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LETTER

Dear Friends and Colleagues,

The scientific program of the Italian Melanoma Intergroup (IMI) Congress, held in Turin in 2021, was characterized by presentations and comparisons of the latest research carried out by various disciplines dealing with melanoma and complex non-melanoma skin cancers. The abstracts published in this issue of Dermatology Reports represent the basis and "soul" of the Italian Melanoma Intergroup, which is increasingly being affirmed as a vital reality in research, clinical practice, and the advancement of young researchers. One such young researcher is Federica Zamagni, a biostatistician of the IRCCS IRST (Romagna Cancer Institute). Dr. Zamagni was awarded the Elvo Tempia Prize 2021 for her work on the historical improvement in melanoma patient survival related to the impact of new therapeutic strategies; conferral took place during the Congress of the International Association of Cancer Registries (IACR). The research, a continuation of a joint study by AIRTUM (Association of Italian Tumor Registries), was supported by funding from IMI and the Italian Health Ministry. Once again, a multidisciplinary approach in the diagnosis and treatment of melanoma proved successful.

Ignazio Stanganell, *President*
Italian Melanoma Intergroup (IMI)

EPIDEMIOLOGY, GENETICS AND PATHOGENESIS

A01

RISK FACTORS IN PEDIATRIC MELANOMA: A RETROSPECTIVE STUDY OF 39 CASES

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Objective: Pediatric melanoma is a rare form of tumor whose epidemiology is widely increasing thanks to the improvement of dermoscopic and anatomopathological diagnostic techniques. Although it is a tumor of considerable interest in adults, little has been described about the pediatric field. The objective of our study was then to identify the possible risk factors for the development of melanoma in the pediatric population

Setting: We performed a retrospective study conducted in the Melanoma and Skin Cancer Unit and Unit of Dermatology (Livorno, Italy).

Patients: We analyzed a population of 38 children under 21 years with a diagnosis of melanoma. This population was compared with a control population of 114 children followed up in our dermatological clinic.

Results: From our combined univariate-multivariate statistics analysis, the number of nevi [Regression Coefficient (RC) of 1.04 and Odds Ratio (R) of 2.8 (Cl 1.2-6.6)], exposure to environmental pollutants [RC of 1.24 and OR of 3.5 (CI 1.3-9.4)] and familiarity [CR of 1.99 and OR of 7.3 (Cl 2.3-22.7)] emerged as possible risk factors for the development of melanoma.

Conclusions: The identification of these elements would allow the physician to carry out a more targeted preliminary assessment of the patient, potentially decisive in cases of diagnostic doubt of the lesion. Our study also lays the foundations for identifying those children who, despite not having received a diagnosis of melanoma on histological examination, should be considered as patients susceptible to a focused follow-up, because of the presence of the risk factors that emerged from our research.

A02

GORLIN SYNDROME: A CASE SERIES WITH CLINICAL AND GENETIC PROFILE

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Background: Gorlin Syndrome (GS) is a rare autosomal dominant disorder mainly characterized by the early development of multiple basal cell carcinomas (BCCs), increased risk of other benign or malignant tumours, and developmental anomalies. GS is inherited with a high degree of penetrance but variable expression.[1] The estimated prevalence is 1 in 31.000,[2] however, it may be higher as milder phenotypes may be underdiagnosed. In nearly 70% of cases, GS is caused by germline mutations in the human homolog of the patched (PTCH1) gene, which encodes a receptor for the secreted hedgehog ligands. Rarely, mutations in the suppressor of fused (SUFU) gene and PTCH2 have been identified.[3] In this study we aimed to describe the clinical and genetic profile of GS patients that are followed-up in our department.

Methods: We conducted a retrospective analysis including all the patients with a diagnosis of GS[4] that were followed-up in our department between January and 2006 and January 2020. Data was collected through available electronic medical records and interviews using a questionnaire.

Results: We enrolled a total of 25 patients: 16 adults (mean age 46 years) and 9 paediatric (mean age 13 years), with a female to male ratio of 4:1. All our patients had a pathogenic mutation of the PTCH1 gene. Family history was positive in 71% of cases, and 12 of them belonged to 5 families. Regarding BCCs, the mean age of onset in the adult group was 30 years, and 25% of them were diagnosed before the age of 20 years. Only one paediatric patient had a BCC (skin-tag type). Most of our patients (12/25) had 1 to 20 BCCs, two patients had more than 20 BCCs, and one patient had more than 50 BCCs. Regarding the presence of other major diagnostic criteria: 72% of patients had odontogenic keratocysts (average of 3.5 lesions per patient), 48% had palmar/plantar pitting, 25% had lamellar calcification of the falx cerebri, and two pediatric patients had a desmoplastic medulloblastoma. Minor criteria and additional comorbidities were also assessed.

Conclusions: The overall assessment of our patients' clinical and genetic profile is comparable to other published studies. There is contrasting evidence in the literature regarding genotype-phenotype correlation in GS, and the issue of whether the involved gene or the type of mutations is related to certain clinical manifestations or to the severity, must be a matter of future, multicentric studies.

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A03

OUTCOMES AND COSTS COMPARISON IN A 2015 AND A 2017 MELANOMA COHORT IN VENETO REGION

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Background: The burden of melanoma constitutes a major concern for healthcare systems throughout the world,[1] yet real-world data analysis on the costs of the management of patients affected by cutaneous melanoma and their survival reveals mixed results. The long-term effects of these standardized treatment pathways are still lacking and may be of great relevance to guide policy makers and also offer some insights to the whole Italian healthcare system.[2] Thus, we performed a population-level comparison of cases diagnosed before (2015) and after (2017) the introduction of a disease management pathway, covering all the latest diagnostic and therapeutic strategies.[3]
Methods: This work was conducted considering 1279 incidental cases of melanoma diagnosed in 2015 and 1368 recorded in 2017, including patients from all over the Veneto region registered by the Veneto Cancer Registry. Cox's regression models were performed to determine whether overall mortality was associated with index year, adjusting by sex, age and stage at diagnosis. Secondly, Mann-Whitney test, a non-parametric analysis, was performed to investigate whether total and single-item costs sustained in the two years following diagnosis of melanoma and the monthly costs by stage were associated with the index year.
Results: The mortality rate was lower in the 2017 cohort compared to the 2015 one. In addition, there was a decrease in total costs for the 2017 cohort in the two years following the patient's diagnosis. Single item cost analyses showed a clear decrease in average inpatient and outpatient costs for patients in the 2017 cohort.
Conclusions: Italian national healthcare system has prioritised melanoma targeted therapies in the last decade and the long-term effects in melanoma-related survival and overall costs have rewarded the earlier economic investment.

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A04

ALTITUDE EFFECT ON MELANOMA EPIDEMIOLOGY IN THE VENETO REGION: A PILOT STUDY

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Background: In the Veneto region (Italy), melanoma cases have more than tripled in the last 30 years, with a heterogeneous incidence within the regional territory.[1] This area is characterized by a mixed morphology including hills (15%), mountains (29%) and plains or coastal areas (56%), with altitudes ranging from sea level up to 3,383 meters above sea level, but negligible differences in latitude.[2] Therefore, this seems a suitable area for exploring the association between melanoma and altitude within a population with similar pigmentation characteristics. We investigated the clinico-pathological characteristics in a cohort of melanoma patients living in the Veneto region (Italy) according to the different geographical areas of residency.
Methods: This retrospective cohort study included 2752 melanoma patients who were diagnosed and/or treated at Veneto Institute of Oncology (IOV) and at the University Hospital of Padua (UHP) between 1998 and 2014. Categorical data were compared between groups using the Chi Square test or Fisher's exact test, while continuous data used Mann–Whitney test and Kruskal-Wallis test. Since the participating centers are the hubs for most patients living in the plain area, a sensitivity analysis including only referred patients was performed to strengthen the findings of the main analysis.
Results: The vast majority of patients lived in plain area (87.3%), followed by patients living near the coast (9.5%), in the hills (2.0%) and in the mountains (1.2%). The sensitivity analysis confirmed the differences in terms of primary site (p-value <0.0001), Breslow (p-value <0.0001), ulceration (p-value 0.03), number of mitoses (p-value <0.0001) and pTNM stage (p-value <0.0001) among patients living in different geographical areas.
Conclusions: Results from our study show a "coast-plain-hill" gradient, characterized by a progressive increasing number of melanomas involving the head/neck site and progressive reducing number of melanomas involving the trunk and the lower limbs. These data suggest that geographical area of origin of melanoma patients represents an interesting factor which may help to estimate pattern and level of sun exposure of melanoma patients. Further studies including data regarding host risk factors as Fitzpatrick phototype, number of melanocytic nevi, familiar history and genetic susceptibility are needed to better evaluate the role of altitude in melanoma epidemiology.

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A05

NOVEL PREDISPOSITION GENES DOUBLE A DECREASING CDKN2A MUTATION RATE: FIVE YEARS OF (TELE)-COUNSELLING AND GENE PANEL TESTING FOR HEREDITARY MELANOMA WITHIN THE ITALIAN MELANOMA INTERGROUP

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Background: During the last 5 years, routine application of next-generation sequencing in cutaneous melanoma (CM) genetic testing has been running in parallel with increasing melanoma incidence in Italy. Therefore, candidate gene mutation rate and criteria for genetic assessment may need to be revised according to the technological and epidemiological context.
Methods: Starting 2016, a germline gene panel, shared within IMI, including *CDKN2A, CDK4, BAP1, POT1, ACD, TERF2IP, MITF, ATM*, was applied to 879 melanoma patients from 25 different Italian centers, also through IMI genetic telecounselling. Patients were selected for a personal/family history of at least another melanoma and/or associated cancer (pancreatic adenocarcinoma (PDAC), kidney cancer, mesothelioma, uveal melanoma for a total of at least 2 cancer events). Pathogenic and likely pathogenic variants in candidate genes were considered for the mutational rate (MR).
Results: Overall, *CDKN2A* MR was 5.4%. The addition of other candidate genes doubled MR to 10.5%. In CM families, *CDKN2A* MR ranged from 4.5% (2 cases) to 9.8% (≥3 cases), rising to 9.2% and 14.7%, respectively, including other genes. In non-familial multiple primary CM cases, *CDKN2A* MR ranged from 3.6 % (2 CM) to 7.9% (≥3 CM), rising to 6.9% and 12.3%, respectively, including other genes. Counting CM events, *CDKN2A* mutational rate ranged from 4% (2 CM) to 6% (≥3 CM) (6.6% and 10.8%, including other genes). In cases with 2 or more CM and PDAC events, *CDKN2A* MR ranged from 9.7% to 13.1%, respectively (19.4% and 22.6%, including other genes). In contrast, in those with 2 or more other selected cancer events (kidney cancer, uveal melanoma, mesothelioma), *CDKN2A* MR ranged from 0% to 1.3%, while the inclusion of other genes (mainly *BAP1*) increased MR from 3.5% to 13.9%. *CDKN2A* age-related MR falls below 2.5% in patients diagnosed with melanoma over the age of 60 (below 1% if over 65).
Conclusions: our data suggest avoiding genetic testing when the earliest age of diagnosis is over 60 years. The presence of PDAC in the proband or the family is strongly predictive of a germline predisposition. The presence of 3 or more cancer events, including CM and the other associated cancers, is predictive of *BAP1* pathogenic variants. Compared to single gene testing, gene panel doubled *CDKN2A* MR, which is decreasing, in parallel with increasing melanoma incidence.

A06

GENETIC PROFILING OF ATYPICAL DEEP PENETRATING NEVI (DPN)

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Background: The recent WHO classification of melanocytic tumors requires the implementation of combined phenotypic–genotypic diagnostics. Deep penetrating nevi (DPN) are rare melanocytic neoplasms consisting of pigmented spindled or epithelioid melanocytes with a distinctive wedge-shaped configuration showing activation of the WNT pathway, with unusual cyto-architectural features. However, there is insufficient information regarding genetic status of DPN, and it is not yet clear whether the observed unusual morphological cyto-architectures reflect a distinct genomic profile or are associated with an increased metastatic potential and aggressive clinical behavior.
Methods: We report a comprehensive next-generation sequencing (NGS) analysis of a series of atypical DPN, showing their mutational profile with some specific signatures for these rare and diagnostically challenging tumors. In particular, we describe a cohort of 21 atypical DPNs analyzed by next-generation sequencing using the Ion AmpliSeq™ Comprehensive Cancer Panel.
Results: We found that β-catenin exon 3 was mutated in 95% and MAP kinase pathway genes in 71% of the cases. Less frequent mutations were observed in HRAS (19%) and MAP2K1 (24%). Isocitrate dehydrogenases 1 (IDH1) mutations, including R132C, V178I, and S278L, were identified in 38% of cases and co-existed with BRAF/HRAS mutations. The only case with progressive nodal disease carried alterations in the β-catenin pathway and mutations in IDH1 and NRAS (codon 61).
Conclusions: By a comprehensive mutation analysis, we found low genetic heterogeneity and a lack of significant associations between specific gene mutations and histopathological features, despite atypical features. Whether the acquisition of an NRAS or IDH1 mutation in an atypical DPN may represent a molecular evolution implying a pathway to melanoma progression should be confirmed in a larger series.

PREVENTION AND DIAGNOSIS

A07

ULTRA HIGH FREQUENCY ULTRASOUND MONITORING OF MELANOMAS ARISING IN CONGENITAL MELANOCYTIC NEVI: A CASE SERIES

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Background: Ultra high Frequency Ultrasound (UHFUS) is a non-invasive diagnostic technique that allows to differentiate between benign and malignant melanocityc lesions with high resolution and a frequency between 30 and 100 MHz.[1] The aim of our study were to evaluate with UHFUS Vevo®MD the different ultrasound features of congenital melanocytic nevus (CMN) and malignant melanoma (MM) arising on CMN and the correlation between ultrasonographic thickness and histological thickness in MM.
Methods: We evaluated 10 patients with CMN and 10 patients with MM arising on small-medium CMN. We collected patient's data, clinical and dermoscopic features. Following the clinical-dermoscopic examination, the UHFUS was performed using a 70 MHz frequency probe to study the ecostructure, and vascularization.
Results: In the MM group the following dermoscopic features were described: hyperpigmentation (n=9), regression area (n=6), whitish-blue veil (n=5), thickened network (n=5), irregular globules (n=3), inverse network (n=2) and striae (n=1). Hyperpigmentation (n=9), thickened network (n=7), irregular globules (n=5), regression area (n=5), striae (n=1) and whitish-blue veil (n=1) were found in the CMN group. The multicomponent pattern was present in both MM (n=4) and in CMN (n=5). Moreover, the parameters indicative of suspected malignancy (thickened network, regression area, striae, hyperpigmentation, irregular globules, multicomponent pattern) were variously combined in the two groups, without showing significant differences in the statistical analysis; with the exception of the blue veil that correlated with the diagnosis of MM (p-value=0.141). MMs showed an inhomogeneous hypoechogenic structure. All MMs presented intralesional vascularization, in particular in 50% medium intensity and 50 % of high intensity. CMN had a less inhomogeneous hypoechogenic structure. Intralesional vascularization was not detected in (n=6) CNM, while (n=4) CMN showed low intensity intralesional vascularization.
Conclusions: In our study we observed numerous dermoscopic criteria in common in the group of MM and CMN. Multicomponent pattern generally has good specificity for MM, but in our study we found it also in CMNs. Vascularization was ever-present parameter in MM (100%), with high intensity of intratumoral signal, as opposed to CMN. We also found a statistically significant correlation between ultrasound thickness and Breslow thickness.

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A08

A SEGMENTATION ALGORITHM FOR SKIN MELANOMA REGRESSION

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Background: The absolute prognostic significance of regression and its predictive role on sentinel node status is still widely debated, and the histopathological quantification of regression still represents a problem and indeed an unsolved point in managing cutaneous melanoma.
Methods: We explored an Artificial Intelligence approach in processing histopathological images of regressed cutaneous melanomas. Our aim was to train a neural network to define a deep learning algorithm able to recognize the regression areas in histological preparations of skin melanoma, highlighting and quantitazing them by color maps.
This work is part of an IMI multicenter project which currently has collected cases from the Pathological Anatomy Unit of the "Federico II" University of Naples, and the Pathological Anatomy Section of the University of Catania.
Our analysis was carried on archived FFPE histopathological images of skin melanomas at various stages of regression, digitalized at 40x with an Aperio AT2 digital slide scanner, and manually annotated by expert pathologists.
Results: We based the training of UNet network on a starting dataset of 51 Whole Slide Images for a full account of 22,464 tiles and validated the algorithm on 10 Whole Slide Images for a full account of 816 tiles, achieving on the validation set a mIoU of 0.64 and an accuracy of 89%. The case series on which the study is based is currently being expanded.
Conclusions: The proposed algorithm represents a valid computer aided diagnostic tool in the definition and quantization of the regression phenomenon in cutaneous melanomas, in order to facilitate the pathologist's work and normalize this evaluation by reducing elements of individual variability.

A09

IMPACT OF THE COVID-19 PANDEMIC ON PRIMITIVE MELANOMA DIAGNOSES AT THE IDI-IRCCS OF ROME

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Background: Due to the COVID-19 pandemic, some planned medical activities have been postponed, for both national directives and out of concern of the patients who were afraid to go to hospitals.[1] In our study we tried to evaluate if the pandemic has had any detrimental effect on melanoma diagnosis both in 2020 and 2021.
Methods: We collected all consecutive primary melanoma from the Pathology Registry of IDI-IRCCS of Rome (Breslow, ulceration and other main histological features). During year 2020 we divided the COVID-19 Italian pandemic into three phases: pre-lockdown (1 January-9 March), lockdown (10 March-3 May), post-lockdown (4 May-6 June). We compared these data with the same period of year 2021.

Results: In the year 2020 mean number of melanoma diagnoses per day were as follows: 2.3 in the pre-lockdown phase, 0.6 during the lockdown and 1.3 after the lockdown (in 2018–2019, we had 2.3/day). Mean Breslow thickness was 0.88 (95% CI, 0.50–1.26) pre-lockdown and 1.96 (95% CI, 1.16–2.76) post-lockdown. Proportion of ulceration was 5.9% (95% CI, 2.4–11.7%) pre-lockdown and 23.5% (95% CI 10.8–41.2%) post-lockdown. During the same period of year 2021 we observed a constant number of new melanoma cases, with a daily number similar to the 2020 pre-lockdown period. Overall, we observed a higher number of nodular melanoma and superficial spreading melanoma with nodule compared to 2020 pre-lockdown period. The proportion of in situ melanoma in 2021 (about 28%) is constant and it is very close to the observed values for 2018 (23.8%), 2019 (26.4%) and 2020 (25%).

Conclusions: Our data support the hypothesis that during the COVID-19 lockdown period of year 2020, melanoma diagnoses may have been delayed. In 2020 a significant increase has been observed for men (from 0.96 to 2.70) but not for women (0.79 to 1.44), and in patients 50 years old or older. Regarding the year 2021, our data support the hypothesis that the number of new melanoma diagnoses returned to the pre-lockdown period, but the higher Breslow thickness and the largest number of thicker melanomas (nodular and superficial spreading with nodule) suggest it could be caused by the postponed prevention during the previous year. The constant proportion of in situ melanoma indicate that more 'health-conscious' people were more likely to defy the 2020-2021 lockdown limitations than people who might have been underestimating the severity of their lesions.

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A10

A NOVEL ALGORITHM COMBINING STATIC AND DYNAMIC FEATURES TO IDENTIFY MELANOMA IN DIGITAL DERMOSCOPY MONITORING

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Background: Early diagnosis is the most effective intervention to improve the prognosis of cutaneous melanoma. Even though the introduction of dermoscopy has improved the diagnostic accuracy, it can still be difficult to distinguish some melanomas from benign melanocytic lesions. Digital dermoscopy monitoring can identify dynamic changes of melanocytic lesions: to date, some algorithms where proposed, but a universally accepted one still lacks.[1,2]

Objectives: To identify independent predictive variables associated with the diagnosis of cutaneous melanoma and develop a multivariable dermoscopic prediction model able to discriminate benign from malignant melanocytic lesions undergoing digital dermoscopy monitoring.

Methods: We collected dermoscopic images of melanocytic lesions excised after dermoscopy monitoring and carried out static and dynamic evaluations of dermoscopic features. We built a multivariable predictive model based on logistic regression.

Results: We evaluated 173 lesions (65 cutaneous melanomas and 108 nevi). Forty-two melanomas were in situ and the median thickness of invasive melanomas was 0.35 mm. The median follow-up time was 9.8 months for melanomas and 9.1 for nevi. The logistic regression model performed with AUC values of 0.87, which was substantially higher than those of the static evaluation models (ABCD TDS score, 0.57; 7-point checklist, 0.59).[3,4] Finally, we built a risk calculator, which translate the proposed model into user friendly application, to assist clinicians in the decision-making process.

Conclusions: The present study demonstrates that the integration of dynamic and static evaluations of melanocytic lesions is a safe approach that can significantly boost the diagnostic accuracy for cutaneous melanoma. We propose a diagnostic tool that significantly increase the accuracy in discriminating melanoma from nevi during digital dermoscopy monitoring.

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SURGERY

A11

NON-SENTINEL LYMPH NODE DETECTION MEANWHILE SENTINEL LYMPH NODE BIOPSY IN NOT-COMPLETE LYMPH NODE DISSECTION ERA: A NEW TECHNIQUE FOR BETTER STAGING AND TREATING MELANOMA PATIENTS

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Background: Sentinel lymph node biopsy has been demonstrated to be an effective staging procedure since its introduction in 1992.[1] The new AJCC classification did not consider the lack of information that will result from the less usage of the complete lymph node dissection as for diagnostic purpose.[2] Thus, this will make difficult the correct staging and would leave about 20% of the further positive non-sentinel lymph nodes in the lymph node basin. In this paper we aim to describe a new surgical technique that, combined with SPECT-CT, allows a better staging of melanoma patients.
Methods: This is a prospective study that includes 104 patients, with cutaneous melanoma. Sentinel lymph node biopsy was offered according to AJCC guideline. Planar lymphoscintigraphy has been performed in association with SPECT-CT, identifying and removing all non-biologically "excluded" lymph nodes, guiding surgeon's hand in detection and removal of lymph nodes.
Results: Even if identification and removal of non-sentinel lymph nodes is not able to increase the overall survival, it gives a better control disease in the basin.
Conclusions: With a "classic" setting the risk of leaving further lymph nodes out of the sentinel lymph node procedure is around 20%, so basically the surgical sentinel lymph node of first and second lymph nodes would have therapeutic as well as the complete lymph node dissection classically performed.

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A12

SENTINEL LYMPH NODE BIOPSY IN SQUAMOUS CELL CARCINOMA

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Background: Squamous cell carcinoma (SCC) is the second most common skin cancer. While the surgical cure rate for SCC is approximately 95%, a proportion of patients are considered to be at high risk for recurrence.[1] The progression for SCC is about 5%, but ranges from 16% to 85% depending on whether it is a low-risk or high risk cancer.[2] The progression of SCC appears to be stepwise from local recurrence to regional metastases and then distant metastases.[3] In high-risk SCC lymph node involvement is detected in 20-25% of patients.[4] Patients with lymph node metastases have a poor prognosis with a 5-year survival of 26-34%. However, if treated early, when only a single node is involved and extracapsular spread has not yet occurred, 5-year survival reaches 70% to 75%.[2] We report herein our experience on SLNB in SCC patients and the criteria to define 'high-risk' SCC and to select patients for SNB will be discussed.
Methods: SLNB was performed following the standard procedure using pre-operative lymphoscintigraphy, Patent-blue and intra-opeartive gamma-probe in 28 patients with SCC.
SCC patients were considered at low or high-risk according AJCC, BWH, NCCN criteria.[4,5,6]
Results: Seventeen patients were males and eleven were females. Age ranged from 62- to 84- years. The SLN was detected in all patients. Three patients had a positive SLN (10,7%) and complete lymph node dissection was then performed.
Conclusions: SLNB should be considerd in patients with high risk SCC. The different criteria used to define high risk SCCs still represent a limitation to select patients for SLNB and more studies are needed in order to identify those criteria related to lymph node metastases.

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THERAPY

A13

CORRELATION BETWEEN PNI, NLR, SII AND CLINICAL COURSE AND SURVIVAL IN METASTATIC MELANOMA PATIENTS TREATED WITH BRAF/MEKI TARGETED THERAPY: A MONOCENTRIC RETROSPECTIVE OBSERVATIONAL STUDY

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Background: inflammation plays a key role in the development of neoplastic disease. Several indices have been proposed as prognostic markers in immunotherapies for melanoma, while there are few data regarding target therapies. The aim of this study is to evaluate the values of PNI (prognostic nutritional index), NLR (neutrophil to lymphocyte ratio) and SII (systemic inflammatory index) at the beginning of treatment with Dabrafenib and Trametinib, and establish any correlations with response, progression and survival.
Methods: data of 130 melanoma patients were retrospectively evaluated. The distribution of markers according to clinical characteristics was compared with the Mann-Whitney U-test. Subsequently, in the group of patients with ongoing disease PNI, NLR and SII were dichotomized based on their median value. Associations between these groups and response, progression and death were analyzed with the Chi-square test. PFS (progression free survival) and OS (overall survival) in months were evaluated by study of Kaplan-Meier curves compared with log-rank tests. Validity as prognostic factors for OS was investigated by univariate and multivariate analysis with the Cox regression model.
Results: age under 65 is associated with higher values of PNI, advanced stage of disease is associated with higher NLR and SII and lower PNI, and presence of active disease shows a similar association.
In the group of patients with active disease high NLR and SII are associated with a higher percentage of progressions (74% vs 47%) and deaths (87% vs. 53%), and lower median times of PFS and OS. A low PNI is associated with age above 65, higher mortality (87% vs 55%), lower response rates (ORR 33% vs 68%; DCR 50% vs 87%), lower PFS and OS; it is also the only marker that has shown significance as a PFS and OS predictor with the multivariate analysis with Cox regression model (HR=0.235, 95% CI 0.111-0.499).
Conclusions: NLR, SII and especially PNI are promising markers for predicting prognosis and response to therapy at the beginning of BRAF/MEKi treatment in patients with metastatic melanoma. Prospective studies are needed to further the knowledge about the distribution of these parameters in different stages of disease.

A14

CUTANEOUS SIDE EFFECTS AND TYPES OF DERMATOLOGICAL REACTIONS IN METASTATIC MELANOMA PATIENTS TREATED BY IMMUNOTHERAPIES OR TARGETED THERAPIES: A RETROSPECTIVE SINGLE CENTER STUDY

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Background: Immunotherapy and target therapy have revolutionized treatment of Stage III/IV melanoma. Both treatments show a favourable toxicity profile even if cutaneous adverse events are frequent (30-40% of cases).[1]
Methods: this is a retrospective single center cohort study that included patients with stage IV or inoperable stage III metastatic melanoma (AJCC 8th) who received BRAFi+MEKi therapy or immunotherapy with Checkpoint inhibitors. All cutaneous AEs were ascertained by a dermatologist based on clinical and histological findings.
Results: a total of 286 patients with stage III-IV metastatic melanoma were included: 146 received immunotherapy and 140 target therapy. In the immunotherapy cohort, 63 (43.1%) cutaneous reactions were observed whilst 33 skin reactions (23.6%) were identified in patients treated with target therapy. All the skin toxicities observed were grade I, excepted four cases: an erythema multiforme-like eruption, a grade III psoriasis and two grade III rashes. Patients were analysed also on the basis of concomitant therapies, and it was observed that levotyroxine was associated with a significant higher risk to develop skin reactions during immunotherapy (p=0.01); whilst insulin in target therapy. Immunotherapy in older age resulted statistically related to skin toxicities (p=0.011), meanly in metastatic setting (p=0.011). Cumulative incidence of skin toxicities is 65.63% in immunotherapy cohort (p=0.001).
Conclusions: Cutaneous adverse events are characterised by heterogeneous manifestations, are more often seen in patients on immunotherapy and dermatologists can play a crucial role in multidisciplinary care.

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A15

NEOADJUVANT IPILIMUMAB/NIVOLUMAB COMBO IMMUNOTHERAPY IN LOCALLY ADVANCED OR OLIGOMETASTATIC MELANOMA

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Background: We investigate the efficacy of Ipilimumab and Nivolumab combination in the neoadjuvant setting for locally advanced or oligometastatic melanoma patients (pts). This is an open label, single arm study performed at the European Institute of Oncology in Milan and at the Dermatologic Clinic, University of Turin. Treatment schedule consists in 4 neoadjuvant cycles of Ipilimumab 1 mg/kg and Nivolumab 3 mg/kg every 3 weeks, followed by surgery and adjuvant Nivolumab 480 mg every 4 weeks for 6 cycles. Primary objective was pathological complete remission (pCR) rate, according to Neoadjuvant Melanoma Consortium criteria, while secondary objectives were: safety, feasibility and efficacy; QoL; identification of molecular and immunological biomarkers of response and resistance; degree of immune activation; evaluation of microbioma.
Methods: From March 2019 to April 2021, 35 pts were treated within the trial. 4 pts were withdrown during primary phase for progression (2), toxicity (1) and consent withdrawal (1). One pts is waiting for surgery. 30 pts underwent to surgery after neoadjuvant phase: pCR was reached in 17 (57%), pCR/near pCR was reached in 19 (64%), pathological partial remission in 4 (14%) and pathological no response (pNR) in 7 (24%) pts. 23 pts concluded the adjuvant therapy. With a median follow-up of 13 months, 33/35 pts are alive. Relapses occurred in 2 pts after neoadjuvant and in 7 pts (1 pCR and 6 pNR at surgery) during/after adjuvant phase. 6 pts (17%) developed related G3-4 adverse events (AE): 3 transaminitis, 1 pneumonitis, 1 myocarditis, 1 CPK increase and 1 miositis; all of them but two underwent to surgery after toxicity resolution. One patient died 5 months after the end of therapy due to ischemic stroke, and one other six month after progression
Conclusions: In conclusion neoadjuvant Ipilimumab/Nivolumab is a feasible therapeutic option, able to achieve a high pCR/near pCR rate as expected (primary objective met). Toxicity in this study was lower than that previously reported. Translational data evaluated longitudinally during therapy on each patient will be available and presented at IMI.

A16

5-YEAR OVERALL SURVIVAL (OS) IN COLUMBUS: A RANDOMIZED PHASE 3 TRIAL OF ENCORAFENIB PLUS BINIMETINIB *VERSUS* VEMURAFENIB OR ENCORAFENIB PATIENTS (PTS) WITH BRAF V600-MUTANT MELANOMA

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Background: Combined BRAF/MEK inhibitor therapy has demonstrated benefits on progression-free survival (PFS) and OS and is standard of care for the treatment of advanced BRAF V600-mutant melanoma. Here we report a 5-year update from the COLUMBUS trial.
Methods: In Part 1 of COLUMBUS, 577 pts with advanced/metastatic BRAF V600-mutant melanoma, untreated or progressed after first-line immunotherapy, were randomized 1:1:1 to encorafenib 450 mg QD + binimetinib 45 mg BID (COMBO450), encorafenib 300 mg QD (ENCO300), or vemurafenib 960 mg BID (VEM). An updated analysis including PFS, OS, objective response rate (ORR; by blinded independent central review), and safety was conducted after minimum follow-up of 65.2 months (mo). Data are as is; study is ongoing.
Results: At data cut-off (Sep 15, 2020), there were 131 (68%), 117 (60%), and 145 (76%) deaths in the COMBO450, ENCO300, and VEM treatment arms, respectively. The median OS (95% CI) and 5-year OS rate (95% CI) with COMBO450 were 33.6 (24.4–39.2) mo and 34.7% (28.0–41.5), respectively (median follow-up: 70.4 mo). The 5-year OS rate (95% CI) in COMBO450 pts who had normal lactate dehydrogenase (LDH) levels at baseline was 45.1% (36.5–53.2). Median OS and 5-year OS rates for ENCO300 and VEM, as well as for pts with normal and high LDH levels and > 3 organs involved at baseline, are shown in the table. For COMBO450, ENCO300, and VEM, the 5-year PFS rate was 22.9%, 19.3%, and 10.2%; ORR (95% CI) was 64.1% (56.8–70.8), 51.5% (44.3–58.8), and 40.8% (33.8–48.2); and the median duration of response (DOR) was 18.6, 15.5, and 12.3 mo, respectively. Safety results were consistent with the known tolerability profile of COMBO450. Additional efficacy and updated safety analyses will be presented. Following study drug discontinuation, the most common subsequent treatment in all arms was checkpoint inhibitors.
Conclusions: Updated OS and DOR results with COMBO450 demonstrate continued long-term benefits in pts with BRAF V600-mutant melanoma. Clinical trial information: NCT01909453.

	COMBO 450			ENCO 300			VEM		
	Events/pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)	Events/pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)	Events/pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)
All pts	131/192 (68.2)	33.6 (24.4–39.2)	34.7% (28.0–41.5)	117/194 (60.3)	23.5 (19.6–33.6)	34.9% (27.9–42.0)	145/191 (75.9)	16.9 (14.0–24.5)	21.4% (15.7–27.8)
LDH normal	81/137 (59.1)	51.7 (36.8–67.3)	45.1% (36.5–53.2)	79/147 (53.7)	35.3 (23.7–60.5)	41.8% (33.3–50.1)	95/139 (68.3)	24.5 (18.6–29.1)	28.4% (20.9–36.4)
LDH high	50/55 (90.9)	11.4 (9.0–17.4)	9.1% (3.3–18.4)	38/47 (80.9)	9.2 (7.0–16.2)	13.8% (5.6–25.6)	50/52 (96.2)	9.6 (8.5–11.5)	4.0% (0.7–12.1)
> 3 organs involved	35/42 (83.3)	11.6 (9.1–20.8)	–	32/44 (72.7)	15.7 (7.9–19.7)	–	39/45 (86.7)	10.9 (8.6–15.7)	–

*Unstratified Cox regression model

A17

A DIGITAL COMPANION FOR PATIENTS WITH BRAF-MUTANT ADVANCED MELANOMA TREATED WITH TARGETED THERAPIES: TAVIE SKIN APP

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Background: Patients with advanced melanoma are facing questions regarding their disease, their treatment, or potential signs and symptoms that are common, though predictable. Strategies to control symptoms include targeting patient education and unhealthy behaviors. In the context of an increasingly digital healthcare system, it is worth considering the role of mobile health applications (mHealth) as patient empowerment tools for routine care, patient education and treatment management. To support patients in their daily-life, a digital solution, called TAVIE Skin, was developed; dedicated to all BRAF-mutant unresectable or metastatic melanoma patients who are treated with targeted therapies.

Methods: The intended goal of the TAVIE Skin app is: I) to deliver the necessary information and education support to the patient in regards with their disease and medications, through virtual nurse coaching; II) to keep track of medications to improve adherence; III) to assist patients in identifying side effects using the virtual nurse coaching and side effects library, and; IV) to engage them towards sustainable healthy behaviors thanks to lifestyle interventions, health trackers and real time coaching.

In addition, an optional patient survey is incorporated into the TAVIE Skin app to assess patient reported outcomes, after an e-consent is signed via the app. Ethics approval will be obtained before data collection as per local regulations.

Results: The application is available in France since January 2021 and will be available in 5 additional European countries throughout 2021. The survey will include 400 patients and will allow for describing the users' profile of TAVIE Skin app, for assessing HRQoL, including physical, emotional, social, and functional well□being, treatment adherence, as well as work productivity and activity impairment upon targeted therapy. The patients' satisfaction toward their melanoma treatment, and toward the application will be also assessed.

Perspectives: To the best of our knowledge, TAVIE Skin is the first mHealth application dedicated to patients with BRAF-mutant advanced melanoma. This is a description of the app, the survey and their objectives.

A18

THE ROLE OF TERT PROMOTER MUTATIONS IN BRAF V600E MUTANT METASTATIC MELANOMA PATIENTS TREATED IN FIRST LINE WITH BRAF/MEK INHIBITORS

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Background: Combination of BRAF/MEK inhibitors results in rapid response and improved progression free and overall survival in advanced BRAF V600-mutant melanoma. However significant response is not universally observed, and the majority of BRAF-mutant melanoma develops resistance while under BRAF/MEK inhibition. TERT promoter mutations have emerged as prominent somatic alterations and markers of poor survival in melanoma.[1] Tan et al showed that dabrafenib and trametinib (D+T) robustly induce shrinkage of xenograft tumors harboring both BRAF V600E and TERT promoter mutations, but they have little effect on tumors harboring only BRAF V600E mutation.[2]

Methods: We performed a single center retrospective analysis of adults with cutaneous metastatic melanoma (MM) with BRAF V600E mutation, which received first line treatment with BRAF/MEK inhibitors. DNA was extracted from formalin-fixed paraffin-embedded (FFPE) specimens. All samples were analyzed using a customized Next-Generation Sequencing multi-gene panel, which allows the mutational analysis of 75 target regions in 25 genes, including BRAF and TERT. Response rate (RR) and progression-free survival (PFS) in response to BRAF/MEK inhibition were assessed. Differences in RR and PFS were compared using Kaplan-Meier and Log-Rank.

Results: We analyzed FFPE tumor samples from 39 pts eligible for the study. 9 were not evaluable, due to poor DNA quality or quantity. We found the presence of TERT promoter mutations in all the analyzed samples (30/30). TERT -146C >T was present in 20/30 (66.7%), -124C > T in 6/30 (20%), -138_-139CC > TT in 3/30 (10%) and c.-124_125CC>TT in 1/30 (3.3%). Mean age at the start of treatment was 58±5 years and 57% (17/30) were female. 23 pts received D+T and 7 vemurafenib + cobimetinib. Partial response was observed in 11/30 pts (37%) and no complete responses were recorded. 11 pts (37%) had stable disease and 8 pts (27%) had progressive disease as best response, showing a primary resistance to BRAF/MEK inhibitors. Median PFS was 8 months (95% CI, 4.2-11,8). Overall no significant differences in PFS were observed among different TERT promoter mutations. Among responders (11/30), TERT -146C > T was the most frequent mutation (7/11, 64%), TERT c.-124C>T in 2 and TERT c.-138_139CC>TT in the remaining 2. Among responders, median PFS was significantly longer in TERT c.-146C > T mutated when compared with TERT c.-124C>T (49 vs 7 months, p=0.046).

Conclusions: Preclinical data observed an improved response to BRAF/MEK inhibition in genetic duet tumors. However, in our study, which is the largest to report on outcomes of first line BRAF/MEK directed therapy in BRAFV600E/TERT co-mutated cutaneous MM, RR and PFS are worse than expected. The role of TERT promoter co-mutations in melanoma has still to be defined.

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A19

PROGNOSTIC AND PREDICTIVE FACTORS IN ADVANCED MERKEL CELL CARCINOMA PATIENTS TREATED WITH IMMUNOTHERAPY: TOWARDS A PROGNOSTIC TOOL

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Background: Factors associated to immunotherapy (IT) response ad survival in Merkel Cell Carcinoma (MCC) patients (pts) are unknown: their identification and the elaboration of a prognostic score is the aim of our study.
Material and Methods: Between 17.02 2017 and 02.08 2021 27 MCC pts started IT at our center. We studied the association between overall survival (OS), progression free survival (PFS), tumor best overall response (BOR) and baseline: a) clinical patients' features as age, gender, stage, num of metastatic sites, visceral mets (VM), ECOG PS, systemic pretreatment b) candidate biomarkers as sum of largest diameter of target lesions (SLD), disease free interval (DFI), LDH, total WBC and leukocytes subpopulations, PTL, NLR and PLR. We also evaluated the associations among the different variables analyzed. Tumor assessments were performed according to RECIST 1.1 criteria. IBM *SPSS* Statistics for Windows was used for statistical analyses.
Results: Six pts (22%) had a locally advanced disease, 21(78%) distant metastases, 10 (37%) VM and 4 (15%) were pretreated. At data cut off 4 pts (15%) discontinued ICI because of a confirmed CR, 14 (52%) for death or progressive disease (PD) and 2 (7%) for toxicity while 7 (26%) were still on IT. Median follow up was 18 months (mo) (95% CI 11.1-24.5), m-OS 14.3 mo (95% CI 7.1-21.5) and m-PFS 2.8 mo (95% CI 2.4 -3.1). ORR was 37% (4 CR and 6 PR). OS and PFS significantly correlated with: 1.PS (0.023 KS p-value (p-v)-0.004 MW p-v OS), 2. VM (0.107 KS p-value-0.023 MW p-v OS), 3. SLD (0.004 SR p-v OS), 4. DFI (0.019 SR p- OS) and 5. LDH (0.004 SR p-v OS). Response (SD/RP/RC vs PD) was associated with: VM (0.042 FE p-v), SLD (0.001 FE p-value according to median value) and LDH (0.001 FE p-v according median value). Kaplan Meier (KM) OS curves confirmed the prognostic impact of variables significantly associated with survival. We then divided subjects in: a.pts with 1- 2/5 and b. pts with 3 or more/5 negative prognostic factors and compared the survival curves of the 2 groups using KM, obtaining a statistically significant difference in OS (Log Rank p-v 0.000164). Among correlations between the variables we found: PS and absolute lympho count, PS and PLR, DFI and SLD, SLD and LDH.
Conclusions: To obtain a larger data set for a multivariate analysis and to build a tool useful to counsel patient and guide trial eligibility/design, we are starting a research collaboration involving all Italian centers interested in this tumor.

A20

DECIPHERING THE HETEROGENEITY OF CIRCULATING MELANOMA CELLS AND TUMOR DNA THROUGH A MULTI-PLATFORM APPROACH

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Background: Melanoma heterogeneity has been well established, being a major hindrance for the management of metastatic melanoma patients. Even if the advent of targeted therapy has significantly improved patient outcome, despite the high response rate, the frequent occurrence of resistance makes the monitoring of tumor genetic landscape mandatory, to detect drug-resistant clones and possibly allow for an earlier therapy change. As a sum of the systemic disease, liquid biopsy could be an important biomarker for real-time tracing of disease evolution. The recent development of high-sensitive techniques applied to Circulating Melanoma Cells (CMCs) and circulating tumor DNA (ctDNA) has provided tools for an in-deep definition of melanoma heterogeneity.
Methods: In this pilot study, 18 stage IV melanoma patients, treated with BRAF/MEK inhibitors, have been prospectively enrolled, and followed for up to 18 months for monitoring disease evolution and timing/mechanisms of resistance. A longitudinal screening at different time points has been applied to study the dynamic changes in the liquid biopsy during response to treatment and/or at progression (50 samples in total). For this purpose, starting from a single blood draw, we devised a multi-platform (CellSearch, Next Generation Sequencing, droplet digital PCR) approach, which encompassed the tracking and count of CMCs and ctDNA, together with their customized genetic analysis and copy number variation (CNV) assessment.
Results: Missense mutations (single nucleotide variants, SNVs) known/suspected, to confer resistance (involving, among others, *MEK1, PTEN, FBXW7, NRAS* genes) were detected by NGS in ctDNA and/or CMC DNA of 75% of patients, some of them were also putatively targetable. *BRAF* mutations were detected by ddPCR in 78% of patients; moreover, we tracked a decrease in ctDNA level during response, and a BRAF-mutated fraction rebound that preceded/overlapped the radiological detection of progression. In parallel, the levels of other SNVs increased before recurrence.
Conclusions: This study provides the proof-of-principle of the power of a multiparameter liquid biopsy approach. Indeed, this kind of analysis was able to provide cfDNA tracking/profiling, together with CMC count variation, and genetic landscape, useful for capturing tumor heterogeneity and evolution, while assessing sensitivity to specific drugs. Overall, our analysis showed informative SNV/CNV profiles, useful for early detection of relapse and therapy resistance.

A21

CIRCULATING RNA (CTRNA) FROM TUMOR-EDUCATED PLATELETS (TEPS) AS A NOVEL TOOL TO MONITOR RESPONSE TO TARGET THERAPY IN PATIENTS WITH METASTATIC MELANOMA: A PROOF-OF-CONCEPT STUDY

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Background: circulating tumor DNA (ctDNA) assessment has emerged as a strong biomarker to monitor and predict response to combined BRAF and MEK inhibition in patients with metastatic melanoma (MM) carrying BRAF V600E mutations.[1] However, ctDNA analyses are not capable to detect gene expression signatures predicting sensitivity or resistance to targeted therapies. Hence, we first explored the feasibility of transcriptome analysis using ctRNA from Tumor-Educated Platelets (TEPs) derived from patients' blood samples.[2] Next, we investigated the potential role of gene signatures derived from ctRNA analysis to predict response to targeted therapy.
Methods: five patients with BRAF V600E mut MM were treated with dabrafenib plus trametinib. Blood samples were collected at baseline (T0) and after 3 cycles of treatment (T1). We developed our own protocol to extract and purify ctRNA from TEPs. Next, we employed a 770-genes panel for essential cancer pathways (Multiplex Code Barcode Technology) to investigate gene expression.[3]
Results: before to proceed with multiplex color code barcode analysis, the quality and quantity of extracted RNA was evaluated by using a microfluidic technology (TapeStation 4200, Agilent) with RNA HD kit. The median quantity of RNA was 2,6 ng/µl and the median quality, reported in term of RNA Integrity Number (RIN), was 5,6. Then, Hallmark Gene Set Enrichment Analysis (GSEA) of the transcriptional data obtained from Nanostring platform revealed a significant down-regulation of RAS-related signature (Normalized Enriched Score, NES=2.14; FDR=0.017) in T1 samples, confirming the on-target effects of the therapy. Consistently, in all T1 samples we detected significant reduced expression of genes typically regulated by MAPK signaling pathway, such as *CD14, HSPA1A, MAP2K4, MAPK8, PDGFD, STMN1*.
Conclusions: our results demonstrate that ctRNA extraction and purification from TEPs is a feasible method. Hence, ctRNA analysis could become a novel non-invasive tool to monitor response to BRAF and MEK inhibitors, in addition to standard clinic-radiological evaluation. We are currently enrolling more patients in our study. We also plan to collect blood samples from patients at time of disease progression, to investigate peculiar gene signatures associated with treatment failure.

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A22

A REAL-WORD EXPERIENCE WITH ANTI-PD-1 ANTIBODIES IN PATIENTS WITH ADVANCED MELANOMA

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Background: The programmed cell death-1 (PD-1) receptor inhibitors nivolumab (N) and pembrolizumab (P) have demonstrated significant clinical activity in *BRAF*^{V600} mutant or WT metastatic melanoma patients (pts).[1-3] We report a single-Institution real world experience on the efficacy of therapy with N and P in metastatic melanoma pts.
Methods: A retrospective analysis was conducted in pts with metastatic melanoma treated (March 2016 – June 2020) with N 3 mg/kg, 240 or 480 mg or with P 2 mg/kg or 200 mg, at the Center for Immuno-Oncology of Siena, Italy. Median Overall Survival (OS), Progression Free Survival (PFS) [months (mo), 95% CI], 1- and 2-year survival rates, and Objective Response Rate (ORR), Disease Control Rate (DCR), and Duration of Response (DOR) (mo, 95% CI) based on iRECIST criteria, were recorded, along with safety profiles of N and P therapy.
Results: Ninety-one pts with melanoma (78 cutaneous, 9 ocular, 4 mucosal) were evaluated. Patient's characteristics were: unresectable Stage III (2 pts), Stage IV M1a (21 pts), M1b (18 pts), M1c (38 pts), M1d (12 pts) (58 male, 33 female); median age 60 years (range: 31-89), ECOG performance status 0 (68 pts) or 1 (23 pts); BRAF mutant or WT (27/62); untreated o pre-treated (56/35). With a median follow-up of 39 mo, median OS was 31 mo (95% CI: 13-49), 1- and 2-year survival rates were 70% and 58%, respectively; median PFS was 18.8 mo (95% CI: 6.1-31.5), DCR and ORR were 73% and 38%, respectively. Median DOR was not reached, objective responses were ongoing at 3 years in approximately 90% of pts who achieved a PR/CR. Any grade immune-related adverse events were reported in 74% of pts, and were G3-4 in 10%.
Conclusions: Treatment with anti-PD-1 antibodies is feasible, safe and clinically effective also in the daily practice in pre-treated metastatic melanoma pts, with a sizeable proportion of pts experiencing durable clinical benefit and long-term survival. Comprehensively, these results demonstrate that the efficacy and safety profiles of anti-PD-1 antibodies in the real-world setting are consistent with those of clinical trials.

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A23

THREE SUBPOPULATIONS OF CIRCULATING EXTRACELLULAR VESICLES AS PROMISING BIOMARKERS FOR THE RESPONSE TO ANTI-PD1 THERAPY IN METASTATIC MELANOMA

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Background: Metastatic melanoma (MM) is one of the most aggressive types of cancer. First-line therapy in patients with BRAF-V600 mutation is targeted therapy with a combination of BRAF-V600 inhibitors and MEK inhibitors or immunotherapy with immune checkpoint inhibitors (ICI), instead patients without BRAF mutations are candidates for ICI therapy. The immunotherapy together with the target therapy has provided substantial survival benefits in patients with MM, however most of them develop resistance and indeed a durable response is limited to 30-40% of patients. Nowadays cell-free circulating nucleic acids, exosomes and microvesicles released into the peripheral blood emerged as new biomarkers of resistance to ICI. For these reasons it would be useful to identify easily detectable circulating biomarkers for the selection of MM patients with a high probability of response to anti-PD1 treatment.

Methods: This is a prospective study enrolling 71 MM patients in the IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy. All patients were treated with immune check point inhibitors. The EVs were isolated from plasma before treatment by ultracentrifugation and characterized by Nanoparticle tracking analysis (NTA), Transmission Electron Microscopy (TEM) imaging, Dynamic Light Scattering (DLS) analysis and by FCM. This research is supported by the Puglia Region (Italy) within "Tecnomed-Tecnopolo per la Medicina di Precisione" project (CUP B84I18000540002).

Results: We isolated and characterised EVs from plasma of MM patients for their size, positivity to the three tetraspanins CD9/63/81 and site of origin. The analysis of the distribution of both PD-L1$^+$ EVs and PD1$^+$ EVs subpopulations in responders and non-responders showed that the level of PD-L1$^+$ EVs from melanoma cells and CD8$^+$ T cells and that of PD1$^+$ EVs of any origin were always higher in non-responders then in responder. The analysis of the PFS and OS categorizing patients for the presence of EVs positive for PD-L1 and PD1 demonstrated a strong correlation between higher levels of PD-L1$^+$ EVs from melanoma cells and T cells and of PD1$^+$ EVs of any origin and worst PFS and OS. Finally, the multivariate analysis identified the high content of PD1+ EVs from CD8+ T cells, of PD-L1+ EVs from melanoma and of PD1+ EVs from B cells as independent biomarkers.

Conclusions: For the first time we have identified three subpopulations of circulating PD1$^+$ EVs and PD-L1$^+$ EVs, which are promising biomarkers of response to anti-PD1 therapy. Our research has demonstrated that these specific subpopulation of circulating EVs could be dosed in liquid biopsy with the great advantage of a minimally invasive procedure and used for monitoring the response to ICI in metastatic melanoma patients.

A24

CEMIPLIMAB BEYOND CLINICAL TRIALS: A SINGLE CENTER REAL-LIFE SERIES OF AN ELDERLY AND FRAIL POPULATION OF PATIENTS WITH LOCALLY ADVANCED OR METASTATIC CUTANEOUS SQUAMOUS CELL CARCINOMA

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Background: Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer whose incidence is growing parallel to lengthening of average lifespan. Cemiplimab, an antiPD-1 monoclonal antibody, is the first approved immunotherapy for patients with locally advanced (laCSCC) or metastatic (mCSCC) CSCC thanks to phase I-II studies showing high antitumor activity and good tolerability. Nevertheless, at present very few data are available regarding cemiplimab in real life settings with frail, elderly, and immunosuppressed patients as well as clinical features or biomarkers able to predict response guiding therapeutic choices.

Methods: We built a retroprospective cohort study including 30 non-selected patients with laCSCC (25) and mCSCC (5) treated with cemiplimab from August 2019 to November 2020. Clinical outcomes, toxicity profile and correlations with disease, patients and peripheral blood parameters are explored.

Results: Median age was 81 years (range 36-95); 24 males; 5 patients having an immunosuppressive condition while frailty prevalence was 83% based on index deriving from age, ECOG performance status and Charlson Comorbidity Index (CCI). We reported 23 responses (76.7%) with 9 CR (30%). A higher response rate was observed in head and neck primary tumours and in patients with haemoglobin level >12 g/dL. No difference was observed with respect to frailty, median age, sex, body mass index. Baseline low

neuthophils/lymphocytes ratio and low platelets/lymphocytes ratio resulted also correlated with a better response. Moreover, lymphocytes, neutrophils and monocytes behaviors had an opposite trend in responders and non-responders. An overall response was reported in 4 of 5 immunosuppressed patients. Seventeen patients (57.6%) still have an ongoing response and still alive. Two responders interrupted treatment (for toxicity) but maintaining their response.

The treatment was well tolerated by the majority of patients. The most common adverse events were fatigue in 7 patients (23.3%) and skin toxicity in 10 patients (33.3%) including pruritus in 6 patients, rash in 3 patients, bullous erythema in 1 patient.

Conclusions: In our real-life experience, cemiplimab showed high antitumor activity with acceptable safety profile similar to those in selected patients of trials. Moreover, its antitumor activity resulted not impaired in very elderly patients and in those with immunocompromised status.

A25

RETROSPECTIVE OBSERVATIONAL MULTICENTER STUDY ON SKIN TOXICITY INDUCED BY IMMUNO THERAPIES

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Background: Cutaneous toxicity related to oncological therapies is a common scenario in daily clinical practice and has gained new importance after immunotherapy and target therapy has emerged as revolutionary cancer treatments.[1]

Methods: This is a retrospective observational study collecting the data of patients treated with immune checkpoints inhibitors (ICI) as nivolumab, pembrolizumab, ipilimumab or their combination, in 4 different Italian centers. The data reported in the database included the type, severity and duration of treatment-related toxicities. In particular, all the possible skin toxicities were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Data on clinical outcome were also collected.

Results: Of 323 patients, 305 were evaluable for this analysis; 182 patients (59.7%) had been treated for a metastatic cutaneous melanoma, 99 (32.5%) for a lung carcinoma and 24 (7.8%) for a kidney carcinoma.

The most frequent skin toxicities in all the 3 types of cancer included pruriginous rash (10.2%), vitiligo-like areas (7.2%), psoriasiform rash (6.2%), asymptomatic rash (4.6%), pruritus without rash (4.3%).

Vitiligo-like areas occurred more frequently in patients with melanoma (11.5%) compared to lung (0.0%) and kidney (4.2%) cancers, while pruritus without rash was more frequently observed in patients with kidney cancer (12.5%) compared to melanoma (2.2%) and lung cancer (6.1%).

Interestingly, treatment interruption was related to drug-induced cutaneous toxicity in 15.4% of melanoma patients and 0.0% of lung and kidney patients.

Considering overall response rate (ORR), progression free survival (PFS) and overall survival (OS), patients developing a cutaneous adverse event had a higher ORR, median PFS and 12-month OS than the patients without cutaneous adverse events (53.7% versus 26.6% for ORR, 18.8 versus 3.9 for PFS and 89.2 versus 51.7 for OS), considering all cancer sites together, with $p<0.001$

Conclusions: Our study has many interesting learning points to explore in further study: i) vitiligo-like areas are associated to ICI treatment in melanoma patients; ii) pruritus without rash is associated to ICI treatment in kidney cancer patients; iii) treatment interruption related to drug-induced cutaneous toxicity is more frequent in melanoma patients than in patients affected by lung and kidney cancers; iv) the occurrence of skin toxicities is associated with a better ORR, PFS and OS in all considered cancer sites.

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