XXVIII CONGRESSO NAZIONALE IMI

FIRENZE
30 SETTEMBRE, 1-2 OTTOBRE
2022

PALAZZO DEGLI AFFARI
Piazza Adua, 1

intergruppo italiano melanoma imi

PATROCINI

XXIII CONGRESSO NAZIONALE IMI

ADOI
ASSOCIAZIONE DERMATOLOGI-VENEREOLOGI OSPEDALIERI ITALIANI e della SANITÀ PUBBLICA

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A.I.L.M.A.G.

aimame. Associazione Italiana Malati di Melanoma e tumori della pelle

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SIAPEC - IAP

SICPRE

SIDCO
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Società Italiana di Radiologia Medica e Interventistica

Care colleghe, cari colleghi,

Siamo molto lieti di annunciare la XXVIII edizione del Congresso annuale della nostra società scientifica che si terrà a Firenze dal 30 Settembre al 2 Ottobre 2022.

Seguendo una consolidata tradizione il Congresso si articola in sedute plenarie, con esperti nazionali che affronteranno argomenti scientifici di particolare interesse quali la prevenzione, le strategie diagnostiche innovative, l'inquadramento del melanoma ad alto rischio, i consolidati e nuovi approcci terapeutici sia chirurgici che farmacologici (adiuvante e neoadiuvante) nelle varie fasi della malattia, avanzata e localmente avanzata. Una specifica enfasi verrà data alla immunoterapia e terapie a bersaglio molecolare, con l'illustrazione del profilo di efficacia e sicurezza delle varie strategie prescrittive (somministrazione in sequenza o combinazione). Si incontreranno i colleghi esperti e si conosceranno le nuove leve, che rappresentano il futuro di questa nostra Società.

Le Tavole Rotonde multidisciplinari rappresentano un classico riferimento per l'aggiornamento dei colleghi che operano nell'intero territorio nazionale. Nella oramai consolidata tradizione IMI, anche quest'anno il Congresso organizzerà sessioni Focus On con numerosi temi di aggiornamento sulle terapie mediche per melanomi uveali e mucosali con attività interattiva relatore-discenti, oltre a promuovere un confronto fra modelli organizzativi e gestionali, e ad analizzare competenze e collaborazione multidisciplinare.

Il tema dei carcinomi della cute (carcinoma a cellule squamose, carcinoma a cellule basali, carcinoma a cellule di Merkel) non verrà ovviamente trascurato implementando vari momenti di confronto multidisciplinare con altre società scientifiche partner di IMI (ADOI, SIAPEC-IAP, SICPRE) per discutere l'elaborazione di documenti di consensus, per monitorare e ottimizzare le varie attività relative alla qualità dell'assistenza ed all'adesione alle linee guida, in base alle recenti innovazioni normative.
Le riunioni del Comitato Scientifico dei Coordinatori di Area costituiranno il momento saliente per approfondire, monitorare e promuovere nuovi studi multicentrici sviluppati in vari centri IMI.

Il rapporto tra IMI e Associazioni dei pazienti è strategico per tutte le iniziative della nostra associazione in particolare quelle con i decisori amministrativi e politici. Saranno quindi presenti A.I.L.M.A.G., A.I.Ma.Me., Associazione Melanoma Day, APaIM, Carolina Zani Melanoma Foundation, Comitato Emme Rouge ONLUS, MiO e Melanoma Patient Network Europe.

Quest'anno durante il Congresso 2022 si terranno le elezioni per il nuovo Consiglio Direttivo ed il Presidente eletto, occasione anche per ulteriori riflessioni su quanto IMI potrà fare nella continuità della nostra tradizione affiancata da un intenso impegno sempre in un'ottica multidisciplinare. Il lavoro, il confronto, la collaborazione, e l'amicizia saranno i veri protagonisti del Congresso e Firenze vi accoglierà per un soggiorno sia ricco di aggiornamenti professionali che di momenti di piacevole fruizione della sua impareggiabile cornice di arte e cultura.

Vi aspettiamo, con la stima e l'affetto di sempre.

Ignazio Stanganelli
Presidente IMI

Daniela Massi
Presidente del Congresso

EPIDEMIOLOGY, GENETICS AND PATHOGENESIS

GERMLINE VARIANTS AND PROGNOSTIC FACTORS FOR CUTANEOUS MELANOMA IN CHILDREN AND ADOLESCENTS

S. Raimondi[1], S. Vignati[1], C. Pellegrini[2], P. Ghiorzo[3], M. Rodolfo[4], A. Ferrari[4], M.C. Fargnoli[2], L. Pastorino[3], M. Berwick[5], V. Hoiom[6], E. Nagore[7], C. Menin[8], S. Puig[9], E. Passoni[10], A.M. Manganoni[11], L. Kandolf Sekulovic[12], S. Brugnara[13], G. Guida[14], G. Palmieri[15], A. Stratigos[16], F. Baldini[1], G. Tosti[1], P. Quaglino[17], M. Capone[18], R. Fernandez de Misa[19], F. Ozdemir[20], G. Ribas[21], A. Romanini[22], E. Migliano[23], I. Stanganelli[24], M.T. Landi[25], P. Kanetsky[26], M.A. Pizzichetta[27], A. Gaeta[1], P. Queirolo[1], D. Massi[28], S. Gandini[1] for the IMI Study Group, the GEM Study Group and the M-SKIP Study Group

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Background: Although the role of several genes in cutaneous melanoma (CM) prognosis has been studied in adult patients, to our knowledge no study has investigated the relationship between genetic alterations and CM prognostic factors in children and adolescents.
Methods: A retrospective cohort of children and adolescents (<21 years old) with histologically confirmed CM was assembled through an established international collaboration between the M-SKIP (*MC1R*, Skin cancer and Phenotypic characteristics) consortium and the Italian Melanoma Intergroup (IMI). Genetic information was available for *MC1R* gene and, for a subset of Italian cases, on *CDKN2A*, *CDK4*, *MITF* and *POT1*. The present study included 290 subjects with available data on Breslow thickness (BT). Other investigated prognostic factors were ulceration (N=171 subjects with available data), presence of mitosis (137), regression (123), and tumor infiltrating lymphocytes (TILS, 140). Univariate association analyses were carried out with Wilcoxon-Mann-Whitney and Chi Square tests for continuous and categorical variables, respectively. Logistic regression models were used to determine the corresponding Odds Ratios (OR) with 95% Confidence Intervals (CI).
Results: Subjects carrying any *MC1R* non-red hair colour variant, i.e. *r* variant, had on average thinner melanomas (BT=1.33mm) than those with consensus *MC1R* sequences (BT=1.71mm, p=0.02). Accordingly, the odds of having a CM with BT>1 is almost halved for subjects carrying *MC1R r* variants (OR=0.58, 95%CI 0.35-0.94). This result is likely attributable to the *R163Q* variant, which was associated with significantly thinner CM (p=0.02). Regression was more often observed in carriers of the *D294H* variant compared to non-carriers (57% vs 21%, OR=4.97, 95% CI 0.97-25.57). Finally, subjects carrying any *MC1R r* variant were more likely to have TILS (79% vs 61%, OR=2.41, 95%CI 1.02-5.67). No further association between any investigated genetic alterations and prognostic factors was found.
Conclusions: *MC1R r* variants, which are mainly present in darker pigmented Caucasian populations like Italy, were associated with thinner CM and a higher probability of TILS, being suggestive of CM with better prognosis. Further data on other genetic alterations and prognostic factors, along with survival data, will help to better clarify the role of genetic alterations in CM prognosis for children and adolescents.

ASSOCIATION BETWEEN POLYGENIC RISK SCORE AND MULTIPLE PRIMARY MELANOMA

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Background: In addition to the known high/medium-penetrance genes involved in melanoma susceptibility; recent Genome-Wide Association Studies (GWAS) have identified many common allelic variants (SNPs) that may affect the risk of developing the disease. Each of these variants alone has a weak effect, but their combination, according to a polygenic risk score (PRS) model, may increase the risk by three-fold, and even more in association with other risk factors (*i.e.* nevus count and skin phototype). The PRS has been deeply evaluated in population studies; however, little is known about its role on the risk of multiple primary melanomas (MPM).
Methods: A total of 64 SNPs was analyzed in 164 MPM, 95 single melanoma cases, and 296 healthy individuals as controls. All melanoma cases did not carry pathogenic variants in high-penetrant melanoma genes (CDKN2A, CDK4, POT1, BAP1, ACD, TERT, TERF2IP).
The SNPs were selected from previous independent GWAS analyses and genotyped by NGS sequencing in the Illumina MiSeq platform, using a custom multi-gene panel. The PRS was calculated using the β value for each SNP (β is the per-allele log

OR for melanoma associated with the SNP alternative allele). Logistic regression, and Chi-Square or Fisher exact test were applied to assess the association between PRS and melanoma risk and to compare PRS between the subgroups respectively.
Results: We found a significantly higher median PRS in all melanoma cases than controls (0.43 vs 0.03, p=0.0001) and a double median PRS in multiple vs single melanoma cases (0.56 vs 0.25, p=0.031). On the other hand, familial vs sporadic cases did not show a significantly different median PRS (0.45 vs 0.37, p=0.7). In particular, an association between PRS and multiple melanoma risk was found with a per-SD OR of 1.4 (95% CI 1.06-1.79, p=0.016) corresponding to almost tripled risk (OR 2.78, 95% CI 1.18-6.61, p=0.0189) for individuals in the highest PRS quintile compared to those in the lowest quintile.
Conclusions: This study highlights the importance of including in the genetic testing carefully selected SNPs useful in the calculation of PRS. Individuals with a high PRS are not only more likely to develop melanoma, but also to develop subsequent melanomas. Therefore, the PRS can be a useful tool for selecting patients without pathogenic variants in currently known high-risk melanoma genes, who should be addressed to more stringent protocols of surveillance.

POROCARCINOMA: AN EPIDEMIOLOGICAL, CLINICAL, AND DERMOSCOPIC 20-YEAR STUDY

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Background: Porocarcinoma is a rare cutaneous adnexal tumor with a variable metastatic potential. Given the paucity of data, guidelines and specific recommendations for porocarcinoma are not yet well-established. In this study, we evaluate the disease-specific characteristics and outcome of this rare and often underestimated tumor.
Methods: A retrospective study of the epidemiological, clinical, and dermoscopic characteristics among cases of histopathologically diagnosed porocarcinoma, collected from the database of two skin cancer clinics in Italy (Firenze, Pistoia) from 2000 to 2020, was conducted.
Results: Among the 52 patients with 53 tumors, 31 were men (59.6%) and 21 were women (40.4%) with an age range of 49-96 years (median age 82 years). The most common locations were the head/neck region in men (34% in men vs. 17% in women) and the lower limb in women (17% in women vs. 9% in men). Forty-eight cases (91%) underwent local excision. Of these patients, two (4%) experienced local recurrence, and one (2%) developed a second porocarcinoma on a different anatomical site 1 month after the primary tumor's excision. Lymph node metastases were present in three cases (6%). Two of them have been treated surgically with adjuvant radiotherapy (both are disease-free after a 2-year follow-up period), whereas the third case developed visceral metastases followed by porocarcinoma-related death (Table 1).
Conclusions: This study, with 52 patients with 53 tumors covering a follow-up period of more than 5 years, shows a less aggressive behavior of porocarcinoma with 4% local recurrence, 6% nodal metastases, and 2% mortality.

	n	Percent
Sex		
F	21	40.38
M	31	59.61
Age at diagnosis, years		
<70	10	18.87
>70	43	81.13
Primary site		
H&N	25	47.17
Trunk	8	15.09
Upper limb	5	9.43
Lower limb	13	24.53
NOS	2	3.77
Preoperative diagnosis		
SCC	14	26.42
BCC	13	24.53
EPC	5	9.43
Bowen	1	1.89
SK	2	3.77
CCA	1	1.89
Ulcerative cyst	1	1.89
KA	2	3.77
Pyogenic granuloma	1	1.89
NOS	13	24.53
Stage		
In situ	3	5.66
Localized	47	88.68
RegionalDistant	31	5.661.88
Treatment		
Surgery alone	51	96.22
Surgery and radiotherapy	2	3.77
Nodal dissection	2	3.77
Metastasisa		
Yes	3	5.66
No	50	94.34

PRIMARY CUTANEOUS MELANOMA AND COVID-19: A HOSPITAL-BASED STUDY

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Background: The COVID-19 pandemic prompted drastic containment measures and a rearrangement of healthcare services, with reduction of melanoma diagnoses and related activities.[1] It has been hypothesized that the lockdown may have led to a delay in diagnosis, resulting in an increase in melanoma upstaging cases and healthcare costs.[2] Several series of melanoma management have been published in various Italian centers with variable results.[3,4]
Methods: We collected melanomas and melanocytic nevi diagnosed from January 2019 to December 2021 at Azienda Ospedaliero-Universitaria di Parma. Differences in the number of diagnoses, histopathological characteristics, diagnostic-therapeutic pathway and staging were evaluated.
Results: There were no significant differences between 2019 and 2020 in the number of melanomas, while there was a decrease in 2021 (540 vs 554 vs 407), determined by a reduction in melanomas in situ (395 vs 412 vs 238, $p<0.001$) rather than invasive melanomas. The Breslow thickness, excluding melanomas in situ, was not significantly increased in 2020 and 2021. A reduction of ulcerated melanoma was observed in 2020 (13.6% vs 5.3% vs 9.3%, p 0.04), contrary to the literature in the Covid-19 era (4). No significant differences were observed in the type and duration of diagnostic-therapeutic pathway and the staging. On the other hand, there was a reduction in the number of nevi between 2019 and 2020 (2608 vs 1452, $p<0.001$), with an increased percentage of dysplastic/atypical vs common nevi (6.6% vs 83.5% in 2019 and 21.3% vs 67.6% in 2020, $p<0.001$).
Conclusions: Unlike other studies, we analyzed both melanomas and nevi for a longer period than lockdown. In particular we observed a marked decrease of nevi (especially common nevi), but no worsening of invasive melanomas, Breslow thickness, diagnostic-therapeutic pathway and staging. These data corroborate the results of a patient-based IMI survey (5), in which no worsening of melanoma management was observed during the COVID-19 pandemic in Italy.

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EPIDEMIOLOGY OF MERKEL CELL CARCINOMA IN TUSCANY (ITALY), 2006 TO 2021

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Background: Merkel cell carcinoma (MCC) represents a rare but aggressive tumor still hampered by an unfavorable prognosis[1]. MCC incidence has increased in recent years worldwide[2].
Methods: The aim of our study is to perform an epidemiological retrospective study and evaluate the impact of MCC clinic-pathological features on overall survival (OS) in a specific geographical area. We retrospectively collected all reports dated 2006-2021 from the pathology archives of the University Hospital of Pisa and from the Hospital of Livorno. Within this Italian area has been already reported a higher incidence of melanoma[3]. We collected 94 cases.
Results: The most frequently affected site was the face. Laterality was different according to the site and almost half of the lesions were T1 and almost half of the patients had a clinical stage III considering 19 cases of MCC diagnosis were a lymph node localization with unknown primary site. We registered a dramatic increase of MCC diagnoses in the last 5 years in comparison with previous period observed, with a crude incidence rate of 1,15/100000 inhabitants, almost doubling the last reported data in Italy[4]. We found a 1:1 ratio between the two sexes and the age groups above 70 y.o. were highly affected. In the univariate analysis, we considered sex, age, site, maximum tumor diameter, T, status of the excisional margins, and presence of ulceration. The female sex showed an increased risk of death, increased by each 1 cm of tumor size and above age over 78 y.o. Surgical margins status and ulceration were not related to OS. In the multivariate analysis, only tumor size and age remained statistically significant. Half of the patients died within the first 3 years. The 2-year survival rate was almost 60%, the 3-year survival rate was 50% and the 5-year survival was 48%.
Conclusions: We have noticed that we have patients with fast progressing disease and many showing a slower progression and the investigation of specific biomarkers or other features may elucidate this striking difference in PFS and can potentially identify different subtypes of MCC. Considering the generally low incidence of MCC worldwide, a lot of efforts must be done to create or merge larger cohorts to validate our data, obtaining a better prognostic stratification.

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PREVENTION AND DIAGNOSIS

ATYPICAL SPITZ TUMOURS: AN EPIDEMIOLOGICAL, CLINICAL AND DERMOSCOPIC MULTICENTRE STUDY WITH 16 YEARS OF FOLLOW-UP

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Background: Atypical Spitz tumours (ASTs) are regarded as an intermediate category distinguished from prototypical Spitz naevus by presenting one or more atypical features and often by an uncertain malignant potential (1), (2), (3). Clinical and dermoscopic features may play a relevant role in the diagnostic approach (4), (5). Our aim was to evaluate the clinical and dermoscopic features of ASTs, and their evolution over time.
Methods: This was a descriptive, multicentre study of the clinical and dermoscopic characteristics of ASTs. Data on clinical and dermoscopic characteristics, histopathology, local extension, therapy and follow-up, lymph node staging, complete lymph node dissection, and outcome were collected from the databases of four Italian Dermatology Units for the period 2004-2021.
Results: The study population consisted of 99 patients (62 female, 37 male) with a histologically confirmed diagnosis of AST, including age at presentation ranged from 2 to 70 years (mean 28.1 years, median 24 years). Of the 99 patients, 29 (29.3%) underwent sentinel lymph node biopsy, which showed evidence of micrometastases in three cases (10.3%); all three patients underwent complete lymph node dissection with no evidence of further metastasis. Considering the whole study population, the clinical outcome was excellent, as all of the patients have no evidence of recurrence or distant metastasis. The follow-up period ranged from 6 to 216 months (mean 81.6 months, median 78 months). In addition, we collected data on the clinical and dermoscopic features of 26 lesions. The most frequent dermoscopic pattern observed was the multicomponent pattern (34.6%), followed by homogeneous (26.9%) and nonspecific (23.2%). In 66.7% of amelanotic ASTs, we observed glomerular (coiled) vessels uniformly distributed within the entire lesion, without asymmetry.
Conclusions: The results of our study with a long follow-up show no recurrence or distant metastases, confirming the good clinical outcome, even in the case of sentinel lymph node positivity. From a diagnostic point of view, our series identified a typical dermoscopic picture for amelanotic ASTs, with a glomerular vascular pattern throughout the lesion in the absence of other dermoscopic parameters, making the correct diagnosis possible.

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PEDIATRIC MELANOMA: AN EPIDEMIOLOGICAL, CLINICAL AND DERMOSCOPIC MULTICENTRE STUDY

E. Magnaterra[1], F. Silvestri[1], F. Venturi[1], B. Zuccaro[1], J. Colombo[1], M. Magliulo[1], S. Magi[2], M. Medri[2], L. Mazzoni[2], F. Savoia[2], L. Trane[3], M. Gola[1], P. Covarelli[4], L. Stingeni[5], I. Stanganelli[2], V. De Giorgi[1]

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Background: Pediatric melanoma (PM) is defined as a malignant melanocytic lesion which occurs during child's growth up before the age of 18 or 21 years, depending on the cutoff employed for defining adulthood.[1] Cutaneous Melanoma (CM) is uncommon among children, occurring before the age of 18 years in only less than 1% cases, accounting for about 1-3% of all pediatric cancers.[1,2,3] Few studies investigated differences between children's and adults' melanoma and literature about this topic is lacking. Our understanding of the natural history, clinical and dermoscopic features of PM is limited due to the low number of studies about this topic. Moreover, currently the management of this disease is based on the adult guidelines, as specific treatment guidelines for children are unavailable.
Methods: We conducted a retrospective analysis of patients under 18 years from 3 different dermatology units in Italy (Florence, Ravenna, Perugia) diagnosed with melanoma between 1995 and 2021. All lesions were diagnosed by dermatopathologists specialized in the diagnosis of melanocytic neoplasms at the originating institution. Data on socio-demographic and histopathological variables were collected and retrospectively analized.
Clinical and dermoscopic images were evaluated jointly by three experienced reviewers, in order to identify specific dermoscopic patterns of PM.
Results: A total of 39 cases of PM were collected. Since melanoma in pre-pubertal children may act differently than in post-pubertal children, we decided to divide patients by age as a surrogate for pubertal status. We divided patients in two different age groups: group A including patients aged 12 years and younger and group B including patients aged from 13 to 18 years. Of the cohort of 39, 8 subjects (20,5%) were aged 12 years or younger (group A) and 31 (79,5%) were aged 12 to 18 years (group B). Histopatologically,

nine lesions were in situ (23,1%); and 30 were invasive (76,9%) with mean Breslow thickness of 1.05mm (SD 0,23). Furthermore, all the melanoma in situ cases were diagnosed after age 12.
Conclusions: Results from this retrospective study suggest a higher frequency of melanoma in situ after menarche, testifying a possible hormonal effect. No substantial dermoscopic differences between children's and adults' melanoma were observed, nor a greater frequency of pink lesions.

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RECURRENCE-FREE SURVIVAL PREDICTION IN MELANOMA PATIENTS BY EXPLOITING ARTIFICIAL INTELLIGENCE TECHNIQUES ON MELANOMA WHOLE SLIDE IMAGES

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Background: recently, adjuvant therapy has become a standard of care in high risk melanoma with the advent of immune and target therapy. However, the burden of financial toxicities and potential permanent side effects related to these treatments raise questions about the assessment of benefit-risk profile.[1-2] An improvement in defining the risk of recurrence through reliable and noninvasive methods is critical to avoid medical overtreatments.
Methods: we designed a deep learning-based model with the aim of learning prognostic biomarkers from melanoma whole slide images (WSIs) to predict 1-year recurrence-free survival in stage I-III cutaneous melanoma patients. We analyzed histological slides referred to a cohort of 43 patients with stage I-III melanoma selected from the Clinical Proteomic Tumor Analysis Consortium Cutaneous Melanoma (CPTAC-CM) public database.[3] At 1-year follow-up, 12 patients showed recurrence and 31 patients did not. WSIs were firstly annotated by expert pathologists and then split into 12575 crops which were then employed to train and validate the proposed model.
Results: the best predictive performances were obtained in terms of AUC and accuracy with values of 70.1 3.0% and 72.7 6.8%, respectively, by implementing a soft-voting procedure to combine quantitative imaging biomarkers automatically extracted from WSIs via deep learning with some clinical data regarding T, age, gender, primary tumor site.
Conclusions: these promising preliminary results suggest that our proposal could be a valuable noninvasive tool to better define the prognosis of patients, complementary to current genetic and histopathological methods. Therefore, it could help physicians better select patients to be treated with adjuvant therapy.

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ULTRA-HIGH FREQUENCY ULTRASOUND AND MACHINE LEARNING APPROACHES FOR THE DIFFERENTIAL DIAGNOSIS OF MELANOCYTIC LESIONS

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Background: Malignant melanoma (MM) is characterized by high morbidity and mortality[1]. Advanced MM is associated with poor long-term survival and early MM detection improves prognosis and survival rates[2]. Differentiating between MM and atypical melanocytic nevi (MN) can often be difficult, therefore additional non-invasive methods could assist with diagnostic accuracy. The aim of this study was to present a potential new method for the differential diagnosis of MM from melanocytic naevi (MN).
Methods: We examined 20 MM and 19 MN with a new ultra-high frequency ultrasound (UHFUS) (Vevo MD, Fujifilm, Visualsonics, Toronto, Canada), equipped with a 70 MHz linear probe. Ultrasonographic images were processed for calculating 8 morphological parameters (area, perimeter, circularity, area ratio, standard deviation of normalized radial range, roughness index, overlap ratio and normalized residual mean square value) and 122 texture parameters. Color Doppler images were used to evaluate the vascularization. Features reduction was implemented by means of principal component analysis (PCA), and 23 classification algorithms were tested on the reduced features using histological response as ground-truth.
Results: MN and MM appear as hypoechoic fusiform (84% of MN; 95% of MM) or oval (16% of MN, 5% of MM) inhomogeneous lesions, with a variable degree of intralesional vascularization most frequently found in MM instead of MN (85% of MM; 26% of MN). Best results were obtained using only the

first component of the PCA and the weighted k-nearest neighbour classifier; this combination led to an accuracy of 76.9%, area under the receiving operating characteristic (ROC) curve of 83%, sensitivity of 84% and specificity of 70%.
Conclusions: Our best classifier performed very well in terms of accuracy and area under the ROC curve (AUC). The histological analysis still remains the gold-standard, but the UHFUS images processing using a machine learning approach could represent a new non-invasive approach to differential diagnosis of melanocytic lesions.

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COM'È CAMBIATO LO SCREENING PER MELANOMA E TUMORI CUTANEI PRIMA E DURANTE L'ERA COVID

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Background: Lo screening e il follow-up è fondamentale in termini di prevenzione dei tumori cutanei. Riportiamo i dati di uno studio condotto in una singola Istituzione, su 9.397 pazienti ambulatoriali visitati nel periodo Gennaio 2019 – Giugno 2022, confrontato il periodo pre- con il periodo post-pandemia da Sars Cov 2.
Methods: I dati sui pazienti e la storia familiare e personale di melanoma e tumori cutanei non-melanoma sono stati raccolti un database strutturato per la refertazione delle prestazioni ambulatoriali dermato-oncologiche. Le seguenti caratteristiche sono state considerate: fenotipo dei pazienti, storia personale e familiare di melanoma cutaneo e tumori cutanei non-melanoma, motivo dell'accesso ambulatoriale (visita di screening o visita per una lesione cutanea sospetta). Riportiamo le frequenze con p-values dell'analisi di regressione logistica multivariata.
Results: Complessivamente sono state effettuate 13.205 (11.294 visite di screening e 1.911 visite per una lesione cutanea sospetta). Nel caso di lesioni cutanee sospette il paziente è stato visto o per richiesta diretta del paziente o perché inviato dal medico curante o perché riferito da uno specialista sul territorio.6.934 soggetti hanno avuto un singolo accesso dall'inizio della raccolta dei dati, mentre 2.463 soggetti hanno effettuato almeno due accessi. Paragonando il primo quadrimestre del 2019 con il primo quadrimestre del 2020, si è osservata una diminuzione del numero di visite effettuate pari al 32.5%. L'analisi multivariate mostra che durante il periodo pandemico, il numero di accessi singoli è diminuito per i soggetti con capelli rossi rispetto al periodo pre-pandemico (65% vs. 61%, p<0.001), mentre è aumentato il numero degli accessi dei soggetti che hanno dichiarato di avere utilizzato lettini abbronzanti (20% vs. 28%, p<0.001), che hanno un numero elevato di nei (37% vs. 22%, p<0.001) o che presentano lentiggini (32%vs40%, p<0.001). Gli accessi per lesioni cutanee sospette sono diminuiti rispetto alle visite di screening durante il periodo pandemico rispetto al periodo pre-pandemia (17% vs. 11%, accesso per lesione sospetta vs. accesso per screening p<0.001). I soggetti di età > 60 anni si sono sottoposti a un numero di visite di follow-up significativamente inferiore nel periodo pandemico rispetto al periodo pre-pandemico (35% vs. 25%, p=0.03), in maniera similare ai soggetti con una storia personale di tumori cutanei (22% vs. 14%, p=0.02).
Conclusions: Le caratteristiche degli individui che hanno avuto accesso alla nostra Istituzione per visita dermatoncologica sono cambiate tra il periodo pre-pandemico e il periodo post-pandemico. I soggetti che si sono sottoposti a visita perché presentavano una lesione sospetta e i soggetti di età > 60 anni hanno effettuato un numero inferiore di visite durante la pandemia.

CLINICOPATHOLOGIC AND DERMOSCOPIC FEATURES OF 20 CASES OF SPARK'S NEVUS, A DERMOSCOPIC SIMULATOR OF MELANOMA

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Background: Spark nevus is a particular type of melanocytic nevus, with histology that shows features of both Spitz's and Clark's nevus. Detailed dermoscopic features in a series of Spark nevi have not been described yet.
Methods: We performed a monocentric retrospective observational study on 20 lesions of Spark nevus excised to 19 patients (M:F=10:9; mean age: 37,6 years;), reviewed by five experts in dermoscopy and two dermatopathologists.
Results: The histological review confirmed that Spark nevi were mostly symmetric (80%), well circumscribed (100%), mainly compound (65%) melanocytic lesions with either epithelioid (55%) or spitzoid (45%) cell morphology and bridging of the nests (100%). Spark nevi were more frequently found on the trunk (85%) in patients with a history of sunburns in childhood (84%), skin phototype III (79%) and with high nevus count (>100 nevi, 7 patients (36%). Upon dermoscopy we observed different general pattern: multicomponent (40%), reticular-globular-homogeneous (15%), globular homogeneous (15%), reticular (15%), reticular-globular (5%), homogeneous (5%) and globular (5%). Spark nevi showed frequently dermoscopic asymmetry (63%), brown color (90%) with areas of central hyperpigmentation (41%) and peripheral hypopigmentation (28%), atypical pigment network (48%), irregular globules (42%), irregular dots (31%), irregular blotches (16%), blue whitish-vel (13%), peripheral island (25%), irregular hyperpigmented areas (12%), regression (33%). BRAF mutation was present in seven of the 10 analyzed cases (70%); all these cases presented a history of evolution.

Conclusions: Spark nevi occur on the trunk of young adults with high nevus count and history of sunburns; dermoscopic features are protean, oft atypical and suspicious of melanoma.

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PATHOLOGICAL AND MOLECULAR CLASSIFICATION

GENETIC DETERMINANTS OF RESPONSE TO THERAPY IN A REAL-WORLD SETTING OF ADVANCED/METASTATIC MELANOMA PATIENTS: WHOLE-EXOME SEQUENCING AND CFDNA ANALYSIS

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Background: Despite a large number of studies addressing the molecular landscape of metastatic melanoma, genetic determinants of resistance are still largely unknown. Therefore, predicting patients showing a durable response vs patients relapsing is an urgent clinical need.
Methods: Thirty-six advanced/metastatic melanoma patients (19 BRAF V600+ and 17 BRAF V600-), treated in adjuvant or advanced setting according to clinical practice with targeted therapy or immunotherapy, were recruited prospectively and followed up during therapy. For each patient, clinical benefit was assessed according to the treatment setting, and both germline and somatic DNA from fresh tissues were analyzed by Whole-Exome Sequencing (WES). For 12 patients (4 BRAF V600+ and 8 BRAF V600-), matched pre-therapy and post-therapy biopsies underwent WES. Circulating free DNA (cfDNA) was also sequenced by targeted Next Generation Sequencing (NGS) in 14 patients; for 3 patients, multiple cfDNA samples were sequenced during therapy.
Results: In BRAF V600+ patients, copy number variations and mutations in 33 melanoma driver genes were higher in non-responders than in responders. Conversely, no differences in both driver melanoma and interferon pathway genes were found in BRAF V600- patients, but responders showed a doubled tumor mutational burden compared to non-responders (30.5 *vs* 15.9). Several determinants of intrinsic/acquired resistance were identified (*i.e.*, ARID2, KIT, PREX2, RAC1, FBXW7 mutations, PTEN deletion, BRAF amplification). Concordance between cfDNA and matched biopsy was close to 70%, considering BRAF p.V600E and KIT p.K642E hotspot mutations. Furthermore, a novel germline variant in ATM was identified and classified as pathogenic with proof of concept functional data.
Conclusions: Despite an extensive deep investigation of metastatic melanoma genetics, little data is available on how to discriminate between patients who could benefit from one treatment over another. Indeed, literature on prospective real-world WES studies conducted analyzing fresh tissues during treatment is scant.
Driver and resistance-associated mutational profiles point out known and novel gene mutations encouraging functional in vitro/in vivo studies to confirm their pathogenicity.
ctDNA-derived data confirm the clinical utility of liquid biopsy in following dynamic changes in response to therapy. Germline findings support the clinical relevance of performing germline testing secondary to somatic WES.

THE EORTC PROTOCOL FOR SENTINEL LYMPH NODE BIOPSY (SLNB) REVEALS A HIGH NUMBER OF NODAL NEVI AND A STRONG ASSOCIATION WITH NEVUS-ASSOCIATED MELANOMA

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Background: The diagnosis of nodal nevi (NN) is challenging as they mimic melanoma metastases (MM), with a detection rate mostly ranging between 1% and 11% in sentinel lymph node biopsy (SLNB). Herein, we assessed the incidence of NN and the association with the clinical-pathological features of primary melanoma, adopting the updated European Organisation for Research and Treatment of Cancer (EORTC) protocol for SLNB.
Methods: All cases of paired melanoma and SLNB were retrospectively evaluated (April 2019-May 2020). Appropriate statistical tests were adopted, with significant variables included in the logistic regression model.
Results: 81 patients and a total of 186 lymph nodes (LNs) were included. Eleven patients had only NN and 4 had both NN and MM (18.5%); 29 LNs (15.6%) showed at least one NN and 12 (6.5%) showed more than one NN (a total amount of 43 NN was detected). All NN and none MM stained for p16. NN were associated with age < 60 years (p: 0.042), no ulceration (p: 0.025) and nevus-associated melanoma (NAM) (p: 0.018), with this latter being the only predictor at the logistic regression model (p: 0.022).
Conclusions: The updated EORTC protocol shows a high number of NN and highlights a strong association with NAM.

BRIGHT-FIELD MULTIPLEX IMMUNOHISTOCHEMISTRY ASSAY FOR TUMOR MICROENVIRONMENT EVALUATION IN MELANOMA TISSUES

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Background: The tumor microenvironment (TME) plays a crucial role in melanoma development, progression, and response to treatment. As many TME most relevant cell phenotypes are defined by simultaneous detection of more than two markers, the bright-field

(BF) multiplex immunohistochemistry (IHC) technique has been introduced for quantitative assessment and evaluation of spatial relative distances between immune cells and melanoma cells.
Methods: In the current study, we aimed to validate BF multiplex IHC techniques in Ventana Discovery Ultra Immunostainer to be applied to the evaluation of TME in variably pigmented melanoma tissues. The BF multiplex IHC staining was performed using different combination of 6 immune cell markers: CD3, CD4, CD8, CD20, CD68 and CD163 and the melanoma cell marker SOX10.
Results: Our results showed that the BF double IHC Yellow/Purple protocol guarantees the maximum contrast in all cell populations tested and the combination SOX10 (Green) CD8 (Yellow) CD163 (Purple) of the BF triple IHC protocol ensures the best contrast and discrimination between the three stained cell populations. Furthermore, the labeled cells were clearly distinct and easily identifiable by the image analysis software.
Conclusions: Our standardized BF IHC multiplex protocols can be used to better assess the immune context of melanoma patients with potential applications to drive therapeutic decisions within clinical trials.

THE MOLECULAR CHARACTERIZATION OF ANIMAL-TYPE MELANOMA

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Background: Animal-type melanoma (ATM) is a rare melanoma subtype, classified as "pigmented epithelioid melanocytoma" in the latest edition of the WHO Skin Tumors. The histopathological features include hyperpigmented spindle, epithelioid cells with the presence of melanophages. In immunohistochemistry, the loss of cytoplasmic staining for the PRKAR1A protein is distinctive and loss of expression of the R1α subunit results in dysregulation of melanocyte function. However, studies on the genetic profile of this entity are limited and driver mutations in the pathogenesis of ATM are unknown. Our study aims to explore the genetic landscape of ATM and to identify gene variants as potential prognostic and therapeutic biomarkers.
Methods: We enrolled 26 patients with ATM from different IMI centers. The DNA extracted from paraffin-embedded tissue, was amplified with Next Generation Sequencing using an IMI-validated Somatic DNA (IAD79062) multi-gene panel. Target regions were analyzed by Ion Torrent Suite Software used as control for conventional melanoma.
Results: 40 pathogenetic variants were isolated: 20 % involved the BRAF gene and 20% NF1 gene. ARID2, NRAS and CDKN2A mutations were detected in 12.5%, 10% and 7.5% of cases, respectively. Mutations in KIT, TP53 and KRAS genes are present in two cases, while BAP1, CDK4, ERBB4, MET, GNAQ, and DDX3X variants were unique. Most of the variants are missense (82.5%) and nonsense (15%). Nonsense variants result in NF1 (10%), ARID2 (5%) alterations, or in a loss of function mutation in GRD region (GTPase-activating protein-related domain). In 50% of the patients analyzed, we found 'UV signature' (nucleotide variations of type C> T). In our cohort, BRAF variant was observed in not chronically UV-exposed melanoma, mainly in men (87.5%) without a correlation with age.
Conclusions: Our data provide additional information on ATM molecular landscape thus suggesting a more appropriate diagnosis and prognostic evaluation of these variant. However, further larger studies are required for understanding the genetic background and its correlation with outcome.

SEMAPHORINS AS PREDICTIVE/PROGNOSTIC FACTORS AND PROMISING DRUGGABLE TARGET IN MELANOMA

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Background: Semaphorins are a family of 20 secreted or transmembrane proteins with cleavable extracellular domain, initially identified for their pivotal role in neuronal plasticity.[1] We previously demonstrated that Semaphorin 5A, Sema5A, promotes cell migration and invasion properties of melanoma cells, is expressed in metastatic melanoma specimens, while in situ melanoma specimens showed a focal positivity, and its expression is regulated by Bcl-2.[2] Here we evaluate the expression of Sema5A transcript in melanoma specimens and the level of circulating semaphorins in serum samples of melanoma patients under treatment or follow-up at IRE. Moreover, we investigate the role of Sema5A in the response to drug treatments.
Methods: qRT-PCR of Sema5A mRNA in melanoma tumor sam-

ples. ELISA assay of different semaphorins in sera of melanoma patients. Murine B16/F10 melanoma clones transduced with shSema5A and the corresponding control shRNA lentiviral particles were used to evaluate the effect of Sema5A on colony formation and cell viability assay in response to drug treatment.
Results: A trend of higher level of the Sema5A transcript was found in patients with more advanced melanoma, pT>2b, respect to patient with pT=2b. In sera samples of patients collected at T0 (time of lymph node evaluation), the levels of Sema5A, Sema3A and Sema4D were not found to be modulated respect to a cohort of healthy donors, while Sema7A was not detectable. Segregating patients with advanced melanoma (pT>2b; N≥1; Breslow thickness>1.6) based on BRAF status, an increased trend of Sema5A, Sema3A, and 4D level was observed in patients with mutated BRAF gene, respect to patients carrying the wild type gene. Finally, we observed a significant reduction of Sema4D protein in sera of patients with positive lymph node at diagnosis respect to patients with negative lymph node. Sema5A downregulation in murine B16/F10 melanoma cells reduced ability to form colony and increased resistance to ventoclax, a Bcl-2 specific inhibitor, respect to control cells, while none differences were observed after treatment with dabrafenib, a BRAF inhibitor.
Conclusions: Overall our data provide evidence supporting a role played by semaphorins in melanoma.

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2. doi: 10.1186/s13046-018-0933-x

MUTATIONAL STATUS OF SUPERFICIAL SPREADING AND NODULAR PRIMARY MELANOMAS IN PATIENTS WITH DISEASE RECURRENCE TOWARD THE CORRELATION WITH CLINICAL, DERMOSCOPIC, AND HISTOLOGICAL FEATURES: AN IMI STUDY (CARAMEL)

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Background: Literature data indicate that more than half of primary cutaneous melanomas (CM) in patients with metastatic disease were superficial spreading (SSM), while the remaining of them had a nodular melanoma (NM) at diagnosis. Moreover, a high proportion of deaths can be attributable to thin melanomas - 1 mm or less - in both the United States (27%) and Australia (23%). Thus, there is a subset of SSM at high risk of metastasis; thin melanomas with worst prognosis seem to be those located on the back and with large regression affecting at least 50% of the lesion. We here investigated the mutational profile in two series of patients with primary SSM or NM who were further stratified for disease progression.
Methods: Paraffin-embedded tumor tissues of the CM lesions were retrieved from the archives of the institutions participating in the study. NGS was performed using a specific multiple-gene panel constructed by the Italian Melanoma Intergroup (IMI) to explore the mutational status of selected regions (343 amplicons; amplicon range: 125-175 bp; coverage 100%) within the main 25 genes involved in CM pathogenesis; sequencing was performed with the Ion Torrent PGM System. For each group of primary SSM and NM, the mutational profile is being compared with dermoscopic and histopathological parameters as well as with clinical outcome within 5 years after the diagnosis.
Results: Overall, the median and average rates of pathogenic mutations were 2 and 3,23 for NM samples vs. 1 and 1,42 for SSM samples, respectively. BRAF-V600 mutations were found in 20/42 (47,6%) NM vs. 17/31 (54,8%) SSM; a NRAS mutation was detected in 15/42 (35,7%) NM vs. 1/31 (3,2%) SSM. One case carried both BRAF-V600E and NRAS-Q61R mutation but with different allele frequencies (6,3% and 18,8%), respectively. The SSM lesions presented a higher frequency of wild-type status in both BRAF and NRAS genes (13/31; 42%) as compared to the NM lesions (8/42; 19%). Considering the AJCC stage classification, no significant differences were observed in mutation frequency for BRAF or NRAS in NM and SSM samples (see Table 1 below). Interestingly, a variant allele frequency (VAF) ≥ 40% was observed in 9/20 (45%) BRAF-V600 mutated NM cases *vs.* 2/17 (11,8%) BRAF-V600 mutated SSM cases.
Conclusions: In our series, the SSM lesions were found to lack NRAS mutations. Although the prevalence of BRAF-V600 mutations was similar in both subsets (roughly, half of NM and SSM), a significantly higher level (more than three times) of the BRAF-V600 mutant allele frequency was observed in NM lesions as compared to SSM lesions. Correlation of these different subgroups of mutated cases with clinical and pathological parameters is under progression.

Table 1.

NM						SSM					
Stage	No.	$BRAF^{V600}$	%	$NRAS^{mut}$	%	Stage	No.	$BRAF^{V600}$	%	$NRAS^{mut}$	%
IA/IB-IIA	13	5	38,5%	5	38,5%	IA/IB-IIA	26	14	53,8%	1	3,8%
IIB/IIC-IIIA	15	6	40,0%	6	40,0%	IIB/IIC-IIIA	2	1	50,0%	0	0,0%
IIIB/C/D	14	9	64,3%	4	28,6%	IIIB/C/D	3	2	66,7%	0	0,0%

MULTI-PLATFORM ANALYSIS OF THE HETEROGENEITY OF CIRCULATING MELANOMA CELLS AND TUMOR DNA AS USEFUL TOOL TO TRACK DISEASE EVOLUTION AND TARGETED THERAPY RESPONSE

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Background: Melanoma heterogeneity is one the main obstacles for the management of metastatic melanoma. Although the advent of targeted therapy has significantly improved patient outcome, the occurrence of resistance makes the monitoring of tumor genetic landscape mandatory. Liquid biopsy, being a sum of the systemic disease, is currently evaluated as an important biomarker for the real-time tracing of disease evolution.

Methods: In this pilot study, 17 stage IV melanoma patients, treated with BRAF/MEK inhibitors, have been enrolled, and followed for up to 24 months. A longitudinal screening at different time points (52 samples) has been applied to identify liquid biopsy dynamics during response to treatment and progression. Considering that resistance develops at a median time of 11-12 months, blood has been collected before starting the therapy, after 6 and 10 months to test the ability of our approach to detect early signs of tumor escape, and at relapse. We devised a multi-platform approach exploiting high-sensitivity techniques (NGS, ddPCR) and an FDA-cleared platform (CellSearch) to analyze circulating tumor DNA (ctDNA) trend, circulating melanoma cell (CMC) count, together with their customized genetic analysis and copy number variation assessment.

Results: BRAF mutant ctDNA was detected by ddPCR in 82% of patients, and its amount prior to the beginning of therapy was significantly correlated with response to treatment; a cut-off was also identified for a fast translation to the clinic. Moreover, when considering on-treatment changes, patients without ctDNA clearance up to the first 6 months had a significant correlation with early progression/no response, suggesting a further endpoint for this biomarker. In addition, single nucleotide variants (SNVs) known, or suspected, to confer resistance (involving, among others, MEK1, PTEN, NRAS genes) were identified by NGS in ctDNA and/or CMC DNA in 60% of patients. Finally, CMC number was confirmed to be a prognostic biomarker as a significant correlation between CMC count >0 at baseline and worse overall survival/progression free survival was identified.

Conclusions: This study provides the proof-of-principle of the power of this multi-platform analysis. Indeed, it can provide ctDNA tracking and profiling, together with CMC count variation, and genetic landscape, useful for capturing tumor evolution. Although a validation of this data in a larger cohort is mandatory, this kind of strategy opens new scenarios for the management and real time monitoring of melanoma patients.

SURGERY

RADIOGUIDED OCCULT LESION LOCALIZATION TECHNIQUE (ROLL) FOR NON-PALPABLE SUBCUTANEOUS AND LYMPH NODE METASTASES FROM MELANOMA REMOVAL

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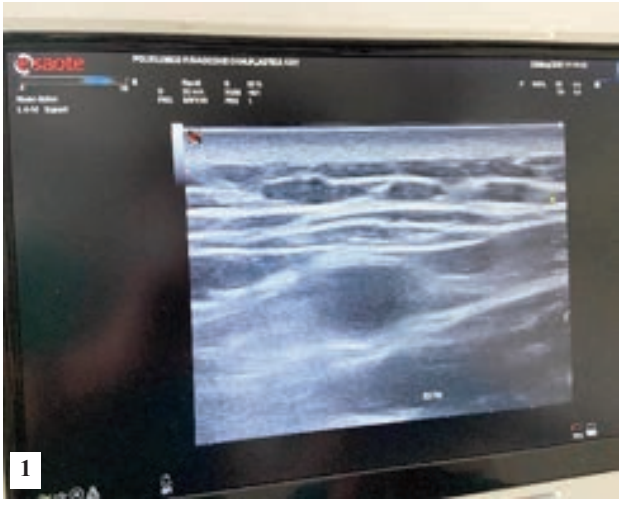
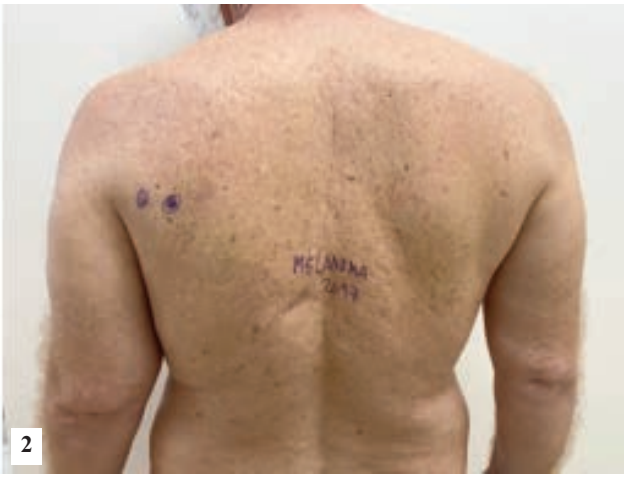
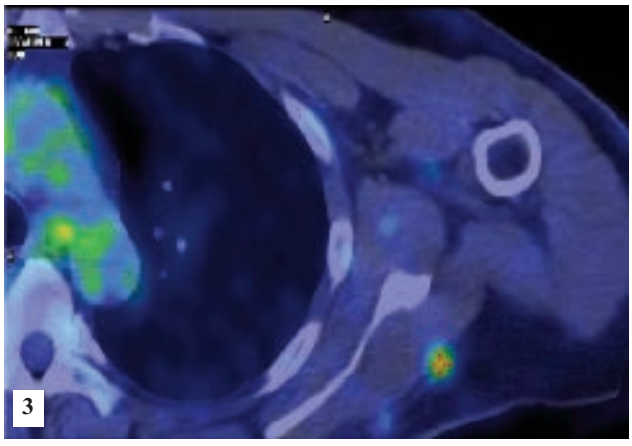
Background: The ROLL is an innovative technique for non-palpable breast lesions detection, which are evident on imaging studies. The technique involves the ultrasound-guided introduction within non-palpable lesions (small nodules or microcalcifications) of a radio-drug containing macro-aggregates of human albumin conjugated with Tc99m. This technique can be applied in patients with melanoma who have non palpable subcutaneous or lymph nodes metastases, evident on imaging studies deserving of histological characterization. The technique allows an exact localization of the lesion and a following minimally invasive but radical surgical resection.

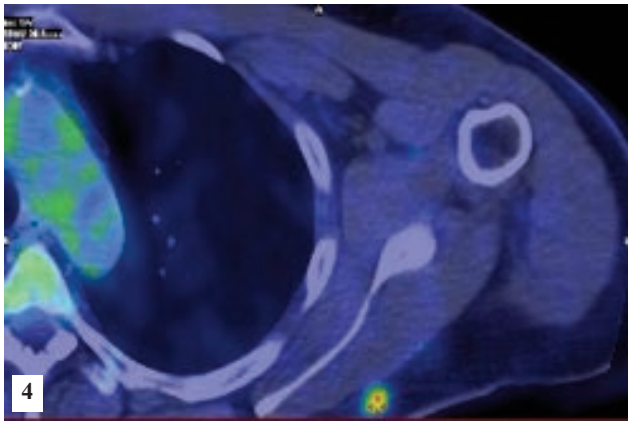




Figures 1 and 2. US-guided identification and skin marking of the two non-palpable lesions.

Methods: The day before surgery the interventional radiologist identifies suspicious and non-palpable lesions by ultrasound (Figures 1,2), highlighted previously on CT-Pet or MRI (Figures 3,4,5), and injects a minimal amount of radio-drug into their context (Figures 6,7). The radioactive tracer injected into the lesion emits signals that are picked up by a probe, the same used for sentinel lymph node biopsies. The gamma camera analyzes the signal picked up by the probe by emitting a sound whose intensity is proportional to the intensity of the signal picked up. The probe identifies the point of maximum uptake which corresponds to the center of the lesion. Moving the probe towards the periphery, the signal is reduced until it disappears completely; in this way the limits of surgical resection are defined (Figure 8).





Figures 3 and 4. PET-TC: Two uptake areas in the left chest wall, posterior to the infraspinatus muscle.

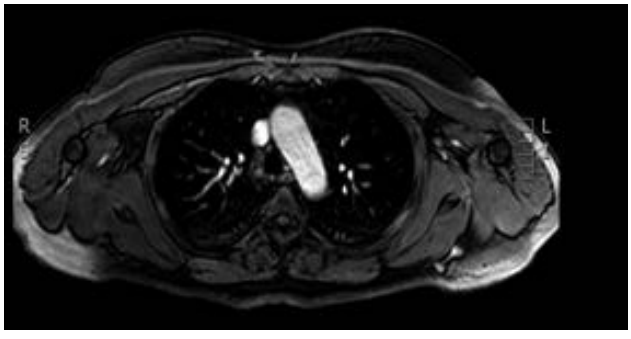
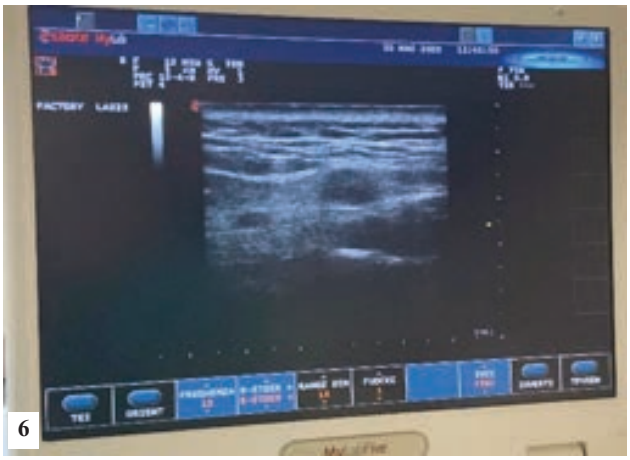


Figure 5. RMN TORACE: Two nodular lesions of 1.6 x 1.3 cm and 1.4 x 1.2 cm with post-contrast enhancement, in the left chest wall posterior to the infraspinatus muscle.



Figures 6 and 7. US-guided radio-drug inoculation within the two non palpable lesions (Figure 6. Before the inoculation of the radiopharmaceutical; Figure 7 after the inoculation of the radiopharmaceutical).

Figure 8. Surgical piece with the two non-palpable lesions in the center.

At the end of the procedure, you must check the emission of radioactivity in the operating piece and the total absence of residual uptake on the treated anatomical area. In terms of radioprotection, the procedure is safe both for the low levels of radioactivity of the substance introduced into the lesion that is removed during surgery, and for the dose absorbed by the patient and the surgeon. This technique has been found to be useful in patients who are overweight or have severe edema.
Results: The ROLL provides: oncological radicality, first intention wound healing, rapid recovery of the patient, absence of lymphedema secondary to biopsy, no worsening of limbs oedema, identification of stage III patients candidate for adjuvant therapy.
Conclusions: The ROLL allows the radical removal of non-palpable metastases from melanoma. The ROLL's aim is not only therapeutic but also of staging, since the minimally invasive removal of the lesions has allowed to restage the disease, allowing the patient to access adjuvant therapies, without exposing him to the risk of secondary lymphedema.

MODIFIED MOHS MICROGRAPHIC SURGERY IN SKIN TUMORS

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Background: Microscopically controlled surgery allows intraoperative histological analysis of 100% of the circumferential margins and the bottom of a neoplasm, while traditional histological examination analyzes approximately 1% of the tumor margins.[1] Therefore, Mohs micrographic surgery allows to obtain higher cure rates than traditional techniques and in addition reduces the surrounding healthy tissue removed.[1] Numerous variants of the technique have been described over the years with the term "modified Mohs surgery" (MMS).[2] The experience on the use of microscopically controlled surgery in the treatment of skin tumors is reported and the different variants used in relation to the type, location and size of the tumor are described.
Methods: Retrospective analysis of 503 cases of skin cancers treated with MMS. The techniques used were: the Mohs and 'muffin' techniques, which analyze the entire lesion in horizontal sections; the Tubingen technique, which analyses the margins in vertical sections and the bottom in horizontal sections; the PDEMA, the 'spaghetti technique', the staged surgical excision.
Results: Among patients, 287 (57%) were men and 216 (43%) were women. The average age was 72 years. Forty-five cases were lentigo maligna and 458 cases were non-melanoma skin cancers: 342 basal cell carcinomas, 86 squamous cell carcinomas and then dermatofibrosarcoma protuberans, porocarcinomas and other adnexal tumors. The Tubingen technique was the most used. The PDEMA was preferentially used in large tumors. The spaghetti technique and the staged surgical excision were used in selected cases of large malignant lentigo of the face. The negativity of the margins was obtained in 312 patients (62%) with one "stage", in 130 patients (26%) with two stages, in 61 patients (12%) with three or more stages. We observed 3% of recurrence during follow-up (mean 30 months).
Conclusions: MMS has been shown to be effective in the treatment of skin cancers with a reduced number of relapses. MMS offers the advantage of allowing microscopically proved complete surgical excision of the tumor and immediate reconstruction, with economic advantages for the health system (single hospitalization) and psychological advantages for the patient (one procedure with immediate reconstruction). Moreover, MMS allows the removal of the minimum amount of surrounding healthy tissue reducing scarring, particularly useful in aesthetically sensitive areas such as the face.

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TREATMENT OF NON-MELANOMA SKIN CANCERS WITH MOHS MICROGRAPHIC SURGERY AND ITS VARIANTS: A SINGLE CENTER EXPERIENCE

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Background: Mohs micrographic surgery (MMS) allows the real-time evaluation of 100% of the surgical margins during skin cancer excision. Moreover, MMS leads to the complete removal of the tumour, with a minimum loss of surrounding healthy cutaneous tissue. For these reasons, MMS represent the gold standard for treating high-risk non-melanoma skin cancers (NMSC).[1,2] Nevertheless there are still no clear indications regarding MMS variants.
Methods: Retrospective analysis of all MMS performed for non-melanoma skin cancers (NMSC) at the Dermatology Unit of Santo Stefano Italy, between 1 September 2021 and 31 July 2022.
Results: During the investigated period, a total of 94 patients underwent MMS. In all cases dermoscopy was used for demarcation of surgical margins.[3] All patients had a histologically confirmed NMSC. 68% were men, and the remaining 32% were women (Figure 1). In most cases, the initial diagnosis was basal cell carcinoma (Figure 2). The most common anatomic site was the face (56%), followed by the scalp (15%) (Table 1). After the first incision, 75 % of surgeries had clear margins, and 25% needed a second round re-excision (Table 2). There were 3 cases of cancer recurrence after a median 5 months of follow-up (Figure 2); all these latter were squamous cell carcinomas with perineural invasion. There were no severe adverse events or complications related to MMS procedure.
Conclusions: Analysing our MMS cases we find that tumor histological type and location play an important role in determining the number of steps necessary to achieve negative surgical margins, defect size and closure type resulting in better patient outcomes.

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THERAPY

BRAFV600 VARIANT ALLELE FREQUENCY PREDICTS OUTCOME IN METASTATIC MELANOMA PATIENTS TREATED WITH BRAF AND MEK INHIBITORS

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Background: The prognostic impact of variant allele frequency (VAF) on clinical outcome in BRAFV600 mutated metastatic melanoma patients (MMPs) receiving BRAF (BRAFi) and MEK inhibitors (MEKi) is unclear.
Methods: A cohort of MMPs receiving first line BRAFi and MEKi was identified by inspecting prospectively collected electronic databases of 3 Italian Melanoma Intergroup (IMI) centers. Clinical outcome and response rate were retrieved. VAF was determined by next generation sequencing in pre-treatment baseline MM tissue samples. The correlation of VAF with BRAF copy number variation (CNV) was analysed in an ancillary study by using a training and a validation cohort of melanoma tissue sam-

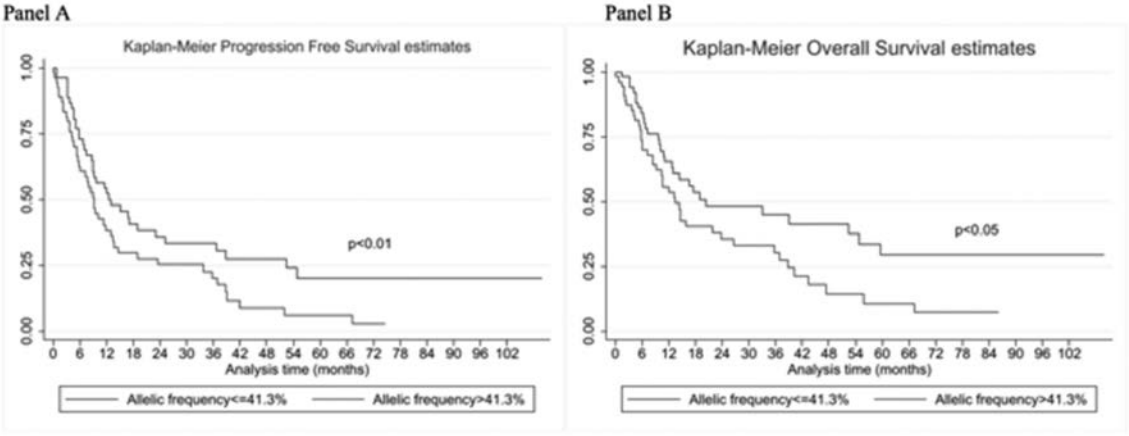

Figure 1. Progression free and overall survival according to BRAFV600 allele frequencies in melanoma patients treated with MAPKi.

ples and melanoma cell lines.

Results: Overall, 107 MMPs were included in the study. The VAF cutoff determined by ROC curve and Liu approach was 41.3%. At multivariate analysis, PFS was significantly shorter in patients with M1c/M1d [HR 2.16 (95% CI 1.31-3.56, p<0.01)], in those with VAF >41.3% [(HR 1.62 (95% CI 1.03-2.56, p<0.05)], in female [(HR 1.77 (95% CI 1.09-2.87, p<0.05)] and in those with ECOG PS ≥1 [(HR 1.89 (95% CI 1.16-3.07, p<0.05)]. At multivariate analysis, overall survival (OS) was significantly shorter in patients with M1c/M1d [(HR 2.06 (95% CI 1.23-3.47, p<0.01)]. Furthermore, OS was shorter in patients with VAF >41.3% (HR 1.59 (95% CI 0.98-2.58), and in patients with ECOG PS [3]1 [(HR 1.47 (95% CI 0.88-2.44)]. BRAF gene amplification was found in 11% and 7% of samples in the training and validation cohort, respectively.

Conclusions: High VAF is an independent poor prognostic factor in MMP receiving BRAFi and MEKi, and alternative treatment strategies are needed. VAF and BRAFV600 gene amplification are different biological phenomena in most of patients.

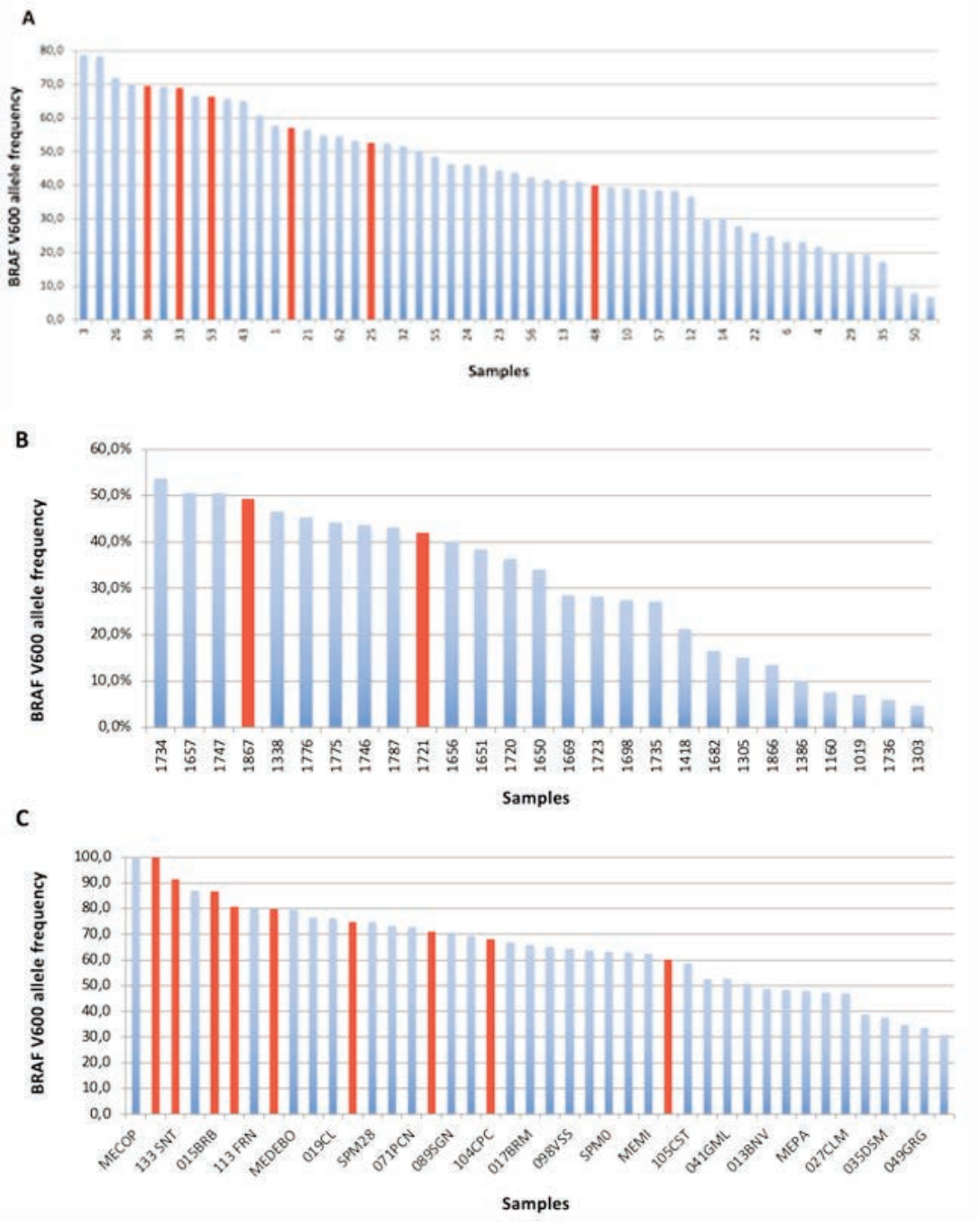

Figure 2. Distribution of melanoma samples according to the BRAF V600 mutated allele frequency. In red, samples carrying the *BRAF* gene amplification (>4 copies; see Methods). a) Results on melanoma tissues from the discovery (a) and validation (b) cohorts as well as on melanoma cell lines (c).

Table 1. Univariable and Multivariate analysis: prognostic factors for PFS and OS.

	Progression Free Survival (95%CI)		Overall Survival (95%CI)	
Characteristic	**HR Univariate**	**HR Multivariate**	**HR Univariate**	**HR Multivariate**
Gender				
Male (ref.)	-	-	-	-
Female	1.16 (0.74-1.51)	1.77 (1.09-2.87)*	1.06 (0.66-1.71)	
ECOG Performance status				
0 (ref.)	-	-	-	-
≥ 1	1.54 (0.96-1.95)	1.89 (1.16-3.07)*	1.58 (0.96-2.61)	1.47 (0.88-2.44)
Metastasis				
M1a+M1b (ref.)	-	-	-	-
M1c+M1d	2.22 (1.39-3.53)**	2.16 (1.31-3.56)**	2.16 (1.29-3.61)**	2.06 (1.23-3.47)**
Variant allelic frequency				
≤ 41.3% (ref.)	-	-	-	-
> 41.3%	1.6 (1.03-2.48)*	1.62 (1.03-2.56)*	1.7 (1.05-2.74)*	1.59 (0.98-2.58)
Histology type				
Superficial spreading (ref.)	-	-	-	-
Nodular melanoma	1.31 (0.83-2.08)	1.38 (0.84-2.29)	1.21 (0.74-1.98)	

Multivariate models were adjusted for age and estimated after backward-selection method (p<0.3)
*p value<0.05 **p value<0.01

CIRCULATING CYTOKINES AS PREDICTORS OF RESPONSE AND SURVIVAL IN MELANOMA (MEL) PATIENTS (PTS) TREATED WITH IMMUNE CHECKPOINT INHIBITORS (ICIS)

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Background: The identification of factors influencing ICI efficacy in cancer PTS and the elaboration of a prognostic score based on circulating biomarkers could optimize treatment selection and outcomes in metastatic melanoma treated with this approach.
Methods: Our multicentric prospective study enrolled advanced stage MEL and NSCLC PTS treated with ICI with the primary endpoint of evaluating the association between circulating cytokines (Il-1b, Il-2, Il-4, Il-5, Il-6, Il-8, Il-10, TNFA, GM-CSF) and: i) Disease Control Rate (DCR), ii) Progression Free Survival (PFS) and iii) Overall Survival (OS). PTS underwent a blood sample at baseline, before the first 6 ICI cycles (T1-T6) and at each tumor assessment until Disease Progression (PD) or for maximum of 2 years. Biomarker levels are assessed by lumine xmap based technology using r&d high sensitivity kits.
Results: Here we report the analyses of the T1(baseline)- T2 samples from the first 43 MEL PTS enrolled (M:F 20:23, median age 71). Median follow-up, PFS and OS times are 10.6 (95% CI 8.5─13.1), 6.9 (95% CI 2.8─15.9) and 12.6 (95% CI 4.7─ne) months (mo), respectively. Il-6 and Il-8 were significantly higher at baseline and at T2 for PD PTS (Kruskal-Wallis test). The median relative increase (RI) from T1 of Il8 was 32% for PD PTS and it was significantly higher than for PTS with Disease Control (DC) (decrease of 11%). Likewise, il-10 median RI was 104% for PD PTS and of 41% for DC PTS (p=0.002). Each marker was categorized according to high and low levels by maximizing its discriminative ability, and the association with the outcome was tested in univariate and multiple variate analyses. The multiple logistic analysis confirmed that Il8 at T2 and the its RI were independent factors of DC, with an overall accuracy of 81.1%. In detail, high levels of Il-8 at T2 and a higher RI were associated with a low probability of DC (OR=0.01, 95%CI: 0.00─0.15 and OR= 0.06, 95%CI: 0.00─0.53, respectively). In the multiple Cox regression model: elevated Il-8 and Il-10 at T2 (HR=7.89, 95%CI: 2.66─25.78, HR=2.99, 95%CI: 1.09─8.49) and a higher RI of Il-8 (HR=3.61, 95%CI: 1.27─13.81) remained significantly associated with a worse PFS. Higher levels of Il-10 at T1 (HR=11.06, 95%CI: 2.05─74.73), of Il-8 at T2 (HR=6.38, 95%CI: 1.69─30.76) and a higher RI of Il-8 (HR=11.86, 95%CI: 2.97─66.38) were significantly associated with worse OS.
Conclusions: Higher T2 or RI of Il-8 levels are strongly associated to PD, PFS and OS. Higher T1 and T2 Il-10 levels are associated to shorter OS and PFS, respectively. The accrual of planned patients (166, included NSCLC) was now completed and the analyses in all patients will allow to evaluate if cytokines levels and

their ri are histology or treatment related, and a possible gender relationship, in the aim of risk-based tailored treatments.

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PATIENTS WITH STAGE IV MELANOMA TREATED WITH IMMUNOTHERAPY FOR MORE THAN 2 YEARS: IS AN END TO TREATMENT POSSIBLE?

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Background: Immune checkpoint inhibitors Anti-Pd-1 have significantly improved prognosis of patients with advanced melanoma. treatment duration in patient who achieved a durable Complete Response (CR) is still debated. On the basis of some literature findings, it is generally agreed that in CR patients treatment can be interrupted after two years. however, a few data are available for those patients who achieved a long-lasting partial response or stable disease after two years of treatment in a real-life setting.
Methods: This multicentre study included 328 stage iv melanoma patients from 23 Italian referral centres belonging to IMI (Italian Melanoma Intergroup) who underwent an Anti-Pd1 treatment for more than 2 years discontinued the treatment after the obtaining of a CR or due to drug-related toxicity or for patient decision.
Results: Out of 328 patients, 237 discontinued treatment because of complete response, toxicity or patient's decision after two years of treatment. 78 patients continued treatment more than two years. among those patients, we observed a CR in 16 patients, Partial Response (PR) in 47 patients, Stable Disease (SD) in 14 patients and Disease Progression (PD) in 1 patient. Among the group of patients who interrupted therapy after two years (n 237), 128 patients were in CR. Out of 128 patients in CR discontinuing treatment, only 10 patients (7.8%) developed relapse and 8 patients (6.3%) died. Moreover, 16 patients of this group (12.5%) underwent surgery and 19 patients (14.8%) received radiotherapy.
Conclusions: In this multicentre study, treatment interruption is a safe decision in patients who achieved CR. Since a great number of patients in CR took advantage of surgery and/or radiotherapy in order to achieve complete response, same benefits can be supposed for the group of patients with PR and SD that are still in therapy since many years. Otherwise, treatment interruption is not advised in this group since, considering our experience, a greater risk of relapse has been proved to be associated with PR and SD at the discontinuation of immunotherapy.

META-ANALYSIS OF RANDOMIZED TRIALS EVALUATING TRIPLET COMBINATIONS OF IMMUNOTHERAPY AND TARGETED THERAPY FOR BRAF V600–MUTANT UNRESECTABLE OR METASTATIC MELANOMA

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Background: Immune-Checkpoint Inhibitors (ICI) and Targeted-Therapies (TT) are both considered standard options for Braf-V600 Metastatic Melanoma (B-MUT MM) Patients (PTS). However, still more than 50% of those PTS do not respond or relapse due to primary or secondary resistances and though, innovative strategies are needed. Preclinical and translational data suggest that ICI plus TT may improve treatment outcomes in PTS with B-MUT MM, but with conflicting results in the clinical setting.
Methods: We performed a systematic review and meta-analysis of phase ii-iii Randomized Controlled Trials (RCT) published until July 2022 comparing first-line TT+ICI *vs* TT alone in B-MUT MM. We obtained summary estimates through random-effects models. Summary Hazard Ratio (SHR) for Overall Survival (OS) and Progression-Free Survival (PFS) were the main outcomes retrieved but we look also at differences in clinical responses and adverse events by treatments arms.
Results: The summary estimate indicates a significant 28% decrease in risk of progression (SHR=0.72, 95%CI:0.54-0.95) and a significant 20% reduction in risk of death (SHR=0.80,95% CI:0.68-0.94) with TT+ICI vs TT alone. no difference was shown between arms in terms of summary objective response rate (TT 65.4% *vs* ICI+TT 67%, p=0.56). ECOG PS 1 PTS, compared to ECOG PS 0, have a greater benefit with a significant reduction in risk of death with TT+ICI compared to TT (HR=0.55; 95%CI

0.37-0.83; HR=0.80; 95%CI 0.50-1.27, for ECOG PS 1 and 0 respectively). Furthermore, those with Neg Pd-L1 status, compared to Pos one, seem to benefit more in terms of OS with TT+ICI vs TT (HR=0.62; 95%CI 0.43-0.89; HR=0.91;95%CI 0.65-1.28, with Pd-L1 Neg Vs Pos respectively). No significant differences were observed in SHRS for PFS by prognostic factors. Significant greater frequency of grade 3 or more adverse events was observed in arms TT+ICI compared to TT (summary odd ratio=2.04, 95%CI:1.34-3.12).

Conclusions: This study supports and extend the discussion on first-line combinations to be offered to B-MUT MM PTS. Combining ICI with TT demonstrated an effective advantage on both PFS and OS, although augmenting toxicities. further biomarker-driven investigation may identify PT subpopulations who could benefit from TT+ICI combinations to expand their window of therapeutic opportunities.

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PHASE III STUDY OF ADJUVANT ENCORAFENIB PLUS BINIMETINIB VERSUS PLACEBO IN FULLY RESECTED STAGE IIB/C *BRAF*V600-MUTATED MELANOMA: COLUMBUS-AD STUDY DESIGN

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Background: Encorafenib+binimetinib (E+B) is a well-tolerated and effective treatment option in advanced BRAFV600-mutant melanoma, providing sustained progression-free and overall survival benefit in unresectable or metastatic setting. The focus has shifted to early-stage disease to prevent recurrence as it has been estimated that 18% of stage IIB and 25% stage IIC patients (pts) die due to melanoma within 10 years from the diagnosis[1] indicating an unmet medical need.

Methods: COLUMBUS-AD (NCT05270044) study is an international randomized, placebo-controlled, triple-blind, multicenter Phase III trial evaluating adjuvant E+B against placebo in pts with fully resected stage IIB/C BRAF V600-mutant melanoma. Around 815 pts will be enrolled. More than 160 sites in up to 26 countries worldwide will participate in the study conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC). Pts will receive E+B or placebo for 12 months, or until disease recurrence and will be followed monthly during treatment period, then every 3 months up to year 3, and then at regular intervals. The participants will be followed for a total of 10 years. Pts included in the study must have undergone resection of a stage IIB/C cutaneous melanoma with a BRAFV600E/K mutation, confirmed on resected tumor sample by a central laboratory, and a negative result on sentinel node biopsy. Pts must have fully recovered from the surgery, a good performance status ECOG 0/1, and adequate hematologic, hepatic, cardiac, coagulation and renal functions. Eligible pts will be randomized 1:1 to receive either active treatment with E:450 mg once daily + B:45 mg twice daily or matching placebos. The primary objective is to evaluate the efficacy of the combination of E+B for prolonging recurrence-free survival. The secondary objectives are to compare distant metastasis-free survival, overall survival, health-related quality of life and safety and tolerability between the 2 arms and to provide additional pharmacokinetic data.

Conclusions: COLUMBUS-AD is the first study to evaluate a combination of BRAFi/MEKi in high-risk stage II adjuvant melanoma. This study will evaluate whether the combination of E+B can decrease the risk for recurrence and improve distant metastasis-free survival and overall survival versus placebo in completely resected IIB/C BRAFV600E/K-mutant cutaneous melanoma.

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ACTIVITY AND SAFETY OF FIRST LINE TREATMENTS FOR ADVANCED MELANOMA: A NETWORK META-ANALYSIS

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Background: Treatment options for advanced melanoma have increased with the Food and Drug Administration (FDA) approval of the anti-LAG3 and anti-PD-1 relatlimab/nivolumab combination. To date, ipilimumab/nivolumab is the benchmark of overall survival (OS), despite a high toxicity profile. Furthermore, in *BRAF*-mutant patients, BRAF/MEK inhibitors and the atezolizumab/vemurafenib/cobimetinib triplet are also available treatments, making the first-line therapy selection even more complex. To address these issues, we conducted a systematic review and network meta-analysis comparing the activity and safety of ipilimumab/nivolumab with relatlimab/nivolumab and all the other available first-line treatment options in metastatic melanoma.

Methods: Randomised clinical trials (RCTs) of patients with unresectable stage III or IV, previously untreated melanoma, were included if at least one intervention arm contained a targeted (BRAF with or without MEK) or an immune checkpoint (CTLA-4 or PD-(L)1) inhibitor. The aim was to indirectly compare the ICIs combinations ipilimumab/nivolumab and relatlimab/nivolumab, and these combinations with all first-line treatment options for advanced melanoma (irrespective of BRAF status) in terms of activity and safety. The co-primary endpoints were progression-free survival (PFS), overall response rate (ORR), and grade ≥3 treatment-related adverse events (≥ G3 TRAEs) rate, defined according to Common Terminology Criteria for Adverse Events

(CTCAE). PROSPERO: CRD42022303279.
Results: A total of 9070 patients treated in 18 RCTs of metastatic melanoma were included in the network meta-analysis. No difference in the risk of disease progression and response between ipilimumab/nivolumab and relatlimab/nivolumab was observed (HR=0.99 [95%CI 0.75 – 1.31] and RR=0.99 [95%CI 0.78 – 1.27], respectively). The PD-(L)1/BRAF/MEK inhibitors triplet and BRAF/MEK inhibitors combinations were superior to ipilimumab/nivolumab in terms of PFS (HR=0.56 [95%CI 0.37 – 0.83] and HR=0.73 [95%CI 0.50 – 1.06], respectively) and ORR (RR=3.07 [95%CI 1.61 – 5.85] and RR=2.99 [95%CI 1.58 – 5.67], respectively). Ipilimumab/nivolumab showed the highest probability to have the highest risk of developing ≥ G3 TRAEs. Relatlimab/nivolumab trended to a lower risk of ≥ G3 TRAEs (RR=0.71 [95%CI 0.30 – 1.67]) vs. ipilimumab/nivolumab.
Conclusions: Relatlimab/nivolumab showed similar PFS and ORR compared to ipilimumab/nivolumab, with a trend for a better safety profile.

PATIENT-REPORTED OUTCOMES AND QUALITY OF LIFE IN MELANOMA PATIENTS WITH ASYMPTOMATIC BRAIN METASTASES: RESULTS FROM THE PHASE III NIBIT-M2 TRIAL

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Background: The phase III trial NIBIT-M2 study showed a 41% 5-year overall survival (OS) of melanoma patients (pts) with asymptomatic brain metastases (BM) treated with ipilimumab plus nivolumab (*1*). In spite of the significant efficacy of ipilimumab combined with nivolumab, no data are available on patient-reported outcomes (PROs) and Health-Related Quality of Life (HRQoL) in this patient population.
Methods: The NIBIT-M2 study recruited pts 18 years with *BRAF* wild type or mutant melanoma, and active, untreated, asymptomatic BM from nine Centers in Italy. Eligible pts were randomized (1:1:1) to fotemustine (Arm A), ipilimumab plus fotemustine (Arm B), or ipilimumab plus nivolumab (Arm C). Primary endpoint was OS. PROs were assessed at week (W)1 and W12 using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30Version 3.
Results: Between January 2013 and September 2018, 80 pts were enrolled and 76 received fotemustine (23), ipilimumab plus fotemustine (26), and ipilimumab plus nivolumab (27). Seventy-twopts completed a baseline QLQ-C30 questionnaire, and 34 pts completed it at W12; compliance rates were 95% at baseline and 45% at W12. No statistically significant differences were observed in global health score (GhS) and most functional scales were preserved from baseline to W12 (Table 1). A lower decrease in the mean QLQ-C30 scores was recorded from baseline to W12 in pts receiving ipilimumab plus nivolumab (Table 1). Notably, when assessing as clinically meaningful a variation in GhS of 10-point, a worsening ≥10-point was observed in 44% of patients for Arm A and B and in 29% for Arm C.
Conclusions: HRQoL was comprehensively preserved in all treatment arms of the NIBIT-M2 study. Treatment with ipilimumab plus nivolumab in melanoma pts with asymptomatic BM led to a lower decrease in the mean QLQ-C30 scores as compared to pts treated with ipilimumab and fotemustine and fotemustine alone.

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Table 1.

Change From Baseline to Week 12 in QLQ-C30 Scores	ARM A N = 22	ARM B N = 25	ARM C N = 25
GHS/QoL	- 7.9% (74 to 67)	-5.8% (78 to 64)	-7.1% (77 to 71)
Physical functioning	-9.4% (94 to 86)	-7.7% (93 to 86)	-6.1% (94 to 89)
Role functioning	-14.4% (98 to 83)	-13.3% (93 to 80)	-6.2% (93 to 87)
Emotional functioning	-14.1% (78 to 69)	-4.3% (79 to 75)	+11.1% (80 to 79)
Cognitive functioning	-10.4% (94 to 83)	-3.3% (94 to 89)	-2.1% (96 to 93)
Social functioning	-14.1% (96 to 81)	-12.3% (88 to 77)	-6.9% (100 to 93)

For GHS/QoL and functional scales, a positive score indicates improvement.

HEDGEHOG INHIBITORS (HHI) IN THE MANAGEMENT OF MULTIPLE BCCS IN PATIENTS WITH NEVOID BASAL CELL CARCINOMA SYNDROME: A SINGLE CENTRE EVALUATION OF SONIDEGIB EFFICACY AFTER VISMODEGIB DISCONTINUATION

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Background: Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome (GS), is a rare genetic condition characterized by the early development of numerous cutaneous basal cell carcinomas (BCCs).[1] Although most BCCs are surgically treated with total resection, some of these lesions may proceed to a locally advanced or metastatic stage. Systemic treatment with a HHI, such as Vismodegib or Sonidegib, is indicated in this population.[2,3,4]
Methods: We report the case of two patients with confirmed diagnosis of NBCCS. Both patients previously underwent multiple surgical excisions and have been treated with oral Vismodegib 150

mg/day for a locally advanced tumor. They both discontinued the therapy due to its specific adverse effects (AEs) and they are now being treated with oral Sonidegib with better tolerability and complete response. Case 1: 54-year-old male with NBCCS evaluated for a tumor located on the left nasal fold and multiple BCCs on the back, previously treated with Vismodegib 150mg/day for 13 months and discontinued for AEs such as G2 muscular cramp, G2 alopecia, and moderate dysgeusia now under treatment with Sonidegib 200mg/day with overall complete response (CR) and no drug-related AEs; Case 2: 74-year-old woman referred to our clinic for diffuse spreading BCCs located on the back treated with Vismodegib 150 mg/day for 36 months then halted due to its specific AEs, specifically G2 alopecia, G2 muscular spasm, G1 dysgeusia, and nausea now under treatment with Sonidegib 200mg/day with overall (CR) and no drug-related AEs**.**

Discussion: Antagonistic effect on Hedgehog signaling is a major treatment possibility for patients with locally advanced, metastatic BCCs as well as NBCCS patients who have a high risk of developing numerous BCCs throughout their lives. The half-life of Sonidegib is longer than that of Vismodegib, but both Vismodegib and Sonidegib have strong overlapping class-dependent AEs. However, In the case of Sonidegib, dose adjustments are viable options for reducing the need for treatment discontinuation without jeopardizing its specific efficacy. Considering patients with NBCCS, a recent report showed the promising efficacy of Sonidegib in all patients treated, with partial or total clinical clearance of target BCCs, as well as pathological clearance in 57% of cases.[5]

Conclusions: Sonidegib should be considered in all respects a first line treatment for patients with NBCCS not amenable for surgery or radiotherapy, and for sure a second line option in patients previously treated with other HHI.

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CEMIPLIMAB FOR LOCALLY ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA IN ELDERLY PATIENTS: REAL-LIFE DATA FROM THE DERMATO-ONCOLOGY UNIT OF TRIESTE

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Background: Cemiplimab is a human IgG4 monoclonal antibody directed against the programmed death 1 (PD-1) receptor, approved for the treatment of metastatic (mcSCC) or locally advanced cutaneous squamous cell carcinoma (lacSCC).[1] Despite information from the registration trials, only few real-life data on the effectiveness and safety profile of cemiplimab are currently available. For this reason, we describe our experience with cemiplimab in a cohort of 7 elderly patients with several comorbidities, treated for lacSCC at the Dermato-Oncology Unit of Trieste.

Methods: We retrospectively analyzed the medical records of 7 patients treated with cemiplimab between March 2021 and June 2022 in our Unit. All individuals were affected by lacSCC, none had mcSCC. For each patient, epidemiological data, as well as response to treatment (according to RECIST criteria)[2] and adverse events were collected.

Results: The group included 4 men (57.2%) and 3 women (42.8%), with a mean age of 86.6 years (range 83-92). Many patients had several comorbidities, including heart disease and chronic kidney disease. Almost all lesions were located in the head and neck area (n = 6/7, 85.7%), only one case arising on the inferior limb (1/7, 14.3%). All patients received cemiplimab at the dosage of 350 mg every 3 weeks intravenously, most of them as first-line therapy (n = 5/7).

Five patients (71.4%) achieved complete response (CR), while 2 patients (28.6%) achieved partial response (PR). Overall, we observed rapid and significant results in all patients. The median time of response consisted in 3 cycles of therapy.

Averse events were few and mild in severity, including only fatigue (n =1/7, 14.3%) and skin toxicity with grade 2 pruritus, rash and fever (n =1/7; 14.3%).

Conclusions: In our cohort, we observed 5 CRs (71.4%) and 2 PRs (28.6%), therefore our data showed an overall response rate (100%) higher than previously reported in controlled trials and other real-world series (overall response rate: 31-76.7%).[3] Tumor location in the head and neck area and use of cemiplimab as first-line therapy in the majority of patients could also have led to improved results, since these two features are predictors of better response.[3,4] Our case series demonstrates that cemiplimab can be effective and safely used in real-life patients with poor performance status and relevant comorbidities, improving their quality of life.

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EXTENSIVE "HALO NAEVI" PHENOMENON AND REGRESSION OF MELANIN DURING NIVOLUMAB TREATMENT IN METASTATIC MELANOMA: A PREDICTOR OF A BETTER OUTCOME?

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Background: Vitiligo-like depigmentation in stage III-IV melanoma patients, treated with immune checkpoint inhibitors (ICI), has been associated with improved overall survival, pointing to depigmentation phenomena as a proxy of response to immunotherapy.[1,2] Conversely, halo nevus, or Sutton phenomenon, is a rarer clinical manifestation and its prognostic value, as well as any differences from the classical form, remains undefined. As of today, descriptions on extensive halo nevus development (defined as involvement on more than 50% of pre-existing naevi) during ICI treatment are lacking.
Methods: The case of a 63-year-old man with metastatic melanoma in treatment with anti-PD1 nivolumab is herein presented along with a comprehensive overview on the current knowledge on ICI-related halo phenomena.
Results: After 12 weeks on anti-PD1 nivolumab (480 mg every 4 weeks), an achromic halo appeared on our patient's left arm around a pre-existing nevus (Figure 1). The halo phenomenon progressively involved more than 50% of naevi on the body during the following months. In few cases, the sudden disappearance of pre-existing naevi was observed, resulting in achromic macules only (Figure 2). The dermoscopic evaluation revealed complete regression of the melanin in some other naevi (Figure 3). The patient has remained progression-free after 120 weeks of immunotherapy.
Conclusions: Extensive halo phenomenon has been previously reported during pembrolizumab and ipilimumab treatment.[3,4] In both cases, complete remission of metastatic melanoma was later obtained. This first case of extensive Sutton phenomenon during treatment with nivolumab supports the hypothesis that extended Sutton phenomenon and melanin regression may be associated with a better prognosis, as it has been previously observed for vitiligo-like depigmentation. Immune-mediate responses against shared melanocytic antigens (i.e., MART-1, gp100, and tyrosinase-related proteins 1 and 2) are likely responsible for the observed phenomenon.[5,6]

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RESCUE ADDITION OF IPILIMUMAB TO PEMBROLIZUMAB OR NIVOLUMAB IN METASTATIC MELANOMA AFTER RESISTANCE TO ANTI-PD-1 MONOTHERAPY: A MONOCENTRIC CASE SERIES

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Background: Most patients (pts) with advanced melanoma are resistant to anti-PD-1 monotherapy. Significant antitumor activity was demonstrated by the addition of ipilimumab (ipi) immediately after progression to pembrolizumab (pembro) monotherapy.[1] A retrospective study reported response in 21% of pts with combination therapy after progression to nivolumab (nivo) *vs.* 16% with ipi monotherapy.[2]
Methods: Hypothesizing that a subset of anti-PD-1 resistant pts would benefit from rescue combination with anti-CTLA-4, after authorization by the local regulatory entity, we administered salvage ipi in addition to ongoing pembro or nivo in 6 pts with advanced melanoma.
Results: 2 pts had uveal, 1 mucosal, and 3 cutaneous melanoma; 3 were females; the age range was 51-72 years. All received anti-CTLA-4 + anti-PD-1 after primary (3 pts) or acquired (3 pts) resistance to I-line with anti-PD-1 monotherapy (Table 1); 2 pts received pembro 200 mg q21 followed by ipi 1 mg/kg + pembro 2 mg/kg q21,[3] 4 received nivo 480 mg q28 followed by ipi 4 mg/kg + nivo 1 mg/kg q21.[4] Monotherapy maintenance was resumed after combination therapy in 2 pts with clinical benefit (CB). Disease-control rate was 50%: 2 patients achieved stable disease with CB after combination salvage therapy, 1 is still ongoing with CB; 3 had progressive disease. At the median follow-up of 16 months, time-to-treatment failure ranged from 3 to 26 months, overall survival from 7 to 21 months. No additional toxicity was reported after ipi introduction.
Conclusions: Rescue combination therapy with anti-CTLA-4 in addition to ongoing anti-PD-1 is feasible and potentially beneficial for patients with advanced melanoma after primary or acquired resistance to I-line monotherapy.

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Table 1. Treatment sequence, duration, and outcome for each patient of the case series.

Patients and disease	Anti-PD-1 monotherapy & duration	Rescue combination therapy & number of cycles	Monotherapy maintenance & duration	Best response to the rescue	TTF*	OS*
Patient 1 MM	Nivo 9 months	Ipi+Nivo 4 cycles	Nivo 2 months	SD	26 months	30 months
Patient 2 CM	Nivo 3 months	Ipi+Nivo 1 cycle	-	PD	3 months	7 months
Patient 3 CM	Nivo 17 months	Ipi+Nivo 4 cycles	-	PD	19 months	20 months
Patient 4 CM	Nivo 3 months	Ipi+Nivo ongoing (1 cycle)	N/A	NE	censored at 3 months	censored at 3 months
Patient 5 UM	Pembro 3 months	Ipi+Pembro 4 cycles	-	PD	5 months	12 months
Patient 6 UM	Pembro 9 months	Ipi+Pembro 4 cycles	Pembro 4 months	SD	17 months	21 months

TTF = time-to-treatment failure; OS = overall survival; MM = mucosal melanoma; CM = cutaneous melanoma; UM = uveal melanoma; Nivo = nivolumab; Pembro = pembrolizumab; Ipi = ipilimumab; N/A = not applicable; SD = stable disease; PD = progressive disease; NE = not evaluable *calculated from anti-PD-1 monotherapy start

SURVEY OF THE IMPACT OF BOLT-TRIAL DATA ON ONCOLOGISTS' AND DERMATOLOGISTS' DECISION MAKING IN TREATING PATIENTS WITH LOCALLY ADVANCED BASAL CELL CARCINOMA

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Background: We did a national survey where oncologists and dermatologists from reference hub structures for laBCC were asked questions on which efficacy and tolerability data of the pivotal phase-II BOLT trial they consider relevant to choose Sonidegib in their clinical practice.

Methods: We conducted a survey among Italian oncologists and dermatologists to collect opinions on which efficacy and tolerability data of the pivotal phase-II BOLT trial[1,2] they consider relevant to decision making in the treatment of patients with laBCC. 15 oncologists and 18 dermatologists from 27 hub hospitals accepted to participate in the survey which was conducted between Nov. 1 and Nov. 18, 2020 by email, anonymously, consisting of two multiple-choice questions on clinical efficacy and safety data of Sonidegib.

Results: When asked about efficacy outcomes from BOLT trial affecting treatment decision, oncologists stated duration of response, objective response rate and progression-free survival are influential factors (28%, 24% and 20% respectively. The percentage of dermatologists is similar, but they tend to prioritize objective response rate (35%) than duration of response (DoR) (24%). Disease control rate and time to response are perceived by the responders as less important outcomes for the efficacy. Disease control rate was rated higher by oncologists than dermatologists (16 % *vs*. 6%) but time to response scored higher for dermatologists (12% *vs*. 4%).

Both oncologists and dermatologists identified incidence and severity of AEs of high relevance to Sonidegib treatment. A slightly higher percentage of oncologists focused on incidence of AEs,

rather than their severity. Overall, a total of 23% to 31% of the respondents identified alternative dosing of high relevance and importance for choosing Sonidegib to treat laBCC patients.
Conclusions: This survey shows that overall response and the DoR are the most expected results from sonidegib and vismodegib across dermatologists and oncologists. The different pharmacokinetic profile of the two HhIs are behind their diverse toxicity spectrum, dose and schedule modification seem to address the choice between vismodegib and sonidegib among dermato-oncology prescribers.

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ADJUVANT IMMUNOTHERAPY IN MUCOSAL MELANOMA: AN OBSERVATIONAL RETROSPECTIVE STUDY FROM THE ITALIAN MELANOMA INTERGROUP

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Background: Anti PD-1 immunotherapy is considered a standard of care for patients with stage III melanoma. However, few data are available regarding subjects with mucosal melanoma (MM) who were originally excluded from registrational studies.
Methods: This retrospective multicenter study analyzed data from 23 patients referred to IMI (Italian Melanoma Intergroup) with stage III mucosal melanoma and undergoing adjuvant immunotherapy from January 2019 to December 2021. Two patients were on treatment at the time analysis and thus were excluded from the analyses.
Results: We observed a prevalence of female gender with a F:M ratio 3:1. The mean age was 57 years (38-82 yrs). The sites involved were vulva (8), anal canal (6), glans (3), nasal mucosa (3), and 1 patient with conjunctival localization. According to the AJCC 8th edition 6 patients have a stage IIIA, 1 IIIB, 12 IIIC and 2 IIID. Twelve months adjuvant treatment was completed in 11 patients, while in 10 patients was interrupted early after a median time of 5 months (range 2-11 mo). The main cause of discontinuation was disease progression, while only two patients discontinued due to toxicity Overall, 3 patients had skin toxicity, 2 gastrointestinal toxicity and 1 patient endocrine toxicity. Among patients who concluded the 12-mo adjuvant treatment, we observed a median PFS from the end of treatment of 5 months (range 2-11). Overall, 12 patients had a recurrence: 4 locally, 7 distant metastasis and 1 patient had a synchronous local and distant recurrence. Interestingly, of the 4 patients who continued anti PD-1 treatment after progression, none achieved a clinical response. 1 patient continues treatment with Ipilimumab, for two patients target therapy was used (Imatinib for a patient with c-Kit and Dabrafenib and Trametinib for a patient with BRAF mutation) achieving partial response. The other patients were switched to best supportive care.
Conclusions: MM has a very poor prognosis and significantly worse outcomes than cutaneous melanoma (CM). In fact, immunotherapy is less effective in MM than in CM, even for stage III disease in adjuvant setting. The high rates of progression suggest that MM deserves an early molecular characterization. Moreover, patients should be closely monitored to identify recurrences that could benefit from local-regional treatments.

THE IMPORTANCE OF CAREGIVING IN PATIENTS WITH ADVANCED BASAL CELL CARCINOMA IN TREATMENT WITH HEDGEHOG-PATHWAY INHIBITORS: AN OBSERVATIONAL PROSPECTIVE STUDY

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Background: Oral target therapy with hedgehog-pathway inhibitors **(**HPIs) has revolutionized the standard of care for patients with advanced basal cell carcinoma.[1,2] Two HPIs are currently available: vismodegib (Erivedge®; Genentech) and sonidegib (Odomzo®, Sun Pharmaceutical Industries); both HPIs share a number of class-related adverse events (AEs).[3] Most advanced basal cell carcinoma (BCC) patients are frail and elderly patients with various comorbidities and on pharmacological polytherapy.[4,5] This scenario requires the clinician to manage the AEs that can have a significant impact on therapeutic adherence.[6]
Methods: All patients included in this observational prospective study have histologically confirmed metastatic or locally advanced BCC and were treated with HPIs from January 2016 to December 2021 at the Department of Dermatology at the University of Florence, Italy. The collected patient data included age, sex, BCC site and extension, marital status (single, divorced, married/live-in, widow/widower), and information such as living with someone, and the presence of any caregivers. Other information regarding number of cycles, dose, duration and tolerability of the therapy were collected during a monthly follow-up visit during which any AE were recorded.
Results: The most important data that emerged from our study was that BCC patients treated with HPIs, patients who were married or

lived with a care-giver could better tolerate the therapy relative to single patients who live alone. Indeed, married/live-in patients and/or those with an adequate caregiver experienced greater therapeutic adherence and tolerated AEs better. (Figure 1)

Conclusions: Information regarding civil status, co-habitation, and the presence of a partner during follow-up visits are basic in predicting therapeutic adherence and managing the timing of control visits. Furthermore, given the greater therapeutic adherence of married/live-in patients whose caregiver is the partner, it is essential to consider patient's marital status. It is advisable to involve the caregiver upon enrollment. There should be a training discussion on the various possible adverse events and the best way to mitigate them. Success in therapy is linked not only to an informed patient but also to a trained caregiver. Patients who live alone should have closer and more frequent checks and psychological support to avoid interruption of therapy.

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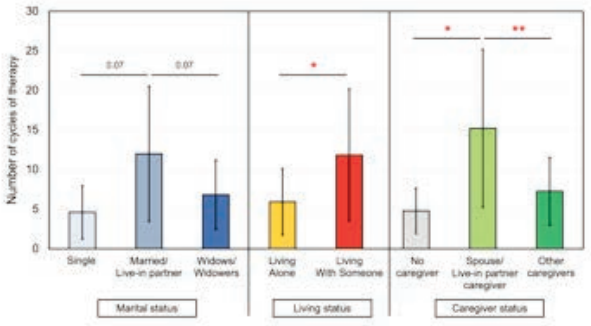

Figure 1. Number of cycles of therapy with HPI before discontinuation according to marital, living and caregiver status.