with poor prognosis with no target agent available. New biomarkers are needed in order to improve the outcome of these patients.

C21

LOCALLY ADVANCED GASTRIC CANCER: DOES HISTOLOGY SUGGEST STRATEGY IN PAN-CANCER ERA?

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Background: Surgery is the only potentially curative treatment for locally advanced gastric cancer (LAGC). Evidences suggest that perioperative CT (pCT) plus surgery is superior to surgery alone, whereas studies on adjuvant CT (aCT) are controversial. Guidelines recommend a perioperative approach in pts with stage II/III, nevertheless in real-life many pts receive immediate surgery followed by aCT. Histology influences survival and pathological response with worse prognosis and lower pathological response among diffuse LAGC. No trial has compared pCT and aCT or investigated the impact of histology on the outcome of these different approaches. We hypothesized that histology may predict a different benefit from CT administered in the 2 settings, allowing to define the optimal strategy. We performed a study comparing the two approaches according to histology.
Material and Methods: We retrospectively analyzed pts with stage III (c for pCT, p for aCT) LAGCs treated at our Institution between Jan-09 and Jan-17. The objective of the study was to evaluate the impact of histology (intestinal and diffuse) on survival according to strategy approach (pCT *vs* aCT). Primary endpoints were DFS and OS. Differences were compared with the use of log-rank test, considering statistically significant *p*value <0.5.
Results: 81 pts had diffuse LAGC (29 received pCT and 52 aCT) and 60 intestinal LAGC (32 received pCT and 29 aCT). All pts underwent adequate D2-lymphadenectomy. CT dose intensity was balanced between groups. In the intestinal cohort both DFS and OS were significantly higher in pts treated with pCT compared to aCT (DFS:HR 0.3, 95%CI0.1-0.78, p=0.02; OS:HR 0.3, 95%CI0.1-0.8, p=0.03). On the contrary in the diffuse cohort both DFS and OS were significantly lower in pts receiving pCT compared to those receiving aCT (DFS:HR 2.4, 95%CI1.3-4.7, p=0.0014; OS:HR 2.6, 95%CI1.3-5.2, p=0.0012).
Conclusions: Our study, although retrospective and small-sized, shows that the survival benefit of pCT is limited to intestinal LAGC, whereas in diffuse LAGC the administration of pCT appears detrimental. Indeed, diffuse LAGC is known to be chemoresistant and pCT might delay surgery allowing metastasization. Despite the arising of recent molecular classification, still far from modifying clinical practice, histotype might represent an easy factor to discriminate pts benefitting from pCT (intestinal) to those in whom upfront surgery might be recommended (diffuse). Our hypotheses need to be confirmed in prospective trials.

C22

FLOT AS PERIOPERATIVE TREATMENT IN GASTRIC CANCER PATIENTS: PRELIMINARY RESULTS FROM MONOINSTITUTIONAL REAL-LIFE EXPERIENCE

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Background: The optimal treatment for resectable locally advanced gastric (GC) or gastroesophageal cancer (GEJ) remained to be defined. However, the docetaxel-based triplet FLOT recently showed to increase the rate of curative resections and the outcomes of these patients (pts) if compared to standard ECF. The aim of this analysis was to evaluate the safety and efficacy profile of FLOT regimen in a real-life population.
Methods: We analyzed the data of 21 pts affected by locally advanced GC and GEJ treated with a perioperative approach from January 2015 to April 2018 at our institution. Pts received docetaxel 50 mg/m2/iv, oxaliplatin 85 mg/m2/iv, leucovorin 200 mg/m2/iv and 5-fluorouracil 2600 mg/m2 24h infusion (FLOT schedule) on day 1 every 2 weeks for 4 cycles. All pts received G-CSF. After 4-6 weeks, pts were evaluated for surgery followed by 4 cycles of FLOT. Statistical analysis was performed by SPSS 21.0 software.
Results: Pts characteristics were the following: median age: 62 years (range 36-77 yo), male/female ratio: 16/5, PS ECOG 0: 100%; primary tumor location: Siewert I: 23.8%; Siewert II and III: 38.1%, stomach: 38.1%; adenocarcinoma with signet ring cells (SRC): 33.3%; Lauren's type: intestinal: 23.8%, diffuse: 28.5%, unknown: 47.6%; stage at diagnosis: IB: 4.8%, IIA: 19%, IIB: 42.8%, III: 33.3%. Median treatment duration was 2 months (4 cycles). The most frequent grade 3 adverse event (AE) was neutropenia (4.8%) and 28.5% of pts discontinued perioperative treatment due to AE or progression disease (PD). The perioperative treatment is ongoing in 19% of pts; 71.4% underwent to surgery, whereas 4.8% continued chemotherapy due PD. 86.6% and 13.3% of resected pts had a R0 and R1 resection, respectively. After surgery, among evaluable pts, 9.5% reported TRG1, 33.4% TRG 3, 28.6% TRG 4 and TRG was not reported in 9.5% of cases. 47.6% of pts received a complete postoperative treatment, requiring a dose reduction in 28.6%. With a median follow-up of 17 months (95% CI: 5-29), median OS was 14 months (95% CI: 8.4-19.5) and median PFS was 11 months (95% CI: 8.3-13.7). Median OS was higher in pts without SRC

tumors (NR vs 12 months in case of SRC) and in pts with intestinal Lauren's histotype (NR vs 9 months in case of diffuse one).
Conclusions: Our preliminary results showed that FLOT regimen was well tolerated in the perioperative treatment of pts affected by GC in the clinical practice.

C23

PROGNOSTIC VALUE OF SYSTEMIC INFLAMMATION SERUM BIOMARKERS IN RESECTED PANCREATIC CANCER

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Background: Pancreatic cancer (PC), is characterized by an immunosuppressive behavior, in particular lack of inflammation and abundance of fibrosis within tumor microenvironment (TME), play a crucial role in disease pathogenesis and progression. The prognostic value of several serum biomarkers of systemic inflammatory status have been evaluated but none of those is currently used in clinical practice.
Material and methods: a retrospective analysis of 67 consecutive PC patients (pts) undergone surgery from January 2012 to December 2017 in a single academic hospital was performed. Aim of the study was evaluating the inflammation and immune suppression serum biomarkers prognostic role, in terms of disease free survival (DFS) and overall survival (OS). Tumor staging was based on the *AJCC Cancer Staging Manual, 7th Edition*. Lymphocyte-to monocyte ratio (LMR), neutrophils-to-lymphocyte ratio (NLR) and LDH levels were analyzed at PC diagnosis, at adjuvant chemotherapy (AC) start, and at first metastatic disease evidence.
Results: Overall, 47 (73%) pas achieved a R0 surgery. The most common histotype was represented by ductal adenocarcinoma (61%). 6% of the pts received neoadjuvant chemotherapy and 58% received adjuvant treatment. Median OS, DFS and follow up were respectively 35.2, 17.1 and 29 months. All the known prognostic factors were associated with OS at univariate analyses: pT ($p<0.001$), nodal status (p=0.004) and Performance Status (p=0.01), analyzed continuously, Grading=3 (p=0.037), AC received (p=0.01). According to this preliminary analysis, LMR, NLR and LDH were not significantly associated with survival outcomes (DFS and OS).
Conclusion: No prognostic role was observed for LMR, NLR and LDH levels in patients with early stage pancreatic cancer. Although definitive conclusions cannot be drawn, due to the small sample size, the strongest, and already known, prognostic factors confirmed their value in the present study. Further analyses are ongoing to investigate the role of fibrosis and inflammatory cells in TME in predicting PC patients' outcome.

C24

PROGNOSTIC FACTORS ASSOCIATED WITH SURVIVAL AND RECURRENCE IN A VERY LARGE COHORT OF GASTRIC CANCER PATIENTS RESECTED OVER A DECADE AT A SINGLE ITALIAN CENTRE: THE CREMONA EXPERIENCE

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Background: Surgical resection is the only curative option for non-metastatic gastric cancer (GC). A large cohort of GCs from a high-volume Italian centre was analysed to describe clinical outcomes and prognostic factors.
Methods: 379 GC patients (pts) undergoing curative resection from 2007 to 2016 were considered. Variables analysed were: age, sex, tumour location, histology, TNM stage, resection margins (R) status, grade (G), (neo)adjuvant (adj) chemotherapy (CT), adjuvant chemoradiotherapy (CTRT), oligometastatic disease, recurrence, type of surgery and types of lymphadenectomy.
Results: Male to female ratio was 1.5:1. Median age was 75 years (ys) (41-92). Histology was intestinal in 68.5% and 11.5% had cardia as primary site. Disease stages I-II were present in 46.9%pts, 36.3% stage III and 16.8% oligometastatic disease. Grouping data by year of surgery (2007-2011 for 195 and 2012-2016 for 184 cases) there was a significant difference in lymphadenectomy type ($p<0.001$) with D1 decreasing from 64% to 26% as compared with D2 (increased from 36 to 74%); 6.9% pts received neoadj CT, 37% adj CT and 16.7% adj CTRT. At 24.13 months of median follow-up, median overall survival (OS) was 29.7 months (IC95%, 23.4-36.0) with no significant difference between year groups. Variables significantly associated with OS at multivariate analysis were: stage ($p<0.001$, 3d.f.), positive R (HR=3.02, $p<0.001$), adj CT (HR=0.61, p=0.010), age > 65ys (HR=2.01; p=0.002) and non-cardia primary (HR=0.60; p=0.029). Disease recurrence (info available in 56% pts) was registered in 32% of cases, with no significant differences between ysof surgery.
Conclusions: This large retrospective analysis confirms the prognostic value of stage, R status and adjCT on OS. Elderly pts and those with proximal disease showed a

worse prognosis and may deserve specific treatment strategies.

C25

PROGNOSTIC VALUE OF SERUM BIOMARKERS IN RESECTED GASTRIC CANCER: A SINGLE-CENTER RETROSPECTIVE ANALYSIS

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Background: despite potentially curative surgical resection, the prognosis of gastric cancer (GC), after local or distant recurrence, still remains poor. Several prognostic factors, including inflammation-based prognostic scores, have been investigated, but pattern of recurrence needs to be more extensively explored.
Material and methods: a retrospective series of 138 consecutive patients (pts) with gastric cancer (GC) who underwent potentially curative resection between Jan 2012 and Dec 2017 at the Udine academic hospital was analyzed. Aim of the study was to evaluate the prognostic role of serum biomarkers in terms of disease free survival (DFS) and overall survival (OS). Hemoglobin (Hb), monocyte-lymphocyte ratio (MLR), neutrophils-lymphocyte ratio (NLR) and monocyte-platelet ratio (MPR) were analyzed at GC diagnosis and at first metastatic disease evidence. Univariate Cox regression analysis was conducted (Stata Corp LP STATA v14).
Results: overall, 72 (56%) pts had a diagnosis of GC in pathological TNM stage I-II and 57 pts (44%) in stage III. The most common histotype was intestinal type (55%). Neoadjuvant chemotherapy (CT) was administered to 37 pts (27%) and 71 pts (51%) received adjuvant treatment. Cancer recurrence occurred in 47 pts (34%); most frequent recurrence site were lymphnodes (44%) and liver (31%). Median DFS and OS were not reached. Known strong prognostic factors, pT and pN, were associated with both OS and DFS at univariate analysis ($p<0.001$). A lower Hb level and a higher MLR were significantly associated with worse OS ($p=0.008$ and 0.025 respectively) and worse DFS ($p=0.006$ and $p=0.020$ respectively). Higher MPR was associated to better DFS ($p=0.029$). Pts who received neoadjuvant or adjuvant CT had better DFS ($p=0.007$ and $p=0.021$ respectively). MLR was associated with disease stage in resected GC pts ($p=0.049$).
Conclusion: this study confirmed the prognostic value of pT and pN and the association of neoadjuvant or adjuvant CT with better pts outcome. Higher MPR was associated with longer DFS. Conversely, higher MLR was associated with worse DFS and OS. Also lower Hb levels predicted an unfavorable outcome. Of note, in these selected pts MLR was associated with disease stage. Further efforts are needed to validate the prognostic value of these biomarkers.

C26

PROGNOSTIC ROLE OF NEUTROPHIL TO LYMPHOCYTE RATIO IN PATIENTS WITH GASTRIC CANCER

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Background: Markers of inflammation and in particular neutrophil-lymphocyte ratio (NLR) have been associated with outcomes in cancer; preliminary data show correlation between NLR and gastric cancer prognosis.
Methods: We retrospectively analyzed data from 119 patients affected with gastric cancer treated in Surgical Department and Oncology Unit in Varese between January 2011 and December 2016.

We included 57 patients with early stage who underwent surgery and 62 patients with metastatic disease at the diagnosis. We evaluated cellular blood count at the diagnosis and periodically during chemotherapy treatment and every 6 months in operated patients.

Considering data available from the literature, we used NLR cut-offs: $< 2{,}20$, $\geqslant 2{,}20$ and < 3, $\geqslant 3$ and < 4, $\geqslant 4$. Data regarding age, sex, stage, metastatic sites, chemotherapy regimen, haemoglobin value, platelets number, absolute value of neutrophils, absolute value of lymphocytes were collected.

In surgical patients, overall survival (OS) and disease free survival (DFS) were calculated with a median follow-up of 38 months (12-50), while in metastatic patients overall survival (OS) and progression free survival (PFS) were calculated with a median follow-up of 10 months (3-19).

Descriptive statistical analysis has been made with median (range interquartile). The variation in time of NLR has been calculated with d'agostino-pearson test. Univariate analysis using cox's regression model were performed. The survival analysis has been calculated by kaplan meier limited product.
Results: The median value of NLR at the diagnosis in patients with early cancer before surgery was 2,28 (1,83–3,69), while the median value of NLR at the diagnosis of metastatic disease was 3,17 (2,15–4,39). NLR was statistically different in the two groups ($p=0{,}01$).

Variations in time of NLR considering the entire sample didn't show a significant change in time ($p=0{,}60$), while considering only the group of patients with metastatic disease

we found a significant increase of NLR in time (p<0,0001). This increase was not correlated with prognosis.

Using all cut-offs, no correlation was found between NLR values and survival in the two groups of patients.

Conclusions: Comparing patients with early disease and advanced disease we found significant different median value of NLR. In contrast with the available data from the literature, in our cohort NLR was not predictive of survival. Further prospective studies are needed.

C27

CLINICAL OUTCOMES IN GASTRIC CANCER (GC): DO THEY DEPEND ON TREATMENT CHOICES OR HISTOTYPES?

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Background: Currently, medical management of patients (pts) with GC is mostly dependent on prognostic assessment which is based on tumor stage (TNM) and clinical patients' characteristics. Prognostic and predictive factors beyond disease stage are clearly needed, and histology could be proposed as a surrogate marker of disease biology. The aim of our analysis is to compare clinical outcome according to different histotypes (diffuse, intestinal and signet ring cells type) in metastatic GC patients receiving first-line chemotherapy.

Patients and methods: Advanced GC pts treated with first-line combination chemotherapy were included in our analysis. Pts were divided in three subgroups according to different histotypes.

Results: A total of 135 advanced GC pts were included: 24.4% of them had a diagnosis of signet ring cell GC, 57.7 % of diffuse type, while intestinal type was diagnosed in 17.7%. Pts received a fluoropyrimidine-based chemotherapy doublet containing Cisplatin or Oxaliplatin; in three drugs regimens the anthracycline was added. Diffuse type GC, when treated with Oxaliplatin regimens, had a significant statistically difference in terms of OS (13.3 months vs 7.1 months of Cisplatin; p=0,001) and PFS (6.6 months vs 4.2 months in Cisplatin group; p=0,0004). Among pts with intestinal type we didn't detect any difference in comparing first line schedules (OS was 12.3 months and 12.1 months with Oxaliplatin and Cisplatin respectively, p=0,08; PFS was 5.4 months in Oxaliplatin group vs 5.1 months in Cisplatin one, p=0,095). Pts with signet ring cell GC when treated with Oxaliplatin, if compares with Cisplatin regimens, had a better clinical outcomes both in terms of OS (12.1 months with Oxaliplatin and 5.6 months with cisplatin; p= 0,03) than PFS (6.3 months and 2.9 months in pts with Oxaliplatin and Cisplatin respectively; p= 0,0005).

Conclusions: On the basis of our data, we could decide whether to use oxaliplatin or cisplatin according to histology as well as clinical conditions, comorbidities and toxicity profile. Although promising, there is not yet a consensus about the clinical role of molecular biomarkers, beyond HER-2 status, in advanced GC, due to technical issues (availability, reproducibility, reliability). In this scenario, the prognostic and predictive value of histology could play a significant role in future and above all in daily clinical practice.

C28

PHASE II CLINICAL STUDY FOR THE PREOPERATIVE TREATMENT OF OPERABLE OR BORDERLINE OPERABLE ADENOCARCINOMA WITH CHEMOTHERAPY AND CARBON ION HADROTHERAPY (TERAPIA PREOPERATORIA CON IONI CARBONIO PER IL TUMORE DEL PANCREAS OPERABILE O BORDERLINE, PIOPPO TRIAL): FEASIBILITY RESULTS

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Background: A strong rationale exists for the investigation of preoperative CT in pts with resectable or borderline resectable pancreatic ductal adenocarcinoma (R/BRPC). Aim of the PIOPPO trial is to assess the role of combination CT followed by carbon ion hadrotherapy (CIRT), a promising approach for treatment of pancreatic cancer, as suggested by the favorable results, in terms of resectability rate and survival, obtained in this setting at the National Institute of Radiological Sciences (NIRS), Chiba, Japan (Shinoto, Int J Radiat Oncol Biol Phys 2016).

Patients and methods: PIOPPO trial is a prospective, phase II, multicentre, single-arm study aimed to assess the feasibility and efficacy of 3 cycles of FOLFIRINOX CT followed by CIRT at the dose of 38.4 Gy [RBE] as neoadjuvant therapy for R/BRPC. The dose of CIRT (carried out in 8 fractions, 4 fractions per week) derives from the conversion of the dose used at NIRS taking into account the radiobiological model employed at CNAO, the National Centre for Oncological Hadrontherapy, located in Pavia, Italy. Four to 6 weeks after completion of CIRT pts will undergo conventional pancreatic resective surgery. Primary endpoint of this study is local progression free survival (LPFS) and secondary endpoints are overall survival (OS), R0 resectability rate, treatment toxicity

including intra and perioperative toxicity. Thirty pts will be enrolled in the study, the sample size being defined with an expected probability of success at 24 mo of 60% vs 35% (H0: p <= 0.35-H1: p> 0.35). Subjects who meet the enrolment criteria but eventually decline to participate in the study will serve as controls. In the post-operative period, adjuvant CT with single agent gemcitabine is given according to clinical practice.

Results: Since January 2018 four pts have been so far enrolled and two have completed the surgical phase. No significant acute toxicities, including surgery-related, were observed. Our preliminary results, including 6 patients (with local recurrence only) treated before the study was approved by Bioethical Committee of IRCCS San Matteo Foundation of Pavia, suggest that CIRT does not affect negatively the surgical approach.

Conclusions: Our results provide initial evidence of the feasibility of the combined CT and CIRT neoadjuvant approach in R/BRPC.

C29

GEMCITABINE PLUS NAB-PACLITAXEL AS FIRST LINE THERAPY IN METASTATIC PANCREATIC CANCER PATIENTS RELAPSED AFTER ADJUVANT TREATMENT

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Background: Gemcitabine plus Nab-paclitaxel represents one of the standard regimen for first line therapy of metastatic pancreatic cancer (mPC).

Very few data on its efficacy and safety are available in mPC patients (pts) relapsed after a gemcitabine-based adjuvant treatment. Our analysis aims to evaluate the efficacy and feasibility of gemcitabine plus nab-paclitaxel as first line treatment for mPC in pts previously resected and treated with adjuvant treatment.

Materials and methods: We retrospectively analyzed the safety and efficacy data of 28 PC pts, from two Italian centers, diagnosed from September 2007 to April 2018 who received 6 months of adjuvant Gemcitabine after curative surgery. A combination of Gemcitabine and Nab-Paclitaxel was administered as first-line at the time of relapse until death or progression of disease (PD).

Results: Median age of our cohort is 63 years old (range 41-75), with a male/female ratio: 1/1. Other pts' characteristics are: ECOG performance status 0/1: 35.7/64.3%; stage at diagnosis: IA: 3.6%, IB: 3.6%; IIA: 25%; IIB: 42.8%; IIIA: 17.8%; IIIB: 7.1%. All pts were resected with curative intent and received gemcitabine as adjuvant treatment with a median of 6 cycles (range 2-6); moreover, 14.2% of pts received also adjuvant radiotherapy. Median time between the end of adjuvant treatment and PD was 5.5 months (range 1-66); median DFS was 13 months (95% CI: 9.2-16.8).

Most frequent sites involved at relapse were peritoneum (35.7%), liver (35.6%), lymphnodes (32%) and lung (21.3%). Pts received a median of 4 first-line cycles (range 1-25) with a treatment still ongoing in 17.8% of pts.

No grade 4 toxicity was recorded and the most common adverse events was G2 anemia (10.7%). Stable disease was observed in 32.1% of pts, with a disease control rate of 46.4% and objective response rate of 14.3%.

With a median follow-up of 94 months, median first-line Progression free survival (PFS) was 11 months (95% CI: 8.4 – 13.6), whereas median overall survival (OS) was 40 months (95% CI: 31.5 – 48.5). Median OS was higher in pts with a relapse = 5 months after the end of adjuvant treatment (40 months); however also in pts who relapsed earlier (< 5 months) the OS was substanzial (27 months).

Conclusions: Our results, although preliminary, show that first-line Gemcitabine plus Nab-paclitaxel schedule is effective and feasible also in pts previously treated with gemcitabine as adjuvant chemotherapy, with a remarkable median PFS of 11 months.

C30

USE OF THE PHYTOSOME COMPLEX OF CURCUMIN AS COMPLEMENTARY THERAPY OF LOCALLY ADVANCED OR METASTATIC PANCREATIC CANCER TREATED WITH GEMCITABINE: A PHASE II PROSPECTIVE STUDY

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Background: A large body of biomedical evidence indicates that activation of Nrf2 by curcumin increases the nucleophilic tone and damps inflammation cumulatively supporting the malignant phenotype. Conversely, genetic analyses suggested a possible oncogenic nature of Nrf2 activation since an increased nucleophilic tone is alleged increasing chemoresistance of cancer cells. Aiming to contribute to solve this paradox, this study addresed the issue

of safety and efficacy of curcumin as complementary therapy of Gemcitabin (GEM) on pancreatic cancer (PC).
Material and methods: This is a single centre, single arm prospective phase II trial. Patients received gemcitabine and Meriva®, a patented preparation of curcumin complexed with phospholipids. Primary endpoint was response rate (RR), secondary endpoints were progression free survival (PFS), overall survival (OS), tolerability and quality of life (QoL). Analysis of inflammatory biomarkers was carried out. Fifty-two consecutive patients were enrolled. Forty-four (13 locally advanced and 31 metastatic) were suitable for primary endpoint evaluation. Median age was 66 years (range 42-87); 42 patients had ECOG PS 0-1. The median number of treatment cycle was 4.5 (range 2-14).
Results: We observed 27.3% of RR and 34% of cases with stable disease, totalizing a disease control rate (DCR) of 61.3%. The median PFS and OS were 8.4 and 10.2 months, respectively. Higher IL-6 and sCD40L levels before treatment were associated to a worse OS ($p<0.01$). Increases in sCD40L levels after 1 cycle of chemotherapy are associated with a reduced response to the therapy. Grade 3/4 toxicity was observed (neutropenia, 38.6%; anemia,6.8%). There were no significant changes in QoL.
Conclusions:, the complementary therapy to GEM with phytosome complex of curcumin is safe and efficiently translate in improved RR in first line therapy of advanced PC.

C31

CARBON IONS RADIOTHERAPY FOR PATIENTS WITH PANCREATIC ADENOCARCINOMA (PA): ACUTE TOXICITY AND PRELIMINARY OUTCOME

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Background: Even if the surgical resection is complete, prognosis of pancreatic adenocarcinoma (PA) in terms of local control (LC) and survival is very poor. Chemotherapy and/or radiotherapy represent the standard of care in unresectable disease, but due to its inherent chemoradio-resistance, the LC remains poor. Depth-dose curves of carbon ions radiotherapy (CIRT) offers potential advantage in terms of efficacy and safety. The aim of this study is to evaluate the toxicity and clinical outcome of CIRT for treatment of pancreatic adenocarcinoma (PA).
Methods: Thirteen patients with PA have been evaluated. Six (46%) patients presented a recurrent disease and 7 (54%) had a locally advanced tumor. All of them have been treated with CIRT at National Center of Oncological Hadrontherapy (CNAO), located in Pavia, Italy, between September 2014 and March 2017. Median total dose was 57.6 GyE (range: 43.2-57.6 GyE) delivered in median number of 12 fractions (range: 8-12 fractions). Median dose for fraction was 4.8 GyE (range: 4.6-4.8 GyE). Toxicity was recorded according to CTCAE 4.0.
Results: All patients completed the scheduled treatment. Acute toxicity was mild, no grade 3/4 acute or late side effects were observed. Overall survival rates at 1 and 2 years were 68% and 20%, respectively. We observed LC in 6 (46%) patients translating into estimated *1-* and *2-year LC* rates of 38%. Progression Free Survival and Metastasis Free Survival were documented in 4 of 13 (31%) patients, the estimated *1- and 2-years rates* being 23 % and 51%/34%, respectively.
Conclusions: CIRT is feasible, safe and well tolerated treatment for PA . For its radio-resistance, PA could be an ideal disease to test this therapeutic approach and, since CNAO is the only carbon ion facility in Italy, a close cooperation with existing oncological centers is of paramount importance to investigate the biological and clinical efficacy of hadrontherapy.

C32

POOR OUTCOME FOR PATIENTS WITH GASTRIC CANCER AND LUNG METASTASES TREATED WITH RAMUCIRUMAB AND PACLITAXEL

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Purpose. The aim of this report is to describe the activity of ramucirumab in combination with paclitaxel in patients with metastatic gastric cancer and lung metastases.
Methods. Treatment consisted of ramucirumab 8 mg/kg intravenously (i.v.) on days 1 and 15, plus paclitaxel 80 mg/m² iv on days 1, 8, and 15 of a 28-day cycle. Patients received study treatment until disease progression, unacceptable toxicity, or withdrawal of consent.
Results. Thirty-one patients were retrospectively evaluated. Five (16.1%) patients had lung metastases. The median progression free survival was 132 days (95% CI, 93- 186 days); 156 days in patients without lung metastases versus 54 days in patients with lung metastases ($p<0.01$) No complete tumour response was observed, while documented partial responses were observed in 9

patients in the group without lung metastases and in 0 patients in the lung metastases group.
Conclusions. Despite the small number of patients and the retrospective nature of the data, our analysis showed relatively poor efficacy of ramucirumab as second line treatment in patients with lung metastases from gastric cancer. Further studies are awaited to evaluate novel treatments in this subset of patients.

C33

EDUCATIONAL INTERVENTION FOR THE MANAGEMENT OF NUTRITION IN PATIENTS WITH CARCINOMA OF THE UPPER GASTROINTESTINAL TRACT (GI) SUBJECTED TO ACTIVE TREATMENTS (SURGERY, CHEMOTHERAPY, RADIOTHERAPY): A PILOT PROJECT

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Background: Patients with upper GI cancer are a group sensitive to nutritional complications worsened by incorrect diet regimens. Surgical and chemo/RT treatments contribute alter the ability to feed with worsening of the nutritional framework. Malnutrition may compromise the performance of antineoplastic treatments by negatively interfering with the prognosis. This pilot project is direct to patients and their families with an educational and theoretical approach. The course allows you to set up a proper diet, even with the reduction of consumption of industrial foods and refined sugars.
Material and methods: 25 patients with GI tumors were enrolled. From October 2017 to March 2018, 3 editions of the course were held with a theoretical meeting and a practical meeting in a professional kitchen by a trained chef. At T0 and T2 were found: anthropometric data, chair test and walk test. Topics in the theoretical course: preventing weight loss and to counteract the adverse effects of treatments. Menus were created with "seasonal" raw materials. They all cooked. At the end of meeting the patients and their families tasted the different preparations. A practical manual was delivered to address the symptoms related to treatments in progress and the recipes made.
Results: There was a reduction in the percentage of slimming from 6% to 2% in all patients. The muscle strength did not undergo significant worsening by recording the following values: for the test of the chair from 2.69 "to 2.82" to T0 and to the test of the walk from 3.88 "to 3.96" at T2. The main symptoms at T0 were nausea, lack of appetite, constipation, dysgeusia, diarrhea manifested by 44% of patients; at T2 16% of patients experienced nausea, early repellency, pain at meals. During the 7 months of the pilot project no patient interrupted or reduced therapies due to reduction in weight or weight loss.
Conclusions: The nutritional education intervention in patients undergoing oncological treatments has recorded an increase in the average BMI and a reduction in the percentage of slimming, together with a slight increase in the daily kcal taken. There was a reduction in gastrointestinal symptoms related to treatments (from 44% to 16% of patients), an almost unchanged course of physical strength. Nutritional counseling helped to avoid interruption or reduction of therapies. Furthermore, cooking together, a medical-nursing team with patients and family members, turned out to be a phenomenal "team-building".

C34

FOLFIRI AS A THIRD-LINE THERAPY IN PATIENTS WITH RAMUCIRUMAB-PRETREATED GASTRIC CANCER: AN OBSERVATIONAL PHASE II STUDY

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Background: The aim of this phase II study is to evaluate the efficacy and safety of the FOLFIRI regimen as a third-line chemotherapy in metastatic gastric or gastroesophageal junction cancer.
Methods: Treatment consisted of biweekly irinotecan 150 mg/m^2 as a 1-hour infusion on day 1, folinic acid 100 mg/m^2 intravenously on days 1–2, and 5-fluorouracil as a 400 mg/m^2 bolus and then 600 mg/m^2 continuous infusion over 22 hours on days 1–2.
Results: Twenty-six patients were enrolled. The median progression free survival (PFS) was 52 days (95% CI:42-74), and the median overall survival was 117 days (95% CI: 94-154). Longer PFS and OS were observed in patients who had achieved PFS $\geqslant$ 3 months during prior ramucirumab treatment.
Conclusions: The present analysis seems to suggest the best efficacy of the FOLFIRI regimen in third line of treatment is for patients who responded to prior ramucirumab-based therapy.

C35

SORAFENIB IN HEPATOCELLULAR CARCINOMA (HCC): OUR EXPERIENCE

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Background: The kinase inhibitor Sorafenib evidenced antitumor activity in hepatocellular carcinoma (HCC). The international multicentric phase III study (SHARP) showed statisticaly significant increased Overall Survival (OS,10.7 months vs 7.9 months) and Time to Progression (TTP,5.5 months vs 2.8 months) in patients treated with Sorafenib then placebo. Aim: to evaluate efficacy and safety of Sorafenib 400 bid p.o. continuosly in patients affected by biopsy-proven HCC not previously medically and/or surgically trited and not eligible for surgical treatment, until progression.

Patients and methods: From October 2015 to November 2017 we treated a total of 21 patients (male/female:15/6), median age: 67 years (range 59/76), ECOG performance status 0-2, Child-Pugh A. Patients had underlying cirrhosis of various etiologies, including hepatitis B virus, C virus, alcohol and non alcolic fatty liver disease (5). Tumor responce was assessed every three cycle using RECIST criteria.

Results: The treatment continued until PD with evidence of: 6 partial responce (RP, 28%), 5 stable disease (SD, 24%). Median OS was 8,4 months and median TTP 3.9 months. Grade 3/4 drug- related toxicities included Hand-Foot Syndrome (30%), mucositis (25%), rash (15%) and arterial hypertension (20%). This effects were corrected with the reduction of the dose of Sorafenib in the 20% of cases.

Conclusions: Monotherapy with Sorafenib, in our experience, was well tollerated and with a manageable safety profile.

C36

GRANISETRON TRANSDERMAL DELIVERY SYSTEM (GTDS): A SINGLE INSTITUTE EXPERIENCE IN GASTROINTESTINAL CANCER PATIENTS

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Background: Chemotherapy-induced nausea and vomiting (CINV) occurs in 10-90% patients, based on the different emetic risk of chemotherapeutic agents.

CINV has a negative impact on patient's quality of life, with a considerable cost because of the loss of workdays and in some cases delayed chemotherapy administration.

A new formulation, the granisetron transdermal delivery system (GTDS) Sancuso ProStrakan Pharmaceuticals), was developed to extend release of granisetron over 7 days. GTDS showed efficacy and not inferiority to oral granisetron in a multicenter randomized double-bind phase III trial. It was included in antiemetic guidelines for mild/moderate chemotherapy.

Transdermal delivery is not invasive option for better compliance and, in particular, for patients with uncertain absorption of oral medications, such as with gastrointestinal surgery.

Material and methods: From May 2017 in our institution, 12 consecutive patients with gastrointestinal cancer were treated with GTDS. All patients reported CINV G2/3 in the first cycle of chemotherapy.

GTDS was applied to upper outer arm 24 hours before chemotherapy administration and patients were requested to keep the patch on for 3-7 days after chemotherapy.

All subjects received a three-day chemotherapy regimen (FOLFOX/FOLFIRI).

Results:12 patients were included in our analysis, 33% female, 67% male.

The median age was 67 (range, 33-79). 58% of patients had metastatic disease and about 50% were pre-treated. Eleven patients showed their satisfaction for complete control of vomiting and nausea. It didn't require any use of rescue medication. One patient removed early the GDTS for headache. The median application period before removal was 5 days. No local skin irritation was observed with this patch formulation.

Patch adhesion was very good and no serious AE was reported. The most common reported AE was mild constipation.

Conclusions: GTDS was effective and safe for CINV prevention in patients receiving moderately multiday emetogenic chemotherapy, in particular for pre-treated patients with previous CINVG2/3.

C37

FOLFIRI REGIMEN AS SECOND LINE TREATMENT IN METASTATIC PANCREATIC CANCER: OUR EXPERIENCE

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Background: In Italy the incidence of pancreatic cancer (PC) is 13500 new cases year. It is the 5th most fatal cancer with an estimated 5-year survival rate of 7% although

recent progress on treatments. At the date, there is no defined 2nd line standard treatment for patients (pts) progressing after first line failure. Several studies have analyzed the role of FOLFIRI (irinotecan, 5fluorouracil, folinic acid) regimen in 2nd line.

The purpose of the present study was to evaluate the activity in terms of DCR (CR+PR+SD) and the tolerability of the FOLFIRI regimen, administered as 2nd line chemotherapy in pts with metastatic pancreatic cancer (MPC) after the 1st line nab-paclitaxel-gemcitabine failure in the clinical practice.

Methods: From June 2016 to April 2018 we retrospectively collected the data of 18 pts MPC treated with second line chemotherapy FOLFIRI regimen progressed after the nab-paclitaxel-gemcitabine. Median age was 58 yrs (range 47-75); 8 pts (44%) were over 70 years old; 7 pts (39%) were male and 11 (61%) female. They received a median of 7 (range 1-14) drug administrations.

Results: Of 40 pts with PC previously treated with nab-paclitaxel-gemcitabine, 18 pts (45%) received 2nd line chemotherapy with FOLFIRI regimen. The most frequent site of metastases was liver. Median PFS was 5 months (range 1-10). The DCR was 33 % (we recorded only SD).

No toxic death or grade 4 toxicity were recorded. Hematologic G3 toxicity included: Neutropenia 2 pts (10%). Non Hematologic G2 toxicities included diarrhea 3 pts (15%) and nausea 1 pt (5%).

Conclusion: Our previously experience showed that nab-paclitaxel-gemcitabine in the first line is an active and well tolerated regimen. 18/40 pts (45%) received a second-line therapy with FOLFIRI. This regimen in 2nd line showed a modest activity and discrete tolerance.

We are waiting for new drugs, in clinical practice, to improve the survival. New prognostic factors should be identified for guiding the choice of treatment.

D - Thoracic Cancer

D01*

PHASE II STUDY OF NAB-PACLITAXEL IN SENSITIVE AND REFRACTORY RELAPSED SCLC (NABSTER TRIAL)

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Background: Despite high sensitivity to first-line chemotherapy, most small-cell lung cancer (SCLC) patients relapse and have a poor clinical outcome. In this contest, Topotecan demonstrated a modest activity counterbalanced by significant haematological toxicity. Paclitaxel-based regimens have demonstrated to be active for the treatment of relapsed SCLC. Nab-paclitaxel, compared to paclitaxel, has a reduced incidence of hypersensitivity reactions and of neutropenia. However, its safety and efficacy in relapsed SCLC have not been prospectively studied yet.

Methods: This open-label, multicentre, phase II study enrolled patients with extensive- (ED-SCLC) or limited-stage disease (LD-SCLC) with disease progression during or after cisplatin/carboplatin and etoposide first-line chemotherapy with the aim to assess the activity and safety of Nab-paclitaxel. Patients were classified according to treatment-free interval (TFI) as refractory (TFI $<$ 60 days) or sensitive (TFI $=$ 60 days). Eligible patients received Nab-paclitaxel 100 mg/mq weekly on days 1,8,15 every 28 days until a maximum of 6 cycles or progressive disease or intolerable toxicity. Tumor assessment by using computed tomography (CT) scan was performed every 2 cycles. The primary endpoint was objective response (OR), evaluated according to standard RECIST v1.1 criteria. The secondary endpoints were toxicity, measured according to NCI-CTCAE v4.03, progression-free survival (PFS) and overall survival (OS).

Results: From January 2017 to March 2018, 68 patients (25 refractory and 43 sensitive) were enrolled in the modified intention-to-treat (mITT) population. Median age was 68.5 years (range 44-80). 44 (65%) patients were males and 57 (84%) had ED. Median follow-up was 5.8 months (IQR 3.3-7.1). Objective responses are currently being reviewed by an independent radiology panel. Most common toxicities (of all grades) have been: anemia (39%), leukopenia (27%), neutropenia (28%), nausea (19%), diarrhoea (21%), fatigue (52%), peripheral neuropathy (19%). The only severe toxicity (grade $\geqslant$3) has been neutropenia (9%). In 13 patients treatment is presently still ongoing while 3/55 (5%) patients permanently discontinued treatment for toxicity.

Conclusion: To our knowledge, this is the first prospective study of Nab-paclitaxel for relapsed SCLC. Nab-paclitaxel demonstrated a manageable toxicity profile. Final activity data will be available at the time of the meeting.

D02*

MOLECULAR SIGNATURE IN MALIGNANT PLEURAL MESOTHELIOMA (MPM): PRELIMINARY DATA OF ITALIAN RAMES STUDY

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Background: MPM is a highly aggressive pleural tumor associated with asbestos exposure. To date, most clinical trials have focused on cytotoxic agents rather than targeted therapies. The ability to analyze entire genomes opens the door to global mapping of normal variation and mutations of all types for correlation with doscare propensity, diagnosis, treatment, prognosis, as well as identification of new targets for interventional therapy discovery and development.

Methods: RAMES is a ongoing phase II study to evaluate the efficacy and the safety of the addition of ramucirumab to gemcitabine as the second-line treatment in 160 pts with MPM. We designed a custom panel covering 1040 amplicons spanning 33 genes frequently altered in MPM. To establish the genetic asset of MPMs we used an amplicon-based next generation sequencing approach.

Results: To date, 40 FFPE mesothelioma cancer tissues were successfully sequenced A total of 2930 variants passing quality filters were detected. Focusing on potentially functional alterations, polymorphisms and non-coding variants were excluded, leaving 143 alterations in 23 of the analyzed genes. Of these, 59.4% (85/143) were missense mutations, 22.4% (32/143) lead to frameshift alteration of the gene sequence, 13.3% (19/143) were splice variants, while the remaining 4.9% (7/143) were start loss, stop gain alterations and deletion. 97.5% of patients (39/40) displayed at least one mutation, while the average number of mutations per sample was 3.6 (range 0-8), confirming the high mutational load of these tumors. The most frequently altered genes identified were PIK3CA (62.5%), RDX (40%), MXRA5 (20%), BAP1 (15%), NF2 (15%). Molecular analyses have been correlated with Histology and Stage (thoracic vs extrathoracic MPM).

We found the following NF2, PIK3CA, RDX altered genes in 9 biphasic tumor and MXRA5, NF2, PIK3CA, RDX, CUL1, BAP1, NF2, TAOK1 altered genes in 31 ephitelioid tumor. We observed a significant correlation between mutations in RDX gene (23.1%) and extrathoracic MPM. CUL1 and RDX genes were found in pts with progression free survival ⩾6 months from prior treatment.

Conclusions: This preliminary data supports the generation of a genetic signature based on tumor mutational status useful to discriminate MPM with different clinico-pathological features and possible correlation with treatment choice.

D03*

EFFECT OF BONE METASTASES ON IMMUNOTHERAPY EFFICACY IN PRETREATED ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: Bone is a common site of metastatic spread in advanced NSCLC, with 35-40% of patients developing bone metastases (BoM) during the course of the disease. Beyond its supportive role, bone is a critical hematopoietic organ with active functions in regulating immune system and trafficking of immune cells, such as myeloid-derived suppressor cells and mesenchymal stem cells. To date, no trial evaluated the role of BoM in modulating response to immunotherapy. Aim of the present study was to investigate whether presence of BoM impact on immunotherapy efficacy.

Methods: Two different cohorts of pretreated NSCLC patients (cohort A: Non-squamous; cohort B: Squamous) were evaluated for nivolumab efficacy in terms of objective response rate (ORR), progression free survival (PFS), and overall survival (OS) according to presence or absence of BoM. All patients received nivolumab at standard dose of 3 mg/kg every 2 weeks within the Italian Expanded Access Program.

Results: Cohort A accounted for 1588 patients with non-squamous NSCLC: 626 (39%) with (BoM+) and 962 (61%) without BoM (BoM-). Cohort B accounted for 371 patients with squamous histology: 120 BoM+ (32%) and 251 BoM- (68%). In Cohort A, BoM+ had a significantly lower ORR (12% versus 34%; $p < 0.0001$), shorter PFS (3.0 versus 4.0 months, $p < 0.0001$) and shorter OS (7.4 versus 15.3 months, $p < 0.0001$). In cohort B, BoM+ had significantly lower ORR (13% versus 22%; $p < 0.04$), shorter PFS (2.7 versus 5.2 months, $p < 0.0001$) and shorter OS (5.0 versus 10.9 months, $p < 0.0001$). Presence of BoM negatively affected outcome irrespective of performance status (PS; OS cohort A: PS-0 BoM+ 12.0

versus 20.9 months in PS-0 BoM-, p<0.0001; OS cohort B: PS-0 BoM+ 5.8 versus 16.4 months in PS-0 BoM-, p<0.0001). In multivariate analysis, PS, presence of liver metastases and BoM independently associated with higher risk of death. In cohort A and B, BoM+ patients had HR for survival of 1.50 and 1.78, respectively.
Conclusion: Our results, the first assessing BoM in patients treated with immunotherapy, suggest that presence of BoM is a negative prognostic factor and could predict lower efficacy of immunotherapy in pretreated NSCLCs irrespective of histology. Baseline bone assessment should be performed in all clinical trials with immunotherapy.

D04*

HIGH MRNA EXPRESSION LEVELS OF PD-L1, AND IDO2 ARE ASSOCIATED WITH WORSE OVERALL SURVIVAL IN RESECTED NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: Programmed death ligand 1 (PD-L1) expression is a predictive biomarker of the success of PD-1/PD-L1 inhibitor therapy for patients with advanced non-small cell lung cancer (NSCLC) but its role as a prognostic marker for early stage resectable NSCLC remains unclear. Here, we studied gene expression levels of immunologic factors in fresh tumor tissue of resected NSCLC and we correlated the finding with clinicopathological features and patient outcomes.
Material and methods: A total of 191 consecutive stage I-II-III NSCLC patients who underwent curative pulmonary resection were studied. The mRNA expression levels of PD-1, PD-L1, PD-L2, IDO1, IDO2 and IFN-gamma were evaluated by quantitative reverse transcription polymerase chain reaction (qRT-PCR) using RT2 Profiler PCR Arrays (Qiagen). The Cox proportional hazards model was used to evaluate the prognostic role of each single studied parameter on Overall Survival (OS) and Disease-Free Survival (DFS), in univariate and multivariate analyses.
Results: Median age was 67 years (range 38-84 years), M/F: 137/54, PS 0/1: 188/3, stage I/II/III: 101/56/34, squamous/adeno/adeno-squamous: 120/68/3, smoker/never: 175/16. PD-L2, IDO2 and PD-1 gene expression were significantly lower in patients with adenocarcinoma (p=0.048, p=0.0001 and p=0.001, respectively). The PD-L1 gene expression was significantly higher in patients with higher TNM stage (p=0.048) while IDO2 and PD-1 gene expression were significantly lower in those with stage I (p=0.002 and p=0.005, respectively). The univariate analysis for DFS and OS showed that patients with higher levels of PD-L2, IDO2 and IFN-gamma (p=0.05, p=0.028 and p=0.04, respectively) were associated with a worse DFS, while patients with higher levels of PD-L1 and IDO2 were associated with a worse OS (p=0.04 and p=0.03, respectively). At median follow-up time of 43 months, 60 patients died and 131 were still alive. The multivariate interaction model adjusted for sex and stage confirmed that higher levels of PD-L2, IDO2, IFN-gamma were significantly associated with worse DFS (HR: 4.56, p=0.01) and higher levels of PD-L1 and IDO2 with worse OS (HR: 8.01, p=0.04).
Conclusions: PD-L1 and IDO2 were independent negative prognostic factors for survival in resected NSCLC. These features may have important implications for future immune-checkpoint therapeutic approaches.

D05*

PRELIMINARY EFFICACY AND SAFETY RESULTS OF THE SENECA (SECOND LINE NINTEDANIB IN NON-SMALL CELL LUNG CANCER) TRIAL: AN ITALIAN REAL-LIFE EXPERIENCE

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Background: Nintedanib is a multi-target anti-angiogenic agent. Used with docetaxel nintedanib confers longer progression free survival (PFS) and overall survival (OS) than chemotherapy alone as second-line in non-squamous

Table 1. Patients' characteristics at baseline.

Median Age	N 167	
	T1 (N 82)	T2 (N 85)
	63.9 yrs (range 35-86)	63.9 yrs (range 35-80)
ECOG PS		
0	75.6%	69.4%
1	24.4%	30.6%
Smoking history		
Never	13.4%	17.6%
Former	69.5%	54.1%
Current	17.1%	28.3%
Relapse-timing		
C1	81.7%	83.5%
C2	18.3%	16.5%

Non-Small Cell Lung Cancer (nsNSCLC) patients. Considering the greater safety profile of weekly docetaxel than docetaxel q3wks in real life, the SENECA trial, a phase IIb, open label, Italian multicentre study, aims to explore efficacy and safety of nintedanib with the two different docetaxel schedules for nsNSCLC patients.

Methods: Patients from 18 Italian oncologic centres, with advanced nsNSCLC non-oncogene addicted, progressing after first-line chemotherapy, have been treated with docetaxel (T1: 33 mg/mq on days 1 and 8 in a 21-days cycle; T2: 75 mg/mq q3wks) plus oral nintedanib, with the possibility of maintenance. Primary endpoint was PFS (by investigator's assessment); secondary endpoints were OS, safety and QoL. Study stratifies patients into two cohorts according to relapse-timing, within or over 3 months (C1 and C2, respectively) from the end of first-line chemotherapy.

Results: From January 2016 to 30th March 2018 (data cut-off), 197 patients have been evaluated: 30 were screening failures, mainly for contraindications to nintedanib use. Patients' characteristics are summarized in Table 1. According to investigator's choice, patients were assigned to T1 or T2. No significant differences in median PFS have been observed between T1 and T2 (3.83 vs 4.32 months, respectively; HR 0.889 [95% IC 0.598-1.321], p-value=0.559). After a median follow-up of 7.28 months (standard deviation=5.55), a trend of similar OS emerged in both T1 and T2 (6.63 vs 7.91 months, respectively; HR 0.770 [95% IC 0.484-1.225], p-value=0.270). Survival data of relapse-timing cohorts are not yet mature. Main toxicities in T1 and T2 were: fatigue (53.6% vs 65.9%, respectively), diarrhea (50.0% vs 47.0%), afebrile neutropenia (13.4% vs 52.9%) and ALT elevation (29.3% vs 20.0%).

Conclusion: Preliminary results of the SENECA trial confirm that docetaxel plus nintedanib could be effective and safe as second-line option for nsNSCLC patients, regardless docetaxel schedule, suggesting higher toxicities for docetaxel q3wks.

D06

UPFRONT OR SEQUENTIAL STRATEGY FOR NEW GENERATION ANAPLASTIC LYMPHOMA KINASE (ALK) INHIBITORS: AN ITALIAN RETROSPECTIVE STUDY

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Background: Anaplastic lymphoma kinase (ALK) rearrangement confers sensitivity to ALK inhibitors (ALKis) in non-small-cell lung cancer (NSCLC). Although several drugs provided an impressive outcome benefit, the most effective sequential strategy is still unknown.

Methods: We retrospectively collected 242 ALK-positive advanced NSCLC diagnosed between 2010 and 2018 in 23 Italian institutions (expanded data collection from Gobbini et al. Lung Cancer 2017). 138 patients received exclusively crizotinib as ALKi (not considered for this analysis). 78 patients received crizotinib and a new (second or third) generation ALKis as further treatments (group A). 26 patients performed a new generation ALKi as upfront agent (group B).

Results: Study population clinical features and treatments received are summarized in Table 1.

With a median follow-up of 22.6 months (CI 95% 20.09-25.10), 33 patients had died (32%). In group B, the progression free survival (PFS) for new generation ALKis administered as first (median 14.0 months, CI 95% 9.52-18.471), second (12.7 months, CI95% 7.22-18.17) or third-line (12.8 months, CI95% 6.24-19.35) was not statistically different (p= 0.522). The time from the start of crizotinib to the disease progression after the new generation ALKi sequentially performed (group A) was longer than that one detected in group B for the upfront new generation ALKis (median 29 vs 14 months, HR 0.40 [CI95% 0.22-0.74],

Treatments per line n(%)	Group A Crizotinib followed by new generation ALKis N= 78				Group B Upfront new generation ALKis N=26				
	1°	2°	3°	4°	1°	2°	3°	4°	
Crizotinib	28(36)	50(64)	–	–	–	–	2(8)	–	
Alectinib	–	11(14)	18(23)	5(17)	7(27)	–	–	–	
Ceritinib	–	(9(12)	23(30)	3(4)	8(31)	8(31)	1(4)	–	
Brigatinib	–	(6(8)	6(8)	2(3)	–	2(8)	–	2(8)	
Lorlatinib	–	–	4(5)	5(6)	–	–	1(4)	–	
Chemotherapy	50(64)	(2(3)	10(13)	na	11(42)	6(23)	1(4)	Na	
Clinical features n(%)									
IHC[a] test	13(17)				(6(23)				
FISH[b] test	40(51)				13(50)				
IHC and FISH test	21(27)				(3(12)				
Age (range)	58(27-83)				55 (24-82)				
Male	37(47)				10(38)				*p*= 0.42
Female	41(53)				16(62)				
Current smoker	8(10)				(5(19)				*p*= 0.23
Never/former smoker	70(90)				21(81)				
ALKi beyond progression	27(34)				(4(15)				*p*= 0.06

a. Immunohistochemistry.
b. Fluorescence In Situ Hybridization.

p=0.003). This result was confirmed even considering the time lost between the two treatments in group A. The median overall survival (OS) was not reached. The 12-months OS rate was 97% in group A and 84% in group B.

Conclusion: New generation ALKis maintain their efficacy regardless of the treatment setting considered. With the obvious limitation of retrospective comparison, the sequential strategy using crizotinib as first ALKi seems to provide a substantial benefit, but a longer follow-up and larger samples are needed to clarify the survival impact.

D07

THE AMOUNT OF ACTIVATING EGFR MUTATION IN CIRCULATING TUMOR DNA IS A BIOMARKER OF RESPONSE TO OSIMERTINIB

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Background: p.T790M is responsible for about 50% of cases of resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs) and can be successfully targeted by third-generation TKIs, such as osimertinib. Treatment monitoring by means of circulating cell-free tumor DNA (cftDNA) may help understand the molecular response to pharmacologic treatment and provide important information on the evolution of clonal heterogeneity of NSCLC. For these reasons, this study evaluated the changes of activating EGFR mutations (act-EGFR) and p.T790M in cftDNA at baseline and after 3 months of osimertinib treatment in patients with advanced NSCLC resistant to gefitinib, erlotinib or afatinib in relation to treatment outcome.

Patients and Methods: Thirty-four subjects positive for both act-EGFR and p.T790M in cftDNA at study entry were included. Plasma samples were obtained at osimertinib baseline and after 3 months of therapy. CftDNA was extracted from plasma and EGFR mutations were analysed by ddPCR (BioRad).

Results: At osimertinib baseline, the amount of the act-EGFR compared to p.T790M was significantly higher with a median allele frequency (AF) of 2.6 for act-EGFR vs 0.575 for p.T790M ($p<0.0001$). The baseline AF of act-EGFR was correlated with disease control rate (CR+PR+SD vs PD, p=0.02) during osimertinib treatment, and it was dependent from the number of previous lines of TKIs treatment (=1 vs >1, p=0.01). The baseline p.T790M/act-EGFR ratio was correlated with disease response (CR vs PR vs SD vs PD p=0.02) and an AF cut-off of 0.22 was identified to stratify patients as per PFS (>0.22 vs =0.22, not reached vs 3 months; p=0.01). In all patients achieving a CR or partial

response PR, a disappearance or strong reduction of both act-EGFR and p.T790M mutations were found. A significant decrease of both act-EGFR and p.T790M mutations was also observed in patients with stable disease (SD), although the decline of act-EGFR was less pronounced compared to p.T790M ($p=0.002$ and $p<0.0001$, respectively). In 8 patients with disease progression, 4 showed a strong increase in act- EGFR, although the amount of p.T790M decreased in all but one, and p.C797S was detected. Of them, 5 were re-biopsied and 2 had SCLC transformation, one presented c-MET amplification, one had the C797S mutation whilst another one had ex19del only.

Conclusion: Act-EGFR amount may be a good early predictive biomarker of response to osimertinib, better than p.T790M does, and this finding should be considered for treatment monitoring.

D08

BE-TEAM: AN ITALIAN REAL-WORLD OBSERVATIONAL STUDY ON 2ND-LINE THERAPY FOR EGFR-MUTATED NSCLC PATIENTS (PTS)

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Background: Introduction of 3rd generation tyrosine kinase inhibitors (TKI) in epidermal growth factor receptor (EGFR) T790M mutated pts imposes a molecular characterization after disease progression to 1st and 2nd generation EGFR-TKIs. Be-TeaM is an observational study aimed to understand the diagnostic approach after progression to EGFR-TKIs. Data from an interim analysis are presented.

Material and methods: Pts affected by advanced NSCLC with an activating EGFR mutation who progress to 1st- and 2nd-generation EGFR-TKI therapy were enrolled. The study was designed with a retrospective phase (from the start of first TKI until disease progression) and a prospective phase (within 3 months from disease progression). Primary objective is to describe the Italian real-world practice of diagnostic approaches and treatment strategies in NSCLC pts who progressed to EGFR-TKI therapy. Results are presented descriptively.

Results: From July 2017 until February 2018 174 pts were enrolled in 50 centers and 97 have been analyzed. Mean age was 66 (range 33-88) years; 70% were female. Regarding data on first EGFR-TKI treatment, 57 pts (59%) received gefitinib, 29 (30%) afatinib and 11 (11%) erlotinib, with an overall median treatment duration of 11.9 months (range 8.5-20.8). Eight patients (8.2%) received also a chemotherapy prior to EGFR-TKI. For the diagnosis of progression, only RECIST criteria were applied in 70 pts, while only clinical evaluation was applied in 7; for 16 pts both RECIST criteria and clinical evaluation were used. At disease progression, 58 (59.8%) pts had new metastases with central nervous system being the site of progression in 24 pts (25%). Performance status at disease progression was 0-1 in 86 (89%), 57 (59%) had symptoms at enrollment (mainly bone pain and dyspnea). A total of 85 pts (88%) performed a biopsy: liquid in 63 pts (74%) and tissue in 27 (32%); 13 pts were firstly prescribed a liquid biopsy, and subsequently a tissue biopsy. Among the 85 pts, 48 (56%) resulted T790M+, 37 (44%) were T790M-. In the T790M- cohort, 16 pts (43%) received a TKI (9 gefitinib, 4 afatinib, 3 osimertinib) and 18 (49%) a chemotherapy (10 platinum-pemetrexed, 4 other platinum-based doublet, 4 single agent); among the 12 pts without T790M test, 4 had a targeted therapy.

Conclusions: BE-TeaM is an Italian multicenter observational study reporting bioptic attitude after progression to 1st and 2nd generation EGFR-TKIs. Updated data will be presented at the congress.

D09

PRELIMINARY RESULTS FROM A MULTICENTER ITALIAN OBSERVATIONAL PROSPECTIVE STUDY OF PATHOLOGIC UNITS FROM THE "RETE ONCOLOGICA PIEMONTE E VALLE D'AOSTA" AND FURTHER ITALIAN CENTERS LOOKING AT MOLECULAR ALTERATIONS IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PTS) IN A CRUCIAL TIME WINDOW

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Background: At present time, systemic treatment for stage IV NSCLC have changed considerably, primarily as a result of a better patient selection on the basis of histology and availability of molecular markers, with consequent innovative treatment approaches including immunotherapy. The implementation of tests in the diagnostic algorithm is not carried out homogeneously at regional and national level and sometimes, therapeutic changes are introduced faster in clinical practice compared to corresponding changes in pts screening. This prospective evaluation has been made in a crucial window time, when several improvements appeared in the treatment setting.

Material and methods: From May 2017 until October 2017 pts diagnosed with NSCLC referring to 12 Italian institutions were, only for those in advanced stage, prospectively evaluated with specific end-points being: the percentage of diagnoses performed on cytological and histological material, the proportion of pts undergoing Epidermal Growth Factor (EGFR) mutational status, those who were EGFR mutated, progressed and then were evaluated for resistance mutations by both liquid biopsy or solid one, the proportion of pts undergoing Anaplastic lymphoma kinase (ALK) rearrangement, ROS-proto-oncogene (ROS1) and Kirsten RAt Sarcoma (KRAS) determinations, finally the proportion of those who underwent Programmed-Death Ligand-1 (PDL-1) determination. Furthermore, these data will be compared to a similar evaluation performed in a previous window time, to evaluate the evolution of diagnostic work-up.

Results: In this preliminary analysis 1306 NSCLC pts were included. The majority of them presented with adenocarcinoma histology (n= 857, 65,6%). The prevalent alterations requested or performed were: PD-L1 in 906 pts (69,3%), ALK and ROS1 in 846 and 518 (64,7% and 39,6%) pts respectively, EGFR in 704 cases (53,9%) and KRAS in 464 cases (35,5%). Even in the small interval of time stated by protocol, re-biopsies for detecting EGFR resistance mutations, for confirming ALK traslocations or searching new ALK mutations were n = 44 and n = 8, respectively.

Conclusions: The data collected represent an updated tool with potential utility in order to define points of weakness in clinical practice and to give the size of future needs both in diagnostic and therapeutic setting for advanced NSCLC.

D10

ANALYSIS OF PD-L1 AND CTLA-4 SINGLE NUCLEOTIDE POLYMORPHISMS: CORRELATIONS BETWEEN GENOTYPE AND OUTCOME IN ADVANCED NSCLC PATIENTS TREATED WITH NIVOLUMAB

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Background: Nivolumab has demonstrated improved patient outcome over docetaxel in previously treated advanced NSCLC but predict treatment benefit still remain an unsolved problem. Role of single nucleotide polymorphisms (SNPs) in conditioning treatment outcome are emerging thanks to genome-wide study approach. Here, we investigate the role of *CTLA4* and *PD-L1* polymorphisms in predicting clinical outcomes of advanced

	PD#	CB#	p	TTF*	p	PFS*	p	OS*	p
CTLA4 rs231775			0.362		0.677		0.971		0.687
AA	33 (49%)	34 (51%)		59		55		168	
AG+GG	20 (59%)	14 (41%)		66		56		195	
PD-L1 rs2282055			0.722		0.476		0.540		0.611
TT	36 (68%)	17 (32%)		56		56		189	
TG+GG	31 (65%)	17 (35%)		61		53		192	
PD-L1 rs4143815			0.07		0.192		0.820		0.374
GG	36 (75%)	12 (25%)		59		55		189	
GC+CC	31 (59%)	22 (41%)		66		56		192	

#number of pts and (%) *median survival in days.

NSCLC patients (pts) treated with nivolumab after first-line of chemotherapy.

Material and methods: NSCLC pts treated with nivolumab were evaluated for *PD-L1* (rs2282055, rs4143815) and *CTLA4* (rs231775) SNPs. Genomic DNA was extracted from blood and analyzed with quantitative PCR. We investigated the association between genotypes and outcome measures: clinical benefit (CB: complete response, CR; partial response, PR; stable disease, SD, of at least of 6 months according RECIST criteria v. 1.1), progressive disease (PD), time to treatment failure (TTF), progression-free survival (PFS) and overall survival (OS).

Results: Among the advanced NSCLC 101 pts enrolled in this study from August 2015 to January 2018, 20 were females and 81 males, with 42 squamous carcinomas and 59 adenocarcinomas. Median age at nivolumab initiation was 69 years (range 43-85) and the drug was administered in 2nd to 7th treatment line (2nd 65 pts, > 2nd 36 pts). As best response to nivolumab, 2 pts achieved CR, 15 PR, 21 SD, 63 PD. Median PFS, TTF and OS in overall population were 61 (95% confidence interval [CI] 41.4-81.5), 56 (95%CI 51.9-60) and 192 (95%CI 153.8-230.1) days, respectively. None of analyzed SNPs were statistically significant associated with clinical benefit and survival outcome (see table).

Conclusions: Although no statistically significant correlation was observed between SNPs investigated and outcome measures, a trend for *PD-L1* rs4143815 and clinical benefit was evidenced: patients with rare allele (GC+CC) presented a better response respect those with ancestral one (GG). This study is ongoing and other patients have been enrolled after January 2018, final data with larger simple size will be available at the time of the meeting.

D11

IMMUNOTHERAPY IN THE TREATMENT OF ADVANCED, PRETREATED, NON-SQUAMOUS NON SMALL CELL LUNG CANCER. SYSTEMATIC REVIEW OF RANDOMIZED CLINICAL TRIALS WITH NETWORK META-ANALYSIS

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Background: To assess the role of Immunotherapy (I) in second line treatment of Advanced, Pre-treated, Non-Squamous Non Small Cell Lung Cancer (APNS-NSCLC).

Methods: A pooled analysis of the final data of the CA209057, the KEYNOTE-010 and the OAK trial was performed. Overall Survival (OS) was the primary end point of the trial. The outcomes of patients with PD-L1 expression of 1%-49% (PD-L1 1%-49%), PD-L1 expression <1% (PD-L1<1%) or mutated-EGFR (EGFR+) were analyzed comparing any checkpoint inhibitor with standard chemotherapy. An indirect comparison with network meta-analysis was performed between the different checkpoint inhibitors whenever a significant difference was observed in the pooled analysis. Direct and indirect comparisons were performed using a random effect model.

Results: The outcome of 1720 patients was analyzed. 313 patients had been treated with Atezolizumab (A), 292 with Nivolumab (N), 270 with Pembrolizumab (P), and 845 with Docetaxel (D). The preliminary results were detailed in the table.

	OS Hazard Ratio	CI95%	
A vs D (PD-L1 1%–49%)	0.571	0.423–0.771	P<0.001
N vs D (PD-L1 1%–49%)	0.62	0.467–0.882	P=0.001
P vs D (PD-L1 1%–49%)	0.76	0.604–0.956	P=0.019
I vs D (PD-L1 1%–49%)*	0.66	0.555–0.786	P<0.001
A vs N (PD-L1 1%–49%)**	0.921	0.609–1.392	P=0.696
A vs P (PD-L1 1%–49%)**	0.751	0.541–1.043	P=0.087
N vs P (PD-L1 1%–49%)**	0.816	0.597–1.116	P=0.491
N vs D (PD-L1<1%)	0.9	0.66–1.214	P=0.491
A vs D (PD-L1<1%)	1.04	0.619–1.747	P=0.882
I vs D (PD-L1<1%)*	0.933	0.72–1.21	P=0.601
P vs D (EGFR+)	0.88	0.453–1.71	P=0.706
N vs D (EGFR+)	1.18	0.693–2.004	P=0.542
I vs S (EGFR+)*	1.052	0.695–1.594	P=0.81

Legend. CI95%: 95% Confidence Interval; *: Pooled Analysis; **: Network Meta-Analysis.

Conclusions: Our data seem to confirm the role of I for APNS-NSCLC with PD-L1 1%-49%. On the contrary, not-significant benefits in terms of OS seem to emerge for patients with PD-L1<1% or EGFR+ expression. Likewise, no significant differences seem to emerge from the indirect comparisons between A, N and P for patients with a PD-L1 1%-49% expression. Although all these data need to be analyzed with caution, as expression of indirect comparisons, waiting further conformations from clinical trials they can support clinicians for daily clinical practice.

D12

CLINIC-PATHOLOGICAL PREDICTIVE FACTORS TO PLATINUM-BASED CHEMOTHERAPY IN THYMIC EPITHELIAL TUMORS: THE ROLE OF PARANEOPLASTIC AUTOIMMUNE SYNDROMES

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Background: Thymic epithelial tumors (TETs), including thymomas and thymic carcinomas (TCs), represent a heterogeneous group of neoplasms of the anterior mediastinum with extremely variable clinical behaviour. Many cases present paraneoplastic syndromes associated, mostly autoimmune syndromes.
Patients and methods: We enrolled 82 patients with TETs, 75 thymomas ant 7 TCs, who were treated in our institution from 1994 and 2017. Response to chemotherapy was evaluated according to RECIST1.1. criteria. The association between clinic-pathological data and objective response to chemotherapy was evaluated by Fisher exact test.
Results: M/F ratio was 0.87, median age at diagnosis was 51 years (range 21-81), 27 patients reported concomitant autoimmune diseases, including 27 cases of myasthenia gravis and single cases of myositis (dropped head syndrome), undifferentiated connective tissue disease, haemolytic Coombs-positive anemia and polyneuritis. 78 patients underwent surgery, 27 out of them performed post-operative radiation therapy and 13 patients presented disease recurrence. 53 patients received chemotherapy, including neoadjuvant and first line treatments and 38 patients received platinum-based chemotherapy. In this group, 17 patients achieved a response to chemotherapy and 21 patients experienced no response. Response to platinum-based chemotherapy resulted significantly associated with age at diagnosis (<60 years, p=0.0081), concomitant autoimmune diseases (p=0.0334), carcinoma and thymoma B3 histology (p=0.0219).
Conclusion: No previous studies reported predictive factors to chemotherapy in TETs. Our study showed that a lower age at diagnosis seems to improve the response to chemotherapy, presumably because a younger population could allow to perform full-dose and well-scheduled treatments, maintaining an adequate dose-intensity. Furthermore, carcinoma and B3 thymoma histology were associated with a better response, probably due to their more aggressive behaviour and their related higher proliferative activity. The association between autoimmune concomitant syndromes and a better response suggests that an immune activation might improve the antitumoral activity of chemotherapy, supporting future investigation about the possible anticancer activity of immunotherapy associated with chemotherapy in TETs.

D13

5 YEARS INTO THE IMMUNE-THERAPY ERA FOR ADVANCED STAGE NON-SMALL CELL LUNG CANCER (ANSCLC): NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) AS A PREDICTIVE MARKER FOR EFFICACY AND FOR DEVELOPMENT OF IMMUNE-RELATED ADVERSE EVENTS (IRAES)

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Background: Immune checkpoint inhibitors (ICIs) have changed clinical practice for aNSCLC treatment (trt). The only predictive marker currently available, PD-L1 TPS, have shown several limitations. Clinical factors and circulating markers, such as NLR, have been recently suggested as relevant in predicting clinical benefit. In our study we reviewed the impact of irAEs in patients (pts) treated with ICIs and evaluated NLR as predictive tool for trt benefit and irAEs occurrence.
Patients and methods: We retrospectively reviewed clinical data of aNSCLC pts treated with ICIs at our Institution between August 2013 and January 2018. Pre-ICI NLR was calculated and dichotomized between high (H) and low (L) using the pre-identified cut-off of 3 for survival analysis.
Results: A series of 115 pts was evaluated: median follow-up was 54,6 months (m), range (r) 2,4-56,8m, median age 67 years (r: 37-83 years), most of them were smokers (83%) and had ECOG performance status (PS) 0-1 (78%). 16 (13,9%) pts had PD-L1 TPS>/=50% and received pembrolizumab upfront; the others received nivolumab

(76,5%), pembrolizumab (3,5%) or atezolizumab (6%). Median number of ICI administrations was 7 (r: 1-59). Median PFS and OS were 2,9m (95% CI: 2,1-3,8m) and 21,3m (95% CI: 15,4-27,1m) respectively. IrAEs occurred in 38 pts, mainly G1-2 (68,4%), and caused trt interruption in 31 cases. 17 pts definitively withheld ICI after irAE with no impact on PFS (4,1m; 95% CI: 1,1-7,2m), when compared with pts who resumed it (5,6m; 95% CI: 1,4-9,7m, p=0,99). Median PFS and OS were significantly longer for pts who had any irAE: 5,5m (95% CI: 3,9-6,9m) versus (vs) 2,3m (95% CI: 1,9-2,6m, p<0,001) and 49,9m (95% CI: 17-82,8m) vs 17,1m (95% CI: 10,8-23,4m, p=0,001) respectively. H-NLR pts (55,6%) had both worse PFS (2,8m; 95% CI: 2,0-3,5m) and OS (17,8m; 95% CI: 10,7-24,9m) compared to L-NLR population (PFS 5,1 m; 95% CI: 2,0-8,1 m, p=0,021 and OS 49,9m; 95% CI: 14,1-85,6m, p=0,004). In multivariate analysis, including PS, previous trts and occurrence of irAEs, NLR maintained association with OS (HR 1,194; 95% CI: 1,118-1,276;p<0,001). L-NLR was able to identify pts with higher risk of irAEs development (p=0.021, Chi-square test). In pts receiving ICI after chemotherapy, PD-L1 had no predictive impact on OS, both as continuous and as dichotomized variable.

Conclusions IrAEs were associated with survival benefit. NLR might be a useful predictive marker of response and of irAEs occurrence in aNSCLC pts receiving ICIs.

D14

CONCOMITANT IMMUNOTHERAPY AND RADIOTHERAPY FOR METASTATIC NON SMALL CELL LUNG CANCER: A SINGLE INSTITUTION EXPERIENCE

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Background: The advent of immunotherapy (IO) for metastatic non small cell lung cancer (mNSCLC) led to a significant improvement in disease outcome. Nonetheless, prognosis of mNSCLC remains unsatisfactory. Preclinical data suggest that combination of radiotherapy (RT) and IO may increase their efficacy. This synergy may be mediated by immune response stimulation due to antigen unmasking after radiations. Herein we retrospectively analyze a single Institution case series of mNSCLC patients (pts) treated with IO and RT.

Material and methods: We retrospectively collected data of pts treated with IO at Istituto Nazionale dei Tumori, Milan, Italy, from April 2013 to January 2018. We divided the cases in the following subgroups: those who underwent RT within 1 month before the beginning of IO or during IO (group RIT), and all the other pts (group IT). Clinical data were extracted from Institutional database. Progression free and overall survival (PFS and OS, respectively) were estimated with Kaplan-Meier method. Fisher exact test was used to compare paired proportions.

Results: We identified 50 pts in RIT group, 125 pts in IT group. The subpopulations were balanced for sex, smoking, performance status, PD-L1 expression and line of IO. EGFR was mutated in 4.0% of RIT cases, and in 6.4% of IT cases. Nivolumab was the most frequently prescribed IO (68.0% in RIT group, 54.4% in IT group), followed by durvalumab (12.0% in RIT group, 21.6% in IT group), and atezolizumab (4.0% in RIT group, 11.2% in IT group). RT target were bone (50.0%), brain (26.0%), lung/mediastinum (22.0%) and other sites (2.0%). Median RT dose was 20 Gy, in a median of 5 fractions. No differences in disease control rate (DCR) were observed between the groups (44.8% for IT, 56.0% for RIT; *p* 0.5). Median PFS was 3.8 months (mos) for IT group, 5.6 mos for RIT group (*p* 0.9). Median OS was 7.5 mos for IT group, 7.7 mos for RIT group (*p* 0.4).

Conclusions: In our series, no synergy was apparently observed between RT and IO. Maybe the limited number of cases impaired the statistical significance of the analysis. Furthermore, the difference in RT schedule, target, doses and timing from IO may have influenced the results. However, given the growing broadening in IO indications for mNSCLC and the discordant literature data, this topic warrants further investigation with prospective studies.

D15

CORRELATION BETWEEN B7-H4 AND OUTCOMES OF PATIENTS RECEIVING NIVOLUMAB FOR ADVANCED NON-SMALL CELL LUNG CANCER

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Background: While immunotherapy has emerged as a standard of care in non-small cell lung cancer (NSCLC), reliable predictors of benefit are currently lacking and even PD-L1 has a limited role, especially in second or further line setting. Apart from the PD-1/PD-L1 axis, other immune checkpoints might play a role in tumor immune escape. This study aims to determine whether the expression of selected molecules involved in immune response might be associated with outcomes of NSCLC patients

receiving nivolumab in second or further line of treatment.

Patients and methodS: Tumor samples from 46 NSCLC patients receiving nivolumab (Nivolumab Cohort) underwent immunohistochemistry (IHC) to determine the expression of PD-L1, PD-L2, PD-1, B7-H3, and B7-H4; correlations between protein expressions and clinical outcomes were explored. Additionally, the prognostic biomarkers observed in the Nivolumab Cohort were subsequently assessed in a population of 27 NSCLC patients receiving platinum-based chemotherapy (Chemotherapy Cohort).

Results: Samples from 17 patients (37.0%) in the Nivolumab Cohort (n= 46) were positive for B7-H4 expression. At univariate analyses, B7-H4 expression was associated with significantly decreased progression-free survival (PFS; 1.7 *vs.* 2.0 months; *p*-value= 0.026) and with a disadvantage in terms of overall survival (OS) close to statistical significance (4.4 *vs.* 9.8 months; *p*-value= 0.064). At multivariate analyses, B7-H4 was significantly associated both with PFS (hazard ratio (HR)= 2.28; *p*-value= 0.021) and OS (HR= 2.38; *p*-value= 0.022). In the Chemotherapy Cohort (n= 27), no correlation between B7-H4 expression and outcomes in terms of PFS or OS was observed at univariate or multivariate analyses. With regards to the other immune-related biomarkers, no significant association between the expression of PD-L1, PD-L2, and PD-1 and outcomes was observed in the Nivolumab Cohort, while the number of patients expressing B7-H3 was too limited to draw clinically meaningful conclusions.

Conclusions: A negative correlation between B7-H4 expression and outcomes was observed in a cohort of NSCLC patients treated with nivolumab, while no correlation was observed in a cohort of NSCLC patients treated with chemotherapy. These results encourage further studies exploring the potential predictive role of B7-H4 in NSCLC patients receiving nivolumab.

D16

PRELIMINARY RESULTS OF THE ARPA (AZD9291 IN RELAPSED PATIENTS AFTER EGFR-TKI) STUDY. PSYCHOLOGICAL ISSUES IN A REAL-LIFE POPULATION OF NON-SMALL CELL LUNG CANCER PATIENTS

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Table1. Pts' characteristics at baseline.

N 32 (100%)

Median age 66,8 years (range 39-84 years)

Gender		*ECOG PS*	
Male	11 (34,4%)	0	22 (68,7%)
Female	21 (65,6%)	1	10 (31,3%)
Smoking		*Line of osimertinib*	
Current	0 (0%)	II	25 (78,1%)
Former	8 (25,0%)	III	6 (18,7%)
Never	24 (75,0%)	IV	1 (3,2%)

Background: Literature shows a low quality of life (QoL) in Non-Small Cell Lung Cancer (NSCLC) patients (pts) due to disease and therapy, which may influence psychological distress, sleep and depression. Osimertinib is a third-generation Epidermal Growth Factor Receptor (EGFR) inhibitor, which confers longer progression free survival (PFS) vs standard of care in treatment-naïve NSCLC EGFR mutated pts, such as in pretreated T790M+ ones. In this context, the ARPA study, a phase II monocentric observational study, aims to evaluate pts' perception of treatment-related symptomatic Adverse Events (sAEs), their impact on QoL and psychological issues, being these aspects never explored in depth before.

Methods: A real-life population of NSCLC EGFR T790M+ pts received osimertinib: multiple previous therapies and silent brain metastases (mts) at baseline were allowed. Pts' perception of sAEs and the matched medical/psychological evaluation was performed q3wks with dedicated questionnaires. Functional Assessment of Cancer Therapy-Lung (FACT-L) was used to assess QoL, Beck Depression Inventory II (BDI-II) for depression, Psychological Distress Inventory (PDI) for distress and Pittsburgh Sleep Quality Index (PSQI) for sleep quality.

Results: From February 2016 to January 2017, 34 pts were evaluated (2 screening failures for brain mts and lack of compliance). Main pts' characteristics are listed in Table1. At 1st May 2018, average therapy was 10,3 months (standard deviation [DS]=6.0) and median PFS, in this early evaluation, 12,8 months (DS=7,1). Data about pts' perception of sAEs are not yet mature. Here we present results of psychological evaluations performed at baseline. The BDI-II showed depression symptoms in 18,5% of cases. The 96,9% of pts had medium-high QoL (FACT-L) and 57,1% low distress (PDI). Gender differences was found in QoL and distress, judged high and of low level, respectively, in 72,7% and 70,0% of men vs 38,1% and 50,0% of women. Sleep quality (PSQI) was poor in 80,6% of pts (81,8% in men, 80,0% in women).

Conclusions: Preliminary data would seem to confirm that the NSCLC diagnosis is associated with high psychological burden. Final data will be available upon reaching study completion.

D17

LUNG ADENOCARCINOMA WITH SYNCHRONOUS/METACHRONOUS BRAIN METASTASES: A RETROSPECTIVE ANALYSIS OF A SINGLE INSTITUTION SERIES

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Background: Brain metastases (BM) may be a life-threatening complication for lung adenocarcinoma. In patients (pts) with BM, prognosis depends on many clinical and pathological features. Aim of the present study is to analyze risk factors for BM developing and prognostic factors in pts with BM in a homogeneous case series.

Material and Methods: We retrospectively reviewed 152 pts with new diagnosis of lung adenocarcinoma from January 2014 and December 2016 in our Institution who developed synchronous (SBM) or metachronous BM (MBM) confirmed radiologically. We described their clinical and pathological features and type of radiotherapy (RT).

Results: The incidence of BM in our Institution was 19.5% (152/781): 61.8% presented SBM while 38.2% developed MBM (median time of presentation 8.2 months). 62.5% of pts were male, 23.7% had an ECOG PS =2 and median age at diagnosis was 66 years old (range 36-93) with 43.4% of pts =70 years old. Median Body Mass Index (BMI) was 24.8 (range 16.0-39.2). 15.8% were never smokers. 19.1% had T status <3 cm and 63.2% were N2-3. 17.1% were EGFR mutated and 3.3% carried ALK translocation. 64.5% presented 1-3 BM. Most BM occurred in a supratentorial site (65.1%) and 51.3% were symptomatic. 42.1% received brain RT: 43 pts whole brain RT (WBRT), 18 stereotactic RT and 3 both.

At the time of the data cut-off, 125 pts (82.2%) died and 13 (8.6%) were lost to follow up; median overall survival (mOS) was 10 months (range 0-40 months). Subgroups with better mOS (in months) were: female (12.8 vs 8.2), pts <70 years old (11.1 vs 8.5), ECOG 0-1 (11.9 vs 4.9), BMI ⩾18.5 (10.5 vs 9.0), non-smokers (11.6 vs 9.7), T <3cm (12.7 vs 9.4), N0-1 (11.6 vs 9.2), EGFR mutated (12.2 vs 9.7), KRAS wt (10.9 vs 8.4), ALK traslocated (12.4 vs 10.2). Regarding BM, mOS improved for MBM (13.3 vs 7.9), 1-3 lesions (10.8 vs 8.4), supratentorial site (10.9 vs 9.3 for subtentorial and 8.0 for both or leptomeningeal) or asymptomatic pts (11.0 vs 9.0). mOS improved with RT (11.9 vs 8.5) and in particular in 3 pts treated with both stereotactic and WBRT (21.0 months).

Conclusions: Pts with T>3 cm and N2-3 presented a major risk for BM development. ECOG PS confirms its role as main prognostic factor in pts with BM, but also other factors seem to have a prognostic role (sex, age, BMI, characteristics of BM and primary tumor). We cannot draw significant conclusions on the basis of our monocentric retrospective analysis, but there should be more extensive studies with focus on BM.

D18

CELL-FREE CIRCULATING TUMOR DNA(CTDNA) ANALYSIS BY NEXT GENERATION SEQUENCING (NGS) PANEL IN NON SMALL CELL LUNG CANCER PATIENTS (NSCLC): IMPLICATIONS IN CLINICAL PRACTICE.

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Background: The treatment of NSCLC has evolved into precision medicine that needs the implementation of biomarkers testing. In the last years, the number of potentially actionable molecular alterations has rapidly increased. Diagnostic samples are frequently not sufficient for molecular definition of NSCLC but with NGS can be analyzed many genes simultaneously. So we evaluated the feasibility of using ctDNA NGS in clinical practice to better identify alterations that may predict response and toxicity to the therapies.

Material and methods: We performed a retrospective study about adults patients with advanced non squamous NSCLC. A cohort of 45 non squamous NSCLC was profiled using a NGS panel targeting 56 actionable and cancer related genes.45 plasma samples obtained were subjected to manual cell-free circulating tumor DNA extraction with Helix Circulating Nucleic Acid Diatech pharmacogenetics kit, NGS with Illumina MiSeq-Myriapod NGS-IL 56G Onco panel kit. Relationships between gene mutations, tumor response and grade of toxicity were evaluated using standard Recist Criteria and Common Terminology Criteria for Adverse Events (CTCAE) version 4.02. We used a database and analyzed the data using nonparametric methods.

Results: Of 45 enrolled non squamous NSCLC patients,18 (40%) patients showed gene alterations. Recurrent alterations were observed in KRAS, TP53, MET, KDR, KIT, SMAD4 and MET genes, whereas the remaining genes (ERBB4, CTNNB1, EGFR) were mutated in <5% of the cases. The overall treatment response was higher in patients with SMAD4 mutation. Instead for KIT mutated patients we showed a poor prognosis associated to an

increased gastrointestinal (G3/4) and haematological toxicity (G3/G4), according to CTCAE v. 4.02.

Conclusions: Despite the low sample size the results seem to confirm the importance of more accurate analysis of genomic alterations. We highlighted that NGS panel represent an effective diagnostic tool showing the interesting role of some genes alterations that may predict responsiveness and toxicity to standard NSCLC regimens. There is interest in literature for potential applications of NGS-based liquid biopsy in the treatment of NSCLC despite the gap between theoretical and practice medicine. Further studies are needed to monitor tumor evolution, response and resistance to targeted therapies and to facilitate translational medicine.

D19

LOCALLY ADVANCED NSCLC (LA-NSCLC): RESULTS FROM A NATIONAL SURVEY ON TREATMENT PRACTICE FROM ITALIAN THORACIC ONCOLOGIST COMMUNITY

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Background: In LA-NSCLC the recommended treatment is concomitant Radio-Chemotherapy (cRT-CHT), but it is often variously managed due to different and heterogeneous presentations at diagnosis. Recently significant results were obtained with the addition of Immunotherapy (IT) to standard treatments.

Material and Methods: A dedicated survey, made by 15 multiple choice web questionnaires about diagnostic-therapeutic course of LA-NSCLC, was submitted to Italian Pneumologists (PN), Thoracic Surgeons (TS), Radiation Oncologists (RO) and Medical Oncologists (MO) actively involved in thoracic oncology between February and April 2018. Questions regarded demographic characteristics of participants, diagnostic approaches and treatment management (through explicative clinical cases). Aim of the survey was to evaluate the predominant pattern of care of LA-NSCLC and a presence of a real multidisciplinary management.

Results: Most of participants were RO (42%), followed by PN (22%), MO (20%) and TS (15%) with 69% of specialists with more than 5 years' experience in treating NSCLC; 80% of responders perform at least fortnightly multidisciplinary discussion, and 72% even weekly. An adequate cytological or histological evidence of malignancy was considered a proper condition for an appropriate integrate treatment by 63% of specialists, while 37% of them also consider addictive bio-molecular characterization mandatory. Clinical cases exemplifying stage III A NSCLC evidenced a preference for surgical treatment in cN2 single nodal, while in multinodal involvement, 48% of responders would prefer cRT-CHT. Inoperable patients with partial response or stability after neoadjuvant treatment are mostly addressed to radical RT-CHT (48%). When RT-CHT is the elective treatment, 54% of thoracic oncologists choose a concomitant approach, while 46% decide for sequential therapy, mostly due to better toxicity profile and logistical issues.

Conclusions: The critical point of interest emerging from our survey is the need for adequate patient selection for cRT-CHT. Furthermore, a real multidisciplinary approach through regular meeting needs to be increased and widely spread in all Italian Centers, particularly in the era in which very promising results were obtained by the associations with immunotherapy.

D20

THE DIAGNOSTIC ACCURACY OF CIRCULATING TUMOR DNA FOR THE DETECTION OF EGFR-T790M MUTATION IN NSCLC: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: This meta-analysis aims at evaluating the diagnostic accuracy of circulating tumor (ct) DNA for the detection of epidermal growth factor receptor (EGFR)-T790M

mutation in patients with EGFR-positive advanced non-small cell lung cancer (NSCLC) who progressed to prior EGFR-tyrosine kinase inhibitors (TKIs).

Methods: Data from published studies collecting matched blood and tumor tissue samples from patients with EGFR-positive advanced NSCLC who progressed to prior EGFR-TKI were collected by searching in PubMed, Cochrane Library, American Society of Clinical Oncology, European Society of Medical Oncology and World Conference of Lung Cancer meeting proceedings. Studies which evaluated both sensitivity and specificity of plasma-based EGFR-T790M mutation testing by ctDNA analysis were included and pooled sensitivity and specificity with 95% confidence intervals (95% CIs) were calculated.

Results: A total of twenty-one studies, with 1639 patients, were eligible. The pooled sensitivity of ctDNA analysis was 0.67 (95% CI: 0.64-0.70) and the pooled specificity was 0.80 (95% CI: 0.77-0.83). The positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 2.67 (95% CI: 1.86-3.82) and 0.46 (95% CI: 0.38-0.54), respectively. The pooled diagnostic odds ratio (DOR) was 7.27 (4.39-12.05) and the AUC of the sROC curve was 0.77. Subgroup analysis by different detection platforms showed that sensitivity, specificity and AUC of ctDNA analysis by real-time (RT)-PCR were: 0.61 (95% CI: 0.57-0.65), 0.82 (95% CI: 0.77-0.87), and 0.70; sensitivity, specificity and AUC of ctDNA analysis by digital (d)PCR were: 0.72 (95% CI: 0.68-0.76), 0.73 (95% CI: 0.67-0.79), and 0.77; sensitivity, specificity and AUC of ctDNA analysis by by next-generation sequencing (NGS) were: 0.87 (95% CI: 0.76-0.95), 0.89 (95% CI: 0.82-0.94), and 0.88, respectively.

Conclusions: The ctDNA analysis represents a promising, non-invasive approach to detect and monitor the T790M mutation status in patients with EGFR-positive advanced NSCLC, with NGS emerging as the most accurate detection platform. Development of standardized methodologies and clinical validation are recommended.

D21

CIRCULATING TUMOR CELLS AND CIRCULATING FREE DNA. IS THERE A PREDICTIVE ROLE FOR NSCLC PATIENTS TREATED WITH IMMUNE CHECK POINT INHIBITORS?

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Policlinico San Martino, genova

Background: Nivolumab represents now the standard of care in pretreated non small cell lung cancer (NSCLC), but prognostic and predictive factors of response are still under debate. It has been observed that circulating biomarkers might have a prognostic role in lung cancer. The aim of this study was to determine whether circulating tumor cells (CTCs) as well as circulating free DNA (cfDNA) might predict the outcome of patients with advanced NSCLC treated with Nivolumab.

Methods: From May 2015 to April 2017 89 NSCLC patients were treated with Nivolumab as a second or further line of therapy. All patients underwent blood sample collection before the start of treatment (baseline) and after 4 and 7 cycles of Nivolumab to evaluate both biomarkers. CTCs were isolated from 3mL of blood by the ?ltration-based device ScreenCell Cyto (ScreenCell) according to manufacturer's protocol. cfDNA was extracted from plasma using the QIAamp DNA Blood Mini Kit (Qiagen) and quanti?ed (ng/mL) by qPCR method, using hTERTsingle copy gene. The median baseline CTC number and cfDNA content were used as cut-off values to discriminate patients with different outcomes. An univariate analysis was done to evaluate the overall survival (OS) in the study population based on CTC and cfDNA using the Kaplan Meyer method.

Results: The median CTC number and cfDNA at baseline were 2/3mL and 836.5 ng/mL, respectively. Median OS was 8.8 and 6.2 months for patients with baseline CTC $\leqslant$2 and $>$2, respectively (HR 1.53, 95% CI 0.96-2.42; p=0.072). Similarly, patients with high level of cfDNA $>$ 836.5 ng/mlshowed a worse OS as compared with those having lower cfDNA: 5.1 vs 9.4 months (HR 1.63, 95% CI 1.02-2.59; p=0.040). Patients with both CTC and cfDNA over the median had worse OS (HR 2.23, 95% CI 1.21-4.11; p=0.037) than patients with both markers under the median.

Conclusion: A statistically significant advantage in terms of OS was observed in the group of patients with lower baseline cfDNA. A longer survival of borderline significance was observed in the group of patients with baseline CTC =2. Furthermore, the combined presence of high CTC and cfDNA was associated with worse OS.

D22

"ACTION!"... CANCER MOVIES AND LUNG TUMOURS: MEDICAL, PSYCHOLOGICAL AND SOCIAL IMPLICATIONS

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Background: Malignant tumors are the leading causes of death particularly lung tumors. In recent years the theme of cancer has been at the center of national and international movies with the main intent to represent not only the effects of pathological condition, but above all the dynamic

transformation of the patient in personal life and interpersonal relationships. The objective of this study is to evaluate the impact of psychological and social implications that emerge in the movies focused on lung tumours.
Methods: To perform this study, we have searched filmography related to lung cancer on the main databases present (Allmovie, IMDb, Movieplayer, MyMovies, TMDb). Each movies was seen by a team composed by a communication expert to identify the communicative context through a semiotic investigation, an oncologist to better define the clinical-therapeutic approach reported and a psyconcologist, in order to evaluate the emotional and psychological impact of lung cancer management.
Results: 110 films focusing on the theme of cancer producted in the last 12 years have been analyzed. The first aspect emerging from the analysis is the theme of cancer movies center predominantly around hematological malignancies, particularly leukemia (23%). Despite high rates of incidence and mortality, lung cancer is not frequently represented in cancer movies. In the our evaluation the theme of lung cancer is reported only in five movies (The Bucket List, Gran Torino, Beginners, Saç aka Hair, Truman). The limited interest of cinematography for lung cancer could be explained considering the negative feeling of people due to the combination of social discrimination related to the stigma of smoking and hopelessness for high mortality rate. Moreover, a peculiar psychological theme has been evaluated the "AIR HUNGER" fear, as the concept of life is strictly related to the act of breathing, representing not only an internal body function, but also a main relationship with the external environment. In the five movies, both aspects are overcome through the intense relational dynamics between patients and "caregivers" and the pour diagnosis becomes an opportunity to review their life experiences and search for new goals.
Conclusions: Filmography can be an useful tool for lung cancer awareness and support communication and emotional exchange in cancer patient-caregiver relationship.

D23

METABOLIC MICROBIOTA PROFILE PREDICTS RESPONSE TO NIVOLUMAB IN NSCLC PATIENTS

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Background: Despite the efficacy of Immune Checkpoint Inhibitors (ICIs), only the 20-30% of treated patients present long term benefits. The identification of predictive markers of response and toxicity is a challenging approach for drug selection in order to obtain the best clinical benefit. The changes occurring in the microbiota composition have been proposed as a mechanism potentially influencing the response and the toxicity to immunotherapy.
Material and methods: The metabolomic profile of microbiota was characterized in an age-matched control-case study of 11 patients affected by non-small cell lung cancer (NSCLC) treated with Nivolumab in 2 line. The stool samples of NSCLC patients were collected at cycle 1, 3 and 5. The metabolomic analysis were performed by GC-MS/SPME and1H-NMR in order to detect volatile and non-volatile metabolites. Metabolomic data will be submitted to statistical profiling and chemometric analyses and the correlation networks will be created to individualize potential biomarkers.
Results: Four out of 11 patients (36%) presented early progression (defined as progression of the disease within 3 months from the beginning of Nivolumab treatment) while 6 out of 11 (54%) presented progression of disease after 12 months . The inter-individual variability of metabolites levels resulted high. Alcohols, esters and phenols were significantly associated with fast progression and on the contrary organic acids and SCFAs were significantly associated with long term benefit.
Conclusions: Our preliminary data suggest significant role of specific microbiota metabolic profile in influencing response to immunotherapy. The metabolic approach could be a promising strategy to stratify patients in responder and resistant.

D24

RADIOTHERAPY (RT) AND NIVOLUMAB IN NON-SMALL-CELL LUNG CANCER (NSCLC): A MULTICENTER REAL-LIFE EXPERIENCE

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Background: The combination of RT and programmed death 1 (PD-1) inhibitors seems augment antitumor immune responses. The aim of this study was to assess the outcome of patients (pts) with NSCLC previously undergone to RT before receiving nivolumab, a PD-1 inhibitor.

Material and methods: We conducted an observational, retrospective analysis of 95 consecutive pts with advanced NSCLC who received any RT within 10 months prior nivolumab, as clinically indicated, at seven Italian institutions. Tumor response to treatment was defined according to RECIST criteria version 1.1. Median overall survival (OS) and the 95% confidence interval (CI) were estimated with the Kaplan -Meier method.

Results: 95 pts (median age 66 years [range 41-82]; male:63.2%) with advanced NSCLC (adenocarcinoma [adc]:66.3%; squamous cells [sqc]:33.7%) were treated with nivolumab after RT. Median OS was 11.9 months (mo) [95% CI, 6.6-17.2 (adc: 13.0 mo [95% CI,6.7-19.3], sqc 10.5 mo [95%CI,3.9-17.1]). Median progression free survival (PFS) was 6.3mo [95% CI,4.6-8.0] (adc: 6.4 mo[95% CI,4.5-8.3]; sqc: 3.7 mo [95% CI,0.0-8.3]). A better performance status (PS) according to ECOG scale was associated with an improved OS (PS 0[38 pts]: 17.9 mo [95% CI,12.3-23.5; $p<0.0001$]; PS1[50pts]: 6.9 mo [95%CI,3.2-10.6]; PS2[7pts]: 4.4 mo [95% CI, 3.9-4.9]). Median OS in 70 pts who received $\leqslant$ 1 previous systemic therapy was 13.0 mo [95% CI, 10.4-15.6] and in 25 pts who received $\geqslant$2 prior lines was 7.4 mo [95% CI, 1.8-12.9]. Median OS in 69 pts (72.6%) receiving extracranical RT was 12.0 mo [95%CI,6.6-17.4] and in 26 (27.4%) pts with cranial RT was 11.7 mo [95%CI, NE]; p=0.31. Median OS was shorter in 36 pts receiving bone-RT [7.3 mo; 95% CI, (0-15.3)] when compared with 59 pts receiving extra-bone RT [14.4 mo; 95% CI, (10.3-18.5); p=0.007]. Median OS in 68 pts aged $<$ 70 years was 11.9 mo [95% CI,6.5-17.3] and in 27 elderly ($\geqslant$ 70 years) was 12.0 mo [95% CI, 3.8-20.1]. 1 (1.0%) complete response, 25(26.3%) partial response, 28(29.5%) stable disease and 41 (43.2%) progressive disease have been observed.

Conclusions: This study shows that combining irradiation with nivolumab for the treatment of advanced NSCLC leads to improve OS and promote tumor control both locally and distantly. This potentially synergistic effect was comparable among pts regardless previous lines of therapy, histology, type of RT and age.

D25

ASSOCIATIONS BETWEEN ORAL VINORELBINE CLINICAL OUTCOME AND MULTI-DRUG RESISTANCE 1 GENE POLYMORPHISMS IN NSCLC PALLIATIVE SETTING

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Background: Vinorelbine (VNR) is a substratum of P-glycoprotein (P-gp), a molecular pomp that drives drug efflux outside of cells. P-gp is located on the luminal sides of enterocytes, where hinders oral drug absorption, and on renal tubules and hepatocytes, where increases drug elimination. MDR1 gene codes for P-gp and is characterized by at least 30 polymorphic variants. Two single nucleotide polymorphisms (SNPs), MDR1-2677G>T and MDR1-3435C>T, have been associated with P-gp pump activity, VNR clearance, chemotherapy response and risk of progression upon intravenous administration. We assessed whether MDR1 SNPs can affect the efficacy of oral VNR.

Patients and Methods: Elderly and/or pretreated patients affected by advanced lung cancer received 20-50 mg of oral VNR with a metronomic schedule. Time of Treatment Duration (the time between treatment start and stopping from any cause, TTD) and Clinical Benefit (persistence of the clinical well-being without evidence of progression for at least 12 weeks, CB) were evaluated. Genomic DNA was extracted from peripheral blood and MDR1 SNPs were studied by RFLP analysis. VNR blood concentrations were determined after one month of drug intake by LC-MS/MS.

Results: Eighty-three patients (68 males), median age of 73 years (range 29-88; 65% over 70), 48 with adenocarcinoma histology, were enrolled. Median TTD was 15 weeks (range 1.3-144) and was not statistically different according to line of therapy, age or histology. CB was obtained in 59% of patients. VNR blood concentrations was highly variable (mean 3.1 ± 2.2nM); patients with MDR1 2677TT-3435TT had significantly higher levels compared with the other genotypes (4.9 vs 2.8 nM, p=0.015).

Associations were found between MDR1 polymorphisms and outcomes of treatment: patients with MDR1 2677GG and 3435CC (n=21) had a significantly shorter TTD (9,6 vs 16,0 weeks, p=0.001) with an HR of 2.2, and a lower percentage of clinical benefit (42.8% vs 64.5%, p=0.001). Moreover, in the haplotype 2677GG-3435CC only 38.6% of the patients continued treatment over 15 weeks, compared with 57% of the other haplotypes (p= 0.04).

Discussion: The aplotipe MDR1 2677G-3435C has a negative impact on the response to oral VNR. Polymorphisms of MDR1 may provide a useful pretreatment indicator of P-gp-mediated VNR intestinal absorption and systemic clearance and could predict the clinical outcome in advanced lung cancer patients.

D26

DERIVED NEUTROPHIL-TO-LYMPHOCYTE RATIO AS PROGNOSTIC FACTOR IN ELDERLY NSCLC PATIENTS TREATED WITH ANTI-PD-1 IMMUNOTHERAPY: A MULTICENTER, EXPLORATORY ANALYSIS

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Background: Immune checkpoint blockade (ICB) with anti-PD-1 monoclonal antibodies (mAbs) therapy is a new standard of care for advanced non-small-cell lung cancer (NSCLC) patients, although only a small subset of patients significantly benefits from this therapy. Derived neutrophil-to-lymphocyte ratio (dNLR) is an emerging marker of response to ICB in NSCLC. However, its accuracy as predictive biomarker of response to immunotherapy in elderly NSCLC patients has not been explored so far. We therefore decided to evaluate dNLR among elderly NSCLC patients treated with anti PD-1 therapy.

Patients and methods: This is a retrospective cohort study of NSCLC patients treated at seven Italian institutions. Inclusion criteria were: diagnosis of advanced or metastatic NSCLC, age ⩾75 years and treatment with anti-PD-1 mAbs (nivolumab or pembrolizumab) in first or subsequent lines. dNLR was calculated with the following formula: ANC/(WBC-ANC). A dNLR⩾3 was defined as high and indicative of increased risk of disease progression and death. The primary end-point was to assess the impact of dNLR on disease-free and overall survival (DFS and OS).

Results: From July 2015 to December 2017, 72 patients were included in the analysis. Mean age was 78 years (75-86). Sixty patients (83.0%) were males. ECOG PS was 0-1 for 49 out of 72 patients (68.0%). Squamous and non-squamous histologies were diagnosed in 27 (37.5%) and 45 cases (62.5%), respectively. Nivolumab represented the most used agent (80.5%), being second or advanced lines the prevalent settings (59/72, 81.9%). A dNLR⩾3 was found in 21 out of 72 patients (29.2%). After a median follow-up of 6.4 months (1.7-25.5), disease progression occurred in 44 patients (61.1%) and 36 tumor-related deaths (50.0%) were observed. Median PFS were significantly lower in the dNLR⩾3 group as compared to dNLR<3 group (8.9 vs 2.8 months; HR 0.54, 95% CI 0.29 - 1.00; p=0.049). No difference in terms of OS was found between the two groups.

Conclusions: An elevated pre-treatment dNLR could be an independent prognostic biomarker for PFS in elderly patients with advanced NSCLC treated with anti-PD-1 immunotherapy. These preliminary results need to be confirmed in a larger cohort of elderly NSCLC patients.

D27

COST-CONSEQUENCE ANALYSIS OF THREE DIFFERENT DIAGNOSTIC STRATEGIES IN THE FIRST- AND SECOND-LINE TREATMENT OF LOCALLY ADVANCED OR METASTATIC NON-SMALL-CELL LUNG CANCER

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Background: Unlike the tissue one, liquid biopsy is a less invasive diagnostic method for the assessment of possible mutations of the tumor, based on the analysis of circulating free DNA (cfDNA) present in the plasma component of the blood. Because blood samples are easily obtainable, plasma biopsy is a non-invasive method, supplementing the more traditional biopsy techniques.

A cost-consequence analysis (CCA) was conducted to compare the adoption of three different diagnostic strategies in the first- and second-line treatment of locally advanced or metastatic (mNSCLC): i) tissue strategy (only tissue biopsy for first and second line); ii) combined strategy (first line: tissue biopsy, if its outcome is unknown proceed with liquid biopsy; second line: liquid biopsy, if its outcome is negative proceed with tissue biopsy); iii) potential strategy (first line: tissue biopsy and liquid biopsy for tissue ineligible patients, if the outcome of tissue biopsy is unknown proceed with liquid biopsy; second line: liquid biopsy, if its outcome is negative proceed with tissue biopsy).

Methods: A decision-analytic model was developed considering the Italian NHS's perspective. We only evaluated direct medical costs (tissue biopsy, management of complications associated with tissue and liquid biopsies) borne by the NHS. The CCA was conducted over a time horizon of 1 year, assuming that for each patient with mNSCLC the diagnostic pathway ends within such period. Key variables were tested in the sensitivity analysis.

Results: The results of the model are shown in: number of correctly identified cases, the total cost of the strategy and average cost per correctly identify cases. Considering both the first and the second line of treatment, the potential strategy constitutes the cost-effective alternative, characterized by an average cost per correctly identified case (€ 685) lower than that estimated for the combined strategy (€ 732) or for the tissue strategy (€ 1,004). The potential strategy remains cost-effective, also considering the results referred to the first- or second-line treatment only.

Conclusion: The choice of a correct diagnostic strategy is crucial in order to optimize cancer therapies in the first- and second-line treatment of mNSCLC. The addition to the diagnostic pathway of the liquid biopsy would

correctly identify a greater number of cases, supporting the prescription of the most effective oncological therapy.

D28

HIGH BLOOD SERUM AMYLOID (SAA) PREDICTS RESISTANCE FROM FIRST-LINE PEMBROLIZUMAB (P) IN PATIENTS (PTS) WITH ADVANCED NON-SMALL-CELL LUNG CANCER (ANSCLC)

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Background: In cancer pts, including those affected by ANSCLC, blood SAA level reflects not only the liver production but also the direct synthesis by tumor cells. In melanoma pts, SAA inhibits the anti-tumor immune response by the expansion of anti-inflammatory IL-10-secreting neutrophils. We aimed to investigate the potential role of SAA as resistance factor from P in pts with ANSCLC.

Patients and Methods: From September 2017, pts with ANSCLC (PD-L1⩾50%) receiving upfront P at our institution, were prospectively evaluated for baseline blood SAA before starting treatment. Disease progression (PD) to P was assessed according to Immune-related Response Evaluation Criteria in Solid Tumors (IrRECIST). The most accurate SAA cut-off to predict PD was established with a ROC-analysis.

Results: We enrolled 26 consecutive pts. Pts characteristics: male/female (81/19%), number of sites <3/= 3 (30/70%), ECOG PS 0/= 1 (42/58%); smokers/never or former smokers (50/50%); median age 70.5 (range 35-86) years. After a median follow-up time of 4.9 months, 14/26 (54%, 95%CI 34.6-73.0) pts had an early PD, while 4 partial responses (15%) and 8 stable disease (31%) were observed. No relationship between baseline SAA and PD-L1 was found (rho=0.0089, *p=0.979*). Baseline SAA was significantly higher in pts experiencing an early PD (93.3 ng/ml, 95%CI 14.7-188.4) than in those achieving disease control (10.5 ng/ml, 95%CI 5.17-28.6) (*p=0.03*). Adopting the ROC-derived cut-off (12.6 mg/L, AUC 0.75, 95% CI 0.54-0.90, *p=0.01)*, 6-months progression-free-survival (PFS) rate was significantly reduced in pts with high SAA in comparison with those having lower level (8%, 95% CI 0-24 vs 71%, 95% CI 43-99;*p=0.01*). A correlation between SAA higher than the fixed cut-off and early PD was found (Odds Ratio 11, 95%CI 1.77- 68.3, *p=0.01).* At multivariate analysis, a trend towards significance for SAA as independent predictive factor of PD *(p=0.055*) and PFS was found (*p=0.051*); PD-L1 expression as continuous variable significantly predicts PD (*p=0.03*).

Conclusion: High baseline SAA represents a potential resistance factor to 1st line P in ANSCLC pts, predicting early progression and worse 6-months PFS rate. This prospective study is currently ongoing and the sample size will be enlarged with external pts series to increase the power.

D29

ANTIBIOTIC USE BEFORE PEMBROLIZUMAB AS FIRST LINE TREATMENT IN NON-SMALL CELL LUNG CANCER (NSCLC): EXPERIENCE OF MODENA CANCER CENTER

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Background: Immune checkpoint inhibitors induce clinical response in NSCLC, but primary resistance develops in about half of patients. Gut microbiome may have a role in the development of resistance and growing evidences suggest that it may be altered by antibiotics administration prior to immunotherapy. This study evaluates the impact of antibiotic therapy (AT) on survival in patients with stage IV NSCLC treated with programmed death-1 (PD-1) inhibitor pembrolizumab as first line treatment.

Material (patients) and methods: We performed a retrospective review of stage IV NSCLC patients treated with pembrolizumab at our Institution between July 2017 and February 2018. We evaluated antibiotic exposure within 4 weeks before initiating immunotherapy. Patients with performance status (PS) ⩾2 according to Eastern Cooperative Oncology Group (ECOG) were excluded. Primary outcome was overall survival (OS), secondary outcomes were progression-free survival (PFS) and time to treatment failure (TTF).

Results: A total of 21 Caucasian patients were included in the analysis. Median age at diagnosis was 69 years old (range 49-81 years old). The majority of patients were male (66.7%), had adenocarcinoma histology (71.4%),

and were active smokers at time of diagnosis (57.1%). 61.9% of patients had a PS 1. All patients had PD-L1 expression ⩾60%. 4 patients (19%) received antibiotics (penicillin or cephalosporin) prior to pembrolizumab. At data cut-off, 7 patients (33.3%) were still on treatment and none of them had received antibiotics prior to immunotherapy. Patients treated with antibiotics had worse OS compared to patients who did not received AT (median OS 4.23 months vs 5.65 months). Median PFS and TTF were also inferior with antibiotic use (PFS 3.76 months vs 4.88 months and 2.93 months vs 4 months, respectively).

Conclusions: Although this is a small retrospective study, its peculiarity is that it evaluates exclusively patients treated with pembrolizumab in first line and with a good PS. No statistically significant differences were noted probably due to small number of cases. In this subgroup of patients, our results are consistent with other evidences that suggest that the alteration of gut microbiome induced by antibiotics may reduce immunotherapy efficacy.

D30

METRONOMIC ORAL VINORELBINE FOR THE TREATMENT OF ADVANCED NON-SMALL-CELL LUNG CANCER: A MULTICENTER RETROSPECTIVE ANALYSIS

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Background: Metronomic oral vinorelbine (MOV) could be a treatment option for unfit patients with advanced non small cell lung cancer (NSCLC) based on its safety profile and high patient compliance.

Patients and Methods: We retrospectively collected data on 245 patients (median age 76[range 48-92]yrs, M/F 184/61, PS 0(22)/1(100)/⩾2(123), median of 3 serious comorbidities) with stage IIIB-IV NSCLC treated with metronomic oral vinorelbine as first(T1) (67%), second(T2) (19%) or subsequent(T3) (14%) line. Schedules consisted of vinorelbine 50mg (129), 40mg (55) or 30mg (61) three times weekly continuously.

Results: Patients received an overall median of 6 [range 1-25] cycles with a total of 1133 cycles delivered. ORR was 17.9% with 42 partial and 2 complete responses, 107/245 experienced stable disease >12 weeks with an overall clinical benefit of 61.6%. Median overall time to progression was 5 [range 1-21] months (T1 7[1-21], T2 5,5[1-19] and T3 4[1-19]months) and median overall survival 9 [range 1-36] months (T1 10[1-31], T2 8[1-36] and T3 6,5[2-29]months). Treatment was extremely well tolerated with 2% (23/1133) G3/4 toxicity (mainly G3 fatigue and anemia) and no toxic deaths. We observed longer OS 14[range 7-36]months in a subset of squamous NSCLC patients receiving immunotherapy after metronomic oral vinorelbine.

Conclusions: MOV confirmed as an extremely safe treatment in a larger patient population of advanced NSCLC with an interesting activity mainly consisting in long-term disease stabilization. We could speculate a synergistic effect with subsequent immunotherapy.

D31

PROGNOSTIC AND PREDICTIVE ROLE OF HYPONATREMIA IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH IMMUNOTHERAPY

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Background: In metastatic non-small cell lung cancer (mNSCLC), immunotherapy (IO) significantly improved patients (pts) outcomes. Hyponatremia is a common finding in cancer pts, and it has been associated with poor clinical outcomes in mNSCLC. In this study we aimed at assess the predictive and prognostic role of hyponatremia in pts with mNSCLC treated with IO.

Methods: We retrospectively reviewed all pts with mNSCLC treated with IO at our institution and collected demographics, clinical and pathological data of pts with at least one instrumental response assessment and the availability of baseline serum sodium. Hyponatremia was defined as the presence of serum sodium values below institutional lower limits of normal (i.e. < 136 mEq/l). Chi-square test or Fisher's exact test were used to analyze the association between hyponatremia and pts' characteristics. The Kaplan-Meier method and the Cox proportional-hazards model were used for survival analyses. The reverse Kaplan-Meier method was used for follow-up quantification.

Results: Baseline hyponatremia was observed in 15 (10%) out of 149 pts included and was not associated with any evaluated pts' characteristic (gender, age, smoking status, ECOG PS, histology, PD-L1 status, number of previous treatment lines and number of metastatic sites). Disease control rate and response rate did not significantly differ between the two groups. With a median follow-up of 28.6

months, the presence of baseline hyponatremia was associated with a poorer median overall survival (OS) (5.1 vs 13.1 months, HR 2.10, 95% CI 1.10-3.90, $P = .02$). In the multivariable model including the only other covariate significantly associated with survival (ECOG PS), hyponatremia was confirmed to be independently associated with poorer OS (HR 2.23, 95% CI 1.18-4.21, $P = .01$). Median progression-free survival (PFS) was 2.3 and 3.5 months for pts in the hyponatremia and control group, respectively (HR 1.90, 95% CI 1.10-3.40, $P = .02$). In the multivariable model (including ECOG PS and PD-L1 status), hyponatremia failed to be independently associated with PFS.

Conclusions: In our study, baseline hyponatremia significantly impaired OS in mNSCLC pts treated with IO. Even if hyponatremia conferred a poor PFS at univariate analysis, it failed to confirm its independent predictive role in the multivariable model. Based on our findings, the role of hyponatremia as prognostic and predictive factor in this setting warrants further investigation.

D32

EVALUATION OF PATTERN OF RESPONSE IN PATIENTS WITH STAGE IIIB-IV NSCLC TREATED WITH NIVOLUMAB IN TWO ONCOLOGY UNITS

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Background: Immune checkpoint inhibitors represent a real breakthrough in non-small cell lung cancer (NSCLC) treatment. However, a novel challenge for oncologists is the evaluation of new patterns of radiological response such as pseudoprogression and hyperprogression. Clinicians have to be careful in the management of treatment and consider also clinical benefit and individual patients' features.

Methods: The aim of our analysis was to evaluate the pattern of response in a cohort of patients with stage IIIB-IV NSCLC treated with nivolumab in two different oncology units, with special focus on pseudoprogressive and hyperprogressive diseases. According to iRECIST criteria and RECIST 1.1 criteria, we performed radiological evaluations and compared the pattern of response with clinical benefit.

Results: We retrospectively observed 54 patients with NSCLC stage IIIB and IV, treated with nivolumab, in second-line (36 pts) or further line treatment (18 pts), between December 2015 and December 2017 (36 males and 18 females); they were considered for radiological review, made by a senior and a junior radiologists. The cohort was composed of 26 adenocarcinomas and 28 squamous cell carcinomas, 15 patients were stage IIIB and 39 stage IV. The best objective response was partial response in 10 cases (18%), stable disease in 15 (28%) and progression disease in 29 (54%). No complete response was observed. Pseudoprogressive diseases were observed in 3 patients (5%). Only one patient (2%) experienced hyperprogressive disease with an increase in tumour burden of more than 50%, associated with a worsening of clinical conditions. According to iRECIST criteria, 31 patients experienced an unconfirmed progressive disease at the first evaluation. In this population, performance status was preserved in 16 patients and treatment was continued because of clinical benefit.

Conclusion: Atypical patterns of response to nivolumab occurred in NSCLC. Pseudoprogression and hyperprogression represent a relevant challenge in clinical practice and there is a strong need of collaboration between clinicians and radiologists with great expertise. Interestingly, a discrepancy between clinical benefit and radiological response was frequently observed at the first evaluation and clinicians have to be careful regarding treatment discontinuation, in presence of clinical benefit.

D33

THE ROLE OF COMPUTERIZED TOMOGRAPHY TEXTURE ANALYSIS AS BIOMARKER OF BENEFIT FROM NIVOLUMAB IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: While immune checkpoint inhibitors (ICIs) have revolutionized the management of advanced non-small cell lung cancer (NSCLC), response assessment is a challenging task. Indeed, due to the peculiar mechanism of action of ICIs, the currently employed response evaluation criteria based on dimensional assessment might underestimate their activity. Computerized tomography texture analysis (CTTA) is an emerging approach belonging to the field of "radiomics" and based on the analysis of quantitative data extracted from imaging features; recently, correlations between CTTA and histopathologic as well as molecular characteristics of solid tumors were observed. Our aim is to determine whether parameters derived from CTTA might be used to assess the benefit from ICIs in advanced NSCLC.

Methods: Among 74 patients (Pts) treated with nivolumab for advanced NSCLC, 35 had CT scans evaluable for CTTA and had undergone at least two assessments (at baseline and after 4 cycles). Each pulmonary lesion was evaluated by a radiologist experienced in CTTA, blinded to clinical and temporal data; 295 texture analysis parameters were obtained from each image using an open source software (MaZda, version 4.6). The variations of parameters derived from pre-set gray-level co-occurrence matrices (GLCM) before and after 4 cycles of nivolumab were determined and compared with clinical outcomes. Statistical analyses were performed using MedCalc Statistical Software (version 18).
Results: After a median follow up of 9.9 months, variations of GLCM features describing entropy were directly associated with overall survival (OS). Most notably, Pts with increase of entropy above the median value between baseline and the subsequent CT scan identified with a specific GLCM combination had longer OS (15.3 vs. 6.2 months; p= 0.044). This finding suggests that increased tissue heterogeneity during treatment, possibly caused by immune cells infiltration, might be associated with improved outcomes.
Conclusion: CTTA might have a prognostic/predictive role during treatment with ICIs for NSCLC. Further analyses including clinical and histopathologic features are currently ongoing, in order to enlighten the biological mechanisms at the basis of our observations.

D34

NSCLC, IMMUNOTHERAPY AND PERIPHERAL BLOOD BIOMARKERS AS PREDICTOR OF RESPONSE: A RETROSPECTIVE STUDY FROM A SINGLE CENTER EXPERIENCE

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Background: Peripheral blood biomarkers (PBBs) as predictor of response to immunotherapy (IO) in Non-small cell lung cancer (NSCLC) is an emerging field, easy and costly. The aim of this study is to explore the role of these complete blood biomarkers (CBC) in clinical practice in patients (pts) treated with anti-programmed death-1 (anti-PD-1) in NSCLC.
Material and Methods: we analysed data from119 pts a single cancer center: squamous/non-squamous (46/73). We collected CTC results at baseline (within two weeks from IO start), after 1st (for 112 pts) and 2nd course of anti-PD-1 (for 103 pts). Univariate analysis using Kaplan Maier were performed and also adjusted cox progression analysis to estimate correlation between survival and PBBs.
Results: median age were 67 years (y), (31-86 y), male/female (80.7%/19.3%), most were smokers (79%), and Eastern Cooperative Oncology Group (ECOG) were 0-1 in 63% and 2 in 37%. Median progression-free survival (mPFS) and overall survival (mOS) were: 3.8 months (mo) and 9,6 mo, respectively. Only 38% of pts performed anti-PD-1 in 2nd line, while the remaining performed it in 3rd, 4th or further line. Worse PFS (3.2 vs 4.5 mo, p=0.05) were seen in pts with baseline absolute neutrophil count (ANC) $\geqslant$ 7500/μL. Neutrophil to lymphocyte ratio were evaluated at baseline, after 1 and 2 IO-courses and NLR$\geqslant$5 correlate with a worse PFS (HR 1.9, p=0.004, HR 3.2 p$<$0.0001, HR 1.76 p=0.03, respectively) and in a multivariate analysis its role especially after one IO-cycle seems to be an independent negative factor predictor (p=0.05). An emerging role were seen for monocyte count (AMC) $\geqslant$1000/μL which seems to correlate with a worse PFS (HR 2.19, p=0.002). Also in pts with lymphocyte monocyte ratio (LMR)$\geqslant$1,5 after one course IO were observed a better survival 5.6 vs 2.8 mop$<$0.001 and adjusted analysis confirmed its positive predictive role (HR 0.34, p$<$0.001).
Conclusion: This is a retrospective study which demonstrated the role of PBBs in clinical practise and especially the role ofNLR and LMR as predictor biomarkers of response to IO. Prospective studies are need to validate their role in NSCLC pts treated with anti-PD-1 drugs.

D35

THE DISCRIMINATIVE VALUE OF COMPUTED TOMOGRAPHY (CT) RADIOMIC FEATURES FOR METASTATIC NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH IMMUNOTHERAPY: A FEASIBILITY STUDY

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Background: Radiomic's goal is developing models to predict response in a non-invasive manner, extracting quantitative imaging features not visually detectable. Texture analysis of CT images has potential for enabling differentiation between lesion with various pathologic characteristics. The purpose of this preliminary study is to evaluate the reliability of correlation between texture

feature of CT images and clinical and radiological disease progression of advanced NSCLC patients treated with immunotherapy.

Materials and methods: 13 patients treated with nivolumab after failure of first line platinum-based chemotherapy were evaluated. All patients underwent CT scan at the beginning of the treatment and every 4 cycles of nivolumab treatment. CT protocols were set in order to guarantee homogeneity of acquisition and reconstruction parameter. CT data were collected to extract radiomic features from primary and secondary lung cancer lesions. All tumor lesions were manually segmented and texture feature were extracted using LIFEX (www.lifexsoft.org), an open access software. Than we assigned clinical score to classify patients performance status and a radiological score to characterize lesion progression. Statistical analysis of texture results was performed using R, an open access software. Texture features were correlated with clinical and radiological scores.

Results: The results of the statistical analysis are in good agreement with macroscopic radiological characteristics, as tumor volume and shape. Moreover, the differential analysis of our data suggests a set of texture parameters, not evaluable by classical radiologic criteria, associating with the response to the therapy (e.g. Entrophy)

Conclusions: To optimize patient specific therapeutic strategy, the development of a model which enables treatment response stratification in patients with similar prognosis can be very useful. According to RECIST criteria (increment of tumor diameter) some patients are characterized by disease progression, while clinical status improves (pseudo-progression). Even immune-related RECIST criteria rarely identify the true responders. The addition of radiomic features to the radiological evaluation and to clinical factors (including patient performance status) may have a higher discriminative power in response evaluation to immunotherapy, contributing to better therapeutic decision for individual patients. Further studies are warranted to confirm these interesting preliminary data.

D36

DETECTION OF EGFR MUTATIONS IN PLASMA CELL-FREE DNA BY THREE METHODOLOGIES, DIGITAL PCR, PANAMUTYPER AND THERASCREEN, IN EGFR-TKI TREATED ADVANCED NSCLC PATIENTS

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Background: Among advanced non-small cell lung cancer (NSCLC) patients with acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI), about 50% carry the T790M mutation. Circulating cell-free tumor DNA (cftDNA) in plasma has emerged as a specific and sensitive blood-based biomarker for detection of EGFR mutations. Although several methodologies are available to detect EGFR mutations from cftDNA, there is not a widely accepted and approved methods for cftDNA analysis.

Material and Methods: We monitored EGFR mutations in plasma samples of 31 NSCLC patients treated with EGFR-TKI, at baseline and serially, during the treatment with EGFR-TKIs (baseline, 8 days and 20 days after treatment, clinical evaluation and progression). We compared the ability of three technology platforms, Therascreen EGFR Plasma RGQ PCR Kit-QIAGEN, QuantStudio 3D Digital PCR System-Thermo Fisher Scientific and PANAMutyper EGFR-PANAGENE, to detect EGFR mutations (L858R, exon 19 deletion, T790M) in cftDNA from NSCLC patients. Furthermore, we evaluated the sensitivity and specificity of each method and we compared at baseline time point the results of tumor tissue with those of plasma cftDNA.

Results: For L858R and T790M EGFR mutations, there were no differences between the three methods. Instead, the comparison Digital PCR versus PANAMutyper have shown a higher overall concordance rate (80%) respect to Digital PCR versus Therascreen (60%) and Therascreen versus PANAMutyper (70%) for Del19 EGFR mutation. The specificity was 100% for all three methods for all three mutations. Sensitivity for L858R and T790M were the same in the three methods (42.86%). Sensitivity for Del19 were different for the three methods (Therascreen 45%, Digital PCR 85% and PANAMutyper 75%). Del19 with Digital PCR showed the highest diagnostic sensitivity. Concordance rate between plasma cftDNA and tissue samples for all mutations was: 46.4% for Therascreen, 75% for Digital PCR, and 67.8% for PANAMutyper. L858R mutation showed a concordance rate of 42.86% for the three methods; Del19 was of 45%, 85%, 75% for Therascreen, Digital PCR and PANAMutyper, respectively; T790M was of 100% for all three methods.

Conclusions: Digital PCR, compared to other methods would be more suitable for quantification of samples in a longitudinal way, allowing to better monitor the evolution of mutations over time. Furthermore, Digital PCR showed best correlation data with tissue and highest sensitivity.

D37

HIGH-GRADE TREATMENT-RELATED ADVERSE EVENTS IN NON-SMALL-CELL LUNG CANCER PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITOR: A RETROSPECTIVE OBSERVATIONAL STUDY IN A "REAL LIFE" POPULATION

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Background: Immune checkpoint blockade (ICB) is a dominant strategy for treating locally advanced or metastatic non-small-cell lung cancer (NSCLC). Phase III studies demonstrated that ICB improves overall survival (OS) with a lower incidence of adverse events (AEs) than chemotherapy. According to the literature 10% of patients experience high grade immune related adverse events (IrAE). The aim of the study is to determine the percentage of IrAEs in a real-life population and assess whether the incidence of IrAEs is of the same order of magnitude of that observed in clinical trials.

Patients and methods: We retrospectively analyzed a cohort of patients with advanced NSCLC who received nivolumab or pembrolizumab between 2015 and 2018. We measured the incidence of TRAEs graded according to the common terminology criteria for adverse events (CTCAE) version 5.

Results: We collected data from 118 patients with advanced NSCLC, 70% of whom with stage IV. Thirty patients (25%) had squamous histology, 88 (75%) had non-squamous tumors. Seventy-nine patients (67%) received nivolumab in second line, 39 (34%) received pembrolizumab, of whom 25 (65%) received pembrolizumab as first-line, and 14 (35%) as second-line. Fifty-eight patients (50%) developed AEs of any grade (36% G3 or more). Among patients who developed high grade AEs, drug was discontinuedin 79%, and 21% of deaths was observed. In patients receiving nivolumab, 9 (11%) experienced AEs of G3 or more. Of these, two patients developed pneumonitis. In patients receiving pembrolizumab in first line 9 (36%) experienced AEs of G3 or more. Of these, 6 (66%) developed pneumonitis.

Conclusions: The current retrospective analysis demonstrates that in a real-life population, the percentage of IrAE is higher than that reported in phase III clinical trials. These results call for confirmation in a larger cohort of patients to correlate IrAEs with the clinical characteristics of the patients.

D38

ESTIMATING RENAL FUNCTION IN A COHORT OF OLDER PATIENTS WITH NON SMALL CELL LUNG CANCER: A COMPARISON OF THREE METHODS

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Background: With the increasing of age about 70% of patients have a progressive reduction in renal mass and function. The evaluation of renal function in older patients is however, somewhat complex. Several formulas have been developed to estimate the creatinine clearance however most of them are not validated in elderly patients. We therefore evaluated the relationship and the impact of there different measure of CrCl in a cohort of patients with advanced lung cancer (NSCLC).

Methods: This is a retrospective cohort study. Inclusion criteria were: diagnosis of advanced or metastatic NSCLC, age $\geqslant$70 years and treatment with Platinum based chemotherapy or monotherapy in first line setting; PDL-1 status $<$ 1%, EGFR wild type and no ALK rearrangement. Three formulas were used to estimate CrCl: Cockroft-Gault (C-G), MDRD and CKD-Epi. The primary end-points were to evaluate the concordance between the three methods and the impact of their values on treatment toxicity and discontinuation of treatment.

Results: 152 patients were evaluated. Mean age was 76 (70-89, SD 4.1). Mean number of drugs was 4,56 (0-14, SD 2.96), with a median CIRS-G score and index of 4 and 2 (range 0-11 and 0-8 with SD 2.49 and 0.42) respectively. 6 (2.6%) and 56 (37%) patients had some form of disability in ADLs e IADLs. Mean values of creatinine clearance according to C-G, MDRD and CKD-Epi were: 67.8 (20-149), 86.7 (29-168), 76.2 (26-106) ml/min. ECOG PS was 0-1 for 148 out of 152 patients (97 %). Squamous and non-squamous histologies were diagnosed in 42 (28 %) and 110 cases (72%), respectively. Monotherapy with Gemcitabine/Vinorelbine represented the most used regimen (99/152, 65%). Median number of cycles administered was 3.9 (1-11, SD 1.74). 79 patients (52%) had dose reduction and 52 (34%) had premature treatment discontinuation. Grade 3/4 hematological and no hematological toxicity occurred in 19 (12%) and in 5 (3%) patients. Correlation between the three methods was: C-G/MDRD 0.77; C-G/CKD/Epi 0.76; MDRD/CKD-Epi 0.94 (p 0.0001). Low correlation and no impact on dose reduction or treatment discontinuation was found at regression analysis.

Conclusions: In our series we found a good correlation between three different methods to estimate creatinine clearance, especially between MDRD and CKD-Epi. No impact on treatment outcomes was found.

D39

WEEKLY IRINOTECAN (CPT11) AS THIRD-LINE CHEMOTHERAPY IN PATIENTS WITH SMALL CELL LUNG CANCER (SCLC)

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The role of salvage chemotherapy still remains controversial in SCLC.

The aim of this study was to evaluate the activity and safety of weekly CPT11 in SCLC previously treated with two chemotherapy lines.

Methods: Patients with histologically documented SCLC previously treated with two chemotherapy lines were eligible for the study.

All patients received CPT11 100 mg/m2/ week.

Results: The study enrolled 19 patients: 14 (74%) had distant metastases whereas 5 (26%) had disease localized to the chest. All of the patients had received Cisplatin or Carboplatin + VP 16 as first-line treatment. Two patients (10%) had partial response to treatment, eight patients (40%) had stable disease or minor response at the time of first re-evaluation, whereas nine patients (50%) had progressive disease. The median time to progression was 5 months (range 2-9) and the median survival was 7 months (range 3-11). No patients developed grade 4 toxicity. Grade 3 neutropenia occurred in 3 patients and grade 3 anemia in 4 patients. Grade 3 diarrhoea occurred in 2 patients. Grade 3 fatigue/asthenia occurred in 5 patients. No treatment-related death was reported. Quality of life (EORTC-C30) was maintained relatively well, reflected by the fact that there were no significant differences between the mean global quality of life scores at baseline and the 3 and 5.

Conclusions: The study suggest that weekly CPT 11 in effective and well tolerated, and may prolog survival with a relatively good quality of life in patients with SCLC previously exposed to two chemotherapy lines.

D40

METRONOMIC ORAL VINORELBINE: AN ALTERNATIVE SCHEDULE IN ELDERLY AND UNFIT PATIENTS WITH LOCALLY-ADVANCED AND METASTATIC NSCLC NOT-ONCOGENE ADDICTED?

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Background: MILES and ELVIS study showed that vinorelbine is one of the best option in elderly patients with advanced NSCLC. Oral vinorelbine at standard schedule (60 – 80 mg/m²/weekly) documented good activity in terms of response rates and progression-free survival (Jassem et al 2001). In the last years, a metronomicchedule of oral vinorelbine (40 – 50 mg/m² three times a week, continously) has been studied in phase II trials, especially in unfit and elderly patients. In MOVE trial (Camerini et al, 2015), metronomic oral vinorelbine documented a clinical benefit (PR + SD > 12 weeks) in 58% of patients with mild toxicity. On these bases, we thought to start a phase II study with metronomic oral vinorelbine in elderly (over 70 years) or unfit (ECOG 2 with co-morbidities) locally-advanced and metastatic NSCLC patients. Primary aims were Clinical Benefit (PR + SD = 6 months) and Toxicity; secondary aims were Progression-free survival and Overall survival.

Material and methods: to date 16 patients entered the study: 8 locally-advanced and 8 metastatic NSCLC (5 squamous and 11 adenocarcinoma). All patients were not-oncogene addicted (EGFR mutations, ALK translocation, and PDL-1 expression were tested for adenocarcinoma; PDL-1 expression was tested for squamous). Median age was 81 years (range 44 – 90). ECOG 0 in 7 pts, 1 in 5 pts and 2 in 4 pts. Oral vinorelbine was administered at the dose of 40 mg/m²/three times a week continously.

Results: Clinical Benefit was achieved in 6 pts (37.5%). Objective responses were as follow: Partial Remission in 3 pts (21%), Stable Disease in 4 pts (29%), Progressive Disease in 4 pts (29%). 3 pts were not evaluable for response (21%) and 2 pts are still ongoing. Progression-free survival was 4 months; Overall survival is not still evaluable. Toxicity was mild: no patient experienced grade 2-3 neutropenia or piastrinopenia; 1 pt gr. 3 asthenia, 1 pt gr. 2 asthenia, 1 pt gr. 2 mucositis, 1 pt gr. 2 diarrhoea, 1 pt gr. 2 anorexia. In 3 pts the dose was reduced to 30 mg/m²/three times a week.

Conclusions: These preliminary results confirmed activity and safety of metronomic oral vinorelbine in patients with "wild type" locally-advanced and metastatic NSCLC not suitable to be treated with standard iv chemotherapy, allowing a comfortable home therapy and avoiding several hospital visits to patients.

D41

IMPACT OF DNLR ON TREATMENT OUTCOME IN NSCLC PATIENTS RECEIVING SALVAGE CHEMOTHERAPY AFTER PD-1/PD-L1 INHIBITORS

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Background: Immune checkpoint inhibitors (ICI) are effective in advanced non-small lung cancer (aNSCLC) patients (pts). Pretreatment derived neutrophils/(leukocytes – neutrophils) ratio (dNLR) is associated with outcome to ICI in aNSCLC. We investigated the predictive and prognostic role of dNLR and previous irAEs in pts receiving salvage chemotherapy (Cx) following ICI.

Materials and Methods: We retrospectively collected clinical data from aNSCLC pts receiving salvage Cx after ICI at our Center from January 2013 to January 2018. dNLR at different time points was analyzed. The previously identified cutoff of 3 was used to define low (L) versus high (H) dNLR. R software was used for statistical analysis.
Results: 24 (20%) out of 118 pts received ⩾1 line of Cx following 2nd ± line ICI. Median follow up was 32.5 months (m) since diagnosis, 17 m since starting ICI. Any grade immune-related adverse events (ir-AEs) occurred in 13 (54%) of pts, mainly low grades (85% G1-2). 22 pts (92%) had L-dNLR pre- ICI; 7 pts (29%) had L-dNLR pre-salvage Cx. 6 (67%) pts with H-dNLR at the end of ICI had received steroids for ir-AE. Median Overall Survival (mOS) was 20m (17m-NA) from aNSCLC diagnosis, 10m (6m-NA) from ICI, 3m (3m-NA) from 3rd ± line Cx. Median Progression Free Survival (mPFS) from ICI was 4m (2-6m), from 3rd ± line Cx was 2m (2-5m). In univariate analysis, L-dNLR pre-ICI and ir-AEs were associated with prolonged OS (respectively 10 vs 4.5 m, p=0.035, and 12 vs 5 m, p=0.025) and PFS (respectively 4.5 vs 1.5 m, p=0.048, and 5 vs 2 m, p=0.021) to ICI, whereas L-dNLR before starting salvage Cx was associated with prolonged OS and PFS to 3rd ± line Cx (7 vs 3 m, p=0.05, and 5 vs 2 m, p= 0.009, respectively). The latter was confirmed as independent prognostic factor for PFS to 3rd ± line Cx in multivariate analysis.
Conclusions: Our retrospective study evaluates a prognostically favorable subgroup of aNSCLC pts. Though the small sample size, we showed a possible role of dNLR in predicting treatment outcome of pts receiving salvage Cx following ICI agents. The predictive and prognostic role of dNLR to each treatment line will be further investigated in a larger cohort.

D42

THE HARD CHOICE OF THE SECOND-LINE CHEMOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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Background: Malignant pleural mesothelioma (MPM) is a poor-prognosis tumor that correlates with asbestos exposure. Despite therapeutic progresses, international guidelines did not define a standard second-line treatment. The aim of this study is to define the role of second-line treatment and the possible advantage of a chemotherapy agent compared to others in terms of outcome, evaluating a real-life series.

Material and methods: This monocentric, retrospective analysis included patients treated for MPM at Medical Oncology Department of Ospedali Riuniti di Ancona-Università Politecnica delle Marche (Italy) between January 2003 and December 2017. Overall survival (OS) was calculated from date of histologic diagnosis to death or last follow-up visit, while progression free survival (PFS), evaluated after first- (PFS1) and second-line treatment (PFS2), was calculated from chemotherapy treatment's start to disease progression or death. PFS and OS were estimated using Kaplan-Meier method. The Cox multivariate proportional hazard regression model was used to detect the effects of clinical and laboratory parameters on OS and PFS.
Results: 97 patients were included. All patients were treated with first-line chemotherapy (mOS=16 months; range 1.1-132 months). We found a significant correlation between OS and histology: median OS was 21.4 months for epithelioid subtype vs 7.8 months for sarcomatoid subtype vs 10.4 months for biphasic subtype, P<0.0001. Median PFS1 was 5.4 months (range 0.5-56). No difference was found between cisplatin and carboplatin in association with pemetrexed in first-line setting: mOS was 17 vs 14.8 months respectively (P=0.4). 55.6% of the sample underwent a second-line chemotherapy, predominantly gemcitabine-based. Median PFS2 was 3.3 months (range 0.5-92). Subjects who performed second-line chemotherapy showed a longer survival (19.1 vs 12.1 months P=0.01: HR 0.58: CI 0,3242-0,8775). No statistical difference of OS and PFS2 was found stratifying patients according to the second-line regimen (pemetrexed vs gemcitabine-based chemotherapy with mOS: 24.4 vs 19.7 months respectively, P=0.45 and for PFS2 5.6 vs 2.1 months respectively, P=0.10).
Conclusions: We demonstrated a benefit on survival in those patients receiving a second-line chemotherapy for MPM independently by the schedule. We confirmed the prognostic and predictive role of histology in patients treated by first- and second-line chemotherapy for MPM, according to literature data.

D43

PREVALENCE AND EVOLUTION OF RENAL CYSTS IN PATIENTS TREATED WITH CRIZOTINIB IN OUR CENTRE

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Background: Anaplastic Lymphoma Kinase (ALK) gene rearrangement is found in approximately 6.7% of patients (pts) with Non small cell lung cancer (NSCLC). Crizotinib is an inhibitor of ALK and several receptor tyrosine kynases, including MET and ROS1. Among the side effects (SE), renal cysts (RC) are found in 4 % of pts during Crizotinib treatment in clinical trials. These pts generally do not require dose reductions, nor permanent discontinuation and most of them continue treatment with clinical benefit. The aim of our study is to assess the prevalence and the evolution of complex renal cysts (CRC) in pts treated with Crizotinib in our center, exploring the impact on drug administration.
Patients and methods: We conducted a retrospective radiological analysis of RCs of all pts with stage IV NSCLC treated with Crizotinib in our institution between 01/2013 and 04/2018. The analysis was performed with computed tomography CT scan by two independent radiologists. The morphological classification of RCs was assessed using Bosniak criteria and we considered as significant only dimensional decrease/increase greater than 3 mm in diameter. Pts clinical characteristics, tumor stage and outcomes were evaluated.
Results: Among 33 pts eligible for this analysis, 12 were males and 21 females, with median age 56 years. 29 pts were ALK rearranged, 2 ROS-1 rearranged and 2 MET mutated. Median follow-up was 7.6 months (mo). RCs at baseline were found in 16 pts (48,4%); in 13 of them (81,2%), RCs remained stable during Crizotinib treatment, while in 3 pts (18,8%) significant changes were observed, consisting in the enlargement from baseline of pre-existent RCs and in the growth of new cysts, after a median time of 4,57 mo (2,97 to 6,17 mo). One of these pts also developed a mixed blood-fluid collection in the left paravertebral muscles, associated with edema of thoracic and abdominal soft tissues; only in this case we discontinued Crizotinib and after two mo CT scan showed a decrease of the CRCs and the complete regression of the abscess.
Conclusions: This analysis suggests that development of RCs is a common SE and Crizotinib discontinuation is not always necessary. In a single case we observed an unexpected SE consisting in a paravertebral abscess complicated by fever unresponsive to antibiotic therapy and CRCs development. The radiological evidence of CRCs, invading peripheral tissues, leaded physicians to consider the drug suspension with a resolution of abscess and RCs size decrease.

D44

ADDITIONAL STEREOTACTIC BODY RADIO THERAPY (SBRT) FOR OLIGO-RECURRENCE AD-NSCLC PATIENTS

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Introduction: Oligo-recurrence is defined as the state in which cancer pts have <5 metastasizes or recurrent lesions with controlled primary lesion. SBRT is considered a good treatment option for local disease control.* This study evaluates retrospectively the records of pts underwent SBRT after first line chemotherapy.
Material and methods: All pts underwent at least 4 cycles of platinum based chemotherapy or 3 months of tirosin kinase inhibitors with Disease Free Intervall (DFI) > 3 months. RT was delivered to a median dose of 48 Gy (range 24-60), with a median fraction dose of 12 Gy by a X-ray linear accelerator. CT scan was performed every 3 months in first year after RT and than every 6 months.
Result: A total of 38 pts who received SBRT between 2011 to 2017 were enrolled. They were 26M/12F, median age 71 y (Range 50-80); PS O-1:85% - PS 2:15%; 11 SQM + 27 ADK (4 pts expressed EGFr mutation); 30 pts had N2-N3 stage while only 5 pts had >5 sites of metastasis. The extra thoracic disease's sites are snc, bone, adrenal gland in 17 cases. They were syncronous (S) with primary lesion in 22 cases and methacronous (M) in 16. After first line treatment there was mDFI of 9 months (3-12) while the mPFS after SBRT was 12 months (4-36). The PFS for S pts was 18 m (4-36) while for M pts was 12 m (3-30). Four pts underwent to surgical resection also, and they are still alive. Today 22 pts are alive over 18 m while 16 pts are died with mOS of 24 m. OS rate at 24 m was 100% in stage N0-N1 and 60% in N2-N3. OS rate at 3 years was 38% but it may be improve by the follow up of alive pts. SBRT was well tolerated with only 3 cases (10%) of radiation pneumonitis resolved by steroids
Conclusion: SBRT is a good and well tolerated option for local treatment in oligo-recurrence advanced NSCLC, we confirm the better prognosis for syncronous metastatic and stage N0-N1 pts.

*Juan O., Popat S : Ablative therapy for oligometastatic Non Small Cell Lung Cancer . Clin Lung Cancer, 2017

D45

DETECTION OF T790M MUTATION IN PATIENTS (PTS) WITH EGFR-POSITIVE METASTATIC LUNG ADENOCARCINOMA (MLA): A SINGLE INSTITUTION ANALYSIS OF CONCORDANCE BETWEEN ASSESSMENT ON TISSUE AND THAT IN CIRCULATING TUMOR DNA

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Background: About 60% of pts with EGFR-positive mLA shows a T790M mutation on EGFR exon 20 at progression of treatment with first or second generation EGFR Tyrosine Kinases Inhibitors (TKIs). These pts may benefit from osimertinib, a third generation EGFR TKI, in terms of both response and survival. When tumor tissue is limited or a rebiopsy is not feasible, the presence of T790M mutation may be evaluated by circulating tumor DNA (ctDNA).
Methods: We considered as eligible patients with cytologically confirmed EGFR positive mLA progressing on treatment with first or second generation TKIs. All patients were evaluated by a liquid biopsy assay to detect EGFR mutations in ctDNA. Plasma was analyzed by Real Time PCR (RT PCR). The degree of concordance between EGFR mutational analysis in blood and on tissue was evaluated. The T790M detection rate and the percentage of rebiopsy performed at disease progression following first line treatment were also reported.
Results: Between April 2015 and May 2018, a consecutive series of 31 patient underwent liquid biopsies before and/or after treatment with EGFR TKIs (erlotinib, gefitinib or afatinib). All pts had a diagnosis of adenocarcinoma and stage IV disease, and the median age was 69 years (range 41-82); most of them were female (68%) and never smokers (71%). Before starting first line treatment, liquid biopsy was performed in 19 pts: no pt showed T790M mutation and the concordance between ctDNA and tissue was 100%. After disease progression, 24 pts underwent liquid biopsy with a T790M positivity rate of 54.2% (13 pts). In these pts a rebiopsy was performed in 29.1% of cases (7 pts) with 3 pts showing T790M mutation. Among the three tissue-positive pts, concordance between tissue and ctDNA detection was found only in one pt, while in the remaining two the mutation was found only on tissue. Osimertinib was administered to 12 of 13 T790M positive pts (92.3%); the remaining patient received best supportive care due to poor performance status.
Conclusions: Our experience confirms that liquid biopsy is a valid method to detect the T790M mutation in pts with mLA before and after treatment with first and second generation EGFR TKIs. In particular, RT PCR showed high sensitivity and specificity in detection of T790M at disease progression, when T790M positive pts may benefit from osimertinib treatment. Nevertheless, in presence of negative ctDNA analysis, a rebiopsy should be performed whenever possible to confirm this result.

D46

DOUBLE TROUBLE. IMPACT OF A DOUBLE EGFR MUTATION IN CLINICAL OUTCOMES FOR FIRST LINE THERAPY IN ADVANCED NSCLC

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Background: Lung cancer (LC) is the leading cause of cancer-related death. However, in recent years the discovery of driver mutations and the introduction of targeted therapies has radically changed the natural history of LC oncogene addicted.

Mutations in the epidermal growth factor receptor (EGFR) are detected in about 25% of Non-Small Cell Lung Cancer (NSCLC). The two most frequent mutations of EGFR are the Delection in Exon 19 and the L858R mutation of exon 21. In these patients, the standard of care for first line treatment in advanced disease are the EGFR tyrosine kinase inhibitors (EGFR-TKis).

However, exons 19 and 21 are often the only ones analyzed. Furthermore, several clinical trials with EGFR-TKis included only pts harboring these mutations. Moreover, other mutations in the EGFR gene are rarely detected; these last have a different spectrum of sensitivity to EGFR-TKis. Indeed, it has been described few patients with a double EGFR mutation in the same tumor sample.

The frequency of this event and the efficacy of EGFR-TKI in this subgroup of patients are still unclear.

The purpose of this study is to evaluate the outcomes of the first line treatment for advanced disease with EGFR-TKis in double-EGFR mut NSCLC pts.
Methods: In this retrospective observational study, we enrolled 62 pts with histological diagnosis of stage IV NSCLC EGFR mut treated in first-line therapy with EGFR-tkis (gefitinib, erlotinib, afatinib) at Sant'Andrea Hospital in Rome.
Results: Overall, 62 pts were included in the study. The median age at diagnosis was 65 years (range 47-85); Female pts were 37 (60%). 20 Patients (33%) had the L858R ex21 mutation, 26 pts had the Del19 (42%), in 4 pts (6%) a G719X ex20 mutation was detected, in 3 cases (5%) the L861Q ex21 and in 2 pts (3%) an insertion in exon 20. In total, 55 pts had a single EGFR mut.

In 7 patients (11%) it has been identified a double-EGFR mutation.

Overall, with an EGFR-Tki first line treatment, in the cohort of single-mutation group we observed a median PFS of 10 months and a median OS of 16 m. Conversely, the double-mutations group showed a median PFS of 5 m and a median OS of 9 m.
Conclusion: In our experience NSCLC with double mutation EGFR seems to be less rare than described in the literature and with a worse outcome in first line treatment with EGFR-tkis.

However, this retrospective study is limited by the low number of patients enrolled; a multi-center study is ongoing to confirm or reject our observation.

D47

SAFETY OF CHEMOTHERAPY FOR ADVANCED NON-SMALL-CELL LUNG CANCER IN DIALYTIC PATIENTS

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Background: little evidence is available about the feasibility and safety of chemotherapy for the first-line treatment of advanced non-small-cell lung cancer (NSCLC).
Patients and methods: database retrospective search looking for dialysis patients with a diagnosis of stage IIIB/IV NSCLC undergone first-line chemotherapy five years back. All available clinical informations about toxicity according to Common Toxicity Criteria adverse Events (CTCAE) were collected.
Results: we identified 10 pts (M/F 8/2; median age 75[range 65-80]yrs; ECOG Performance Status 0-1/2 7/3); PS 0/1 pts (7 out of 10) received a low dose platinum doublet (5 carboplatin/2 cisplatin) with pemetrexed or gemcitabile while PS 2 pts (3 out of 10) were treated with single agent metronomic oral vinorelbine (40mg x3/week continuously). Platinum treated pts showed a higher than expected G3/4 toxicity rate requiring prolonged hospitalization (71% G4 neutropenia, 43% G3 thrombocytipenia, 43 % G4 nausea ad vomiting) recovered after long time. Toxicity were lower with metronomic oral vinorelbine (33% G3 nausea and vomiting, 33% G2 asthenia).
Conclusion: First-line treatment of advanced NSCLC appear to be challenging in dialytic patients; oral metronomic vinorelbine seems to be a safer option.

D48

ARE THERE DIFFERENCES IN OVERALL-SURVIVAL IN SQUAMOCELLULAR-NSCLC PATIENTS TREATED WITH NIVOLUMAB ASSESSED WITH RECIST1.1 AND IRECIST?

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Background: The discovery of immune checkpoint inhibitors such as PD-1 inhibitor Nivolumab had revolutionized the treatment of advanced NSCLC.

Instead the radiological response to immunotherapy wasn't always easy to assessment: therefore it's necessary to use new evaluation criteria for the response, such as I-Recist.

The purpose of this study is to compare the survival data, consisting of overall-survival (OS), for squamocellular-NSCLC patients treated with Nivolumab with RECIST1.1 and iRECIST criteria response categorisation.
Material and methods: After IRB approval, the CT-images of 15 squamocellular-NSCLC patients treated with Nivolumab were retrospectively evaluated at baseline, 3-months and 6-months by RECIST1.1 and iRECIST criteria. Patients were categorised as responders and non-responders as per RECIST1.1. For iRECIST, patients showing complete-response, partial-response or 6-months ongoing stable-disease were considered responders, while those showing progressive-disease were considered non-responders. Unconfirmed progressive-disease by iRECIST was considered as stable-disease for categorisation purposes. Kaplan-Meier analysis for these response categories was performed for OS.
Results: According to RECIST1.1, 5/15 (33.3%) patients were categorised as responders and 10/15 (66.6%) patients as non-responders.

According to iRECIST, 11/15 (73.3%) patients were categorised as responders and 4/15 (26.6%) patients were categorised as non responders. Significant differences between responders and non-responders for OS were observed for both radiological response criteria (Log-rank test: $p<0.05$). Median OS following RECIST1.1 was 22 months for responders and 10 months for non-responders (HRs: 0.5796; 0.2101-1.5991). Median OS following iRECIST was 21 months for responders and 7 months for non-responders (HRs: 0.1774; 0.02127- 1.4795).
Conclusions: The OS curves for RECIST1.1 were similar to the one observed in iRECIST. For non-responders, the OS observed in RECIST1.1 was longer than the one observed in iRECIST; this difference may suggest that iRECIST better identifies progression of disease.

D49

NEGATIVE AND POSITIVE PREDICTOR CLINICAL AND BIOCHEMICAL FACTORS OF RESPONSE TO ANTI-PD-1 AGENTS IN NSCLC: A SINGLE CENTER EXPERIENCE

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Background: Baseline (prior immunotherapy) clinical characteristics in non-small cell lung cancer patients (NSCLC) patients (pts) treated with immunotherapy (IO) is an interesting field to select pts for IO. In this retrospective, monocentric study we aim to demonstrate the role of bone, liver and nervous central system (NCS) metastases

(mets) as predictor factors to anti-programmed death-1 (PD-1) drugs in NSCLC. Also we investigate the role of baseline (bl) serum lactate dehydrogenase (LDH) to predict response to anti-PD-1.

Material and Methods: We included for the analyses 137 evaluable patients with NSCLC which performed at least one IO-course, in 2nd or further line setting from a monocentric database. Kaplan Maier was used to perform univariate analyses and to estimate progression-free survival (PFS) and overall survival (OS). Also cox proportional hazard model was used for multivariate analyses.

Results: Characteristics: median age was 67 years (y) (31-86 y), 43/137 were ⩾70 y, male (81%) and smoker (81%), ECOG 0-1 was62% and 2 in 38% of pts. mPFS and mOS were 3.8 months (mo) and 7.5 mo respectively. Univariate analyses demonstrated a correlation between worse PFS and bl-bone (p=0.001), liver (p=0.003) and NCS (p=0.022) mets. No differences in PFS and OS was seen for pts ⩾70 y. While bl-LDH level of < 400 mg/dl (evaluable in only 80 pts) seems to be a positive predictor to anti-PD-1 agents (5.8 vs 2.6 mo, HR 0.34, p<0.0001). Significant univariate variables were included in a multivariate analysis which identified liver and bone mets as negative predictor (HR 2.87 p=0.003 and HR 2 p=0.031, respectively) to IO (and confirmed LDH <400 mg/dl as positive predictor of response to anti-PD-1 drugs (HR 0.30 p=0.001). NCS mets has a trend but is not confirmed as statistically significant in multivariate analysis (p=0.052). Also as previously reported ECOG 2 is a poor predictor of response (HR 3.2 p<0.001).

Conclusion: Despite the retrospective nature of this study we observed that some baseline features as bone and liver mets and also ECOG 2 are associated with a poor response to anti-PD-1 drugs. While LDH <400 mg/dl can correlate with a better PFS. We also observed that older pts had the same benefit form IO as young pts.

D50

OVERALL SURVIVAL AND DETECTION OF ALK POSITIVE PATIENTS IN LUNG ADENOCARCINOMA

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Background: Anaplastic lymphoma kinase (ALK) in lung adenocarcinoma is targetable by ALK inhibitor. To date these drugs have improved the survival.. In this monocentric retrospective study we investigated the relation between detection of ALK rearrangement by fluorescent in situ hybridization (FISH) or immunochemistry (IHC) and survival in NSCLC pts.

Material and Methods: Of 44 evaluable patients, 41 pts were included in the analyses which performed at least one ALKi.

Kaplan Maier were used to calculate univariate analysis and estimate survival. Statistically significant variables were included in a multivariate analysis using Cox proportional hazard model.

Results: Pts characteristics were as follow: median age 61 years (y) (27-85y), pts < 65 were 51.5%. male/female (21/20), smoker/never smoker (%) (61/39), ECOG prior start ALKi was: 0 (14.6%), 1 (65.8%), 2 (19.6%), stage IVA/IVB (20/21). 14 pts performed ALKi in 1st line, 21 in 2nd line and 6 pts in 3rd or further line and 26.9% performed more than one ALKi. Baseline nervous central system (NCS) metastases (mets) were identified in 26.8%. For the detection of ALK rearrangement FISH only was used in 43.9%, IHC in 31.7% and both methods in 24.4%. The overall response rate (RR) to the 1st ALKi was 51.2% and disease control rate (DCR) was 61%. Local radiotherapy during ALKi was performed in 12/41 pts. Univariate analyses demonstrated that pts which experienced oligoprogression had better survival (HR 0.31 p=0.041). FISH test were used in 28 pts, in these pts we observed that positive FISH test with >40% of rearranged cells confer a better OS (HR 0.26 p=0.003). The adjusted analyses for age, sex, smoke, ECOG-PS, Stage, ALK line identified pts with FISH > 40% as independentpositiveprognostic (HR 0.13 p=0.001) and predictor (HR 0.14 p<0.0001) factor.

Conclusion: This retrospective study interestingly reported a role of % of rearranged cells in lung adenocarcinoma ALK positive pts treated with ALKi. Despite these results prospective study with important samples are needed to validate these results.

D51

A SINGLE CENTRE EXPERIENCE OF ARNAS CIVICO PALERMO WITH NIVOLUMAB ADMINISTRATION IN NSCLC. WHAT NEW?

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Background: The addition of anti-PD-1 antibody change the paradigm of treatment and the landscape of NSCLC. Immunotherapy using monoclonal antibody anti-PD-1

(Nivolumab) offers another possibility to improve tumor control in patients with NSCLC. We present a single cente experience of all patients with NSCLC treated with Nivolumab since this treatment became available via AIFA reimbursement.

Methods: We present our first analyses with Nivolumab experience, Nivolumab tolerability, and DCR in 58 Patients. Data was retrospectively collect using our hospital database.

Results: We identify 58 patients, 30 male and 28 female. The median age is 66 years old (range 48-73). Histologically was as follow 28 squamous NSCLC, 30 Non-squamous NSCLC. Of these patients 35 patients have a PS =1 and 23 a PS of 0. Nivolumab was administered as second line treatment in all patients. The median number of cycles administered was 9 (range 2-36). The median follow up was 12 month (range 2-38) with a median OS squamous and non-squamous NSCLC of 10,6 month and 9,6 month respectively. The 1 years OS is 65% and 58% for squamous and non squamous respectively. DCR of squamous and non squamous NSCLC is 45% and 50% respectively with a median duration of responds not reached and a median time to responds of 2 month. Adverse events grade 3-4 were 8% and all grades 55%, one of this patient have had pneumonitis and one colitis. We have done an analysis by PS divided in PS 0 vs PS 1 and this have no statistical significance.

Conclusion: Although the small number of patients the results of real-world audit appear to be in line qith the clinical trial. The median OS was similar to checkmate 017 and checkmate 057, and also other parameters as incidence of G3-4 and DCR were similar to the findings of the registrational trials. We think that Nivolumab should be administered in all patients candidable to the treatment.

D52

PSYCHOLOGICAL RESOURCES IN THE ELDERLY PATIENT LIVING WITH LUNG CANCER

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Most lung cancer patients are elderly. Disease prognosis, treatments impact, further problems related to age and other contextual factors can negatively influence them functionality and subjective well-being, affecting motivation and compliance degrees. Our aim is to have a deeper knowledge about which psychological resources are the most recognized in this critical context. It could be relevant to all care process: patients could identify personal strengths they can refer to, and healthcare staff could better understand which dimensions help lung cancer patients, also the older ones, to cope and maintain high levels of compliance.

Resilience, optimism, hope, future orientation, courage and life satisfaction have been explored. We proposed a test battery to 29 patients with lung cancer from Camposampiero and Cittadella's Oncology (mean age=67,52). We analysed the degree to which patients identify them: like resources, strengths, or vulnerability areas. Then we identified specificities in relation to age (<70 or $\geqslant 70$ yrs.) and stage of disease (treated with TKI/chemo/immunotherapy or under control).

All participants recognized the presence of at least one resource. Most recognized strengths were Courage, Social Resources and Family Cohesion (about over the 41,4%). Vulnerability areas were, like expected, Optimism, Hope and Future planning. No significant differences emerged between different therapeutic conditions or different ages ($p>.05$).

Results highlight the importance of courage and interpersonal context to lung cancer patients, also the older ones. Healthcare staff could intervene keeping support these areas and enhancing especially emerging vulnerabilities, related to vision about future, to improve motivation and compliance.

E - International Studies

E01*

CABOZANTINIB VERSUS PLACEBO IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA WHO HAVE RECEIVED PRIOR SORAFENIB: RESULTS FROM THE RANDOMIZED PHASE 3 CELESTIAL TRIAL

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Background: Cabozantinib (cabo), an inhibitor of MET, VEGFR and AXL, has previously shown clinical activity in patients with advanced hepatocellular carcinoma (HCC). This double-blind, global, phase 3 trial (NCT01908426) evaluated cabo vs placebo (pbo) in patients with advanced HCC previously treated with sorafenib.
Patients and Methods: Patients were randomized 2:1 to receive cabo (60 mg qd) or matched pbo; randomization was stratified by disease etiology (HBV, HCV, other), geographic region (Asia, other), and presence of extrahepatic spread and/or macrovascular invasion (EHS/MVI). Eligible patients had a pathologic diagnosis of HCC, Child–Pugh score A, ECOG PS $\leqslant$ 1, and must have received prior sorafenib. Patients could have received up to two lines of prior systemic therapy for HCC and must have progressed following at least one. The primary end point was overall survival (OS). Secondary end points were investigator-assessed progression-free survival (PFS) and objective response rate (ORR) per RECIST 1.1. The study was designed to detect a hazard ratio (HR) for OS of 0.76 (90% power, two-sided, $\alpha = 0.05$) at the final analysis, with two prespecified interim analyses at 50% and 75% of the planned 621 events.
Results: Overall, 707 patients were randomized. As of 1 June 2017, 484 deaths had occurred (cabo, 317/470; pbo, 167/237). Baseline characteristics were balanced between the two arms: median age was 64 years, 82% were male, 38% had HBV, 24% had HCV, 25% were enrolled in Asia, 78% had EHS, 30% had MVI, 85% had EHS/MVI, and 27% had received two prior systemic therapy regimens for advanced HCC. The study met the primary end point at the second planned interim analysis, with a median OS of 10.2 months for cabo vs 8.0 months for pbo (HR 0.76; 95% CI 0.63–0.92; $p = 0.0049$). Median PFS was 5.2 months for cabo vs 1.9 months for pbo (HR 0.44; 95% CI 0.36–0.52; $p < 0.001$), and ORR was 4% vs 0.4%, respectively ($p = 0.0086$). The most common grade 3/4 adverse events (predominantly grade 3) with a higher incidence in the cabo vs pbo arm included hand–foot skin reaction (17% vs 0%), hypertension (16% vs 2%), increased aspartate aminotransferase (12% vs 7%), fatigue (10% vs 4%), and diarrhea (10% vs 2%).
Conclusions: Cabo significantly improved OS and PFS vs pbo in previously treated patients with advanced HCC. Adverse events were consistent with the known safety profile of cabo. Clinical trial information: NCT01908426.

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E02*

REACH-2: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF RAMUCIRUMAB VERSUS PLACEBO AS SECOND-LINE TREATMENT IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC) AND ELEVATED BASELINE ALPHA-FETOPROTEIN (AFP) FOLLOWING FIRST-LINE SORAFENIB

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Background: Patients (pts) with advanced HCC and elevated AFP have a poorer prognosis compared to the general HCC population, and need effective, well tolerated treatment options. Increased VEGF and VEGFR2 expression is associated with high AFP expression in HCC tumors. Ramucirumab (RAM), a human IgG1 mAb, inhibits activation of VEGFR2. REACH-2 was designed to confirm the benefit of RAM treatment observed in the REACH study in pts with baseline AFP $\geqslant$400 ng/mL.
Materials and Methods: Eligible pts were $\geqslant$18 yrs, had HCC with BCLC stage C or B disease refractory or not amenable to locoregional therapy, baseline AFP $\geqslant$400 ng/mL, Child-Pugh A, ECOG PS 0 or 1, adequate hematologic and biochemical parameters, had progressed on or following, or were intolerant to sorafenib. Pts were randomized (2:1) to receive RAM 8 mg/kg iv or placebo (PL) Q2W plus best supportive care, until disease progression or unacceptable toxicity. Primary endpoint was overall survival (OS). Secondary objectives included progression-free survival (PFS), objective response rate (ORR) per RECIST v1.1 and safety.
Results: 292 pts were randomized to RAM (197) or PL (95). Baseline characteristics were generally balanced between arms. RAM treatment significantly improved OS (median OS 8.5 mo vs 7.3 mo PL; HR 0.710; 95% CI 0.531, 0.949; p=.0199). RAM significantly improved PFS (median PFS 2.8 mo vs 1.6 mo PL; HR 0.452; 95% CI 0.339, 0.603; p<.0001). ORR was 4.6% RAM vs 1.1% PL (p=.1156) and disease control rate (ORR + stable disease) was 59.9% RAM vs 38.9% PL (p=.0006). Grade $\geqslant$ 3 adverse events occurring in $\geqslant$ 5% pts in the RAM arm

were hypertension (12.2% RAM, 5.3% PL) and hyponatremia (5.6%, 0%).

Conclusions: REACH-2 met its primary endpoint showing a significant survival benefit, with RAM treatment reducing the risk of death (29%) in pts with HCC and AFP = 400 ng/mL who progressed on or were intolerant to sorafenib. Treatment was well tolerated, with a safety profile consistent with the established profile for single agent RAM. REACH-2 is the first positive phase 3 study conducted in a biomarker-selected pt population with HCC.

E03*

FINAL RESULTS OF NEOMONARCH: A PHASE 2 NEOADJUVANT STUDY OF ABEMACICLIB IN POSTMENOPAUSAL WOMEN WITH HORMONE RECEPTOR POSITIVE (HR+), HER2 NEGATIVE BREAST CANCER (BC)

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Background: Abemaciclib is a CDK4 & CDK6 inhibitor dosed on a continuous schedule. NeoMONARCH (Phase 2 trial in women with stage I-IIIB, HR+/HER2- BC) met its primary endpoint showing abemaciclib, alone or in combination with anastrazole (ANZ) significantly reduced Ki67 expression vs ANZ alone after 2 weeks (wks) of neoadjuvant treatment. Final results are presented here.

Methods: 223 pts were randomized (1:1:1) to 2 wks abemaciclib (150 mg PO Q12H) + ANZ (1 mg PO QD), abemaciclib or ANZ alone followed by 14 wk combination treatment. Pts were treated with loperamide (2 mg PO Q12H) for 4 wks while receiving abemaciclib. Tumor biopsy was collected at baseline, wk 2 and 16. Primary objective was Ki67 change from baseline to wk 2. Secondary objectives were radiologic/pathological/clinical responses, safety and pharmacokinetics at wk 16. Mutational analyses at baseline were exploratory objectives.

Results: Table 1 shows subgroup analyses of percent change in Ki67 from baseline to wk 2 by disease stage, baseline lymph node (LN) involvement, tumor grade, and tumor size in Ki67 evaluable (KE) population (baseline Ki67 ⩾ 5%) comparing combination to ANZ alone. Data for abemaciclib arm will be shown at the meeting. 185 pts completed treatment; radiological response rate was 46.4%, caliper 53.6% and pCR 3.7% (pts who completed BC surgery assessment). Ki67 end of treatment analysis in

Table 1. Subgroup Analyses at wk 2 of KE population.

	Combination		ANZ		Subgroup Treatment Comparison	
	Pts, n	GM % Change	Pts, n	GM % Change	GMR (95% CI)	*P*
KE Population	59	−92.86	56	−62.78	0.19 (0.13, 0.28)	<0.001
Disease Stage						
I/II	51	−92.56	46	−65.84	0.22 (0.14, 0.34)	<0.001
III	7	−95.28	8	−54.91	0.10 (0.04, 0.27)	<0.001
Baseline LN Involvement						
No	29	−93.18	26	−62.21	0.18 (0.11, 0.31)	<0.001
Yes	29	−92.75	28	−69.02	0.23 (0.13, 0.42)	<0.001
Tumor Grade						
1 or 2	33	−92.88	37	−69.61	0.23 (0.15, 0.36)	<0.001
3	16	−92.79	10	−59.68	0.18 (0.05, 0.60)	0.011
Tumor Size						
< 2 cm	9	−93.25	8	−65.46	0.20 (0.08, 0.50)	0.004
⩾2 cm and < 5 cm	39	−91.22	29	−62.16	0.23 (0.14, 0.40)	<0.001
⩾ 5 cm	11	−94.24	19	−59.73	0.14 (0.07, 0.28)	< 0.001

Abbreviations: GM, geometric ratio; GMR, geometric mean ratio.

138 pts and further results for secondary/exploratory objectives will be presented.

The most common adverse events, were diarrhea, constipation and nausea

Conclusions: Abemaciclib + ANZ is an effective treatment with manageable toxicities in pts with HR+/HER2- early BC. Abemaciclib-driven change in Ki67 was not associated with disease stage, baseline LN involvement, tumor grade, or tumor size.

E04*

PHASE 1B/2 STUDY OF OLARATUMAB PLUS GEMCITABINE AND DOCETAXEL FOR THE TREATMENT OF ADVANCED SOFT TISSUE SARCOMA (STS) (ANNOUNCE 2): PHASE 1B RESULTS

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Background: In a phase 2 study, Olaratumab (O) in combination with doxorubicin (dox) demonstrated a significant improvement of overall survival (OS) over dox alone in patients (pts) with advanced STS. We report safety, tolerability and recommended phase 2 dose (RPTD) of O plus gemcitabine (G) and docetaxel (D) (O+G/D).

Methods: Pts with advanced/metastatic STS, ⩽2 prior lines of systemic therapy, no prior G, D or O, and ECOG PS 0-1 were enrolled. Pts received O on Days 1&8 at 15 mg/kg (cohort 1) or 20 mg/kg (cohort 2) with G (900 mg/m^{2}Days 1&8) and D (75 mg/m^{2}Day 8) on a 21-day cycle. Primary objective was to determine RPTD of O+G/D, with dose-limiting toxicity (DLT) in Cycle 1 at rate <33%. Safety and pharmacokinetics (PK) were secondary objectives.

Results: 54 pts (cohort 1/2=21/33) received at least one dose of treatment. No DLT occurred in cohort 1. In cohort 2, 5 pts experienced 6 DLTs (ALT increase, bacteremia, neutropenia [2 pts], and thrombocytopenia [2pts]). Treatment-related adverse events (TRAEs) for cohorts 1 and 2 included all grades (90.5% and 93.9%), Gr 3 (14.3% and 42.4%), Gr 4 (0 and 18.2%), and serious AEs (9.5% and 15.2%), respectively. Common TRAEs (all grades, Gr⩾3) occurring in ⩾25% of pts were fatigue (66.7%, 11.1%), anemia (61.1%, 18.5%), thrombocytopenia (35.2%, 18.5%), nausea (29.6%, 0%) and diarrhea (27.8%, 3.7%). 1 pt discontinued due to study-related fatigue (cohort 1). Following 2 deaths unrelated to study treatment, cohort 2 was expanded to 33 pts. PK profile of O+G/D was similar to O in combination with other chemotherapies.

Conclusions: Both dose levels were tolerated with higher incidence for known toxicities of G/D in cohort 2. Based on safety and exposure-response analyses across O studies, RPTD for O+G/D is 20 mg/kg at Days 1& 8 in Cycle 1, followed by 15 mg/kg at Days 1&8. Randomized, double-blinded phase 2 part of the study is enrolling and will compare OS of pts with STSreceiving G/D+O vs G/D+placebo (ANNOUNCE 2).

F - Brain Tumours

F01

FINAL RESULTS OF REGOMA: A RANDOMIZED, MULTICENTER, CONTROLLED OPEN-LABEL PHASE II CLINICAL TRIAL EVALUATING REGORAFENIB IN RELAPSED GLIOBLASTOMA (GBM) PATIENTS (PTS)

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Background: There is no established treatment regimen for recurrent GBM. GBMs have activation of multiple signaling pathways in the tumor microenvironment, including the receptor tyrosine kinases, VEGFR, FGFR, and PDGFR. REG, an oral multikinase inhibitor, inhibits these angiogenic kinases and the mutant oncogenic kinases KIT, RET, and B-RAF.

Methods: We present, after the first analysis, the final results of REGOMA trial. The primary aim of this trial was to assess REG activity in prolonging overall survival (OS) in PTS with relapsed GBM after surgery and Stupp regimen (a = 0.2, 1-sided; ß = 0.2). Secondary objectives were PFS, disease control rate (DCR), safety, quality of life (QoL); exploratory objectives included analysis of metabolic tissue biomarkers as possible predictors of response. PTS with histologically confirmed GBM, ECOG PS 0-1, documented disease progression were randomized

1:1 to receive REG 160 mg/day (3 weeks on, 1 week off) or lomustine (LOM) 110 mg/m2 (every 6 weeks) until disease progression or unacceptable toxicity. Tumor response was evaluated by brain MRI every 8 weeks according to the RANO criteria.

Results: 119 PTS were randomized (n = 59 REG; n = 60 LOM) and stratified for surgery at recurrence; baseline characteristics, including MGMT methylation status, were balanced. Median age was 57.3 yrs; 27 PTS (22.7%) had surgery at recurrence, 22% and 23.3% in REG and LOM arm. At the time of analysis (cut-off date: Dec 31, 2017), median follow up was 15.4 months(m), 99 PTS had died. Median OS was 7.4m (95% CI 5.8-12.0) for REG and 5.6m (95% CI 4.7-7.3) for LOM (HR = 0.50, 80%CI 0.38-0.65; p = 0.0007; 1-sided Log-rank test); 12m-OS rates were 38.9% and 15.0% for REG and LOM. 6m-PFS rates were 16.9% and 8.3% (HR = 0.65; 95% CI 0.45-0.95; p = 0.0223) for REG and LOM, DCR was 44.8% and 21.1% (p = 0.009) for REG and LOM. Grade =3 adverse events were reported in 56% and 40% for REG and LOM, no treatment-related deaths were reported.

Conclusions: In this multicenter, randomized study, REG significantly improved OS, PFS and DCR in recurrent GBM PTS. REG treatment was feasible and well tolerated. QoL and biomarker analyses are ongoing. A phase 3 study will be planned.

F02

MISMATCH REPAIR DEFICIENCY (MMRD) IN GLIOMA PATIENTS (PTS): FREQUENCY AND CORRELATION WITH CLINICAL, HISTOLOGICAL AND MOLECULAR CHARACTERISTICS

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Background: Immune-checkpoint inhibitors (ICI) represent a new interesting approach in oncology. The presence of DNA MMRd would seem to be a predictor of ICI efficacy. We analyzed MMRd frequency in glioma PTS and its correlation with clinical, histological and molecular characteristics.

Methods: From July 2017 to May 2018, we prospectively analyzed histologically confirmed glioma PTS for the presence of MMRd by immunohistochemistry (IHC): MSH2, MSH6, PMS2, MLH1. Clinical, histological and molecular characteristics (MGMT methylation and IDH mutational status, PD-L1 expression) were recorded. Chi-square test was used for analyzing their correlations with MMRd.

Result: 167 PTS were enrolled: 78% glioblastoma (GBM), 14% anaplastic astrocytoma (AA), 1% ependymoma, 2% anaplastic oligodendroglioma (OD) and 5% LGG. The analyses were assessed on tissue samples of first (82% of the cases), second surgery (18%). All PTS performing a second surgery received radiotherapy and temozolomide as first-line therapy. 134 PTS were analyzed for IDH status: 99 were IDH wt; 117 for MGMT status: 68 were methylated. 27 PTS (16%) showed MMRd by IHC (MSH2 in 48%, MSH6 in 55.6%, PMS2 in 18.5% and MLH1 in 14.8%): 33% of AA, 14% of GBM, 33% of OD and 0% of LGG (p=0.2). MMRd was found in 13% and 32% on first and second surgery samples (p=0.03). PD-L1 expression analysis was performed in 60 cases: no expression was showed in 58% of cases, = 1% and <50% in 38%, > 50% in 10%. MMRd was not correlated with PD-L1 expression (p=0.3). MMRd was found in 10% and 29% of IDHwt and IDHmut gliomas (p=0.008); MMRd was showed in 10% and 21% of PTS with unmet and met-MGMT (p=0.1). Among MMRd tumors, 7 were also investigated by molecular analysis (PCR) of mononucleotide markers: in only 1 PT (14%) was confirmed MMRd in agreement with IHC analysis (p=0.1.).

Conclusions: We showed a small group of glioma PTS have MMRd by IHC, expecially at second surgery. Correlation was observed between IHC MMRd and IDH mutational status. No association was demonstrated between IHC MMRd and histology, MGMT status, PD-L1 expression or molecular analysis of MMRd. A prospective study analyzing ICI efficacy in MMRd PTS should be warranted.

F03

HIGH DOSE SIB VMAT RADIOTHERAPY PLUS TEMOZOLOMIDE IN GLIOBLASTOMA PATIENTS: PHASE I STUDY (ISIDE-BT-2) INTERIM ANALYSIS

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Background: Glioblastoma multiform (GBM) is an aggressive and resitant disease with rather short overall survival. The multidisciplinary treatment consists of surgical resection followed by post-operative chemoradiation with concurrent then adjuvant temozolomide (TMZ). Standard radiotherapy (RT) dose is 60 Gy in 2-Gy fractions (RTOG). Although TMZ can improve the efficacy of RT alone, a relapse is very common mostly within the irradiation field. Several studies are exploring different RT schedules and doses. The aim of this phase I study was to determine the maximum tolerated dose (MTD) of RT with Volumetric Modulated Arc Therapy (VMAT) technique plus standard concurrent and sequential-dose TMZ in resected patients with GBM.
Methods: Histological proven GBM patients underwent VMAT dose escalation. VMAT was delivered over 5 weeks with the simultaneous integrated boost (SIB) technique to the two planning target volumes (PTVs) defined by adding 5-mm margin to the respective clinical target volumes (CTVs). CTV1 was defined by adding a 10-mm isotropic margin to the tumor bed plus any MR enhancing residual lesion; CTV2 was defined as the CTV1 plus 20-mm isotropic margin. Radiation dose was escalated to the PTV1 with the SIB-VMAT strategy. Four dose levels were planned for PTV1: level 1 (77.5/3.1 Gy), level 2 (80/3.2 Gy), level 3 (82.5/3.3 Gy) and level 4 (PTV1: 85/3.4 Gy); PTV2 was treated by the same dose (45/1.8 Gy). All treatments were delivered in 25 fractions. Patients were treated in cohorts of between three and six per group using a Phase I study design. The recommended dose was exceeded if two of the six patients in a cohort experienced dose-limiting toxicity within 3 months from treatment. TMZ chemotherapy was administered according to Stupp's protocol.
Results: Eleven consecutive GBM patients (male/female: 7/4; median age: 59 years) were treated, 9 of them at first dose level, with none of them experiencing a dose-limiting toxicity (DLT) (grade >3). Being the MTD not exceeded, the PTV1 dose was escalated to the higher planned dose level (80/3.2 Gy) and accrual is actually ongoing. After a median follow-up time of 7 months, no grade >2 late neurological toxicity was recorded.
Conclusions: The SIB-VMAT technique plus TMZ was found to be feasible and safe at the recommended doses of 45Gy to PTV2 and 77.5Gy (biological effective dose –BED- of 157.6 Gy, alpha/beta 3) to PTV1 in the postoperative treatment of patients with GBM. Efficacy data are as well under evaluation.

F04

THIRD-LINE THERAPY IN GLIOBLASTOMA: LAST BUT NOT LEAST

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Background: About 21-62% of GBM patients (pts) access to 3rd line therapy. In this setting, there is no defined standard. In this study we evaluated the outcome of pts who received 3rd line therapy for recurrent GBM.
Methods: We analyzed data from our Institutional data warehouse from consecutive GBM pts who received 3rd line therapy between 2005 and 2016.

Disease assessment was reviewed according to RANO criteria. Survival was calculated from diagnosis to death from any cause (OS) and from the beginning of 3rd line therapy to death from any cause (OS3). Progression-free survival was calculated from the beginning of 3rd line therapy to progression (PFS3).
Results: 184 pts (11.9%) received 3rd line therapy and were included in the study. Median age was 50.5 years (range: 20 to 72). Treatments administered in 3rd line were nitrosourea-based (NU) in 81 pts (44.0%), TMZ in 43 (23.4%), Bevacizumab (BEV) in 25 (13.6%) and carboplatinum-etoposide (CE) in 35 (19%). mOS from GBM diagnosis was 30.3 months, median PFS3 was 2.7 months and median OS3 was 7.0 months. In univariate analysis, the BEV group showed longer mPFS3 (4.6 vs 2.4 months, p= .014) and mOS3 (8.0 vs 7.0 months, p= .038) with respect to NU (table 1). In multivariate analysis age <65 years (HR 0.50, 95%CI 0.30 – 0.84, p= .008) and mMGMT (HR 0.62, 95%CI 0.43 – 0.89, p= .01) significantly improved OS3.
Discussion: Favorable prognostic factors for pts who received 3rd line treatments are younger age and methylated MGMT promoter. Third line therapy with BEV was associated with longer PFS3 and OS3.

	n	mMGMT %	PFS 3 (mos)	OS 3 (mos)
BEV	25	41.2	4.6	8.0
CE	35	48.3	2.6	6.0
NU	81	47.5	2.4	7.0
TMZ	43	71.4	3.0	6.0

F05

SHOULD BEVACIZUMAB BE ADDED TO NITROSUREA CHEMOTHERAPY IN PATIENTS WITH RECURRENT GLIOBLASTOMA? A SYSTEMATIC REVIEW

AND META-ANALYSIS OF RANDOMIZED TRIALS

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Background: Nitrosurea chemotherapy is to be considered a standard treatment option for patients with glioblastoma multiforme (GBM) whose disease recurs following Stupp regimen. On the other hand, antiangiogenic treatment with bevacizumab as single-agent has also been reported to be active in this clinical setting. We conducted a systematic review and meta-analysis of published trials in order to evaluate whether the addition of bevacizumab to nitrosurea could improve the clinical outcome of recurrent GBM patients.

Materials and Methods: Trials published in english language between 2008 and 2018 were identified by an electronic search of MEDLINE. We included retrospective and prospective studies (randomized and single-arm) that reported on patients with primary GBM who were treated with either nitrosurea alone or nitrosurea plus bevacizumab at first disease recurrence after Stupp regimen. Demographic data, objective response rate, median progression-free survival (PFS), PFS rate at 6 months (PFS-6), median overall survival (OS), 1-year OS and grade 3/4 toxicities were extracted. Pooled random effects analysis was performed and heterogeneity assessed.

Results: We pooled eligible PFS-6 data from 13 nitrosurea studies (n = 821) and 4 nitrosurea plus bevacizumab studies (n = 570). The pooled PFS-6 did not significantly differ between nitrosurea alone (25%, 95% CI = 19% to 32%) and nitrosurea plus bevacizumab treated patients (35%, 95% CI = 28% to 41%). Heterogeneity was large in both nitrosurea alone (I-squared = 73%) and nitrosurea plus bevacizumab studies (I-squared = 56%). When we focused on randomized studies we found a decrease in heterogeneity and the pooled PFS-6 was significantly higher for nitrosurea plus bevacizumab treated patients (30%, 95% CI 26% to 35%, I-squared = 0%) compared to nitrosurea alone (21%, 95% CI 13% to 21%, I-squared = 3%). Only two randomized controlled studies provided head to head comparison, resulting in a higher risk of not reaching PFS-6 for nitrosurea alone (RR = 0.87, 95% CI = 0.77 to 0.98, I-squared = 45%).

Conclusions: The present meta-analysis shows that the addition of bevacizumab to nitrosurea significantly improves PFS-6 in patients with recurrent GBM following Stupp regimen. Results on other key endpoints of clinical outcome, including OS, will be presented at the meeting.

F06

COMPREHENSIVE GERIATRIC ASSESSMENT (CGA) FOR OUTCOME PREDICTION IN ELDERLY PATIENTS (PTS) WITH GLIOBLASTOMA (GBM): A MONO-INSTITUTIONAL EXPERIENCE

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Background: Treatment for GBM elderly PTS is still a challenge in neuro-oncology. Clinical tools, including CGA, are needed for improving treatment decision and outcome. To date, few studies exploring the impact of CGA on outcome have been performed in these PTS. The aim of this study was to evaluate CGA as a prognostic tool in terms of PFS and OS in elderly GBM PTS.

Methods: we performed a retrospective analysis of elderly PTS ⩾ 65 years, treated at Veneto Institute of Oncology between January 2011 and January 2018, with newly histologically diagnosed GBM and receiving a baseline CGA after 3-4 weeks from surgery. CGA included the following domains: age, activities and instrumental activities of daily living (ADL, IADL), cognitive status (MMSE), mood (GDS), nutritional status (MNA), number of drugs, comorbidity (cumulative Illness Rating Scale-CIRS), presence of geriatric syndromes, presence of caregiver. PTS were classified according to Balducci's criteria into Fit or Unfit (Frail and Vulnerable).

Results: 113 PTS were enrolled: 72 (64%) were male, KPS were ⩾ 70 in 90 PTS (80%); 37 PTS (33%) had a radical surgery, 63% partial surgery and 4% received a biopsy. 90 PTS (80%) received Stupp treatment, 16 (14%) temozolomide or radiotherapy alone and, only 7 (6%) received no treatment. MGMT methylation status was analyzed in 96 PTS: 44% were metMGMT. According to CGA evaluation: 40 PTS (35.4%) were classified as Fit and 73 PTS (64.6%) Unfit. PFS was 11.2 (95% CI 6.0-16.4) and 7.2 (95% CI 5.8-8.6) months for Fit and Unfit PTS (p=0.1). On multivariate analysis, adjusted for type of surgery, MGMT methylation status and type of therapy, PFS was significantly different between the two groups (HR=0.6, 95% CI 0.2-0.9; p=0.04). OS was 16.4 (95% CI 14.6-18.2) and 10.6 (95% CI 8.3-12.8) ms for Fit and Unfit PTS (p=0.04); on multivariate analysis the HR was 0.51 (95% CI 0.2-0.9; p=0.04).

Conclusions: CGA demonstrated significant outcome prediction in terms of OS and PFS, regardless of therapy. It could be a useful treatment decision-tool suggesting to

treat FIT PTS with radiochemotherapy while a prospective study to evaluate the best treatment in Unfit PTS should be warrant.

F07

THE CONTINUUM OF CARE STRATEGY FOR RECURRENT GBM: DOES THE SEQUENCE OF TREATMENTS MATTER?

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Background: The improvement in the treatment of GBM (glioblastoma) patients (pts) has contributed to progressively increase the median life expectancy, being survival at 2 years in the range of 30-40%.

This survival increase has supported, as in other cancer types, the concept of continuum of care as the optimal palliative therapy strategy. However, the best treatment strategy after the first disease progression is unknown.

Methods: We retrospectively analyzed data from our Institutional data warehouse from consecutive GBM pts who received at least 2 line of systemic therapy at disease progression after RT/TMZ. Survival was calculated from diagnosis to death from any cause (Overall Survival, OS)

Results: 1552 consecutive GBM pts underwent standard RT/TMZ from 2005 and 2016. One hundred eighty-four pts (11.9%) received at least 2 lines of systemic therapy at disease progression.

MGMT methylation status was available for 142 patients (77.2%): MGMT was methylated in 75 pts (mMGMT, 52.8%) and unmethylated in 67 (nmMGMT, 47.2%). We grouped patients by Bevacizumab (BEV) treatment as follows: pts who never received BEV (NoBEV, n=123), pts who received BEV in 2nd line (BEV2, n=36), pts who received BEV in 3rd line (BEV3 n=21), pts who received BEV in 2nd and 3rd line (n=4). OS was significantly longer in the NoBEV than the BEV2 group (33.0 vs 24.7 months, p= .023). Treatments outcome is summarized in the Table.

Treatment sequence	N	Median OS (Months)	95% CI
No BEV	123	33.0	27.7–38.2
BEV2	36	24.7	17.6–31.8
BEV3	21	30.1	26.3–34.0
BEV-BEV	4	34.2	2.3–66.1

Discussion: Continuum of care might have a role in the treatment of GBM pts. Future strategies should take into account the sequence of treatments for patients with recurrent GBM.

F08

THE SOCIOECONOMIC IMPACT OF GLIOMAS: A SURVEY QUESTIONNAIRE

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Background: Socioeconomic status (SES) is associated with survival in many cancers but the effect of disease on SES and access to care for patients with gliomas has not been well studied.

Methods: A questionnaire was designed and administered to 202 consecutive patients treated in our Institution, with diagnosis of diffuse glioma (grade II, II IV). The 22-item survey questionnaire included items related to demographics, personal history, personal concern of cancer, impact of cancer on SES and self-consciousness. All responses were summarized descriptively. Frequency distributions of responses for each question were calculated.

Results: Completed surveys were returned by all the 202 glioma patients (male/female: 62.4% – 37.6%). Overall, 42.1% of patients still work, while 38.1% retired; 38.9% of patients retired due to the disease, 21.3% needed to reduce working time. In 46.3% of patients the disease had an impact on the economic status. Female patients were significantly less likely to feel attractive when compared with male patients (68.7% vs 37.8%, P=0.001). Moreover, sexual activity was worsened both in male and female patients (53.7% vs 43.8%, P=0.364).

Conclusions: The impact of gliomas on patients is burdensome and multidimensional. These diseases heavily impact SES and self-consciousness.

F09

CLINICAL PROGNOSTIC FACTORS IN LOW GRADE GLIOMAS: CONCORDANCE BETWEEN RTOG AND EORTC CRITERIA

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Background: Low grade gliomas (LGG) are a heterogeneous group of brain primary tumors. The EORTC and the RTOG criteria are the most valuable scores to evaluate risk factors and for treatment decision. However, there is no data about concordance between criteria.
Methods: We conducted an analysis on LGG patients treated in our Institution from 1998 to 2015. The population was stratified by both RTOG and EORTC risk factor criteria.
Results: Median follow up (mFU) was 91 months. We evaluated 50 patients with histologically diagnosed LGG. All the patients were stratified by both RTOG and EORTC criteria. with a concordance of 54.0% (K = 0.111, p = 0.086). All the EORTC high risk patients (n =24, 48%) were high risk also with RTOG criteria. Among the 26 EORTC low risk patients (52%), only 3 (11.5%) were low risk with RTOG criteria, while 23 (88.5%) would have been deemed as high risk. Statistical difference regarding OS and PFS was documented applying either RTOG or EORTC criteria, probably due to the limited population.
Conclusions: The concordance between RTOG and EORTC criteria is low, especially in the evaluation of low risk patients. So far, we cannot compare clinical trials adopting different risk criteria.

F10

A NEW TOOL FOR RADIOGUIDED SURGERY IN MENINGIOMA AND NEUROENDOCRINE PATIENTS: FIRST RESULTS FROM EX-VIVO EXPERIENCE WITH A BETA- RADIATION PROBE

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Background: An almost complete surgery in fundamental in meningioma and neuroendocrine tumors, in terms of survival and local control of disease.

Radioguided surgery (RGS) is a technique aimed at assisting the surgeon to reach a complete resection of the tumour, while minimizing the amount of healthy tissue removed. RGS with beta- radioisotopes, is a novel approach focused on developing a new probe which provides a clearer delineation of the margins of lesions with low radiation exposition for surgeons. To validate this RGS procedure, we first performed ex-vivo tests on meningioma and then on gastro-entero-pancreatic neuroendocrine tumors (GEP NET), which highly express somatostatin receptors.

Materials and Methods: We studied these tumors due to the high uptake of a beta- emitting radiotracer already in use in clinical practice as ^{90}Y-DOTATOC in peptide receptor radionuclide therapy (PRRT). Patients were enrolled according to the tumour Standard Uptake Value (SUV>2) and the expected Tumour to Non-tumour Ratio (TNR>10) estimated from ^{68}Ga-DOTATOC PET/CT images. So far, after giving written informed consent, 4 meningioma and 4 GEP NET patients, received ^{68}Ga-DOTATOC/PET and CT/MR scans, two weeks prior to surgery. Twenty-four hours before surgery, meningioma pts received a median activity of 4.5 mCi; NET pts received 5 mCi of ^{90}Y-DOTATOC.
Results: Surgery was performed as clinical and radiological indicated. Tumors and the around tissues were sectioned in different samples and were examined with the beta- detecting probe. All the tumor samples showed high counts of radioactivity, with difference from surrounding healthy tissues. 11 surgical removed NET lesions identified on CT (8 lesions) or ^{68}Ga-DOTATOC PET/CT (11 lesions) were found to have foci of elevated activity at RGS. The CT missed 1 peripheral nodule and 2 nodules at the hepatic hilum but the complementary evaluation of ^{68}Ga-DOTATOC PET/CT increased the overall accuracy.
Conclusions: These first ex-vivo RGS tests showed that through this probe we can discriminate very strongly between tumor and nearby healthy tissues by the administration of low activities of ^{90}Y-DOTATOC. We are planning to complete the trial in NET patients, as a complete surgery could better the prognosis of this disease. The association of morphological (CT or MRI) and functional (^{68}Ga-DOTATOC PET/CT) imaging, remains mandatory to obtain a correct minimal invasive surgery.

F11

LENALIDOMIDE AS TREATMENT FOR RELAPSED PRIMARY CNS LYMPHOMA

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Background: Primary CNS Lymphoma (PCNSL) is an aggressive form of diffuse large B-cell lymphoma (DLBCL). Lenalidomide is an immunomodulatory agent which has shown activity in Relapsed/Refractory (R/R) GCB non-CNS DLBCL and R/R CNS DLBCL (primary and secondary). Although little is known about the capacity of Lenalidomide to cross the blood-brain barrier this drug appears to be potentially active in PCNSL.
Methods: Here we describe two patients with Relapsed PCNSL and one patient with relapsed primary intramedullary spinal cord lymphoma who were treated with lenalidomide. All patients had a pathological diagnosis of PCNSL

(subtypes: 2 GCB, 1 non-GCB), immunocompetent status, Relapsed status despite at least 2 previous therapies including intravenous methotrexate and rituximab. One of the patients failed autologous stem cell transplant . Lenalidomide was administered orally, 25mg/day on days 1-21 of a 28-day cycle .

Results: Median age was 56 (range 44-64). Median PS 2. Patient 1 achieved complete response (CR) after cycle 8 and he is in remission after 8 months. Patient 2 achieved partial response (PR) after cycle 5; dose reduction after cycle 6 (20mg-day) for Grade 3-Neutropenia, presently after 8 mounth he is well in stable partial remission . Patient 3 achieved PR after cycle 4 and she is well in stable partial remission after 7 months. Toxicity was mainly hematologic and reversible after dose reduction

Conclusions: This case series shows lenalidomide has single agent activity in heavily pre-treated relapsed PCNSL. All three patients had clinical and radiographic response to treatment, Hematologic toxicities occurred at the higher dose, however even at reduced dose, lenalidomide was effective in maintaining remission. Currently the outcome of CNS lymphoma is unsatisfactory and the search for more effective and less toxic regimes is a big challenge. The detection of the drug in the CSF further support the experimentation of lenalidomide in patients with PCNSL . Further prospective studies are warranted to determine the efficacy and optimal dose of lenalidomide in patients with newly diagnosed and R/R PCNSL.

G - Genitourinary Tumours

G01

POTENT NATURAL KILLER (NK) AND MYELOID BLOOD CELL REMODELING BY CABOZANTINIB (CABO) IN PRETREATED METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS

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Background: Cabo is an emerging tyrosine kinase inhibitor in mRCC but its impact on systemic tumor immunity is unknown. We investigated the activity of Cabo in modulating blood innate and adaptive immunity in mRCC patients (pts).

Methods: 15 mRCC pts receiving Cabo (60 mg per os/daily) as per clinical practice were prospectively analyzed at baseline and 3 months for blood immune profiling by 13-color cytofluorimetry on peripheral blood mononuclear cell (PBMC). Pts had clear (n=12) or non clear cells (n=4) histology, with intermediate (n=7), poor (n=8) and good (n=1) risk according to Heng prognostic score, and received at least 2 (n=9), 1 (n=2) or none (n=5) previous therapies, including Nivolumab (n=4).

Results: A significant reduction of myeloid immunosuppressive cell subsets in favor of protective antitumor adaptive and innate immunity was detected in most post vs pre PBMC. Specifically, granulocytic myeloid-derived suppressor cells (MDSC) (CD11b+CD15+HLA-DRneg), monocytic MDSC (CD11b+CD14+HLA-DRneg) and TIM3+ myeloid cells (CD15+TIM3+ and CD14+TIM3+) were remarkably reduced. Total CD11b+CD14+ cells were also decreased, while classical protective (CD14+CD16-HLA-DRhigh) and patrolling (CD14+CD16dimCX3CR1+) monocytes showed a clear boost. Concomitantly, higher frequency of cytolytic and activated NK cells (CD3-CD16+CD56dim vs CD3-CD56+CD16+PD-1+, respectively), paralleled by a decrease of anergic NK cells (CD3+CD16+CD56+TIM3+), was detected in post-Cabo samples. Activated CD8+ and CD4+ T cells (CD3+CD8/CD4+ CD69+ cells) were also raised by treatment along with a specific increase of ADCC-prone CD3+CD16dimCD56-T cells. These latter data indicate that Cabo could intensify direct and Ab-mediated enhancing tumor killing potential in NK and T cells, either as direct effect or through the reduced immunosuppressive pressure exerted by myeloid populations.

Conclusions: Cabo administration is associated with a remarkable priming of circulating cytotoxic and activated NK and T cells, together with a broad remodeling of myeloid cells from an immunosuppressive to a antitumor phenotype. These data indicate that even in advanced disease, Cabo can contribute to reset systemic immune conditions, possibly favoring potential combination with immunotherapy.

G02

ARE ADVERSE EVENTS (AES) PREDICTIVE OF NIVOLUMAB ACTIVITY? DATA FROM THE ITALIAN EXPANDED ACCESS PROGRAM IN METASTATIC RENAL CELL CARCINOMA (MRCC)

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Background: The Italian Renal Cell Cancer Early Access Program was an expanded access program that allowed access to nivolumab, for patients (pts) with mRCC prior to regulatory approval.
Methods: Pts with mRCC previously treated with agents targeting the vascular endothelial growth factor pathway were eligible to receive nivolumab 3 mg/kg once every 2 weeks. Pts included in the analysis had received ⩾ 1 dose of nivolumab and were monitored for AEs using CTCAE v.4.0. Association between sex, age, Body Mass Index (BMI), metastatic sites, number and kind of previous therapies, ECOG PS and related toxicity were evaluated with a logistic regression model that identified only age ⩾ 65 years (Odds Ratio= 1.54 (1.00-2.38; P=0.05).
Results: A total of 389 pts were enrolled between July 2015 and April 2016, 79% after 2 or more lines of therapy. The most common any-grade treatment-related AEs were fatigue (13%) and rash (9%). Twenty-two (5.7%) pts discontinued treatment due to AEs. There were no treatment-related deaths. Treatment-related AEs (grade 1-4) were reported in 32% of pts. Median time to appearance of AEs was 1.4 months (range 0-11.4). Grade 3–4 AEs occurred in 27 (7%) pts. Of the 22 serious AEs who induced treatment discontinuation, 11 (50%) were considered irAEs including: grade 4 hyperglicemia with grade 3 diarrhea (n=1), grade 3 pulmonitis (n=1), grade 3 bronchiolitis obliterans organising pneumonia (BOOP) (n=1), grade 3 asthenia (n=1), grade 3 hypertension (n=1), grade 3 skin toxicity (n=1), grade 3 tremor (n=1), grade 2 eyelid ptosis (n=2), grade 2 liver toxicity (n=1), grade 2 hypothyroidism (n=1). AEs were generally manageable with treatment as per protocol-specific guidelines. At a median follow-up of 12 months, the median progression-free survival was 4.5 months (95% CI 3.7 - 6.2), the 12-months overall survival rate was 63%. Pts with toxicity (124 pts) had a significant (P=0.01) longer survival (1 year OS 69%) in comparison to pts who did not experience AEs (1 year OS 59%).
Conclusions: The appearance of AEs strongly correlates with survival benefit in a real-life population of mRCC pts treated with Nivolumab.

G03

SAFETY AND EFFICACY OF CABOZANTINIB FOR METASTATIC NON-CLEAR RENAL CELL CARCINOMA: REAL WORLD DATA FROM AN ITALIAN MANAGED ACCESS PROGRAM

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Background: Final results from the randomised phase III METEOR trial confirmed a survival benefit of cabozantinib over everolimus in patients with advanced clear-cell renal cell carcinoma (RCC) who progressed after at least one previous antiangiogenic inhibitor. However, in the METEOR study, as previous clinical trials, non-clear cell histologies were excluded, thus no efficacy and safety data are reported to this setting of patients.
Methods: Data were collected across 24 Italian hospitals. Cabozantinib was available, upon physician request, from September to December 2016. Patients were aged 18 years and older with advanced non-clear cell RCC and measurable disease, with an Eastern Cooperative Oncology Group Performance Status 0 to 2, who had relapsed after one or more prior systemic treatment for metastatic RCC. Cabozantinib was administered orally at 60 mg once a day in 28 days-cycles. Dose reductions to 40 or 20 mg were made after onset of toxicity. Patients were also monitored for adverse events using CTCAE v.4.0.
Results: 17 patients were enrolled. 3 (18%) patients were diagnosed with type I papillary RCC, 9 (52%) type II papillary, 3 (18%) chromophobe and 2 (12%) with Bellini duct carcinoma. 11 patients started with full dose of 60 mg. Due to clinical conditions, age and comorbidity, 6 patients started from a lower dose of 40 mg. Median progression free survival was 7.83 months (0.4 – 13.4) while median overall survival was not reached but one-year overall survival was about 60%. 6 patients (35%) reached a partial response to treatment and other 6 patients (35%) showed a stable disease. In the remaining 5 patients (30%) we observed progressive disease. Grade 3 and 4 AEs were observed in 36% of patients. Among 20 patients, only 1 (6%) discontinued treatment due to AEs. Asthenia (41%), diarrhea (35%), aminotransferase increasing (35%), mucosal inflammation (35%), hand and foot syndrome (24%) and hypothyroidism (24%) were the most frequently AEs observed.
Conclusions: Our data showed that in patients with non-clear cell RCC, cabozantinib is a well-tolerated treatment with demonstrated promising activity that needs further investigation in a larger population, better within randomized prospective clinical trials.

G04

CAN THE LYMPHOCYTE MICRORNA EXPRESSION PROFILE HELP US TO IDENTIFY NOVEL PREDICTIVE BIOMARKERS OF IMMUNOTHERAPY RESPONSE IN METASTATIC RENAL CARCINOMA PATIENTS?

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Background: The recent understanding of the central and dynamic role of immune system contributed to the revolution in the renal cell carcinoma (RCC) treatment, resulting in a greater number of therapeutic opportunities. The currently available drugs do not benefit every patient equally. Biological factors specific for some individuals affect this variation in therapy response. The main aim of our study was to analyze the lymphocyte microRNA expression profile in metastatic RCC patients, in order to investigate the molecular mechanisms and signaling pathways involved in the immunotherapy response.

Patients and Methods: Total RNA and miRNAs from peripheral lymphocytes were isolated using the miRNeasy Mini Kit, and their quality and quantity were assessed using the 2100 Bioanalyzer and spectrophotometer NanoDrop ND-1000. Using a TaqMan Low Density Array A human microRNA microarray analysis, the expression profile of 377 lymphocyte miRNAs was analyzed in 10 metastatic clear cell RCC (ccRCC) patients before and after Nivolumab treatment. A cut off of fold change >2 was considered for up-regulated and <0.3 for down-regulated miRNAs.

Results: Microarray analysis showed that a subset of 59 miRNAs, including miR-22, miR-24, miR-99a, miR-152, miR-183, miR-194, miR-155, miR-214, miR-383, miR-484, miR-486, miR-492, miR-708 and miR-885-5p, involved in several cancer-related processes, including cell cycle regulation, HIF-1, PI3K/Akt, p53, Wnt, and FOXO signaling pathways, was differentially expressed in peripheral lymphocytes of metastatic ccRCC patients respondent to Nivolumab. Among these deregulated miRNAs, 22 were found to be up-regulated in their expression and 37 down-regulated. Finally, the expression of specific peripheral lymphocyte miRNAs such as miR-22, miR-24, miR-155, miR-484, miR-335 and miR-492 was analyzed by Real-time PCR in a cohort of independent samples from 10 metastatic ccRCC patients who showed a stable disease or partial response over 12 months, confirming the coherence of our results.

Conclusions: Recent findings reported in literature regarding variations in expression of some tissue miRNAs involved in proliferation, metastasis development, prognosis, and therapy response of RCC patients have confirmed the coherence of our results. Our data, in future, could help to identify potential predictive biomarkers of response to Nivolumab treatment useful for clinical management of patients subjected to immunotherapy.

G05

PERCUTANEOUS MICROWAVE THERMO-ABLATION (MWTA) OF KIDNEY CANCER UP TO 5 CM: A CLINICAL EXPERIENCE

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Background: The standard treatment of T1 renal cell carcinoma is surgery. The aim of this clinical experience is to evaluate the percutaneous microwave thermo-ablation (MWTA) for patients where surgery could not be the treatment of choice

Materials and methods: Were evaluated 204 patients (139 males) with 210 renal neoplasms from 10 to 52mm Inclusion criteria: kidney neoplasms with largest diameter (Ø) up to 5cm, presence of comorbidities or surgical/anesthetic risk, renal failure, solitary kidney, refusal of surgical therapy, technical feasibility of RFTA/MWTA (AMICA™ MW Ablation System; probes from 14G to 16G), PT$>$50%, PLT$>$50.000/mm^3

FUP was established in contrast enhanced CT or MRI at 1 month from treatment and afterwards every 6 months until 24 and then abdominal US or CEUS every 6 or 9 months, CT or MRI if US or CEUS were unclear

Results: From April 2008 to December 2017, 146 patients (101 males and 45 females, mean age 62.05yrs) with renal tumors from 21 to 50mm (mean Ø 31.9mm), according to the protocol (RFTA for nodules $<$20mm and MWTA from 21 to 50mm), underwent to MWTA. 93.1% of treatments were US-guided and biopsy was performed in all cases: 84% clear-cell carcinomas, 9.2% non clear-cell and 6.8% non-diagnostic

Complete Response (absence of contrast enhancement within the treated lesion and/or presence of avascular area with diameter lager than the treated lesion) was found in 139 patients after the first treatment (95.2%) and in 145 patients (99.3%) after re-treatment

2 long-term local-recurrences ($>$12months from treatment) were found: 1 patient with clear-cell histology was re-treated with MWTA while the second patient, papillary histology, underwent to surgery

In 1 patient was found a metastatic para-aortic LN after 24 months from treatment of a clear-cell carcinoma (Ø 48mm) without evidence of loco-regional relapse and has been started a 1st line with sunitinib. 2 deaths were noted, 1 due to pulmonary embolism and 1 due to acute pulmonary edema, in absence of loco-regional relapse, respectively at 28mos and 34mos. Complications: 1case of

macroscopic hematuria, 1case of renal sub-capsular hematoma, 2traumatic injury of pelvis with formation of urinomas, 1case of paraesthesia in the area of the left genitofemoral nerve.

The median FUP time was 42.6 months, from 4 to 116.

Conclusions: MWTA seems to be a safe and effective treatment and could be the first choice treatment for kidney tumors up to 5cm. Comparison trials with nephron-sparing surgery are desirable

G06

RADIUM-223 RE-TREATMENT IN AN INTERNATIONAL, OPEN-LABEL, PHASE 1/2 STUDY IN PATIENTS WITH CASTRATION-RESISTANT PROSTATE CANCER AND BONE METASTASES: 2-YEAR FOLLOW-UP

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Background: Radium-223 (Ra-223) treatment (tx) is indicated for patients (pts) with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases (mets) (6 × 55 kBq/kg IV injections [inj]; 1 inj q4wk). Early results of an international, open-label, phase 1/2 study (NCT01934790) showed that re-treating pts with Ra-223 was well tolerated with favorable effects on disease progression. Here we report safety and efficacy findings from a 2-year follow-up.

Methods: Pts with CRPC and bone mets who completed 6 initial Ra-223 inj with no disease progression in bone and later progressed were eligible for Ra-223 re-tx (6 additional Ra-223 inj), provided that hematologic parameters were adequate. No concomitant cytotoxic chemotherapy was allowed; other concomitant agents for prostate cancer (including abiraterone and enzalutamide) were allowed at investigator discretion. The primary objective was safety. Exploratory objectives were time to radiographic bone progression, radiographic progression-free survival (rPFS), overall survival (OS), time to first symptomatic skeletal event (SSE), and SSE-free survival, all calculated from re-tx start. Pts will be followed for safety up to 7 years after last Ra-223 dose; an active 2-year follow-up evaluated exploratory objectives. Safety results from the active follow-up period and updated efficacy are reported.

Results: 44 pts were re-treated with Ra-223; 29 (66%) completed all 6 inj (median number inj = 6). 34 (77%) of 44 pts entered active follow-up, during which no new safety concerns were noted. There were no serious drug-related adverse events. 26 (59%) of 44 pts had an rPFS event (radiographic progression or death); median rPFS was 12.0 months. Only 5 (11%) of 44 pts had radiographic bone progression; median time to radiographic bone progression was not reached. Median OS was 24.4 months. Median time to first SSE and SSE-free survival were 16.7 and 12.8 months, respectively.

Conclusions: Re-treating with Ra-223 was well tolerated in this select pt population, led to minimal hematologic toxicity, and provided continued disease control in bone at 2-year follow-up.

G07

A PROSPECTIVE REAL-LIFE STUDY EVALUATING ABIRATERONE ACETATE PLUS PREDNISONE EFFECTIVENESS IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (ABITUDE)

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Background: There is an emerging need to investigate abiraterone acetate plus prednisone (AAP) effectiveness in routine clinical practice: the ABITUDE study was designed to evaluate hard endpoints in a real-world setting on chemotherapy-naïve patients with metastatic Castration-Resistant Prostate Cancer (mCRPC). Here we present the main results of the first interim analysis.

Methods: ABITUDE is a prospective, observational cohort study. Patients were consecutively enrolled in 49 Italian centers at the beginning of AAP and are being followed for 3 years. The primary objective is to evaluate PSA decline rate and radiographic progression-free survival (rPFS) during AAP. Patient's quality of life and pain were measured every 6 months with the Functional Assessment of Cancer Therapy–Prostate (FACT-P; score range: 0-156) and the Brief Pain Inventory (BPI; score range: 0-10).

Results: Among 481 enrolled patients, 453 (94.2%) were evaluable for analyses. Mean age at enrolment was 75.9±7.5 years; patients aged >=80 years were 164 (36.2%). Median (25^{th}-75^{th} percentile) observation

Table 1.

Comorbidities, N (%)	307 (67.8)
Hypertension, N (%)	219 (48.3)
Hypercholesterolemia, N (%)	52 (11.5)
Diabetes, N (%)	48 (10.6)
Gleason score ⩾8 at diagnosis, N (%)	232 (59.2)
Metastases, N (%)	
Bones	318 (70.2)
Lymph nodes	230 (50.8)
ECOG PS, N (%)	
0	250 (56.4)
1	170 (38.4)
⩾2	23 (5.2)

duration per patient was 8.8 (5.8-12.2) months. Baseline characteristics are shown in Table 1.

During AAP treatment 242 patients (60.3%) had a ⩾50% PSA decline (N=401). In 439 patients with available follow-up data the 1-year probability for no radiographic progression was 73.9% (standard error: 2.9%; median time to event not estimable).

At enrolment median (25^{th}-75^{th} perc.) FACT-P total score was 110 (95; 120) points (N=421); during observation period 218 patients (71.9%) did not show functional decline (N=303). Median (25^{th}-75^{th} perc.) baseline BPI worst pain score was 2 (0; 4) points (N=388); the 1-year probability for no pain progression was 70.9% (N=439). Adverse reactions occurred in 10% of patients, the vast majority being non serious (9.4%).

Conclusions: These data suggest that AAP was active and safe in a real-world patient sample with comorbidities.

G08

RESULTS FROM A LARGE, MULTICENTER, RETROSPETIVE ANALISYS ON RADIUM 223 USE IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER (MCRPC) IN THE TRIVENETO ITALIAN REGION

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Background: Radium223 was introduced for the treatment of mCRPC with bone lesions, based on the results of a randomized trial showing reduction of the risk of death and skeletal events. Our aim is to evaluate outcome of patients (pts) receiving Radium223 in a real-world setting.

Methods: We conducted a multicentre retrospective analysis on pts treated with Radium223 in the Triveneto Region. Key inclusion criteria are: histological diagnosis of PC, presence of symptomatic bone lesions without visceral metastases, at least one cycle of Radium223.

Results: Since its introduction in Italy, 158 pts have received Radium223 in our Region. Baseline characteristic are outlined in table 1. After a medial follow-up time of 9.5 months (mos), 75 pts have died. Median OS was 14.2 mos, median PFS was 6.2 mos. 71 (45%) pts achieved progression as best response; ORR was 11%; clinical benefit rate was 28%. 37 pts (23%) early stopped the treatment because of disease progression.

Table 1. Baseline patients' characteristics.

Median age (range)	72 years (52–82)
Median PSA (range)	335.6 ng/ml (0.33–4552)
Median ALP (range)	256 U/L (19.2–3028)
Prior prostatectomy	70 (44%)
Prior radical radiotherapy	60 (38%)
Baseline lymph node disease	46 (26%)
Treatment line	
− First line	41 (26%)
− Second line	37 (23%)
− Third line	33 (20%)
− Fourth or further line	47 (30%)

ECOG performance status was prognostic for survival (median OS 18.4 vs 12.3 vs 7.5 mos; 0 vs 1 p=0.0062; 0 vs 2 p=0.0002) while previous prostatectomy or docetaxel exposure were not. A neutrophil to lymphocytes ratio (NLR) greater than 3 significantly impacted on OS (18.1 vs 9.7 mos; $p<0.001$) and slightly on PFS (6.6 vs 5.6 mos; p=0.05). Pts with a baseline ALP value ⩾ 220 had worse OS and PFS (24.1 vs 10.5 mos; 7.2 vs 5.5 mos; $p<0.001$). Pts with ALP value reduction during treatment achieved better OS (p=0.029) and PFS (p=0.002). There was no difference according to the line of therapy (0 vs ⩾1, p=0.490).

Main G3/4 toxicities were anemia (13%), asthenia (6%), thrombocytopenia (3.5%).

Conclusion: At the best of our knowledge, this is the largest Italian report on Radium223 in real-word setting; moreover, it confirms comparable OS and PFS data of the pivotal study, as well as the predictive role of ALP and NLR. Definition of the optimal position of Radium223 in the treatment of mCRPC has still to be defined.

G09

WHEN AND HOW TO FOLLOW-UP: AN ITALIAN SURVEY ON TESTICULAR CANCER

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Background: Testicular cancer (TC) is a common disease in patients (pts) between 15 and 40 years. National and international guidelines are not unanimous as to how often, for how long and with what exams to carry out the follow-up (FU) of pts with a diagnosis of TC. Aim of this study was to investigate the attitudes of Italian urologists and oncologists in strategies of surveillance for seminoma (S) and non-seminoma (NS).

Methods: We developed and conducted an online survey including 42 items evaluating the FU of S and NS and investigating any other strategies based on the individual center's experience. Questions focused on FU schedule (FUS) for stage I and II S and NS in pts treated with surgery alone or with adjuvant chemo- or radiotherapy. We proposed multiple choice tests with agreement scored in 5 points (from very little to very much) or open-ended questions.

Results: A total of 27 Italian health care centers completed the survey with 33 respondent physicians (RE). As results, 78.8% of RE have expertise with TC for more than 10 years, and 39.4% follow more than 10 pts with TC per year. In the first instance, specialists prefer to follow the national guidelines of AIOM (71%) than the European EAU (11.5%) and American NCCN (10.7%) or European ESMO (10.3%). Tumor dimension >4 cm (much – 55.2% of cases), rete testis invasion (much – 58.6%) and patient's choice (much – 51.7%) seem to drive timing and exams to follow-up stage I S pts (85.7% of RE). Instead, lymph-vascular invasion (very much – 61.5%) and patient's choice (much – 69.2%) represent the main factors that drive adjuvant therapy versus close surveillance and affect timing and exams to follow-up stage I NS pts (76.9% of RE). FUS varies widely among centers with 75.0% and 68.7% of RE that alternate first- and second-level exams such as CT scan and chest x-ray or abdominal ultrasound. Depending on year of FU, 66.6% and 69.2% of RE follow-up their pts over 5 years for stage I S or NS, respectively. For stage IIB-III S and IB-III NS, after curative treatment, FUS seem to have a large variability as well as for stage I S or NS. Moreover, most of the RE (41.7-90.0%) prescribe testicular ultrasound at least once a year regardless of stage, therapy or year of FU.

Conclusion: This real world survey discloses a wide FUS heterogeneity among Italian centers and physician attitudes. Further investigations are urgent needed to define clear and physician-friendly guidelines demonstrating a long-term clinical outcome.

G10

IRAENE TRIAL: A RETROSPECTIVE STUDY OF CORRELATION BETWEEN IMMUNO-RELATED ADVERSE EVENTS (IRAES) OCCURRENCE AND DISEASE CONTROL RATE IN METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS (PTS) TREATED WITH NIVOLUMAB

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Background: Immunotherapy (IO) has brought dramatic clinical benefits to patients with mRCC. In particular, Nivolumab has become the standard of care for the second and third line of mRCC. Most patients tolerate IO, but serious irAEs have been reported. Some studies indicate the correlation of irAEs and clinical response in different cancer types. For mRCC treated with nivolumab, the impact of irAEs on clinical outcome is unknown.

Methods: A retrospective review of pts with mRCC treated with nivolumab in clinical practice between March 2017-January 2018 from 14 Italian centers of the IGO group (Innovators in Genitourinary Oncology) was performed. Pts enrolled in clinical trial or expanded access program were excluded. IrAEs were assessed based on the treating physician diagnosis.

Results: Totally, 144 pts met inclusion criteria. Median age was 67 years, 108 pts (75%) were male. Histology was clear cell in 131 pts (91%) and non clear cell in 13 pts (9%). IrAEs were noted in 59 pts (41%) (Table 1) with steroid required in 29/59 pts (49%). The median time from the beginning of nivolumab treatment to the irAE occurrence was 10 weeks.

In pts who developed irAEs, we observed a disease control rate of 67% with 4% of complete response (CR), 21% of partial response (PR), 42% of stable disease (SD) (according to RECIST criteria) while in pts who did not develop irAEs, the disease control rate was 52% with 2% CR, 12% PR, 38% SD. Development of irAEs had a statistically significant impact on disease control rate (p=0.047). There was also no significant association of steroid use with disease control rate (p = 0.54).

Table 1. Incidence of Immuno-related Adverse Events.

Immuno-related Adverse Events	Any grade
gastrointestinal	15%
renal	5%
polmonar	15%
hepatic	3%
endocrinopatic	15%
skin	20%
neurologic	2%
general (fatigue/astenia, anoressia, iperpiressia)	25%
Other	10%

Conclusions: The development of irAEs may be correlated with better response to nivolumab. This data may be limited by retrospective nature. A long-term follow-up is required to determine the impact of irAEs on survival in mRCC patients treated with nivolumab.

G11

PROGNOSTIC IMPACT OF EARLY PSA DECLINE IN CASTRATION-RESISTANT PROSTATE CANCER PATIENTS TREATED WITH ABIRATERONE OR ENZALUTAMIDE

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Background: Previous studies demonstrated a predictive value of prostate-specific antigen (PSA) kinetics for treatment outcomes. Our study aimed to evaluate the prognostic role in terms of progression free survival (PFS) and overall survival (OS) of early PSA decline in docetaxel-naïve and docetaxel-treated mCRPC patients (pts) receiving abiraterone acetate (AA) or enzalutamide (E).
Methods: We retrospectively collected data of CRPC pts treated with AA or E between 2010 and 2018, with available early PSA value (defined as a PSA detected between 28±7 and 60±7 days). Pts were divided in early responders and non-early responders according to early PSA response (defined as a PSA decline ⩾50% from baseline). PFS and OS were measured from the start of AA or E, both in pre- and post-docetaxel setting. Univariate and multivariate analyses (adjusted for baseline PSA, ALP, LDH, haemoglobin, albumin, ECOG PS, use of opioids, presence of visceral disease, treatment with AA or E and pre- or post-docetaxel setting) were performed.
Results: 219 pts were analysed, and 103 had information about early PSA value. 43 pts (42%) received E (pre-docetaxel 26, post-docetaxel 17) and 60 (58%) received AA (pre-docetaxel 29, post-docetaxel 31). 49 pts (47.6%) achieved early PSA decline. In patients treated with AA or E in pre-docetaxel setting (n=55), median PFS was 18.9 (with early PSA decline) vs 6.1 months (without early PSA decline, p=0.001), while in the post-docetaxel setting (n=48) median PFS was 11.9 vs 4.0 months (p<0.001). In the whole cohort, median PFS was 14.9 vs 4.6 months in patients with and without early PSA decline, respectively (p<0.001).

In pre-docetaxel setting pts who achieved early PSA decline during AA or E had a median OS of 39.5 vs 17.6 months (p=0.063), while in post-docetaxel setting median OS was 29.6 vs 11.4 months (p=0.013). Considering both pre- and post-docetaxel AA or E treatment, median OS was 30.4 vs 15.1 (p=0.003) in patients with and without early PSA decline, respectively. At multivariate analysis, early PSA decline confirmed an independent association with PFS (HR 0.20; 95%CI: 0.11-0.39, p<0.001) and OS (HR 0.21; 95%CI: 0.10-0.46, p<0.001).
Conclusion: In this retrospective series, metastatic CRPC pts treated with AA or E both in pre- and post-docetaxel setting who achieved an early PSA decline had a significantly better OS and PFS. These data could be helpful in the early identification of pts with resistance to new generation hormone therapy.

G12

MANAGEMENT AND SAFETY OF CABOZANTINIB (CABO) IN METASTATIC RENAL CELL CARCINOMA (MRCC): RETROSPECTIVE ANALYSIS

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Background: CABO significantly improves outcomes in mRCC pts, but management of adverse events (AEs) represents a crucial point to optimize treatment. The aim of this study was to describe safety profile of CABO in clinical practice
Methods: Data from mRCC patients (pts) treated at Gustave Roussy with CABO have been analyzed. Patient characteristics, prognostic factors and outcome data were retrospective collected. AEs were described according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Only AEs leading to dose reduction or dose discontinuation were analyzed
Results: Data from 66 pts have been collected. The median age was 55 years (26-72). The majority of pts had clear-cell histology (77%). CABO was administered as second

line therapy in 15 pts (23%), as third line in 17 pts (26%), as fourth line 12 pts (18%) and as further lines in the remaining 22 pts (33%). At time of starting CABO International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic classification was available in 56 pts: 6 (11%) were in the good risk group, 34 (61%) in the intermediate risk group and 16 (28%) in the poor risk group. Median PFS was 9 months (95% CI 6–11) and median OS was 18 months (95%CI 12-23). Among 26 pts that discontinued the treatment, in 4 pts (15%) reason was an AE. 22 pts (33%) experienced at least one AE requiring dose adjustment or drug discontinuation: 7 were grade 2, 9 were grade 3, 1 was grade 4. Eleven pts synchronously experienced one second AEs: 8 were grade 2, 3 were grade 3. Four patients presented also a third AEs (all grade 2). In 23 pts (35%) dose reduction were required. One dose reduction occurred in 20 pts (30%) and in 3 pts (5%) a further reduction was required. Fatigue and diarrhea were the most frequent AEs leading to dose reduction or discontinuation. In this analysis median OS was not different between pts who experienced reduction versus pts continued with full dose. No different frequencies of AEs emerged across different lines of treatment

Conclusion: CABO represents an important option for the treatment of mRCC. This study confirms safety of CABO in clinical practice but about one third of pts experienced a significant AEs. Correct management of safety profile, including dose adaptation and alternative schedules, may improve pts tolerance and long-term benefits from CABO

G13

TYROSINE KINASE INHIBITORS IN RENAL CELL CARCINOMA WITH BRAIN METASTASES: CABOZANTINIB IS A SAFE AND EFFECTIVE OPTION IN A REAL-WORLD POPULATION

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Background: In a real-world experience of metastatic renal cell carcinoma (mRCC) patients (pts) treated in second and further lines, cabozantinib revealed promising efficacy and a manageable toxicity profile. Here we report the sub-analysis of pts with brain metastases (BM) treated with cabozantinib within the Italian Managed Access Program (MAP).

Methods: Data were collected across 24 Italian hospitals. Cabozantinib was available, upon physician request, from September to December 2016. Ninety-six pts progressing after at least one prior regimen were treated with cabozantinib at standard dose. Clinical data on treatment compliance, symptoms as well as radiological assessments were retrospectively reported from patients' charts.

Results: Twelve pts presented with BM. Despite predominant high tumour burden, poor performance status and heavily pre-treated disease, 50% of pts experienced partial response (PR) as best response. Pan-encephalic radiotherapy was safetly administered for BM within a multimodality approach before, after or concurrently to cabozantinib treatment. The main cause of treatment discontinuation was progressive disease except for one case of severe gastrointestinal bleeding. Toxicity was comparable to overall MAP population: 83% of pts experienced grade 1/2 toxicity; grade 3 and 4 adverse events (AEs) accounted for 36% of pts. Most common AEs included hypertension (30%), asthenia (25%), aminotransferase elevation (25%), hypothyroidism (16%), nausea (16%), emesis (16%), diarrhea (16%). Median progression-free survival and median overall survival were respectively 5.8 months (95% CI, -) and 8.8 months (95% CI, -).

Conclusions: Our study proves cabozantinib antitumor activity in patients with brain involvement from RCC. It represents a valid and tolerable treatment option even in highly pre-treated pts, with high tumor burden. A combined modality approach for RCC with BM, whenever feasible, is recommended to improve oncological outcomes.

G14

EARLY AND LATE PSA AS PREDICTIVE MARKER IN ADVANCED LINES IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER (MCRPC)

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Background*:* The standardization of the use of the Prostate Specific Antigen (PSA) in the evaluation of responses to treatment and the correlation with OS and PFS in metastatic castration resistant prostate cancer (mCRPC) is still debated topic; especially related to the timing of evaluation (after the fist ore third cycle) and the rate of decrease (-30% or-50%).

Material (patients) and methods*:* A retrospective analysis involving 285 patients with histological diagnosis of mCRPC treated in first line, second and third line with current therapeutic options at Santa Chiara Hospital in Trento was conducted.

The primary objective of the study was the assessment of the potential predictive value, effectiveness (PFS and OS) of the PSA marker after the first cycle of therapy (at 3 weeks with chemotherapy and at 4 weeks if hormonotherapy) defined as ' early PSA ' and after 3 cycles (12 weeks) defined as ' Late PSA '.

The associations between qualitative variables have been evaluated using the Chi-Quadro test or testExactly Fisher's. In the case of quantitative variables, the analysis of the using maximally selected log-rank statistics. The median duration of the responses and survivals were calculated by the method of Kaplan-Meier and the comparisons between the curves were made through the log-rank test. All statistical analyses were performed by SPSS (version 17.0).

Results: At fist line an early reduction of the marker, regardless of the rate, are not significantly demonstrated for PFS and OS. A reduction of $>$ 30% at 12 weeks was instead significantly correlated with PFS and OS (PFS 10 months (CI95% 6-10 p 0.002), OS 25 months (IC 95% 24-27 $p < 0.0001$)).

In advanced line both early and late PSA reduction was significantly correlated with OS and PFS. In particular at second line patients with a reduction$>$ 50% after the first cycle have 8 month PFS (CI95% 6-11 p 0.003).

At third line the early reduction of the marker has been shown to be significant for PFS (PSA early reduction of $>$ 30% PFS 7 months (CI95% 4-9 p 0.001)) and also confirms significant for OS with a median of 31 months (IC 95% 12-50 p 0.003).

Conclusion: In conclusion, our analysis highlights early PSA as a predictive marker in advanced lines and confirms the meaning of late PSA regardless of the treatment line.

However, it is necessary to underline the intrinsic and extrinsic confounding factors present in the first lines and the need to validate the data by prospective studies.

G15

EVEROLIMUS AND BONE TARGETED THERAPY IN THE INHIBITION OF THE CROSS-TALK BETWEEN CLEAR-CELL RENAL CELL CARCINOMA AND OSTEOCLASTS IN AN IN VITRO CO-COLTURE MODEL.

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Background: The skeleton is one of the most common site of metastatic spread from advanced clear-cell renal cell carcinoma (ccRCC). Most of the bone lesions observed in advanced RCC patients are mainly classified as osteolytic, causing severe pain and morbidity due to bone pathological destruction. Targeting the mammalian target of rapamycin (mTOR) is an efficient treatment option for advanced renal cell carcinoma patients. Moreover, bone targeted therapy could benefit bone metastatic patients from advanced RCC. However, data is needed to support a beneficial effect of a combined therapy. The aim of this work is to investigate the effect of targeting mTOR and the sequential combination with bone targeted therapy in the inhibition of the interplay between RCC cells and bone stromal cells.

Materials and Methods: A previously optimized co-colture model is used to reproduce the interplay between Caki-2 cells (ccRCC cell line) and osteoclasts. Human osteoclasts are obtained from the differentiation of monocytes isolated from peripheral blood mononuclear cells (PBMCs) of healthy donors by Ficoll density gradient. For co-colture assays Caki-2 cells are seeded in transwell inserts and they are following plated over the mononuclear cultures for 14 days. Cells are treated at fixed timing with Everolimus, Zoledronic Acid and Denosumab as single or sequential combined treatment. Doses of drugs are selected on the basis of plasma levels from pharmacokinetic clinical data.

Results: We show that Caki-2 cells can secrete soluble factors able to induce osteoclast cells differentiation from isolated human monocytes, as showed by specific tartrate-resistant acid phosphatase (TRAP) staining and f-actin ring formation, in a statistically significant manner. Moreover, differentiated osteoclasts showed to be functionally active by Pit Formation Assay. Interestingly, Caki-2 cells co-coltured with osteoclasts acquire a more aggressive phenotype based on gene expression analysis. Moreover, the sequential combined treatment with Everolimus and Zoledronic Acid is the most effective in the inhibition of both Caki-2 cells survival and osteoclastogenic potential.

Conclusions: At preclinical level, we confirm the value of our in vitro co-colture model as an useful tool to mimic the bone microenvironment and to assess drug sensitivity in vitro. A better understanding of the molecular mechanisms involved in the tumor-bone stomal cells cross-talk will be next investigated.

G16

VINFLUNINE IN PRE-TREATED PATIENTS WITH METASTATIC UROTHELIAL CANCER (MUC): A SYSTEMATIC REVIEW OF SEVEN REAL-WORLD (RW) EUROPEAN STUDIES

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Study	German study	French study	Greek study	Scandinavian study	British study	Italian study	Spanish study
Patients	n = 77	n = 134	n = 71	n = 100	n = 49	n = 217	n = 102
Median OS, mo	7.7	8.2	11.9	6.3	9.1	8.1	10.0
[95% CI]	[4.1-10.4]	[6.5-9.4]	[7.4-21]	(NP)	[6.0-12.7]	[6.3-8.9]	[7.3-12.8]
Median PFS, mo	NP	4.2	6.2	2.8	5.1	3.2	3.9
[95% CI]		[2.8-4.8]	[4.4-8.8]	[NP]	[4.3-8.7]	[2.6-3.7]	[2.3-5.5)
ORR %	23	22	15	23	29	13	25

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Background: Vinflunine is the only chemotherapy agent for which there is a marketing authorization in Europe for platinum-pretreated patients (pts) with UC, based on a randomized phase III clinical trial. However, RW data regarding long-term efficacy and safety of vinflunine in unselected populations is needed. We conducted a systematic review gathering RW data from published observational European studies.

Methods: Controlled studies and case series were excluded. We systematically explored the following endpoints: Overall Response Rate (ORR), Progression-Free Survival (PFS), Overall Survival (OS) and toxicity.

Results: From 2014 to 2017, seven post-marketing studies including 750 pts were published: one was prospective and six were retrospective. Median ORR and median OS ranged from 13% to 29% and 6.3 to 11.9 months (mo) respectively (see Table below). In long-term survivors, OS reached 20.5 mo. Initial doses ranged from 250 to 320 mg/m^2 adapted to patient's conditions. In multivariate analysis, OS was found to be associated with the following risk-factors at baseline: ECOG PS > 0, hemoglobin < 10 g/dl, and presence of liver metastasis. The favorable safety profile demonstrated in randomized trials was confirmed. Main toxicity was hematological: neutropenia (G 3/4 in 1% to 23%) and anemia (G 3/4 in 4% to 33%). Constipation seemed to be less frequent than previously reported (G 3/4 in 5% to 22%).

Conclusion: Our data reinforce the role of vinflunine as standard single-agent CT in platinum-pretreated mUC, as the only agent validated both by phase III and extensive RW evidence.

G17

CAN DIARRHEA DURING TKI TREATMENT AFFECT NIVOLUMAB EFFICACY IN SECOND LINE TREATMENT OF METASTATIC RENAL CELL CARCINOMA? PRELIMINARY DATA FROM AN OBSERVATIONAL STUDY

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Background: Diarrhea is a common adverse event of treatment with tyrosine-kinase inhibitors (TKi) for metastatic renal cell carcinoma (mRCC), occurring in about half of the patients. Diarrhea of any grade could influence quality of life, causing discomfort. Recently, the correlation between diarrhea and stool bacteriomic profile was explored, revealing the influence of TKi-related microbiota alteration on the onset of diarrhea. Furthermore, specific microbiota profiles were associated with the efficacy of immune checkpoint inhibitors. Based on these data, we conducted this study to investigate the efficacy of Nivolumab as second line therapy for mRCC considering the TKi-related diarrhea.

Patients and methods: We analyzed the efficacy of Nivolumab at standard dose of 3 mg/kg every 2 weeks as second line therapy for mRCC. We evaluated response rate and progression-free survival (PFS) according to the diarrhea of any grade reported during the first line TKi-treatment.

Results: We collected the data of 22 consecutive mRCC patients. 2 patients obtaining an objective response with Nivolumab did not experience diarrhea during the first line treatment. Among the 11 patients with stable disease, only 4 patients experienced diarrhea during TKi-treatment, while 8 of the 9 patients with progressive disease had diarrhea during the first line therapy. PFS with Nivolumab was 4.3 months for the patients who experienced diarrhea as TKi adverse event and 7.8 months for the patients without diarrhea (p=0.018). Median OS was not reached.

Conclusions: Our results suggested that diarrhea could affect the efficacy of second line Nivolumab, probably through microbiota alteration. Updated data and stool bacteriomic profile will be presented at the meeting.

G18

SECOND-LINE THERAPY FOR METASTATIC UROTHELIAL CARCINOMA: DEFINING THE BEST TREATMENT OPTION AMONG IMMUNOTHERAPY, CHEMOTHERAPY, AND ANTI-ANGIOGENIC TARGETED THERAPIES. A SYSTEMATIC REVIEW AND META-ANALYSIS

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Backgroud: There is no second-line standard of care universally accepted for platinum-refractory metastatic urothelial carcinoma (mUC). Single agent chemotherapy (taxanes and vinflunine) is frequently used, with a modest benefit. Two noteworthy strategies showed promising though inconclusive results; combining anti-VEGF(R) targeted therapies with chemotherapy and immunotherapy with anti-PD-1/PD-L1 inhibitors. We perform a systematic review and meta-analysis of the available data in order to investigate the more active second-line treatment of mUC.
Patients and Methods: Searching the MEDLINE/PubMed, Cochrane Library and ASCO Meeting abstracts prospective studies were identified. Data extraction was conduced according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The measured outcomes were OS and PFS.
Results: Seven randomized controlled trials were selected for final analysis, with a total of 2451 patients evaluable. Chemotherapy with vinflunine did not reduce the risk of progression (HR=1.11; 95%CI 0.78–1.57; p=0.56) or death (HR=0.97; 95%CI 0.70–1.34; p=0.87) compared to taxanes. Immunotherapy was associated with improved OS over chemotherapy (HR=0.81; 95% CI 0.71–0.92; p<0.0009). The OS benefit of immunotherapy was retained when compared to taxanes, but not compared to vinflunine, although without a significant difference between the two subgroups (p=0.30). A lack of PFS (HR=0.73; 95%CI 0.53–1.02; p=0.08) and OS (HR=1.0; 95%CI 0.79–1.28; p=0.99) benefit was observed with the association of anti-VEGF(R) plus chemotherapy compared to chemotherapy. No PFS (p=0.14) or OS (p=0.13) differences were detected when comparing anti-VEGF(R) +/− chemotherapy and immunotherapy.
Conclusions: Immunotherapy significantly improved OS compared to chemotherapy in mUC unselected for PD-L1 status. The addition of anti-VEGF(R) to chemotherapy did not provide any statistically significant PFS or OS benefit. No substantial differences were observed between anti-angiogenic targeted therapies and immunotherapy. Taxanes or vinflunine could be taken into account considering the same efficacy with a different toxicity profile.

G19

ONCONEPHROLOGICAL MULTIDISCIPLINARY EVALUATION IN RENAL CANCER PATIENTS TREATED WITH TARGETED THERAPY

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Introduction: The anti-vascular endothelial growth factor tyrosine-kinase inhibitors (TKi) and the mammalian target of rapamycin (mTORi) inhibitors showed survival benefit in patients (pts) with metastatic renal cell cancer (mRCC). These targeted therapies (TTs) may cause renal toxicity. Incidence of renal toxicities and TTs mechanism of damage is still unknown. A multidisciplinary evaluation and early nephrological intervention could prevent treatment discontinuation and improve survival.
Patients and Methods: Pts with mRCC treated with TTs and subjected to nephrological evaluation from December 2013 to January 2018 at two Italian Centres, were enrolled in this study. Renal toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.0. We evaluated Time to Renal failure (TRF), as the time from starting TTs to the first renal event, defined as a grade >=1 of creatininemia or proteinuria, progression free survival (PFS) and overall survival (OS).
Results: 29 pts with mRCC (median age 68 ys, 65% male) were treated with TTs: 22 (75,9%) TKi (sunitinib, pazopanib); 7 (24,1%) mTORi (temsirolimus, everolimus). With a median follow-up of 27 months (mo), 18 (62,1%) pts reported any grade renal event (6 and 12 pts with mTORi and TKi, respectively), including 8 events of grade 2 (5 hypercreatinine, 3 proteinuriae) e 3 proteinuriae of grade 3. None grade 4 event or death occurred. 20 pts discontinued TTs for nephrotoxicity, but after a median of 30 days, toxicity regressed in 7 (35%) pts who resumed

treatment at lower dosage. Median PFS was 14,5 mo and median TTRF was 6±12 mo regardless of TTs class. Median OS in pts who experienced a renal event was 53,9 mo and in pts who not reported renal events was 33,3 mo (HR= 0.37, 95%CI 0.09-1.40; P=0.14). A subgroup analysis of pts selected for TKi (mOS 52,9 mo and 36,2, respectively) and mTORi (47.3 mo and 9 mo, respectively) showed similar difference.

Conclusion: This study suggests that early detection of renal effects may be associated with a better survival. A clinically relevant risk reduction between pts who have reported renal events compared to who have not was described. An onconephrological evaluation should lead to an early diagnosis of renal alterations, a prompt intervention on toxicity and to carry out the established treatment, determining a longer response and better outcome.

G20

ERDAFITINIB COMPARED WITH VINFLUNINE OR DOCETAXEL OR PEMBROLIZUMAB IN PATIENTS WITH METASTATIC OR SURGICALLY UNRESECTABLE UROTHELIAL CARCINOMA AND SELECTED FGFR GENE ALTERATIONS: THE PHASE 3 THOR STUDY

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Background: Patients with metastatic or surgically unresectable urothelial carcinoma (M/UR UC) have poor prognoses. Programmed death (ligand)-1 (PD-[L]1) inhibitors have improved outcomes in some patients, but responses vary based on genotypic subtype. *FGFRalt* are present in 20% of patients with UC, and may reflect an immunologically "cold" tumor that does not respond well to immunotherapy.[1] In early phase 2 data, the pan-FGFR (1-4) inhibitor erdafitinib (ERDA, 8 mg/d continuous) demonstrated tolerability and a favorable 42% objective response rate (ORR) in patients with M/UR UC and *FGFRalt*; uptitration to 9 mg/d was feasible. Activity of single-agent ERDA will be compared with chemo or pembrolizumab in patients with M/UR UC in this randomized phase 3 study.

Trial design: Adult patients (ECOG performance status </= 2 and adequate bone marrow, liver, and renal function; no uncontrolled cardiovascular disease, known HIV, hepatitis B or C, or baseline phosphate persistently above the upper limit of normal allowed) with stage 4 M/UR UC and specific pathogenic *FGFRalt* (*FGFR3* mutations or *FGFR2/3* fusions) who have received 1 line of prior systemic therapy are eligible. Patients will be screened for *FGFRalt* and assigned to cohort 1 or 2 based on prior therapy. In cohort 1 (n ~280), patients with prior chemo and PD-(L)1 inhibitor (prior PD-[L]1 inhibitor alone allowed for cisplatin-ineligible patients) in combination or in maintenance setting will receive 8 mg/d continuous ERDA vs chemo (randomized 1:1) with docetaxel or vinflunine. In cohort 2, patients (n ~350) with prior chemo but no prior PD-(L)1 inhibitor will receive 8 mg/d ERDA vs pembrolizumab (randomized 1:1). Uptitration of ERDA to 9 mg/d is recommended in patients with serum phosphate </= 9 mg/dL. Primary end point: overall survival. Secondary end points: progression-free survival, ORR, duration of response, patient-reported outcomes, safety, and pharmacokinetics. PD-(L)1 expression level per immunohistochemistry and UC subtype per RNA sequencing or other methods are exploratory end points. Patients are being enrolled at sites in 25 countries. For additional information on specific sites/countries: https://clinicaltrials.gov/ct2/show/NCT03390504.

Reference:

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G21

IMMUNE-CHECKPOINT INHIBITORS IN PREVIOUSLY TREATED PATIENTS WITH ADVANCED OR METASTATIC UROTHELIAL CARCINOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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Background: Management of patients with advanced/metastatic urothelial carcinoma progressed on or unfit for standard platinum-based therapy represents an open challenge, due to the absence of therapeutic options resulting in a clinically relevant survival benefit. Immunotherapy represents a new promising approach for these patients. However, to date, only one of two completed randomized trials with immune checkpoint inhibitors showed a clear survival advantage compared to chemotherapy. Moreover, the role of

PD-L1 (Programmed Death Ligand 1) expression as predictive factor of activity and efficacy remains unclear.
Material and methods: We performed a systematic review and meta-analysis of clinical trials exploring single agent immunotherapy in UC, published on Pubmed/Medline, Cochrane library or presented at main International meetings between 2014 and 2018. The aims were: (i) to evaluate the efficacy, in terms of overall survival, of single-agent immune-checkpoint inhibitors vs. single-agent chemotherapy as second-line treatment of patients with advanced urothelial cancer; (ii) to describe the activity of single-agent immune-checkpoint inhibitors in patients with advanced urothelial cancer, in terms of ORR; (iii) to explore the predictive value of patients' selection according to PD-L1 expression for the activity and efficacy of immune-checkpoint inhibitors.
Results: Systematic review included randomized (n=2) and non-randomized (n=9) clinical trials. Among the latter, we restricted meta-analysis to trials exploring these agents in patients previously treated with platinum. In randomized trials, immune checkpoint inhibitors were associated with a significant improvement of overall survival compared to chemotherapy in unselected patients, with pooled Hazard Ratio [HR] 0.80 (95% confidence interval [CI] 0.69 – 0.93, p=0.003), while the difference was not statistically significant in the subgroup of patients selected for the highest PD-L1 expression (HR 0.72, 95% CI 0.48 – 1.09, p=0.12). Considering all trials, pooled probability of objective response was 0.18 (95% CI 0.16 – 0.20) in unselected patients and 0.27 (95% CI 0.25 – 0.32) in patients selected for the highest expression of PD-L1.
Conclusion: Meta-analysis of randomized trials showed a significant survival advantage for immunotherapy in patients not selected for PD-L1 expression. Both OS and ORR analysis showed that the predictive value of PD-L1 expression is far from being optimal.

G22

abstract withdrawn

G23

RETROSPECTIVE MONOCENTRIC STUDY ON THERAPY SEQUENCES IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

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Background: Several life-prolonging drugs are available for the treatment of metastatic castration-resistant prostate cancer (mCRPC), but the right sequence has not been explored in randomized, prospective trials.
Material and Methods: We considered mCRPC patients (pts) who received at least two life-prolonging drugs (among abiraterone (A), enzalutamide (E), docetaxel (D), and cabazitaxel (C)) at our centre. We identified three groups: pts who received D followed by either A or E (D > A/E), pts who received either A or E followed by D (A/E > D), and pts who received D followed by C (D > C). We finally performed a comparison between the two most represented groups: A/E > D versus D > A/E.
Results: 56 pts received at least two life-prolonging treatments at our centre. 33 pts received D > A/E, 14 pts received A/E > D, and 9 received D > C. We made a comparison between the two most represented groups (A/E > D vs D > A/E). In the D > A/E group 48% of pts had a locally advanced disease and 48% a metastatic disease at the time of diagnosis, whereas in the A/E > D group only 29% of pts had a locally advanced disease and 35% a metastatic disease at the moment of diagnosis. In the D > A/E group 85% of pts had a Gleason score (GS) = 7 at the moment of diagnosis, whereas in the A/E > D group 72% of pts had a GS = 7. We observed no statistically significant differences in time to progression to the first line (TTP1, 10 months in A/E > D vs 9 months in D > A/E, p = 0.519), time to progression to the second line (TTP2, 8 months in A/E > D vs 5 months in D > A/E, p = 0.107), and time from the beginning of first line and progression to second line (TT2P, 21 months in A/E > D vs 16 months in D > A/E, p = 0.108). However, we observed a statistically significant advantage in OS in the A/E > D group (31 vs 22 months, p = 0.021).
Conclusions: With the limits of a retrospective analysis we observed a statistically significant advantage in OS in pts who received a novel hormonal agent in first line (either A or E) followed by chemotherapy (D) compared to pts who received the reverse sequence. However, this difference might be related to the fact that pts in the D > A/E group had worse prognostic features (e.g. stage, GS) at the moment of diagnosis. Prospective, randomized trials should be performed with this aim.

G24

NEW AGENTS FOR MCRPC : A "REAL LIFE" RETROSPECTIVE STUDY

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Introduction: Metastatic CRPC is considered a non-chemosensitive tumor with poor prognosis.

		HR	CI 95% per HR min	max
ECOG PS	0,004	0,367	0,154	0,729
Time to failure on ADT	0,077	1,517	0,935	5,521
New agents	0,000	0,186	0,082	0,422
Lines of therapies	0,494	0,880	0,610	1,269
PSA	0,047	0,512	0,265	0,990

In last few years Abiraterone, Enzalutamide, Cabazitaxel, Radium 233 have shown to be safe and effective in different settings of mCRPC therapy.

However in the lack of direct comparaison trials and therapeutic sequences studies, we don't know how these new agents have changed mCRPC outcome.

Patients and Methods: In this "real life" study we retrospectively compared the survival between pts treated with "new agents" and pts who only received "old chemotherapies" for mCRPC at our Oncology Unit in the last 10 years.

Furthermore we assessed the impact on survival of known prognostic factors Gleason score, PS, PSA, Hb, LDH . We also evaluated if Neutrophils/linphocytes ratio, time to failure on ADT and the number of treatments are related with the outcome.

Results: Seventy mCRPC patients were treated in last 10 years: 29 pts only received "old therapies", 41 pts performed "new agents". We report below statistically significant differences found in univariate analysis:

medianOS from mCRPC diagnosis was 31 months for pts who performed new agents vs 11 months for pts receiving only old chemotherapies.

The median survivals for pts treated with 4, 3, 2 or 1 lines of therapy were respectively 44, 31, 27 and 16 months .

MedianOS for pts with ECOG PS 0-1 was 33 months instead mOS for pts with ECOG PS 2-3 was 8 months. mOS for pts who failed ADT in less than 22 months was shorter than mOS for those who experienced a longer hormonosensitivity (respectively 14 months and 31 months); mOS for pts with PSA levels $>$ 25,78 ng/ml was 12 months, mOS for pts with PSA levels$<$ 25,78 was 30 months.

Survivals for pts with N/L ratio $<$ 2,68 and pts with N/L ratio $>$ 2,68 were respectively 30 months vs 14 months.

In multivariate analysis ECOG PS, "new agents", time to failure on ADT, PSA levels demonstrated to be indipendent prognostic factors for mCRPC:

Conclusion: In this retrospective study we found that new agent Abiraterone, Enzalutamide, Cabazitaxel, radium 233 prolonged survival of mCRPC pts . ECOG PS, time to failure on ADT, lines of therapies, PSA confirmed to be prognostic factors. N/L ratio may impact on survival too.

G25

REDUCED DOSE OF CABAZITAXEL IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC): FROM PROSELICA TRIAL TO THE REAL LIFE. A SINGLE INSTITUTION EXPERIENCE

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Background: The phase III TROPIC trial investigated the efficacy of cabazitaxel 25 mg/m2 (C25) in patients (pts) with castration-resistant prostate cancer (mCRPC), who had progressed during or after docetaxel. C25 improved the overall survival (OS) compared to mitoxantrone, but almost 82% of pts in C25 arm experienced grade 3 neutropenia. Subsequently, the phase III PROSELICA trial showed that cabazitaxel 20 mg/m2 (C20) was not inferior and better tolerated compared to C25. Here, we report on a real-world retrospective analysis concerning the safety and the activity of C20 schedule in pts with mCRPC treated at our Institution.

Material (patients) and methods: We identified 24 pts with progressive mCRPC who received C20 as baseline dose treatment because they were frail pts or they experienced serious toxicities to previous treatments. Adverse events (AEs) assessment was performed at each visit during the treatment. Progression-free survival (PFS) and OS curves were obtained using the Kaplan–Meyer product-limit estimator.

Results: Median pts' age was 72 years. All patients received a previous treatment with docetaxel; moreover 11 pts (46%) received two previous lines of therapy and 6 pts (25%) more than two lines. Our pts received a median of 4 cycles. In our analysis only one patient experienced a grade 3 neutropenia (5%), one patient a grade 3 fatigue and two pts were treated with prophylactic G-CSF. The most frequent AEs of all grades were fatigue (33%), anemia (29%) and pyrexia (19%). Median PFS was 3.7 months [95% CI: 3.26-4.14] and OS was 7.3 months[95% CI: 6.16-8.51]. Our results in terms of AEs were apparently better than those observed in PROSELICA C20 pts (grade 3 neutropenia in 42% of pts) but this could be related to the small number of our group of pts; PFS in our patients was longer than PFS obtained in the PROSELICA C20 group (2.9 months [95% CI: 2.79-3.45]) but OS was shorter compared to PROSELICA C20 pts (13.4 months [95% CI: 12.19-14.88]). These results could be explained observing that our pts had higher median age compared to PROSELICA trial (72 vs 68 years) and they were highly pre-treated pts.

Conclusions: Our real-world study confirms that C20 is a feasible option for elderly and heavily pre-treated pts with

mCRPC, showing activity and good tolerability. Actually studies are ongoing to identify a better cabazitaxel regimen capable to maximize its activity and minimize its toxicity.

G26

VISCERAL METASTASES ARE UNCOMMON DURING RA223 TREATMENT IN PATIENTS WITH METASTATIC PROSTATE CANCER AND BONE METASTASES

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Background: Radium-223 dichloride (Ra223), improved overall survival (OS) in patients(pts) with castration-resistant prostate cancer (CRPC) and bone metastases and no visceral metastases (lymph nodes<3 cm were allowed). Because Ra223 targets specifically bone metastases, it was important to evaluate onset of visceral metastases during the six cycles of Ra223 therapy.
Materials and Methods: Between August 2016 and January 2018, 47 pts with metastatic CRPC (mCRPC) received Ra223 therapy in our Institution. Ra223 was administered at 55 kBq/Kg every 4 weeks for 6 cycles. Visceral and bone evaluation included choline PET-CT and bone scan performed at baseline and 4-weeks after the six treatment cycles. In pts with increasing pain and ALP progression in the course of treatment or in pts with aggressive disease (high Gleason score at diagnosis, PSA doubling time<6months before starting radium-223, ADT progression ?12 months), visceral evaluation was repeated using PET-CT scan after the third cycle. The aim of this analysis was to evaluate the number of patients with visceral progression during the six cycles of Ra223 therapy. Additional assessments included OS, pain (BPI-SF evaluation), and safety.
Results: Patients (n=47) were >65 yrs (range 53-89). Gleason score of 7(n=12), 8(n=14) or 9(n=13). Twenty six pts (55%) completed 6 cycles of treatment; 21 (44%) discontinued treatment after 1(n=4), 2(n=7), 3(n=1), 4(n=3) or 5(n=6) cycles, 7 pts were under treatment during data collection. Patients presented bone mets only at baseline, excepted for one patient who presented bone and metastatic lymph-nodes (<3 cm). Among 47 evaluable pts, visceral disease were observed in 3 pts (6%). Two pts developed liver metastases and 1 pt liver and lymph-nodes metastases. None of the three pts had documented < 3 cm lymph-nodes at baseline. Visceral lesions were detected after 2 cycles (2pts) and 5 cycles (1 pt). Mean OS was 13.7 months; median OS had not been reached at time of reporting. BPI-SF pain score remained unchanged in 4 pts and improved in 27 patients. Grade 3-4 AEs were anemia (5 pts, 10%) and thrombocytopenia (2pts, 4%), all these patients received a previous chemotherapy or presented a bulky disease.
Conclusions: Visceral metastasis during Ra223 treatment is an uncommon. Monitoring symptoms, transaminases and ALP progression may suggest to perform supplementary imaging modalities before the end of treatment, specifically in patients with bulky or aggressive disease.

G27

FIRST-LINE TREATMENT WITH PAZOPANIB IN METASTATIC RENAL CELL CARCINOMA PATIENTS: IMPACT ASSESSMENT OF DOSE REDUCTIONS ON CLINICAL OUTCOMES

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Background: Pazopanib is an orally available multitargeted tyrosine kinase inhibitor that inhibits tumor angiogenesis and cell proliferation. The safety and efficacy of Pazopanib in patients with advanced or metastatic renal cell carcinoma (mRCC) have been demonstrated in several clinical trials but the question of clinical experience outside controlled trials is less clear. In this retrospective observational study, we analyzed the clinical outcomes of patients with mRCC who received Pazopanib as first line treatment, assessing the impact that dose reductions may have on progression free survival (PFS).
Material and methods: mRCC patients treated with first-line Pazopanib were retrospectively analyzed for demography, response, outcomes and toxicity. Two patient groups were compared: the first group received a standard dose of 800 mg/day; the second group started with 800 mg/day and then reduced the dose to 400 or 600 mg/day due to toxicity. The response to treatment was evaluated using RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1. Toxicity was evaluated according to CTCAE (Common Terminology Criteria for Adverse Events) version 4.0. Statistical analysis was performed using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/)
Results: A total of 29 patients (21 male, 10 female) were evaluated: 20 in the first group, 9 in the second. Mean age was 65 years (50 - 79). After a median follow-up of 8.1 months (range 0.4-20.1), 16% of patients had disease progression, 57% stable disease, 24% partial response, 3% complete response, for a disease control rate of 84%. Median PFS of the patients was 7.3 months for the first

group and 8.1 months for the second group, with a Hazard Ratio of 0.78 (IC: 0.34 - 1.79) and 1.27 (IC: 0.55 - 2.91), respectively. The grade 3-4 toxicities observed in more than 10% of the sample examined were Fatigue (13%), diarrhea (11%) and AST/ALT increase (10%).
Conclusions: Our observations may suggest that patients with mRCC receiving a lower dose of first-line Pazopanib may not have significant differences of PFS compared to those receiving a standard dose. These results show the crucial role of treatment-related side effects management, which leads to consistent clinical outcomes while preserving patients' quality of life.

H - Gynaecological Tumours

H01

PATHOLOGICAL AND MOLECULAR CHARACTERIZATION IN HEREDITARY AND SPORADIC OVARIAN CANCER PATIENTS

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Background: Ovarian cancer (OC) represents the leading cause of cancer deaths among gynaecological malignancies. Germline mutations in the BRCA1 and BRCA2 genes are associated with hereditary predisposition to breast and OC and account for 10-15% of OC cases. Hereditary OC patients (pts) have improved clinical outcomes compared to BRCA-wild type OC, due to greater response to platinum-based treatments and tailored therapeutic options, such as PARP inhibitors. The present study evaluates pathological and molecular features of BRCA-wild type (sporadic) and BRCA-mutant (hereditary) OC pts in Marche Region.
Patients and methods: we determined the prevalence of germinal BRCA1 and BRCA2 variants in OC pts undergoing genetic counselling and testing between June 1996 and April 2017 at Centro Regionale di Genetica Oncologica, Ancona. Risk assessment was made relying on clinical criteria and prediction tools such as BRCApro and Manchester Scoring System. We proposed BRCA test to all pts affected by OC regardless of familiarity according to 2015 AIOM recommendations. BRCA genes were studied by sequencing and Multiplex Ligation Probe Amplification. We referred to Breast Cancer Information Core committee, IARCs databases and ClinVar archive.
Results: 227 OC pts were included in the study; among them 68 (30%) carried a pathogenic variant while 35 (15.4%) had a Variant of Uncertain Significance (VUS). Pathogenic variants were significantly more frequent in the BRCA1 gene (83%) vs BRCA2 gene (51%) ($p = 0.00012$). High grade serous OC was the most frequent histotype (57%), followed by endometrioid OC (17%).

Median age at diagnosis was 52 years (range 16-83). No significant differences in terms of age at diagnosis were observed between BRCA-mutant and BRCA-wild-type pts, neither between BRCA1- and BRCA2-mutant pts. Positive family history for BRCA-related cancers was reported in 160 (70%) pts, while 67 (29%) had negative family history. In the first group 64 (28%) had a pathogenic BRCA variant, while in the second group only 4 (2%) was carrier of a pathogenic mutation. Detection rate, defined as the probability to detect pathogenic BRCA variants, resulted higher (40%) in OC pts with positive family history vs pts with negative family history (6%) ($p = 0.0009$).
Conclusions: our results highlight the importance of BRCA status analysis in Marche Region OC pts as to perform comparisons among mutational and clinic-pathological features between our Region and other geographical areas.

H02

RISK REDUCING SALPINGO-OOPHORECTOMY (RRSO) IN HIGH-RISK WOMEN: BEYOND BRCA

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Background: Previous experiences have demonstrated that RRSO reduced the risk of ovarian cancer in BRCA1-2 carriers[1], and the rate of occult neoplasia in RRSO specimen ranges from 2.5 to 9%[2]. Serous tubal intraepithelial carcinoma (STIC) is an establish precursor of pelvic serous carcinoma, and pre-neoplastic lesions (STIL) has the same aberrant expression of p53 mutations, suggesting a link between these two lesions[3]. Overexpression of p53 mutations (called p53 signature), is also found in normal areas, and it may represent a role in cancerogenesis.
Patients and Methods: From February 2012 to March 2018, ninety-one high-risk women (median age 49 yrs; range 31-71 yrs) underwent RRSO; fifty-seven women were BRCA1-2 mutation carriers, 9 were VUS and 25 women had family history of ovarian or breast cancer. Sixty-nine (76%) women had a previous history of breast cancer (BC), and 7 of them (10%) had a bilateral BC.
Results: No surgical adverse events were recorded, following RRSO. Six cases of occult cancer were detected giving an overall incidence of 6.5% (median age was 55 yrs). Concerning non invasive lesions, we identified five STIL (5.4%), and eight p53 signature (8.7%), that represent 14.2% of all pre-neoplastic lesions (median age of

women was 50 yrs). Among BRCA1-2 mutant carriers (n=57), 4 women (7%) had occult carcinoma and 9 (16%) had pre-neoplastic lesions (STIL and p53 signature), while in high risk women non BRCA-carriers (n=34), the pre-neoplastic lesions were identified in 4 of them (11.7%).

Conclusions: Our data confirm previous experience in high-risk women undergoing RRSO. Furthermore due to the prevalence of pre-neoplastic lesions, careful ongoing studies about the role of p53 signature, are necessary to make such a conclusion.

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H03

ROLE OF PARP INHIBITORS IN OVARIAN CANCER: SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Ovarian cancer is the leading cause of death among gynaecological malignancies. The gold standard of treatment still remains the combination Carboplatin and Taxol, while the platinum free interval is considered the major prognostic factor. Moreover, platinum-sensitive patients recognize in 40% of cases a germline or somatic BRCA1/2 mutation. Recently, a new class of drugs, the PARP inhibitors (PARPis), was able to significantly modify the progression free survival (PFS) of these patients when used in a maintenance setting. We performed a systematic review and meta-analysis in order to verify the impact of these agents both in term of efficacy and safety.

Patients and Methods: By searching "Pubmed" database and abstracts from cancer meetings clinical trials were identified within a time frame January 2008 - April 2018. PFS was the primary end-point, toxicities were secondary end-points. Hazard ratios (HRs) of PFS, with confidence intervals, and risk ratios (RR) of grade 3-4 toxicity rates were extracted from retrieved studies and included in the current analysis. Meta-analysis was carried out by fixed and random effect models. An indirect comparison in term of efficacy (PFS) was also performed.

Results: Six randomized trials for a total of 1879 patients were selected and included in the final analysis. In particular, we evaluated a BRCA-mutant cohort (911 patients) with a pooled HR 0.26 (95%CI 0.21-0.31) and the BRCA-wild type cohort (836 patients) with a pooled HR 0.41 (95%CI 0.31-0.55), respectively. Regarding the safety profile, no significant differences were detected in all grade toxicities, however considering the 3-4 grade toxicities and severe adverse events (SAEs) we showed that rucaparib-treated patients, reported major abdominal pain events, while we reported the highest percentage of haematological toxicities for niraparib, hypothesizing a "drug effect" for the safety analysis. In the indirect comparisons, significant differences were not detected on PFS for the different agents.

Conclusions: We confirm the significant benefit in survival outcome of PARPis for EOC patients both in the pair-wise meta-analysis and indirect comparisons ("class-effect"). Particularly, we highlighted that the major effect of this strategy remains in BRCA-mutated patients. Thus, a better selection by genetic testing at diagnosis is needed with the added social value of individualized prevention in BRCA-mutated families.

H04

PLATINUM-SENSITIVITY IN HIGH-GRADE SEROUS OVARIAN TUMORS WITH BRCA1 AND BRCA2 MUTATIONS

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Background: Approximately 10-15% of patients with ovarian cancer (OC) are carriers of genetic mutations in BRCA1 or BRCA2 (BRCA+); these patients show greater sensitivity to platinum-containing chemotherapy (CT). We analyzed the response data to CT and survival of patients in our center by comparing cases of carriers of BRCA genetic mutation with the wild type (WT) population.

Material (patients) and methods: We examined 94 patients undergoing genetic investigation for BRCA1/2 genes, aged between 37 and 76 years, with OC undergoing CT between 1998 and 2018. 22 patients were BRCA+: 19 with BRCA1 mutation and 3 with BRCA2 mutation; 72 patients were WT. Progression free survival (PFS) and the platinum sensitivity were compared between the 2 groups by Kaplan-Meier curves. Patients were all at the III stage of the disease at the diagnosis time. 70% of all patients had primary radical surgery before CT (carboplatin and paclitaxel), while the remaining 30% received neoadjuvant CT with the same drugs, with subsequent interval surgery.

Results: In this study, we evaluated PFS at the first and at the second recurrence in the 2 distinct groups (BRCA+, WT) by median calculation. Platinum-sensitivity (appearance of disease recurrence after >6 months from the end of the first platinum-containing CT) was observed in 20/22 (90,9%) BRCA+ patients and 64/72 (88,8%) WT patients for such mutations. In BRCA+ patients the median of PFS

at the first disease recurrence was 23,9 months and at the second disease recurrence was 16,6 months. In WT patients the median of PFS at the first disease recurrence was 21,7 months and at the second disease recurrence was 15,7 months. No statistically significant difference was found in terms of PFS in the 2 groups, but medians PFS were better in the BRCA+ patients group.

Conclusions: According to literature studies BRCA + patients have a greater response to the first and subsequent lines of platinum-based CT, compared to WT patients. This suggests that patients with BRCA 1/2 mutations have a higher sensitivity to platinum-containing CT. On the other hand it has been observed that also many WT patients are platinum-sensitive (BRCAness). Platinum sensitivity may be due to non-genetic factors, or to the presence of somatic BRCA mutations or of mutations in other genes involved in homologous recombination repair. Finally research into BRCA1/2 genetic mutations may allow to identify more personalized treatments that could improve OC prognosis in this patients setting.

H05

NIRAPARIB IN RECURRENT PLATINUM SENSITIVE HIGH-GRADE OVARIAN CANCER: A MONOCENTRIC EXPERIENCE

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Background: NOVA trial has demonstrated that Niraparib as maintenance treatment significantly prolongs progression-free survival in patients (pts) with platinum-sensitive recurrent ovarian cancer (PSROC) regardless of BRCA mutational status.

Methods: This is an observational single-institution experience, which included pts with PSROC (high-grade, endometrial or serous) treated with Niraparib as maintenance therapy after complete or partial response to the most recent platinum-based chemotherapy. Drug availability was made possible thanks to the Compassionate Use Program.

Results: From September 2017 to April 2018, Niraparib was administered to 13 pts: 5 (38%) as 2nd line maintenance treatment, 3 (24%) as 3rd line and 5 pts (38%) as >4th line. With regards to BRCA mutational status, 1 pt (8%) was BRCA1 mutated, 11 pts (84%) were wild type, and for 1 pt (8%) the test is ongoing. Treatment started within 12 weeks from the last cycle of platinum therapy for all pts, at the standard dose (300 mg/die) for 8 pts (62%), whereas 5 (38%) received Niraparib starting dose of 200 mg/die because the weight was <58Kg, as indicated in drug data sheet. A total of 44 cycles have been administered, with a median of 3 cycles. Six pts (46%) experienced adverse events (AEs) >G3. Hematological toxicity was the most frequent AE: a >G3 thrombocytopenia was observed in 3 pts (33%), G3 and G2 anemia in 1 pt (11%) and 2 pts (22%) respectively and G2 neutropenia in 1 pts (11%). The only non-hematological toxicity observed was fatigue G3 (1 pt, 11%). All the AEs >3 resulted in drug dosage reduction. At the time of the present report in 3 pts (23%) a further radiological partial response was observed; among the remaining 10 pts, 1 (8%) had a disease stabilization, 3 (23%) discontinued treatment due to disease progression and for 6 pts re-evaluation of disease status is pending.

Conclusions: In this real life experience, the treatment with Niraparib has shown a good tolerability. The observed >G3 hematological toxicities were as expected and were easily managed with temporary drug interruption. In our PSROC pts, although included patients treated with multiple lines of therapy, Niraparib maintenance treatment was effective in maintaining prior platinum response and also in improving tumor shrinkage.

H06

abstract withdrawn

H07

ADVANCED UTERINE CERVICAL SQUAMOUS CELL CANCER (AUCSCC). HIGH RESPONSE RATE USING A DOSE-DENSE CHEMOTHERAPY WITH TAXOL, IFOSFAMIDE AND PLATINUM (TIP-DD)

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Background: AUCSCC represents an aggressive tumor with a poor prognosis. To date, no studies have identified the best chemotherapy regimen. Dose-dense chemotherapy is an effective treatment modality for many tumors but the efficacy of this approach in this population is unknown. Aim of this study was to assess the efficacy and tolerability of the TIP-dd regimen given with a dose-dense approach.

Patients and Methods: We performed a retrospective review of all cases with a diagnosis of locally advanced or metastatic cervical cancer seen at the Oncology Division of the Istituti Ospitalieri of Cremona from November 2004 to December 2018. Chemotherapy consisted of Ifosfamide 2500 mg/m2 and Mesna 2500 mg/m2, on day 1; Paclitaxel 175 mg/m2 and Cisplatin 70 mg/m2, on day 2; every 2

weeks for a maximum of 6 cycles with prophylactic pegfilgrastim on day 3. Complete staging before chemotherapy was available in all patients. Response rate was evaluated using the RECIST 1.1 criteria; acute and late toxicity of chemotherapy, time to progression (TTP) and overall survival (OS) were recorded.

Results: 17 patients were identified so far. Median age was 52 years (range 25-71), PS 0 (100%),16 (94.1%) squamous histology and 1 adenocarcinoma; FIGO Stage was IIB in 2 (11.7%), IIIA in 1 (5.8%); IIIB in 3 (17.6%) and IV in 11 (64.7%). Median number of TIP-DD cycles was 6 (range 1 to 7). 16 patients were evaluable. Following chemotherapy, ten patients underwent surgery (62.5%) and five patients received pelvic radiotherapy (31.2%). We observed 7 (43.7%) complete responses and 8 (50%) partial responses for a overall response of 93.7%. At this time nine patients have recurred (56.2%) and five patients are still alive (31.2%). Six patients have performed further treatment lines (37.5%). Median TTP was 44.4 months (IC95%: 0.5-NR) and median overall survival was 33 months (95% CI: 23 -236). Treatment was delayed in 10 patients (62%). Toxicities included grade 3-4 neutropenia: 6% (0% febrile neutropenia), grade 3-4 thrombocytopenia: 6%, grade 2 neuropathies 12%; grade 2 asthenia/fatigue 12%, and no treatment-related deaths. 5 patients are still alive (median overall survival = 40,3 months)

Conclusions: These excellent results from a retrospective case series represent a hint for further research with a view to get a possible cure for metastatic cervical cancer. However, due to limitations of the trial design, this approach should be studied in prospective trials prior to drawing any conclusions.

H08

EFFICACY, TOXICITY AND QUALITY OF LIFE OF WEEKLY CHEMOTHERAPY REGIMEN IN ELDERLY PATIENTS WITH GYNECOLOGICAL CANCER

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Background: Several studies revealed a strong association between increasing age and decreased use of chemotherapy. The aim of this study is to investigate in elderly patients with gynecological cancer the efficacy and toxicity (CTCAE version 4.0) of weekly chemotherapy regimen with Carboplatin AUC 2.5 plus Paclitaxel 80 mg/m² on days 1,8 +/− Bevacizumab 15 mg/kg on day 1 (if indicated for stage and site of cancer) every 21 days. Secondary endpoints are quality of life (QoL) and the correlation between safety, efficacy and G8 evaluation at baseline and at the end of treatment.

Patients and methods: We have designed a monocentric phase II non randomized study. Patients eligibility criteria: age⩾70; ovarian, endometrial or cervical cancer; no previous systemic therapy for cancer; adequate baseline functional parameters. Patients are stratified on the basis of: age (⩾70-75 vs >75-80); site of cancer (ovarian vs endometrial vs cervical); stage (IIA-IIIA vs IIIB-IV for ovarian, III-IV for endometrial, relapsed-IV for cervical cancer); G8 score (>14 vs ⩽14). G8 screening tool is used at baseline. Patients with a score ⩽14 (high risk) are submitted to the CGA (Comprehensive Geriatric Assessment); frail patients are excluded. Safety is recorded in all patients that receive at least 1 cycle. The efficacy endpoints are ORR, PFS, OS. Only patients that complete at least 3 cycles are evaluable for ORR. Tumors are assessed by CT at baseline and every 3 cycles. QoL is measured by SF 36 at baseline and every 3 cycles.

Results: From March 2018 to May 2018 six patients are enrolled: median age 77,5 (range 76-80); 5 ovarian cancer (1 stage IIA, 1 stage IIIA, 3 stage IVB) and 1 cervical cancer (stage IV). Two of six patients with score ⩽14 at G8 screening was evaluated with CGA. No patient resulted frail at CGA. Only G1-G2 hematological toxicity are observed: G1 neutropenia in 33,3% of patients, G1 anemia and thrombocytopenia in 16,7%; G2 neutropenia in 16,7%. Between non hematological toxicities, G1 fatigue and neuropathy are observed in 33,3%. No patient has delayed or interrupted chemotherapy due to toxicity. The study is ongoing, the required sample size is 62 patients in 24 months.

Conclusions: The study aims to demonstrate that the weekly regimen in elderly patients to be as effective as standard 3-week scheme but with significantly lower toxicities and better tolerance, adherence to planned treatment and QoL.

L - Head & Neck Tumours

L01

REAL WORLD SURVIVAL RESULTS OF PATIENTS WITH RECURRENT AND/OR METASTATIC (RM) HEAD AND NECK CARCINOMA (HNC) TREATED WITH CETUXIMAB PLUS CHEMOTHERAPY: A FINAL REPORT ON 340 PATIENTS

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Despite modern treatment approaches, survival of patients (pts) with RM HNC remains low and it is difficult to identify patients who derive optimal benefit from treatment. We analyzed which clinical parameters may help improving the prognostication in first line palliative treatment for patients with RM HNC.

All pts included in this retrospective analysis were diagnosed with RM HNC and were treated with Cetuximab in combination with chemotherapy as first line palliative treatment from 1/2007 to 12/2016 in 6 Italian Centres. The following baseline prognostic factors were investigated: sex, age, site of disease, tumor grading, HPV status for oropharyngeal cancer, performance status (PS), weight loss in the previous 3 months (less/more than 5%), comorbidities (according to ACE-27), residual tumor at primary site, previous chemotherapy or cetuximab in curative setting, previous radiotherapy, platinum type (cisplatin/carboplatin, CBDCA), chemotherapy schedule (weekly/3-weekly), platinum and cetuximab doublet or with a third drug (i.e. 5FU or paclitaxel). For each potential predictor variable, Kaplan-Meier curves for OS and PFS were estimated, and a Log-rank test was used to compare survivorship in different levels of the variable. A Cox proportional hazard model was run including only predictors characterized by a significant ($p<0.05$) Log-rank test.

We analyzed 340 pts, with a median PFS/OS of 5.0/10.6 months. The 1-year and 3-year OS rate for all pts was 44.2% (CI: 39.1-50.0) and 7.8% (CI: 5.1-12.0). Only one out of two pts received a second-line therapy. In univariate analysis lower OS was associated with PS>0 ($p<0.001$), residual tumor at primary site ($p<0.001$) and CBDCA use ($p=0.012$) while lower PFS was associated with paranasal sinus site ($p=0.008$), PS>0 ($p=0.001$), CBDCA use ($p=0.035$) and residual tumor at primary site ($p<0.001$). All these predictors except for platinum type remained significant at multivariate analysis. Pts with clinical response to treatment carried a more favorable prognosis, while progressive disease as best response had a dismal median OS of 5.8 months.

Median PFS and OS of 5.0 and 10.6 months in this retrospective real life study are comparable to the results reported in Extreme trail (Vermorken et al. 2008). At baseline, PS and residual tumor at primary site could be used to define pts prognosis. Pt selection is essential in tailoring treatment intensity, so to balance treatment toxicity with expected clinical benefit.

L02

ADOPTIVE T-CELL THERAPY IN RELAPSED EBV-RELATED NASOPHARYNGEAL CARCINOMA

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Background: Epstein-Barr virus (EBV)-related Nasopharyngeal carcinoma (NPC) is a highly chemo-radiosensitive cancer. However, when relapsing without surgical or reirradiation options, NPC carries a dismal prognosis; survival >2 years being reported in 7-14% metastatic pts (1,2). We have previously achieved disease control using autologous EBV-specific cytotoxic T lymphocytes (CTL) in refractory/relapsed pts following conventional treatments. The aim of the present study was to evaluate outcomes in pts receiving T-cell therapy after first line chemotherapy (CT) for recurrent disease.

Patients and Methods: Sixteen patients (13 males, median age 41 yrs) with metastatic (n=12; 7/12 with visceral metastasis, and 5/12 with bone and nodes lesions) or locally recurrent (n=4) NPC received 2 administrations of EBV-specific CTL at a total cell dose/infusion of 1.5-3 x 108, following completion of first line CT. The best response after first-line CT had been progressive disease (PD) in 4 pts, stable disease (SD) in 3, partial response (PR) in 5 and complete response (CR) in 4.

Results: No severe adverse events were recorded, following CTL therapy. Among patients in CR after first-line CT, 3 remain in CR at 58, 76 and 77+ months, while one patient relapsed, but attained a long-lasting CR after treatment with 2nd-line CT. In the 12 patients treated with persistent disease (PR, SD, PD), the best response observed after CTL therapy, in some cases (3/12) associated with 1subsequent line of CT or radiotherapy, was PD in 8 patients, and CR (range 39-78+ months) in 4. At a median follow-up of 64 months, 8/16 patients are alive with no evidence of disease. Among the factors associated with positive outcome are response to first-line CT, and metastatic disease with limited tumor burden.

Conclusions: EBV-specific CTL therapy administered following first line CT for recurrent NPC, is safe and associated with remarkable clinical benefit in some patients, including long-lasting CR.

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L03

RECOMMENDATIONS FOR AN APPROPRIATE CLINICAL USE OF CIRCULATING EBV-DNA IN NASOPHARYNGEAL CARCINOMA: COMPREHENSIVE CLINICAL PRACTICE GUIDELINES EVALUATION

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Background: In Epstein–Barr virus (EBV)-related nasopharyngeal cancer (NPC), quantitative determination of circulating EBV DNA can potentially be applied as marker. Its potential application are: (i) in the screening of asymptomatic individuals in endemic areas for NPC, (ii) in the initial work-up of NPC to assess the risk of progression after curative-intent radiation or chemoradiation therapy and (iii) in the detection of recurrence during the follow-up of patients who have received curative intent therapy. The aim of the present study was to investigate if the clinical utility of circulating EBV DNA is established in clinical practice guidelines (CPG) and if recommendations are provided to standardize the quantitative determination of circulating EBV DNA.
Materials and methods: A systematic literature search for existing guidelines for NPC published between 2011 – 2017 in English or Italian was undertaken using PubMed, National Guideline Clearinghouse and websites of 10 organizations and scientific societies producing CPGs. The search strategy was built with keywords related to NPC and guidelines. Any guideline containing information and recommendations for clinical practice pertaining to diagnosis, work-up, management, treatment or follow-up of NPC was included.
Results: From 1104 title and abstract identified by the search, a total of 79 potentially relevant documents were selected, for which full texts reports were evaluated. We included a final set of 18 guidelines concerning NPC. The selected documents were further clustered as either being based on a systematic revision of the literature to generate recommendations (4/18) or not (14/18).

Plasma EBV-DNA was evaluated in only one guideline based on a systematic revision and in 8 guidelines without systematic revision. Even if methods were discussed in 5 guidelines, none of them produced recommendations on the preferred method.
Conclusions: In spite of the potential usefulness of circulating assay of EBV-DNA in NPC, only 44% of available CPGs provide recommendation for its clinical use. Only 28% discuss methodological issues on EBV-DNA determination, but, surprisingly, do not provide any recommendations on method standardization. Guideline producers need to take into more consideration methodological aspects impacting the actual reliability and generalizability of laboratory results.

L04

CONCURRENT CHEMORADIATION VS CETUXIMAB/RT IN LOCALLY ADVANCED HEAD AND NECK CANCER. FINAL RESULTS OF A RANDOMIZED PHASE II-III TRIAL

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Background: Concomitant platinum-based chemoradiation (cCRT) is the standard treatment of locoregionally advanced Head and Neck Squamous Cell Carcinoma (LASCCHN). Currently, cetuximab/RT (CET/RT) is considered an alternative treatment option to cCRT. This is a 2x2 factorial trial comparing concomitant treatment (cCRT or CET/RT) vs. induction chemotherapy (IC) followed by concomitant treatment (cCRT or CET/RT). We aimed at assessing 2 primary endpoints: 1) overall survival (OS) of IC vs no-IC; 2) Grade 3-4 in-field mucosal toxicity of cCRT vs. CET/RT. The present paper focuses on the safety analyses of cCRT vs. CET/RT.
Methods: Patients with LAHNSCC were randomized to receive cCRT [2 cycles of concomitant cisplatin +5Fluorouracil (PF)] or CET/RT preceded or not by 3 cycles of induction docetaxel/cisplatin/5Fluorouracil (TPF). The superiority hypothesis of OS comparison of IC

vs. no-IC required 204 events from 420 patients (HR=0.675; power 0.80, α=0.05, two-sided), allowing to detect a 10% difference in G3-4 in-field mucositis for the safety comparison of CET/RT vs cCRT.

Results: 384 out of 421 patients were evaluable for safety. G3-4 in-field mucositis was 38.7% for cCRT vs. 37% for CET/RT (p=0.739). No statistically significant difference was observed in G3-4 in-field skin toxicity too (p=0.667). RT completion, median RT duration and median RT dose were similar in both arms, however, less patients in the cCRT arm required RT delays and permanent discontinuation of the medical treatment. No significant differences for cCRT vs CET/RT were detected in Loco-regional failure (p=0.620), PFS (p=0.718) and OS (p=0.768).

Conclusions: No significant differences were observed for in-field toxicities for cCRT vs. CET/RT. Compliance to RT was similar in both arms. No significant differences were observed in activity and efficacy although no conclusions can be drawn for survival data because the trial was not powered for the efficacy comparison.

L05

PROGNOSTIC ROLE OF INFLAMMATORY INDEX IN HEAD AND NECK SQUAMOUS-CELL CARCINOMA PATIENTS IN FIRST LINE CHEMOTHERAPY

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Background: Inflammatory index, carried out of neutrophils, lymphocytes and platelets count, has been shown to be prognostic in different malignancies. Also in head and neck squamous-cell carcinoma (HNSCC) a prognostic role has been demonstrated in patients who were candidates for radical treatment. The purpose of this study is to evaluate retrospectively the prognostic role of these markers in patients receiving a first-line chemotherapy.

Methods: From 2003 to 2017 One hundred and fifty-eight HNSCC patients have been treated with first-line chemotherapy at our institution. Among these, 54 patients were selected excluding patients that received concomitant radiotherapy, corticosteroid therapy for more than 10 days or GCSF. Patients characteristics for site and treatment are summarized in table 1. Information on blood counts were carried out the day before the first cycle of therapy and after the last one. NLR and PLR were computed as the ratio of the absolute neutrophil count and absolute platelet count by the absolute lymphocyte count respectively. Cut-off from literature for NLR and PLR were considered.

Table 1.

Characteristics	Total - N (%)
Age, Median (iqr range)	61 (53-68)
Gender	
Male	42 (77.8)
Female	12 (22.8)
Site of disease	
Oral cavity	24 (44.4)
Larynx	10 (18.5)
Nasopharynx	11 (20.4)
Other	9 (16.7)
Chemotherapy	
Cisplatin+Fluoruracil+CETUXIMAB	31 (57.4)
Cisplatin+Fluoruracil	8 (14.8)
Other	15 (27.8)

Results: NLR and PLR showed a statistically significant reduction from beginning to end of therapy (p-values 0.006 and 0.059 respectively) but this reduction wasn't correlated with an improvement in overall survival (OS) or progression-free survival (PFS).

Patients with baseline NLR $<$ 2.5 (11 patients) had a better OS respect to patients with baseline NLR$\geqslant$2.5(40 patients) (median OS 60 vs 26 months p-value 0.0296) but not a different PFS. Results for PLR values wasn't statistically significant.

Conclusion: For our knowledge this is the first study that evaluate the prognostic validity of NLR even in the advanced metastatic setting in HNSCC patients.

Further analyses to correlate these data to the type of treatment, location of diseases and HPV/EBV positivity will be performed.

L06

CONSENSUS IN HEAD AND NECK CANCER PATIENTS' MANAGEMENT: AN EXPERT OPINION MEETING OUTCOME

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Background: Squamous cell carcinoma of the head and neck (SCCHN) accounts for 6% of all malignancies.

The majority of SCCHN patients are diagnosed with loco-regional disease, while 10% of patients present with metastatic disease at diagnosis. About 40% of the locally advanced patients experience a recurrence of disease.

There are still several unmet medical needs in head and neck (H&N) cancer patient's management and a lack of clinical criteria and consensus in defining: patient populations suitable or unsuitable for concurrent chemoradiotherapy; platinum refractory patients' population; the best management of recurrent H&N cancer according to patients' clinical history and status.

Material and Methods: 10 Italian experts in SCCHN treatment, with previous experience from consensus initiatives using risk assessment models, promoted the whole initiative and proposed the set of scenarios, besides having participated in the meeting as chairpersons. An Expert Panel of 40 specialists with extensive experience in SCCHN patient management participated in the Expert Opinion meeting. Finally, a total of 50 medical specialists with special experience in the treatment of SCCHN were involved, in order to evaluate the appropriateness of clinical scenarios.

A comprehensive evaluation of the results obtained from the Expert Opinion meeting was performed.

Results: A group of 50 experts in the field of H&N cancer (oncologists, radio-oncologists, surgeons) from 24 Italian medical centers convened in 10 April 2018 in Rome to discuss a set of clinical criteria by 71 scenarios analyzed with the RAND Appropriateness Method,[1] to fill the knowledge gap and with the aim of improving clinical decision making.

Conclusions: Of 71 proposed scenarios, 52 met a common consensus and 19 did not. The further work and focus on these unmet needs will better define the best approach to head and neck cancer patients in the Italian clinical practice.

Acknowledgement

The Expert Panel Meeting was funded by Merck Serono.

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L07

TREM-1 EXPRESSION IN HPV RELATED OROPHARYNGEAL SQUAMOUS CELL CARCINOMA (OP-SCC)

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Background: immunotherapy in head and neck SCC is a hot topic and PD-1/PDL-1 checkpoint blockade in recurrent/metastatic tumors is a promising approach, however there is a lack of robust predictive/prognostic biomarkers and treatment benefits on OS are variable. Aim of this study is to evaluate the co-expression of PD-1, PDL-1 and Triggering Receptor Expressed on Myeloid cells 1 (TREM-1) to better understand the immunophenotype of OP-SCC.

Materials and Methods: 17 surgical specimens of advanced stage primitive OP-SCC resected between 2004 and 2012; bony invasion, recurrent/metastatic disease, previous RT/CT for HNSCC, previous CT for other site solid and/or hematological tumors and immunosuppressive therapy were exclusion criteria. Immunohistochemistry (IHC) for p16 and E6 (0negative;1+,1-30%of positive cells and 2+, 31-100%), CD4 and CD8 (0negative; 1+, <10% positive cells; 2+, 10%-20%; 3+, >20%), PD-1 and PDL-1 (0, negative; 1+, <20% positive cells; 2+, 21-50%;3+,>50%) and TREM-1 (0, negative, 1+, 1-50% positive cells and 2+, >50%) was performed on consecutive sections. The McNemar test was used to asses differences between intra- and peritumoral environment.

Results: p16 was positive in 60%pts (24%+;36%++) and negative in 41% of pts; E6 was positive in 100%pts (59%+;41%++); intra-tumoral environment (ITE): CD4 was positive in 100%pts (12%+;24%++;64%+++) as CD8 (12%+;36%++;53%+++), PD-1 was negative in 29% and positive in 71%pts (71%+;0%++;0%+++), PDL-1 on tumoral cells was positive in 100%pts (53%+;48%++;0%+++), TREM-1 was negative in 82% and positive in 18% (12%+;6%++); peri-tumoral environment (PTE): CD4 was positive in 100%pts (6%+;24%++;71%+++) as CD8 (48%+; 41%++; 12%+++), PD-1 expression was negative in 59% and positive in 41%pts (41% +;0%++;0%+++), PDL-1 expression was positive in 100%pts (6% +;59%++; 36%+++) TREM-1 was negative in 18% and positive in 82% (64%+;18%++). Statistical analysis showed a concordant expression of CD4, CD8, and PDL-1 both in ITE and PTE, while TREM-1 was more expressed in PTE (p=0.001) and PD-1 in ITE (p=0.12)

Conclusion: as expected, our data shows that HPV+ OP-SCC growth is promoted by inflammatory infiltrate anergy caused by high expression of PDL-1. For the first time, we described a high expression of TREM-1 in the PTE and this finding could have a clinical relevance because TREM-1 triggering reverses the M2-polarizing effect of hypoxia imparting a M1-skewed proinflammatory phenotype to macrophages that controls tumor growth.

L08

PATTERNS OF USE OF CETUXIMAB + PLATINUM-BASED THERAPY AS A FIRST-LINE TREATMENT FOR PATIENTS WITH RECURRENT/METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (R/M SCCHN) IN THE ITALIAN COHORT OF THE OBSERVATIONAL ENCORE STUDY

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Background: The EXTREME regimen (cetuximab + platinum + fluorouracil [5-FU], followed by cetuximab maintenance until progressive disease [PD]) was the first treatment to significantly improve survival and response in patients with R/M SCCHN in over 30 years. ENCORE (EMR 062202-566) is a multinational, observational, prospective, open-label study to investigate the real-world treatment practices for cetuximab plus platinum-based chemotherapy (PBT) for first-line (1L) R/M SCCHN. Here we report the findings of the Italian cohort of ENCORE.

Methods: Previously untreated patients with R/M SCCHN were enrolled in Algeria, France, Italy, Portugal, Russia and South Africa; this analysis focuses on the Italian cohort. The study looked at patients who were planned to receive 1L treatment with cetuximab + PBT, with or without local palliative treatments, at the sole discretion of the investigator. Patient characteristics, planned regimens and schedules were recorded. The primary objective of ENCORE was to collect data on how cetuximab is used to treat R/M SCCHN. Secondary endpoints include clinical benefits, safety, and subsequent therapies.

Results: Treatment-planning practices in Italy were collected for 144 evaluable patients. 91 patients (63.2%) had treatment decisions made by a multidisciplinary team. 15 patients (10.4%) were tested for human papillomavirus infection prior to treatment. 144 patients (100%) were planned to receive cetuximab maintenance until PD. Furthermore, 83 patients (57.6%) were planned to receive PBT per the EXTREME label (ie, either cisplatin + 5-FU or carboplatin + 5-FU). 80 patients (55.6%) continued cetuximab maintenance treatment after PBT treatment. Median progression-free survival and overall survival were 7.2 months (95% CI, 5.8-8.7 months) and 11.2 months (95% CI, 8.4-16.2 months), respectively. Serious adverse events (SAEs) and SAEs related to cetuximab occurred in 31.3% and 3.5% of patients, respectively.

Conclusions: This study shows that a real-world R/M SCCHN patient population treated with the EXTREME regimen in Italy derives a clinical benefit from first-line cetuximab + PBT comparable to that observed in the EXTREME study.

This trial was sponsored by Merck KGaA, Darmstadt, Germany.

L09

DATASET OF NASOPHARYNGEAL CANCER PATIENTS IN NON-ENDEMIC SETTINGS

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Background: Nasopharyngeal carcinoma (NPC) has got unique epidemiological features, being endemic in Southern China and Southeast Asia and a rare cancer in most areas including Europe. Data regarding natural history, prognostic factors and treatment opportunities in NPC patients (pts) are derived from studies conducted in endemic settings. Also, the prevalence of EBV-related disease in non-endemic setting is not clearly described in literature.

Materials: Through the web portal www.npcportal.org, designed to implement information and sharing data about NPC, this ongoing study will collect clinical data from consecutive NPC pts treated in non-endemic countries. As first analysis, the study will be retrospective and limited to all consecutive pts treated with curative intent from 2005 till 2015, while data of recurrent and/or metastatic pts will be collected till 2016.

Main objective of the study is to collect clinical and biological parameters able to describe the characteristics of the disease in non-endemic settings and to correlate them with the outcome.

Results: Through this dataset, we expect to improve the knowledge in non-endemic areas about:

- global outcome of NPC patients with early and locally advanced disease, in term of locoregional control, distant metastatization and overall survival

- global outcome of NPC patients with recurrent/metastatic disease
- prognostic factors in the different setting of disease, comparing them with prognostic factors, prognostic score index and nomogram already studied in endemic settings
- prevalence of EBV-positive and HPV-positive NPC
- prevalence of assessment of plasmatic/blood EBV DNA and its prognostic factor in the different setting of disease
- use of conventional RT or IMRT techniques and its impact on locoregional control
- late toxicities recorded by physicians

Conclusions: The dataset is currently ongoing in 80+ Centers in Italy and abroad and it is open to participation. Results will inform about prognostic factors and outcome in non-endemic areas and it will be referral for building new prospective trials.

On behalf of the NPC Portal Investigators Group

L10

PROGNOSTIC IMPACT OF TAILORED NUTRITIONAL SUPPORT IN PATIENTS (PTS) AFFECTED BY HEAD AND NECK CANCER (HNC) UNDERGOING CHEMOTHERAPY AND/OR RADIOTHERAPY

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Background: Patients affected by HNC reported a high risk of malnutrition, with an unintentional weight loss and several nutritional challenges at diagnosis, during and after the end of treatment. Despite this high prevalence, the nutritional assessment and management are not routinely integrated into cancer care in these pts. Consequently, the aim of the present study was to explore the prognostic impact of the nutritional intervention in pts affected by HNC undergoing chemotherapy and/or radiotherapy.

Material and methods: Data from pts affected by HNC (stage II-IV), diagnosed between April 2010 and August 2016 at the AOUI of Verona and undergoing chemotherapy and/or radiotherapy, were retrospectively analysed. Descriptive statistics was adopted. Clinical, pathological and nutritional data were correlated to Overall Survival (OS) using a Cox model. Kaplan-Meier curves were compared with Log-Rank analysis.

Results: Data from 87 pts (68 males [78.2%] and 19 females [21.8%]) were gathered (median age 63 years [range 35-83 years], with a median follow-up of 23 months (range 3-116 months)). Forty-one pts (47.1%) received an individualized nutritional intervention (including tailored nutritional counselling and oral nutritional supplements according to pts' need) and 46 pts (52.9%) did not receive that, without a significant difference for baseline characteristics. In particular, the median weight loss in the last 6 months was 6.7% (6.7% vs. 7.0%, respectively) and the median Body Mass Index (BMI) was 23.7 kg/m2 (22.7 kg/m2 vs. 23.9 kg/m2, respectively). At the multivariate analysis, the response or stable disease after the first line treatment (HR 4.62, 95% CI 2.12-10.90, $p<0.0001$), the nutritional intervention (HR 3.72, 95% CI 1.86-7.42, $p<0.0001$), the Performance Status <1 (HR 2.06 95% CI 1.04-4.06, p=0.037) and the BMI $\geqslant 25$ at baseline (HR 2.85 95% CI 1.35-6.02, p=0.006) were significant independent predictor for better OS. Particularly, the 3-year OS was 59.0% in pts receiving the nutritional support and 34.9% in pts who did not receive that (p=0.007). In the context of pts with unplanned hospital admissions $^{3}2$ (37 pts [42.5%]), the nutritional intervention significantly discriminated the OS (61.5% vs. 25.5%, p=0.006).

Conclusions: Despite the retrospective design of the study, our results support the prognostic relevance of the nutritional management in pts affected by HNC undergoing chemotherapy and/or radiotherapy.

L11

DIAGNOSTIC WORKUP OF CERVICAL UNKNOWN PRIMARY (CUPS) OF THE HEAD AND NECK (HN)

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Background: CUPs in the HN area are rare and their therapeutic approach remains controversial. The current retrospective series investigates the management of patients (pts) with HNCUPs.

Methods: From 2005 to 2017, 61 HNCUPs were examined and treated in our Institution. The diagnostic workup consisted in HN office-based endoscopy and imaging with MRI and/or CT-PET. P16 and HPV DNA as well as EBV DNA were assessed on true cuts performed on the N in each case.

Results: The majority of pts were males (88%), with a median age of 61 years (range: 25 – 84) and ECOG 1 (range: 0 – 1). 64% were smokers with a median of 30 pack/years. The most common cN categories were cN2b and cN3 (56%), while23% had distant metastases. Hence,

93% of pts had a stage IV disease (according to the TNM AJCC VII ed). Tumoral HPV/p16 and EBV DNA assessment had not been performed in 17 cases. 26 out of 44 (59%) pts were positive for high risk HPV and/or p16 and 3 (7%) were EBV positive. HNCUP were staged by MRI, CT-PET or both respectively in 83%, 75%, and 69% of cases. Primary tumor was identified in 31% of cases by MRI and in 26% by CT-PET . Pathological primary tumor assessment was performed heterogeneously, being the targeted biopsy on the base of radiological suspicion the most common approach (33% of pts). In 28% of cases, diagnosis of HNCUP was performed exclusively by imaging (23%). At the end of investigations, only 13 primary tumor (21%) were identified.

Conclusions: HPV-related tumors represent the majority of HNCUPs. HPV and EBV assessment is mandatory in each HNCUP. MRI to search for primary tumor and pathological confirmation of the suspicious imaging is advisable in each case.

L12

PERINEURAL INVASION AS INDEPENDENT PROGNOSTIC FACTOR IN RADICAL RESECTED ORAL TONGUE SQUAMOUS CELL CARCINOMA: A SINGLE-INSTITUTION, RETROSPECTIVE STUDY

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Background: Oral tongue squamous cell carcinoma (OTSCC) is one of the most frequent and aggressive cancer among all head and neck malignancies. After radical surgery, about 20-40% of patients develops tumor relapse. The histological identification of perineural invasion (PNI) is generally considered as a poor prognostic factor in OTSCC, but its role in the management of patients with OTSCC is still controversial. The purpose of this study was to evaluate the impact of PNI on survival outcomes of OTSCC patients.

Patients and methods: Clinical records of treatment-*naive* patients with OTSCC who underwent radical surgery were analyzed. Patients received adjuvant radiotherapy or chemoradiotherapy based on standard clinical and pathological determinants. The association between the presence of PNI and clinical characteristics were evaluated through the chi-squared or Fisher's exact test. Disease-free survival (DFS) was calculated according to Kaplan-Meier method and differences between groups were screened by log-rank test. Cox proportional hazards regression model was performed.

Results: Between January 2005 to December 2017, 109 patients were included in the study. Median age was 61.1 years (18 - 87). Sixty-eight patients (62,4%) were men. Eighty-nine patients (81,7%) had T1 or T2 tumors. Thirty-eight patients (34,9%) had nodal involvement and 17 (15,6%) of them presented extra nodal extension (ENE). PNI was found in 14 patients (12.4%). PNI+ patients were more likely to have higher tumor dimension [8/89 (9.0%) in T1 or T2 vs 6/20 (30.0%) in T3 or T4; p=0.006] and lymph node metastases [8/38 (21.0%) in N+ vs 6/71 (8.4%) in N-; p=0.049] with a more frequent presence of ENE [7/17 (41.2%) in ENE+ vs 7/88 (8.0%) in ENE-; $p<0.001$]. After a median follow-up of 95.5 months (5.6 - 143.4), a total of 19 patients (17.4%) experienced tumor relapse, including 12 loco-regional (63.2%) and 7 distant recurrences (36.8%). In this group seven patients (36.8%) had PNI+ carcinoma. Patients with PNI+ tumors presented a decreased DFS as compared to PNI-negative subjects [74.9 months vs not reached; hazard ratio (HR) 0.201, 95% CI 0.079 - 0.512; $p<0.001$].

Conclusions: In OTSCC, the presence of histological evidence of PNI has a significant impact on survival outcome in OTSCC patients after radical surgery, independently of adjuvant therapy. Further investigations are required to evaluate possible interactions with other risk factors and the opportunity of intensified treatments.

L13

PSYCHOLOGICAL INTERVENTION IN THE CARE OF HEAD AND NECK CANCER PATIENTS

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Background: Our goal was to include psychological intervention in taking care of patients with Head and Neck Cancer. Many patients with head and neck cancer have a history of alcohol abuse and/or smoking, and often pre-existing mental-health problems that limit access to psychological intervention.

Patients and methods: During a one-year period patients susceptible to psychological intervention were

sent for psychological evaluation by the Head and Neck multidisciplinary team to the Hospital Psychological Service after communication of the diagnosis and therapeutic plan. The psychologist proceeded to a psychological distress screening through: psychological interview, Distress Thermometer (DT, recommended by NCCN Guidelines), Hospital Anxiety Depression Scale (HADS, recommended by the European Head and Neck Cancer Society) and a socio-demographic card. The psychologist then proceeded with individual care and/or patient placement in group activities (predominantly relaxation activity). Selection criteria for being forwarded to the psychologist were: newly diagnosed head and neck cancer patients, age less than 70 years, ability to access a psychological evaluation (no cognitive deficits or severe psychiatric disorders).

Results: From July 2016 to July 2017 out of 15 selected patients 12 were sent to the Psychological Service, 3 refused. Among the 12 patients sent, one refused to complete the questionnaires. Patients characteristics were: 10 males, 1 female, median age of 60. 73% were married, 27% were separated or single; 46% had an occupation, 54% were retired; 46% were affected by laryngeal cancer, 18% by oropharyngeal cancer, 18% by hypopharyngeal cancer, 9% by salivary gland cancer and 9% by nasopharyngeal cancer. 64% underwent chemo- and radiotherapy. 46% reported dependence on smoking, 27% on smoking and alcohol. The average DT score was 2.6. The HADS had an average score of 4.6 for anxiety and 2.6 for depression.

Conclusions: We would have expected distress, anxiety and depression scores greater than those detected. In our opinion, low scores reflect difficulty by Head&Neck cancer patients to express their moods and emotional problems. We believe that these patients still deserve attention from a psychological point of view, therefore psychological care models should be implemented.

L14

SAFETY AND EFFICACY OF LENVATINIB AT A REDUCED DOSE FOR METASTATIC RADIOIODINE- REFRACTORY DIFFERENTIATED THYROID CANCER: OUR EXPERIENCE

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Background: Final results from the phase III SELECT trial confirmed a survival benefit of lenvatinib in patients (pts) with metastatic radioiodine refractory differentiated thyroid cancer but 67.8% of pts required a dose reduction due to toxicity.

Material (patients) and methods: we evaluated 6 patients treated with lenvatinib from February 2017 to April 2018. Pts were aged 18 years and older, with performance status ecog 0-1, relapsed after radioiodine treatment and after sorafenib 800 mg daily in one case. One patient experienced rechallenge with lenvatinib. Three patients had papillary hystotype while the other 3 had follicular type. The most frequent sites of metastases were: lung and bone. Lenvatinib was administered orally at 14 mg once a day in 5 cases due to clinical status of pts, patient having rechallenge started with 10 mg daily. Dose reduction to 10 mg was performed in one case after three months of treatment with dose at 14 mg. Pts were monitored for adverse events. Our aim is to evaluate the safety and efficacy of Lenvatinib in clinical practice.

Results: lenvatinib was related to grade 1-2 adverse events in all patients. Main toxicities included hypertension (2/6 patients), asthenia and decreased weight (6/6 patients), diarrhea (2/6 patients), arthralgia (1/6 patients). A case of heart failure was reported in a patient receiving lenvatinib 14 mg for 10 months but its origin is uncertain. Three patients had partial response, 2 pts had stable disease, 1 patient has no yet an evaluation of response. The median progression free survival was 9.3 months (range 2-14 months) according to data of SELECT trial.

Conclusions: Our experience suggests that Lenvatinib also at a reduced dose is quite safe and effective in patients with progressive radioiodine refractory differentiated thyroid cancer.

L15

PLATINUM UNSUITABLE HEAD AND NECK CANCER ELDERLY PATIENT: EFFICACY AND SAFETY OF RADIOTHERAPY PLUS CETUXIMAB

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Background: In patients with locally advanced head and neck squamous cell carcinoma (HNSCC), chemoradiation (CRT) improves locoregional control (LRC) and overall survival (OS). Cisplatin at a dose of 100 mg/m2 given every three weeks remains the recommended systemic therapy option during CRT. However, addition of this chemotherapy regimen to RT is often associated with significantly increased toxicities that influence the quality of life dramatically. In locally advanced SCCHN, concurrent chemoradiotherapy in patients over 70 years remains a point of controversy owing to its possibly

higher toxicity and questionable benefit. This is a retrospective observational study that evaluates the efficacy and the safety of radiotherapy plus cetuximab for the treatment of unfit elderly patients with loco-regionally advanced squamous-cell carcinoma of the Larynx/Hypopharynx.

Patients and methods: From may 30, 2013 to march 30, 2015, thirty-one consecutive patients (median age 72 years; range 69-87) with squamous-cell carcinoma of the Larynx/Hypopharynx have been enrolled. The treatment included high-dose radiotherapy plus weekly cetuximab at an initial dose of 400 mg per square meter of body-surface area, followed by 250 mg per square meter weekly for the duration of radiotherapy. The primary end point was the duration of control of locoregional disease.

Results: There was a predominance of males (72%), and the median age of the population was 79 years (range, 61 to 87 years). Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1 was present in 25% of the patients, whereas 60% had a PS of 2 and 15% a PS of 3. Primary tumors were located in hypopharynx (33%) and larynx (67%). All patients enrolled had at least one severe comorbidity and one clinical factor for absolute contraindications to cisplatin. The median duration of locoregional control was 17 months among patients treated with cetuximab plus radiotherapy. The incidence of acute adverse effects of grade 3 was 52 percent in the population of the study.

Conclusion: This study shows that the concomitant treatment of radiotherapy and cetuximab is a feasible and useful therapeutic option also for frail elderly patients not suitable for cisplatin chemotherapy. This treatment of locoregionally advanced head and neck cancer has a definite activity and improves locoregional control with a favorable safety profile.

M - Management of Cancer Pain

M01

PALLIATIVE CARE PATIENTS HAD A CIRCADIAN RHYTHMICITY IN THEIR BREAKTHROUGH PAIN (BTP) EPISODES

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Background: Pain intensity, analgesics effect and opioid requirement have all been demonstrated to change considerably across the day. BTP is defined as transitory exacerbations of pain that occur on a background of stable pain adequately controlled by around-the-clock opioid therapy (Caraceni et al., 2012).

In cancer outpatients suffering from chronic severe pain, BTP occurs according to a circadian rhythm with a peak in the late morning (Saini et al, 2013). End-of-life (EOL) cancer patients usually have higher tumor burden with more bothersome symptoms and are frequently bedridden. These conditions may alter their circadian rhythm, including pain perception and BTP occurrence. No data on a possible rhythm in BTP occurrence are available in EOL cancer patients.

The aim of this study was to explore whether EOL cancer patients have a circadian BTP rhythm.

Methods: 101 consecutive home and hospice patients with severe chronic pain followed by two palliative care services and successfully treated using major opioids were longitudinally observed over 7 days and screened for BTP episodes using a BTP diary. BTP characteristics were assessed with a short form of the Italian version of Alberta BTP Questionnaire by nurses and palliative care physicians at day 8 of the observation period (Sperlinga et al., 2015). Patient performance status was assessed using the following tools: ECOG-PS; Palliative Outcome Scale; and Karnofsky Performance Status. Rhythm in the number of BTP episodes was characterized and validated by two-way analysis of variance (ANOVA) and by COSINOR analysis. Cosinor analysis yields three main parameters: MESOR (Midline Estimating Statistics Of the Rhythm of the fitted cosine curve); acrophase (occurrence of maxima in days or months, which may not take place at the time during which maximum concentration was observed); and double amplitude (the difference between the highest and lowest point of the fitted cosine curve).

Results: A total of 658 BTP episodes were recorded. BTP episodes showed a significant circadian pattern, with a peak at 12h30 pm. Circadian rhythm was evident in all subgroup analyses (home or hospice; patients with or without bone metastases; bedridden or not bedridden) with no statistically significant difference between subgroups.

Conclusions: The findings of our prospective study demonstrated that BTP occurrence presents a circadian rhythmicity also in EOL cancer patients.

M02

EARLY PALLIATIVE CARE FOR EARLY BREAKTHROUGH CANCER PAIN TREATMENT

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Table 1. Baseline patient characteristics (n=83).

	n	%
Sex		
F	46	55,4
M	37	44,6
Mean age (range)	69 (40-89 anni)	
Median KPS (range)	70 (40-80)	
PAP score A	83	100
Primary tumor site		
Gastrointestinal	20	24,1
Pancreas, liver or biliary tract	12	14,5
Lung and pleura	11	13,3
Breast	23	27,7
Genito-urinary	9	10,8
Haematological	4	4,8
Other	4	4,8
Treatment		
Chemotherapy	69	83,1
Radiotherapy	10	12,0
Tyrosine Kinase Inhibitors	4	4,8
Other	13	15,7
>1 treatment (last 3 months)	11	13,3

Background: Patients with advanced cancer often develop physical and psychosocial symptoms that require individualized assessment and management. AIOM and SICP indicate that palliative care (PC) services should be present within oncology departments (OD). Indeed, early PC provide better management of symptoms on patients' quality of life and end-of-life care. Four out of ten oncologists consider themselves not fully confident in their choice of the appropriate cancer pain therapy determining a 'time lag" between the initial diagnosis of breakthrough cancer pain (BTcP) and its treatment.
Material and methods: The study was performed in 1 OD (2 hospitals) between 2016 and 2018. Oncologists evaluated the presence of all following conditions: metastatic cancer, active anticancer treatment and Karnofsky performance status (KPS) <90%. Early PC consultation was performed in patients with one or more of following clinical elements: uncontrolled symptoms, psychological distress of patient or his relatives, severe comorbidities, multiple hospital admissions or social difficulties. The evaluation of life expectation and chronic or BTcP were performed by PC physicians using PAP score, ESAS and IQ-BTP questionnaires. Patients with high or intermediate likelihood-BTP level received rapid onset opioids.
Results: Baseline patient characteristics are listed in table 1. 58% (n=48) and 19% (n= 16) of patients had chronic pain and potential-BTcP respectively. The likelihood for BTP diagnosis was 'high' in 31%, 'intermediate' in 44% and, 'low' in 31% of patients with potential BTcP. It was predictable in 56% of cases. In 96% of patients with chronic pain oral oxicodone (± naloxone) or trans-dermic fentanyl were used as around the clock drug. In 67% of them, rescue drug was oral morphine. One or more adjuvants were prescribed in 60% of cases (79% of patients received steroids). Patients with high-potential BTcP received transmucosal or intranasal fentanyl at mean dose of 200 mcg.
Conclusions: Early referral to PC services and the use of IQ-BTP could permit BTcP treatment with right drugs at the right time.

M03

OUTPATIENT MANAGEMENT OF PAIN IN THORACIC CANCER PATIENTS WITHOUT INDICATION TO ACTIVE THERAPY. A SINGLE INSTITUTION EXPERIENCE

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Background: Despite attention paid to patients (pts) quality of life about one third of cancer pts do not receive adequate treatment for pain and near 64% of those with metastatic disease report pain. A subgroup of pts with thoracic tumors are unable to receive "active" treatments, although they maintain discrete general conditions, due to advanced age or co-morbidities. These pts are often followed as outpatients, being palliative care clinics scarce or absent in several Italian contexts.
Materials and methods: Pain incidence and its management have been retrospectively evaluated in pts with thoracic malignancies without indication to active cancer therapy and followed at our institution's supportive care clinic by oncologists and nurses with palliative training.
Results: From March 2016 to March 2018, we analyzed 155 consecutive pts (evaluated on average every 23 days for a total of 604 outpatient visits). Pts mean age was 79 years (range 50-92), 113 were males (73%), 139 pts (89.6%) had an ECOG performance status 1-2. Histologic diagnosis was available in 105 pts (67.7%; 77 lung carcinomas, 28 pleural mesotheliomas), while 50 patients (32.3%) had only a radiological suspicion. Most pts were stage IV (131, 84.5%). Sixty pts (38.7%) had more than 4 comorbidities. At the first visit, 103 patients reported pain (38 pts, NRS scale = 1-3; 53 pts, NRS 4-6; 12 pts, NRS 7-10). Pain therapy was administered to 101 pts. At the last outpatient visit 53 pts (52,4%) reported good pain control (NRS 0-3). The opioids was used in 89 pts (88%; 16 weak opioids, and 73 strong opioids) with excellent tolerance. A breakthrough pain medication has always been prescribed

(1/6 of the daily opioids dose) to every patient treated with strong opioids. Pain management required dosage increasing (37 pts), introduction of a different analgesic (5 pts), pharmacological switch in 21 (15 between strong opioids and 6 from weak to strong opiates). The switch was performed for ineffective treatment and for poor tolerance in 16 and in 5 pts, respectively. The following additional drugs were used: FANS (7 pts), gabapentin (10), benzodiazepines (39), steroids (117), neuroleptics (16), antidepressants (21). All patients treated with strong opioids (73) used laxatives.

Conclusions: Outpatient management of thoracic tumors pts in discrete clinical conditions and not eligible for active treatment is feasible, leading to a good pain control before switching to other palliative settings.

M04

FEASIBILITY AND UTILITY OF PAIN MONITORING BY NUMERIC RATING SCALE IN CANCER PAIN MANAGEMENT

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Background: A regular evaluation of pain in hospitalized cancer patients is required by Italian Law 38/2010 on Palliative Care and Pain Therapy and by the AIOM-SICP guidelines on "Early and simultaneous Palliative Care in Oncology". We report data recorded between April 2015 and January 2016 concerning: pain prevalence, type, frequency of medical interventions for breakthrough cancer pain (BTcP), pain revaluation after therapy for breakthrough pain, efficacy of interventions during patient hospitalization.

Material and methods: Pain were evaluated twice a day in our in-patients by means of numeric rating scale (NRS). We recorded daily data reported in the medical records about number of: pain detections, detections of pain NRS $>$ 4, interventions for pain NRS $>$ 4, number of re-evaluations after intervention for pain NRS $>$ 4, number of missing re-evaluations after intervention for pain NRS $>$4, number of re-evaluation with a NRS value decrease after intervention lower than 30%. Medical intervention was defined as analgesic drug administration according to breakthrough pain therapy planning. Data were analyzed by STATA (v14.0)

Results: We recorded data from 157 in-patients (83 males, 74 females; median age 69 yrs) for 1981 days of hospitalization overall. At admittance, 79 out of 157 patients (70%) had pain: 41%, 18%, 8% and 3% had visceral, bone, somatic or neuropathic pain, respectively. 94 out of 157 patients (59%) were already in analgesic therapy: 10% with non-opioids, 15% with weak opioids and 34% with strong opioids. Breakthrough analgesic treatment was scheduled in 92% of patients: 37% with non-opioids, 20% with weak opioids, 35% with strong opioids. A NRS value $>$ 4 was recorded in 435/3792 (12%) total pain detections and in 410/435 cases (94%) involved a medical intervention by pain relief drug administration. Pain after medical intervention was re-evaluated in 388/410 (95%) cases and a reduction upper than 30% in NRS value was obtained in 358/388 cases (92%).

Conclusions: The breakthrough pain represents a clinically relevant condition with a negative impact on the patient's quality of life.

Our results confirms that twice a day evaluation of pain in hospitalized patients by NRS is feasible and allows to correctly record pain intensity, to timely treat breakthrough pain and to quantitatively evaluate response to analgesic drug administered for BTcP.

Most patients, properly instructed and cooperating, obtained a rapid and effective personal pain management.

M05

THE INTERDISCIPLINARY MANAGEMENT OF PROBLEMATIC RETURN TO WORK AFTER EARLY PHASE ONCOLOGICAL TREATMENTS: A PILOT PROJET PROMOTED BY ONCONAUTI ASSOCIATION AND OCCUPATIONAL DOCTORS NATIONAL ASSOCIATION

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Today over 1,3 million of citizen are living after being diagnosed with tumour. Especially for the 50% of the women operated from breast tumour return to work (RTW) can be problematic, as it is often followed by a severe socio-economic impact as regards absence, excessive sanitary spending and productivity loss. A recent study, carried out by an Ausl Bologna working group and Onconauti Association, allowed to identify the main risk factors, both psycho-social and secondary to the late side effects of the oncologic treatments (OT), of a problematic RTW of women operated at the breast.

Focusing on the available literature, the Working Group identified 4 key points for reduce risk of problematic RTW: 1. Evaluation of the pre-tumor diagnosis health status and the level of psycho-social vulnerability in the choice of OT of early stage of breast cancer. 2. Multidisciplinary assessment

of the higher risk cases of problematic RTW. 3. Sending long survivors to a personalized integrated rehabilitation programs to improve physical and emotional well-being 4. Interdisciplinary training of Occupational Doctors, to activate custom adaptation of the job tasks of cancer survivors at risk of work disability.

Onconauti Association, in collaboration with ANMA, taking into account the positive preliminary results achieved in its integrated "evidence based" oncological rehabilitation programs (Yoga, psychological support and promoting healthy changes in lifestyle) wants to promote a Pilot Project that confirm the feasibility of these interventions in facilitating the RTW of cancer survivors.

Oncological rehabilitative pathways are still lacking in Italy, patients are rarely informed about the possible impact of early phase OT on work skills and about the proved benefits of integrative treatments. INPS welfare services may not to be sufficient to facilitate a full fitness recovery nor to avoid that in many cases the late side effects of the OT become transformed into a more or less pronounced conditions of chronic occupational disability. We believe that the Pilot project could have a positive impact on public spending and the quality of life of patients, favoring a synergic intervention between the different subjects involved in the oncological rehabilitation and RTW path, including Companies, Oncologists, Occupational Doctors and Patients Associations, and also could constitute a innovative model for the RTW of patients affected by other chronic diseases.

M06

SMART4PAIN – CANCER VERSION: EVIDENCE-BASED PSYCHOLOGICAL INTERVENTIONS IN THE MANAGEMENT OF PEDIATRIC CANCER- AND TREATMENTS-RELATED PAIN

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Pain is significant stressor for both child and parents during course of cancer. A good pain management is not only associated with decreased distress and anxiety, but also with less negative attitudes towards future medical procedures and pain episodes. Despite the proven effectiveness of psychologically strategies for pain, too few pediatric patients refer to psychological services due to a lack of available providers, scheduling conflicts, inadequate knowledge of efficacy. These interventions should be planned in a format that is acceptable, closely to the DH routines. The purpose of this preliminary study is to evaluate the efficacy of a psychological program to manage cancer- and treatments-related pain.

Since effective treatments is a collaborative effort among services, University of Trento in partnership with Bolzano's Hospital has been developed the SMART4Pain program to manage chronic pain, started in December 2017. From it we planned this feasibility study with a 1-group, nonrandomized, repeat measures design.

All participants (teens 11-18 ages and their parents) will be in a phase of their treatments and will familiar with the invasive procedures. In addition to their medical care, teens will complete 4 sessions of Biofeedback treatment (a tool that measures and feed-back information about the own physiological activity) to increase awareness of and control over one's physiological processes, like respiration, skin temperature, and heart rate variability (HRV). By visual feedback via computer, they will learn self-regulation skills. The baseline readings will be recorder for each session. A Problem-Solving Skill Training, (PSST - a process to identifies or creates coping strategies in response to a stressful event) will addressed to parents during their child's participation in each session.

We expect that both state-anxiety and pain score will demonstrate a downward trend over the time from Session 1 to 4, as well an increase HRV and Coherence Scores. In an exploratory manner we will examine change in parent distress from pre- to post-treatment.

This combination interventions can be serve as a tool to increase participants' awareness of the connection between emotions, physiological changes, and self-regulation even though the situation itself (eg. invasive procedure) is not entirely under the child's control. Furthermore, although we chose to apply PSST with parents to managing pain problems, it can be implemented at any time for other issues.

M07

CHRONIC PAIN AND BTCP MANAGEMENT IN SIMULTANEOUS CARE: A RETROSPECTIVE STUDY

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Background: Diagnosis and treatment of pain, both in its chronic and acute expressions, are fundamental aspects of the oncologic patient's care path. A Simultaneous Care (SC) approach allows collaboration between the oncologist and the palliative care specialist allowing an overall assessment of the patient's state and of his assistance needs.

Data have shown that palliative care is more effective in oncology when simultaneous approach is applied [Temel, 2010, Maltoni 2016].

Breakthrough Cancer Pain (BTcP) has a negative impact on the quality of life and is a bad prognostic factor of hard to treat pain [Fainsinger, 2009].

We undertook a retrospective study on a SC experience in our Oncology Day Hospital (ODH), in the presence of a dedicated Palliative Care (PC) clinician focused on diagnosis, characterization and treatment of BTcP.

Material and Methods: Patients who performed at least 3 consecutive PC consultations in ODH during 2017 were recruited. Data were analyzed by examining patient's clinical records and counseling reports for the following variables: demographics, pathology, therapy, EOCG Performance Status, features of chronic pain and BTcP, specific therapies prescribed.

Health registry analysis offered data about SC assistance features and outcomes: hospitalizations, activation of Home Assistance, date of death.

Results: During 8 months, 99 patients were observed: 54 performed at least 3 progressive evaluations (F =24; M=30), mean age was 68.6, ECOG average 1.2. The primary cancer site was: pancreas (12), colon (9), prostate (6), pleura-lung (5), ovary-uterus (4), breast (4), urinary tract (4). 53 of 54 had at least 1 site of metastasis. All 54 patients underwent antalgic therapy with a mean oral morphine dose of 100.7mg/day). Baseline pain relief observed at the third assessment was on average 67%. Seventy-seven BTcP episodes were reported and treated, when indicated, with Rapid Onset Opioids (mean fentanyl dosage 207 μgrams). 25 patients are alive at the time of analysis, SC assistance was performed for a mean time of 4.5 months; 43 were never hospitalized, 11 were admitted at least once and 23 had a home care assistance activated.

Conclusions: A SC approach allows to improve pain diagnosis and treatment, optimizing the prosecution of the oncological therapy path. At the presentation of the study results will be completed with inferential part evaluating relation between disease, baseline pain and BTcP, and SC care path features.

M08

EFFICACY OF TAPENTADOL PR IN OPIOID NAIVE CANCER PATIENTS.

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Background: Cancer pain could be the first symptom in cancer patients. Its intensity could be moderate or severe, requiring an effective and well-tolerated treatment. Tapentadol PR is recognised to be a first-line analgesic treatment. First molecule of a new class of painkillers called MOR-NRI, characterized by a double mechanism of action, opioid and noradrenergic. Data shown that tapentadol PR is more effective in different types of pain and better tolerted than traditional opioids. We evaluated the analgesic efficacy and tolerability of tapentadol PR in opioid naïve patients with cancer pain.

Material and methods: 45 opioid naïve patients (21M/24F), median age 60 years (42-82) with cancer pain ⩾4 on NRS were evaluated. They were affected by different neoplasms (20 lung, 12 breast, 9 gastrointestinal, 3 gynaecologic, 1 urological). Tapentadol PR was initially administered at a dose of 50 mg/die based on previous therapy and patient needs. The study lasted 1-2 months with 4 visits (baseline and after 7, 15-20 and 45-50 days). The primary endpoint was the number of responder (patients with at least a 30% reduction of pain intensity at the end of study compared to baseline). Others parameters were pain intensity, QoL, quality of sleep, neuropathic symptoms. All adverse events were recorded.

Results: Pain lasted on average from 2.7 months. ECOG-PS was 0 (17 pts)-1 (28 pts). The disease stage was M1 in 31 cases; 21 subjects underwent chemotherapy, 4 radiotherapy and 1 another type of therapy. The mean basal pain intensity was 5.4 (±0.8); 27/45 cases previously received analgesics (paracetamol alone or in association in 13 pts, NSAIDs in 9, opioids or adjuvants in 1). The mean tapentadol PR dose was: 121.1±43 mg/day at baseline, 108.3±28 at 7 days, 108.3±28 at 15-20 days and 131.1±44 at the end of study; it was administered alone in 35 cases at baseline, in 43 at 7 and at 15-20 days, in 36 at final visit. At baseline paracetamol was associated in 4 cases, while cortisone in 6; the most used ROO was fentanyl (35 pts at baseline and 36 at the last visit). All patients were responders and 87% of patients reported a reduction of pain intensity ⩾50%. A significant reduction in pain intensity was observed (-67% with a final value of 1.8). There was a significant reduction of neuropathic symptoms, a marked improvement in QoL and quality of sleep.

Conclusions: Tapentadol PR showed to be effective and well tolerated in controlling cancer pain in opioid-naïve patients.

M09

IMPROVING SIMULTANEOUS CARE IN THE NETWORK OF "RETE ONCOLOGICA CAMPANA (ROC)"

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Background: Most of the clinical activities in cancer patients are given in an outpatient setting. The concept of simultaneous care, consider concurrently in the need of a specific cancer therapy and treatment of all remaining patient needs. In particular pain management is not only related to the phase of the end of life, but must be followed all over the history of the disease adapting therapy dynamically, especially breakthrough pain, underestimated in the practice. Nutrition is also underestimated and requires continuous assessment. The link among cancer hospitals and the clinical services that manage cancer patient in their area of residence is not fully active in our region. One of the main goal of the ROC is to take care of the oncological needs both in the diagnostic phase and after the therapy is started giving the opportunity to the patients to satisfy all the needs that do not require direct management in the hospital in the services available in the local territorial system

Methods: The aim of this project is to include in the electronic platform of the ROC a module able to promote the path of simultaneous care. The goal of the project is related to the activation of the territorial integrated assistance when the patient after being treated in the hospital go back home and local services are involved in the care. All the patients coming from the Medical Oncology of the NCI of Naples and resident in the area of the territorial services of ASL NA1 are included in the project. Electronically, all the information regarding the needs of the patient that is going to be sent home are reported to the local services close to its residence. A first assessment of nutrition and pain is done in the cancer center and this report is transmitted to the regional services to prepare the following actions required. Than the territorial pain services take care of the patients identifying through specific questionnaires the occurrence of pain and recording also episodes of breakthrough pain. The pilot experience is going to start in May 2018 and is planned to be extended to all patients treated in the ROC in September.

Conclusions: A web based procedure to guide the path of simultaneous care between cancer centers and the territorial assistance has been developed. 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.

M10

CANCER-RELATED WEIGHT LOSS AND CANCER PAIN : SUPPORTIVE CARE AND MANAGEMENT

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Background: Cancer cachexia is characterized by systemic inflammation, negative protein and energy balance, involuntary loss of lean body mass. It is an insidious syndrome, which includes malnutrition, inflammation and anorexia. It not only has a dramatic impact on the quality of life, but also on the prognosis itself. The half of all the patients with cancer eventually develop a syndrome of cachexia, with anorexia and a progressive loss of adipose tissue and skeletal muscle mass. Episodes of breakthrough cancer pain (BPTC) increased until 6 per day, and they are poorly controlled with ROO (Rapid onset Opioids), because fentanyl is a lipophilic drug.

Patients and Methods: We conducted spontaneous observational studies with 47 patients of both sexes, with metastatic disease and neoplastic cachexia (BMI> 18), performance status sec Karnofsky 40/50, cancer pain 8-9 to the NRS and more than 6 episodes of BTCP. We included patients with low Bmi (18-20) and we increased it with nutritional support. We treated them with analgesic opioids at a stable dose of an equivalent of 60 mg of oral morphine to control the background pain. These patients had dysphagia. We then used oral nutritional supplements and parenteral nutrition with intravenous nutritional bags to improve the BMI. Nevertheless, only 2 patients within this group did not reach the BMI cut-off 18 and dropped out. We treated patients who increased the BMI with transdermal fentanyl for the management of cancer pain. We treated these patients with analgesic opioids at a stable dose equivalent to a 60 mg of oral morphine to control background pain. We used oral fentanyl in 34 patients in the 400-microgram formulation and the 67-microgram dose as rescue dose. 11 patients developed mucositis as a result of cytotoxic and radiotherapy treatments: in this pool we used intranasal pecfentanyl (400 micrograms).

Results: Patients with increased BMI reported a measurable pain reduction from 8 to 4 within the NRS scale. BTCP episodes were reduced to 3 per day. Therefore, we reduced the dose of fentanyl used at BTCP from 400 to 267, using the 67 micrograms as a rescue dose.

Conclusion: Clinical evidence suggests to correct malnutrition in the oncohematological patients pool, also with ONS and parenteral nutrition, to use fentanyl for Cancer Pain and BTCP. The safety and tolerance of integrated management in long-term treatment improved the quality of life.

M11

KEEP THE PAIN IN CHECK IN 10 MOVES AT MEDICAL ONCOLOGY UNIT

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Background: To guarantee for all the patients admitted to recovery in the Oncology ward it is necessary a systematic survey of the pain symptom, a prompt pharmacological intervention for breakthrough pain (BTP), an attentive monitoring of the clinical evolution, globally taking charge also of the psychological and emotional impact of the pain symptom.

Material and methods: Since January 2018 we introduced in our Oncology Unit the following multidisciplinary system regarding the pain management, with these criteria:

1) survey of the pain with the NRS scale when the patients enter the recovery and then 2 times a day;
2) compulsory planning in the computerized system of therapy to timetables in case of background pain and rescue therapy for BTP (preferably with two choices);
3) mandatory revaluation (with NRS scale) of BTP after therapy with a value >= 4, to be registered in the computerized scheme;
4) comparison at the morning meeting between the nursing staff and the medical personnel of the Department for pain revaluation of each patients;
5) in the case of pain from bone metastasis, it is mandatory the evaluation of the radiotherapist and the orthopedic specialists;
6) in the presence of difficulty in swallowing or precarious peripheral venous access, it is mandatory a prompt evaluation for indication of stable venous access-assessment at the entrance of the venous heritage;
7) in case of neuropathic pain, prompt consultation with the dedicated neurologist colleague;
8) prompt activation of the pain therapist in case of pain not responsive to opioid treatments at high dose or with side effects which not lead to dose adjustments;
9) compulsory psychological taking charge (unless refusal) for all the patients with pain associated with psychological distress admitted in the Department;
10) in case of risk of pharmacological interactions from other drugs, prompt consultation by the dedicated pharmacologist.

Results: The evaluation of the clinical impact of this system of integrated pain management in 10 points will be available after 12 months from its beginning.

Conclusions: We believe that the systematic items registration (NRS of background pain, daily number and intensity of BTP episodes, analgesic dosage of drugs, real effect on pain, distress scales) could result in a concrete clinical benefit for oncological patients with chronic pain.

M12

MULTIDISCIPLINARY MANAGEMENT OF CANCER PAIN AND BREAKTHROUGH CANCER PAIN: OUR CENTER EXPERIENCE

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Background: Despite improved attention and health interventions, cancer pain (CP) still represents a widespread problem with negative impact on physical and emotional patients' life. CP is more frequent in advanced stages, but not rarely it occurs in early disease. A specific type of CP is the breakthrough cancer pain (BTcP), defined as a temporary exacerbation of algic symptomatology occurring in 64-89% of patients with controlled chronic CP; most episodes are unpredictable, typically arising with rapid onset, short duration and high intensity. Intranasal fentanyl, a highly fat-soluble opioid molecule, showed efficacy and feasibility in BTcP treatment and appreciation by patients thanks to easy spray drug delivery and quick effect. CP and BTcP are often underestimated and consequently undertreated. So, correct identification of CP is the starting point for adequate management and multidisciplinary approach may be helpful. Here, we present management of CP and BTcP with the collaboration of our Hospital's Antalgic Therapy and Palliative Care Clinic (ATPCC).

Material (patients) and methods: We studied 40 advanced cancer patients attending our Oncology Unit from January 2017 to April 2018. They were affected mainly by pancreatic (9), head-and-neck (8) and colorectal (7) tumours. At first visit we screened them for CP and BTcP with ATPCC Colleagues. Patients were asked to quantify CP and BTcP through numerous rating scale (NRS), according to which treatment with maintenance opioid drugs and fentanyl pectin nasal spray (100 mcg or 400 mcg) for BTcP was started. First assessment was made in 5 days with NRS scale; frequency of next evaluations was planned according to grade of achievement of pain control and regular phone calls between visits were made. Patients had to report satisfaction (yes/not) of this joint management and variations on NRS of their CP and BTcP.

Results: All patients were satisfied with CP management shared between oncologist and ATPCC, especially with administration of intranasal fentanyl for BTcP. 27,5% of patients (11) obtained a reduction of pain intensity of 5

points in NRS, 22,5% (9) of 4 points and 20% (8) of 6 points. They reported quick relief from BTcP with fentanyl nasal spray and improvement of daily life quality.
Conclusions: Multidisciplinary management of CP and BTcP lead to improvement of pain control and quality of life. Patients showed satisfaction with this cooperation and good compliance to BTcP treatment with intranasal fentanyl.

M13

MANAGEMENT OF CANCER PAIN AND BREAKTHROUGH PAIN IN LOCALLY ADVANCED AND METASTATIC PANCREATIC CANCER

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Background: Patients affected by pancreatic cancer present during the evolution of the disease uncontrolled pain and breakthrough pain that drastically reduce their quality of life. In particular, the breakthrough pain is not easy to manage. It is defined as a temporary exacerbation of algic symptomatology occurring in 64-89% of patients with controlled chronic cancer pain, mainly unpredictably, with rapid onset, short duration and high intensity. For this reason, a more complete organization has become necessary, with the involvement of our Antalgic Therapy and Palliative Care Clinic (ATPCC).
Material (patients) and methods: We studied 47 patients, 25 of them were affected by locally advanced pancreatic cancer and 22 by metastatic pancreatic cancer, attending our Oncology Unit between March 1, 2016 and May 1, 2018, involving our Antalgic Therapy and Palliative Care Clinic (ATPCC).

At the first consultation they were initiated to pain therapy with our ATPCC colleagues. Patients were asked to quantify cancer pain through several scores, including NRS, and they started opioid-based pain therapy, including fentanyl pectin nasal spray (100 mcg or 400 mcg) for BtcP.

The first check was performed after about 6-7 days with NRS, followed by regular consults during the treatments. Furthermore patients had to report satisfaction (yes/not) of this management and variations on NRS of their CP and BTcP.

Results: Most of patients were satisfied with the management. 44,6% of patients (21) obtained a reduction of pain intensity of 5 points in NRS; 25,5% (12) a reduction of 4 NRS points; 14,9 % (7) 6 NRS points; 10,6% (5) 7 NRS points and 4,2% (2) patients decide not to be included in the program.
Conclusion: Patients who took part in the program achieved good cancer pain and BtcP control, with good compliance with fentanyl pectin nasal spray treatment. This has allowed us to improve the quality of life of the patients and to obtain a good adherence to the treatments.

M14

EFFECTIVENESS OF FENTANYL SUBLINGUAL TABLETS FOR PAINFUL MUCOSITIS DURING CHEMO-RADIOTHERAPY FOR SUPRAGLOTTIC LARYNGEAL CANCER

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Background: In head and neck cancer (HNC), painful mucositis is a common adverse event during radiotherapy ± chemotherapy (RT ± ChT). Intermittent pain is related to oral functions such as eating or swallowing. In the current study, we prospectively analyzed the safety and efficacy of Abstral® (Fentanyl sublingual tablets for Breakthrough Cancer Pain) in a cohort of patients affected by supraglottic larynx submitted to definitive RT + ChT
Methods: Inclusion criteria of the present study were: age > 18 years, KPS > 70; histologically proven carcinoma of supraglottic larynx underwent to RT concomitantly to Cisplatin; moderate/severe painful mucositis appeared during RT + Cisplatin; incidental Breakthrough Cancer Pain (BTP) due to painful mucositis; opioid maintenance treatment for background pain; postmenopausal women or surgically sterile or use a reliable form of contraception during the study period. The period of observation has been 90 days starting from the beginning of RT + ChT. The effectiveness of Fentanyl sublingual tablets in treating BTP was assessed every week during RT + ChT through the evaluation of measuring the body mass index (BMI), oral intake (number of meals/day) and pain intensity measured by means of NRS scale. All the adverse events which occurred during the period of administration of Fentanyl sublingual tablets were registered.
Results: From January 2017 to January 2018, fifteen outpatients affected by supraglottic larynx were enrolled in the present analysis. At the baseline, before starting the antineoplastic treatment, patients were able to feed themselves three times a day, and no patient reported alterations at oral mucosa, such as mucositis, xerostomia and candidiasis. At 18–25 day after the baseline, predictable BTP duene to

painful mucositis appeared in all patients with a mean NRS of 5.73 ± 2.5. At this last time-point, the number of daily main meals decreased to two times per day and the median BMI was slightly decreased from the baseline evaluation. The administration of Fentanyl sublingual tablets (dose 100 mcg) reached a NRS 2.25 ± 2.45. Subsequently, the number of daily meals increased and BMI remains stable. Adverse events were reported in few patients and were mostly mild
Conclusions: In our experience, Fentanyl sublingual tablets for painful mucositis during RT + ChT for supraglottic laryngeal cancer appear effectiveness and safe.

N - Melanoma & Skin Cancer

N01

CLINICAL PREDICTIVE FACTORS FOR EFFICACY OF ANTIPD1 USED IN FIRST LINE IN METASTATIC MELANOMA: AN ITALIAN MELANOMA INTERGROUP STUDY

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Background: AntiPD1 Nivolumab (N) or Pembrolizumab (P) are an option for first line treatment in metastatic melanoma (MM) but predictive factors of efficacy are needed to choose between them or other treatment (antiPd1+ AntiCTLA4, BRAF+MEK inhibitors (BMEi) for BRAF mutated melanoma). Many studies suggest that LDH, ECOG PS, tumor burden can identify BRAF mutated MM patients (pt) in which BMEi show better outcome. Similar data are not available for N or P in first line. We evaluate pt treated with N or P in first line in order to verify if these factors or other factors can be applyed also to antiPD1
Methods: A retrospective multicenter study was conducted in 13 Italian Oncology Centers, evaluating MM pt treated with N or P in first line from 2016. Endpoints were OS and PFS, Kaplan Mayer and Cox regression were applied for survival analysis
Results: 236 pt were analyzed (51% treated with N, 7% BRAF mutated). ECOG PS was 0 in 169 pt, number of metastatic sites (Nu) was less then 3 in 135 pt, in 88 pt there were not visceral metastasis (Vi), LDH was normal in 141 pt, ratio between baseline neutrophils and total leukocytes count (Fr) was less then 0.7 in 152 pt: in univariate analysis, all this factors resulted significantly associated with better OS (all $p<0.0003$) and PFS (all $p<0.003$), the only exeption were pt with Nu less then 3 that resulted not signficantly different in PFS then pt with higher Nu (p 0.13). In multivariate analysis all these factors were confirmed as significantly associated with better PFS and OS (all $p<0.03$), with the exeption of Nu (p 0.22)

A score was counted for every pt considering the number of favorable baseline factors present (normal LDH, ECOG PS 0, Vi 0, Fr < 0.7)

18 months-PFS was 69% in pt with all 4 favorable factors vs 41% in pt without favorables factors (p value 0.0029). 18 months-OS was 90% in pt with all four favoreble factors vs 48% in pt without favorables factors (p value<0.0001)
Conclusions: ECOG PS 0, normal LDH, Fr <0.7, absent Vi are indipendent baseline factors associated with favorable PFS and OS of MM pt treated with N or P in first line (instead of Nu – that was found relevant for BMEi in other study). Subgroup with all these factors has a better prognosis. These data can help first line treatment choice and should be evaluated prospectively

N02

SECOND-LINE AVELUMAB TREATMENT OF SUBJECTS (SBJS) WITH METASTATIC MERKEL CELL CARCINOMA (MMCC): ITALIAN EXPERIENCE FROM A GLOBAL EXPANDED ACCESS PROGRAM (EAP)

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Background: MCC is a rare and aggressive disease linked to exposure to UV light and to the Merkel-Cell polyomavirus (MCPyV). It usually responds to chemotherapy (CT) but responses are transient with a PFS of 94 and 61 days in

1st and 2nd line respectively. MCC expresses PD-L1, a high tumor mutational board or MCPyV neoantigens, making the block of immune inhibitory pathway attractive. Avelumab (anti PD-L1 antibody) in a phase II study in pretreated sbjs, obtained an ORR of 33%, median OS of 12.9 months, 1-year OS of 52%, and 21 % of ongoing responses at a median FU of 16,4 months. Due to MCC rarity, it is relevant to evaluate results observed in the Italian EAP.

Methods: Sbjs ⩾18 year-old, with histologically confirmed stage IV MCC, progressing after ⩾1 line of CT, after Merck Pfizer alliance approval, received Avelumab at 10 mg/kg i.v. q2 wks until unacceptable toxicity or confirmed PD. We analyzed patients' clinical features, disease control rate (DCR), durable responses (DR, >6 months) and discontinuation/delay due to toxicity. All sbjs signed an informed consent form approved by the local E.C. Safety was recorded using NCI-CTCAE version 4.1.

Results: Last database analysis (26th of March, 2018) regarded 67 sbjs (22.4% females, 77.6% males) enrolled in 40 Italian sites. At time of analysis, 18 (26.9%) sbjs were on treatment, 21 (31.3%) stopped therapy, 13 never started it and 15 were waiting to start. The mean age was 71.2 ± 10.0 years. ECOG PS was 0 in 68.8% of sbjs, 1 in 25.0% and 2 in 4.7%. 50 (78.1%) had distant metastases. Evaluable lesions were present at the baseline CT scan in 54 (84.4%) sbjs. The median duration of therapy in who stopped the treatment (21 of 67) was 87 (14-228) days and 205.5 (68-418) days in the 18 sbjs still on treatment. Of 21 sbjs discontinuing the treatment, 2 (9.5%) died, 18 (85.7%) discontinued due to PD, 1 was lost to follow-up. Of 13 sbjs who never started the treatment, 3 (23.1%) died, 2 (15.4%) had a rapid worsening of PS and no reasons were provided for 8 patients. 15 sbjs of 39 (38.5 %) who started the treatment (5 of them interrupted and 10 are still on treatment) received it for more than 6 months. No discontinuation due to toxicity or toxic deaths was reported.

Conclusions: Our experience indicates that sbjs treated with Avelumab did not record any discontinuation due toxicity or toxic deaths in a real life context. DCR, DR and discontinuation/delay due to toxicity will be analyzed and available for presentation.

N03

THE REAL-WORLD IMPACT OF MODERN TREATMENTS ON THE SURVIVAL OF PATIENTS WITH METASTATIC MELANOMA

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Background: Between 2010 and 2015, phase III trials with strict enrolment criteria led to the approval of several new treatments for unresectable or metastatic melanoma (MM). The impact of these treatments on the overall survival of the whole "real world" population of MM is unknown.

Methods: The Danish MM database contains data on the entire unselected population diagnosed with MM within a nationwide area. To evaluate the impact of novel treatments, all MM cases diagnosed in the three non-consecutive years marked by major changes in the availability of 1st line treatments (2012: i.v. IL-2 and BRAFi; 2014: anti-CTLA-4; 2016: anti-PD-1 and MEKi) were retrieved. Patients were grouped into "trial-like" and "trial-excluded" based on seven predefined eligibility criteria, including CNS metastases and PS⩾2, used in all MM registration immunotherapy clinical trials. The database was locked on May 8th 2018, and each patient had a minimum follow up of 12 months.

Results: We retrieved the data of all 837 patients diagnosed with MM (excluding ocular melanoma) in Denmark during 2012, 2014 and 2016. The baseline characteristics of patients diagnosed in 2012, 2014 and 2016 were similar. In the "trial-like" population (39% of all MM), meeting all seven eligibility criteria for trial participation, the median overall survival (OS) was not yet reached in 2016 versus 19.1 months in 2014 (hazard ratio [HR] for death 0.52, 95% CI 0.36-0.76; p = 0.0007) and 16.5 months in 2012 (HR 0.41, 95% CI 0.27-0.63; p<0.0001). A similar survival advantage was observed in a sub-group analysis of BRAF wild-type patients. No major survival differences were observed in 2014 versus 2012 (HR 0.78, 95% CI 0.55-1.09; p=0.1404). In the "trial-excluded" population (61% of all MM), 75% of patients had known CNS metastases and/or PS⩾2. Here, the median OS was improved to 6.9 months in 2016 versus 5.2 months in 2014 (HR 0.66, 95% CI 0.52-0.84; p=0.0008) and 4.2 months in 2012 (HR 0.66, 95% CI 0.52-0.84; p=0.0007). No difference was observed between 2012 and 2014 (p = 0.71). Sub-group analysis of the BRAF wild-type population showed an improved 1-year survival rate in 2016 versus 2014 (35.9% vs 18.8%, p=0.0153).

Conclusions: "Trial-like" patients represent only 39% of the total MM population in the real world. Our data show that the introduction of modern treatments led to an improved survival of real world patients with MM, regardless of their clinical trial eligibility or BRAF status.

N04

IMMUNE-RELATED ADVERSE EVENTS CORRELATE WITH IMPROVED SURVIVAL IN PATIENTS UNDERGOING ANTI-PD1 IMMUNOTHERAPY FOR METASTATIC MELANOMA.

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Background: A dramatic improvement of the prognosis of metastatic melanoma patients has been observed in the last years following the introduction of new therapies, including antibodies targeting programmed cell death protein-1 (PD-1). However, response rate to anti-PD1 is relatively modest (40%) and immune-related adverse events (irAEs) can be of concern. Here, we aimed to assess the prevalence of irAEs and survival outcomes in a large series of MM undergoing anti-PD1 into a "real world" clinical experience.

Patients and Methods: Data of consecutive pts treated with anti-PD1 (nivolumab or pembrolizumab) for MM were collected. irAE were graded according to CTCAE4.02 criteria. Survival outcomes (progression-free (PFS) and overall (OS) survivals) were assessed using Kaplan-Meier and Cox models.

Results: Overall, 173 pts were included. Therapy was administered for a median of 6 (range, 2-46) mo. At the time of this analysis 56 (32%) pts were still on treatment. Mean PFS and OS were 9.7 (±11.5) and 12.8 (±11.9) mo, respectively. 103 (60%) pts experienced irAEs; 10 (6%) of which severe (grade 3-5). The most frequent irAEs were: fatigue 16%, cutaneous rash 13%, endocrinopathies 9%, arthralgyas 7%, and neurologic syndromes 6%; 8% pts developed vitiligo. Multivariate analysis showed that PFS was influenced by =3 metastatic sites (HR:1.83 (95%CI:1.01,3.43);p=0.048) and baseline increased LDH value (HR:2.11 (95%CI:1.02,4.38);p=0.043). The increased neutrophil/lymphocyte (N/L) ratio was associated with a trend toward worse PFS (HR:1.06 (95%CI:0.99,1.13);p=0.066 per 1-unit increase). Pts experiencing irAEs had better PFS (HR:0.47 (95%CI:0.26,0.86);p=0.016). Non-cutaneous melanoma (HR:2.34 (95%CI:0.93,5.84);p=0.068), baseline increased LDH (HR:2.85 (95%CI:1.26,6.42);p=0.012) and N/L ratio (HR:1.08 (95%CI:1.01,1.15);p=0.028) independently correlated with the risk of death. Presence of irAEs was the only factor associated with a favorable OS (HR:0.39 (95%CI:0.18, 0.81); p=0.007). The development of vitiligo was associated with an improvement of PFS (p=0.029) and OS (p=0.061).

Conclusions: Anti-PD1 therapy can offer disease control in a subset of pts with MM. Well known baseline clinical and biochemical factors are associated with worse outcomes. irAEs onset correlates with improved PFS and OS. Further prospective studies are needed in order to better select the patients and to define the best therapeutic strategy for minimizing treatment related toxicity.

N05

VITILIGO ARISING DURING CHECKPOINT INHIBITORS THERAPY IN METASTATIC MELANOMA (MM) PATIENTS (PTS): WHICH SIGNIFICANCE? ON BEHALF OF THE ITALIAN MELANOMA INTERGROUP STUDY (IMI)

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Background: Vitiligo is an autoimmune skin disorder reported in MM patients who undergo immunotherapy with an incidence of about 10%. So far, very small case studies have been published in pts treated with antiCTLA-4/antiPD-1 antibodies and its significance is still controversial.

Patients and methods: *W*e conducted a study on MM pts which developed vitiligo during checkpoint inhibitor treatment with the aim to evaluate its impact on clinical outcomes. Our population included 139 pts with MM treated with ipilimumab (41pts), antiPD-1 (80pts), ipilimumab + nivolumab regimen (18pts). 94 pts were male and 45 female; median age: 60 ys (range 23-83); primary: cutaneous/non-cutaneous./unknown 118/8/13; M1a,b,c 34%/ 17%, 48% (high LDH 28% and 8 pts with brain involvement); BRAF wt 76%, mutated 19%; unknown 5%; NRAS mutated 9%; checkpoint inhibitors. as first line in 76 pts, as 2nd line in 53 pts, as 3th line in 31 and 10 pts as 4th line. The 57% of pts received a 2nd line therapy, the 30% a 3th line, and the 9% a 4th line therapy.

Results: The appearance of vitiligo included about 15% of treated patients with a median time of 26 weeks (24 for Ipi, 27 for anti-PD1, 17 for regimen). After a median follow up of 50 months, the mOS from metastatic disease was not reached with the 60% of pts yet alive whereas the mOS from the vitiligo appearance was 55 months with no difference among diverse therapies used. The mPFS was 40 months from the starting of therapy inducing vitiligo and 37 months from vitiligo appearance. mPFS was significantly longer for ipilimumab when calculated from

therapy starting. Nevertheless, this advantage was lost when vitiligo appeared. BRAF mutated pts had a significantly longer OS compared with wt pts, but PFS was not different among these two groups. Finally, both the OS and PFS were significantly longer in BRAF than NRAS mutated pts. Regarding ORR, we reached statistical significance for pts treated with Ipilimumab (CR: 33.3%; PD: 7.7%; PR: 35.9%; SD: 23%) *vs* pts treated with antiPD1 (CR: 20%; PD: 0%; PR: 63.7%; SD: 16.2%) (p-val=0.01). We observed a significant better ORR in antiPD1 treated pts with respect to those ones treated with regimen (CR: 22.2%; PD: 16.6%; PR: 44.4%; SD: 16.6%; p-val= 0.01).
Conclusion: This is the largest study regarding vitiligo arising in MM pts during checkpoint inhibitors therapy. We confirm that vitiligo is an important indicator of robust antimelanoma immunity associated with a significant clinical benefit and better prognosis.

N06

SINONASAL MUCOSAL MELANOMAS FROM THE SOUTHERN ITALIAN POPULATION ARE MUTATED IN THE BRAF GENE

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Background: SinoNasal Melanoma (SNM) is a rare and aggressive type of mucosal melanoma. It can be diagnosed late and has a poor prognosis. Unlike to cutaneous melanomas which incidence is increasing, the incidence of mucosal melanomas is believed to remain stable (RARECARENet). Due to SNM rare incidence, we currently have a limited understanding of its genetic component and the most effective targeted treatments. Mutations of several genes involved in the MAPK and PI3K-AKT pathways have been mostly associated with cutaneous melanoma. Here we analysed a panel of 25 genes associated with cell cycle progression as well as cell differentiation and survival underlying melanoma pathogenesis.
Materials and Methods: Primary tumour tissue samples from a cohort of 25 patients affected with SNM were analysed for mutational status by next generation sequencing (NGS) assays. A custom panel, the IMI Somatic Panel, targeting 25 genes associated with melanomagenesis was designed. This panel consists of 343 amplicons of max 175bp in length, organized in 3 pools of primers to identify variants in coding region and splice sites for intron and exon boundaries for candidate genes. Mutations classified as pathogenic for their deleterious effects on gene products were confirmed by conventional screening approaches (Sanger sequencing or real-time PCR assays).
Results: We identified a total of 125 of non-synonymous single-nucleotide variants (ns-SNVs), with a median of 3 (range, 1-26) ns-SNVs per patient. Strikingly, 7/25 (28%) of our patients carried the $BRAF^{V600E}$ gene mutation, whereas other three (12%) cases presented a deleterious mutation in *RAS* (2 *NRAS*, 1 *KRAS*) genes. These finding suggest a strong association between activation of the MAPK pathway and the SNM pathogenesis. As expected, the identified mutations mostly lack the typical UV signature, which is usually associated with the cutaneous melanoma. To a less extent, we observed an association between mutations in *KIT, CDKN2A, ARID2, CDK4, NF1, CCND1, PTEN*, and *PPP6C* genes with SNM.
Conclusions: We propose that the mutation analysis of the *BRAF* gene should be included in the routine diagnostic test to better classify the SNM subtype and improve the choice of therapeutic strategy.

This work was presented on behalf of the Italian Melanoma Intergroup (IMI)

N07

IS THERE A CORRELATION BETWEEN PLASMA PD-1 LEVELS AND TUMOR-INFILTRATING LYMPHOCYTES IN METASTATIC MELANOMA PATIENTS?

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Background: Tumor-infiltrating lymphocytes (TILs), generally categorized into brisk (infiltrating the base of vertical growth of tumor), non-brisk (infiltrating melanoma only focally) and absent (not present or not infiltrating tumor), have been shown to locally influence the immune response to melanoma. Experimental evidences suggested that a higher abundance of TILs, especially brisk, in primary melanoma is associated with a more favorable prognosis and better survival, while others studies showed an immunophenotypic and functional heterogeneity of TILs. Since recent studies demonstrated an association between plasma PD-1 expression and antitumor immune response, our work was aimed to study the

correlation between plasma PD-1 expression levels and presence/typology of TILs in metastatic melanoma patients.

Patients and Methods: The PD-1 levels were analyzed in plasma of 28 patients with metastatic melanoma by a specific ELISA assay. An immunohistochemistry analysis was performed for the characterization of TILs in tumor tissue. T-Student and ANOVA tests were used for the statistical analysis. Survival curves were estimated by using the Kaplan-Meier method and log-rank test to evaluate significant differences among them.

Results: The presence of TILs was detected in primary tumor of 16 out of 28 patients, 10 of which brisk and 6 nonbrisk. Three different analyses were performed analyzing the plasma PD-1 levels based on the presence/absence of TILs (p=0.022), their efficiency (brisk TILs *versus* nonbrisk/absent TILs; p=0.014), and their typology (brisk *vs* nonbrisk *vs* absent; p=0.032). In particular, brisk TILs in primary melanoma have been shown to be correlated with low plasma PD-1 levels, nonbrisk TILs with intermediate values, and absent TILs with high expression levels. Although the small number of analyzed samples did not allow us to demonstrate a statistically significant association between overall survival and plasma PD-1 levels in relation to the absence/presence of TILs, however the median survival of patients with brisk TILs and low plasma PD-1 levels was five months higher than other 2 groups of patients with absent and nonbrisk TILs, respectively.

Conclusions: This work suggests, for the first time, the potential role of the plasma PD-1 levels to predict prognosis also in patients with metastatic melanoma at diagnosis for which it is not possible to identify the primary tumor and obtain information about the presence/typology of TILs.

N08

NGS-BASED MUTATIONAL STATUS AMONG PRIMARY TUMORS AND METASTASES IN PATIENTS WITH MELANOMA

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Background: The prevalence of mutations in main genes involved in tumorigenesis during melanoma progression - moving from primary to metastatic lesions - remains a crucial issue to assess the levels of tumor molecular hetrogeneity. Different melanoma tissues from the same patients were investigated for prevalence and distribution of mutations in these genes.

Materials and Methods: Ninety-eight tumor tissues from 36 patients with metastatic melanoma patients were screened for sequence variants in a panel of 25 genes associated with cell cycle progression, cell differentiation, angiogenesis, and tumor growth by next generation sequencing (NGS) assays. Paired samples of primary melanomas (n=36) and synchronous or asynchronous metastases from the same patients (n=62) were included. Secondary lesions included lymph nodal (n=28), subcutaneous (n=19), and visceral (n=15) tumor samples.

Results: *BRAF, CDKN2A, RAS*, and *TP53* genes were the most frequently mutated genes. Deleterious mutations were also found in also in *ARID2, CDK4, NF1, CCND1*, and *PTEN* genes. Of 28 patients with lymph node metastases, 23 (82%) presented consistent mutation patterns in paired primary and secondary tumor samples. For visceral metastases, 11/15 (73%) patients showed a similar mutation spectrum between primary and secondary tumors. A significantly less consistency was observed in skin metastases (11/19; 58%).

Conclusions: Our findings are consistent with previous studies from our group (Colombino, *JCO* 2012; Casula *JID* 2016) indicating a low heterogeneity in matched primary and lymph node metastatic samples. Assessment of the prevalence of mutations in genes involved in melanomagenesis among paired tumor lesions from patients with metastatic melanoma may further improve the management of such a disease.

This work was presented on behalf of the Italian Melanoma Intergroup (IMI).

N09

DABRAFENIB/TRAMETINIB COMBINATION IN BRAF-MUTANT METASTATIC MELANOMA PATIENTS IN REAL-WORLD CLINICAL PRACTICE: PROGNOSTIC FACTORS ASSOCIATED WITH CLINICAL OUTCOMES

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This retrospective observational study investigates the effectiveness and safety of Dabrafenib/Trametinib combination in patients with metastatic melanoma.

We analyzed the data of 76 consecutive patients (34 males; median age 55 years, range 24-86) treated with dabrafenib/trametinib combination (150 mg twice a day/2 mg once a day) from November 2013 to February 2017. In total, 15 (20%) patients were >70 years old and 23 (30%) presented elevated LDH before treatment. The most frequent mutation was V600E (n=61; 80%). Most patients (n=42; 55%) had >1 metastatic sites and 15 (20%) showed CNS metastasis. Among previously treated patients, dabrafenib/trametinib was administered as a second-line systemic therapy in 16 subjects (66%), in the third-line setting in 3 (13%) and as a fourth-line treatment in 5 (20%). Median follow-up was 12 months (range 4-49) and median treatment duration was 11 months (4-44). The primary endpoints were PFS, OS and RR. Safety considerations were also performed.

Median PFS was 9 months (95% CI 7-11) and median OS was 14 months (95% CI 11-16). At 12-month follow-up, 46 patients were still alive (60%). DCR was 72%, with partial response being the most frequently observed response (n=42; 55%). Nine patients (12%) experienced a complete response. Of these, 7 presented only one metastatic site, none had lung or CNS metastasis, and none had elevated LDH levels at baseline. Their median OS was 17 months, with a 1-year survival rate of 66%. Among patients with CNS metastasis, we recorded 7 PRs and no CR; the overall RR was 48% and mean response duration was 12 months (range 5-12). The multivariate analysis showed that baseline LDH levels (HR 3.2; 95% CI 1.4-7.1, p=0.006) and number of metastasis (HR 2.8; 95% CI 1.0-7.8; p=0.04) were significantly associated with patient's prognosis. The most frequently-reported ADR was fever (n=33; 43%), followed by cutaneous reactions (n=24; 31%). However, in the wide majority of cases ADRs were graded as G1-2 and were manageable with supportive care, symptomatic medications or, in case of fever, brief treatment interruptions.

Dabrafenib/trametinib combination can be effective and well-tolerated also in a heterogeneous "real-life" population comprising patients with adverse prognostic features.

N10

ACTIVITY OF PLATINUM AND CETUXIMAB IN CUTANEOUS SQUAMOUS CELL CANCER NOT AMENABLE TO CURATIVE TREATMENT

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Background: Cutaneous squamous cell cancer (cSCC) is the second most common skin cancer. Even if rare, unresectable or metastatic cSCC is a potential life-threatening disease. In this setting, systemic therapy has a palliative intent. This retrospective study aim at reviewing outcomes in patients (pts) treated with platinum-based chemotherapy (CT) and cetuximab (cet).

Materials and Methods: we collected data of twelve patients (pts) with non-curable cSCC, (11 M, 1 F; median age 73 years, range 46-82) treated between June 2010 and March 2016 with CT+cet. Cet was associated with cisplatin (5 pts, one of them received also 5-fluorouracil) or carboplatin (7 pts). ECOG PS was 0 in 2, 1 in 9 and 2 in 1 pts. Most pts (83%) had a primary disease localized in the head and neck area and the remaining ones in the gluteal region. Histological characteristics showed poorly differentiated aspects in one case and pseudosarcomatous traits in two cases. All patients received previous surgery, while radiotherapy was performed in seven out of twelve pts. Other previous treatments consisted in: CT with cisplatin and 5-fluorouracil (8%), metastasectomy (8%), concurrent chemoradiation (8%), gefitinib (8%) and sirolimus (8%). Median disease-free interval from the first curative treatment was 4.5 months (95% CI 2.0-18.9). One-third of pts had metastatic disease.

Results: Overall response rate (RR) was 50% (complete response CR 8%, partial response PR 42%), disease control rate (DCR) was 67%. After systemic treatment, 25% of pts (1 PR, 2 PD) received surgery and 33% RT (3 PR, 1 CR). Median duration of response was 2.73 months (95% CI: 1.28-3.52). Median PFS and OS were 6.6 (95% CI 1.9-8.4) and 14.6 (95% CI 9.4-20.1) months, respectively. In 67% of responders further surgery or RT was subsequently delivered. The most frequent toxicities were skin reactions (58%) and anaemia (10%). Grade 3 adverse events occurred in 25% of pts (skin rash 25% and neutropenia 8%), no G4 toxicities were observed.

Conclusions: Cet and platinum-based CT showed to be feasible and active in cSCC. In comparison to previous series treated with single antiEGFR agents (RR 28-31%), the combination of cet and CT showed higher responses (50%). Responsive pts might benefit from adding further local therapy.

N11

PEMBROLIZUMAB AS FIRST LINE TREATMENT FOR METASTATIC UVEAL MELANOMA: A PHASE II CLINICAL TRIAL

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Background: No standard treatment has yet been defined for metastatic uveal melanoma (mUM). Although randomized clinical trials exploring the role of Nivolumab/Pembrolizumab for cutaneous melanoma did not include melanoma from uveal origin, anti PD-1 agents are commonly used for the treatment of mUM. We explored efficacy and safety of Pembrolizumab as first line therapy for mUM.

Patients and methods: Patients with diagnosis of mUM included in this study were treated with 2 mg/kg of Pembrolizumab intravenously every 3 weeks. Pembrolizumab was the first treatment for metastatic disease for all the patients. The efficacy of anti PD-1 treatment was evaluated in terms of response rate, progression free survival and overall survival. Toxicity was also evaluated.

Results: 16 patients were enrolled. All the patients had not resectable liver metastases. 7 patients showed extrahepatic disease. A median of 8 cycles were administered (range 2-28). Three patients achieved a partial response (18.7%), 6 a disease stabilization (37.5%), while 7 (43,8%) patients have a progression at first tumor assessment. Among responding patients, 2 experienced a pseudo progression at first evaluation. For these patients, a partial response was revealed at the following tumor assessment. No complete responses were observed. PFS of the whole population was 4.8 months. For the patients with more than 5 years from diagnosis of primary tumor and metastatic disease PFS was 9.1 months, while for patients with less than 5 years PFS was 3.1 months – p=0.013, HR 0.2523 (95% CI 0.0579-0.4593). Median OS of the whole population was not reached. All responding patients (3 patients) are alive after a median follow up of 16 months. Considering the patients with clinical benefit survival was 12.8 months, while median survival for progressive patients was 8 months. Toxicity was mild. No grade 3-4 adverse events were observed. Grade 2 hypophysitis occured in one patient, grade 1 hypothyroidims in 2 patients.

Conclusion: The efficacy of Pembrolizumab seems to be not particularly different when compared to other agents used for mUV. Responding patients have a remarkable time of disease control. The treatment was well tolerated.

N12

ROLE OF TUMOR BURDEN ON THE OUTCOME OF PATIENTS WITH METASTATIC MELANOMA

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Background: Nowadays, the definition of tumor burden (TB) and its prognostic role in metastatic melanoma patients has not been well clarified, yet. The aim of this study was to create a score, including parameters of TB and LDH, to identify metastatic melanoma patients that could benefit from first line therapy.

Patients and methods: 42 patients with advanced melanoma, treated with first-line anti-BRAF +/− MEK or immuno-therapy (IT) at our institution from 2011 to 2017 were included into the study. We considered as an expression of TB: site and number of metastasis, sum of diameters of target lesions (SLD) according to RECIST and immune-RECIST 1.1 and site and dimension of the biggest metastasis (DBM).

We analyzed PFS to the first line therapy with "MedCalc Statistical Software" version 14.10.2.

Results: We identified as indipendent prognostic factors for PFS: F/M, p= 0.005; DBM, p= 0.016; SLD, p= 0.025; LDH, p= 0.009. Median f-u: 12.9 months (m) (1.57-55.18).

A novel score was retrospectively calculated assigning a grade to the aforementioned clinical-laboratory parameters, according to their influence on PFS at first line.

Prognostic parameters	Influence of PFS
Sex (0= M; 1 = F)	21
DBM (0= <2; 1= > 2 cm)	11
SLD (0= < 66; 1= >66 mm)	10
LDH (1= <240; 2= >240<480; 3= > 480 U/l)	6
Score: (Sex x 21) + (DBM x 11) + (SLD x 10) + (LDH x 6)	

Listing in numerical order the results of the score products, we obtained 4 categories (quartiles) with different prognosis. With regard to target therapy, we showed a statistical significance difference between the first category (PFS not reached) vs. the third one (7.4 months). In patients treated with IT we recorded a median PFS of 13.7 m (2thquartile (q)) vs. 6.7 (3th) vs. 1.6 m (4th), p= 0.0009 (we didn't consider 1thq with only two patients).

Conclusions: Our study identified groups of patients that take advantage, in term of PFS, of first line therapy. LDH and SLD, represent routine parameters in clinical practice (CP). Adding DBM, potentially included in TB and easy to measure, the calculation of our prognostic score is immediate. It could be a useful tool for patients' selection for first line of therapy. A superior statistic power and a great

applicability in the CP of our results, could be reached, probably, widening our series and prolonging the considered f-u.

N13

CHECKPOINT INHIBITORS IN MELANOMA TREATMENT: COSTS AND SAFETY AFTER FOUR YEARS OF CLINICAL PRACTICE

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Introduction: This survey was performed using melanoma data of the National Cancer Institute G. Pascale Foundation, which is a reference center for melanoma cancer. Since the recent introduction of immune checkpoint inhibitors in melanoma treatment, the aim of this work was to evaluate changes in melanoma treatment over the years, analyzing ipilimumab(Ipi), nivolumab(Nivo) and pembrolizumab(Pem) treatments in term of costs and drug safety from their introduction in clinical practice up to December 2017.
Materials and methods: The number of treated patients(pts), consumption and cost data relating to the period under review were collected from the hospital database. The adverse reactions (ADR) were obtained from the Italian Agency of Drug network for Pharmacovigilance. In primis it was performed an assessment of the total consumption and cost per year; then was evaluated the most used antibody for a therapeutic indication when different strategies were allowed. Finally ADR and their outcomes were evaluated.
Results: In the period 2013-2015 Ipi was the only immune checkpoint inhibitor approved for melanoma therapy. In this period we observe an increase in treated pts for year, 79, 149 and 198 with a corresponding increase in costs €2.955.002, €6.132.764 and €8.418.396 respectively.

In 2016 not only Ipi but also Nivo and Pem were approved for melanoma. Number of pts treated was 201, so 3 pts more were treated and €3.133.225 less were spent thanks to the introduction of lower cost drugs. Nivo was the most used drug with 116 pts and €1.917.595 spent. Instead 83 pts received Ipi with €2.999.721 and 18 pts received Pem with €367.879 spent.

In 2017 the scenario has changed. An increase in consumption and costs was observed because the treatments with Pem were increased and the others with Nivo and Ipi were reduced. Nivo remained the most used drug with 104 pts and €3.285.957 spent. However pts treated with Pem increased to 66 with €1.831.166. Differently only 35 pts with Ipi and €1.128.635 spent.

Analyzing the ADR reported in our Institute since the introduction in clinical practice, it was observed that 35 ADR were reported but none of these is serious, in particular 28 ADR to Ipi,1 reaction to Pem and 6 to Nivo.
Conclusions: Pts treated with checkpoint inhibitors increased significantly over the years. Nowadays anti-PD1, Nivo and Pem, were the most used therapeutic strategy; although they were recently introduced in clinical practice they seem to be well tolerated and safe.

N14

TELOMERASE REVERSE TRANSCRIPTASE (TERT) PROMOTER MUTATIONS IN MELANOMA

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Background: Melanoma is characterized by recurrent mutations of oncogenes such as BRAF, NRAS, and KIT . Recently, TERT promoter mutations were identified at high frequencies in cutaneous and mucosal melanoma and it seems to correlate to a poor prognosis.
Material and Methods: We retrospectively investigated the mutational status of BRAF V600 codon and hTERT promoter (position -124 bp and -146 bp) in 28 melanomas of 28 different patients (pts), by Idylla BRAF kit (Biocartis) and Sanger sequencing respectively. The first line treatment of these pts was: targeted therapy (anti BRAF +/− anti MEK) for 15 pts (54%), immunotherapy (anti CTLA-4 or anti PD1 treatment) for 11 pts (39%), chemotherapy and radiotherapy in 2 cases (7%). A correlation between mutational status and the response to therapy was investigated.
Results: V600 mutation was found in 16 melanomas (57%). Fifteen of these cases were also mutated in hTERT; specifically, 3 in -124 bp position and 12 in -146 bp position. Conversely, BRAF wt cases (n=12) resulted predominantly mutated in -124 bp position (n=7); 3 cases were mutated in -146 position and 2 cases were hTERT wt. A major number of hTERT -146 bp mutations was observed in BRAF mutated melanomas respect to BRAF wt (P=0.0249). In 22 pts a disease control was obtained, of these 63% were characterized by the presence of BRAF mutation; 6 patients (including 5 pts BRAF wt) progressed. There was no correlation between hTERT mutations and clinical response to treatment, which instead appears predominantly determined by the presence of the BRAF V600 mutation (p 0,0725).
Conclusions: With the limit of these retrospective and small series, our analysis did not allow to identify a clear correlation with the main hTERT mutations and the response to cancer treatments. It could be hypothesizes that the -146 bp hTERT mutation correlate with BRAF mutational status; the meaning of this correlation and the functional difference between the two different hTERT

mutations is not known today. Larger population of melanoma patients is needed to better understand hTERT mutations and their clinical implications.

N15

EFFICACY AND SAFETY OF NIVOLUMAB MONOTHERAPY IN ADVANCED OR METASTATIC MELANOMA: A REAL LIFE EXPERIENCE

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Background: The therapeutic landscape of advanced melanoma has changed with approval of checkpoint inhibitors (nivolumab/ipilimumab) and targeted therapies (TT). The anti-PD1 antibody nivolumab (NIVO) is a standard option for first line treatment in patients with metastatic melanoma regardless of BRAF mutational status. Real life data are increasingly available and can help clinicians in decision making process even in patients generally not included in experimental clinical trials due to age, copathologies or poor performance status.
Methods: This is an observational, retrospective, single center study. We analyzed clinical findings of 36 consecutive patients with unresectable stage III or IV melanoma treated with NIVO, at the Regina Elena National Cancer Center, in Rome, Italy, between March 2016 and November 2016. These pts had been administered NIVO at a dose of 3mg/kg every 2 weeks.
Results: Of 36 pts, 12 were treatment naive (cohort 1), 14 were pretreated with ipilimumab (IPI) (cohort 2) and 9 with TT (cohort 3), respectively. Despite BRAF status,12 pts had a BRAF mutation. Median age was 63 (31-80). 23 pts were male and 13 were female. 20 pts had ECOG PS 0. 15 pts had visceral disease included 2 pts with brain metastasis. 3 pts had complete responses (CR), 15 had partial response (PR), 1 patient had stable disease (SD) and 14 pts had progression disease (PD). CRs were observed in pts of cohort 2 who are currently alive. Median PFS was 4,2 months in cohort 1 (95% CI:0-40.9) versus 14 months in cohort 2 (95% CI:1,5-6,9) versus 3,3 months in cohort 3 (95% CI:0-7.3). Pretreatment ECOG performance status (PS) = 1was associated with poor PFS (median PFS was 19.8 months (95% CI:10.6-28.9) among pts with PS 0 versus 3.3 months (95% CI:1.3-5.2) among pts with PS> 1). Pts with the worst LDH levels (=1 X ULN) had the worst response. During NIVO treatment 6 pts (16%) had a G3-G4 toxicity (hyperamylasaemia, pancreatitis, pneumonitis, cutaneous rush, asthenia, gastrointestinal toxicity (GI). One patient with pre-existing reumathoid disease has permanently discontinued due to GI toxicity with colon perforation.
Conclusions: Within this real world cohorts, NIVO was mainly used as second-line therapy and appears to have a greater degree of activity in patients previously treated with IPI even if the small number of patients do not consent to draw any definitive conclusions. Despite a good toxicity profile, attention should be paid in patients with known autoimmune disease.

P - Neuroendocrine Tumours

P01

SOMATOSTATIN ANALOGUES (SSAS) IN ASSOCIATION TO PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT) AFTER SSAS PROGRESSION. A MONOCENTRIC RETROSPECTIVE EVALUATION IN WELL-DIFFERENTIATED (WD) ENTERO-PANCREATIC (EP) NEUROENDOCRINE TUMORS (NETS)

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Background: In advanced WD-NETs with high somatostatin type receptor (SSTR) expression, treatment with SSAs is the gold standard. Moreover, the efficacy of PRRT with 177Lu-DOTATATE in association to Octreotide LAR (OCT) has been recently demonstrated in the NETTER-1 trial in SSTR positive midgut NETs, progressing to OCT. The aim of this analysis was to evaluate the role of SSA in association to PRRT beyond progression disease (PD) or after switch to other SSA at PD.
Methods: Out of 107 WD EP-NETs, treated with PRRT (90Y-DOTATOC/DOTATATE and/or 177Lu-DOTATOC/DOTATATE) at the Istituto Nazionale Tumori of Milan, from 2008 to 2017, 69 patients (pts) treated with the combination of PRRT and SSA (OCT or Lanreotide, LAN) after SSA treatment failure, were evaluated for present analysis. We identified 2 groups: S1, pts who kept the same SSA treatment beyond first PD; S2, pts who switched the SSA with another SSA after first PD. Median Progression Free Survival (mPFS) (from the start of first SSA) and Overall Survival (OS) have been evaluated using the Kaplan-Maier method.
Results: In S1 (n=47) and S2 (n=22) groups median age and sex were 58 ys (range 29-78) and 59.5% males vs 52.5 ys (range 35-78) and 45.4% males, respectively. We had a

P-NETs percentage of 34% vs 40.9% in the S1 vs S2 groups, respectively. The most of pts (82.9% in S1 and 86.3% in S2) received PRRT with alternate radionuclides (90Y/177Lu). Overall the median number of PRRT cycles was 4.2 in S1 and 4.8 in S2 (p=0.09). In the S1 (SSA beyond PD) group PRRT was associated with OCT in 74.5% and LAN in 25.5% of pts. In the S2 group (SSA switched with other SSA) PRRT was associated with OCT in 27.3% and LAN in 72.7% of pts. In the overall population the mPFS and OS were 70 (CI95% 52.8-87.1) and 82 (CI95% 66.7-97.2) months (mo), respectively. The difference on mPFS was 53 and 127 mo, in S1 and S2 respectively (p= 0.001; HR: 0.31; CI95% 0.15-0.63). In S1 group the OS was 69 mo vs 150 mo in S2 (p= 0.004; HR: 0.32; CI95% 0.14-0.71).

Conclusions: Despite the retrospective nature of the analysis and the low number of pts, we found a significant difference on mPFS and OS between S1 and S2 groups. In pts with advanced WD EP-NETs treated with PRRT plus SSA after SSA failure, the "switch" strategy of SSA after PD, might improve PFS and/or OS. Further large retrospective and/or prospective study are needed to confirm or discharge these preliminary data.

P02

POST-HOC ANALYSIS OF CLARINET PHASE III STUDY TO INVESTIGATE THE INFLUENCE OF DIABETIC STATUS ON PROGRESSION-FREE SURVIVAL (PFS) OF PATIENTS WITH NEUROENDOCRINE TUMOURS (NETS) TREATED WITH LANREOTIDE (LAN) OR PLACEBO (PBO)

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Background: Diabetes mellitus (DM) is a risk factor for pancreatic NETs, but its prognostic role in stage IV NETs is less defined. We evaluated the impact of diabetes on PFS in patients with advanced, non-functioning GEP-NETs.

Methods: Post hoc analysis of data from the phase III double-blind, placebo-controlled CLARINET study (NCT00353496) to investigate association between DM (any of: medical history of type 1 or 2; use of antihyperglycemic medication; HbA1c ⩾6.5%, fasting plasma glucose ⩾7mmol/L; non-fasting plasma glucose ⩾11.11mmol/L [at baseline or during study]) and PFS (Kaplan-Meier). Multivariate Cox analysis including treatment (LAN vs PBO), DM at baseline, previous therapy and progression at baseline was used to test interaction between DM and LAN efficacy.

Results: The overall population (total, n=204; LAN, n=101; PBO, n=103) had well-differentiated (Ki-67 <10%) foregut (45%), midgut (36%), or hindgut (7%) and unknown (13%) NET. 79 patients had DM, 125 did not (N-DM); 24 received metformin in combination with LAN (n=14) or PBO (n=10). Median PFS (mPFS) was 96.0 months (mo) [95% CI: 70.4; not reached (NR)] for DM vs 98.0 mo [72.1;NR] for N-DM (HR 1.20 [0.79;1.82], p=0.38). For DM, mPFS with LAN (n=42) was NR [95.9;NR] vs 60.0 mo [48.0;74.4] with PBO (n=37) (HR 0.27, [0.13-0.57], p=0.0002). For N-DM, mPFS with LAN (n=59) was NR [96.0;NR] vs 72.1 mo [52.0;NA] with PBO (n=66) (HR 0.64 [0.35-1.15], p=0.04). In multivariate analysis, DM at baseline was not significantly associated with PFS (HR 1.64 [0.95;2.84], p=0.08). Significant impact of LAN on PFS was confirmed (HR 0.53 [0.31;0.89], p=0.02), without significant interaction between LAN efficacy and DM (p=0.62).

Conclusions: DM did not emerge as a negative prognostic factor in advanced stage IV NETs. Efficacy of LAN in DM and N-DM was confirmed. Although LAN–DM interaction was not significant, LAN efficacy seemed particularly favorable in DM compared to N-DM patients, in terms of HR. These findings, along with a potential favorable association with hypoglycemic drugs such as metformin, should be evaluated and validated in prospective biomarker studies.

P03

STUDY OF PLASMATIC EXPRESSION OF IMMUNE CHECKPOINT PD-1 IN NEUROENDOCRINE NEOPLASMS (NENS)

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Background: PD-1 and its ligand PD-L1 are critical immune checkpoint molecules that negatively regulate T cell activation. Their blockade with specific antibodies is emerging as an effective and promising treatment option against several solid tumors. Unlike other tumors, the expression and potential role of immune checkpoints in NENs are still unknown. Our main objective is to detect plasmatic expression levels of PD-1 in NENs patients,

evaluating their potential role in prognosis and clinical evolution of disease.

Patients and Methods: This prospective pilot study was conducted by analyzing blood samples from 64 individuals divided into 3 groups: 1) patients with localized disease surgically excised; 2) metastatic NEN patients receiving a medical treatment; 3) control group with healthy individuals.

In each plasma sample we analyzed the protein expression of PD-1 by ELISA assays. Results: Our analysis showed that PD-1 is differentially expressed in plasma of individuals into 3 groups, with higher levels in the group of metastatic NEN patients than patients with localized disease and the control group. Another relevant difference is found into metastatic NEN patients group in relation to the site of origin of the tumors: patients with NEN of the lung (L-NEN) have higher expression levels than gastro-enteropancreatics (GEP-NEN) and this difference is statistically significant ($p = 0{,}0001$)(ng/ml mean:

L-NEN 14.5, GEP-NEN 8.2, Merkel cell carcinoma 3.8).

Conclusions: The identification of plasma PD-1 levels, correlated to specific site of origin of the tumors, could have a significant predictive value, representing a promising tool to select clusters of patients who may benefit from specific immunotherapy.

P04

EVEROLIMUS AND OCTREOTIDE LAR AS FIRST LINE TREATMENT IN WELL DIFFERENTIATED GASTRO-ENTERO-PANCREATIC (GEP) AND OF THE LUNG NENS: UPDATE AFTER 5 YEARS

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Background: We previously presented data about a phase II study showing that the combination of Everolimus and Octreotide LAR for advanced neuroendocrine tumors (NETs) of the gastro-entero-pancreatic (GEP) tract and of the lung in the first line setting, is an active and safe treatment. Currently we performed an update after 5 years.

Patients and methods: We performed an Italian, multicenter, phase II study. Patients with advanced well differentiated, previously untreated, neuroendocrine tumors of the gastro-entero-pancreatic (GEP) tract and of the lung, received Octreotide LAR 30 mg every 28 days in combination with Everolimus 10 mg per day, continuously. The primary endpoint was objective response rate (ORR).

Results: A total of 50 patients (58% males) were enrolled. The median exposure to study drugs is 519,5 days weeks (range 48-2024) and 17 (34%) of these patients have received treatment for more than 2 years. The primary tumor site was: pancreas 14 pts, small intestine 11 pts, lung 11 pts and unknown in 14 pts. The ORR (RC+RP) was: 18% (95% CI 7.4 - 28.6): 1 RC, 8 RP (16%), 37 SD (74%). The median TTP is 33,6 months (95% CI 18,7 – 41,2) and the median OS is 61,0 months (95% CI 49,8 – n.d.).

Conclusions: The current analysis showed an interesting prolongation of TTP and OS in patients treated with everolimus and octreotide LAR as first line treatment. Patients had a long exposure to the study drug, without unexpected side effects in the long term.

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P05

A RANDOMIZED PHASE II TRIAL OF CAPTEM OR FOLFIRI AS SECOND-LINE THERAPY IN NEUROENDOCRINE CARCINOMAS AND EXPLORATORY ANALYSIS OF THE PREDICTIVE ROLE OF PET IMAGING AND BIOLOGICAL MARKERS (SENECA STUDY)

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Background: Patients with metastatic or locally advanced, non-resectable, grade 3 poorly-differentiated neuroendocrine carcinoma (NEC) of the lung or gastroenteropancreatic system (GEP NEC) are usually treated with first-line platinum-based palliative chemotherapy. However, there is no standard second-line treatment when progression occurs. Different second-line chemotherapy combinations have been evaluated retrospectively, but with poor results. In particular, FOLFIRI was evaluated in a retrospective monocentric study, showing a disease control rate (DCR) of 62%. In another retrospective study, temozolomide-based chemotherapy obtained a DCR of 71%.

There is growing evidence that the current grading system for NECs has a number of inconsistencies, highlighting the need for more accurate biomarkers to better understand the natural history of this very aggressive disease.

Study design: The SENECA study is a randomized, non-comparative, multicenter phase II trial designed to evaluate the efficacy and safety of FOLFIRI or capecitabine plus temozolomide (CAPTEM) after failure of first-line treatment in lung and GEP NECs. The primary objective is to assess the DCR of the regimens, with safety as a co-primary objective. Secondary objectives are the evaluation of overall survival (OS), progression-free survival (PFS) and quality of life. It is also planned to assess Gallium-PET/CT and tissue and circulating biomarkers as prognostic and predictive factors.

Eligibility criteria are age ⩾18 years, metastatic (synchronous or metachronous) or locally advanced, non-resectable, grade 3 lung or GEP NEC, and documented evidence of progressive disease during or after first-line platinum-based chemotherapy (cisplatin/carboplatin and etoposide; FOLFOX4 or CAPOX). Each patient is randomized to receive FOLFIRI or CAPTEM, considering Ki-67 (21-55 % vs. > 55%) and primary tumor site (lung vs. GEP) as stratification factors. The randomized study design allows for two active treatments to be evaluated in a comparable patient population. Analysis will be performed for each regimen separately. 56 patients will be enrolled in each arm of the study (total of 112 patients). Sixteen centers are taking part in the study and recruitment is ongoing. The first patient was randomized on March 6, 2017.

R - Sarcomas

R01

TRABECTEDIN AND OLAPARIB COMBINATION IN PATIENTS WITH ADVANCED AND UNRESECTABLE BONE AND SOFT TISSUE SARCOMAS (TOMAS TRIAL): A PHASE 1B STUDY FROM THE ITALIAN SARCOMA GROUP

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Background: Advanced bone and soft tissue sarcomas (BSTS) still represent an unmet medical need. In robust BSTS preclinical models, we demonstrated that trabectedin antitumor activity can be significantly boosted by the combination with the PARP1-inhibitor olaparib. On these bases, we run a phase 1b trial in advanced BSTS progressing after standard treatments.

Methods: This was an open-label, multicenter, phase 1b study recruiting patients with histologically-confirmed, unresectable BSTS. In a typical 3+3 design, patients received trabectedin 24-h infusion every 3 weeks and olaparib tablets orally twice daily across 6 dose-levels (trabectedin 0.675-1.3 mg/m^2, olaparib 100-300 mg bid). Intermediate dose-levels were allowed to better define safety. Primary endpoint was the determination of recommended phase 2 dose (RP2D). Secondary endpoints were pharmacokinetics, pharmacodynamics, preliminary signs of activity, overall toxicity, and exploratory biomarkers. ClinicalTrials.gov NCT02398058.

Results: 50 patients (29 males), median age 53 (range 19-80), median previous lines 2 (1-8), were enrolled between 11/2014 and 1/2017. Patients received a median of 4 cycles (1-17+) with a median follow-up of 10 months. Dose-limiting toxicities were grade 4 thrombocytopenia, grade 4 neutropenia >7 days, and febrile neutropenia. Dose level 4b (trabectedin 1.1 mg/m^2+ olaparib 150 mg bid) was selected as the RP2D, and 28 patients were treated at this dose level. Overall, the most common grade 3/4 adverse events were lymphopenia, neutropenia, thrombocytopenia, anemia, fatigue, AST/ALT elevation, and hypophosphatemia. No treatment-related deaths occurred. One (2%) patient interrupted treatment without progression. Overall, in 50 patients response rate was 14% with no responses reported in the 11 patients with bone sarcomas, and 7 partial responses (18%) observed in the 39 patients affected by STS. In these patients disease control rate and progression-free survival at 6-month were 56% and 38%, respectively. No significant drug-drug interactions were detected by pharmacokinetics analyses. Pharmacodynamics data showed effective PARP1 inhibition.

Conclusions: Trabectedin and olaparib combination is feasible at active doses for both drugs with encouraging preliminary data on antitumor activity. This combination deserves further clinical development and two dedicated phase 2 studies will assess its activity both in platinum-resistant ovarian cancer and advanced soft tissue sarcomas.

R02

A PILOT STUDY EVALUATING THE EFFICACY OF ONE SHOT NEPA (NETUPITANT PLUS PALONOSETRON) PLUS DEXAMETHASONE TO PREVENT CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV) IN SARCOMA PATIENTS RECEIVING MULTIPLE-DAY CHEMOTHERAPY (MD-CT)

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Background: Nowadays, chemotherapy-induced nausea and vomiting (CINV) is still one of the most feared and disturbing adverse events of cancer treatment. When poorly controlled, CINV negatively impact the patient's ability to tolerate chemotherapy and can affect their quality of life.

For high-risk soft tissue sarcoma patients, undergoing multiple-day chemotherapy (MD-CT), antiemetic guidelines recommend a combination of 5HT3-RA, NK1-RA and dexamethasone (Dex) on each day of the antineoplastic treatment and for 2 days after completion of chemotherapy.

NEPA is the first oral fixed-dose combination of a highly selective NK1-RA, netupitant, and palonosetron, an established pharmacologically and clinically distinct 5HT3-RA with a safe cardiac profile. So far, no data has been published in literature about the efficacy of a single dose of NEPA in MD-CT.

Patients and methods: At the Oncology department of Palermo University, we performed a prospective, non-comparative study. 18 patients were administered 1 oral capsule of NEPA immediately before chemotherapy administration and Dex 12 mg on days 1-3. A dose escalation of Dex was done: 4 mg/bid on days 4-6 and 2 mg/bis on days 7-9.

Results: The main objective of the study was to assess the efficacy on CINV of one shot of NEPA plus Dex, in sarcoma patients scheduled to receive a MD-CT of epirubicin 35 mg/m2days 1-3 and ifosfamide 3000 mg/m2days 1-3 every 21 days, analysing the complete response (CR: no emetic episode and no use of rescue medication) during the overall phase (0-120 h) in cycle 1. The main secondary endpoints were CR during the overall phase of cycle 2 and 3.

The primary endpoint was reached in 88.9% of patients. Cycle 2-3 overall CR rates were 88.9% and 82.4%, respectively (Table 1). The antiemetic regimen was well tolerated and no neurotoxicity was detected in patients.

Conclusions: This pilot study showed the benefit of single NEPA administration to control CINV associated with MD-CT. In the setting of MD-CT, the choice of one shot NEPA schedule would allow the simplification of therapy by decreasing the number of individual dose units to be taken by the patients, simplifying therapy and improving patient compliance.

Table 1. Patients achieving a complete response (CR) during acute, delayed and overall phases.

Cycle	% CR Acute phase (0-24h)	% CR Delayed phase (25-120h)	% CR Overall phase (0-120h)
1(n=18)	100%	88.9%	88.9%
2(n=18)	99.4%	99.4%	88.9%
3(n=17)	94.1%	88.2%	82.4%

R03

OLARATUMAB AFTER TREATMENT WITH OLARATUMAB + DOXORUBICIN: MONOTHERAPY (MONO) OUTCOMES FROM THE JGDG PHASE 2 CLINICAL TRIAL

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Background: Olaratumab is a PDGFRα targeting monoclonal antibody blocking PDGFRα signaling. In a phase 1b/2 study (NCT01185964) olaratumab + doxorubicin (dox) demonstrated significant progression-free survival (PFS) and overall survival (OS) benefit versus Dox in patients (pts) with advanced unresectable or metastatic soft tissue sarcoma. Pts who had not experienced progressive disease (PD) after 8 cycles of olaratumab + dox in this study continued with olaratumab mono. Pts in the dox alone arm were allowed to receive olaratumab mono after PD. Here we report the results of the subgroup analysis for Phase 2 pts who received olaratumab monotherapy.

Methods: Patients eligible received olaratumab mono 15mg/kg IV on days 1 and 8 of each 21-day cycle until PD or other discontinuation criteria were met. The primary objective was to assess PFS. Additional objectives included OS, safety, and PK. PFS and OS were measured from randomization and tumor response was assessed according to RECIST (v1.1).

Results: Of 133 pts enrolled, 64 pts received olaratumab mono (34 pts post-olaratumab+dox; 30 pts post-dox). Baseline characteristics were similar to the overall study population, although a slightly increased proportion of women received olaratumab mono. Pts post olaratumab+dox received a median of 4.5 cycles of olaratumab mono. 10 pts received ⩾12 cycles. The 2-year survival rate was 67.6% (95% CI; 49.2, 80.6); median PFS and OS were 9.8 months (m) (95% CI, 7.2, 13.2) and 31.7 m (95% CI, 23.3, NE), respectively. Most pts discontinued due to PD (n=25); only 2 patients discontinued due to AE.

Most frequent related AE (in >2 pts) included diarrhea (n = 4) and fatigue (n = 3).

Pts post-dox received a median of 2.0 cycles of olaratumab mono; 3 pts received ⩾10 cycles. The 2-year survival rate was 28.7% (95% CI; 13.6, 45.7). Median OS was 13.5 m (95% CI, 8.4, 21.7). The only related AE reported in >2 pts was nausea (n = 3).

The pharmacokinetics of olaratumab was similar in all pts who received olaratumab mono, and consistent with that of olaratumab combined with doxorubicin.

Conclusion: Olaratumab mono was safe and well tolerated in the patient population. Pts treated with olaratumab mono following olaratumab+dox had efficacy outcomes longer than any historically reported OS for pts with advanced or metastatic soft tissue sarcoma. There do not appear to be any particular baseline characteristics that predict which pts would continue on to olaratumab mono.

R04

EXPRESSION OF PDGFRA, LIGANDS, AND RELATED GENES VERSUS CLINICAL OUTCOMES IN A PHASE 1B/2 STUDY OF OLARATUMAB PLUS DOXORUBICIN IN SOFT TISSUE SARCOMA

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Background: Post hoc analyses explored associations of biomarkers related to PDGFRa signaling pathway with progression-free survival (PFS) and overall survival (OS) in the randomized, controlled Phase 1b/2 study of doxorubicin (DOX) with or without olaratumab (OLARA) in metastatic soft tissue sarcoma.

Material and Methods: Archived tumor samples were collected at baseline as formalin-fixed, paraffin embedded slides or tissue blocks, from which RNA was extracted. A novel multiplex RT-PCR method was used for relative quantification of PDGFRa, PDGFRb, PDGF-A, PDGF-B, PDGF-C, PDGF-D, Gli1, EGFR, EGF, VEGFA, TGFa, TGFb, TOPO2A, PTEN and CXCR4 expression. Expression of these genes was explored for associations with efficacy endpoints.

Results: Evaluable samples from 77 patients (37 OLARA+DOX; 40 DOX). Demographics of this subset were similar to the overall study. No significant association observed for PDGFRa or PDGFRß expression and OS or PFS. Low PDGF-B or CXCR4 expression was associated with improved PFS in the combination arm (HR=0.51 [90% CI: 0.28, 0.91], HR=0.48 [90% CI: 0.26, 0.87], respectively). Low CXCR4 was associated with improved OS (HR=0.32 [90% CI: 0.17, 0.60]). In contrast to previous studies, poorer outcome among DOX-only treated patients with low CXCR4 expression was observed.

Conclusions: While PDGFRa gene expression on archival pre-treatment samples was not linked to PFS or OS of OLARA-treated patients, some statistical associations for PDGF-B and CXCR4 and efficacy endpoints were identified. The discrepancy with published data for outcome in patients with low CXCR4 treated with DOXO alone introduces uncertainty regarding findings of this exploratory analysis which was limited by sample age, numbers and heterogeneous mixture of primary and metastatic tumor samples. Further biomarker analyses of tissue samples from the ongoing Phase 3 study of OLARA+DOX in STS (ANNOUNCE) of both tumor and stromal expression of PDGF receptors and related ligands are warranted.

R05

PHARMACOLOGICAL THERAPY IN LIPOSARCOMA PRIMARY CULTURES

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Background: Liposarcoma (LPS), one of the most common types of soft tissue sarcoma (STS), has four subtypes, including well-differentiated/atypical lipomatous tumor (ALT/WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid/round cell liposarcoma (MLPS/RCLPS) and pleomorphic liposarcoma (PLS). The spectrum of pathological variations directly impacts on the biological characteristics, prognosis and response to chemotherapy of disease. However, the response of the different LPS subgroups to chemotherapy is not well documented.

Methods: The study has enrolled six patients with low/high grade LPS (1 ALT/WDLPS and DDLPS, 1 DDLPS, 2 MLPS, 1 RCLPS and 1 PLS). Patient-derived primary cultures were established after surgery. The drugs used for the treatment of the cultures were ifosfamide, epirubicin, trabectidin, eribulin, that represent the current systemic treatment options for LPS. Drug concentrations were selected following the human plasma peak in patients with solid tumors. Percentages of cellular survival were assessed by MMT and TUNEL assays.

Results: The results demonstrated the sensitivity of the cultures to the drugs used. The association of ifosfamide and epirubicin exhibited the major activity statistically

significant of the regimen among cultures. Ifosfamide did not show any effect on the cells survival, except in RCLPS suggesting its role in this LPS subtype. Epirubicin showed a comparable activity of the combination regimen in DDLPS (28%) and RCLPS (14%) while displayed a lesser cytotoxic effect in ALT/WDLPS and DDLPS (83%) and MLPS (65%). Trabectidin had no effect on the cells survival in DDLPS, while the drug showed a comparable activity in ALT/WDLPS and DDLPS and MPLS (61% and 65%). In RCLPS there was an important activity (28%). Trabectidin exhibited a higher efficacy in ALT/WDLPS and DDLPS and a similar trend in MLPS compared to epirubicin. Eribulin proved a similar activity of trabectidin in ALT/WDLPS and DDLPS (70%), MLPS (68%) and RCLPS (26%) while was more active in DDLPS (83%). Finally, cells survival of PLS was not affected by all the drugs.

Conclusions: This study explored the role of chemotherapy in a very heterogeneous disease, showing the response to the main drugs used in clinical practice for the treatment of LPS to improve clinical patient outcomes. Further confirmation of these results can represent a potential future direction for the management of this disease.

S - Miscellanea

S01

ROLE OF LIFESTYLE (OR BEHAVIOURAL FACTORS) CHANGES IN CANCER SURVIVORS: RESULTS FROM FUCSAM PROJECT

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Background: Lifestyle factors can benefit not only the quality of life of cancer survivors, but also overall survival, and decrease the risk of recurrence from cancer. Integrating life-style support into standardised models of aftercare for cancer survivors is a challenging purpose. The FUCSAM project aims to assess the impact of a prevention intervention on changing lifestyles in patients after treatment of colorectal and breast cancer followed by interdisciplinary team of care.

Material and Methods: All patients, participating in screening programs, with diagnosis of breast or colorectal cancer, at first follow-up after surgery and adjuvant medical therapy, free of disease, able to walk and with informed consent, were included in the study. Every three months in the follow-up visit (for 3 years) are collected data on: therapies, co-morbidity, anthropometry, clinical and biological parameters, adherence to programs for lifestyle changes. Information pamphlets on lifestyles were delivered to all patients and it was recommended to join the programs offered.

Results: Until September 2017 26 local hospitals have joined the FUCSAM project. Patients enrolled were 1,753 (296 colorectal cancer, 1385 breast cancer), 82% female and 78% are $<$ 70 years old. Analysing Body Mass Index (BMI), at the follow-up visit (six months) decreases the proportion of overweight (from 52,8% to 47,9%, p=0,03) and increases the normal-weight proportion (from 43,5% to 47,2%, p=0,03). Instead there are no differences in waist circumference. About lifestyle in same period we observe for diet, a decrease of red-meat and sausages consumption with an increase of vegetables and legumes consumption, and for physical activities a reduction in use of car with an increase in walks, use of bicycle, and use of stairs.

Conclusions: Although at the follow-up, the study results show an improvement of the diet and an increase in a physically more active lifestyle (great reduction in car use), in line with the recommendations. During the same period it is observed a BMI reduction. These partial results are very encouraging but we need to assess their long-term maintenance (one and two years of follow-up).

S02

EARLY 7-DAY SUPPLEMENTAL PARENTERAL NUTRITION IMPROVES BODY COMPOSITION AND MUSCLE STRENGTH IN HYPOPHAGIC CANCER PATIENTS AT NUTRITIONAL RISK

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Purpose: The international guidelines recommend the use of supplemental parenteral nutrition (SPN) in cancer patients when they are malnourished, hypophagic and enteral nutrition is not feasible. However, there is limited evidence on the short-term effects of SPN on body composition and muscle strength in this patients' population.

Methods: The aim of this bicentric single arm clinical trial (NCT02828150) was to evaluate the effects of early 7-day SPN on bioimpedance vectorial analysis (BIVA) derived body composition, handgrip strength (HG) and serum prealbumin (PAB) in 131, hypophagic, hospitalized cancer patients at nutritional risk.

Results: One-hundred-eighteen patients (90.1%) completed the 7-day SPN support regimen.

SPN induced a significant improvement of phase angle (PhA, +0.25 [95%CI, 0.11, 0.39]; p=0.001), standardized phase angle (SPA, +0.33 [95% CI, 0.13, 0.53], p=0.002), HG (+2.1 kg [95%CI, 1.30, 2.81]; $p<0.001$) and PAB (+3.8 mg/dl [95%CI, 2.1, 5.6]; $p<0.001$).

At multivariable analysis, these effects on BIVA parameters were more pronounced in patients (N=90, 76.3%) in whom estimated protein and calorie requirements were both satisfied (adjusted difference: PhA, +0.39 [95%CI, 0.04, 0.73], p=0.030); SPA, +0.62 [95%CI, 0.16, 1.09], p=0.009).

No significant changes in hydration status were detected and no severe metabolic or other complications occurred.

Conclusions: Early 7-day SPN improved body composition, muscle strength and serum prealbumin levels in hypophagic, hospitalized cancer patients at nutritional risk in the absence of any relevant clinical complication. Full satisfaction of both calorie and protein requirements may be a key point for the initial improvement of nutritional status in this patients' population. Further trials aimed at verifying the efficacy of this early nutritional approach on mid and long term primary clinical endpoints in specific cancer types are warranted.

S03

CONFLICT OF INTEREST AMONG ITALIAN MEDICAL ONCOLOGISTS. A NATIONAL SURVEY SPONSORED BY CIPOMO

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Background: Conflict of interest (COI) increasingly affects every aspect of medicine, including care, education, research integrity, patient trust, guideline formulation, regulatory approval and scientific prominence. Collaboration between industry and clinicians and/or researchers creates challenges and opportunities. While these relationships are regulated by the Physician Payment Sunshine Act in the US, little is known about this issue in Europe. We assessed the Italian medical oncologist's opinion regarding the implications of COI on medical education, care and research and evaluated their direct financial relationships.

Materials and Methods: The Italian College of Medical Oncology Chiefs sponsored a cross-sectional survey between March and April 2017 among Italian oncologists through its web site. Italian oncologists filled out an anonymous questionnaire including 19 items and individual and working characteristics. The main outcome measures were the proportion of medical oncologists perceiving COI as an outstanding issue and those receiving direct payments from industry.

Results: The number of responders were 321, representing 13% of Italian tenured medical oncologists. Overall, 62% declared direct payments from pharmaceutical industry in the last 3 years. Sixty-eight percent felt the majority of Italian oncologists have a COI with industry but 59% suppose this is not greater than that of other specialties. Eighty-two percent consider that most oncology education is supported by industry. More than 75% believe that current allocation of industry budget on marketing and promotion rather than research and development is unfair but 75% consider it appropriate to receive travel and lodging hospitality from industry. A median net profit margin of 5.000€ per patient enrolled in an industry trial was considered appropriate for the employee institution. Sixty percent agree to receive a personal fee for patients enrolled in industry trials but 79% state this should be reported in the informed consent. Over 90% believe that scientific societies should publish a financial report of industry support. Finally, 79% disagree to being co-author of an article written by a medical writer when no substantial scientific contribution is made.

Conclusions: COI is perceived as an important issue influencing costs, education, care and science among Italian oncologists. These findings support a more rigorous policy on COI at individual and institutional level.

S04

CURRENT NEEDS OF ADULT CANCER SURVIVORS AFFECTED BY SOLID OR HEMATOLOGIC TUMORS ENROLLED IN HUMANITAS RESEARCH HOSPITAL'S SURVIVORSHIP CARE MODEL

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Background: The growing population of cancer survivors (CS) represents a challenge to clinicians that should be able to address the different lifetime health need of this population. While there are different studies investigating the quality of life (QoL) of cancer pts during active treatment, few studies report QoL of CS after at least 5 years (yrs) from achieving complete remission. We have investigated QoL and concerns about physical\psychological symptom of CS enrolled in our survivorship program from April 2015 to December 2016.

Methods: We included pts > 18 yrs affected by hematologic or solid tumors after at least 5 yrs from achieving complete remission. A cross-sectional survey was carried out using validated scales: Cancer Survivors Survey of Needs subscale and a single-item measure of global QoL perception.

Results: We analyzed data from 191 CS. The median age was 63 yrs (52 yrs at diagnosis), 70% were females. The most frequent histological types were breast (50%), colorectal (19%) and hematologic tumors (18%). Most pts received both chemotherapy and radiation therapy. With a median observation time of 139 months, the 10-yrs cumulative incidence of second neoplasm and cardiac adverse event was 8% and 7% respectively. 127 pts (66%) reported a good QoL (score ⩾3). The most frequent symptoms reported were dental\mouth problems (50%), memory\concentration deficit (48%), sleep disturbance (47%). The most common physical\psychological symptoms were fear of relapse (68%), genetic counseling (56%), living with uncertainty (46%). A positive statistically significant association ($p < 0.05$) was observed between previous hormonal therapy and the following concerns (score ⩾2): sleep disturbance (59% vs 36%); weight gain (34% vs 27%), osteoporosis (46% vs 28%), living with uncertainty (58% vs 37%). Female reported more fear of relapse (p 0.005), sense of uncertainty (p 0.004), pain (p 0.013), sleep disturbance (p 0.003), weight gain (p 0.009), osteoporosis ($p < 0.001$), body changes ($p < 0.001$) than males. 94% of pts have fully or partially adhered to the survivorship care plan.

Conclusions: Most CS have a good QoL perception but we observed a high percentage of pts with a low score indicating different needs to be addressed. Female pts treated with hormonal therapy are at higher risk of having both physical and psychological concerns representing a subgroup of patient with a wide range of needs. So far, the compliance of pts with the program was high.

S05

GENETIC VARIANTS OF NR1I3 AND UGT2B7 ADME GENES ARE PREDICTIVE BIOMARKERS OF TAXANE NEUROTOXICITY AND RETAIN PROGNOSTIC VALUE

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Background: Taxane-based schedule is the gold-standard of breast cancer (BC) treatment. Genetic polymorphisms in drug-transporters and drug-metabolizing enzymes (ADME) may influence taxane associated neuropathy (TAN), known as dose-limiting toxicity. By the drug metabolizing enzyme and transporter (DMET) Affymetrix microarray genotyping platform, we investigated, in a learning set (LS) of BC taxane treated patients, the correlation between single nucleotide polymorphisms (SNPs) in ADME genes and grade (G)⩾2-3 TAN. Then, all recognized SNPs were validated in an independent set (Validation Set, VS) of BC patients. Moreover, we identify a genetic signature of prognostic relevance for BC outcome.

Patients and methods: Seventy nine advanced BC patients, who received docetaxel or paclitaxel, were enrolled in the LS as a retrospective case-control study; 27 experiencing TAN (⩾ grade2-3 according to NCI criteria) were the case group, while 52, who never experienced TAN, were controls. DNA from peripheral blood cells was genotyped by DMET. Primary end-point was the association between SNPs and TAN; SNP association with Overall Survival (OS) was the secondary endpoint. Genotype association was evaluated by Fisher exact test. By receiver operating characteristics (ROC) curves, we validated the G⩾2-3 TAN related biomarkers in an independent series (54, 17 cases and 37 controls) of BC patients (VS), identified by direct sequencing. Validated SNPs were subsequently classified by association rulesas input for the Random Tree classifier (Weka ver. 3.8.1), in order to explore the five SNPs as predictive signature for BC outcome. We classified patients into two groups: the group 0 (G0) for time to relapse< 12 months, and group 1 (G1) for patients who relapsed longer than 12 months.

Results: 21 SNPs were associated to TAN. After Bonferroni's correction for multiple testing, 5 SNPs, mapping on two genes, NR1I3 (rs11584174) and UGT2B7*2c (rs7438284, rs7662029, rs7439366 and rs7668258), were significantly associated with protection from G⩾2-3 TAN ($p \leqslant 0.002$). Internal cross-validation of the LS confirmed the predictive value of TAN-related SNPs. NR1I3 was correlated to Paclitaxel-TAN and UGT2B7 to docetaxel-TAN both with a protective effect. Lastly, we recognized a prognostic genetic signature able to predict OS.

Conclusion: Polymorphic variants in NR1I3 and UGT2B7*2c genes predicted for TAN protection. These results could suggest information for personalized treatment.

S06

PREVALENCE, SEVERITY, AND SELF-REPORTED CHARACTERISTICS OF TASTE ALTERATIONS EXPERIENCED BY PATIENTS RECEIVING CHEMOTHERAPY

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Background: TAs can lead to malnutrition and weight loss, and affect the quality of life (QoL). This study aimed to describe the prevalence, severity, and self-reported characteristics of TAs induced by chemotherapy (CT) and to investigate TAs across CT regimens. It further aimed to describe the impact of TAs on QoL and the predictors of TAs.

Methods: This cross-sectional study included consecutive outpatients with cancer who received CT at five hospitals in Northern Italy between April and June 2014. Patients with CT-related TAs were asked to self-report their TAs in the previous week using the Italian version of the Chemotherapy-induced Taste Alteration Scale (CiTAS). The overall CiTAS score ranged from 4 (no TAs) to 20 (maximum severity of TAs). They were then asked to rate the impact of TAs on their QoL in the previous week using a Numerical Rating Scale (NRS, 0-100). Overall CiTAS was classified as: ⩽6 insignificant; 6-10 mild; 10-14 moderate; and 15-20 severe. The correlation between the NRS and CiTAS scores was assessed using Pearson correlation (r). Predictors of TAs were identified using a multivariate linear regression analysis.

Results: In all, 243 patients were included with an overall prevalence of TAs of 65.6%. The mean overall CiTAS score was 8.5/20 (SD=2.3). TAs were insignificant, mild, moderate or severe in 30 (12.3%), 156 (64.2%), 51 (21%) and six (2.5%) patients, respectively. Tasting saltiness was the ability most affected (39.5%), followed by alterations in umami (34.2%), sweetness (30%), bitterness (26.7%) and sourness (20.6%) perception. Feeling nauseated (63%), having a reduced appetite (61%), and having difficulty eating meat (51%) were the most frequent and distressing problems. Gemcitabine, cisplatin/pemetrexed and epirubicin/cyclophosphamide caused the most severe TAs, while low levels of TAs were found with GEMCARBO and CISGEM. Overall CiTAS score correlated with QoL ($r=0.31$, $p<0.001$). A 21-day chemotherapy schedule increased the overall CiTAS score by 1.41 points ($p<0.001$) compared to a 7-day schedule, while for each 10-year age increase the overall CiTAS score decreased by 0.37 points ($p=0.002$).

Conclusion: CT-related TAs were a frequent side effect with moderate to severe symptoms in almost one-fourth of the patients. TAs were often associated with unpleasant symptoms and negatively affected QoL. CT impacted all the tasting qualities and the severity of TAs was influenced by the CT regimen.

S07

EMERGENCY CANCER RELATED VISITS: GENERAL AND DEDICATED EMERGENCY ROOM

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Background: "Acute Oncology" refers to intensive care of acute side -effects of therapies or severe complications from a known or new cancer diagnosis. Specialists rapidly recognize emergencies providing specific treatment, improving quality of care and reducing inpatient stay. Local services configuration may reflect number and type of admissions often referred to General Emergency Room (GER). Onco-Hemato Emergency Room (OHER) in Modena Hospital, operative since 2001, is a service completely dedicated to cancer patients (pts) needs integrated with Oncology Department. Medical team is composed by oncologists and hematologists with a nurse active from Monday to Friday (08, 00-18, 00) and Saturday (08, 00-12, 00). Otherwise pts must refer to GER.

Objective: to describe clinical features of pts admitted to OHER between January, 1, 2007 and December, 31, 2017, percentage of hospitalizations comparing GER

Methods: Data were obtained through the query of a relational database used to collect medical records, concerning all disease history including prior hospitalizations and planned evaluations. Pts were received regardless disease stage from suspected tumor to palliative care setting.

Results: We reported 28.680 admissions; of 11.239 evaluated pts, 5326 (47%) had a single access, the most recurrent one had 51 visits, 165 (0.6%) died during OHER stay. According to the site of primary malignancy: digestive tract 24%, lung 16.5%, lymphoma 9%, acute and chronic leukemia 10%, breast 7.2%, colon-rectal 8.4%, urological 8%, myeloma 5%, head neck 4%, melanoma 1.4%, sarcoma 1.7%, hematologic 2.3%, thrombotic purpura 0.2%, other 2.3%. Most common reasons determining OHER visits were worsening of disease (14.6%), pain (12%), therapy toxicities (8.6%), suspected tumor (5.6%), deferrable (7%). January was the most crowded month (2900, 10%), December the less one (1952, 6.8%). Monday (6926) was the most haunted day of the week. Appropriate hospitalizations in Oncology Department were 6.781 (23%), 1.710 (5.8%) in others. 10. 246 onco-hematologic pts acceded to GER in the same period (1.4% of all pts); 5961(58%) were hospitalized.

Conclusions: OHER is the first place pts turn in case of unexpected worsening; specialist adequately trained are required to quickly stratify clinical needs and start intensive treatment. Rapid control of symptoms and prompt stabilization of acutes should enhance quality and safety of care decreasing avoidable hospitalizations.

S08

THE DIAGNOSIS AND PROGNOSIS AWARENESS IN TERMINALLY ILL CANCER PATIENTS: ASSESSMENT AND CLINICAL IMPLICATIONS.

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Objective: To examine the level of awareness of diagnosis and prognosis in a sample of terminally ill cancer patients, and to investigate the impact of the disease awareness on the psychological, physical, social and spiritual aspects.
Material and Methods: Participants have been recruited in "Vittorio Valletta" Hospice of Turin and in Città della Salute e della Scienza Hospital of Turin. Inclusion criteria were: cancer diagnosis, life expectancy $\leqslant$ 4 months, Karnofsky Performance Status (KPS) $\leqslant$ 40, score at the Mini-Mental State Examination (MMSE) $>$ 19, comprehension and speaking of Italian language. The level of patients' awareness has been indicated by the psychologists at the end of the consultancies. The following validated rating scales were administered: Hospital Anxiety and Depression Scale (HADS), Visual Analogue Scale for pain (VAS), McGill Pain Questionnaire (MPQ), Functional Assessment of Cancer Therapy (Fact-G), Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale (Facit-sp 12) and Brief-COPE (BC).
Results: Sample was constituted by 443 patient-caregiver dyads. Only the 17.9% (n=79) of the patients were aware of both the diagnosis and the prognosis, the 22.6% (n=100) were completely unaware, and most of them overestimated the prognosis (42.2%, n=187). On the contrary, the 81.9% (n=363) of the caregivers were aware of patient's diagnosis and prognosis. With the increasing of the awareness levels, patients' depressive symptomatology and experienced sensorial, affective, and total pain enhanced, and emotional and spiritual wellbeing reduced. However, higher awareness corresponded to higher levels of socio-familiar well-being and active coping, acceptance and planning, and to lower levels of denial and behavioral disengagement. Finally, the spiritual well-being linked to faith and the religious coping style were not associated to the level of awareness.
Conclusions: Results highlight the relevance of interventions on the topic, both focused on the physician-patient communication and relative to the clinical sensitization to the theme. It could be interesting to observe whether an earlier process of informative communication is associated to better emotional and physical outcomes. An appropriate level of awareness might let patients to use the end phase of their lives in a fruitful and active way. Finally, a therapeutic focus on spirituality could be clinically relevant for both the aware and the not aware patients nearing death.

S09

WOMEN WITH SYNCHRONOUS OR METACHRONOUS LUNG AND OVARIAN CANCERS: A MULTI-INSTITUTIONAL REPORT

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Background: In women, lung cancer (LC) and ovarian cancer (OC) are, respectively, the second and eighth malignancies for incidence. Despite increasing incidence and mortality of LC, association with OC is rare, with lack of literature data. The aim of this report is to describe a series of patients with synchronous or metachronous LC and OC and to identify common clinical and pathological patterns.
Methods: We retrieved the medical charts of patients who referred to 30 Oncological Institutes, from 2008 to 2018. When patients with synchronous (up to 3 months of time interval in onset) or metachronous LC and OC were found, we collected medical history, pathological features and clinical outcomes. Whenever available, formalin fixed paraffin embedded tumor tissue was collected for centralized pathology revision with an immunohistochemical marker panel including TTF-1 and PAX-8. In ambiguous cases, a broader panel was performed (p40, CK-7, WT1, CA125, Calretinin, EMA,

CEA, CgA, Vimentin, Napsin-A). Whenever tested, genetic alterations in LC and OC were also reported.
Results: As of May 2018, 11 Institutes retrieved 19 cases with a history of LC and OC in the last 10 years. Paired specimens were available in 7 cases. One patient was excluded, since pathology revision revealed that lung lesions were metastases from serous OC. Thus, analyses were performed on 18 patients. In 12/18 cases, LC and OC were metachronous and, in 7/12 cases, OC preceded LC diagnosis, with a median interval of 6.5 years. Median age at diagnosis of the first malignancy was 62 years, the majority of patients (66.6%) were never-smoker, 7 had cancer familial history. Interestingly, 5 patients (27.7%) reported also a third or fourth malignancy. After a median follow-up of 6.8 years, 11 patients are alive. Regarding histology, most LC were adenocarcinoma (83.3%). Molecular status was available in 9/15 cases: 4 had EGFR mutation, 1 B-RAF mutation and 2 ALK translocation. OC were mostly high-grade serous (77.7%). BRCA status was available in 7 patients: 3 mutated, 2 wild-type and 2 affected by variants of unknown significance (USV). Moreover, one synchronous case presented both BRCA-USV and B-RAF mutation.
Conclusions: In our series, synchronous and metachronous LC and OC were often driven by genetic alterations and most never-smokers also had cancer familiarity. Further genetic analysis with next generation sequencing technology has been planned.

S10

THE COPPI (CARDIO-ONCOLOGY PROTOCOL OF PREVENTION AND EARLY INTERVENTION) PROGRAM: ASSESSMENT OF CARDIOVASCULAR RISK, CLOSE MONITORING AND CARDIOPROTECTIVE DRUG THERAPY IN CANCER PATIENTS

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Background: The number of anticancer drugs with potential acute and long-term cardiotoxicity has been continuously increasing. Cardiovascular diseases related to anticancer treatments may impair patients' physical and psychological status, raise costs and ultimately compromise patients' ability to receive further active treatments. Thus, cardiac monitoring is becoming a fundamental support to oncology practice.
Methods: Since 2016, at our Department all cancer patients were stratified using a cardiovascular risk assessment score at their first visit and then assigned to a standard or intensive protocol of cardiovascular monitoring (**COPPI** program). Risk factors were divided in three categories: general cardiovascular (GCV), established heart disease (EHD) and therapy-related (TR). GCV risk factors were: age $>$ 60, female sex, hypertension, metabolic and electrolyte disorders, diabetes since $>$ 10 yrs or uncontrolled diabetes, past or current smoking. Two or more GCV risk factors or one only between EHD or TR risk factors prompted intensive monitoring. This consisted of baseline cardiologist's visit, EKG and echocardiogram plus NT-pro-BNP and HS-troponin T. Blood markers were repeated according to cancer therapy protocol. Significant changes in baseline parameters, e.g. serum markers higher than normal, prompted a new visit and a cardioprotective drug intervention, mainly consisting of low dose enalapril and bisoprolol with the addition of diuretics (furosemide and low-dose potassium canrenoate) if there were either clinical signs of fluid retention or further increase of serum markers.
Results: Since 2016 120 patients who had to begin chemotherapy or other potentially cardiotoxic treatments were deemed as high risk and underwent intensive monitoring. Ten of them had baseline alterations and had cardiac therapy changes before starting treatment. 26 further patients (21.6%) had elevations of serum markers during treatment and underwent early introduction of cardioprotective drugs. No case of heart failure, ischemic heart disease or significant arrhythmia occurred. One case of asymptomatic decrease of left ventricular ejection fraction $<$ 50% was intercepted during trastuzumab/paclitaxel.
Conclusions: A program of strict cardiac monitoring in patients undergoing anticancer therapy is feasible, allows early therapeutic intervention and completion of anticancer therapy and prevent patients from physical and psychological damage due to cardiovascular toxicity.

S11

30-DAY MORTALITY AFTER SYSTEMIC ANTI-CANCER THERAPY FOR BREAST CANCER (BC) AND NON-SMALL CELL LUNG CANCER (NSCLC) IN A SINGLE INSTITUTION IN ITALY

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Background: 30-day mortality after systemic anti-cancer therapy (SACT) might be considered as a measure for evaluating the appropriateness of decision to treat with SACT and the incidence of treatment-related deaths.

Several retrospective mono-institutional studies have been published, with reported 30-day mortality after SACT ranging from 3-4% to 13%. More recently, a large population-based study conducted in England with the aim to establish national benchmarks, reported a 30-day mortality after SACT of 2% among BC patients and 8% among lung patients (pts). Data on 30-day mortality after SACT in Italy are lacking. Here we report data from our institution.
Methods: We retrospectively searched our electronic database for pts with BC or NSCLC treated with SACT from 1st January 2017 to 31st December 2017. Pts receiving endocrine therapy for BC as the only SACT were excluded. The following data were collected: intent of therapy (curative or palliative), type of treatment, the date when treatment was started, the date of last administration and, if the patient was deceased, the date of death. Fisher's exact text was used for comparison of categorical variables.
Results: In 2017, 156 pts with BC and 63 pts with started a new SACT. 30-day mortality after SACT was 2.3% in the overall population (5/219), with higher mortality among pts treated with palliative intent (5/112, 4.5%) compared with those treated with curative intent (0/107, 0%; p=0.06). 30-day mortality after SACT was significantly higher among NSCLC pts (4/63, 6.4%) than among BC pts (1/156, 0.6%; p=0.03). In the cohort of pts with BC, 30-day mortality was 0% (0/98) and 1.7% (1/58) for those treated with curative and palliative intent, respectively (p=0.38). In the cohort of pts with NSCLC, 30-day mortality was 0% (0/9) and 7.4% (4/54) for those treated with curative and palliative intent, respectively (p=0.06).
Conclusions: 30-day mortality after SACT in pts with BC and NSCLC observed at our institution compares favorably with that reported by other mono-institutional studies and also by the large population-based English study. As expected, mortality was higher among pts with NSCLC and those treated with palliative intent. Further research may provide additional information on factors associated with early mortality with the aim to improve the standard of care. We encourage similar audit in other centers across Italy, in order to establish national benchmarks.

S12

CAN THE SAFETY OF CHEMOTHERAPY BE IMPROVED BY PHARMACOVIGILANCE?

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Background: Pharmacovigilance in Oncology Day Hospital of University-Hospital of Udine is an important activity, because through the reporting of the adverse drug reactions (ADRs) it is possible to obtain indications on the frequency of the known adverse reactions, discover new information about the unknown ADRs or, in the case of large numbers of ADRs for the same product, use a different product batch or even change the producer of the drug.
Material and methods: We monitored the occurrence of ADRs in patients who underwent chemotherapy sessions reporting them on Vigifarmaco, an Italian pharmacovigilance platform.
Results: The results indicate 62 ADRs on a total of 8836 chemotherapy sessions administered in 2017. The most involved oncology drugs were, in order: paclitaxel, oxaliplatin, carboplatin, trastuzumab, docetaxel, nivolumab, cisplatin and irinotecan. It was noted that, out of the 21 ADRs to oxaliplatin, 10 occurred at the end of the chemotherapy session. Among the ADRs detected, precious data comes from the unknown ADRs, meaning reactions that are not already present in the drug's technical data sheet. Examples are pruritus, laryngospasm, a throat tingling sensation, sweating, sialorrhea, epigastric weight and fainting sensation for oxaliplatin. For paclitaxel, the unknown reactions were jugular constriction, choking sensation, low back pain, retrosternal and renal pain, broncho and laryngospasm. All of these reactions have been reported through the Vigifarmaco platform and are used to implement the safety of each drug. In addition to this, on a total of 8836 chemotherapy sessions only three chemotherapic drug extravasion took place (0.03%);of these one was with a vesicant drug, one with an urticant drug and the last one with a neutral one (neither vescicant nor urticant).
Conclusions: The pharmacovigilance activity in Oncology Day Hospital Department is very useful. By observing the reactions that arise to patients undergoing chemotherapy sessions, we can acquire new information and transmit them to the physicians and nurses in order to improve the clinical practice. Since half of the detected ADRs registered for the oxaliplatin drug occurred at the end of the chemiotherapy session, the data collected suggest the benefit of patient's monitoring for a longer period of time. Improving information on drug safety is important for everyone, even more for this category of patients, already debilitated by cancer.

S13

SERUM MARKERS ASSOCIATED WITH IMMUNE RELATED ADVERSE EVENTS OF IMMUNE CHECKPOINT INHIBITORS: A REAL WORLD SCENARIO

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Background: Immunotherapy is one of the most exciting advance in anticancer treatment. Immune checkpoint inhibitors (ICI) represent a novel and well tolerated class of drugs. However, because of their mechanism of action, ICI may cause immune related adverse events (irAEs). Currently, no data exist about predictive markers associated with the occurrence of irAEs.
Methods: We retrospectively analyzed a series of 130 consecutive patients (pts) treated with anti PD-1/PD-L1 or anti CTLA-4 agents from Jan 2012 to Dec 2017. IrAEs were graded according to CTCAE v.4.0. The aim of the study was to evaluate changes in serum markers in pts with irAEs onset. Wilcoxon's signed rank test was used to assess the statistical significance of changes in biomarkers. Gray's test to assess differences in the cumulative incidence function of irAEs among groups of pts.
Results: Pts with a diagnosis of NSCLC n=64 (49%), melanoma n=55 (42%), kidney n=9 (7%) and others n=2 (2%) were investigated. Median age was 69 years. ICI represented first line cancer treatment for 27% pts, second line for 57% and third or further line for the remaining 16%. In detail, 18% were treated with ipilimumab and 82% with anti PD-1/PD-L1 agents (nivolumab 60%, pembrolizumab 21%, atezolizumab 1%). For pts who received more than one ICI, we analyzed only irAEs occurred during the first ICI treatment. Among all pts who received first ICI treatment, we detected 41 irAEs (36% of pts), 39% of those were grade 1, 39% grade 2, 15% grade 3 and 7% grade 4. Among pts who developed irAEs, 50% (21 pts) required immunosuppressive treatment, 25% (11 pts) needed hospitalization and 25% (11 pts) required ICI discontinuation.

In patients with irAEs, eosinophilic count increased significantly from the therapy start (p=0.03). Higher NLR (neutrophil to lymphocytes ratio) was associated with lower risk to develop colitis or diarrhea (p=0.04). Additionally, absolute lymphocytic count decreased in patients with irAEs (p=0.07) and monocyte count increased in patients with irAEs (p=0.07) and endocrine irAE (p=0.06).

No statistically significant differences in irAEs incidence were seen according to age ($>$ or $\leqslant$ 65 years) or sex. Ipilimumab had higher rates of irAEs (p=0.03)
Conclusion: These results suggest changes in the white cell subpopulation count may be associated with a higher risk for irAE. Further studies are needed to confirm our findings.

S14

PRIMARY AND SECONDARY PREVENTION TO EFFECTIVELY REDUCE THE RISK OF BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW IN PATIENTS WITH BONE METASTASES

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Background: Bone is one of the most frequent sites of metastasis in patients with advanced cancer. Nearly all patients with myeloma, 65–75% of patients with prostate or breast cancer, and 30–40% of patients with lung cancer or other solid tumors, eventually develop bone metastases. Bisphosphonates (BP), particularly zoledronic acid and denosumab, were demonstrated to effectively reduce skeletal complications in patients with bone metastases. However, bisphosphonate-related osteonecrosis of the jaw (BRONJ) can occur spontaneously, favored by dental extraction, dental implant surgery, or denture wearing. The purpose of this study was to underline the role of dental prevention as an effective tool to reduce the risk of BRONJ.
Material and methods: BRONJ was identified with the standardized query "osteonecrosis" among all data from patients treated at Modena Cancer Center from 2005 to 2016. For each case, demographic and medical information were analyzed, as well as data about notification (year of occurrence, outcome), type and duration of BP exposure, and associated risk factors (dento-alveolar surgery, chemotherapy, antiangiogenics). Data were differently analyzed taking into account the implementation of a Dental Prevention Service in patients who are candidates for BP therapy.
Results: Among 1663 patients treated with BP, 63 cases of BRONJ were identified (3.8%). 44 female and 19 men with a median age of 69 years (range 47-90 years), have been treated with BP for bone metastases from breast cancer (54%), hematologic malignancy (21%), prostate cancer (13%), renal cancer (5%), lung cancer (2%) and other tumors (5%). 15 maxillae and 48 mandibles were involved. The trigger event was a dental extraction in 29% of the cases, being spontaneously the other 71%. The median time to BRONJ was 28 months (range 1-89.1 months) from the first dose of BP, and 25 was the mean number of BP doses administered before BRONJ. Overall, a preliminary odontoiatric evaluation was performed in only 14 cases (22%). All but one of these dentistry opinions were obtained after 2010 when the Dental Prevention Service was created, which is a drop out of the risk of BRONJ from 4.1 to 1.9%.
Conclusions. Prevention of the BRONJ is critical in in bone metastatic patients. The incidence of BRONJ over time can drop to 1.9% when primary and secondary prevention measures are implemented in routine clinical practice.

S15

DELIRIUM DIAGNOSIS, EVOLUTION, PHENOMENOLOGY IN ADVANCED CANCER PATIENTS: AN OBSERVATIONAL PROSPECTIVE STUDY IN TWO DIFFERENT PALLIATIVE CARE UNITS

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Background: Delirium is a neuropsychiatric disorder frequent in Palliative Care patients. The Memorial Delirium Assessment Scale (MDAS) is a 10-item severity delirium assessment questionnaire. Each item scores from 0 to 3 according to its severity. The aim of this study is to compare frequency, evolution and phenomenology of delirium in advanced cancer patients with palliative care assistance in two different settings: Hospice (HS) and Oncology Ward.
Methods: We conducted a prospective observational study of consecutive advanced cancer patients admitted at a HS, and attended by a Palliative Care Supportive Team (ST) at an Oncology Ward. MDAS was employed for delirium diagnoses (cut-off >7) and evolution, using it within 48 hours to admission and once every week. When delirium was diagnosed, we compiled a checklist of causes and therapies. Frequency analysis was employed to describe the population, Fisher test to compare the two groups, Anova Test for the phenomenology.
Results: 582 patients were evaluated, 227 were enrolled (176 in 10 months in HS, 51 in 6 months by ST). The median age was 73 years. The groups differed in Karnofsky performance status (KPS): KPS= 30-40 88% HS, KPS >50 63% ST ($p<0.001$). Delirium prevalence at admission was in 46/176 (26%) patients HS and in 11/51 (22%) patients ST ($p<0.585$). During hospitalization delirium was diagnosed in 31/176 (18%) patients HS and in 4/51 (8%) patients ST ($p<0.208$). At the time of discharge/death, delirium was present in 65/176 (37%) patients HS and in 3/51 (6%) patients ST ($p<0.001$). The causes of delirium were the same in two settings. Haloperidol was the drug most administered. At statistical analysis KPS and different center influence delirium evolution ($p<0.015$). In the subgroup of 32 patients with two consecutive MDAS we analyzed the phenomenology. In the patients 22/32(68%) with reversible delirium, all MDAS items improved with a reduction of the level of intensity ($p<0.05$). In irreversible delirium, the level of intensity of all items reminded the same.
Conclusion: Delirium prevalence at admission and during hospitalization was similar in both settings, but evolution showed a greater recovery in patients attended by ST. Delirium early diagnoses in advanced cancer patients with better KPS could help to alleviate this syndrome. Early Palliative Care integration could be key for that. Delirium signs improve in reversible delirium, but with proper treatment do not worsen in irreversible events.

S16

SECOND-OPINION: WHAT ITALIAN ONCOLOGISTS THINK ABOUT?

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Background: Receiving a cancer diagnosis is a life-changing event. The patients (pts) may be experiencing many different emotions, including feeling overwhelmed with all of the decisions you need to make. Sometimes patients think that exploring a second opinion (SO) can help themselves to make a more informed decision about cancer treatment or can also introduce them to advanced treatment options. But what think Italian oncologists about SO?
Materials and methods: Our research want to investigate Italian Oncologists' perception of SO development and how they emotionally feel. We developed a questionnaire and asked to Italian Oncologists to fill-in. More than one answer was permitted to each question.

104 Italian oncologists answered. 67,3% males; mean age 48 years old. We analyzed data in four different groups: male < 50 years old (17,3%), male > 50 years old (50%), female < 50 years old (23,1%), female > 50 years old (9,6%).
Results: 97% of Italian Oncologists gave a SO.

Oncologists think that pts ask SO for the following reasons (see Tab 1).

Table 1.

Why patients ask Second opinion?	Male < 50 yrs	Male > 50 yrs	Female < 50 yrs	Female > 50 yrs
because of their emotional problems, such as fear and anxiety	66,7%	65,3%	75%	50%
because they are very critics and need reassurance	55,5%	50%	50%	50%
because they need more informations	27,8%	19,2%	16,7%	20%
because disease and treatment are very complicated	5,5%	32,7%	20,8%	40%
because the oncologist suggests a SO	5,5%	21,1%	37,5%	30%

Quite all Oncologists (88,5%) report to feel "quiet" when their pts ask a SO, and only 16,3% reported also negative feelings like disappointed, devalued and offended. Negative feeling were more frequently in the group of female > 50 yrs (40%).

Conclusions: SO is considered important in Italy, both by pts and oncologists. We think that is more useful a SO than consulting doctor Google considering the increasing problem of "fake news". We think that is also necessary a shared regulated management of SO between practitioners.

Our data suggest that a greater attention to emotional aspects of communication (especially regarding diagnosis, prognosis, treatments) is needed to improve relationship with our pts.

We suggest that it will be useful to think about ethical and clinical guidelines for SO.

S17

IMPACT OF BODY MASS INDEX AND BODY WEIGHT VARIATIONS ON SURVIVAL OUTCOME IN CANCER PATIENTS : EVIDENCE FROM A RETROSPECTIVE ANALYSIS

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Background: Obesity is one of the main risk factors for cancer development and it is associated with poor prognosis in multiple tumor type; therefore, body weight control rises as one of the primary recommendation for cancer prevention. However there are few studies focusing on the correlation between body weight variation (BWV) and outcome in cancer patients (pts).

The aim of this study was to evaluate the BMI and BWV as prognostic factor in gastrointestinal and breast cancer.

Patients and methods: We retrospectively analyzed 325 pts who underwent chemotherapy or endocrine therapy for gastroesophageal, colorectal and breast cancer between January 1991 and December 2011. The relationship between BMI (kg/m2), Δweight [(usual weight - current weight)/ usual weight]* 100 and clinical outcomes including overall, disease-free and progression-free survival was assessed. We performed survival analysis with a univariate analysis, carried out both on overall population and on tumor site subgroups. In addition, a multivariate analysis was performed to confirm the independent prognostic value of the statistically significant data.

Results: On overall population sex, smoke, ECOG PS, ?weight =5, BMI, tumor site and stage were associated with outcome ($p<0.05$) in the univariate analysis; the multivariate analysis proved phatological stage, ?weight and sex as independent prognostic factors for survival ($p<0.05$).

In subgroup comparison gastrointestinal (GI) cancer pts with ?weight = 5% showed a positive trend in OS, however not statistical significancy was found.

In breast cancer subgroup, instead, ?weight = 5% was associated with significant advantage in OS (p=0,008) in univariate analysis if the confounding factor, represented by long-term survival women, were excluded from the analysis. No significantly differences was observed in terms of toxicity.

Conclusions: Our data demonstrate that, during cancer treatment, strategies aimed to avoid weight gain or weight loss, compared to patient's weight at diagnosis, can provide an advantage in terms of survival in breast cancer pts. Meanwhile we could not document an evident association between BMI or BWV and disease outcome for GI cancer patients, probably due to the limited number of gastroesophageal tumors analyzed. In this regard our study suggests that future efforts should be directed to the application of a nutritional clinical screening to identify cancer pts who can benefit from a personalized nutritional program.

S18

A NOVEL ELECTRONIC TOOL TO IMPLEMENT PALLIATIVE SEDATION (PS) IN A DEPARTMENT OF ONCOLOGIC MEDICINE

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Background: Palliative sedation (PS) is a medical intervention aimed at relieving suffering in terminally ill cancer patients. Although specific guidelines exist, their application is challenging and varies greatly. We systematically collected relevant data concerning PS, including relatives' perception, in order to inform current practice patterns.

Methods: Electronic medical and nursing records of patients with advanced cancers undergoing PS at the Modena Cancer Centre between December 2016 and February 2018 were retrieved. Data regarding patient demographics, disease characteristics, PS details were collected and organized in items to create a personalized electronic PS record for each patient.

Results: A total of 259 deaths were recorded in our Department during the study period. Among them, 88 patients received PS. The median age was 67.6 years old; 71 (81%) patients had solid tumours, while 17 (19%) had hematologic cancers. At time of PS, 35 (39.8%) patients were receiving chemotherapy, 9 (10,2%) patients radiotherapy

and 44 (50%) patients best supportive care alone. Four patients (4.5%) overtly expressed their informed consent to PS. Most frequently treated refractory symptoms were: delirium/agitation (70.5%), dyspnea (34%), intractable pain (16%), and global suffering (4.5%). Midazolam was used in 78 (88.6%) patients and diazepam in 6 (10.4%) patients. Morphine was added to PS in 65 (74%) patients. The Delirium Palliative Prognostic score reported a 30-day survival probability < 30% in 46 (52%) patients, between 30% and 70 % in 31 (35%) patients, >70% in 3 (3.5%) patients. The average duration of PS was 70 hours (range 3-281 hours). Patient's relatives reported peacefulness in 44 (71%) cases, agitation in 10 (16%) cases and concern for suffering in 8 (13%) cases.

Conclusions: The electronic tool permits to have data that provide an auditing of PS practice, facilitate the cooperation among professionals and obtain the standardization of PS. The involvement of patients' family could lead to a more effective communication. We propose this as a user-friendly electronic tool to improve the quality of PS as well as the planning and coordination of end-of-life care in an inpatient setting.

S19

RELEVANCE OF THE CLINICAL RESEARCH COORDINATOR (CRC) IN CONDUCTING OBSERVATIONAL STUDIES

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Background: The increasing complexity of clinical research requires a dedicated multidisciplinary team to assure high quality to study procedures and to respect the timelines. We decided to investigate, for a retrospective observational study on patients with brain metastases for HER2 positive breast cancer and (HERBA Study) activated in 40 italian centers, if the presence of a clinical research coordinator (CRC) has impacted on some indicators: the median form submission to approval by local Ethic Committee (EC) and the probability of sending data at the coordinating center.

Method: Data of the Herba study were collected through the data base set up at the coordinating center. The following endpoints were elaborated: median time to study approval (Tapp) evaluated from submission to approval by local EC; probability of study approval (Papp) at 6 and at 12 months since the submission; and probability of data transmission (Psend) to the coordinating center at 12 months since submission. The achieved outcomes were compared between centers without CRCs (Group 1) and centers with CRCs (Group 2). The chi square test was used for comparison.

Results: Data from 40 centers were analyzed: 17 centers (42.5%) were classified into Group 1 and 23 centers (57.5%) into Group 2. Probability of study approval (Papp) at 12 months was 50.0% (n=20) with a median time to study approval (Tapp) of 6 months in the whole cohort; probability of study approval (Papp) was 17.6% (n=3) and 73.9% (n=17) for Group 1 and Group 2, respectively: this difference was statistically significant ($p<0.001$). Centers that get approval within 6 months were 17.6 % and 43.5 % for Group 1 and Group 2 respectively. Regarding the probability of data sending, the probability of data transmission (Psend) was significantly higher in Group 2 than Group 1 (47.8% vs 17.6%; p=0.048).

Conclusions: Albeit limited by the small sample size and by the inherently self-certified nature of the data, the present study suggests that CRCs are important for achieving quality, both in terms of speeding up the approval procedures and of success of data collection. Although others factors, such as the level of collaboration with physicians and administrative structures, may play a role in influencing the chosen indicators, we believe that our data support the hypothesis, already formulated by other Authors, that is now very difficult to conduct clinical trials without the support from a CRC.

S20

ONCOLOGY CLINICAL RESEARCH MANAGEMENT. TO EACH HIS OWN

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Background: The presence of the professional figure of the Clinical Research Coordinator (CRC) in most of the Italian cancer research centers is now a fact, as well as the evidence that this presence is pivotal in terms of speeding up the submission procedures, increase the potential of accrual and improve the qualitative and ethical standards of the study.

What is less clear, especially due to the lack of professional recognition and of an official learning process, is their specific job description, that often adapt to the specific demands of workplace or chief.

Methods: During the first quarter of 2018, the Gruppo Italiano Data Manager interviewed, through a web survey, 215 CRC. Respondents were asked to select from a list of activities, identified by a scientific committee composed of 7 CRC experts and divided by type of study management (as local site, profit or not profit studies, or as Sponsor for academic studies), which they actually perform.

Results: The majority of respondents work in a Hospital/University (60.0%) or in a Research Institute (35.9%). About activities performed as local site, the three activities that are most frequently performed by CRC are: data collection forms management (95.3%), study documents management (93.5%), interaction with pharma and contract research organization (91.2%) (Fig.1). Only a small portion (44.2%) supports the organization of internal training courses while a large portion carries out activities that should be performed by other professionals, as patient visits' booking (62.%), sample processing (50.2%), budgets and contracts review (46.5%). 83.3% of respondents also deals with academic trials sponsored by their structure. With regard to the individual activities, the most frequently performed is data collection (79.9%), followed by participation in the protocol writing (63.1%) and organization of study meetings (55.9%) (Fig.2). Less than a third is involved in the final paper production.

Conclusions: The road to the definition of an official description of the CRC work is still long, as evidenced by the lack of specific activities (also the one that should be the main one, data entry) carried out by all the interviewees. The lack of a specific job description, in addition to rowing against obtaining an institutional recognition, can cause a dangerous overlap of activities and responsibilities with other professional figures, such as research nurses and biologists.

S21

INTEGRATIVE MEDICINE IMPROVES THE QUALITY-OF-LIFE OF CANCER PATIENTS

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Background: The aim of Integrative Medicine is to treat patients in their entirety to enhance their physical and psychological wellbeing. In order to improve the Quality-of-life (QoL) in cancer patients, we started an Integrative Medicine service for patients from the main oncologic clinics in Genoa area.

Patients and Method: We conducted a single-arm study from January 2017 to April 2018 One-hundred-35 patients were enrolled, 37 males and 98 females. Average age was 58 years (from 31 to 92). The oncological diseases were: breast cancer 50, colorectal 14, ovarian 12, lung 6, pancreas 6, Lymphomas 27, Others 20.

Patients had two or more of the following:

1) extremely low frequency-electromagnetic fields, 2) acupuncture, 3) shiatsu, 4) psychological support, individual and group, 5) diet, 6) music therapy, 7) yoga

Patients no. = 135										
SF 36 area		start n=135	1st FU n=94	start/1st FU	2nd FU n=52	start/2nd FU	3rd FU n=38	start/3rd FU	4th FU n=22	start/4th FU
		median/area			med/a		med/a		med/a	
Physical activity	**AF**	**65**	**85**	$p < 0.0001$	**95**	$p < 0.0001$	**95**	$p < 0.0001$	**95**	$p = 0.0022$
Limitations to personal role due to problems of physical health	**LAF**	**0**	**50**	$p < 0.0001$	**100**	$p < 0.0001$	**100**	$p < 0.0001$	**100**	$p < 0.0001$
Physical pain	**DF**	**41**	**61**	$p < 0.0001$	**74**	$p < 0.0001$	**73**	$p < 0.0001$	**67**	$p = 0.0025$
General health	**SG**	**33**	**52**	$p < 0.0001$	**56**	$p < 0.0001$	**50**	$p = 0.0001$	**51**	$p = 0.0016$
Vitality	**V**	**35**	**55**	$p < 0.0001$	**60**	$p < 0.0001$	**65**	$p < 0.0001$	**65**	$p = 0.0002$
Social activity	**AS**	**37**	**75**	$p < 0.0001$	**87**	$p < 0.0001$	**87**	$p < 0.0001$	**94**	$p < 0.0001$
Limitations to personal role due to emotional problems	**LAE**	**0**	**66**	$p < 0.0001$	**100**	$p < 0.0001$	**100**	$p < 0.0001$	**100**	$p < 0.0001$
Mental Health	**SM**	**55**	**72**	$p < 0.0001$	**80**	$p < 0.0001$	**80**	$p < 0.0001$	**84**	$p < 0.0001$
Areas with reductions > 10 points relative to the normative group		**5**	**1**	**$p < 0.0001$**	**0**	**$p < 0.0001$**	0	**$p < 0.0001$**	0	**$p < 0.0001$**

FU = follow-up.
Statistical tests: Student's t-distribution.

Results: Health-related QoL was assessed using the SF36 questionnaire at the start of treatments and every 2-4 months. The table shows the medians obtained for every SF 36 areas. Scores were compared with normative group for age and gender in trh database of the Istituto Mario Negri. Last line shows the median number of areas with at least 10 points below the normative group (1 SD)
Conclusion: These results showed an impressive improvement of QoL in the patients treated with Integrative Medicine. Integrative Medicine means seeing the cancer patients with two eyes: one focusing on the results of oncologic therapies, and the other focused on increasing the physical and emotional wellbeing of the same patients.

S22

THE MULTIDISCIPLINARY APPROACH: THE INSTRUMENT TO IMPROVE THE SAFETY OF PHARMACOLOGICAL THERAPY

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Background: The oncology field is in continuous development, above all from the pharmacological point of view. In order to make pharmacological treatments as safe as possible, therefore with the best balance between efficacy and adverse effects, it is necessary to monitor them over time and especially in different patients. The collaboration between different professional figures is essential.
Material (patients) and methods: To monitor the safety of the therapies the hospital pharmacist (PH) periodically attended the oncology department and analyzed drug prescriptions using databases as Terap, Micromedex, Stabilis and Epocrates to search for possible drug interactions or incompatibilities. The PH used an operational decision-making model for the management of drug therapies. The data was recorded into an Excel© database and processed using the IBM SPSS23© program. The Shapiro-Wilk test was used to evaluate the sample distribution and the non-parametric Mann-Whitney test to analyze sample means, accepting a value of $p < 0.05$ as significant.
Results: Of 454 patients hospitalized in the department of oncology of University-Hospital of Udine and observed from 14 July 2015 until 18 April 2017, 53% were males and 47% females. The median age was 65 years for males and 63 years for females. Together with physicians and nurses the PH attended to 819 visits to patients, including more than one for the same patient. During hospitalization every patient received an average of 7 drugs per day. In addition to the visits the PH provided 202 consultations.. 328 significant interactions were detected leading to an intervention in 287 cases (87.5%); intervention consisted either in monitoring or modifying daily therapy. Monitoring included a periodic evaluation of the ECG or of a possible adverse drug reaction (e.g. neurological toxicity from ifosfamide, opioid overdose or excessive benzodiazepine sedation). Modifications included change of dosage, suspension, introduction or replacement of a drug.
Conclusions: From a pharmacological point of view limits of the oncology area are the treatment of patients day by day following more than one symptom and the attribution of a causal relationship between pharmacological treatment and side effects. Despite of this a multidisciplinary approach with a team including PH, physicians and nurses determined more appropriate prescriptions and improved safety for the patients.

S23

COMPLEMENTARY AND ALTERNATIVE MEDICINE IN ONCOLOGY (CAM): PERCEPTION AND OPINIONS OF HEALTH PROFESSIONALS OF AN ITALIAN ACADEMIC HOSPITAL

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Background: Patients with cancer show interest in CAM and often use it without sharing their opinion with the oncologist. On the other hand, clinicians and other health professionals often do not ask patients about the use of CAM. The exact size of the phenomenon (i.e. perception and use of CAM) is not known. We conducted a survey in an Italian academic hospital to better understand health care workers' perception and opinions about CAM.
Methods: From June to December 2017 a survey was presented among the employees of the Academic Hospital of Udine using the web-based platform Survey Monkey. The questionnaire included demographic data, interest in CAM and knowledge about it, and statements for which respondents were asked to express a level of agreement. Participation was voluntary and anonymous.
Result: Overall, 1008 employees (about 20% of the total) completed the survey, 773 females (76.7%) and 235 males (23.3%). Median age was 47 years. A total of 52% of

respondents declared they were interested in CAM before the survey; 62 respondents (7.5%) said that they would propose an alternative treatment to cancer patients, while 212 (25.7%) would propose a complementary treatment. Notably, 547 respondents (54.3%) agreed with the statement: "Alternative therapies could be dangerous and their side effects not known". Females and nurses seemed to be more in favor of CAM than males and physicians, especially regarding the following statements: "CAM can help quality of live even if they are not as effective as traditional therapies" ($p<0.0001$), "Even if probably ineffective, alternative therapies are not harmful" ($p<0.0001$).

Conclusions: Healthcare providers face with cancer patients who would need information about CAM or use it. Therefore, they could have a crucial role in promoting appropriate use of CAM (i.e. evidence-based complementary medicine) and discouraging inappropriate use of alternative medicine. The present study offers first insights to implement educational campaigns on CAM for both patients and health professionals.

S24

AN INTEGRATED MODEL OF MANAGEMENT OF ONCO-HAEMATOLOGIC PATIENTS: THE EXPERIENCE OF SANT'ANDREA HOSPITAL-SAPIENZA UNIVERSITY OF ROME WITHIN A UNIT OF SIMULTANEOUS CARE

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Background: Recent evidences have shown that patients receiving supportive care by a dedicated team, improve the quality of life (QoL) and, sometimes, survival. In January 2017, a Simultaneous Care Unit (SCU) was opened at Sant'andrea Hospital of Rome. The aim was to improve QoL by reducing cancer and therapy related symptoms and to respect the time to treatment.

Patients and Methods: from January 2017 to March 2018, 320 patients with symptoms related to treatment toxicities or disease progression, were admitted to SCU. Male/female ratio was 1.3, performance status was 0-3 according to ECOG, median age was 69 (range 20-96). The majority of patients (98%) presented a metastatic or locally advanced disease and were receiving a disesase oriented treatment. The reported main symptoms were pain (38%) and fatigue (17.8%). Symptom assessment was routinely carried out by Edmonton Symptom Assesment scale and Numerical Rating Scale (NRS).

Results: the 320 patients were admitted in the SCU for a total of 3000 outpatient access. At time zero, 223 patients had PS 0/1 and 97 patients had PS 2/3. At one month follow-up we observed an improvement of PS in 60%, a stability in 32% and a worsening in 8%. Of the 122 patients with pain 65 (53%) have achieved a significant reduction of pain (>40% NRS - pain scale), while 30 (25%) a reduction < 40% of the value NRS and 27 patients a stability of pain (22%). A total of 110 patients (34.4%) received specific supportive intravenous therapy and 23 patients (7.2%) bisphosphonates for the prevention of skeletal related events. 35 patients (11%) received transfusion support of hemoderivates (red blood cell and platelets), 8 (2,5%) patients underwent interventional procedures as a paracentesis. Only 19 (6%) patients required hospitalization: 8 (2.5%) patients were refered to the emergency room for intensive care and 20 (6.25%) patients required connection of the hospital with the territorial palliative care services (hospice or home-care).

Conclusions: we confirm that the interventions delivered by a dedicated and indipendent SCU can alleviate physical and psycological morbidity and enhance adherence to the anticancer treatments. Moreover, it reduces the improper access in the emergency settings and the nosocomial infections. We also would like to underline that the significative reduction of hospitalization costs have an important implication for the national health system.

S25

AIFA MINIMUM REQUIREMENTS FOR PHASE I TRIALS CONDUCTION. IS SELF-CERTIFICATION A WORTHY WAY?

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Background: In Jul 2015 the Agenzia Italiana Del Farmaco (AIFA) has issued a new law that established the minimum requirements for clinical structures to perform phase I studies. The intent was the selection of clinical centers and laboratories that were really able to guarantee the high standard required by early phase trials.

This new rules expected that Centers communicated the possession of requirements through a self-certification and that, in case of loss even of only one of the requirements, the legal representative of the structure provided immediate communication of this. The AIFA regulation requires the verification of the self-certifications through appropriate inspections.

We decided to analyze the self-certification of centers and laboratories over time and the outcome of AIFA inspection

Methods: Our analysis was conducted reviewing 11 lists of self-certified structures, published by AIFA between 05 may 2016 and 29 mar 2018.
Results: The first self certification was sent on 08 Apr 2016, three days only after the first applicable date, and covered both centre and laboratory.

Within the first month 13 self certified structures were counted, for a total of 8 centers and 10 laboratories, while in the second month the total were 27 (19 centers,13 laboratories). After about one year self certified structures increased to 88 (54 centers, 49 laboratories) until they becomes 108 (64 centers, 63 laboratories) in the last available report (29 mar 18).

One structure temporary withdraw the self-certification due to loss of requirements (lasting one month) while from Mar 2018 6 structures (3 centers and 4 laboratories), initially self-certified, no longer appear on the lists following AIFA inspection. Two of these facilities submitted self-certification for conducting Phase I studies not only on patients but also on healthy volunteers.
Conclusions: The aim of AIFA determination was to guarantee the conduction of phase I trials only in high qualified centers and in the first period we have witnessed a "race for certification". Our analysis highlights the effort of the Italian clinical centers and laboratories to be able to carry phase I trials however the decreased number of certified structures in the last year, following AIFA inspection, reflect that some requirements were not fully met and were under estimated.

More conclusion will be drawn by the release, not yet happened, of the AIFA inspection results.

S26

COST OF CLINICAL ONCOLOGY AND OUTCOME IN CLINICAL PRACTICE. AN OUTCOME ANALYSIS

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Background: To assess the trend of the costs of Oncology and their relationship with the main outcome of clinical practice.
Methods: The trend of the costs of clinical oncology (CCO) from 2011 to 2017 was assessed in 9 homogenous districts. Likewise, a relationship between the median per-inhabitant costs (PICCO) in any district and the 2013 tumor-related mortality (TRM) in the same district was analyzed. Likewise, 4 areas were identified on the basis of the median costs (MC) and the median-TRM [(PICCO and TRM<MC and median-TRM)=α, (PICCO<MC and TRM>median-TRM=β), (PICCO>MC and TRM>median-TRM=γ), (PICCO>MC and TRM<median-TRM=δ), and the distribution of the 9 district in the 4 areas was analyzed. A comparison of the PICCO in any district were performed using the Friedman non parametric test, and the relationship between PICCO and TRM was assessed using the Spearman non parametric test. An α error of 5% was assumed as index of statistical significance.
Results: The total population of the 9 homogeneous districts was 4,457,318 inhabitants. Between 2011 and 2017 a significant increase of PICCO was observed in all the 9 districts, with a median increase of 88.8% (range 71.5%-103.8%), ($p<0.01$). No significant relationship was observed between PICCO and median-TRM (Rho=-0.6, p=0.08), with a different distribution of the 9 districts in the 4 areas, as detailed in the table.

DISTRICT	PICCO	TRM	AREA
A	22.8	334.7	β
B	30	321.4	β
C	38.1	298	δ
D	32.4	307.5	α
E	33.9	307.3	γ
F	27.7	320.3	β
G	41.1	305.1	δ
H	23.3	304.2	α
I	33.6	301.9	δ

Conclusions: In the recent years the CCO are dramatically increased, and this kind of increase actually represents a problem for all the Healthcare Systems. In our experience we observe a significant increase of CCO in the 9 districts ranging from 71.1% and 103.4% in 7 years, that is coherent with what is reported in literature and justifies the difficulties in its sustainability. Likewise, although no significant relationship has been detected between PICCO and median-TRM, an indirect trend can be hypothesized, and although no major differences can be detected between the different districts, their different distribution in the 4 areas merits further analysis of clinical governance.

S27

OXYGEN-OZONE THERAPY AS SUPPORT THERAPY IN CANCER PATIENTS WITH FATIGUE: PRELIMINARY RESULTS IN 36 PATIENTS

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Ozone, a gas discovered in the mid-nineteenth century, is a molecule consisting of three atoms of and has a capacity to oxidize organic compounds and has well-known toxic effects on the respiratory tract when present in smog. It is administered in precise therapeutic doses, and advocates that it has excellent health benefits in many diseases.

The National Comprehensive Cancer Network describes fatigue as a universal symptom present at different levels in all subjects with cancer undergoing chemotherapy, radiotherapy, bone marrow transplantation. Within the Tumor Center, CFS, Fibromyalgia and Oxygen Ozone Therapy Unit, MEDE Clinic, Sacile, Pordenone (Italy), we decided to undertake a study with the aim to evaluate the efficacy of oxygen-ozone therapy on cancer patients with fatigue, either during cancer therapy or after cancer therapy or in a palliative setting. This work was performed in compliance with the ethical values laid down by the Declaration of Helsinki, and informed consent documentation was reviewed and agreed by the independent ethics committee at the MEDE Clinic.

From February 2016 to December 2017 we have included in the study 36 patients with cancer and fatigue, 10 with breast cancer, 7 with lung cancer, 7 with colon cancer, 5 with renal cancer, 3 with prostate cancer, 2 with melanoma and 2 hepatocellular carcinoma. Among the 36 patients treated, 10 were during neoplastic therapy, 10 had already finished the cancer therapy and 16 were in a palliative setting. To assess the extent of fatigue in patients with cancer we used the Fatigue Severity Scale, which is used to estimate the severity of the symptom with a score from 1 to 7. Patients were treated with auto hemo transfusion (GAE) according to the SIOOT (Scientific Society of Oxygen Ozone Therapy) protocols, twice a week for one month and twice a month as maintenance therapy. No side effects have been found, while 26 patients (72%) achieved a significant improvement (>50% of the symptoms) of fatigue during therapy, or after therapy was finished, or in a palliative setting. Due to the short period of follow up, we did not yet evaluate the duration of response obtained.

In conclusion, at our knowledge, this is the largest study of patients with cancer treated with ozone therapy reported in the literature. Oxygen-ozone therapy seems a valid supportive therapy for fatigue in patients with cancer, without any significant side effects.

S28

THE ROLE OF DIFFERENT FENTANYL ADMINISTRATION: ORAL TRANSMUCOSAL FENTANYL CITRATE (OTFC), FENTANYL BUCCAL TABLET (FBT), AND FENTANYL PECTIN NASAL SPRAY (FNPS) IN BREAKTHROUGH CANCER PAIN (BTCP) TREATMENT

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Background: Breakthrough cancer pain (BTcP) should not be underestimated since untreated pain has important consequences on patient's quality of life and on concomitant treatments efficacy. Fentanyl represents the main therapeutic choice for BTcP, however different site of administration are available. Oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT), and fentanyl pectin nasal spray (FNPS) were evaluated in this study.

Material and Methods: We includes 101 consecutive patients from 2013 to 2017. Eligibility criteria included patients ⩾18 years, histological or cytological diagnosis of cancer, with at least one episode of BTCP per day. The pain intensity was recorded before and after therapy with validated Numeric Rating Scale (NRS). After the initial screening visit, performed at first episode of BTcP, the patients were stratified based on treatment prescribed for BTcP (ARM A:OTFC, ARM B:FBT, and ARM C:FPNS). Difference in NRS (D-NRS) calculated before (NRS1) and 30 minutes after treatment (NRS2) was used to evaluated response to treatment.

Results: A Linear correlation between drugs used and site of primitive tumor was found: FTB was used predominantly in gastrointestinal cancer followed by urogenital and lung cancer, while OCTF in lung and gastrointestinal cancer, FNPS in head-neck cancer (P=0.0001). Considering each ARM we detected a significant relation between NRS1 and ECOG performance status: worse ECOG have higher NRS1 (P=0.006). D-NRS was not significant related to type of fentanyl used (p=0.16). Lower dose was related to lower response on D-NRS in patients treated with OTCF and FNPS (P=0.04 and P=0.011, respectively). A significant correlation was found between type of used drugs and toxicity (P=0.001). We did not found a correlation between dose drug and toxicity (P=0.89), as well as between the used dose and grade 0-1 or 2-3 of toxicity (P=0.92).

Conclusions: The role of BTcP in the management of cancer patients is well known and the choice of the drug depends on physician experience and patients' needs. Our study aimed to identify clinical parameters to drive the therapeutic choice in BTcP treatment. Primitive tumor, basal pain at BTcP, and ECOG performance status should be evaluated in order to choose the most appropriate and effective treatment. Furthermore, toxicity was not influenced by the dose of Fentanyl formulation, but the different site of administration should be considered to prevent side effects.

S29

THE ROLE OF GERIATRIC SCREENING TOOL (G8) IN PREDICTING SIDE EFFECTS IN ELDERLY PATIENTS, DURING THERAPY WITH AROMATASE INHIBITOR

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Background : Endocrine therapy is the main treatment in women affected with ormonosensitive breast cancer; the main side effects of this treatment are arthralgia, ostheoporosys, depression, dyslipidemia, hypertension. G8 is a simple test developed to identify elderly patients undergoing chemotherapy who could benefit from a comprehensive geriatric assessment (CGA). Little is known about its prognostic value and no scientific evidence exists about its role in predicting side effects from other oncologic treatments. The aim of this study is to evaluate the possible role of G8 in predicting side effects from treatment with aromatase inhibitor in women > 65 years old.

Matherial and method : Women aged > 65 years old affected by breast cancer about to start an endocrine therapy with aromatase inhibitor in adjuvant setting were tested. G8 was performed in the day of activation of the treatment. Patients were classified according to the standard G8 evaluation as "fit" with G8 score > 14 or "vulnerable" with G8 score < 14, then started treatment and clinical-instrumental follow-up according to the national guidelines; all the side effects were recorded at every clinical visit.

Results : From April 2016 to February 2018, 50 consecutive patients were screened with G8 test. Median age was 75.1 (range 65-86). G8 identified 30 patients (60%) as "fit" (score > 14) and 20 (40%) as "vulnerable" (score < 14). The grade of concordance between G8 score and the appearance/absence of adverse events were statistically significative (41/50 patients, 82%, p = 0.0002); sensitivity resulted in 78% and specificity was 81%; positive predictive value was 70% and negative predictive value was 87%. The most frequent adverse event was arthromyalgia (60% of patients vulnerable);

Conclusion : In our experience G8 screening tool has a potential role in predicting side effects during a treatment with aromatase inhibitor. Due to his simplicity and speed of execution, G8 could be very useful in everyday clinical practice. A prospective study with a larger number of patients is needed to better define its role.

DATA MANAGEMENT BY SCIENTIFIC SERVICE I.T.M.O. (ITALIAN TRIALS IN MEDICAL ONCOLOGY)

S30

FOUR-YEAR OBSERVATIONAL STUDY ON CANCER PATIENTS WHO GO TO THE EMERGENCY ROOM OF THE LOCAL HOSPITAL

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Background: The aim of this study is to highlight through the access of the oncologic patients to the emergency room of the local hospital the health and socio-assistance criticalities present in the territory that affect this category of patients and to identify potential solutions to mitigate the level

Patients and methods: For this purpose, during the period of 4 years 2014-2017, we examined the total number of patients arriving in the Emergency Room, including the number of cancer patients, distributed by age and sex, the number of oncologic patients given to their home, those hospitalized, the reasons for the hospitalization .

Results:

Total access numbers (2014-2017)	**127.022**	Pts who voluntarily left the emergency room	**13**
Total of oncologic patients(pts)	**405**	Patients who died	**2**
Total of oncologic patients resigned at home	**43**	Pts hospitalized in other departments	**61**
Total of pts oncologic sent in hospice	**14**	Pts hospitalized in to oncology:	**250**
Pts who refused hospitalization	**23**	males: **187** females:**124**	

Reasons for the hospitalization:

Dyspnea	**42**	Pleural effusion ascites	**38**	Jaundice	**15**
Neurological symptoms	**41**	Fever	**32**	Heart problems	**7**
Pain	**40**	Cachexia	**29**	Other	**6**
Blood dyscrasias	**38**	Intestinal disorder	**23**		

Distribution by age groups/ Number of patients

<50	**16**	71-80	**88**
51–60	**20**	81-85	**35**
61–70	**118**	>86	**14**

Conclusions:
Our survey shows:

1. The Admission of oncologic pts to emergency care continues to be a health problem. Pts with potentially manageable home illness access the emergency room: therefore need to provide adequate information to patients about the different health options (hospital, territory, home care, hospice).
2. Increase efforts for better therapeutic continuity: is essential to articulate the care articulate the care program on several levels of care
3. A system model developed around the person tends to involve more lenders (non sectoral assistance, but global and integrated), in which the hospital has a defined and non-exclusive role
4. Improve at home of the pts treatment procedures against pain, which represents > 10% of admissions to the emergency room.

S31

FIRST RESULTS OF CORE-IMMUNO STUDY: CORRELATION, IN A REAL-WORLD SETTING, BETWEEN CLINICAL-DISEASE CHARACTERISTICS AND COMPLIANCE WITH IMMUNOTHERAPY IN SOLID METASTATIC TUMORS

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Background: Monotherapy with Nivolumab, Pembrolizumab and Ipilimumab has shown survival benefits in patients (pts) with melanoma, kidney, lung and head-neck cancer. The aim of this study is to evaluate safety and treatment compliance in terms of delays in the administration or withdrawal of drugs due to toxicity, according to disease and the clinical characteristics of pts in routine clinical practice
Patients and Methods: In this retrospective study, data was evaluated on pts in the Reggio Emilia Provincial Oncology Network who were treated for solid metastatic tumors with monotherapy using Nivolumab, Pembrolizumab and Ipilimumab in clinical practice. The pts included in the study had received at least 1 dose of immunotherapy by December 2017 and were monitored for adverse events (AE) using Common Terminology Criteria for Adverse Events v.4.1
Results: A total of 92 pts were analyzed, of which 42 with lung cancer, 35 with melanoma, 12 with kidney cancer and 3 with head-neck cancer. Seventy-five pts (71%) were treated with Nivolumab, 17% with Pembrolizumab and 12% with Ipilimumab. Overall, 36 pts (39%) experienced an immunorelated adverse event (iAE) of some degree; 33/92 pts (36%) presented a G1-2 iAEs, while only 7% had a G3-4. Out of the 92 pts, the immunotherapy of 17% was delayed due to toxicity, but only 5% of pts discontinued treatment due to iAEs. No statistically significant differences in PFS (9.5 vs. 5.9 months, p=0.12) and OS (21.9 vs. 12.2 months, p=0.15) were found between pts who experienced iAEs and those who did not. The median duration of toxicity and time of toxicity onset were respectively 2,6 and 2,9 months. Cox regression was performed for PFS and OS using sex, performance status (PS), comorbidities, presence of brain metastases, number of previous lines of therapy, number of metastatic sites and age as covariates. For both, only PS (1-2) significantly correlates with poor PFS and OS with respect to PS 0 ($p<0.001$)
Conclusions: The data supports the use of immunotherapy in pts treated in clinical practice for different solid tumors. In particular, such treatments are suitable for elderly pts with multiple comorbidities, pts with brain metastases and heavily pretreated pts. However, the use of these drugs should be evaluated with caution in pts with poor PS

S32

EFFECTIVENESS OF GROUP INTERVENTION ON RARE TUMOR PATIENTS' WELL-BEING

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Background: Patients affected by rare tumors (< 6/100000) are called to significant challenges, not only adopting healthy lifestyles to improve treatment effectiveness but also managing intimate relationships. Literature highlighted that benefits derived from social support, especially caregivers such as partners or parents, help to increase psychological well-being and Quality of Life in chronic disease generally through the perception of not being alone. Low incidence solid cancers were choosen for their specific psychological characteristics and the low

number of research in this field. The present contribution aims at (1) evaluating effectiveness of a group intervention on the patients' well-being, and (2) taking over the impact of the group intervention on the bond between patients and caregivers, in terms of intensity and adaptability.

Material and methods: Twenty-three patients affected by rare tumor meeting inclusion criteria and related caregivers were included. All subjects (patients and caregivers) filled out four questionnaires (Big Five Inventory - BFQ, Beck Depression Inventory - BDI, Mini Mental Adjustment to Cancer – MINI-MAC and Life Orientation Test Revised – LOT-R) and the Inclusion of the other in the self-scale – IOS, in pre, post treatment and follow-up phases and participated to group intervention during 6 months. Descriptive statistical analysis through a paired test t and a Pearson correlation test r were conducted.

Results: Regarding patients, BDI has an initial increase in post treatment (from 6.9 to 7.29), and return on 6.7 value in the follow up, LOT-R decreases in post treatment (from 19.9 to 18) and increase a lot in follow-up (32.4), while MINI-MAC reveals anxiety in all phases. Despair and Fatalism are coping's strategies used equally, while Combativeness and Avoidance are less utilized. Correlation' study shows significant results between BDI and MINI-MAC ($r=0,59$, $p<0,01$), and MINI-MAC and LOT-R ($r= -0,57$, $p<0,01$) in pre-treatment and between MINI-MAC e LOT-R ($r=0,51$, $p<0,05$) in post-treatment, only for patients. IOS reveals that partner is chosen like main caregivers and the illness is put in the intersection of the circles.

Conclusions: Confirming literature, our results suggest benefits on patients' Quality of Life and the relevance of intimate relationships obtained by clinical group treatment is verified.

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S33

SAFETY OF IMMUNOTHERAPY IN ELDERLY PATIENTS: A RETROSPECTIVE ANALYSIS OF A PHASE I UNIT

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Background: Cancer immunotherapy has been used in patients over 70 years old with controversial results. Several age-associated changes including the dysregulation of the immune system could be involved.12 The main goal of our study is to retrospectively investigate the safety of immunotherapy in elderly patients enrolled in early phase studies regardless tumor type.

Materials and methods: We retrospectively reviewed all cases of patients =70 years old enrolled in early phase trials with different immunotherapeutics between January 2016 and March 2018. Eligible patients have received at least one cycle of single agent or a combination of first and/or second generation immune-modulating drugs. The primary aim of the study was to evaluate the safety of such an approach in the elderly population. Toxicity has been graded using the NCI CTCAE v 4.0. Secondary objective was disease control rate (DCR). Fisher test was used to perform the comparison analysis.

Results: We identified 29 patients, of those 21 were eligible and 8 were screening failures. Patients included in the analysis had an ECOG performance status 0-1. Twelve patients were treated with combo regimens (including a backbone of an anti-PD1 in combination with a new generation immune-checkpoint inhibitor) and 9 with monotherapy. Only 2 patients, one treated with combo and one with monotherapy, experienced a grade 3 immuno-related toxicity leading to treatment discontinuation: an autoimmune thyroiditis in one case and an autoimmune hepatitis, histologically proved, in the other one. The most common adverse event (AE) was G1-G2 fatigue that occurred in 33% of patients. Immuno-related AEs of any grade were observed in 22% of patients treated with monotherapy compared to 33% in the combo group. Three out of 9 patients treated with monotherapy had a partial response or a stable disease with a DCR of 33%, whereas in the combo group the observed DCR was 66%. Differences were not statistically significant between the two groups for neither toxicity nor efficacy (p value 0.65 and 0.19, respectively). No complete response was observed.

Conclusions: Our results suggest that immunotherapy is an effective and well tolerated treatment for older patients with solid tumors.

S34

RARE TUMORS: AN ANALYSIS OF CLINICAL PATHWAYS FOR PATIENTS RESIDENT IN REGIONE LIGURIA

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Background: Data Regarding Rare Tumors (RT) patients (pts) are of interest in the actual context, considering the implementation of specific Networks of care (see the regulations of the Italian Ministry of Health, Gazzetta Ufficiale 16.1.2018). In this work, we describe the admissions and hospitalizations of RT pts, in order to obtain information useful for organizing a network of care.

Methods: The Databases of the Hospital Discharge Data (ICD-9-CM) have been explored to identify RTs included in the list published by the Ministry of Health, i.e. RT of the skin, Thoracic RT, Genitourinary RT, Gynecological RT, Digestive RT, Endocrine RT, Sarcomas CNS RT, Head&Neck RT, Hematological RT, Pediatric Tumors. Cases for which the RT could not be individuated by the ICD-9-CM system (eg neuroendocrine tumors) have not been considered. The study has regarded all the residents of Regione Liguria and their hospitalization in any hospital of National Health System. Data obtained from administrative databases will be collected anonymously; a unique patient identifier was used to track each RT patient throughout multiple admissions.
Results: 20985 records with a diagnosis of RT (solid RT or Hematological RT of adults pts) have been retrieved for the period 2010-2016. Each subfamily includes RT with very different incidence, and for some of the RT list (sarcomas, anal cancer, thymic cancer) the records retrieved are $<$50/year. Hospitalizations outside the Region Liguria occur from 13-14% in the majority of the subfamilies to 34% in the case of sarcomas. The regional Hospital and Tumor Inst. (Policlinico San Martino) is the most frequent place of hospitalization for each subfamily ($>$80% of hematological RT, 17% of sarcomas, 20-30% of other subfamilies); however, the number of hospitals involved in the hospitalizations was impressively high (mean 52; range 40-90). Only for sarcomas the admissions seem to concentrate in specific institutions (Univesrity Hospitals, Tumor Institutes). Interestingly, all over the period considered the incidence of admission for malignant mesothelioma has decreased (618 in 2011 to 418 in 2016).
Conclusions: Our results clearly show that the clinical pathways of RT pts are highly heterogeneous and, with the exception of hematological RT and sarcomas, tend to scatter in many different hospitals. These data may be useful for building the Rare Tumors Networks.

S35

INCIDENCE AND SEX RELATED DIFFERENCES OF DISTRESS AMONG CANCER PATIENTS

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Background: Studies indicate a worse prognosis in cancer patients with elevated distress and fatigue. The NCCN guidelines recommend all cancer patients undergo assessment of distress and fatigue. We studied the frequency and level of distress and fatigue in a consecutive population of cancer patients in our outpatient Institution.

Table. Estimated mean distress (95%CI).

	Time		
	0	12	24
F	5.28 (4.84, 5.71)	5.51 (4.89, 6.13)	4.07 (2.74, 5.40)
M	4.32 (3.72, 4.93)	4.88 (4.00, 5.76)	7.23 (4.93, 9.52)

Patients and methods: Patients attending our outpatient clinic were invited to undergo a psychological interview before the medical visit. Distress was assessed by the Distress thermometer and fatigue by the ESAS scale. Patients underwent follow up visits to assess distress and fatigue during time.
Results: Between March 1, 2016 and March 31, 2018, 248 patients were analyzed for distress and fatigue by a psycho-oncologist. Mean age was 64.5$\pm$12.3 years, 66% were women, 75% had a secondary school diploma, 71% were married, 48% had retired and 21% were employed. One third had breast cancer, another third had GU or GYN cancer and 15% had CRC. 51% underwent adjuvant treatment, 37% had advanced disease and 38% was under active treatment. At baseline, women had an higher frequency of elevated distress compared with men (25% vs 10%, p=0.006). Age was inversely related to distress (p=0.022). No other subject and tumor characteristics were associated with distress. During follow-up, there was a significant interaction (p=0.007) between time and gender in that women had a tendency to decreased distress levels whereas men had an opposite behavior (table).

The risk of a higher distress was significantly associated with difficult relationships with children and a variety of emotional factors, including depression, anxiety, fear, worry, grief, anguish, sadness, loss of interest. Moreover, distress was significantly associated with symptoms such as nausea, insomnia, pain, fatigue, dyspnea, loss of appetite, dyspepsia, dysuria and sexual problems. Fatigue showed the same pattern with a decrease in women and an increase in men during time (p interaction=0.027).
Conclusions: Our findings show a high incidence of distress and fatigue in a general cancer population. Women and younger patients are at increased risk. However, women tend to recover during follow-up whereas men tend to worsen, suggesting different gender related coping capabilities. Specific interventions addressing these issues are warranted.

S36

THE SEXSUAL-AFFECTIVE DIMENSION OF LONGTERM ELDERLY MALES CANCER PATIENTS

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Backgroung: Clinical research have given attention to the sexual disorders of female and young patients. Little is know instead of the sexual-affective dimension in elderly males longterm cancer patients.
Material and methods: this is a monocentric and monophasic study; 30 longterm elderly patients with different primivitivities were interviewed. The questionnaire administered were the IOQ and another that evacuate the personal and clinical data collection and the sexual-affective patients dimension.
Results: 17 men and 13 women were recruited. Averege age 68.06 (62-87); the average spent time from diagnosis exceeds 10 years (range 5-26). The 66.6% were married. The 56.6 % of respondents claimed that the disease has changed the intimacy with the partner (item 25 IOQ); 43.4% reported a significant decrease in sex desire, after the cancer diagnosis (item 4 QI) and 50% reported no sexual activity (item 3 QI). None of them searched for a medical supportive treatment (item 6 QI) and only 10% received psychological counseling (item 10 QI).
Conslusions: The results suggest that elderly males cancer patients, as the female and yonger patients, have a sexual-affective dimension that is compromised, even after years from diagnosis, by disease and its treatment. At the same time they highlight the oncologist lack of attention to this need.

S37

CAN SYSTEMIC THERAPY INCREASE THE TOXICITY AND RATE OF RADIONECROSIS IN STEREOTACTIC RADIOSURGERY FOR BRAIN METASTASES?

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Introduction: Stereotactic Radiosurgery (SRS) is an effective treatment for brain metastases (BM) and may be generally safe. The relative risk of toxicity in patients treated with combination target therapy/immunotherapy and SRS has not been well-defined.
Methods and Materials: We analyzed all patients treated between 2010 and 2017 at our institution with SRS for BMs with or without concurrent systemic therapy. We evaluated in this cohort of patients the haematological and neurological toxicity, brain progression free survival and overall survival, stratifiyng patients for yes / no systemic therapy and type of systemic therapy.
Results: Data on 45 patients were obtained. Median age at diagnosis of BM was 66 years (range, 37-90 yrs). At the time of initial presentation of BMs, the majority of patients had ECOG perfomance status of 0-2. The most common primary tumors were lung, breast, melanoma and kidney. Sixty percent of SRS treatments were delivered concurrently with systemic therapy, of which 56% were with conventional chemotherapy and 44% with targeted and immunotherapy agents. Patients were divided in two groups: SRS alone and SRS/systemic therapy. No differences between the two groups of patients in terms of clinical and treatments characteristics were found. Median follow up was 10 months (range, 1-65 months) from the time of SRS. Myelosuppression was minimal after treatment, with 9% grade 2-4 toxicity; grade $>$ 2neurological symptoms were reported in 11% of patients, with one grade 5 neurological toxicity. Histologically confirmed radionecrosis was reported in 2 patients (one in SRS alone and one in SRS-systemic therapy group) and radiologically suspected radionecrosis in 2 patients both in the group of concurrent therapy (one with chemotherapy and one with target therapy). No difference in haematological ($p=0.79$) and neurological ($p=0.96$). Median brain PFS was 12.1 months, without any significant difference between the two group ($p=0.49$). To date 29 patients have died, of which 3 for brain progression, 13 for systemic progression and two for both systemic and brain progression. Nine patients were died for no tumor related causes and 2 patients for unknown causes. Median overall survival for entire group was 8.13 months without any difference between the two group of patients. ($p=0.369$).
Conclusions: Systemic therapy can be safely given concurrently with SRS for BMs without increase of neurological toxicity and radionecrosis risk.

S38

SECONDARY EFFECTS ANALYSIS OF THE NEW IMMUNOTHERAPEUTIC AGENTS USED IN ONCOLOGY

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Background: The approval of anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death protein 1 (PD-1) antibodies resulted in significant improvements in disease outcomes for various cancers. PD-1 and CTLA-4 limit immune activation in physiological conditions and prevent autoimmunity, therefore inhibition of these receptors is associated with a wide range of autoimmune side effects. Interestingly, certain treatment-related auto-immune reactions have been shown to correlate with better prognosis suggesting a correlation between auto-immunity and anti-tumor immune responses. We conducted a retrospective analysis to

explore this relation in an agnostic of cancer site population treated with checkpoint inhibitors.

Patients and methods: We conducted a retrospective analysis of patients with metastatic melanoma (MM), non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC) treated from September 2014 to February 2018 at our Institution (Fondazione Policlinico Universitario "A. Gemelli" - IRCCS) and exposed for the first time (in first or subsequent lines) to monotherapy with checkpoint inhibitor (Ipilimumab or Nivolumab or Pembrolizumab). The aim was to correlate the auto-immune adverse events (AE) with progression free survival (PFS). A multivariate analysis was performed with prognostic factor which could limit this unconventional analysis (line of therapy: 1 vs >1, gender: male vs female, cancer site: melanoma vs non melanoma, immune therapy: anti-PD-1 vs anti-CTLA-4).

Results: 140 patients were enrolled: 71 patients (51%) with NSCLC, 57 patients with MM (40%) and 12 patients with RCC (9%). 39 patients developed auto-immune AEs (28%). The PFS in the population with auto-immune AE was 13.5 vs 7.5 months (HR: 0.41; 95%CI: 0.25-0.67, p 0.001). Multivariate analysis confirmed that only auto-immune AEs statistically impact on PFS.

Conclusions: Despite the limitation of the retrospective nature of this study and the possible bias due to the peculiar selection of patient, our data showed an interesting association between auto-immune AE and outcomes of checkpoint inhibitor therapy in an agnostic of cancer site population

S39

CANCER RISK AFTER EXPOSURE TO PERFLUOROALKYL SUBSTANCES (PFAS): EVIDENCE FROM LITERATURE

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Background: From the literature we know that perfluoroalkyl substances (PFAS) are persistent environmental contaminants. However, their metabolism and distribution in humans tissues are not well studied and few data have documented the accumulation of PFAS in specific issues, such as lung, kidney, brain and bone. Recently, in a monograph, the International Agency for Research on Cancer classified PFOA as "possibly carcinogenic to humans" (Group 2B). In the absence of clear data that can demonstrate the association between PFAS and cancer, it might be interesting to compare the evidence in the literature about the possibile association between PFAS and the different types of human cancer.

Table 1. The relantionship between PFAS exposure and the different types of human cancer in the considered studies.

Cancer	**Mastrantonio et al.** Eur J Public Health2018;28:180-5.	**Vieira et al.** Environ Health Perspect2013;121:1318-23.	**Barry et al.** Eur J Public Health2018;28:180-5.
Bladder	+/−	−	−
Brain	NE	−	+/−
Cervical	NE	NE	−
Colon/rectum	NE	−	−
Esophagus	NE	NE	−
Female breast	+	+/−	−
Kidney	+/−	+	+/−
Leukemia	+/−	−	+/−
Liver	−	−	−
Lung	NE	−	−
Lymphoma	−	+/−	+/−
Melanoma of the skin	NE	−	−
Multiple myeloma	NE	−	−
Oral	NE	NE	−
Ovary	+/−	+	−
Pancreatic	−	−	−
Prostate	−	+/−	−
Soft tissue	NE	NE	−
Stomach	NE	NE	−
Testicular	−	+	+
Tyroid	NE	−	+/−
Uterus	NE	−	+/−

Legend: NE= not evaluated; += statistically significant; +/−= not statistically significant but with positive trend; −= not statistically significant.

Methods: All ecological studies published in peer-reviewed journals up to February 2018 and referring to adult community residents who resided in contaminated water districts or worked at a local chemical plant were considered.
Results: Our analysis evaluated 3 ecological studies, including 25 685 patients affected by different kind of cancers in the contaminated districts (Table 1). In the analyzed studies, significant higher risks were observed for kidney and testicular cancer. Uncertain data were obtained for female breast cancer, leukemia, lymphoma, ovary, bladder, brain, tyroid and uterus. No increase risk for pancreatic and liver cancer was found.
Conclusions: Our analysis indicate that kidney and testicular cancer are positively associated with PFAS exposure. Uncertain and negative results were obtained for the other types of cancer.

S40

NARRATIVE BASED MEDICINE: A DIGITAL DIARY DURING CHEMOTHERAPY TREATMENT TO PERSONALIZE PATIENT CARE (PILOT STUDY)

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Background: In the age of patient(P)-centered care very few data evaluating the role of theme-oriented P narration applied to the path of cure exist.
Objective: Evaluating feasibility (F) and utility (U) of a model integrating P theme-oriented narratives with clinical data during chemotherapy treatment (CT).
Patients and Methods: From May 2017, 26 breast or colorectal cancer P, undergoing CT at the Department of Medical Oncology 1, "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. Two physicians (Ph) read the stories, shared and used them to personalize the cure. P access was gained by invitation from Ph 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 (8 months) to P and Ph. PF items were: friendliness and easiness to diary (to be handle), its adequacy in reflexive writing, compliance with diary; PhF items were: diary friendliness and easiness, time saving, length of visit. UP items concerned: communication, cure relationship, awareness, self-confidence, empowerment; UPh 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: All P agreed to participate; 15(58%) used DNM: they were mostly female (77%.) and aged 58 yrs (range 31-79) on average. A high PF and PhF medium scores emerged (4,5). PhU medium score was high (4,5). PU score was strongly related to Ph behavior, ranging from 3,6 (scarce or no replay) to 4.7. The strongest reported advantage by Ph was the opportunity to disclose relevant data otherwise not detectable. Both P and Ph strongly suggested the introduction of DNM in clinical practice.
Conclusions: The study provided data supporting the need of integrating P narratives with clinical data, encouraging further research. At the same time Ph narrative competence, the involvement of the whole care team and an appropriate health organization are required.

S41

USE YOUR HEAD TO SAY NO! A PROJECT TO PREVENT SMOKING, ALCOHOL AND DRUGS IN SCHOOLS

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Background: Italy is the European country where more teenagers smoke. In our country, smokers represent 22% of the population over 17 years old, men being 27.3% and women 17.2%. Prevention remains the most effective weapon to protect health and life; school is the ideal place to promote prevention because in school exist the necessary conditions for identifying needs, assessing risky behavior and, organizing promotion interventions, training and education to the culture of health and correct lifestyles.
Methods: The Oncology of Piacenza in collaboration with the Associazione Piacentina Malato Oncologico has begun an intervention program aimed to promoting the prevention against smoking, alcohol and drugs starting from the fifth classes of the elementary school. Through the support of audiovisual media, mannequins and practical examples, our aim is to inform teenagers of the damage caused by smoking, alcohol and drugs. From February to April 2018 in each school voluntary accepting the intervention, meeting of two hours are organized and will be repeated for 3 consecutive years. All the training interventions are based

on the constant involvement of the class through particular interactive way techniques, so children will be constantly stimulated and the training will be built according to the needs expressed in that specific context. This approach contributes to generating a high interest as well as stimulating the innate curiosity of children, a fundamental element in the learning principles.

Results: The project has involved 12 elementary schools, 29 classes and about 750 students in the city of Piacenza. Only one school has renounced membership but not for reasons related to the project. This project in the first quarter, was very appreciated by the children and the teaching staff. As a consequence, even the elementary schools of the entire province of Piacenza requested the application of our intervention for their fifths classes.

Conclusions: For healthcare professionals who are confronted every day with the damage and suffering that the cancer disease involves, it becomes a duty to try to prevent this disease by starting intervention educative where possible, from primary school. The project was mentioned in the XIII edition of the Good Practices Award for the Humanization of Healthcare Care, Andrea Alesini, organized by Cittadinanzattiva, Tribunal for the rights of the patient.

S42

WASTE AND INEFFICIENCY IN CANCER PATIENTS TRANSITION FROM CURATIVE TO END OF LIFE CARE: A SINGLE INSTITUTION RETROSPECTIVE COHORT STUDY

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Background: Cancer patients' (pts) transition from hospital-based oncological care to home-based palliative care (PC) is a complex process demanding coordination between different services and compliance with current national legislation. In our institution the process includes 3 main phases: oncologist identification of PC needs and referral to primary care physician (MMG), MMG convocation of a primary care Multi-Dimensional Assessment (UVMD) involving all professionals, subsequent access to PC. A poor quality organization causes delays or lack of access to PC, even though patient's complex needs and limited survival. The aim of this study was the identification of waste and inefficiency in this process.

Patients and Methods: This was a retrospective cohort study enrolling patients who died with cancer as the first cause of death in 2017 in the area served by ULSS8 (West District), Veneto Region. The study collected information from administrative databases: Italian Statistics Institute death registry, oncological, primary care and palliative care records. For each case identified, the data recorded concerned demographic data, place and date of death, date of oncologist first referral to PC services, date and professional composition of UVMD and first access to home by PC team (PCt).

Results: A total of 391 pts were included, mean age was 76 years. In our cohort, 23% of pts died at home and 50% in hospital; 37% (n.145) of all deceased were cared by PCt and these pts were more likely to die at home (49,6% vs 7.3%). Of 145 pts cared by PCt, 49,6% of referrals were oncologist based. The median time from oncology referral to death was 90 days; 25,7% of referrals didn't result in UVMD convocation by MMG. The median time from oncologist referral to UVMD convocation was 20 days, PCt wasn't informed of UVMD convocation and didn't attend in 37% of cases. Median time from UVMD to PCt first access was shorter if PCt was present in UVMD (4,5 vs 28 days). Median time from PCt first access to death was 41 days, 20,6% of pts survived less then 8 days.

Conclusions: This study found a strong association between the involvement of PC services and the place of death. A poorly executed care transitions approaching end of life care may lead to dissatisfaction among patients and inappropriate use of hospital services. There's need to improve the effectiveness of transitional care and find strategies for limiting waste of time and lack of access to PC services.

S43

LEGIONNAIRES DISEASE: THE NEW CHALLENGE FOR THE ONCOLOGIST

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Background: Legionella is an aerobic gram-negative bacillus that is spread through aerosolized water particle. It is a common cause of community and hospital-acquired pneumonia. The mortality rate is about 10% but the incidence has progressively increased nearly 4,5-fold.

Methods: We critically evaluated the incidence of Legionella infection among our oncologic patients, compared to the total cases reported in our hospital, registering three fatal cases in a few months. In view of conflicting laboratory data and high mortality rate in immunocompromised patients, we have set up a multidisciplinary roundtable to outline behavioral guidelines. From October 2015, all urinary antigen positive samples are sent to an external

laboratory for diagnostic confirmation on respiratory material, if available or on peripheral blood; it was decided to perform the urinary antigen test only in case of evidence of pneumonia at the chest X-ray, in the context of a pool of tests indicated as pneumonia profile. Standard antibiotic therapy protocols have been established. Actions were taken to reduce the possible sources of infections throughout the hospital.

Results: In the Hospital of Piacenza from October 2013 to October 2017, the total number of urinary antigen tests for Legionella remained stable, as was for the percentage of positivity (1.4-2.5%). In our Unit from October 2013 to October 2014 were carried out 16 urinary antigen test (positivity percentage 12.5%, mortality rate 70%); in the second year the total number of test done was 28, no one positive.

When an external laboratory was used for diagnostic confirmation and chest X-ray was identified as a filter, the first year the samples tested for urinary antigenwere 122 with (positive 8.2%); the second year on thirty-two patients tested, eight were positive; two cases were community-acquired as verified through water-home investigations; the mortality rate has been stable around 70%. Using filters for water taps and avoiding stagnation of water in the pipes together with the periodic monitoring of the possible environmental sources of contamination reduced the infectious outbreaks throughout the hospital.

Conclusions: Since pneumonia from Legionella can be lethal, every effort is mandatory to optimize diagnosis and start prompt antibiotic therapy. In immunocompromised patients we have to remember that the urinary antigen test is less sensitive. Monitoring and decontamination of possible sources of contamination are essential.

S44

MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS: A SINGLE-CENTER RETROSPECTIVE ANALYSIS IN A REAL WORD SCENARIO

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Background: Immune checkpoint inhibitors (ICI), anti CTLA-4 and anti PD-1/PD-L1 agents, have demonstrated an improvement in survival outcome in several malignancies. Despite the high rate of efficacy, therapy with ICI is characterized by immune-related adverse events (irAEs) as a result of exuberant immune system activation. Recent guidelines have been published for irAEs management.

Methods: A retrospective series of 130 consecutive patients (pts) treated with ICI from Jan 2012 to Dec 2017 was analyzed. Adverse events with a potential immunological etiology were defined as irAEs and graded according to CTCAE v.4.0. The aim of the study was to evaluate irAEs management in a single academic hospital center.

Results: Pts with a diagnosis of NSCLC n=64 (49%), melanoma n=55 (42%), kidney n=9 (7%) and others n=2 (2%) were investigated. Baseline ECOG PS was = 1 in 96% of the pts. ICI represented first line treatment for 27% pts, second line for 57% and third or further line for the remaining 16%. 18% were treated with ipilimumab and 82% with anti PD-1/PD-L1 agents (nivolumab 60%, pembrolizumab 21%, atezolizumab 1%). Overall, 50 (38% of pts) irAEs occurred, 42% of those were grade 1, 38% grade 2, 14% grade 3 and 6% grade 4. The most frequent irAEs were endocrinopathies in 17 pts (34%), followed by cutaneous toxicity in 9 pts (9%) and colitis and diarrhea in 7 pts (14%). Among pts who developed irAEs, 48% (24 pts) required immunosuppressive treatment. IrAEs led to hospitalization in 14 pts (28%) for 118 days, cumulatively. Grade = 2 colitis was the most frequently irAE, it occurred in 4 pts (29%). Colitis and diarrhea required the longest hospitalization (range 4-31 days). Systemic steroids were the most common immunosuppressive agents used for irAEs. Only one patient received infliximab as an additional immunosuppressive treatment because of steroid failure. Totally, irAEs required 67 specialist consultancies and additional diagnostic examinations, in particular, 29 blood tests and 22 imaging exams. 15 pts (30%) required ICI discontinuation because of irAEs.

Conclusion: In our center frequency and severity of irAEs were similar to literature data. Considered the complexity of irAEs management, multidisciplinary approach and hopefully a trained hospital network play a key role for the best choice of diagnostic evaluations and treatment in pts who received ICI treatment and experienced irAEs.

S45

PROCALCITONIN AS AN EARLY SEPSIS BIOMARKER: CORRELATION OF PROCALCITONIN VALUES AND POSITIVE BLOOD CULTURES IN CANCER PATIENTS

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Background: Sepsis is a frequent complication in cancer patients, among whom it causes almost 20% of deaths. Early sepsis biomarkers could be useful to fasten diagnosis

in order to offer patients the best appropriate treatments in the shortest time. In our study we wanted to confirm if procalcitonin (PCT) could be considered an early sepsis biomarker in cancer patients.

Material and Methods: We analyzed patients that accessed our dedicated outpatient supportive care service with a clinical suspicion of sepsis from 2010 to 2016. We considered only patients who were evaluated with both PCT and blood cultures (BCs). We analyzed the concordance between PCT positive levels (⩾ 0.5 ng/mL, according to our laboratory standard values) and a positive BC. We finally performed a ROC study to see which PCT cut-off was the best predictor of a positive BC.

Results: 90 patients were evaluable. 29 patients had a positive PCT: among these, 25 (86.21%) had a positive BC and 4 (13.79%) a negative one; 61 patients had a negative PCT: among these, 45 (73.77%) had a negative BC and 16 (26.23%) a positive one. The ROC analysis showed that the best cut-off for PCT was 0.88 ng/mL. This value was related to a sensitivity of 74.1% (CI95% 55-86.9), a specificity of 85.2% (CI95% 73-92.5%), a predictive positive value of 71.4%, and a predictive negative value of 86.8%.

Conclusions: Our study confirmed the role of PCT as an early sepsis biomarker in cancer patients and its use should be implemented in everyday clinical practice.

S46

CORRELATION BETWEEN G8 TESTS AND PHASES ANGEL (PHA) IN ONCOGERIATRIC TEST: OSSERVATIONAL STUDY RESULTS

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Background: Incidence of cancer increases with age. In older cancer patients, important information may be missed without a Comprehensive Geriatric Assessment (CGA). A validated screening instrument is needed to identify patients for whom a CGA would be beneficial. G8 is a screening tool (8 questions) for older cancer patients in need of a CGA, it explores functional, cognitive, nutritional status and it takes 5 minutes; a score of ⩽14 is considered abnormal. An other screening test is BIA analysis, when we can measure the nutritional performance through the PhA.

Objectives: To prove if exists the correlation between the score of test G8 and the value of PhA in oncogeriatric patients with colon-rectal cancer.

Methods: This study is conducted between April and October 2017, 71 patients aged =70 years diagnosed with colon-rectal cancer is valutated. The G8 tests and PhA results was administered at the first visit in oncological Day Hospital in Vito Fazzi (Le). At all patients was administered the G8 test and the BIA analysis (with the rilevation ofanthropometric measurements: weight, height and BMI). Patients aged 70 years or older treated with chemotherapy for solid tumor and at risk of malnutrition. The PhA (Angol phases) in oncogeriatric patitiens =5°, is considerated abnormal and a severe malnutritional risk.

Results: 20 patients with 76 years median age have a correlation between a G8 test ⩽14 and a PhA<5; in the remaining 51 patients there's not a significative correlation between the score of G8 and PhA.

Conclusion: G8 can be used in order to identify those patients who would benefit from a CGA and those who have a malnutrition risk. The results in to 20 patients show that there's a significative correlation between a G8 test =14 and a PhA<5; this study suggest that for this patients is important to implement and develop strategies for individual nutritional care (24 hours recall, 1 day recall, alimentary diary), in order to prevent and treat malnutrition in elderly people. We can be used the BIA analysis for precouce diagnose of sarcopenia in a oncogeriatric patients.

S47

THE ROLE OF PSYCHOLOGICAL FLEXIBILITY IN CANCER PAIN

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Background: This study is aimed to test psychological flexibility (thereinafter flexibility) in cancer patients with chronic pain. Our hypotheses are that a greater flexibility correlates with less attentional focus on pain, less use of medications, less depression or anxiety symptoms, less distress and less pain interference on the quality of life.

Material (patients) and methods: Patients with cancer presented chronic pain during hospitalization were recruited in the Oncology department of Sacro Cuore-Don Calabria Hospital in Verona, Italy.

Patients were asked to complete questionnaires on clinical state (Distress Thermometer (DT), HADS (Hospital Anxiety Depression Index), Vital statistics form), on pain (Brief Pain Inventory (BPI), NRS (Numerical Rating Scale), Pain statistics form), and on psychological flexibility and acceptance (AAQ-2) (Acceptance and Action Questionnaire II).

Results: Thirty three patients (mean age = 64.7; sd=11.8, 17, 16 female (58.5) were recruited; 78.8% is married, 42.4 % is retired, 90.9 % have sons and middle schooling

age is 9.8. 48.5% of patients is in active treatment, 39.4% is in diagnostic phase and 12.1% in palliative care.

NRS and BPI show these average scores: pain during hospitalization (M=2.69; sd=1.39), average pain during 24h measured by nurse (M=1.86; sd=1.88), average pain during 24h measured by BPI (M=3.09; sd=2.19) and number of days with pain during hospitalization (M=8.03; sd=7.66).

Data show a significant correlation ($p< 0.01$) between flexibility and distress ($\rho=-0.45$), anxiety ($\rho=-0.73$, $p<0.001$), depression ($\rho=-0.59$, $p<0.001$) and HADS total score ($\rho=-0.73$). Results show lower correlation levels ($p<0.05$) for interference of pain on emotions ($\rho=-0.36$) and schooling age ($\rho=0.42$).

Conclusions: This study shows as bigger levels of flexibility correlate with more schooling age, less distress, less anxiety, less depression and less interference of pain on emotions.

Conversely, Age, medications, average pain and pain durability appear not significant. Data seem to confirm results of previous studies about pain in non-cancer patients (McCracken, 1998).

Psychological flexibility can be a new construct to explain adaptation to pain and cancer. However, these are preliminary data and further studies are required to better understand the role of flexibility in cancer patients.

S48

TOGETHER AGAINST CANCER: PREVENTION PROJECTS OF ASL NO

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Background: The European Code against Cancer (ECaC) is a set of recommendations providing such advice on prevention of cancer. This code is also addressed to cardiovascular diseases (i.e. hypertension, diabetes), that represent a leading cause of death in Western Countries, as well as cancer. Nevertheless, the low health-care professionals' knowledge obstacle its dissemination. To this intent, in line with Rete Oncologica del Piemonte e della Valle D'Aosta, in collaboration with Associazione Mimosa Amici del DH oncologico of Borgomanero since 2017 we have planned several activities aimed at promoting the ECaC in our area, involving both patients and healthy ndividuals.

Material and Methods: Up to now, form September 2017 we have disseminated the ECaC by means of:

- Promotion of health diet among infants, parents and teachers (Progetto Materna)
- Focus on environmental and occupational pollutants involving children and students from primary to secondary schools (Progetto Elettrosmog) of Borgomanero
- Dissemination of the ECaC through short conference taking place in local restaurants in order to sensitize customers and restaurateurs to the importance of prevention (La Salute a Tavola)

Results: Progetto Materna included 50 children, 100 parents and 5 teachers, resulted in a deeper awareness of the importance of health diet. **Progetto Elettrosmog** involved 1 nursery, 3 primary school classes, 4 secondary school classes, and 4 high school classes, for a total of about 200 students with their teachers. Each class contributes to the project elaborating an original work on this topic. **Four restaurateurs** joined to La Salute a Tavola, hosting 4 short conference on ECaC, involving public of 150 persons.

Conclusions: The fellowship between our hospital and volunteers allowed a wider dissemination of ECaC as key prevention tool, providing information to the individual on how to reduce their risk of cancer, involving people of different age and profession (teacher, chef and restaurateurs). This approach based on 3 pilot projects resulted in an active participation of all the figures included.

S49

THE IMPORTANCE OF WORK IN CANCER PATIENTS: FROM PSYCHOLOGICAL COUSELING TO SUPPORT, SEARCH AND PRESERVATION JOB

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Background: to preserve employment for cancer patients becomes an economic need, for the high cost of medical care, psychological need due to the increase of anxiety and depression with consequent decrease in self-esteem.

Cancer diagnosis cause a work stop that become a progressive or immediate loss.

Work represent for cancer patients the healthy part of their life, where they feel the same people as always; its loss puts patients in crisis, increase anxiety and depression level up to compromise compliance and outcomes of chemotherapy treatment.

Methods: the professional team (oncologist, psychologist and medical staff) who analyze the case consider diagnosis, therapies and prognosis, to decide the best strategy for each patient in its specificity.

The path is structured through psychological interviews, problem analysis, and evaluation of coping strategies, in which the patients is accompanied to the awareness of oneself.

The goal of cancer patients become:

1. to be able to reconstruct, analyze and evaluate one's life story, in every important part, to find a relationship between these;
2. Recognize and enhance personal skills and resources, increasing self-esteem;
3. Identify the strengths to use as defense weapons against cancer;
4. Plain a work and personal life project, considering the concept of global health (psychophysics) realistic and feasible;
5. Implement the active job search program or back to work.

Access to psychological support and counseling is free and at the discretion of the patient.

Results: one third of the patients is women with breast cancer, aged between 30 and 50 years.

Analysis of interviews and data show that who has undertaken a supportive course for the management of work problems, has applied these strategies also to other contexts of one's own life.

Conclusions: to talk about skills and knowledge of the world of work, bring the patient to a deep analysis of himself and what about the cancer, improves its resilience to stressors.

S50

ESTHETIC PREVENTION AND PHYSICAL ACTIVITY IN WOMEN WELLNESS AFFECTED BY SOLID CANCERS: WHEN THE TUMOR IS NOT ONLY THE TARGET

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Background: Healthy lifestyle, physical activity, esthetical care, and psychological assistance gives an important support to women wellness. Alopecia is considered the most traumatic esthetic side effect of chemotherapy. The presence of hair contributes to define identity of body image and it may cause psychological discomfort. The aim of this project was to underline the role of clinical services to improve wellbeing in women affected by solid tumor.

Table 1. Patients'characteristics.

Patients' characteristics	n. (%)
Married	183(86)
Single	22(10)
Divorced/Widow	9(4)
Upper Intermediate school	103(48)
Middle school	39(18)
Elementaryschool	6(3)
Employes	82(38)
Retired	71(33)
Unemployed	27(13)
Housewife	34(16)

Material and methods: This analysis included patients treated with cancer patients' wellbeing service at our Institution between January 2014 and March 2018. Services included:

1. The "Lifestyle Programme" (since January 2014) that involves oncologists, dieticians and physiatrists
2. The Pink room (since March 2016) which offers free of charge consulting to the patients with female tumors, performed by senologists, dermatologists, nutritionists, psychologists, hair stylists, beauticians, and yoga teachers
3. The DigniCap® system (since July 2017) to prevent chemotherapy-induced alopecia.

Results: "Lifestyle Programme" enrolled 67 women affected by breast cancer between January 2014 and July 2016. Significant anxiety reduction ($p<0.006$) after lifestyle intervention was observed. 653 accesses were recorded on the Pink room activity. 214 women affected by solid tumors were satisfied. Patients' characteristics were summarized in Table1.96 patients started chemotherapy with DigniCap® system supported.11,5% (11) completed treatment with no alopecia,32 patients (33,3%) with alopecia G1-2. 23 patients, treated with anthracycline-based regimen, interrupted early DigniCap® system due to alopecia or clinical problems. To date 30 patients continue treatment with DigniCap® system support. Satisfaction questionnaires showed that all the proposed services were valued by the patients.

Conclusion: Our study showed that wellbeing services are valued and represent crucial options integrating anticancer therapies.

S51

BURNS? NO THANKS

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Over the last decade, WHO and IARC have been concerned with the risk and harmful impact on health by excessive exposure to UV radiation, whether they are of natural origin from the sun, or artificial, such as those emanating from tanning beds, classifying them among carcinogens group1. Unfortunately, in Northern Italy there are 17-20 new cases /100,000/year and it is the neoplasm with the fastest annual growth rate, with an increase in the incidence of about 5% per year. The pathology represents, in subjects under fifty, in terms of frequency, the 1st tumor for the man and the 3rd for the woman. It is known that the therapeutic successes for cutaneous melanoma (a 5-year OS of 85%) are mainly linked to prevention activity and surgery when melanoma is still thin. The neoplasms of the skin are directly correlated with the excessive exposure to ultraviolet rays, whose risk is increased due to the "burns" occurred in childhood and adolescence. This project required an intersectoral activation between the Dept of Environment and Dept of Health. The campaign "Communication on UV radiation exposure" (PNP 2014-2018), it was implemented and financed by the Veneto Region, ARPAV (PRP 2014-2018). The program aims to invite the population to reduce potentially harmful environmental exposures by raising the awareness of parents of children aged 0/10 and that of the very young aged 11/18. Paper and brochure materials, posters, tutorials videos was created to be shown in waiting hospitals rooms, general practitioners', birth points, vaccination centers. Some videos, for teenagers, are posted on social networks, while cartoons are provide for children, in the infant and primary school education plans. This materials contains a decalogue in a simple and exhaustive way to avoid burns, with some images easy to recognize skin lesions. In collaboration with ARPAV a QR code has been printed, which allows the reading in real time of the UV Index situation. In the leaflet there are some coloring comics and puzzle games to be performed by children and parents, also for educational purposes. The posters have been disseminated both in the seaside and in the mountain tourist resorts and were welcomed with enthusiasm by the Tourist Promotion Agencies (APT) which saw the interesting initiative for the health protection of their citizens but also of foreign tourists who often reach the local emergency room with a request for rescue for a nefarious sun exposure. Videos are available to see.

S52

NETUPITANT AND PALONOSETRON IN THE PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING IN PATIENTS RECEIVING CARBOPLATIN AND GEMCITABINE

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Background: Carboplatin and gemcitabine combination chemotherapy (CT) is considered a moderately emetogenic CT (MEC). Currently, antiemetic prophylaxis of carboplatin-based MEC should be done with a 5HT3 receptor antagonist (5HT3-RA), a NK1 receptor antagonist (NK1-RA) and dexamethasone (dex). Netupitant, a novel NK1-RA, in an oral association with palonosetron (NEPA), was shown to get a slightly higher complete response (CR) than aprepitant and palonosetron in patients undergoing multiple cycles of moderately and highly emetogenic chemotherapy. However, a subgroup analysis of patients receiving carboplatin showed a similar CR both in NEPA and control arm. No randomized trial has ever compared NEPA to 5HT3-RA alone in patients receiving carboplatin.
Patients and methods: The aim of this study was to evaluate efficacy and safety of NEPA in the prevention of emesis induced by carboplatin and gemcitabine combination CT, after failure of 5HT3-RA and dex. From January 2016 to September 2017 we enrolled 30 patients (14 stage IV NSCLC, 7 stage IV bladder cancer, 9 platinum-sensitive metastatic ovarian carcinoma, progressed after a first line platinum-based chemotherapy). All patients were treated with carboplatin AUC4 q3w and gemcitabine 1000 mg/mq on days 1 and 8 q3w. 7 patients affected by ovarian cancer also received bevacizumab 15 mg/kg q3w. As primary antiemetic prophylaxis, 22 and 8 patients received ondansetron 16 mg and palonosetron 0.25 mg, respectively, in combination with dex 12 mg on day 1 only. Patients experiencing nausea and/or vomiting after first administration of carboplatin received NEPA (netupitant 300mg-palonosetron 0.5mg) and dex 8mg on day 1 from the second cycle. Primary endpoint was overall CR with NEPA. Adverse events (AEs) were assessed according to CTCAE Version 5.0.
Results: After first cycle of CT, nausea G1 was detected in 10 patients, nausea G2 in 5 patients. After secondary prophylaxis with NEPA, among these 15 patients, 11 patients achieved a CR (73%), while the remaining 4 patients experienced nausea G1. After NEPA, nausea G1 was detected in patients who experienced nausea G2 after primary prophylaxis with 5HT3-RA and dex. 2 patients (13%) who received NEPA experienced constipation G1. No grade 3-4 AEs were recorded with netupitant.

Conclusions: Netupitant has proven to be very effective and well tolerated in the prophylaxis of emesis induced by carboplatin-based chemotherapy.

S53

REPRESENTATIONS AND NARRATIVES DURING PREGNANCY IN WOMEN WITH ONCOLOGICAL DIAGNOSIS

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Introduction: Given the rising trend of delaying pregnancy to later in life, more women are diagnosed with cancer before completing their families (Azim et al, 2011). However, by now psychosocial mechanisms contributing to adjustment during pregnancy in woman with oncological diagnosis have been ignored (Bonassi et al, 2017). Medical risk is associated to poorer representation of herself as mother and of the child-to-be. Women that experience cancer fear for their own and their foetus' health. This may delay or hinder the development of these representations. The aim of this study is to investigate maternal representations and possible other psychological factors linked to these representations in women with oncological diagnosis.

Methods: 10 women with oncological diagnosis (8: breast cancer, 2: hepatic PEComa) during the 3rd trimester of pregnancy were interviewed using the Interview of Maternal Representations (Ammaniti et al., 1990). A 5-point rating scale was used to code 7 dimensions of the women's representations of herself as a mother and of her child-to-be. Women also filled out questionnaires to investigate prenatal attachment, perceived support, resilience and the impact that cancer had on their lives.

Results: Two researchers independently coded transcripts of the interviews. In Table 1 Means and Standard Deviations of the mother's scores in each dimension are reported.

Correlations were found between: (a) prenatal attachment and: Richness (m: $r=.95$, $p<.05$; c: $r=.67$, $p<.05$), Openness to change (m: $r=.61$, $p<.05$), Intensity of involvement (m: $r=.69$, $p<.05$), Coherence (m: $r=.81$, $p<.01$), Differentiation (c: $r=.72$, $p<.05$); (b) perceived social support by family and: Openness to change (m: $r=.69$, $p<.05$), Intensity of involvement (m: $r=.69$, $p<.05$); (c) family cohesion and: Richness (m: $r=.98$, $p<.05$), Intensity of involvement (m: $r=.71$, $p<.05$), Coherence (m: $r=.74$, $p<.01$); (d) the role that cancer had on women's personal identity and: Openness to change (m: $r=-.68$, $p<.05$).

Table 1.

	Representations			
	as mother (m)		of the child-to-be (c)	
	M	SD	M	SD
Richness	3.3	.94	2.8	.63
Openness to change	2.8	.63	2.3	.68
Intensity of involvement	3.5	.71	3.3	.48
Coherence	3.4	.70	3.4	.70
Differentiation	3.1	.74	2.8	.79
Social dependence	2.5	.71	2.7	.68
Fantasy	2.2	.92	2.5	.85

Conclusions: These exploratory results seem to indicate that these women, in addition to medical care, need to be provided with specific psychological support for promoting factors that may have an influence both on representations during pregnancy and on transition to motherhood.

S54

DESCRIPTIVE ANALYSIS FOR CHARACTERISTIC AND DISTRIBUTION OF PHASE I CLINICAL RESEARCH STRUCTURES IN ITALY

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Background: On 05 April 2016 the new law that establishes the minimum requirements for Italian clinical units and laboratories to perform phase I clinical trials (Determina AIFA n. 809/2015), became finally effective. This Determination was issued after an increase (80%) of approved phase I trials in Italy from during the last 4 years and it was intended identifying selected centers that were really able to carry out this type of studies.

In order to verify the trend of self-certification procedures we decided to investigate, 2, 12 and 24 months after the entry into force of this Determination, the characteristics and distribution of the self-certified research structures.

Methods: Our analysis was conducted based on 3 of the periodic lists of self-certified clinical units and laboratories,

published by Italian competent Authority (AIFA) on 16 Jun 16, 06 Jul 17 and 1 Mar 18.

Results: The first self-certification was sent on 08 Apr 16, only 3 days after the first applicable date and the concerned center was able to start all activities on 7 Jul 16.

On 1 Mar 18 a total of 71 clinical units (+500% compared to Jun 16 and +14,5% to Jul 17 respectively) were self certified, for a total of 50 research structures qualify to phase I study conduction. 30 of these structure (60%) were located in the north of Italy, 12 (24%) in the centre while only 8 (16%) in the south.

Interesting, Lombardy and Emilia-Romagna regions host the 46,5% (n=20) of overall self-certified research structure. 36 of self-certified clinical units (50,7%) concern oncology/onco-hematology unit and only 9 (12,7%) are certified for studies on healthy volunteers.

A similar geographical distribution was observed for self-certified laboratories, that were 48 at the last analyzed timepoint (+343% compared to Jun 16 and +9% to Jul 17 respectively).

Conclusions: Despite the Determination has been issued with the intent to select sites of excellence able to deal with phase I studies, we have observed a real "race for self-certification" nevertheless we need the official results of AIFA inspections to really understand how many of these sites really meet all the required criteria and will be able to carry out phase 1 trials.

Our data, admittedly, show the intent of italian clinical research structures to invest in phase I clinical trial for the future (expecially regarding oncology and onco-hematology), but with a typically italian geographical heterogeneity between north and south.

S55

PSYCHOLOGICAL ASSISTANCE IMPROVES THE QUALITY OF LIFE, DEPRESSANT STATUS AND TREATMENT COMPLIANCE OF METASTATIC NON SMALL CELL LUNG CANCER PATIENTS RECEIVING CHEMO AND IMMUNOLOGICAL TREATMENTS

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Background: Depression and anxiety are common symptoms recorded in patients with mNSCLC which worsen their quality of life. In order to provide the best care and improve their compliance to tumor-specific treatments (chemo/immunotherapy), it is important to recognize and control these symptoms. We have then investigated whether older age, male gender and long history of chronic broncho-pneumopathy are associated with a higher frequency of anxiety and depression and whether early treatment may improve their quality of live and survival.

Methods: This is mono-institutional study involving seventy patients (60 male and 10 females) who received front-line chemotherapy for mNSCLC in our Institute since March 2017. Of these 51 received salvage immunological treatment with PD-1 mAb blockade with Nivolumab till progression. The enrolled patients underwent psychometric tests. Quality of life and mood were assessed at baseline and at 12 weeks with the use of the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale and the Hospital Anxiety and Depression Scale (HADS), the distress thermometer (TD) to assess the psychological discomfort, respectively. The primary outcome was the change in the quality of life at 12 weeks.

Results: In our cohort, 15/70 died within 12 weeks and were not evaluated. Early depressant signs were treated with antidepressant and psychotherapy leading to rapid quality of life scale improvement (FACT-L scale). None of the patients abandoned the anticancer treatments and could received the best palliative option. The prevalence of anxiety (HADS-A) was higher in female than males (55% vs 30% with a score $\geqslant$8; P= 0.04), while depression showed a inverse trend (HADS-D) (30% vs 70% with score $\geqslant$ 8; P=0.03). Forty-four cases indicated a stressor rating $\geqslant$ 7, suggesting the presence of clinically relevant psychological discomfort. During the immunological treatment it was recorded a significant rise in both scales (P=0.045) with significant improvement of family relationship and quality of life and sometime return to their own working activity.

Conclusions: These data confirm the relevance of the depressant/anxiety status. This is a preliminary study showing that depression/anxiety can be efficaciously treated with integrated programs and that immunological treatments may open a new scenario regarding the quality of life of these patients

S56

BONE STRUCTURE EVALUATION: PERSPECTIVES IN ONCOLOGY

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Background: Pituitary down regulators, aromatase inhibitors and tamoxifen in pre-menopausal women, and chemotherapeutic drugs all have a negative impact on bone health since, by blocking estrogen or androgen activity, they increase bone turnover leading to a progressively increasing risk of fractures. The global / annual incidence of fracture risk in patients on hormone treatment for breast cancer

varies from 1.37% to 11% and from 1.26% to 2.93% respectively.

Although trabecular bone accounts for only 20% of our skeleton, bone resistance strongly depends also on the micro-architecture, or quality, of bone structure, in addition to bone density.

The recently introduced BESTEST® is an innovative and inexpensive diagnostic method that gives an indication of the quality of the bone structure: it measures the weight-bearing capacity of the bone structure, evaluated from simulated application of loads bone structure images acquired by planar radiograms in the proximal epiphysis of the hand. Results are expressed in statistical terms as BSI_T-score and BSI_z-score, which now refer to the quality of the bone architecture and provide precious add-on information to densitometry. In this work, we discuss the preliminary results obtained in the evaluation of the BSI_T-score in female patients undergoing breast cancer treatment.

Material (patients) and methods: 100 Caucasian women over 20 years, took the BESTEST® as follow-up while undergoing oncological treatment. For a subgroup of 60 patients within this population, the femoral neck DXA T-score value was also available. A subgroup of 10 patients of the original population self-reported an osteoporotic fracture and for 8 of these, the DXA T-score value was available.

A control population of 200 women, accessing the BESTEST® for screening purposes, was also considered. Within the control population, 30 subjects (15%) self-reported an osteoporotic fracture.

No subject was pregnant at the time of the test.

Results: Statistical analyses (T-student test) shows that bone micro-architecture is indeed affected by oncological treatment and that the BESTEST® can provide a precious addition to densitometry in assessing these alterations, especially when associated with fractures.

Conclusions: This preliminary study clearly provides a rational background for further, deeper investigations into the use of a new, rapid and safe technique for monitoring the effect of breast and prostate cancers therapies on bone micro-architecture modifications.

S57

COMPLEX AMBULATORIAL PATHWAY (PAC) OF ONCOLOGIC THERAPY AT ONCOLOGY NETWORK ASL1 ABRUZZO: PRELIMINARY DATA.

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Background: On 09/14 ASL1 Abruzzo established Oncology Network, Integrated Personalized Territorial Oncology program, and Oncology Territorial Care (AOT) Unit, to homogenously enhance cure/prevention, modulate hospitalization vs ambulatory/home care.

Material and Methods: Preliminary data (15 months) showed that 33% patients needed hospitalization for therapies, 67% territorial care: 42% territorial districts L'Aquila-Avezzano-Sulmona, 25% hospital for therapies. Simplified procedures were implemented in diagnostic-therapeutic-care pathway with specialized multidisciplinary cure, according to Abruzzo Region Program of Complex Ambulatory Therapeutic Activity: intravenous PAC2, non-intravenous oral/intramuscle/subcutaneous PAC1. Rembursement was established for all activities related to oncologist visit, treatment administration, safety monitoring, drug prescription, AIFA monitoring, laboratory tests, ancillary therapies: PAC2 135€, PAC1 90€; drugs' costs evaluated in File F. After ASL1 Abruzzo approval (n.487, 8.4.2016), Ambulatory Therapeutic Folder was created for each patient to register anagraphics, patient/familial history, comorbidities, monitor therapies/tolerability, manage related activities. Pharmacy Unit guaranteed drug preparation in Antiblastic Drug Unit, AIFA monitoring, clinical trials. Therapeutic Ambulatory integrated specialized nurses for drug administration, patients' monitoring, Case Manager. Oncologic Therapies were administered at AOT Unit, S. Salvatore Hospital L'Aquila.

Results: In 20 months, 01.08.16-31.03.18, 100% therapies were administered as PAC, 281 patients underwent 3921 PAC: PAC2 3449, 88%; PAC1 472, 12%. Administered therapies 3542: PAC2 3100, 89.8%, PAC1 442, 93.6%. Other clinical related activities 3310. Patients treated only with non-intravenous therapy 53, 321 PAC1, 12%, median 5; administered therapies 299, 95.8%, median 5. Patients treated only with intravenous therapy 191, PAC2 2921, 74.4%, median 11; administered therapies 2609, 89.3%, median 9. Patients treated with non-intravenous and intravenous therapies along disease evolution 37, PAC1/2 688: PAC1 160, 4%, median 2; PAC2 528, 13.4%, median 11; administered therapies 634, PAC1 143 (89.3%), PAC2 491 (92.9%), median 2 and 10, respectively.

Conclusions: PAC is innovative care therapeutic pathway. Efficiency of ambulatorial oncological therapies in terms of efficacy, costs, oncological activity volume will be verified for each Unit and integrated in ASL1 Abruzzo.

S58

WEB APPLICATION FOR CUSTOMER SATISFACTION OF CENTRO ACCOGLIENZA E SERVIZI

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Background: The Centro Accoglienza e Servizi (CAS) collects all patients with a suspicious or a new diagnosis of cancer, who approach for the first time to the hospital. CAS is organised in order to simplify and quicken diagnostic and therapeutic algorithm, but also to guarantee a global management of patients. Indicators for quality improvement of CAS are well established. However, they are not representative of the actual satisfaction and taking charge of patients. In this regard, for the first time between 2013 and 2014, a papery customer satisfaction questionnaire was developed, validated and then applied in the daily clinical practice. However, there were some limits, such as an increasing number of incomplete or even lost surveys. Moreover, it was not always simple to elaborate the answers. To overcome these biases, we sought to develop a web application for tablets to pick up patients' fulfilment.
Materials and Method: From September 2017 to December 2017 by using a software open source, we transferred the papery questionnaire in an electronic format for tablets. This allows saving each answer and prevents to skip to other pages, if some questions have not been fulfilled yet. Furthermore, by this software we have managed to extract data, tables and graphs to monitor in real time patients' satisfaction, and to control the activity of peripheral centres.
Results: Up to now since January 2018, using this app we randomly collected an explorative setting of 63 patients. This cohort matched the whole population referred to our centre in the same frame time for age, sex and culture.
Conclusions: This easy-to-use web application for Customer Satisfaction is able to collect quickly and in real time patients' impression about CAS. Therefore, it should be used as indicator for CAS quality and worth to transfer in the current practice.

S59

MAESTRO CELLULA: A NICE TEACHER EXPLAINS CANCER TO CHILDREN

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Background: The impact of cancer, from diagnoses to therapy and sometimes to dead, has enormous implications for the patient's entire family. The family is called to sustain all the burden of care. Tumor disease determines the need, not only for the patient but also for the whole family system, of profound changes and a continuous adaptive effort, understood as a process of modification of the tasks and related strategies, according to the evolution of the disease itself. Therefore, within this context it becomes important to talk with the child about what it is happening to understand how much he has perceived of the situation, and what he knows about the disease.
Methods: Based on these theoretical assumptions and the experiences of the professionals, the "Il Maestro Cellula" Project is born as a help for parents, children and healthcare professionals. The Oncology of Piacenza has decided to make a journey inside the human body to help talk about the disease cancer, in the belief that we can and should talk about disease. To make communication easier, it was decided to use the drawing accompanied by a story representing a sort of lesson of Maestro Cellula. The booklet was also conceived with a view to prevention, becoming a tool that could be read in the primary classroom schools', and collecting the perceptions of children.
Results: Maestro Cellula will be the chauffeur of the journey that will take the children inside the human body, to help them understand what happens when an organ gets sick and modifies itself, giving start to the tumor. The illness of the mother/father is the main theme and transversal to the whole story. The disease, something great and frightening, is slowly resized and made manageable precisely because it is known and understood.
Conclusions: The communication of "bad news" is a complex and difficult task of medical practice in general and even more in oncology, especially if there are children in the family. This tale is a tool that gently helps adults to tell and explain cancer to children. This is the challenge that the Oncology of Piacenza wants to accomplish by believing it is a possible mission. We must not deny the disease or speak only of certain diseases; all diseases can be told, even to children.

S60

THE TREATMENT OF CANCER PATIENTS NEAR THEIR RESIDENCE IN A TERRITORIAL STRUCTURE "CASA DELLA SALUTE": PRELIMINARY RESULTS IN THE PROVINCE OF PIACENZA, ITALY

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Background. In the field of oncology, we are all stimulated by the desire to improve the lives of patients afflicted with cancer; however there is a little data amount of time and travel discomfort that patients and families typically spend for clinical examinations and for antitumoral/supportive treatments. The purpose of this study was to determine the advantages for cancer patients to receive clinical, test examinations, and anticancer treatment near their residence in a territorial clinical structure called "Casa della Salute" (CdS).

Material and methods. Since July 2016 to all the cancer patients treated at the Oncology Unit of the General Hospital in Piacenza, was offered the possibility to be treated nearest their residence at the Casa della Salute located in the mid valley (Val Nure), or to continue the treatment at the Oncology Unit of the General Hospital in Piacenza. The treatments were delivered by an oncology nurse under the supervision of a medical oncologist.

Results. From 18 July 2016 to 20 July 2017, 54 patients with cancer were managed in the Casa della Salute in Bettola, province of Piacenza in North Italy. All these patients received the planned antitumoral and supportive treatments. The average distance from the patient's residence to the Oncology Unit in Piacenza was 81,65 Km (range 31,6-131 Km), while it was 21,06 Km (range 3-54,2 Km) to reach the Casa della Salute ($p<0,001$). The average time for the round trip to the Oncology Unit in Piacenza was 93,35 minutes (range 40-162) while it was 16,35 minutes (range 10-78) to reach the Casa della Salute ($p<0,001$). 98,5% of patients were very satisfied to receive oncological treatment at the Casa della Salute, and 65% of patients who needed a caregiver to reach the Oncology Unit in Piacenza, could travel alone to the Casa della Salute".

Conclusions. The increase in the incidence of cancer, especially in elderly patients with comorbidity has been accompanied by an increase in the overall survival rate of these patients thus requiring organizational innovations. The results of this study hightlight the possibility of treating cancer patients in territorial structures nearest their residence, with advantages for the patients, their caregivers and for the entire community.

S61

ONCOLOGY FRONT OFFICE: THE RULE OF PSYCHOLOGIST AT THE HOSPITAL ENTRANCE

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Background: At the entrance of oncology department the front office represent the center of requests management, in wich cancer patients and parents turn to ask for information.

Front office task is to monitor and accept any requests from everyone (patients, family and medical staff) welcoming requests and providing possible solutions.

Sometimes persons arrive to the front office with conflicting psychological and emotional condition, angry and depressed at the same time, so the optimal solution is give a chance to elaborate this compicated situation, a cathartic moment in wich accompany the patients to order in his inner world.

Emergency management (often by phone) is another matter of front office work, in wich aggression emotion by cancer patients and their family, caused by long waiting time to start chemotherapy.

Methods: To deal with emotional and psychological loads of those who come at the oncology department, we psychologists, we have taken care of the requests where they emerge agitation, fear, aggression and anxiety feelings.

We have observed and analyzed 40 days of front office activity in wich we counted 5640 contacts, 6,38% of them they were high emotional impact.

Our techniques highlight the importance of comunication (verbal and not verbal), psychological interview structuring with purpose to find psychological balance to improve a high life quality.

In addition to the direct management, we tought communication tecniques to medical and nursing staff, analyzed the strengths and weaknesses of communication between medical staff and patients to improve the quality of interactions.

Results: The psychologist presence has greatly diminished episodes of confrontarion and misunderstanding, improving assessment competence and assertivenes of the subjects involved.

Conclusions: Improve communication and emoziona competence allow better oncology management for all the staff, giving serenity to the patient and family serenity e caregiving.

The identification and immediate management of psycho-oncological dynamics guarantees an improvement of hospital image, like a long-term quality investment.

T - Oncology Nursing

T01*

ITALIAN VALIDATION OF THE CHEMOTHERAPY INDUCED TASTE ALTERATION SCALE

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Background: Chemotherapy-related taste alterations (TAs) can range from a few hours to several weeks or

months after chemotherapy. TAs have been traditionally assessed using objective methods or questionnaires limited to ascertain their occurence. However, none of these methods is appropriate. The Chemotherapy-Induced Taste Alteration Scale (CiTAS) is a 18-item Japanese tool that allows a simple and overall TAs assessment, including the specific kind of alteration (i.e., saltiness, sweetness, sourness, bitterness or umami), symptoms of discomfort, and the impact of TAs on patient nutrition. This study aimed at validating the Italian version of the CiTAS.

Methods: A validation study enrolling consecutive outpatients with cancer who received chemotherapy was conducted at five hospitals in Northern Italy between April and June 2014. Patients with chemotherapy-related TAs (n=243) were asked to self-report their TAs in the previous week using the CiTAS. The overall CiTAS score ranged from 4 (no TAs) to 20 (maximum severity of TAs). They were then asked to rate the severity of TAs and the impact of TAs on their QoL in the previous week from 0 (no impact) to 100 (maximum impact) using a Numerical Rating Scale (NRS). Firstly, cross-cultural, face and content validity were tested. Then, data were analyzed for item consistency (Cronbach alpha) and construct validity (exploratory factor analysis - EFA). Pearson correlation (r) between overall CiTAS score and the severity of TAs and the impact of TAs on QoL was calculated to test discriminant validity. Reliability was also tested re-assessing 50 patients at 3 weeks.

Results: The original CiTAS was not modified since agreement between experts concerning relevance and clarity was higher than 80% for each item. The EFA retained all the items and identified four dimensions with a total variance explained of 67%: 1. Decline in basic taste (n=5; 22%); 2. Phantogeusia and parageusia (n=4; 19%); 3. Discomfort (n=6; 13%); and 4. General TAs (n=3; 13%). The scale showed good validity (Cronbach's alpha=0.82) and discriminant validity (the overall CiTAS score correlated with TAs severity ($r=0.54$, $p<0.001$) and the impact of TAs on QoL ($r=0.45$, $p<0.001$)). Test/retest reliability was moderate ($r=0.41$, $p<0.003$).

Conclusions: The CiTAS enables a valid, simple, time-saving and reliable measurement of chemotherapy-induced TAs. This tool allows health care professionals to tailor dietary and behavioral advices according to the specific TA.

T02*

EMERGENCIES IN CANCER PATIENTS: DESCRIPTIVE STUDY

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Aim: The patients suffering from oncological pathologies often have to enter the hospital in a way that had not been previously planned.

The main reasons are due to the symptoms related to the illness or to the toxicity related to the chemotherapy..

The aim of this study is to identify the main cause that leads the patients affected by cancerous pathologies to enter in the day hospital for oncological emergency.

Methods: Descriptive and quantitative study carried out at the Operative Unit of Oncology Day Hospital of Centro Onco Ematologico Subalpino of the hospital "Città della salute e della scienza of Turin" (hospital unit Molinette) between January and June 2017.

The data were collected from the patient's medical record: age, data admission, gender, nonth of admission in day hospital, reason for admission, type of cancer, concomitant pathologies, drugs, metastasis, number of admission, intervention and support therapies.

Results: The total amount of the patients that entered the day hospital was 162 people with 218 admissions. 63% of the patients were men, the most common oncological pathology was the colorectal cancer (29%) followed by lung cancer (24%) and pancreas cancer (19%). The main reason for which the patients enter in day hospital was pain (40%) followed by asthenia (25%), hyporexia, dysgeusia and weight loss (18%).

Conclusion: Many of the admissions of patients with oncological pathologies ad the day hospital for oncological emergency can be avoid. Understanding the reasons of these visits could be useful in developing specific actions aiming at preventing of avoiding these admission.

Tab. 1. Side effects and symptons.

	n	%
Pain	88	40%
Asthenia	55	25%
Mucositis	7	2%
Temperature	39	18%
Diarrhea	15	7%
Ascites	11	15%
Hyporexia, dysgeusia, weight loss	40	18%
Dyspnoea	21	10%
Nausea e vomiting	29	13%
Not reported	4	2%

Tab. 2. Treatments.

Treatments	n
Therapies in day hospital	30
Emergency care	22
Home therapy	87
Palliative care	17
Admission in oncology	9
General medicine doctor	15
Other	4

T03*

APPLICATION OF THE OTTAWA DECISION SUPPORT FRAMEWORK TO ASSESS THE DECISIONAL CONFLICT IN PATIENTS SCHEDULED FOR INSERTION OF A CENTRAL VENOUS ACCESS DEVICES TO RECEIVE CHEMOTHERAPY: A CROSS-SECTIONAL STUDY

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Background: Decisional conflict is 'the subjective uncertainty about the best choice to make when the options are competing with each other and involve risk, loss, regret or challenge to personal values'. Uncertainty can be intensified by factors such as lack of knowledge, unrealistic expectations, unclear values, pressures from others, social context, lack of support and perception of self-efficacy in shared decision making. An important choice requiring cancer patient involvement is the insertion of Central Venous Access Device (CVAD) to administer intravenous chemotherapy. The choice should be discussed in collaborative processes among patients and health professionals. The Ottawa Decision Support Framework (ODSF) provides a framework for developing interventions for decision support and tools for analysis of the contributing factors such as Decisional Conflict Scale (DCS), Decision Self-efficacy Scale (DSES) and Knowledge Test (KT). Validity and reliability of these self-report scales are well documented. However, DCS and DSES have not yet been culturally adapted and tested in the Italian context.
Materials and methods: The questionnaires DCS, KT and DSES were used in a single centre cross-sectional study with cancer patients scheduled for insertion of a CVAD. The DCS and DSES have been translated into Italian for this study through a process of forward and backward translation. The dimensionality of the Italian versions of DCS (5 subscale, 16 items) and DSES (one dimension) have been investigated with exploratory factor analysis. The study was approved by the Ethics Committee of the 'Istituto Nazionale Tumori, G. Pascale', Naples, Italy.
Results: From May 2016 to February 2018 201 patients were enrolled, 60.2% of which female, with a mean age of 58 years (DS= ±12.9); range 19-83). Factor analysis of the 11-item DSES found a two-factors ('confidence of obtaining information' and 'decisional ability') solution with good reliability. The factor analysis of the DCS will be conducted after reaching the final sample of 250 patients.
Conclusions: Results of this study can provide tools to measure the decisional conflict and associated factors. These are modifiable factors, therefore our results will provide health professionals with helpful tools to improve the quality of shared decision-making in cancer patients scheduled for the insertion of a CVAD.

T04*

A PILOT STUDY ABOUT NURSES' ROLE IN MANAGEMENT OF CUTANEOUS TOXICITY IN PATIENTS TREATED WITH TARGETED THERAPIES

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Background: EGFR-Is (Epidermal Growth Factor Inhibitors) and RTK (Receptor Tyrosine Kinase) are the "Targeted Therapies" with a selective capacity. However their use causes new side effects, such as the skin toxicity, the most prevalent of which is the maculo-papular rash. Several studies emphasize that education and prevention can reduce this toxicity which, if not treated promptly, may compromise the ongoing therapy and have a negative impact on the patient's quality of life (QoL).
Methods: 178 patients will be enrolled in this randomized mono center, two-treatment arms (Arm A experimental group and Arm B control group), and interventional study. Patients will receive intravenous (Cetuximab or Panitumumab) or oral (Erlotinib or Regorafenib) treatment. All patients will receive an "HOC Questionnaire Created" composed by 14 items and Dermatology Life Quality Index (DLQI). The first one will be administered only at the screening, while DLQI Questionnaire will be administered at each time point. Furthermore, only the patients in Arm A group, will receive at the screening a HOC brochure created by the nurses (containing advice and information about skin toxicities and their management) and interviews with nurse at each step, during which they can ask, express thoughts, fears, perplexities and can receive further advice and information about the skin toxicities management.
Results: The sample size will be hypothetical that the incidence of cutaneous toxicity in Arm A group will be lower than that on Arm B group as per CTCAE 5.0. It will be considered clinically relevant to observe a 20%

Study period	Screening phase (-14 to -1)	Every 4 weeks (until at first tumor assessment)
Informed Consent Form	X	X
Inclusion/Exclusion Criteria	X	X
HOC Questionnaire Created	X	
DLQI Questionnaire	X	X
Brochure[a]	X	
Interview with nurse[b]	X	X

Note: a&b only Arm A

reduction in the incidence of cutaneous toxicity, a redistribution of toxicity levels such as to produce an effect size of 0.068 in Arm A group and a better QoL compared to Arm B group.

Conclusions: Oncology nurses play an important role in the identification and management of toxicity, education and patient support. Our project hopes to confirm that allowing patients to be more involved in their treatment and toxicity management related, oncology nurses can help them to promote adherence to treatment, to have lower toxicity's levels and to maintain their QoL.

T05

IMPLEMENTING AN ONCOLOGY NURSE CLINIC FOR ORAL CHEMOTHERAPY: A QI PROJECT IN AZIENDA OSPEDALI RIUNITI MARCHE NORD (AORMN)

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Background: Although the rapid implementation of oral anticancer agents into practice has been widely adapted, patients taking oral chemotherapy (OC) initially could not always receive the appropriate education and information: QI projects in the oncology outpatient setting are needed in order to improve management, monitoring and safe administration.

Material and methods: The AORMN Oncology Department implemented an oncology nurse clinic of taking on the patient that includes: nurse-led medication and adherence education; medication supply assistance; consistent education/ information about side-effects; toxicity monitoring by telephone follow-up and outpatient visits on scheduled basis (grading according CTCAE and nurse clinical judgement); nurse phone line staffed for patients Monday through Friday 8 hours a day; information tools to document the activity and have a data collection for research purposes; educational materials (brochure, information sheets and patient diary to monitor, record symptoms and dosage taken).

Results: Over 7 months, from June to December 2017, 57 patients were taken into care; medication prescriptions were CAPE (37%), VRL (25%), CAPE plus VRL (14%), TEMODAL® (14%), XTANDI® (14%), ZYTIGA® (3%). Outpatient nurse clinic visits, according treatment protocol, was 212 (Mean 4.7 range 2.65 to 8.5): no toxicity for ZYTIGA®, very low for CAPE plus VRL (constipation 2.5%); higher CTCAE score for VINO (mucositis 15,4% and constipation 11.5%) and TEMODAL® (fatigue 16.1%). At the end, 7 patient stopped OC for disease progression (24%), 3 by their own choice (10%),2 due to hospitalization (7%). Nurses phone line received 43 calls (Mean 1.4/week): 27 for organizational reasons (e.g. scheduling blood and medical tests, change the date); 2 only to clarify treatment; 2 to forget medication and 12 for managing side effects. We have related 3 OC regimen and most common failure reasons, CAPE plus VRL vs CAPE vs VRL: in order to fatigue 25% vs 4.7% vs 14.2% ($p>0.05$); vomit: 12.5% vs 4.7% vs 7.1% ($p>0.05$) [Fisher's exact test].

Conclusion: Overall very high patient adherence and lower percentage of side effects. Small sample size to achieve statistically significant results. Oncology nurses had the time to provide patient information/education, to assess, monitor and self manage their symptoms: they can be the pivotal point of contact for the patient and healthcare professional and provide a key source for healthcare organization.

T06

PHYTOTHERAPICS AND DRUGS THE INTERACTION CAN INCREASE SIDE EFFECTS IN ONCOLOGIC PATIENT?

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Aim: To describe the most commonly used phytotherapeutic substances and/or food in the oncologic patient (tab.1) and to identify side effects, mainly gastrointestinal effects.

Methods: Structured questionnaires were distributed, in anonymous and voluntary way, between July 2015 and July 2016 to the cancer patient during chemotherapy treatment, in day hospital. Quantitative data were summarized in descriptive tables. Frequencies were compared with a chi-squared test. The data were processed using programme INSTAT.

Results: A total of 318 questionnaires were compiladed.

The 95% of patients makes use of at least one phytotherapeutic substances and / or foods among those into analysis. 84% developed at least one gastro-intestinal side-effect, of which 95% were taking one or more phytotherapeutic substances. Statistically significant comparison was made between the appearance of side effects and the assumption of specific substances and drugs with $p < 0.05$ (tab.2)

Conclusion: Simultaneous use of phytotherapeutic substances with anti-emetic drugs taken at home can cause an increase of side effects in patients receiving anti - neoplastic treatment. The study shows the need to promote the conscious and safe use of these substances.

Tab. 1. Assumption of phytotherapy and aliments in general population.

	Yes
Eucalyptus	3%(11)
Sage	40,00%
Broccoli	51,00%
Grapefruit	14% (45)
Echinacea	2% (5)
Mint	23,00%
Garlic	62,00%
Pomegranate	19,00%
Licorice	16% (52)
Oats	8% (24)
Pineapple	44,00%
Chamomile	29,00%
Soy	10% (32)
Vinegar	61,00%
St. John Wort	1% (2)
Ginger	31,00%
Valerian	14% (44)
Tobacco	9% (30)
Ginkgo	0,00%(0)
Ginseng	7%(22)
Propolis	9%(29)
Turmeric	21,00%
Aloe	17,00%
Goji barries	5%(15)

T07

THE PRIMARY NURSING MODEL IN ONCOLOGY: A MONO-INSTITUTIONAL EXPERIENCE OF THE ONCOLOGY UNIT OF S. GIOVANNI DI DIO HOSPITAL IN FLORENCE

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Background: A multidisciplinary approach to the patient care is a key aspect in the oncology field. The role of the nurse as a patient interface is central in the different phases of the diagnostic and therapeutic process. The nurse deals with organic, relational, emotional and social aspects that are relevant to the patient and its relatives. Giving such an enabling role, the nurse must operates following a defined, structured and fluid organizational model which integrates in a complementary way with the work of the other professionals. Our medical oncology unit is located in a local hospital. Around 250.000 inhabitants affer to the hospital. The oncologic path encompasses several assistential settings including ambulatory, day service and day hospital with structured and defined links with the medical area for the in-patient setting. Of relevance, the oncology unit actively cooperates with the palliative cure unit for the early simultaneously and the end-of life care of patients. In agreement with the direction of nursing services and the director of the oncology unit, the nurse team operates applying the Primary nursing model.

Matherial and Methods: A primary nurse and an associate nurse are involved in and responsible for the health

Table 2. Correlations to assumption of a substances and gastrointestinal effects.

	Nausea	Vomit	Mucositis	Dysgeusia	Constipation	Diarrhea
Ginger	**p = 0,001**	p = 0,057	**p =0,016**	p = 0,537	p= 0,996	p =0,659
Sage	**p = 0,042**	p = 0,900	p =0,354	p = 0,731	p= 0,336	p =0,488
Broccoli	p = 0,369	p = 0,867	p =0,818	p = 0,648	p= 0,148	**p =0,040**
Pineapple	**p = 0,024**	p = 0,568	p =0,120	p = 0,703	p= 0,127	p =0,773
Chamomile	p = 0,491	p = 0,315	p =0,356	p = 0,05	**p= 0,024**	p =0,680
Mint	p = 0,162	p = 0,242	p =0,440	p = 0,568	p= 0,963	p =0,662
Turmeric	p = 0,638	p = 0,228	p =0,390	p = 0,879	p= 0,626	p =0,218
Pomegranate	p = 0,182	p = 0,540	**p =0,017**	p = 0,678	p= 0,243	p =0,7
Garlic	p = 0,193	p = 0,965	p =0,930	p = 0,471	**p= 0,027**	p =0,301
Vinegar	p = 0,371	p = 0,166	p =0,284	p = 0,915	p= 0,782	p =0,913
Aloe	p = 0,620	p = 0,444	**p =0,017**	p = 0,483	p= 0,492	p =0,599

care pathway of the patient, playing a pro-active role from the beginning of the referral. The primary nurse plans and performs an educational interview, with several aims: introduce the patient in a more human and familiar hospital environment, evaluate organic, relational, emotional and social issues and put the basis for a continuous care. The primary nurse takes care for the patient through scheduled phone contacts in order to monitor the safety and the compliance to the treatment. Specific questionnaires have been administered to the patient at the beginning and at the end of the therapeutic course, exploring emotional impact and the empowerment of the patient.

Results: 208 patients have been managed with this approach during 2017, 1685 phone contacts have been performed and 340 events have been recognized and mainly resolved without hospitalization, with a good feed back from the patients.

Conclusions: The primary nursing model is an effective organizational approach as it allows to ensure a global care of the patient, to integrate the nurse team and the oncologists for a full and complementary management.

T08

PATIENTS REFERRED TO THE "C.A.S." (CENTER FOR ACCEPTANCE AND HOSPITAL SERVICES/ CENTRO ACCOGLIENZA E SERVIZI) WITHIN CITTÀ DELLA SALUTE E DELLA SCIENZA HOSPITAL (MOLINETTE) IN TURIN, BETWEEN JANUARY AND DECEMBER 2017: A RETROSPECTIVE COHORT STUDY

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The C.A.S. ("Centro Accoglienza e Servizi") is an hospital service/unit specifically designed to address, support and sustain patients with a possible or suspect cancer diagnosis. This unit/service ensures to take care of the patient, until the definitive cancer diagnosis and the disease staging. The C.A.S. represents an effective opportunity for patients and their families to avoid a waste of time and resources. Moreover, it improves the quality of provided care, both for patients, in terms of treatment efficacy, and for health care system, in terms of effectiveness. The C.A.S. is characterized by an holistic multidisciplinary approach that provide out-patients visits performed together by medical doctors and nurses. During the visits, the nurse collects, evaluates and identifies the potential medical, psychological and social frailties of every patients, using specific data collection forms that have been validated by the nursing study group of the "Piemonte and Valle d'Aosta Oncology Network".

In January 2018 were retrospectively evaluated and analyzed, using SPSS software for Windows, data about patients referred to the C.A.S. during the period between January and May 2017, and 500 patients were collected. These data were essential to evaluate if the initial goals that we had established for the study were correct and also to describe the cohort, with the aim to elaborate further improvements.

From the analysis of patients needs expressed by the subjects considered in the study it appears the need to reassess the organization of the C.A.S. through the involvement of its main actors, aiming to make the provided service more efficient, effective and personalized on the single patient.

Aim of the study: To analyze the needs and the biological, social and psychological frailties that were collected during visits of patients who were referred to the C.A.S.

T09

ONCOLOGICAL CALL CENTER: A SERVICE OF READY TELEPHONE AVAILABILITY FOR PATIENTS IN ANTICANCER THERAPY

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Introduction: The anticancer therapies generate a series of side effects such as nausea, vomiting, diarrhea, fever, constipation, pain and many others that can worsen the quality of life of the patients and complicate their management at home. The need arises to open a channel of continuous communication, easily accessible and guaranteed that is oriented to the patient, his family and the general practitioner and can help in the management of emerging needs at home.

Materials and methods: A company mobile number is activated with call forwarding to the doctor on duty identified as rotating between the structured physicians of the Oncology Unit. The telephone number is distributed to users at the bottom of the letters of discharge from the DH after therapy and on posters exposed in the waiting rooms of DH and the Oncology clinic. This number is also available at the hospital switchboard which can be referenced by every hospital doctor who needs information on cancer patients entrusted to them. Hourly availability starts at 4 pm on weekdays until the following morning, while it is 24 hours continuous on weekends and holidays. Through a customer satisfaction questionnaire we obtained data related to the satisfaction of patients and their families, the type of problem requested and time slots.

Results: Two hundred questionnaires were recorded. Patients know the service in 95% and used it in 60 % of them; 90 % of the use is over 1 month ago. Only 25 % patients used it only one timem while over 50 % more than 5 tiles. They used it because asking for therapy 20 %, for symptoms 70 %, but 10 % asking for office reasons too. All pts have improved their clinical conditions and there was necessary admitting in Emergency Department only in 10% of cases.
Conclusions: This little pilot study confirm the efficacy of ready phone availability to: a) safe management of acute problem situations related to the side effects of the therapies, b) solve apparently simple, practical but urgent problems at home, c) facilitate access to the E.D. if necessary, avoiding inappropriate appeals to the emergency room, d) only a little part of patients used this service for office reasons.

T10

QUASI-EXPERIMENTAL TRIAL OF COMPLEX NURSING INTERVENTION FOCUSED ON QUALITY OF LIFE ASSESSMENT IN ADVANCED CANCER PATIENTS WITH PALLIATIVE CARE NEEDS: FEASIBILITY, ACCEPTABILITY AND POTENTIAL EFFECTIVENESS (THE INFO-QOL STUDY)

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Background: The standardized application of clinical interventions focused on assessing QoL in clinical practice is limited. This study aims to model and determine feasibility and potential effectiveness of a nurse-led complex intervention focused on Quality of Life (QoL) assessment in cancer patients admitted in hospice.
Material and methods: Development of the intervention (INFO-QoL) was based according to the Medical Research Council framework for developing and evaluating complex interventions in healthcare.

The before-after quasi-experimental study was conducted in two hospice units of the urban district in the north of Italy. The sample included staff members (N=39) and all adult cancer patients newly admitted to the hospice units (N=187). Patients were included after giving their informed consent. Patients too ill to receive the intervention or unable to give informed consent were excluded.

The intervention included: educating staff about QoL and treatments to promote QoL; identifying a nurse to manage the assessment process; assessing patient's QoL using a paper version of the Integrated Palliative Care Outcome Scale (IPOS) at the admittance and a week later; sharing IPOS results during the staff daily briefing, and giving patient's feedback of results and plan of care.
Results: Concerning the feasibility, the INFO-QoL intervention was provided as planned. As for the acceptability, nurses found the intervention relevant, appropriate, and useful. Overall, 229 patients were eligible, 187 accepted to participate to the study (after phase, N= 90). We found that the intervention increased the numbers of activities delivered to patients for the following symptoms: sore/dry mouth (p value: 0.031), patient and family anxiety (p value: 0.019; p value: 0.004, respectively). A significant clinical improvement was found for family anxiety item (d= -0.50; 80%CI -0.88 and -0.11).
Conclusions: The results indicate that the INFO-QoL is feasible and acceptable and showed a positive impact on treatments delivered to patients improving family anxiety.

Our findings confirm that implementing a patient-centred outcome measure intervention improves processes of care. The INFO-QoL highlights nursing contribution to QoL improvement at the process and outcome level.

Our results could help to ensure the highest possible QoL by gathering patient's needs, sharing those needs during the daily staff briefing and developing a plan of care accordingly.(Study funded by the EONS)

T11

IL PROGETTO PROTEZIONE FAMIGLIA UNA REALTÀ IN UN DAY HOSPITAL ONCOLOGICO

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Background: The experience of the cancer involves the patient from a biological point of view but also in a psychological and social context. The multidisciplinary take charge of the oncological individual and of his family, reduces the recovering timespan, improves the coordination of the cure and augments the satisfaction of the patient and of the healthcare professionals. The experience of illness is made particularly complex when characterized by psychosocial fragility. The Project Family Protection is born precisely for helping fragile families.
Material (patients) and methods: The project Protection Weak Families (PPFF) was born in Turin by the F.A.R.O. foundation to sustain the fragile households hit by cancer from a psychological point of view. The project is at present included in the activities of the in-house department. Ultimately PPF exists with purpose of building a psychological support system around the family considered fragile. The aforementioned network is formed with healthcare

professionals (doctors, psychologists, nurses, OSS), social operators (educators, case workers, home attendant) and volunteers.

Results: The project Protection Family has been activated among the Turin S.G. Bosco hospital in 2012 and financed by the piedmontese Oncological Network. In 2013 the project has enabled psychological support to 19 families considered fragile along with an high discomfort and destabilisation risk. In the 2014 the supported families were 50. The assisted households assisted by the Project Protection fragile families were 122 in 2017: 25 in charge of the oncological S.C. of the P.O. Maria Vittoria and 98 in charge of the oncological hospital San Giovanni Bosco. The new take charges were 87 (7.3% of the followed cases). The familiar fragilities in the reference population are distributed as follows: in 51 households (41,8%) only one fragility has been detected; 75 households (61,4%) have more than one fragility; 24 (19,6 %) have more than 2.

Conclusions: The results show an increment in the take charges during the years. This doesn't derive from an augmented fragility from the patients but from a greater sensitivity from the operators in detecting at an early stage the fragilities and from a major investment of resources. The project has led to a better compliance toward the treatment for the patient who feels himself supported not only in the illness care but also from the point of view of the management of the family.

T12

MHEALTH IN ADHERENCE TO ORAL ANTINEOPLASTIC TREATMENTS: A SYSTEMATIC REVIEW

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Background: Digital technology today represents an important resource in the field of health care. The literature illustrates numerous studies conducted on the application of mobile Health as a huge potential to be able to influence the behaviors associated with the management of chronic diseases, especially for monitoring and support for adherence to oral treatments. In the oncological field today many patients are treated with oral formulations consisting of antineoplastic drugs, and nonadherence can reach rates between 26%- 63%. To improve information and counteract unintentional nonadherence, generally represented by the omission of the omission linked to forgetfulness, mHealth is useful in long-lasting therapeutic treatments and in patients not inclined to refer to traditional health services. The objective is to summarize the evidence related to the use of mHealth as a support tool to improve adherence to oral cancer treatments.

Materials and Methods: A systematic review was conducted on Pubmed, Cinahl, Scopus, Wos, Cochrane Library and alternative sources. To process the search the terms mhealth, smartphone, app, sms, adherence, tablets and oncology were used, combined with all the possible synonyms and, in PubMed, with the relative Mesh. A screening was performed, on the basis of eligibility criteria, by two independent researchers who evaluated, in later stages, titles, abstracts and full-text articles. Through the use of a bibliographic software, duplicates were eliminated. The reliability of the inter-judge selection was checked in a second screening phase (abstract assessment) through the calculation of Cohen's Kappa.

Results: 1295 articles were identified, of which 147 were duplicates. Of the remaining 1148, were included, only 3 study protocols 1 pilot study, 1 longitudinal study and 2 RCTs published between 2014 and 2018. Overall, all studies assessed the feasibility, acceptability and effect of the intervention on adherence, while only in the 2 RCTs was patient satisfaction considered.

Conclusion: The interest of researchers in the application of digital treatment adherence is strong but, in the field of oncology, there are still a few studies carried out to evaluate its effectiveness, usability, and feasibility. Furthermore, only studies involving a generic oncology patient target have been identified, without paying particular attention to the differences that characterize every single disease and, with it, every treatment.

T13

ROLE OF THE CASE MANAGER NURSE (CMN) IN THE GOVERNANCE OF SERVICES IN MULTIDISCIPLINARY TEAMS. AN AUDIT-REAUDIT ANALYSIS IN THE TREATMENT OF LOCALLY ADVANCED RECTAL CANCER

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Background: In the recent years multidisciplinary teams are substituting for the traditional model of patient care in clinical oncology and the sequential model of assistance is replaced by the so called "Percorsi-Diagnostico-Terapeutico-Assistenziali (PDTA). This kind of novel model of assistance needs an higher level of coordination between the different disciplines and CMN can probably play a major role in favoring the integration of the different services in the different PDTAs. We report the preliminary results of an "audit-reaudit" analysis in the treatment of locally advanced rectal cancer.

Methods: Rectal cancer represents a model of PDTA where an integration between the services is fundamental

for the best outcome of the patients. Starting from an historical observation that more than 30% of the patients were resected later than 10 weeks after chemo-radiotherapy, we introduced a CMN to govern all the steps of patient assistance from the diagnosis to radical surgery. The trial was planned as a phase II trial using the Simon 2-step model, with a target of reducing the rate of the patients resected after 10 weeks from the end of chemo-radiotherapy of 20%.

Results: We present the preliminary results with descriptive aim of an "audit-reaudit" model of clinical governance. 23 patients were treated before the introduction of the CMN with 7 patients (30.4%) that were resected after more than 10 weeks from the end of chemo-radiotherapy (audit phase). After the introduction of the CMN in clinical practice, in the first stem of the Simon model (6 planned patients), all the enrolled patients were resected within 10 weeks from the end of chemo-radiotherapy, and after 18 enrolled patients (66.6% of the total 27 planned patients) 2 patients (11.1%) were resected after more than 10 weeks from the ending of chemo-radiotherapy.

Conclusions: Although our audit-reaudit trial is still ongoing, and our results are preliminary and with descriptive aim, an interesting reduction of the rate of patients that were resected after 10 weeks from the end of chemo-radiotherapy (as recommended by AIOM clinical guidelines) can be observed after the introduction of the CMN in the governance of the steps of the local PDTA. The datum, that surely needs the confirmation after the ending of the trial, probably suggests the need of a CMN both for the governance of the clinical PDTA of rectal cancer, and for the governance of the main PDTAs where an integration between different disciplines is needed.

T14

ROLE OF THE NURSE CASE MANAGER FOR IMPLEMENTING THE MULTIDISCIPLINARY APPROACH OF PATIENTS WITH HEAD AND NECK CANCER. HEAD AND NECK MULTIDISCIPLINARY TEAM AND SITRA (TECHNICAL AND REHABILITATION NURSING SERVICE), FONDAZIONE IRCCS POLICLINICO SAN MATTEO

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Background: The multidisciplinary team (MDT)-based approach in high-volume centers is beneficial for Head and Neck (HNC) pts and guarantees the best oncological outcome. This approach, which includes multimodality treatment with surgery, if indicated, followed by RT, w or w/o CT/targeted drugs is required for locally advanced (LA) disease. Because of the toxicity of treatments and patient's fragilty, changes in the planned program and overall health path are often required. This must be managed rapidly and in a coordinated manner to avoid severe complication and non-adherence to therapies, which may result in a poorer outcome. Aim of this project is to evaluate the impact of the nurse case manager (NCM) within the MDT in the setting of for managing easily and quickly the clinical needs occurring in course of active therapies.

Patients and Methods: From February 2018 the NCM was introduced in the HNC/MDT team, which includes oncologist, radiotherapist, surgeon, pathologist, radiologist, nutritionist, palliative care specialist. The role of NCM is expected to coordinate the many aspects of pts from initial hospital visit through the treatment and recovery journey; to facilitate access to the necessary services and to ensure they receive all of the clinical and social services they need. Objective of the study is to define if the role of the NCM can result in better clinical outcomes, including reduced hospitalizations for side effects. The NCM records the PS and the ESAS, which facilitates monitoring the symptoms that gradually may appear. In relation to the manifest needs nutritional, vulnological evaluation, psychological support, rehabilitation and vaccination program are proactively activated. In course of treatment pts are monitored during the outpatient accesses and have the possibility to contact the NCM by a dedicated phone and e-mail.

Results: From March 2018 ten pts with LAHNC have been so far enrolled in this new organizational model. These pts have not yet completed their therapeutic program and results will be presented at the meeting.

Conclusions: Our ongoing experience of a model with the NCM at the center of the HNC pt's care path is feasible and, despite preliminary, data suggest better outcomes in clinical field which has to be confirmed in a larger series with adequate follow-up.

T15

NURSES SYMPTOMS EVALUATION IN DAILY ONCOLOGY PRACTICE

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Background: The evaluation of symptoms in cancer patients is very important in order to highlight and correct problems that may limit quality of life and sometimes,

require hospitalization. However it takes time, while the daily oncologic outpatient practice often imposes frenetic rhythms and require speed in the execution of the visits.
Methods: From April 2017 to April 2018, 1,382 patients that accessed to Piacenza's medical oncology Day Service were investigated by a nurse with a data collection form (ESAS scale) for presence of some symptoms: pain, fatigue, nausea, depression, anxiety, drowsiness, loss of appetite, discomfort and dyspnea. The nurse also collect data about sex, age, allergies, cancer, treatment and therapy administration method.
Results: A total of 1,382 data collection form were collected, 638 (46.17%) male and 744 (53.83%) female patients with a median age of 63 years; all cancer were represented. Most of the patients accessed for chemotherapy (72.14%), supportive care (16.28%) or transfusional therapy (6.51%) and received therapy with a central venous catheter (PICC (45.6%) and PORTH (13.7%)) or a peripheral venous catheter (38.2%). A different correlation between the analyzed variables and symptoms was observed: nausea, depression, anxiety, loss of appetite and discomfort were related to the patient's sex and treatment and symptoms reported by female patients had a significantly higher level (p value <0.05) than male patients. Fatigue and drowsiness were related to cancer and to therapy administration methods, pain was related to cancer and treatment and dyspnea to treatment.
Conclusions: Symptoms evaluation is important in order to better manage the patient and to reduce side effects. There are differences in patients symptoms reporting, especially related to sex but the treatment performed by the patient has a greater influence on the severity of the reported symptoms. The nurse symptoms evaluation could be the solution to the oncologist limited time to examine patients in a frenetic ambulatory activity.

T16

NURSING INTERVENTION FOR IMPROVING ADHERENCE TO ORAL ANTINEOPLASTIC AGENTS

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Background: It is estimated that 25% of all the targeted anticancer drugs in development will be available only in oral form and the effectiveness is equivalent to targeted i.v. anticancer medications. The introduction of oral therapy has shown a clear improvement and impact on quality of life, being perceived as an advantage over i.v. therapy, especially avoiding hospitalization and placement of a venous access device. The steady increase in the use of OAs has created important issues in influencing adherence with treatment. The strategies described in literature to improve patient adherence to oral chemotherapy include: diaries, calendars, follow up with short telephone calls, Automatic Voice Response, blister packs, electronic pill bottles and use of MASCC Oral Agent Teaching Tool. We conducted a literature review to assess the effectiveness of nursing interventions on improving adherence to oral antineoplastic therapies.
Material and methods: We conducted a comprehensive literature search on Medline(Pubmed), Embase and Cinahl, using relevant terminology for oral antineoplastic agents. 205 items were found and selected according to inclusion and exclusion criteria. The analysis of the full text allowed to include 6 articles in the review
Results: We identified 3 RCT, 1 cohort study and 2 longitudinal studies, published between 2013 and 2015, including 425 participants on oral antineoplastic therapy. In all the included studies the implemented nursing educational strategies proved to be effective in improving adherence rates, although they did not present statistically significant differences, probably due to the small samples. However, the results are encouraging in clinical terms and health outcomes
Conclusions: The studies analyzed state that nursing interventions are valid in the improvement of adherence to oral antineoplastic treatment in cancer patients. Nevertheless further studies may be necessary to consider, with larger samples and more rigorous methodology. In particular, the use of the mobile phone to receive follw-up calls, text messages and voice calls, used as a reminder, was effective in improvement of ahderence. This shows how they are flexible, easy to use and low cost strategies, but not easily suitable for elderly. This limit can be exceeded with others facilitators, such as calendars, diaries or electromechanical systems (MEMS), alerting on the correct moment in which the assumption should take place, thus preventing any oversights.

T17

EFFICACY OF THERAPEUTIC EDUCATION IN ANTIEMETIC MEDICATION TAKING IN PATIENT TREATED WITH CHEMOTHERAPY: LITERATURE REVIEW.

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Background: Nausea and vomiting are the most well known side effects of chemotherapy; antiemetic medications are used to reduced these symptoms. Empowerment of patients in identification and reporting of nausea and vomiting will be helpful to improve therapy adherence,

infact important difficulties in compliance have been observed in every day life. Therapeutic education has a significant role and nurses have the necessary knowledges to educate patients to facilitate the compliance with therapeutic regimen. Through therapeutic education the nurse improves patients quality of life and confort.

Material and methods: Literature has been reviewed including: RCTs, cohort studies and literature reviews. Various data bases have been consulted in August 2017 (Pub Med, Web of Science, Cinahl, Trip Medical Database, Clinical Trial.gov, Google Scolar). Research question has been supported by PIO-PICO methodology. 13 studies were selected, however only 5 studies responded to research criteria.

Results: Study results demonstrate the efficacy of therapeutic education in reducing nausea and vomiting in patients treated with chemotherapy. The following results were recorded: an improvement in therapy adherence in the assumption of antiemetic medication (from 49% to 79%) and a significant statistical fall in the level of discomfort correlated to episodes of nausea and vomiting ($p<0.001$).

Conclusion: Therapeutic education has shown its efficacy in improving patients adherence to antiemetic medication intake with a consequent better quality of life. In literature there are not many evidences about this topic and perform more severe studies should be necessary to demonstrate the importance of therapeutic education in oncological clinical practice.

T18

MINDFULNESS-BASED STRESS REDUCTION IN EARLY PALLIATIVE CARE FOR ADVANCED CANCER PATIENTS (PTS): AN ITALIAN SINGLE-CENTRE STUDY. MINDEEP

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Background: Early palliative care improves quality of life by reducing pain, anxiety and depression in advanced cancer pts. The objective of this study was to evaluate the acceptability and potential benefits of MBSR for pts with cancer pain in early palliative care setting.

Methods: Main inclusion criteria were: advanced cancer pts in early palliative care; NRS >3 ; PS >60% according to Karnosky, informed consent. A group of 20 advanced cancer pts were enrolled after medical team (nurse and palliative oncologist) evaluation. Each session included different forms of mindfulness meditation practice, mindful awareness during yoga postures and mindfulness during stressful situations and social interactions. Participants enter upon enrolling into a commitment to carry out daily 45-min homework assignments. The MBSR protocol was conducted by two trained Mindfulness Instructors with scientific background. A dedicate nurse with experience in palliative care attended each mindfulness session. Primary outcome was total pain at the end of MBSR intervention evaluated by both VAS and ESAS scales. Secondary outcome was mood state change evaluated by POMS questionnaire. Satisfaction of treatment and compliance were also evaluated. All questionnaires along with a form for collecting personal and clinical data were administered by nurse at baseline and at the end of MBSR intervention.

Results: 19 out of 20 were female with median age 54 years old. 56% were receiving morphine for cancer pain. Preliminary results did show slight reduction in total pain score which however was not statistically significant. The POMS test showed significant changes in the mean scores indicating a statistically significant improvement of mood at the end of mindfulness sessions. Compliance in terms of adherence to MBRS program and homework was 70% while patient's satisfation was 78%.

Conclusions: MBRS program for advanced cancer pts appears to be feasibile and well accepted. The improvements in the mood state suggests that the mindfulness techniques could play a role in helping pts to reduce mood disturbance, leading them to better face the cancer, overall. The role of nurse was optimal to allow critically ill pts to participate in MBRS and to guarantee adherence and satisfation. Moreover nurse was very helful to support the mindfulness trainer in managing cancer pts according to their physical needs. Finally the presence of nurse has been evaluated by pts as part of cancer caring.

T19

CENTRAL VENOUS CATHETERIZATION IN CANCER PATIENTS WITH SEVERE THROMBOCYTOPENIA. ULTRASOUND-GUIDE IMPROVES SAFETY AVOIDING PROPHYLACTIC PLATELET TRANSFUSION

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Background: Prior researches show that introducing ultrasound (US) guide in central venous catheterization is associated with a reduction in complication rate such as pneumothorax and an improved first-pass success when placing central venous catheter (CVC) in the internal jugular vein. We sought to investigate within US-guidance

central venous catheterization, in a subset of cancer patients with severe thrombocytopenia also effects the safety reducing bleeding risk and avoid prophylactic platelet transfusion.

Patients and methods: We retrospectively analyzed the efficacy and safety of US-guided CVC placement in cancer patients with severe thrombocytopenia. From December 2000 to January 2009, 1,660 and 207 patients with cancer underwent US-guided CVC placement into internal jugular vein respectively at the oncology-hematology department, Hospital of Piacenza (Italy). The first group of patients included patients in active antitumor treatment while the second group included patients in the palliative phase. One hundred and ten patients (5.89%) of these 1,867 patients showed severe thrombocytopenia defined as platelet count ⩽ 20x109/L. These 110 thrombocytopenic patients form the basis of this study. All procedures were evaluated for bleeding complications as defined by the National Institute of Health Common Terminology Criteria for Adverse Events (CTCAE 3.0).

Results: In the entire group of 1,867 cancer patients that underwent 2,187 insertional CVC procedure, no pneumothorax, no major bleeding, no nerve puncture were reported, only 6 arterial puncture of 2,187 procedures (0.27%) and 4 (0.18%) of self-limiting hematomas were registered. In the subgroup of 110 patients with severe thrombocytopenia a single needle puncture of the vein was done on 121 of the 122 procedures (99.18%) and not attempts failure were registered. No pneumothorax, no major bleeding and no nerve and arterial puncture were reported, only one self-limiting hematoma (0.90%) at the site of CVC insertion was reported (CTCAE 3.0 grade 1). No platelet transfusion were done in the 110 patients, pre and post CVC placement.

Conclusion: We believe that US-guidance of CVC insertion procedures into the internal jugular vein makes the difference in safety, also in thrombocytopenic patients avoiding prophylactic platelet transfusion

T20

LII: THE PROTOCOL LITERATURE AND IMAGINATIVE INTERPRETATION, FOR DIFFICULT REMOVAL OF A PICC

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Background: The patientcare requires frequently the availability ofa reliable long-medium term venous access, due to the particular complexity of the chemotherapy regimens, the frequent need for a nutritional or transfusional support and for periodic blood sampling. Peripherally Inserted Central Catheters (PICC) are an important innovation technology that has substantially changed the approach to the venous system.

Methods: We reviewed the literature after a case of difficult removal of a PICC. Later we interpreted the few data collected adapting them to the situation in order to avoid invasive approaches.

Results: After one case of difficult removal of PICC we resorted to the interventional radiologist who was able to remove venous access through angiography with cannulation of the femoral vein. When other two case occurred, thanks to the review of the literature and to the "imaginative" interpretation of the scarce data available, we were able to remove both the vascular accesses simply by applying a gentle pulling and a taped tension for a duration of at least 20 minutes on two consecutive days.

Conclusions: PICC represent the best response to the growing need to get in each patient both in hospital and at home, a stable and safe venous access, achieved and maintained with the little risk and the best cost-benefit ratio. Resistance to removal is a rare complication whose causes are still unknown though vasospasm appears the more probable explanation. Gentle pulling, taped tension and warm soaks result almost always the best techniques to apply in order to obtain the removal. Recourse to an interventional procedure may be needed only in rare cases.

T21

HORTICULTURAL THERAPY IN ONCOLOGY: A SYSTEMATIC REVIEW

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Background: The management of cancer patients has until now been entrusted only to traditional medicine. In recent years, however, there has been a growing interest in patients interest towards complementary and alternative medicine (CAM). Some authors say that especially in the palliative phase the same patients tend to resort to this type of care approach to improve their well-being, to increase their self-control and to better manage the different symptoms. A useful way to deal with the emotional and spiritual problems that these patients face daily, are the therapies that allow patients to establish a deep connection with nature and to experience feelings of "life" through, for example, the gardening or meditation in open environments. The objective of this study is to analyze how horticultural therapy can contribute to the management of cancer patients.

Materials and methods: Systematic review of the literature. The databases Pubmed, WOS, Scopus, Cinahl, and Google Scholar were consulted, using the following string

"Horticultural Therapies", "Therapies, Horticultural", "Therapy, Horticultural". Only articles in English or Italian were included for studies conducted on adults with cancer, with no restrictions on the date of publication. The reliability of the selection was evaluated in each phase through the calculation of Cohen's Kappa inter-researcher.
Results: 377 articles were identified and were then subsequently subtracted due to duplicates by referent management software, Mendeley, consequently reducing the number of articles to 324. The abstracts of the articles were translated in twice and only 3 articles were eligible and therefore a pilot study and two systematic reviews were included in the review.
Conclusions: Horticulture has had a beneficial effect on the quality of life of cancer patients, particularly in the perception of health, in vitality, in the emotional role, in mental health ($P < 0.05$) and also on fatigue. One limitation of the study is the small number of scientific articles found in the literature.

T22

THE NEEDS OF THE CAREGIVER DURING THE HOSPITALIZATION OF ONCOLOGICAL PATIENTS

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Background: Cancer is an event capable of destabilizing the individual and the whole family nucleus. In our country, as well as internationally, assistance to cancer patients is largely borne by informal caregivers who in most cases are the closest family members. The literature demonstrates a close correlation between the psycho-physical repercussions of the cancer patient and those of the caregiver in the care pathway, especially in the home or in the Hospice, rather than during hospitalization. The latter is a further problem because the caregiver is not always prepared for the situations they will have to face at this stage of the care process of their loved one. The objective of this study was to identify the needs perceived by the caregiver during hospitalization.
Materials and methods: Observational study. The caregivers of patients who had been in hospital for at least three days were enrolled at an IRCCS in Rome aged> 18 years from December 2016 to March 2017. A standardized questionnaire for evaluating the socio-demographic data was given along with the Caregiver Needs Assessment (CAN) questionnaire to analyse the caregiver needs. A descriptive analysis and association between categorical variables was performed through the Chi-square test with a statistical significance of $p < 0.05$ using the Statistical Package for the Social Science (SPSS) Chicago program. (version 21).
Results: The sample consists of 301 caregivers predominantly women (65.3) with an average age ranging between 41 and 50 years. It has emerged that the caregiver requires training on the care needs of the family members involved (55.4%), as well as to be informed about the treatment care pathway of the sick member of the family by doctors and health care workers (80.2%). The correlational analysis showed that caregivers need information about the disease (p. 0.007) on how to help the patient (p 0.000), as well as psychological support (p.0.000), while they know who to contact in case of economic difficulties linked to the disease (P. 0.000).
Conclusions: Caregivers of hospitalized cancer patients need more information on the therapeutic process and psychological support. The need for effective and clear communication remains a crucial aspect of quality care in the field of oncology, both for the patient and for the family members involved in the treatment process.

T23

"THE MAIN FACTORS INFLUENCING ADHERENCE TO TARGETED AND ORAL THERAPIES AND THE MAIN SIDE EFFECTS: DESCRIPTIVE STUDY"

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Aims: In the last years there has been a significant increase of oral chemotherapy and target therapies in cancer treatment . The transition from an intravenous chemotherapy to as oral one has brought many advantages to the patient, first of all a lower impact of toxicity on the activities of daily life, but it has raised the problem of therapeutic adherence.
Objectives: 1) Identify and describe the main factors influencing adherence to targeted therapies;
2) Identify and describe what are the most common side effects of the drugs used in the study.
Methods: Quantitative descriptive study.
Structured questionnaires were distributed, in anonymous and voluntary way between November 2017 and January 2018 to the cancer patient during oral chemotherapy and targeted treatment, in day hospital. Quantitative data were summarized in descriptive tables. Frequencies were compared with a chi-squared test. The data were processed using programme INSTAT.
Results: A total 103 questionnaires were collected and distributed.72% of patients reported optimal adherence. 30% identified fear of side effects as the main cause of poor

adherence. The most frequently side effects was asthenia (69%), followed by diarrhea (43%) and nausea (32%). For 57.2% of patients side effects have had little influence on daily life activities. Differences were statically significant for: treatments for effects in relation to gender, comparison between gender and manifestation of side effects, comparison between living alone and side effects.
Conclusions: The rate of adhesion, the causes of poor adherence and the main side effects reported in the study, correspond to what is described in the literature. Drug-related toxicities have not had a major impact on patients' daily activities.

T24

"THE CAREGIVERS OF END STAGE CANCER: THE STORY OF THEIR EXPERIENCES, A QUANTI-QUALITATIVE ANALYSIS"

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Introduction: During the last decade health care has been largely a burden of the informal caregivers, who respond to the needs of the patient, in term of basic care and emotional support. The caregiver bears responsibilities that are physically and affectively very challenging even though he or she has not a specialist training. Furthermore the caregiver is involved also from the emotional point of view.
Objectives: The aim of this study is to analyse the experiences, the obstacles and the emotions felt by caregivers during the disease of the patient and to investigate the occupational, economic, emotional and physical impacts of caregiving.
Materials and Methods: The quanti-qualitative descriptive study was conducted in the department of Medical Oncology 1 of the Città della Salute e della Scienza, in the Molinette Hospital of Turin. Data were collected through a questionnaire composed of 8 item, followed by an interview.
Results: The interviewees were 59 caregivers, all of whom had completed the questionnaire. From the analysis of the data, 85% of the sample is female with an average age of 57 years, 41% have a marital relationship with the patient, 32% are their children, 15% are brothers or sisters of the patient, 8% are their parents, 2% are carer and nephews. 92% of the sample states that the experience has had a significant impact on their daily life, in particular: physical tiredness (56%), difficulty in managing home and family (31%), while there were no repercussions on working life and economic situation (56%). 63% of caregivers said they were not ready to play this role, however some positive aspects emerge from the experience, such as: 36% more time and care given to your loved one and 21% rediscovering of the the value of small things . 73% say that the most difficult aspect to deal with is psychological support, followed by 22% sanitation and 5% drug administration. The most common feelings were impotence, sadness and fear.
Conclusions: What emerged from this study was that the caregiver experience of end stage cancer patients has important implications for a person's life. The habits, the schedule and the certainties of the daily routine are going to be altered, to redefine the roles within the family unit. Constant support should be given to caregivers, offering more empathy, active listening, training and adequate psychological support.

Late Breaking Abstracts

*LBA2999

THE HOBOE-2 MULTICENTER RANDOMIZED PHASE 3 TRIAL IN PREMENOPAUSAL PATIENTS WITH HORMONE-RECEPTOR POSITIVE EARLY BREAST CANCER COMPARING TRIPTORELIN PLUS EITHER TAMOXIFEN OR LETROZOLE OR ZOLEDRONIC ACID + LETROZOLE

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Background: Role of aromatase inhibitors and zoledronic acid as adjuvant treatment of premenopausal patients (pts) with hormone receptor positive breast cancer is debated. Letrozole has never been tested in this clinical setting.
Patients and Methods: Women operated for an estrogen/progesterone receptor positive early breast cancer with last menses within 1 year from randomization were eligible. Previous adjuvant and/or neoadjuvant chemotherapy was allowed. Triptorelin 3.75 mg every 4 weeks for 5 years or up to the age of 55 was given to all patients. Pts were randomly assigned 1:1:1 to (T) tamoxifen 20 mg/die, (L) letrozole 2.5 mg/die or (ZL) zoledronic acid 4mg iv every 6 months + letrozole 2.5 mg/die. The primary end-point was disease-free survival (DFS) including locoregional or

distant recurrence, second breast or non-breast invasive cancer and death without cancer as event. Analyses were based on intention to treatment. Pairwise comparisons (with Bonferroni-Holm correction) were allowed if overall test was statistically significant.

Results: From March 2004 to August 2015, 1065 pts were randomized (T: 354, L:356, ZL: 355). Median age was 45. 68% had a pT1 tumor, 55% had negative axillary nodes and 63% had received chemotherapy. After 65 months median follow-up, there were 58, 44, and 32 DFS events and 5 yrs. DFS probability was 0.85, 0.93 and 0.93 in the T, L and ZL arms, respectively (overall Log-rank test P=0.008). Pairwise comparison was statistically significant for ZL vs T (HR 0.52, 95% CI 0.34-0.80, P=0.003) but not for L vs T (HR 0.72, 95% CI 0.48-1.07, P=0.06) and ZL vs L (HR 0.70, 95% CI 0.44-1.12, P=0.22). ZL was more effective than T in all subgroups, but for HER2-positive cases (interaction P=0.002). The HR with ZL vs T was 0.36 (95% CI 0.17-0.73) in under- or normal weight pts and 0.67 (95% CI 0.37-1.19) among those over-weight or obese (P for interaction = 0.18). 26 (7%) pts with T, 26 (7%) with L and 59 (17%) with ZL stopped assigned treatment before than 5 yrs due to toxicity or refusal. Grade 3-4 side-effects were reported in 4%, 7% and 9% of the pts with T, L and ZL, respectively. Four pts had jaw osteonecrosis in the ZL arm.

Conclusions: HOBOE shows that, in premenopausal early breast cancer pts, the ZL+triptorelin combination is more effective than T+triptorelin in terms of DFS, but with a worse compliance.

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A*LBA3266

PROSPECTIVE MULTICENTER STUDY ON THE IMPACT OF THE 21-GENE RECURRENCE SCORE IN ADJUVANT CLINICAL DECISIONS FOR PATIENTS WITH ER POSITIVE/HER2 NEGATIVE BREAST CANCER IN LOMBARDY (BONDX STUDY)

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Background: The BONDX prospective study evaluated the impact of the 21-gene recurrence score (RS) result on adjuvant treatment decisions for patients with early breast cancer (eBC) in Lombardy.

Materials and Methods: 4 large public hospitals in Lombardy (H-Papa Giovanni XXIII in Bergamo, H-Civili in Brescia, H-FBF in Milan, H -St. Anna in Como) participated into the study. All consecutive patients with ER-positive, HER2-negative, T1–T3, N0–N1 eBC were prospectively registered; only those meeting protocol defined clinico-pathological intermediate risk criteria were eligible for the RS test. Initial physician adjuvant recommendation was blinded to the TS results. Final adjuvant recommendation was based also on RS results. Pre-RS and post-RS physicians' adjuvant recommendations and treatment actually received were collected and compared.

Results: A total of 388 (266 N0 and 122 N1) consecutive patients were enrolled and evaluated from Jan 2017 to Jun 2018. The majority had Grade ≤ 2 tumors (73%, G1=4.1%); median age was 62 years, median tumor size was 16 mm, and median Ki67 expression was 20%. According to the ongoing registered OncotypeDx risk classification, the distribution of RS results was <18 in 60.3%, 18–30 in 33.8%, and >30 in 5.9%. The indication before RS was hormonal therapy (HT) alone in 75.3 % of cases. An indication for adjuvant chemotherapy (CT) before the RS results was given in 24.4% of pts, more frequently in N1 versus N0 cases (38.8% vs. 18.1%). After the RS results, the overall rate of change in treatment decision happened in 58 cases (14.9%), either sparing CT in low risk RS (n 46) or adding it in high risk RS (n 12). Adjuvant initial recommendations were not changed in intermediate risk RS results. According to nodal status, rate of change in treatment decision (either sparing or adding CT) was 36 pts for the N0 cohort and 22 pts for the N1 cohort. Adjuvant CT was reduced from before to after RS (24.4% to 12.3%), especially in the N1 cohort.

Conclusion: Despite frequent indication of HT before RS, the use of the RS assay further contributed to sparing CT, especially for patients with N1 tumors. In case of N0 tumors, the implementation of the dichotomous approach of the TAILORx study, eliminating the cohort of "intermediate risk", will be incorporated and analyzed and may produce a major impact in the rate of change in treatment decision.

B*LBA3037

NEGATIVE HYPER-SELECTION OF RAS WILD-TYPE (WT) METASTATIC COLORECTAL CANCER (MCRC) PATIENTS RANDOMIZED TO FIRST-LINE FOLFOX PLUS PANITUMUMAB (PAN) FOLLOWED BY MAINTENANCE THERAPY WITH EITHER 5FU/LV PLUS PAN OR SINGLE-AGENT PAN: TRANSLATIONAL ANALYSES OF THE VALENTINO STUDY

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Background: *RAS* wt unresectable mCRC pts were randomized 1:1 to FOLFOX + Pan induction (8 cy) followed by maintenance with Pan (arm B) or 5FU/LV + Pan (arm A). Exploratory endpoints included biomarkers according to PRESSING panel (Cremolini, Ann Oncol '17), including multiple rare genomic resistance alterations beyond *RAS/BRAF*.

Patients and Methods: Primary endpoint was PFS non-inferiority of arm B vs A. A sample size of 224 pts achieved 90% power to detect 50% 10-month PFS in arm A and max 15% less in arm B, significance level 0.1. Translational analyses: ISH for *HER2/MET*amplification; IHC +/- RNA-seq for *ALK/ROS/TRKs/RET*fusions; NGS (Hotspot Cancer Panel/Ion Torrent®) for low %/atypical *RAS, HER2*and *PI3K/PTEN*mutations; PCR for MSI.

Results: 229 pts randomized (117 arm A/112 arm B). The upper boundary of one-sided 90% CI of HR was 1.857 (exceeding the 1.515 boundary). At updated median follow-up of 18.0 mos, 10-m PFS was 49% for arm B vs 59.9% for arm A (HR=1.51, 95% CI: 1.11-2.07; p=0.009).

Primary sideness analysis (right-sided 19 in arm A and 21 in arm B): mPFS: 7.4 vs 11.2 mos for right- vs left-sided (HR=1.83 [1.26-2.68]; p=0.002). 7.0 vs 8.7 vs 10.6 vs 12.9 mos for right-sided arm B vs right-sided arm A vs left-sided arm B vs left-sided arm A (right-sided B vs A: HR=1.73 [0.85-3.51]; p=0.129/Left-sided B vs A: HR=1.52 [1.07-2.15]; p=0.019/interaction test NS).

PRESSING panel analysis (167 evaluable *RAS* and *BRAF* wt pts up to now, of whom 18 PRESSING pos in arm A and 20 in arm B): mPFS: 7.6 vs 12.4 mos for PRESSING pos vs neg (HR=2.13 [1.42-3.18]; p=0.0002). 7.5 vs 11.1 vs 11.6 vs 13.2 mos for PRESSING pos arm B vs PRESSING pos arm A vs PRESSING neg arm B vs PRESSING neg arm A (PRESSING pos B vs A: HR=2.18 [0.97-4.90]; p=0.059/PRESSING neg B vs A: HR=1.56 [1.02-2.41]; p=0.043/ interaction NS).

Primary sideness and PRESSING *post-hoc* combined analysis: mPFS: 7.9 vs 12.6 mos for predicted resistant (R) vs sensitive (S) (HR=2.08 [1.43-3.02]; p=0.0001). 7.6 vs 9.9 vs 11.8 vs 14.2 mos for predicted R arm B vs predicted R arm A vs predicted S arm B vs predicted S arm A (predicted R B vs A: HR=2.03 [1.03-4.03]; p=0.042/predicted S B vs A: HR=1.55 [0.98-2.45]; p=0.062/interaction NS).

Conclusions: Statistically significant/meaningful inferior PFS was observed in *RAS*/*BRAF*wt, right-sided and/or PRESSING pos pts in Pan alone arm. Future studies on non-inferiority of maintenance with single-agent anti-EGFRs should focus on hyper-selected, *RAS-BRAF*wt, PRESSING neg, left-sided mCRC.

C*LBA3256

MICROSATELLITE INSTABILITY (MSI) IN RESECTED GASTRIC CANCER: CORRELATION WITH CLINICOPATHOLOGIC AND MOLECULAR PROFILE. A TRANSLATIONAL ANALYSIS OF ITACA-S STUDY

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Background and Rationale: While the role of microsatellite instability (MSI) in the adjuvant setting in colorectal cancer is well established, its correlation with the outcome in resected gastric cancer (GC) patients is yet to be determined. Data from a MAGIC trial post-hoc analysis documented that the MSI-high (MSI-H) status can be a good prognostic factor in patients treated with surgery alone and a negative predictive marker of benefit from perioperative chemotherapy. Moreover, the use of adjuvant oxaliplatin-based chemotherapy seems to be ineffective for the MSI-H GC, as showed in the CLASSIC trial. However, the low prevalence of MSI-H tumors and the data in the Eastern population obtained only from retrospective analysis prevent any conclusions. The ITACA-S is a phase III study comparing disease-free (DFS) and overall-survival (OS) in

stage II/III radically resected GC patients treated with adjuvant FU/LV versus sequential FOLFIRI followed by cisplatin and docetaxel. Tumor specimens and clinical information were collected from patients enrolled. The present study is focusing on assessing the association between MSI-H status, clinical-pathological characteristics and patients' outcome.

Methods: Formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks were collected and five quasi-monomorphic mononucleotide markers to assess tumor MSI status. Kaplan-Meier method and Cox's proportional hazards models were used for survival analysis.

Results: 346 tissue samples were collected from 23 Institutions. Of 255 evaluable tumors for MSI status, 25 (9.8%) had MSI-high tumors. Intestinal type (p=0.002) and N stage (p=0.03) were significantly associated with MSI-H status. 3-year RFS was 72.0% (56.4-91.9) in MSI-high subgroup versus 47.3% in MSS one (41.2-54.2) (HR=0.54; 95% CI 0.28-1.02; p=0.057). 5-year OS was 68.7% (51.6-91.6) in MSI-high subgroup versus 42.5% in MSS one (36.2-50.0) (HR=0.47; 95% CI 0.23-0.96; p=0.038). In multivariable analysis of RFS and OS, T, N stage were independent prognostic factors, whereas MSI status was no longer significant. In both MSS and MSI-high subgroups, no major differences were observed in the RFS and OS curves according to treatment arm (test of treatment by MSI status interaction: p=0.842 for RFS and 0.986 for OS).

Conclusion: MSI status may be a useful prognostic biomarker for stratifying patients after D2 gastrectomy for stage II/III gastric cancer and should be used as stratification factor for future trials.

CLBA3286

PROGNOSTIC ROLE OF EARLY NUTRITIONAL SUPPORT IN UPPER GASTRO-INTESTINAL (GI) CANCER PATIENTS UNDERGOING SURGERY AND/OR CHEMOTHERAPY

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Background: patients (Pts) with upper gastro-intestinal cancer (upper-GIC) are a group sensitive to nutritional complications. Chemo/RT treatments and surgery contribute to reduce caloric intake. Malnutrition and weight loss can reduce the tolerability of chemotherapy treatments with an increased toxicity and a reduction in overall survival. An early nutritional assessment can reduce the risk of malnutrition with a positive impact on overall survival (OS).

Material and Methods: Records of patients consecutively evaluated in our institution for upper-GIC from December 2016 to February 2018 were retrieved. 112 Pts (Group A) were evaluated with an early nutritional support within 4 months from the first oncologic observation in order to assess the risk of malnutrition. The remaining 150 Pts (Group B) consisted in the control arm. We have record height, weight and body mass index (BMI) at the first nutritional visit and then after 3 to 6 months. Moreover, we have evaluated the maximum per patient Grade 3-4 toxicity and OS for all patients.

Results: we consecutively evaluated 262 Pts with upper-GIC, 105 females and 157 males, mean age of 67 years; 89 pancreatic cancer (PC), 116 oesophageal-gastric cancer (EGC) and 57 biliary tract cancer (BTC) Pts. 140 Pts had a Stage IV disease and 122 Pts had a non-metastatic disease. 206 Pts had undergone at least one active treatment: surgery or/and chemo-RT therapy. At the first nutritional assessment Group A Pts underwent a nutritional screening with the MUST (Malnutrition Universal Screening Tool): 14 Pts had a low nutritional risk, 64 a medium nutritional risk and 34 a high nutritional risk. Every Pts received a dietary regimen to follow; enteral nutrition together with oral nutrition was indicated for 4 Pts; parenteral nutrition together with oral nutrition for 6 Pts and oral supplements for 14 Pts. A 3-4 grade toxicity (haematological and non-haematological toxicity) was experienced by 35 (39%) Pts of Group A and 25 (37%) Pts of Group B. OS was 11.5 months for Group A and 5.0 months for Group B.

Conclusions: the weight loss registered at the first nutritional assessment could be due to surgery and/or chemotherapy. An early nutritional assessment and nutritional support can lead to a reduction in weight loss and an increase in food and calories intakes. Early nutritional intervention may contribute to improve short-term prognosis of patients affected by upper gastro-intestinal cancer undergoing surgery and/or chemotherapy.

TLBA2877

TELEPHONE INTERVIEW SCHEDULED FOR EARLY DETECTION AND CARE OF SEVERE SIDE EFFECTS FROM CHEMOTHERAPY

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Most of cancer patients underwent chemotherapy and/or radiation therapy with the consequent need to manage associated side effects.

The side effects of chemotherapy are one of the main causes of the worsening of quality of life of cancer patients, as well as the cause of necessary dosage reductions of chemotherapeutic drugs modification of the treatment or even suspension of treatment for more or less prolonged periods of time.

With a view to all-around management of the patient and with the aim of guaranteeing the highest standard of quality of life as possible, the intent is to check whether systematic telephone monitoring 48 hours after the administration of the chemotherapy cycle, can guarantee an early detection and treatment of the side effects, in order to immediately treat them, therefore offering a better quality of life for the patient and better management of the therapies.

After 48 hours from the administration of each cycle of chemotherapy a nurse contacts the patient by telephone in the morning. The phone call made in the early hours of the day will allow patients with evidence of various degrees of side effects to be cared for more quickly.

Patients in whom a ≥2 side effect is detected (during the telephone interview) will be recontacted by telephone after 24 hours.

If the presence of side effects with grade = 3 is confirmed the patients are immediately taken care of by the emergency care doctor in order to arrange a visit to the Oncology Unit or to request

General Physician care or (in the case of patients undergoing palliative care / simultaneous therapies) a home visit of the doctors and nurses of the Service. In the most serious cases the patient will be sent to the Emergency Room where oncologists will collaborate with the ER doctors.

A suitably adapted CTAE (Common Terminology Criteria for Adverse Events) and a NSR (Numerical Scale Rate) for pain assessment is used as a reference tool.

The information will be acquired through a questionnaire that takes into consideration the following side effects: Fatigue Nausea Vomiting Diarrhea, Constipation Mucositis/stomatitis Body temperature Pain.

At 3 months the project demonstrated organizational and effective feasibility: the identification of the degrees of side effect G2 and G3 has proved to be timely, allowing an effective management

The use of telephone conversation emphasizes the centrality of the human relationship between nurse and patient and was appreciated by patients.

TLBA3218

WE, NURSES: FORMED AND INFORMED IN THE FIGHT AGAINST TOBACCO SMOKE

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Background: According to WHO (World Health Organization), smoking habit can be considered a form of epidemic contagious pathology. It causes 5 million deaths worldwide each year, of which 90,000 in Italy. Furthermore, it causes 20-25% of all cases of heart attacks and 30% of deaths due to cancer disease. Nurses' involvement is essential for the fight against smoking, as they play an important role in health promotion. At the Outpatient Ward of Humanitas Gavazzeni a group of nurses, trained by the Health Protection Agency of Bergamo, proposed to all patients a short interview of about 3-5 minutes (minimal advice) to investigate the key points to work on in order to help them to quit smoking. The annual rate of people who spontaneously stop smoking is 2%, but it can increase to 5% if the so-called "short interventions" or "first level" (minimal advice) are implemented by properly trained nurses. The aim of our analysis was to evaluate the perceived effectiveness and the impact on nurses of the interview through a self-assessment questionnaire.

Material and Methods: After "minimal advice" administration the nurse responded a self-assessment questionnaire regarding their own perception of the intervention. We evaluated the percentage of response and the nurse's perception soon after the short interviews.

Results: We proposed the short questionnaire to 158 patients in the Oncology outpatient ward of Humanitas Gavazzeni of Bergamo, from March 2017 to august 2018. For more than 70% of patients who are asked the question "Would you stop smoking, if it was easy?" the reply was affirmative. The perception experienced by the operator during the questionnaire administration, according to the self-assessment questionnaire was as follows: 13 (8.2%) were "at ease", 80 (50.6%) were "at ease and relaxed", 3 (1.8%) were "at ease, relaxed and self-confident", 1 (0.06%) was "at ease and self-confident", 8 times "relaxed", 53 answers were missing.

Conclusions: Nurses can play and important and active role in the fight against smoking, starting from the enhancement of their work and their position of proximity to the individual and the community. According to the self-assessment questionnaire, minimal advice is an effective and easily applicable intervention, if implemented by the properly trained nursing figure, in fact more than 50% of nurses felt at least at ease during the minimal advice administration.

TLBA3220

TABAGISM AND NURSE COUNSELING THROUGH MOTIVATIONAL INTERVIEW IN SMOKER PATIENT, A SINGLE INSTITUTION EXPERIENCE

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Background: A great percentage of cancer patients have smoking habit. We should encourage them to quit smoking, but this can be a quite difficult challenge. In order to help smokers, we should give them adequate information about potential damages deriving from tabagism, but even motivate and support them in quit smoking by providing advices about the possibility of medical, psychological and pharmacological assistance. The aim of our experience was to identify smokers patients and motivate them to stop smoking, through a brief motivational interviews (5-10 minutes) administered by the nurse at the first hospital access.
Matherials and Methods: A short interview about smoking attitude was administered to all patients by the accepting nurses at the time of the first access at the Oncology outpatient ward in Humanitas Gavazzeni (Bergamo). The interview consists in a brief questionnaire (14 questions) aimed to define smoking habits, awareness of damages caused by tabagism and the motivation to quit smoking. Among smokers, we identified 4 different classes, according to the attitude about quitting: former smokers (less than six months) (A), pts trying to reduce smoking (B), pts contemplating the idea of stop smoking (C) and those who have no intention to change their habit (D).
Results: We interviewed a total of 158 pts from march 2017 to august 2018. Patients characteristics were as follows: male/female 79/79 (50% each), smokers/ no smokers or former smokers 55 (34.8%)/ 103 were (65.2%). Among smokers, the attitude to stop smoking was as follows: group A 14 pts (25.5%), group B 12 pts (21.8%), group C 18 pts (32.7%)and 11 pts (20%) in group D. At the end of the talk, 61% of smokers pts were motivated to quit smoking and 75% considered to have had adequate answers about their doubts and needs. The interview lasted less than 5 minutes in 129 pts (82%), from 5 to 10 minutes in 25 (16%) and more than 10 minutes in 4 pts (3%).
Conclusions: Stop smoking can be a difficult challenge, even in cancer patients. We identified a brief questionnaire which can be easily administered by nurses (less than 5 minutes in most cases), with the aim of identifying smoker pts and give them adequate information and support in quit smoking. We observed a good attitude of the pts regarding a short but efficient motivational talk, and a great part of them declared to wish to quit smoking. It can have long lasting impact of smoking attitude deriving from this kind of counseling.

Short Communications

FAST TRACK PAIN CONTROL IN CANCER PAIN: RAPID OPIOID TITRATION FOR CANCER PATIENTS ADMITTED IN AN ONCOLOGICAL WARD.

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Background: Pain is still one of the most common symptoms in the course of malignancies. Assessment and treatment of pain should begin as soon as possible and be strictly followed until pain become tolerable by the patient. Rapid opioid titration (ROT) has been shown to be a safe and effective way of rapidly reaching the effective opioid dose. Herein, we evaluated the role of ROT in cancer patients with pain admitted to oncological department. We hypothesized that a ROT schedule may achieve a shorter time to pain control and may impact on patient's health.
Material and methods: In six month, 57 patients were admitted to the oncology ward for severe cancer related pain. 20 of these patients were treated with the ROT schedule and another 37 were submitted with the standard increase of opiates (NROT). We compared the response to the treatment, length of stay, total opiates dose, and opiates adverse reactions. ROT method consists in subjecting patients to rapid titration throught the intravenous administration of morphine chloridrate. In patients not pretreated with strong opiates 2 mg boluses were repeatedly administreated every 5 to10 minutes until pain were referred to be under NRS 5. In patients undergoing treatment with strong opiates, doses of 5 mg were chosen. Pain was assessed by nurses using NRS scale al least every 8 hours and prophylactic medications for emesis and constipation were routinely prescribed.
Results: Days until NRS $<$ 50% was significantly (p 0.002) higher in patients treated with NROT than those treated with ROT (4.2$\pm$4.3 days vs 0.5$\pm$1.98 days, respectively). Reached oral morphine doses was higher in ROT patients respect NROT group (114$\pm$105.3 mg vs 115$\pm$117.2 mg, p 0.009). The duration of hospital stay was shorter in the ROT group than in NROT group (12,2 days vs 13,2 days), without a statistical significance (p 0.078). The adverse event opioid-related and safety were similar in the two study groups.
Conclusions: ROT could be consider the optimal way to treat cancer pain during hospital admission. Our data support the application of the ROT scheme witch induces a great shortening of the pain management period in comparison to the classic use of analgesic drugs. This is due both to the short time between dose increase and to the higher total dose of opiates. Moreover the control of the quickest pain should improve the overall quality of life, the mood, the nutrition and the mobilization of oncologic patients.

SUBGROUP ANALYSIS AND CIRCULATING BIOMARKERS EVALUATION OF RESORT TRIAL: A RANDOMIZED PHASE 2 STUDY IN METASTATIC RENAL CELL CARCINOMA

(MRCC) PATIENTS (PTS) TO EVALUATE THE EFFICACY OF SORAFENIB AFTER METASTASECTOMY.

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Background: RESORT trial (NCT01444807) was the largest prospective study whose aim was to assess the role of VEGF inhibition in mRCC pts after radical metastasectomy. It showed that sorafenib (SO) was safe and feasible but did not affect Relapse-Free Survival (RFS) compared to observation (OBS) in this population. Early identification of dynamic predictors of outcome, such as Circulating Tumor Cells (CTCs) may be helpful to move up clinical tumor relapse.

Methods: Pts were randomized (1:1) within 12 weeks from surgery to receive SO or OBS for a maximum of 52 weeks or until disease recurrence, with stratification according to time from nephrectomy to metastases (more or less than 12 months), site of disease (lung vs others) and number of lesions (single vs multiple). Blood samples for CTCs were performed at baseline, month 6, end of treatment and at disease relapse. Peripheral blood samples (5 mL) were processed with the AdnaTest Prostate Cancer Select kit for CTC enrichment. CTCs identification was based on expression levels of EPCAM, MUC1 and ERBB2 measured by RT-multiplex PCR (Breast Cancer Detect Adna Test kit) using cutoffs defined on purpose based on expression in healthy donors.

Results: From November 2012 to November 2017, 76 pts were enrolled (32 in SO and 36 in Obs arm); 6 were screening failure and 2 pts never started treatment. A total of 55 pts had single metastasis resected, 26 in SO arm and 29 in OBS arm; the remaining 13 pts had multiple lesions, 6 in SO arm and 7 in OBS arm. Pts with single mets showed a longer median RFS in comparison to pts with multiple resected mets (39 vs 29 months), irrespective of the arm. Pts with single mets had an improved RFS when received SO compared to pts in the OBS arm (39 vs 20 months). A positive CTCs status was observed at baseline in 31% of pts in both arms and was not associated with RFS. Similarly, no associations were observed between CTCs status switches during SO or Obs and RFS.

Conclusions: Pts with single metastasectomy had better prognosis compared to pts with multiple lesions; SO improved RFS in this group of pts. CTC status and its changes during treatment were not associated with RFS.