
XXIX
CONGRESSO NAZIONALE
IMI
NAPOLI
29-30 SETTEMBRE, 1 OTTOBRE
2023
HOTEL ROYAL CONTINENTAL
Via Partenope, 38
intergruppo melanoma italiano
imi

XXIX

PRESIDENTE IMI

Mario Mandalà

PRESIDENTE DEL CONGRESSO

Corrado Caracò

ADOI
ASSOCIAZIONE DERMATOLOGI-VENEREOLOGI OSPEDALIERI ITALIANI e della SANITÀ PUBBLICA

AIDNID

AIFET

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

a.i.ma.me. Associazione Italiana Malati di Melanoma e tumori della pelle

AIOM ASSOCIAZIONE ITALIANA ONCOLOGIA MEDICA

Associazione Italiana Radioterapia e Oncologia clinica

Melanoma Associazione Italia AIMaM

CAROLINA ZANI MELANOMA FOUNDATION

EMME ROSSE
IN RICORDO DI MARIA VANLIN

fondazionemelanoma ONLUS

Insieme con il sole dentro
MELANOMA COMBATTO MELANOMA

FONDAZIONE NIBIT ONLUS
Network Italiano per la Bioterapia dei Tumori

CENTROSTUDI Gised

MELANOMA DAY

MiO MELANOMA ITALIA ONLUS

SIAPEC - IAP

SICPRE

SIDCO
Società Italiana di Dermatologia Chirurgica, Oncologica, Correttiva ed Estetica

SIDeMaST
Società Italiana di Dermatologia medica, chirurgica, estetica e di Malattie Sessualmente Trasmesse

SIF
SOCIETÀ ITALIANA DI FARMACOLOGIA

SIICA
Società Italiana di Immunologia Immunologia Clinica e Allergologia

RSM Società Italiana di Radiologia Medica e Interventistica

SICO SOCIETÀ ITALIANA DI CHIRURGIA ONCOLOGICA
ESSO AFFILIATED

LETTERA DEI PRESIDENTI

Care colleghe, cari colleghi

Siamo molto lieti di annunciare la XXIX edizione del Congresso annuale della nostra società scientifica, che si terrà a Napoli dal 29 settembre all'1 ottobre 2023.

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 alle 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.
Quest'anno abbiamo introdotto tre novità importanti per noi: 1) apriremo il congresso con una sessione dedicata alla comunicazione della diagnosi e della prognosi e all'incontro con le associazioni dei pazienti. La centralità del paziente nel nostro operato viene pertanto ad aprire le sessioni scientifiche e ne diventa idealmente il presupposto etico, relazionale e umano del nostro quotidiano; 2) tre sessioni di controversia, in cui esperti della materia si confronteranno sui dati scientifici e sulle ricadute terapeutiche di scenari clinici considerati aree grigie e di dibattito; 3) il tema della intelligenza artificiale in ambito clinico e patologico sarà ospitato nella sessione dedicata all'area dermatologica e patologica.

Il congresso IMI di Napoli ospiterà anche due speaker stranieri, la professoressa Susana Puig e il professore Piotr Rutkowski, nella sessione IMI incontra l'Europa, nell'ottica di una collaborazione scientifica e di una rete collaborativa essenziale per una medicina moderna.

Le Tavole Rotonde multidisciplinari rappresentano un classico riferimento per l'aggiornamento dei colleghi che operano all'interno del 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 interattive relatore-discenti, con discussione di casi clinici per contestualizzare nell'attività quotidiana le possibili difficoltà decisionali del percorso diagnostico-terapeutico. Si analizzeranno anche i modelli organizzativi e gestionali focalizzando l'importanza cruciale della 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 (AIOM, ADOI, SIAPEC, SICPRE, SIDEMAST) al fine di discutere l'elaborazione di documenti di consensus, per monitorare e ottimizzare le varie attività relative alla qualità dell'assistenza e all'adesione alle linee guida, in base alle recenti innovazioni clinico, diagnostiche e terapeutiche.

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, Emme Rouge, Insieme con il sole dentro e Melanoma Italia Onlus.

Il lavoro, il confronto, la collaborazione e l'amicizia saranno i veri protagonisti del Congresso di Napoli, sede che offrirà un soggiorno ricco di aggiornamenti professionali e di momenti di piacevole fruizione della sua impareggiabile cornice di arte e cultura.

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

Mario Mandalà
Presidente IMI

Corrado Caracò
Presidente del Congresso

EPIDEMIOLOGY, GENETICS AND PATHOGENESIS

HIGH BRAFV600 VARIANT ALLELE FREQUENCY NEGATIVELY INFLUENCES SURVIVAL OF PATIENTS WITH METASTATIC MELANOMA TREATED WITH BRAF/MEK INHIBITORS

Sabino Strippoli[1], Benedetta Apollonio[1], Teresa Squicciarini[1], Paola Ghiorzo[2], Mario Mandalà[3], Pietro Quaglino[4], Vanna Chiaron Sileni[5], Roberta de Penni[6], Iole Natalicchio[7], Michele Del Vecchio[8], Alice Indini[9,10], Virginia Ferraresi[11], Teresa Troiani[12], Paola Queirolo[13], Cristina Pellegrini[14], Melissa Bersanelli[14], Maro Tucci[16], Raffaele Conca[17], Alessandro Minisini[18], Stefania Tommasi[19], Michele Guida[1], Simona De Summa[19], on behalf of the Italian Melanoma Intergroup (IMI)

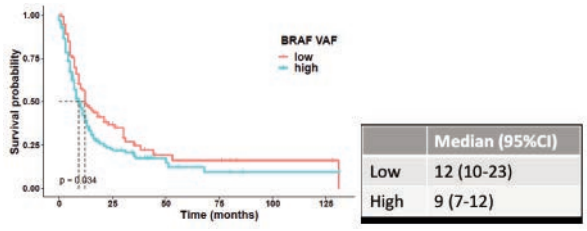
[1]Rare Tumors and Melanoma Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari; [2]Genetics of Rare Cancers, Department of Internal Medicine and Medical Specialties, University of Genoa, Genoa; [3]University of Perugia, Perugia; [4]Department of Dermatology, University of Turin, Turin; [5]Melanoma Unit, Oncology 2 Unit, Veneto Institute of Oncology IOV-IRCCS, Padua; [6]Department of Oncology & Hematology, University of Modena and Reggio Emilia Modena, Emilia-Romagna; [7]Section of Clinic Pathology, Ospedali Riuniti, Foggia; [8]Unit of Melanoma Medical Oncology, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [9]Unit of Melanoma Medical Oncology, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [10]Division of Medical Oncology, Department of Medicine and Surgery, Ospedale di Circolo e Fondazione Macchi, ASST dei Sette Laghi, Varese; [11]Sarcomas and Rare Tumors Unit, IRCCS, Regina Elena National Cancer Institute, Rome; [12]University of Campania Luigi Vanvitelli, Naples; [13]Division of Melanoma Sarcoma and Rare Tumors, IRCCS European Institute of Oncology, Milan; [14]University of L'Aquila, Department of Biotechnological and Applied Clinical Sciences, L'Aquila; [15]Medical Oncology Unit, University Hospital of Parma, Parma; [16]Medical Oncology Unit, Azienda Ospedaliero-Universitaria Policlinico di Bari, Bari; [17]Division of Medical Oncology, IRCCS-CROB, Rionero, Vulture; [18]Department of Oncology, Azienda Sanitaria Universitaria del Friuli Centrale, Udine; [19]Molecular Diagnostics and Pharmacogenetics Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy

Background: BRAF/MEK inhibitors have dramatically increased the response rate in metastatic melanoma (MM) patients harboring BRAF mutation. However, several factors contribute to the great variability in patient outcomes. Among them, BRAF variant allele frequency (VAF), which measures the frequency at which a specific variant is detected in a specimen, has been postulated to influence the quality and duration of response to target therapy. However, currently available data have shown controversial results. Therefore, there is no clear evidence on the impact of allele frequency on the effectiveness of target therapy.

Methods: We retrospectively evaluated 273 MM patients treated with BRAF/MEK inhibitors as first line, enrolled in 20 IMI centers in Italy. BRAF mutation was assessed by Next Generation Sequencing (NGS) and patients had at least 30% tumor cellularity. VAF was correlated with melanoma features, patients' characteristics, and clinical outcomes to treatment, including quality and duration of response, progression-free survival (PFS), and overall survival (OS).

Results: A highly heterogeneous BRAF VAF was identified (2.9%-100%). Mean and median values were 42% and 42.01% respectively. BRAF VAF has been dichotomized using ROC analysis which identified 36.05% as best cut-off value to split responder/non responder patients. Cox regression analyses for OS highlighted high BRAF VAF (HR: 1.66, 95% CI: 0.99, 2.79), LDH>2xULN (HR: 2.54, 95% CI: 1.40, 4.61), and metastatic sites ≥3 (HR: 1.79, 95%CI: 1.03, 3.13) as independent negative prognostic factors. Regarding PFS, high BRAF VAF (HR: 1.5, 95%CI: 0.95, 2.37) and LDH>2xULN (HR:3.03, 95%CI: 1.71, 5.35) confirmed their role as negative prognostic factors together with the metastatic stage (HR: 1.89, 95% CI: 1.15, 3.11). Moreover, logrank test comparing PFS Kaplan-Meier curves (Figure 1) revealed that patients with high BRAF VAF experienced a poorer outcome (median: 9 months) compared to patients with lower VAF (median: 12 months).

Conclusions: Our results confirm the role of the BRAF VAF as negative prognostic and predictive biomarker in MM treated with BRAF/MEK inhibitors.



	Median (95%CI)
Low	12 (10-23)
High	9 (7-12)

Figure 1. Progression-free survival (PFS) of melanoma patients treated with first-line BRAF/MEK inhibitors, and stratified according to BRAF variant allele frequency (VAF). The table shows the median survival for low and high BRAF VAF patients.

OVERALL SURVIVAL OF CHILDREN AND ADOLESCENTS WITH CUTANEOUS MELANOMA: IS THERE AN ASSOCIATION WITH THE MELANOCORTIN-1 RECEPTOR GENE?

Sara Raimondi[1], Silvano Vignati[1], Cristina Pellegrini[2], Paola Ghiorzo[3], Monica Rodolfo[4], Andrea Ferrari[4], Maria Concetta Fargnoli[2], Lorenza Pastorino[3], Marianne Berwick[5], Veronica Hoiom[6], Eduardo Nagore[7], Chiara Menin[8], Susana Puig[9], Emanuela Passoni[10], Ausilia Maria Manganoni[11], Lidija Kandolf Sekulovic[12], Sonia Brugnara[13], Gabriella Guida[14], Giuseppe Palmieri[15], Alexandre Stratigos[16], Federica Baldini[1], Giulio Tosti[1], Pietro Quaglino[17], Mariaelena Capone[18], Ricardo Fernandez de Misa[19], Fezal Ozdemir[20], Gloria Ribas[21], Antonella Romanini[22], Emilia Migliano[23], Ignazio Stanganelli[24], Maria Teresa Landi[25], Peter Kanetsky[26], Maria Antonietta Pizzichetta[27], Aurora Gaeta[1], Paola Queirolo[1], Daniela Massi[28], Saverio Caini[29], Sara Gandini[1] on behalf of the IMI Study Group, the GEM Study Group and the M-SKIP Study Group

[1]IEO, European Institute of Oncology IRCCS, Milan, Italy; [2]University of L'Aquila, Italy; [3]University of Genoa and Ospedale Policlinico San Martino, Genoa, Italy; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]University of New Mexico, Albuquerque, NM, USA; [6]Karolinska Institutet, Stockholm, Sweden; [7]Instituto Valenciano de Oncologia, Valencia, Spain; [8]Veneto Institute of Oncology, IOV-IRCCS, Padua, Italy; [9]Hospital Clinic Barcelona, Spain; [10]Fondazione IRCCS Ca' Granda, Ospedale Maggiore

Policlinico, Milan, Italy; [11]University of Brescia, Italy; [12]Military Medical Academy, Belgrade, Serbia; [13]S. Chiara Hospital, Trento, Italy; [14]Università degli Studi di Bari "Aldo Moro", Bari, Italy; [15]Istituto di Ricerca Genetica e Biomedica (IRGB), CNR, Sassari, Italy; [16]Andreas Sygros Hospital, Athens, Greece; [17]University of Torino, Italy; [18]Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale, Naples, Italy; [19]Hospital Universitario Nuestra Senora de Candelaria, Santa Cruz de Tenerife, Spain; [20]University of Ege (Aegean), Bornova Izmir, Turkey; [20]Fundación Investigación Clínico de Valencia Instituto de Investigación Sanitaria- INCLIVA, Valencia, Spain; [22]Azienda Ospedaliero-Universitaria Santa Chiara, Pisa, Italy; [23]San Gallicano Dermatological Institute, IRCCS, Rome, Italy; [24]IRCCS-IRST Scientific Institute of Romagna for the Study and Treatment of Cancer, Meldola, Italy; [25]National Cancer Institute, NIH, Bethesda, MD, USA; [26]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [27]CRO Aviano National Cancer Institute, Aviano, Italy; [28]University of Florence, Florence, Italy; [29]Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy

Background: The melanocortin-1 receptor (MC1R) gene is known to be associated with cutaneous melanoma (CM) development and prognosis in adult patients. To our knowledge, no study has investigated the relationship between MC1R alterations and CM prognosis in children and adolescents.

Methods: A retrospective cohort of children and adolescents (<21-year-old) with histologically confirmed CM and available genetic information on MC1R gene was assembled through an international collaboration between the MC1R, Skin Cancer and Phenotypic Characteristics consortium and the Italian Melanoma Intergroup. The present study included 207 subjects with collected information on Overall Survival (OS). Univariate association analyses were carried out with Log-Rank test, while multivariable Cox regression models including known melanoma prognostic factors and general patients characteristics were used to determine the corresponding Hazard Ratios (HR) with 95% Confidence Intervals (CI).

Table 1. Univariate and multivariable analyses for the association between MC1R variants and clinical factors with overall survival.

Variable	Univariate Hazard Ratio (95%CI)	Multivariable Hazard Ratio (95%CI) Model 1*	Multivariable Hazard Ratio (95%CI) Model 2∞
Any MC1R variant	0.40 (0.14-1.21)	-	0.20 (0.04-0.97)
Female gender	0.40 (0.13-1.24)	-	-
Breslow thickness (by unit increase)	1.46 (1.24-1.71)	1.32 (1.11-1.58)	1.12 (0.89-1.40)
Ulceration	10.04 (3.16-31.91)	6.28 (1.80-21.89)	22.88 (2.07-252.73)
Sunburns (yes *vs.* no)	3.63 (0.84-13.46)	-	-
Mitotic rate			
1-6	8.99 (1.07-74.40)	-^	4.62 (0.43-49.62)
6+	23.96 (1.99-287.89)	-^	3.88 (0.22-69.02)

*Only significant variables with less than 30% of missing data are included. Missing data indicator is included in the model: N=196. ^More than 30% of missing data. ∞°All variables included in the model with no missing imputation: N=116

Results: Overall, sixteen patients out of 207 (8%) died. Individuals who carried any MC1R variant had a borderline lower risk of death compared to those without variants (p=0.10, Figure 1a). Known melanoma prognostic factors, including Breslow thickness and ulceration, were independently associated with a higher risk of death in childhood and adolescent CM patients (Figures 1b,c and Table 1). A higher mitotic rate (mitoses/mm^2) was associated with a higher risk of death in univariate, but not in multivariable analyses (Figure 1d and Table 1). Interestingly, in the subgroup analysis of patients with available information on these three main prognostic factors, the presence of any MC1R along with ulceration were the only significant factors associated with OS, with HR (95%CI): 0.20 (0.04-0.97) and 22.88 (2.07-252.73), respectively.

Conclusions: Children and adolescents with MC1R variants had a lower risk of death compared to those without MC1R variants. Further data on other genetic alterations and prognostic factors will help to better clarify the role of genetic alterations in prognosis for CM children and adolescents.

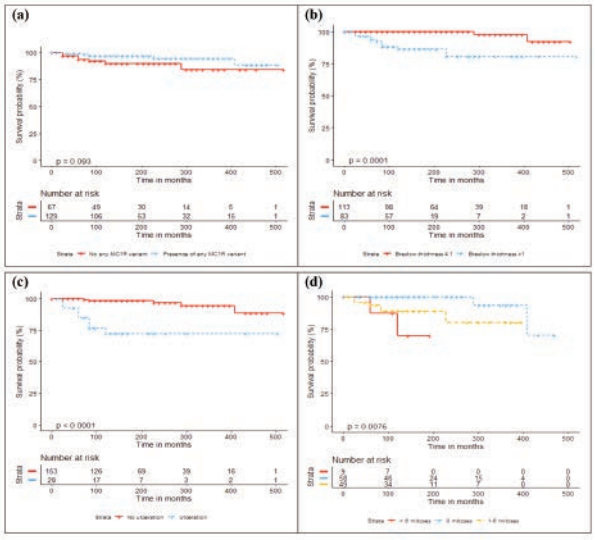


Figure 1. Kaplan Meier curves and Log-Rank test p-value for Overall Survival according to (a) the presence of any *MC1R* variant; (b) Breslow thickness; (c) ulceration; (d) mitotic rate.

EVALUATION OF A TRAINING COURSE FOR GENERAL PRACTITIONERS WITHIN THE MELANOMA MULTIMEDIA EDUCATION PROJECT OF THE ITALIAN MELANOMA INTERGROUP

Federica Zamagni[1], Serena Magi[2], Lauro Bucchi[1], Fabio Falcini[1], Silvia Mancini[1], Rosa Vattiato[1], Stefano Falcinelli[3], Claudio Feliciani[4], Maurizio Lombardo[5], Davide Melandri[6], Patrizia Re[3], Francesco Ricci[7], Rosanna Rita Satta[8], Ignazio Stanganelli[2,4]

[1]Emilia-Romagna Cancer Registry, Romagna Cancer Institute, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Forlì; [2]Skin Cancer Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Forlì; [3]General Practitioner, district of Ravenna, AUSL Romagna, Ravenna; [4]Division of Dermatology, Department of Medicine and Surgery, University of Parma, Parma; [5]Division of Dermatology, Department of Medicine and Surgery, Ospedale di Circolo e Fondazione Macchi, ASST dei Sette Laghi, Varese; [6]Division of Dermatology Cesena/Forli' AUSL Romagna and Department of Medicine and Surgery, University of Bologna; [7]Melanoma Unit, IDI-IRCCS - FLMM, Dermatological Research Hospital, Rome; [8]Department of Medical, Surgical, and Experimental Sciences, University of Sassari, Sassari, Italy

Background: As a part of the National Oncological Plan 2023-2027

on the importance of multidisciplinary and interactive E-learning training, the Italian Melanoma Intergroup (IMI) has developed MelaMEd (Melanoma Multimedia Education), a national project for general practitioners (GPs) on the prevention and detection of cutaneous melanoma through a WEB platform and an online course. MelaMEd enables participants to (1) recognize skin lesions that require specialist dermatological assessment, (2) select patients at high risk of melanoma and (3) be informed of the diagnosis and treatment pathway of patients with melanoma.

Methods: The project is ongoing. A free online platform and online course were developed and launched in June 2022. Before starting the course, enrolled participants fill out a pre-test questionnaire concerning the basic knowledge of the disease and the recognition and management of suspicious lesions. After the course, participants will fill out the same questionnaire again. The online course will end in December 2023. We present an interim analysis of results (January 2023-July 2023). The data have been analyzed descriptively.

Table 1. Characteristic of respondents, numbers and percentages by centre.

	Centre					
	Varese	Parma	Romagna	IDI Roma	Sassari	Total
Enrolled	50	111	1042	33	84	1320
Respondents						
Age group						
<40	23 (58%)	38 (55%)	41 (34%)	6 (60%)	34 (55%)	142 (47%)
40-60	17 (43%)	29 (42%)	45 (37%)	4 (40%)	27 (44%)	122 (40%)
>60	0 (0%)	2 (3%)	35 (29%)	0 (0%)	1 (2%)	38 (13%)
Profession						
GP	13 (33%)	25 (36%)	83 (69%)	2 (20%)	18 (29%)	141 (47%)
Resident GP	27 (68%)	44 (64%)	24 (20%)	8 (80%)	43 (69%)	146 (48%)
Pediatrician	0 (0%)	0 (0%)	14 (12%)	0 (0%)	1 (2%)	15 (5%)

GP, General Practitioner. Percentages might not total 100% due to rounding.

GP, General Practitioner. Percentages might not total 100% due to rounding.

Table 2. Number and percentage of correct answers to theoretical multiple-choice questions and multiple-choice diagnosis for skin tumor images.

Questions	Total N(%)
Theoretical multiple choice questions	
Q1: Identify a risk factor for melanoma	300 (99%)
Q2: choose what is needed for a complete visual examination of the skin	279 (92%)
Q3: explain the acronym ABCDE	291 (96%)
Q4: explain the EFG rule	206 (68%)
Q5: explain what is meant by the "ugly duckling" sign	274 (91%)
Q6: choose a true statement about dermoscopy	190 (63%)
Q7: choose a true statement about Breslow thickness	88 (29%)
Multiple choice diagnosis for skin neoformations images. Percentage of correct answers with respect to the type of lesion	
I1: Thin melanoma	123 (41%)
I2: Congenital nevus	98 (32%)
I3: Seborrheic keratosis	235 (78%)
I4: Nodular melanoma	214 (71%)
I5: Thick melanoma	154 (51%)
I6: Melanocytic nevus	252 (83%)
I7: Congenital nevus	235 (78%)
I8: Melanoma with regression	174 (58%)
I9: Malignant lentigo	108 (36%)
I10: Basal cell carcinoma	262 (87%)

Results: So far, five IMI centers have participated in the project for a total of 1320 participants. Of these, 302 compiled the pre-test questionnaire. Table 1 shows the characteristics of total respondents. Forty-seven percent of them were aged <40 years. Respondents were almost equally divided between GPs (47%) and resident GPs (48%). Table 2 shows the results of the pre-test questionnaire. Among the theoretical questions, the "ABCDE" and "ugly duckling" rules are well known (96% and 91% of correct answers, respectively), but a lower percentage (68%) of respondents knows the "EFG" rule for the recognition of nodular melanomas and the Breslow thickness statement (29%). Among the images, lentigo maligna was recognized correctly by as few as 36% respondents. This lesion poses a differential diagnosis with solar lentigo (diagnosed, incorrectly, by 57%).

Conclusions: Pre-evaluation questionnaire showed a lack of knowledge of the two major points of melanoma diagnosis (EFG) and management (Breslow thickness). We will compare the proportions of correct answers to the questionnaires before and after the course once available.

CUTANEOUS MELANOMA IN OLDER AND ELDERLY PATIENTS

Alessandra Buja[1], Antonella Vecchiato[2], Paolo Del Fiore[2], Saveria Tropea[2], Marco Rastrelli[2,3], Massimo Rugge[4,5], Chiara Trevisiol[2], Manule Zorzi[4], Carlo R. Rossi[3], Luigi Dall'Olmo[2,3], Simone Mocellin[2,3]

[1]Department of Cardiac, Thoracic, Vascular Sciences, and Public Health, University of Padua, Padua; [2]Soft-Tissue, Peritoneum and Melanoma Surgical Oncology Unit, IOV, IRCCS, Padua; [3]Department of Surgery, Oncology and Gastroenterology (DISCOG), University of Padua, Padua; [4]Veneto Tumor Registry, Azienda Zero, Padua; [5]Department of Medicine, DIMED, Pathology and Cytopathology Unit, University of Padua, Padua, Italy

Background: In industrialised countries, the ageing population is steadily increasing. The incidence of cutaneous malignant melanoma (CMM) is higher in the elderly. This study aims to evaluate the clinic-pathological profile of CMM and diagnostic-therapeutic performance indicators in the elderly.

Methods: This retrospective population cohort study included 1,368 incident CMMs registered in 2017 by the Veneto Regional Cancer Registry (north-eastern Italy). The very elderly were categorised as great elderly (≥80 years), elderly (65-79 years) and adult (<65 years). The strength of the association between pairs of variables was tested using the Cramér-V method. Using the age groups as dependent variable, an ordered logistic regression was applied using the variables of the clinical-pathological profile of CMM as covariate. In each of the three age groups, clinical performance indicators were calculated using the Clopper-Pearson exact method.

Results: Compared to patients younger than 80 years of age (1. 187), CMM in the very elderly study population (181; 13.2%) had a different topography of CMM, a higher prevalence of ulceration (43.3% *vs*. 12.7%; p<0.001), a higher Breslow index (p<0.001), a lower prevalence of tumour-infiltrating lymphocytes (64.4% *vs*. 76.5%, p<0.01) and a more advanced stage of pTNM at clinical presentation (p<0.001). Elderly patients underwent sentinel lymph node biopsy (SLNB) and lymphadenectomy less frequently following SLNB-positive (60.0% *vs*. 94.2% and 44.4% *vs*. 85.5%, respectively; p<0.001).

Conclusions: In grgreat elderly patients with CMM, the clinicopathological features present a specific profile. The present results provide critical information to optimise secondary prevention strategies and to refine diagnostic-therapeutic procedures adapted to large elderly patients.

References

1. United Nations, Department of Economic and Social Affairs, Population Division. World population ageing, 2019: high-

lights (ST/ESA/SER.A/430). New York: UN; 2019. Available from: https://digitallibrary.un.org/record/3846855. Accessed April 14, 2023.
2. Whiteman DC, Green AC, Olsen CM. The Growing Burden of Invasive Melanoma: Projections of Incidence Rates and Numbers of New Cases in Six Susceptible Populations through 2031. J Invest Dermatol. 2016 Jun;136(6):1161–71.
3. Van Herck Y, Feyaerts A, Alibhai S, Papamichael D, Decoster L, Lambrechts Y, et al. Is cancer biology different in older patients? Lancet Healthy Longev. 2021 Oct;2(10):e663–77.
4. Ribero S, Stucci LS, Marra E, Marconcini R, Spagnolo F, Orgiano L, et al. Effect of Age on Melanoma Risk, Prognosis and Treatment Response. Acta Derm Venereol. 2018 Jul 11;98(7):624–9.
5. Tas F, Erturk K. Patient age and cutaneous malignant melanoma: Elderly patients are likely to have more aggressive histological features and poorer survival. Mol Clin Oncol. 2017 Dec;7(6):1083–8.
6. Rees MJ, Liao H, Spillane J, Speakman D, McCormack C, Donahoe S, et al. Melanoma in the very elderly, management in patients 85years of age and over. J Geriatr Oncol. 2018 Sep;9(5):488–93.
7. Rees MJ, Liao H, Spillane J, Speakman D, McCormack C, Donahoe S, et al. Localized melanoma in older patients, the impact of increasing age and comorbid medical conditions. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2016 Sep;42(9):1359–66.
8. Ciocan D, Barbe C, Aubin F, Granel-Brocard F, Lipsker D, Velten M, et al. Distinctive features of melanoma and its management in elderly patients: a population-based study in France. JAMA Dermatol. 2013 Oct;149(10):1150–7.
9. Bateni SB, Johns AJ, Gingrich AA, Gholami S, Bold RJ, Canter RJ, et al. Elderly Age Is Associated With More Conservative Treatment of Invasive Melanoma. Anticancer Res. 2020 May;40(5):2895–903.
10. Schuurman MS, Hollestein LM, Bastiaannet E, Posthuma EFM, van Akkooi AJC, Kukutsch NA, et al. Melanoma in older patients: declining gap in survival between younger and older patients with melanoma. Acta Oncol Stockh Swed. 2020 Jan;59(1):4–12.
11. Cavanaugh-Hussey MW, Mu EW, Kang S, Balch CM, Wang T. Older Age is Associated with a Higher Incidence of Melanoma Death but a Lower Incidence of Sentinel Lymph Node Metastasis in the SEER Databases (2003-2011). Ann Surg Oncol. 2015 Jul;22(7):2120–6.
12. Foster AD, Sivarapatna A, Gress RE. The aging immune system and its relationship with cancer. Aging Health. 2011 Oct 1;7(5):707–18.
13. Jones D, Di Martino E, Bradley SH, Essang B, Hemphill S, Wright JM, et al. Factors influencing symptom appraisal and help-seeking of older adults with possible cancer: a mixed-methods systematic review. Br J Gen Pract J R Coll Gen Pract. 2022 Jun 16;72(723):e702-712.
14. Lange JR, Kang S, Balch CM. Melanoma in the older patient: measuring frailty as an index of survival. Ann Surg Oncol. 2011 Dec;18(13):3531–2.
15. Harris E. Meta-analysis: Social Isolation, Loneliness Tied to Higher Mortality. JAMA. 2023 Jun 28;
16. van Bussel MJP, Odekerken-Schröder GJ, Ou C, Swart RR, Jacobs MJG. Analyzing the determinants to accept a virtual assistant and use cases among cancer patients: a mixed methods study. BMC Health Serv Res. 2022 Jul 9;22(1):890.
17. Chuchu N, Dinnes J, Takwoingi Y, Matin RN, Bayliss SE, Davenport C, et al. Teledermatology for diagnosing skin cancer in adults. Cochrane Database Syst Rev. 2018 Dec 4;12(12):CD013193.
18. Imamura T, Nakamura Y, Tanaka R, Teramoto Y, Asami Y, Maruyama H, et al. Cutaneous surgery under local anesthesia in very elderly patients 90 years of age and older is as safe as in elderly patients ranging in age from 75 to 80 years old. Int J Dermatol. 2017 Jun;56(6):681–5.
19. Paredes AZ, Aquina CT, Selby LV, DiFilippo S, Pawlik TM. Increasing Importance of Ethics in Surgical Decision Making. Adv Surg. 2020 Sep;54:251–63.
20. Johnston ME 2nd, Sussman JJ, Patel SH. Surgical Oncology and Geriatric Patients. Clin Geriatr Med. 2019 Feb;35(1):53–63.
21. Rojas KD, Perez ME, Marchetti MA, Nichols AJ, Penedo FJ, Jaimes N. Skin cancer: Primary, secondary, and tertiary prevention. Part II. J Am Acad Dermatol. 2022 Aug;87(2):271–88.

ASSOCIATION OF MIR-146A-5P AND MIR-21-5P WITH PROGNOSTIC FEATURES IN MELANOMA SUBTYPES

Federico Venturi[1-3], Maria Naddeo[1], Martina Lambertini[1-3], Elisabetta Broseghini[1], Milena Pariali[4], Elena Campione[5], Manuela Ferracin[1], Emi Dika[1-3]

[1]Melanoma centre, Dermatology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna; [2]Dermatology, Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna, Bologna; [3]Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna, Bologna; [4]Center for applied Biomedical Research, S. Orsola-Malpighi University Hospital, Bologna; [5]Dermatologic Unit, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Background: In cutaneous melanoma, Breslow thickness (BT) is the main parameter used to define the tumor stage, but also other tumor characteristics are relevant in prognostications. Indeed, specific features have been associated with a worse cutaneous melanoma prognosis, including defined histological parameters (greater BT, presence of ulceration or higher mitotic index), and the tumor histotype. Discrepancies in definition or other obstacles/difficulties in correctly assessing these parameters could lead to tumor misclassification. MicroRNAs (miRNAs) play a role in melanoma carcinogenesis. Given that their expression can be easily measured in archive samples, they could be valid prognostic biomarkers, since from the early stages of disease diagnosis, also paying attention to the different tumor subtypes and localization.
Methods: We quantified the expression of miR-146a-5p and miR-21-5p in 170 FFPE samples of melanoma patients with different BT and prognostic histologic features, including subtype, presence/absence of ulceration and regression, mitotic index and tumor localization, to verify its association with melanoma characteristics that are associated with patients' prognosis.
Results: MiR-146a-5p and miR-21-5p expression was significantly higher in all tumors with higher mitotic rate (≥1/mm^2). Considering the ulceration status, we assessed that miR-146a-5p and miR-21-5p expression was significantly higher in ulcerated melanomas compared to those without ulceration. We did not observe any difference in miRNAs expression when we considered all subtypes and their regression status. We then stratified miRNAs combined expression in different melanoma subtypes and surprisingly the MiR-146a-5p and miR-21-5p expression was was lower in lentigo maligna melanoma (LMM) than in all the other histotypes.

Moreover, given the recognized association of miR-146a-5p and miR-21-5p with tumor thickness, we also stratified the patients according to both BT and tumor histotype and miR-146a-5p and miR-21-5p expression was lower even in LMM with BT ≥0.8 mm. **Conclusions:** miR-146a-5p and miR-21-5p expression has shown to be different in melanoma with different histological parameters and the findings of the study can provide further insights for the diagnosis and treatment of melanomas with specific adverse prognostic features.

IS MC1R-RISK SCORE A USEFUL TOOL TO EVALUATE THE IMPACT OF MC1R SNPS ON MELANOMA RISK?

Debora Tonello[1], Paola del Bianco[2], Stefania Pellegrini[1], Maria Chiara Scaini[1], Antonella Vecchiato[3], Chiara Menin[1]

[1]Immunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua; [2]Clinical Trials and Biostatistics, Veneto Institute of Oncology IOV-IRCCS, Padua; [3]Soft-Tissue, Peritoneum and Melanoma Surgical Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

Background: The melanocortin 1 receptor (MC1R) is a medium penetrance melanoma susceptibility gene affecting skin phenotype according to common SNPs. MC1R variants associated with red-hair phenotype (R alleles) confer a 2-fold risk of melanoma in the general population and a 3-fold risk in familial clusters. Many other common variants, not red-hair associated (r alleles), may modify melanoma risk although to a lesser extent than R alleles. However, the association between MC1R and melanoma risk was often evaluated without taking into account the specific weight of each SNP. Here, we determined an individual MC1R risk score (MC1R-rs) by combining the MC1R risk alleles weighted by the effect size estimate of the most powerful GWAS studies on melanoma.
Methods: MC1R-SNPs were analyzed in 335 single and 263 multiple melanoma cases and 83 controls. MC1R-rs was calculated using the β value for each R/r SNP selected from previous independent GWAS analyses (β is the per-allele melanoma log OR for each SNP alternative allele). The cases with a β-unknown variant were excluded.
Results: At least one MC1R variant was found in the 80% of cases and in the 43% of controls. Moreover, all R variants had a higher allele frequency in cases *vs.* controls, in multiple (MPM) *vs.* single and in familial *vs.* sporadic melanoma. Likewise, we observed a MC1R-rs mean higher in cases than controls (0.21 *vs.* 0.14) and in familial *vs.* sporadic melanomas (0.22 *vs.* 0.18). The MPM subgroup showed the biggest MC1R-rs (0.23).
Conclusions: This study suggests that it might be appropriate to use the MC1R-rs to evaluate the individual melanoma risk according own MC1R profile. However, further analyses should be done by increasing control cohort and including the rare MC1R variants. The goal is to determine a MC1R-rs cut off to identify individuals at high-risk for developing melanoma and multiple melanoma.

PREVENTION AND DIAGNOSIS

DERMOSCOPY AS A TOOL FOR IDENTIFYING POTENTIALLY METASTATIC THIN MELANOMA: A CLINICAL-DERMOSCOPIC AND HISTOPATHOLOGICAL STUDY

Flavia Silvestri[1], Laura Doni[2], Federico Venturi[1], Biancamaria Zuccaro[1], Federica Cosso[2], Vincenza Maio[3], Lorenzo Antonuzzo[2], Daniela Massi[4,5], Vincenzo De Giorgi[1]

[1]Section of Dermatology, Department of Health Sciences, University of Florence, Florence; [2]Medical Oncology, Careggi University Hospital, Florence; [3]Histopathology and Molecular Diagnostics, Careggi University Hospital, Florence; [4]Section of Pathology, Department of Health Sciences, University of Florence; [5]Histopathology and Molecular Diagnostics, Careggi University Hospital, Florence, Italy

Background: Although cutaneous thin melanomas are considered early-stage tumors, they cause a high death toll, due to their increasing incidence. The correlation between metastatic thin melanomas (MTMs) and clinical-dermoscopic and histopathological features may consent an earlier detection of potentially MTMs.
Methods: A retrospective cohort study using databases from two skin cancer referral centers in Italy was performed during a twenty-two years follow-up. A total of 16 patients histologically diagnosed with in situ and primary cutaneous melanoma (≤0.8 mm) who developed regional and/or distant metastases were included. Both clinical and dermoscopic images were analyzed by a group of dermatologists with expertise in dermoscopy and histopathological samples were reviewed by dermatopathologists specialized in the diagnosis of skin cancer.

Table 1. Clinical and dermoscopic data for 15 MTMs patients included in the study.

Patients		N=15
Clinical-dermoscopic features		
>3 colors		12 (80%)
Diameter >10 mm		11 (73.3%)
White patch		11 (73.3%)
Atypical vascular patterns		10 (66.5%)
Blue-gray areas		9 (60%)
Absence of pigment network		8 (53.3%)
Absence of dermoscopic features		4 (26.6%)
Blue-white veil		3 (20%)
Missing		1 (6.6%)

Results: 1.1% of thin melanomas experienced disease progression. The median age at diagnosis was 49 years (range 28-43 years). 56.2% were men and 43.7% were women. The most frequent anatomical site of the primary tumor was the trunk (43.7%). Clinically, all the lesions were pigmented with a diameter >10 mm (73.3%) and at least 3 colors (80%). Dermoscopically, the most frequent features were white patch (73.3%), atypical vascular patterns (66.5%), blue-gray areas (60%) and absence of a pigment network (53.3%) Table 1, Figure 1. Histopathologically, there were 2 pTx and 14 invasive melanomas. All invasive tumors were superficial spreading melanomas (SSM) subtypes. All cases presented at least one histopathological feature such as regression (87.5%), mitoses (66.6%), vertical growth phase (62.5%), and ulceration (12.5%).

Conclusions: Thin melanomas (≤0.8 mm) that present specific clinical-dermoscopic characteristics (diameter >10 mm, at least three colors, regression structures, atypical vascular pattern and absence of a pigment network) might be suggestive of a higher metastatic potential, particularly if coupled with conventional adverse histopathological features (regression, vertical growth phase and mitoses).

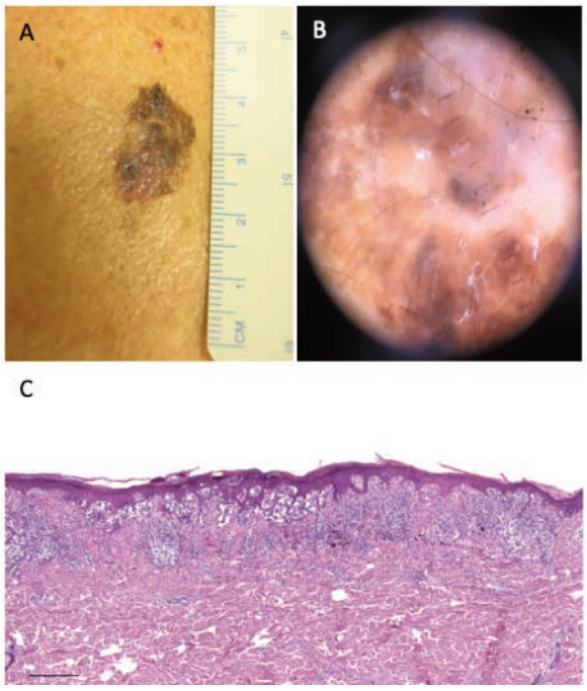


Figure 1. A) Clinical view of a pT1a melanoma: >10 mm diameter (Breslow 0.6 mm, no ulceration) on the trunk of a 62-year-old male patient. B) Dermoscopy of the lesion: absence of pigment network, >3 colors, atypical vascular pattern and peripheral blue-white veil. C) Thin superficial spreading melanoma/low-CSD melanoma associated with regression (partial replacement of the tumor with variably vascular fibrous tissue, accompanied by pigment-laden macrophages and chronic inflammation), original magnification 4x, scale bar 250 m, hematoxylin and eosin stain.

PATHOLOGICAL AND MOLECULAR CLASSIFICATION

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

Maria Cristina Sini[1], Antonella Manca[1], Sara Simi[2], Panagiotis Paliogiannis[3], Caterina Pinzani[4], Vincenzo Canzonieri[4], Stefano Astorino[5], Paola Pasquini[5], Maria Teresa Corradin[6], Sandro Sulfaro[6], Maurizio Lombardo[7], Michele Cerati[7], Giovanna Moretti[8], Marisa Falduto[8], Giovanni Battista Maestrale[1], Jerry Polesel[4], Antonio Cossu[3], Daniela Massi[2], Giuseppe Palmieri[1,9], Maria Antonietta Pizzichetta[4]

[1]Unit of Cancer Genetics, IRGB-CNR, Sassari; [2]Section of Pathology, Department of Health Sciences, University of Florence, Florence; [3]Pathology and Histology Unit, Department of Medicine, Surgery & Pharmacy, University of Sassari, Sassari; [4]CRO-IRCCS, Aviano; [5]Ospedale Celio, Roma; [6]Ospedale di Pordenone; [7]Ospedale di Varese; [8]Ospedale di Messina; [9]Immuno-Oncology & Targeted Cancer Biotherapies, Department of Biomedical Sciences, University of Sassari, Sassari, Italy

Background: More than half of patients with metastatic cutaneous melanoma (CM) is reported to have superficial spreading diffusion (SSM), while two fifths of them have a nodular melanoma (NM) at diagnosis. Furthermore, several reports indicate a high proportion of deaths attributable to melanomas less than 1 mm of thickness at diagnosis. Therefore, a subset of SSM is at a high risk of metastasis. We here investigated the mutational profile in two series of patients with primary SSM or NM who were further stratified for disease progression.

Methods: The NGS analysis was performed on 31 SSMs and 41 NMs retrieved from paraffin-embedded archives of the institutions participating into the study using a multiple-gene panel constructed by the Italian Melanoma Intergroup (IMI) including the main 25 genes involved in CM pathogenesis.

Results: An equal number of males and females categorized into three age groups (<50, 50-69, and >70 years) were analyzed. Nearly all (58/74; 92%) of patients analyzed had no familial history of melanoma and no additional skin lesions (71/74; 96%). For each group of primary SSM and NM, the mutational profile was compared with dermoscopic and histopathological parameters as well as with clinical outcome within 5 years after the diagnosis. In our series, BRAF mutations did not discriminate between the two histological subtypes, whereas NRAS mutations were significantly prevalent in NM (36.6% *vs*. 3.2% in SSM; p<0.01). Moreover, lack of mutated genes is associated with SSM subtype (32.3% *vs*. 7.3% in NM; p=0.02) and, conversely, presence of ≥2 mutated genes is significantly associated with NM (65.9% *vs*. 29.0 in SSM; p<0.01). Finally, absence of mutated genes was significantly associated with low mitotic (<2 mitosis/mm^2; p<0.01), low Clark level (≤2; p<0.01), and absent ulceration (p<0.01). No correlation between the gene mutation status and regression or TILs was found. Correlation analyses with the clinical outcome are ongoing.

Conclusions: The more aggressive phenotype was associated with the presence of mutations in BRAF ± other gene, strongly suggesting a tight relationship between the mutational status and more aggressive features.

MORPHOPHENOTYPIC CHARACTERIZATION OF MELANOMA BRAIN METASTASES IMMUNE MICROENVIRONMENT: A MULTICENTRE RETROSPECTIVE STUDY

Filippo Nozzoli[1], Marco Gessi[2], Filippo Ugolini[1], Luca Tinunin[1], Luigi Iannone[3], Alice Esposito[4], Giovanni Muscas[4], Alessandro Della Puppa[4], Isabella Ciardetti[5], Nicola Pimpinelli[5], Vincenzo De Giorgi[5], Isacco Desideri[6], Lorenzo Livi[6], Laura Doni[7], Giovanni Schinzari[8], Ernesto Rossi[8], Mario Mandalà[9], Daniela Massi[1]

[1]Section of Anatomic Pathology, Department of Health Sciences, University of Florence, Florence; Neuropathology Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica S. Cuore, Roma; [3]Section of Clinical Pharmacology and Oncology, Department of Health Sciences, University of Florence, Florence; [4]Neurosurgery Unit, Department of NEUROFARBA, University of Florence, Florence; [5]Dermatology Unit, Department of Health Sciences, University of Florence, Florence; [6]Radiation Oncology, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence; [7]Oncology Unit, Careggi University Hospital, Florence; [8]Medical Oncology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome; [9]University of Perugia, Perugia, Italy

Background: The role of immune cells (IC) in melanoma brain metastases (MBM) is only partially fulfilled. We aimed at offering a deep focus on the immune microenvironment of MBM including IC distribution and density, and prognostic impact.
Methods: 94 MBM patients were included in a multicentre, retrospective study. Immunohistochemistry for IC microenvironment was performed with the following antibodies: CD4, CD8, CD68, CD163, FoxP3, PD-L1. Score density of immune biomarkers was assessed through a semiquantitative method and as binary variable (high *vs*. low). PD-L1 was assessed in tumour cells as well as percentage and dichotomous variable (cut-off: 1%). Statistical analysis for independent variables were performed with the chi-square test, or the Fisher's exact test. The Kaplan-Meier method was applied to estimate median overall survival (OS), and differences were assessed using the log-rank test.
Results: 65 patients (69.1%) were male and the mean age at diagnosis was 57.5 years. The median follow-up was 12 months, 72 patients (76.6%) died, with a median OS of 20.8 months. 54 patients (57.4%) presented with single MBM at diagnosis. Intratumoral region showed a significantly higher expression of CD4+ (p=0.012) as well as CD163+ was predominant in the peritumoral (p=0.048). 30 patients (31.9%) had PD-L1 expression ≥1%. PD-L1 ≥1% prevailed in high-CD68+ (p=0.047) as well as CD4+ cells were significantly higher in PD-L1 <1% (p=0.030). BRAF mutation occurred in 52 patients (55.3%) and correlated with increased CD68+ macrophages (p=0.038). None of the immune biomarkers was independently associated with prognosis. High-CD68+ showed a favorable impact on OS in multiple MBM (p=0.017), whereas peritumoral high-CD4+ (p=0.041) correlated with prolonged OS in single MBM.
Conclusions: Our findings showed the immune reaction to MBM mainly characterized by a pro-inflammatory expansion of CD4+ regulatory versus $CD8^+$ cytotoxic T-cells. Although we were able to highlight clear topographical correlations of IC in a large retrospective cohort of MBM, our study is limited by heterogeneity in patients' treatment protocols, therefore the prognostic significance should be further explored.

TUMOR INFILTRATING LYMPHOCYTES RECOGNITION IN PRIMARY MELANOMA BY DEEP LEARNING CONVOLUTIONAL NEURAL NETWORK

Filippo Ugolini[1], Francesco De Logu[2], Luigi Francesco Iannone[2], Francesca Brutti[3], Sara Simi[1], Vincenza Maio[1], Vincenzo de Giorgi[4], Anna Maria di Giacomo[5], Clelia Miracco[5], Francesco Federico[6], Ketty Peris[7], Giuseppe Palmieri[8], Antonio Cossu[9], Mario Mandalà[10], Daniela Massi[1], Marco Laurino[3]

[1]Department of Health Sciences, Section of Pathological Anatomy, University of Florence; Florence; [2]Department of Health Sciences, Section of Clinical Pharmacology and Oncology, University of Florence, Florence; [3]Institute of Clinical Physiology, National Research Council, Pisa; [4]Department of Health Sciences, Section of Dermatology, University of Florence, Florence; [5]Medical Oncology and Immunotherapy, Center for Immuno-Oncology, University of Siena, Siena; [6]Institute of Pathology, Sacred Heart Catholic University, Rome; [7]Institute of Dermatology, Sacred Heart Catholic University, Rome; [8]Unit of Cancer Genetics, Institute of Genetic and Biomedical Research (IRGB), National Research Council (CNR), Sassari; [9]Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari; [10]Oncology Unit, Department of Medicine and Surgery, University of Perugia, Perugia, Italy

Background: The presence of tumor-infiltrating lymphocytes (TIL) has been associated with a favorable prognosis of primary melanoma (PM). The recent development of the artificial intelligence (AI) based approach in digital pathology has been proposed for the standardized assessment of TIL on hematoxylin and eosin (H&E)-stained images (whole slide images, WSI).
Methods: Here, we have applied a new convolution neural network (CNN) analysis of PM WSI to automatically assess the infiltration of TIL and extract a TIL score. A CNN was trained and validated in a retrospective cohort of 307 PMs including a training set (237 WSI, 57,758 patches) and an independent testing set (70 WSI, 29,533 patches). After the classification of tumor patches by the presence or absence of TILs, we identified an AI-based TIL density index (AI-TIL).
Results: The proposed CNN demonstrated high performance in recognizing TILs in PM WSI, showing specificity and sensitivity of 100% on the testing set. We demonstrated that the AI-based TIL index correlated with conventional TIL evaluation and clinical outcome. The AI-TIL index was an independent prognostic marker directly associated with a favorable prognosis.
Conclusions: A fully automated and standardized AI-TIL appears to be superior to conventional methods at differentiating PM clinical outcome. Further studies are required to develop an easy-to-use tool to assist pathologists to assess TILs in the clinical evaluation of solid tumors.

A MULTIPARAMETER LIQUID BIOPSY-BASED APPROACH ALLOWS LONGITUDINAL TRACKING OF CUTANEOUS MELANOMA DYNAMICS AND EARLY RESISTANCE TO TREATMENT

Maria Chiara Scaini[1], Cristina Catoni[1], Cristina Poggiana[1], Jacopo Pigozzo[2], Luisa Piccin[2], Kevin Leone[1], Ilaria Scarabello[1], Antonella Facchinetti[1,3], Chiara Menin[1], Lisa Elefanti[1], Stefania Pellegrini[1,3], Valentina Aleotti[1], Riccardo Vidotto[1], Francesca Schiavi[4], Alessio Fabozzi[5], Vanna Chiarion-Sileni[2], Antonio Rosato[1,3]

[1]Immunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua; [2]Melanoma Unit, Oncology 2 Unit, Veneto Institute of Oncology, IOV-IRCCS, Padua; [3]Department of Surgery, Oncology and Gastroenterology, Oncology Section, University of Padua, Padua; [4]Familiar Cancer Clinic and Oncoendocrinology, Veneto Institute of Oncology, IOV-IRCCS, Padua; [5]Oncology Unit 3, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

Background: Melanoma heterogeneity is an obstacle in metastatic disease management. Although the advent of targeted therapy has significantly improved patient outcome, the occurrence of resistance makes monitoring of the tumor genetic landscape mandatory. Liquid biopsy could represent an important biomarker to track the evolution of the disease in real time. Thus, we aimed to correlate liquid biopsy dynamics with treatment response/progression by devising a multiplatform approach applied to longitudinal monitoring.
Methods: We exploited NGS, digital PCR, and CellSearch platforms to analyze circulating tumor DNA (ctDNA) trend and circulating melanoma cell (CMC) count, together with their customized genetic and CNV analysis. The approach was applied to 50 samples from 17 stage IV melanoma patients treated with BRAF/MEK inhibitors, followed up to 24 months.
Results: BRAF mutations were detected in the plasma of 82% of patients. There was a significant difference in ctDNA amount at baseline in responders versus non-responders/early progressing patients (p=0.039). Moreover, a cut-off able to discriminate responders from non-responders was identified. Undetectable BRAF-mutant ctDNA at the first treatment observational point correlated with best overall survival (OS) (p=0.024), and lack of BRAF-mutant ctDNA clearance up to the first 6 months of treatment correlated with non-response or early progression (p=0.015). Single nucleotide variants (SNVs) known or suspected to confer resistance were identified in 60% of patients. Moreover, the number of baseline SNVs correlated with progression free survival (PFS) (p=0.041). Finally, CMCs confirmed to be a prognostic biomarker, as the presence of 1 or more CMCs correlated with worse PFS (p=0.001) and OS (p=0.003).
Conclusions: This work provides proof-of-principle of the power of this approach and paves the way for a validation study to evaluate early ctDNA-guided treatment decisions in stage IV melanoma. The molecular profile complemented the analysis of ctDNA trend and, together with CMC analysis, revealed to be useful in capturing tumor evolution.

EXPLORING BIOMARKERS OF RESPONSE FOR COMBINATION THERAPY WITH PEMBROLIZUMAB AND LENVATINIB IN METASTATIC MELANOMA RESISTANT TO ANTI-PD1 INHIBITOR

Roberta Di Fonte[1], Michele Guida[1], Simona Serratì[1], Sabino Strippoli[1], Livia Fucci[1], Ivana De Risi[1], Rossella Fasano[1], Tania Rafaschieri[1], Andrea Armenio[1], Cosmo M. Ressa[1], Mariateresa Volpicella[2], Amalia Azzariti[1], Letizia Porcelli[1]

[1]IRCCS Istituto Tumori Giovanni Paolo II, Bari; [2]Department of Biosciences, Biotechnologies and Environment, University of Bari, Bari, Italy

Background: Immune checkpoints inhibitors (ICIs) importantly improved the survival of metastatic melanoma (MM) patients, however patients that progress on ICIs represent an expanding population with very limited treatment options. Clinical studies demonstrated relative safety and durable efficacy of multikinase inhibitor lenvatinib and pembrolizumab in MM previously exposed to anti-PD-1. Here, we investigated key features associated with response to single agent and combined treatment with lenvatinib and pembrolizumab in organoids derived from patients who progressed on anti-PD1.
Methods: Organoids were developed from surgical specimens of 9 patients; 6 BRAF wild type receiving first-line PD-1 therapy and 3 BRAFV600 mutant in second-line, after first-line targeted therapy. Tumor killing experiments were performed in co-culture of autologous activated T cells and organoids with and without treatment(s). Organoids viability and apoptosis induction was evaluated using CellTiter-Glo®3D Cell Assay and NucView® 488 Caspase-3 Assay and live cell imaging. Luminex xMAP technology was used to analyze the release of soluble mediators of immunosuppression and immune response in supernatants.
Results: In agreement with clinical response, the organoids of all patients were resistant to pembrolizumab and showed variable sensitivity to lenvatinib. The combined treatment resulted in greater antitumor effect than lenvatinib, by inducing reduction of organoids viability and activation of caspase 3-mediated apoptosis. In almost all organoids combined treatment caused blockade of the release of soluble immune checkpoints PD-1, Tim-3, LAG-3 and BTLA to a greater extent than each drug alone. Notably, no treatment reduced soluble CD73 level, instead both single and combined treatment reduced the level of perforin in co-cultures supernatants.
Conclusions: Collectively, the results suggested both the reduction of CD8+ T cells exhaustion by combined treatment with pembrolizumab and lenvatinib and the reduction of T-cell killing action. Further investigations are warranted to explore the role of CD73 in the response to such experimental immunotherapy.

THE INTERPLAY BETWEEN MIR-579-3P AND MICROPHTHALMIA-ASSOCIATED TRANSCRIPTION FACTOR CONTROLS MELANOMA PROGRESSION AND RESISTANCE TO TARGETED THERAPIES

Domenico Liguoro[1], Luigi Fattore[2], Andrea Sacconi[3], Rachele Frigerio[2], Paolo Antonio Ascierto[4], Rita Mancini[1], Gennaro Ciliberto[5]

[1]Dept of Clinical and Molecular Medicine, Sapienza University of Rome, Rome; [2]SAFU Laboratory, Department of Research, Advanced Diagnostics and Technological Innovation, Translational Research Area, IRCCS Regina Elena National Cancer Institute,

Rome; [3]Clinical Trial Center, Biostatistics and Bioinformatics Unit, IRCCS Regina Elena National Cancer Institute, Rome; [4]Unit of Melanoma, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples; [5]Scientific Directorate, IRCSS Regina Elena National Cancer Institute, Rome, Italy

Background: Therapy of metastatic melanoma has improved dramatically over the last years thanks to the development of targeted therapies (MAPK inhibitors) and immunotherapies. However, drug resistance continues to be a major limitation to the efficacy of these therapies. Our research group has provided robust evidence as to the involvement of a set of microRNAs in the development of non-genetic resistance to target therapy in BRAF-mutated melanoma cell lines. Among them, a pivotal role is played by the newly oncosuppressor miR-579-3p.
Methods: BRAF-mutant WM266 and LOX IMVI cells have been subjected to: a) ChIP and Luciferase assay; b) Cloning and Trasfection; c) Treatments with MAPKi. qRT-PCR and Western Blott analysis were used to evaluate the expression of genes. Crystal violet staining and β-galactosidase assay were used to assess proliferation and senescence features in BRAF-mutant melanoma cells. The use of human samples was approved by Istituto Pascale's Ethical Committee.
Results: Here we show that miR-579-3p and the microphthalmia-associated transcription factor (MITF) influence reciprocally their expression by positive feedback regulatory loops. Luciferase and ChIP studies highlighted that MITF is a positive regulator of miR-579-3p, which is located in the intron 11 of the human gene ZFR. Moreover, we report that miR-579-3p, by targeting BRAF is able to stabilize MITF protein thus inducing its own transcription. As a consequence, upon exposure to MAPK inhibitors, or alternatively upon miR-579-3p transfection, the activation of this newly uncovered miR-579-3p/MITF axis induces block of proliferation and senescence of BRAF-mutant melanoma cells. We also observed that the long term development of resistance to MAPKi is able to select cells characterized by the loss of both miR-579-3p and MITF. We observed their down-regulation also in patients relapsing after targeted therapies treatments.
Conclusions: Altogether these findings suggest that miR-579-3p/MITF interplay potentially governs the balance between proliferation, senescense and resistance to target therapies in BRAF-mutant melanomas.

LOCALLY RECURRENT CUTANEOUS SQUAMOUS CELL CARCINOMA LESIONS OF HEAD AND NECK: A CASE-CONTROL STUDY BASED ON GENETIC ANALYSIS

Maria Colombino[1], Maria Antonietta Fedeli[2], Germana Sini[3], Manuela Rodio[3], Milena Casula[1], Panagiotis Paliogiannis[2], Antonio Cossu[2], Giuseppe Palmieri[1,4], Corrado Rubino[3]

[1]Unit of Cancer Genetics, IRGB-CNR, Sassari; [2]Pathology and Histology Unit, Department of Medicine, Surgery & Pharmacy, University of Sassari, Sassari; [3]Plastic Surgery, Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari; [4]Immuno-Oncology & Targeted Cancer Biotherapies, Department of Biomedical Sciences, University of Sassari, Sassari, Italy

Background: Head and Neck cutaneous squamous cell carcinoma (HNcSCC) is a type of skin cancer with local recurrence rates exceeding 5%, reaching up to 10% in scalp lesions. Predicting recurrent cases in cSCC lesions of this anatomical area, which have intermediate dimensions and no risk factors, remains challenging. In this study, we aimed to identify the main genetic features underlying the clinical behavior of local recurrence in HNcSCC lesions.
Methods: We conducted a retrospective cohort study on patients with T2 HNcSCC (as per AJCC 8 guidelines, tumors that are 2 cm or larger but less than 4 cm in size without any risk factors), treated with standard excision. Cases and controls were selected from a database of surgically treated cSCCs at the University Hospital of Sassari, collected from 2017 to 2020. The study included seven cases with early local recurrence and seven controls with no recurrence during at least 3 years of follow-up. No patient had a history of immunosuppression. NGS analysis was used to assess the mutational status of 25 key genes involved in skin tumor pathogenesis.
Results: Among the 14 cases, all but one were males (93%), with a similar median age of onset (74 years in males and 77 in females). The cSCCs were located in the cheek (43%), scalp (29%), auricle (14%), and lip (14%). A total of 63 mutations were identified, with 37 (59%) in the control group and 26 (41%) in cases. The most frequently mutated gene was TP53, accounting for 31% of all mutations, followed by KIT (15%), KDR (13%), and CDKN2A (11%). The average mutation rate was 3.7 for cases and 5.3 for controls. Excluding mostly-prevalent TP53 mutations, distributed uniformly in both cases and controls, KDR mutations were more common in controls (6/7; 86%), while cases had a lower occurrence of KDR mutations (2/7; 29%). Additionally, mutated KDR was associated with mutations in CDKN2A or KIT or both in 2/7 (29%) of cases and in 6/7 (86%) of controls. Three cases had a history of non-melanoma skin cancer (NMSC) and developed NMSC at other locations during follow-up.
Conclusion: Although our patient sample for T2 HNcSCC is limited, seem to suggest that the occurrence of an increased rate of mutations might be associated with a lower tendency to develop local recurrency in such a cSCC subtype. Moreover, there is a hint about the existence of a pattern of mutated genes associated with reduced local cSCC recurrency.

PREDICTION OF THE RECURRENCE RISK IN STAGE IB-IIC CUTANEOUS MELANOMA THROUGH ARTIFICIAL INTELLIGENCE TECHNIQUES ON HEMATOXYLIN-EOSIN STAIN IMAGES

Maria Colomba Comes[1], Sabino Strippoli[2], Livia Fucci[3], Samantha Bove[1], Ivana De Risi[2], Clara Soranno[1], Annarita Fanizzi[1], Fabio Mele[3], Concetta Saponaro[3], Rosita Tinelli[3], Alfredo Zito[3], Raffaella Massafra[1], Michele Guida[2]

[1]Unità Operativa Fisica Sanitaria, I.R.C.C.S. Istituto Tumori "Giovanni Paolo II", Bari; [2]Unità Operativa Tumori Rari e Melanoma, I.R.C.C.S. Istituto Tumori "Giovanni Paolo II", Bari; [3]Unità Operativa Anatomia Patologica, I.R.C.C.S. Istituto Tumori "Giovanni Paolo II", Bari, Italy

Background: Adjuvant treatments for high-risk melanoma have steadily improved over the years with the advent of immunotherapy and target therapy. Thus, risk stratification and treatment benefit prediction models are urgently needed to improve patient selection and avoid costly and toxic treatments to patients at low risk of recurrence. To this end, the application of artificial intelligence (AI) could help clinicians to better calculate the recurrence risk and choose whether to perform adjuvant therapy.
Methods: We detected quantitative imaging from H&E slides of 71

patients with cutaneous stage IB-IIC melanoma. For each slide, two expert pathologists firstly annotated two Regions of Interest (ROIs) containing tumor cells alone (Tumor ROI) or with tumor-infiltrating lymphocytes (Tumor+TILs ROI). In correspondence of the two kinds of ROIs, two AI-based models were developed to extract information directly from the tiles in which each ROI was automatically divided. This information was then used to predict recurrence-free status (RFS). Performances of the model were computed according to a 5-fold cross validation scheme.

Results: Overall, 20 patients had a recurrence (non-RF cases) and 51 did not (RF cases) with a median RFS of 15 months and 31 months, respectively (Table 1). Tumor ROIs (AUC = 79.1%, sensitivity = 81.2%, specificity = 70.0%, accuracy = 73.2%) have revealed more informative than Tumor + TILs ROIs (AUC = 62.3%, sensitivity = 76.9%, specificity = 43.3%, accuracy = 53.4%). For the best model, the performances were also computed on sub-cohorts by stage: stage IB-IIA (AUC = 80.3%, sensitivity = 55.6%, specificity = 84.6%, accuracy = 77.1%), stage IIB-IIC (AUC = 80.6%, sensitivity = 57.1%, specificity = 85.7%, accuracy = 76.2%).

Conclusions: Our approach represents a valid non-invasive prognostic method to better define the recurrence risk and improve the management of stage IB-IIC melanoma. Validation on larger cohorts of patients is planned.

Table 1. Patients' characteristics.

Characteristic	Distribution
Outcome	
Recurrence Free (abs.; %)	51 (71.8)
non- Recurrence Free (abs.; %)	20 (28.2)
Gender	
Male (abs.; %)	39 (54.9)
Female (abs.; %)	32 (45.1)
Age	
Median [q1; q3]	58 [52; 71]
Tumor site	
Trunk (abs.; %)	37 (52.1)
Extremities (abs.; %)	28 (39.4)
Head and neck (abs.; %)	6 (8.5)
Stage	
IB (abs.; %)	21 (29.6)
IIA (abs.; %)	25 (35.2)
IIB (abs.; %)	16 (22.5)
IIC (abs.; %)	9 (12.7)
pT	
T2a (abs.; %)	21 (29.6)
T2b (abs.; %)	8 (11.3)
T3a (abs.; %)	17 (23.9)
T3b (abs.; %)	9 (12.7)
T4a (abs.; %)	7 (9.8)
T4b (abs.; %)	9 (12.7)

For categorical variables, percentage (%) counts are reported. For continuous values, the median and 1rst and 3rd quartiles values are indicated.

CHANGES IN PERIPHERAL AND LOCAL TUMOR IMMUNITY AFTER CEMIPLIMAB TREATMENT EARLY DESCRIBE CLINICAL OUTCOMES IN PATIENTS WITH CUTANEOUS SQUAMOUS CELL CARCINOMA

Anna Rita Amato, Daniela Esposito, Chiara Barraco, Stefania Belli, Claudia Maria Ascione, Alberto Servetto, Roberto Bianco, Luigi Formisano

Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

Background: Cutaneous squamous cell carcinoma (cSCC) – the second most common skin tumor - accounts for 20% of all deaths from skin cancer. Although the vast majority of patients can be managed with surgical excision, a small percentage of them have locally advanced or metastatic tumors for which programmed cell death 1 (PD-1) checkpoint inhibition was approved and demonstrated substantial antitumor activity. The absence of reliable markers of response and the lacking of a description of immune modulation upon treatment, highlight a clinical need to be addressed.

Methods: We collected tumor and liquid biopsies of 12 patients who underwent to cemiplimab before and after 3-weeks of treatment. We profiled RNA of pre- and post-cemiplimab tumor biopsies using the PanCancer Immunoprofile Panel (Nanostring). We determined cytokines released in blood by multiplex ELISA, and lymphocyte abundance by flow cytometry.

Results: The analysis of transcriptional reprogramming in tumor biopsies showed that PD1 blockade induced the expression of PD1-regulated genes after treatment. Interestingly, cemiplimab treatment boosted immune cell activation only in responders patients (B- and T-cells), according to the host antitumor response expected upon PD-1 targeting. Focusing on peripheral markers, total Tregs early increased in non-responders patients, but dissecting specific antigens of Treg populations, we identified the specific ICOS subpopulation with a different trend in responders and non-responders. ICOS-positive cells, indeed, increased their abundance in the peripheral blood only of responder patients, in line with recent data showing ICOS cells as positive markers of ICI efficacy in lung cancer. Finally, TNF-α *sera* levels decreased after treatment only in responder patients, in line with its role as a determinant of resistance to PD1 targeting.

Conclusions: Our results provided new key elements to monitor response to therapy, determining putative markers to early define responsiveness to ICI in cSCC patients and suggest how to improve their clinical management.

SEX DIFFERENCES IN STAGE II CUTANEOUS MELANOMA: THE IMPACT ON SURVIVAL OUTCOMES.

Ida Taglialatela[1], Giulia Santanelli[1], Alice Indini[1], Benedetta Lombardi Stocchetti[1], Lorenza Di Guardo[1], Roberto Patuzzo[2], Francesco Gallino[2], Andrea Maurichi[2], Ilaria Mattavelli[2], Roberta Ruggeri[2], Mario Santinami[2], Michele Del Vecchio[1]

[1]Melanoma Medical Oncology Unit, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan; [2]Melanoma Surgical Unit, Department of Melanoma and Ocular Tumours Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy

Background: A survival disadvantage in male cutaneous melanoma patients (pts) has been long recognized through the stages. Specifically, we evaluated the role of sex as an independent prognostic factor among pts with stage II melanoma.

Methods: We retrospectively collected clinical, pathological and molecular data of stage II cutaneous melanoma pts referring to our Institution between January 2018 and December 2021. Univariate Cox regression models were used for statistical analysis.

Results: Overall, with a median follow-up of 38 months, 191 patients with stage II melanoma undergoing surgery without systemic adjuvant treatment were analyzed: 43 (22.5%) had stage IIA, 88 (46.1%) stage IIB, and 60 (31.4%) stage IIC disease. Median age was 66 years. 116 (61%) patients were males. BRAF status was available for 140 (73.3%) pts: 51 (36%) were V600-mutant and 89 (64%) wild type. No differences in overall (OS), local relapse-free (LRFS) and distant metastasis-free survival (DMFS) was observed

in terms of BRAF status (HR_{OS} 0.99, p 0.9; HR_{LRFS} 0.82, p 0.4; HR_{DMFS} 0.82, p 0.5). A significant disadvantage for males was observed in risk of local ($mLRFS_{male}$ 47.17 *vs.* $mLRFS_{female}$ 79.57 mo, HR 1.94 [CI 95% 1.22 – 3.09], p 0.005) and distant- relapse ($mDMFS_{male}$ 55.36 *vs.* $mDMFS_{female}$ 152.69 mo, HR 2.69 [CI 95% 1.38 – 5.25], p 0.004). A statistically significant trend for worse OS was observed among male pts (mOS_{male} 122.27 *vs.* mOS_{female} 180.33 mo, HR 2.13 [CI 0.93 – 4.89], p 0.07).

Conclusions: Our study confirms a disadvantage for cutaneous melanoma male pts in survival outcomes, except for OS, for which a longer follow-up is required. Sex, combined with other recognized prognostic factors in stage II melanoma, could potentially become a mean in selecting patients for adjuvant treatments in the near future.

SURGERY

SURGICAL MANAGEMENT OF PREGNANCY ASSOCIATED MELANOMA: A SINGLE INSTITUTION EXPERIENCE

Ilaria Mattavelli[1], Roberto Patuzzo[1], Andrea Maurichi[1], Gianfranco Gallino[1], Bianca Taglione[1], Matteo Matteucci[1], Barbara Valeri[2], Mara Cossa[2], Marco Maccauro[3], Lorenza Di Guardo[4], Alice Indini[4], Ida Taglialatela[4], Michele Del Vecchio[4], Mario Santinami[1]

[1]Melanoma and Sarcoma Surgical Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [2]Department of Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [3]Department of Nuclear Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [4]Unit of Melanoma Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Pregnancy-associated melanoma (PAM) is generally associated with a worse outcome but the prognostic role of pregnancy remains controversial. Surgical approach to melanoma during pregnancy is challenging and there are no established guidelines. Safety of SNB during pregnancy is still argument of debate. We present our experience in management of PAM.

Methods: A series of 32 pregnant women surgically treated for cutaneous melanoma at Istituto Nazionale dei Tumori, Milan, Italy, from 2007 to 2022 was retrospectively reviewed.

Results: During pregnancy - from 7th to 32nd week of gestational age (GA) - 30 patients had a histopathological diagnosis of invasive primary melanoma, while two had a regional nodal recurrence. Twenty-six women (81.2%) received surgical treatment during pregnancy, six (18,7%) were treated after delivery, because diagnosis occurred after 30th week of GA. Twenty-seven women (84.3%) received wide excision and sentinel node biopsy (SNB) during pregnancy or after delivery; three patients (9.3%) were not previously offered SNB and came to our observation with clinical nodal disease. Eleven woman (34.4%) presented with an advanced melanoma at diagnosis (10 stage III, 1 stage IV, M1a); the other 21 (65.6%) had a negative SN (7 stage IA, 8 stage IB, 3 stage IIA, 1 stage IIB, 2 stage IIC according to AJCC VIII Edition). No fetal complications occurred. Median follow up was 61 months. Twenty-four women (75%) were alive without evidence of disease, one (3.1%) was alive with disease (stage IV), and seven (21.9%) died of disease.

Conclusions: Our study showed that SNB can be safely performed during pregnancy after the first trimester without fetal complications. Surgical treatment may be performed during pregnancy without delays since it provides accurate staging and higher prognostic chances.

POTENTIAL RISK FACTORS, CLINICOPATHOLOGICAL FEATURES AND DETERMINANTS OF SURVIVAL FOR MULTIPLE PRIMARY MELANOMA PATIENTS COMPARED TO SINGLE PRIMARY MELANOMA: A LARGE SINGLE-CENTRE STUDY

Ilaria Mattavelli[1], Roberto Patuzzo[1], Carlotta Galeone[2], Claudio Pelucchi[3], Gianfranco Gallino[1], Giuseppe Spadola[1], Elena Tolomio[1], Consuelo Barbieri[1], Bianca Taglione[1], Matteo Matteucci[1], Barbara Valeri[4], Mara Cossa[4], Mario Santinami[1], Andrea Maurichi[1]

[1]Melanoma and Sarcoma Surgical Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [2]Bicocca Applied Statistics Center (B-ASC), Università degli Studi di Milano-Bicocca, Milan; [3]Department of Clinical Sciences and Community Health, University of Milan, Milan; [4]Department of Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Melanoma patients have a high risk of developing subsequent primary melanomas, a condition known as Multiple Primary Melanoma (MPM). We compared risk factors of patients with MPM and Single Primary Melanoma (SPM) treated at Melanoma Surgical Unit of the National Cancer Institute of Milan.
Methods: Primary MPM and SPM consecutively treated at the National Cancer Institute of Milan, Italy, from 1978 to 2021 were retrospectively investigated. Demographic and clinicopathological characteristics were analyzed. Multivariate hazard ratios (HR) and mortality were estimated using Cox proportional hazards regression models.

Table 1. Hazard ratios of multiple primary melanoma by patients and first primary melanoma characteristics.

	Unadjusted HR (95% CI)	Adjusted HR[1] (95% CI)
Age		
10-year increase	0.98 (0.94-1.02)	0.98 (0.94-1.02)
Sex		
Male *vs.* female	1.34 (1.18-1.52)	1.29 (1.13-1.48)
Calendar year		
≥2004 *vs.* <2004	1.56 (1.29-1.89)	1.54 (1.27-1.87)
Anatomic site (*vs.* trunk)		
Head and neck	0.81 (0.65-1.01)	0.90 (0.72-1.13)
Upper extremity	0.75 (0.61-0.93)	0.81 (0.65-1.00)
Lower extremity	0.65 (0.55-0.76)	0.72 (0.62-0.86)
Histologic type (*vs.* SSM)		
In situ	1.65 (1.27-2.15)	1.64 (1.26-2.13)
Nodular melanoma (NM)	0.52 (0.42-0.63)	0.51 (0.42-0.63)
Other	0.57 (0.43-0.76)	0.61 (0.46-0.82)
Breslow[2], mm (*vs.* ≤1.0)		
>1.0 – 2.0	0.52 (0.45-0.62)	0.55 (0.46-0.65)
>2.0 – 4.0	0.40 (0.32-0.49)	0.46 (0.36-0.57)
>4.0	0.44 (0.34-0.57)	0.54 (0.41-0.72)
Mitoses[2] (*vs.* absent)		
present	0.50 (0.43-0.57)	0.54 (0.47-0.63)
Ulceration[2] (*vs.* absent)		
present	0.21 (0.15-0.28)	0.24 (0.17-0.33)
Regression[2] (*vs.* absent)		
present	1.21 (1.03-1.41)	1.09 (0.93-1.29)
Vascular invasion[2] (*vs.* absent)		
present	1.91 (1.59-2.31)	2.20 (1.82-2.66)
Tumor-infiltrating lymphocytes[2] (TIL) (*vs.* absent)		
Non brisk	1.11 (0.94-1.31)	1.05 (0.89-1.25)
Brisk	0.83 (0.66-1.04)	0.75 (0.60-0.95)
Sentinel-node biopsy[2,3] (vs.. negative)		
positive	0.94 (0.75-1.16)	0.98 (0.79-1.21)

SSM, superficial spreading melanoma. [1]Estimated from Cox models including terms for age, sex, calendar year, anatomic site and histologic type of the first primary melanoma; [2]among invasive melanoma only, excludes melanoma *in situ*; [3]among patients undergoing sentinel-node biopsy.

SSM, superficial spreading melanoma. 1Estimated from Cox models including terms for age, sex, calendar year, anatomic site and histologic type of the first primary melanoma; 2among invasive melanoma only, excludes melanoma in situ; 3among patients undergoing sentinel-node biopsy.

Results: Overall, 9122 patients with SPM and 944 with MPM were included. A total of 1437 and 85 deaths occurred in SPM and MPM group, respectively. Of these, 1315 (14.4%) within SPM patients and 60 (6.4%) in MPM group were melanoma-specific deaths (MSD). Males had a higher risk for MPM (HR=1.29), while age was not associated with MPM (HR=0.98) (Table 1). The risk of MPM decreased by about 50% for Breslow thickness >1 mm, and by about 45% and 75% in presence of mitoses and ulceration, respectively (Figure 1). The multivariate HR of death for MPM compared to SPM patients was 0.85 (95% CI: 0.67-1.06), while considering MSD the corresponding HR was 0.93 (95% CI: 0.71-1.22).
Conclusions: Melanoma patients should receive regular follow-up with complete skin examination to early detect subsequent primary melanoma. Patients with more advanced primary have decreased risk of MPM, while males have higher risk. Our study reported no significant difference in mortality between SPM and MPM, but the issue is still open for discussion and further studies.

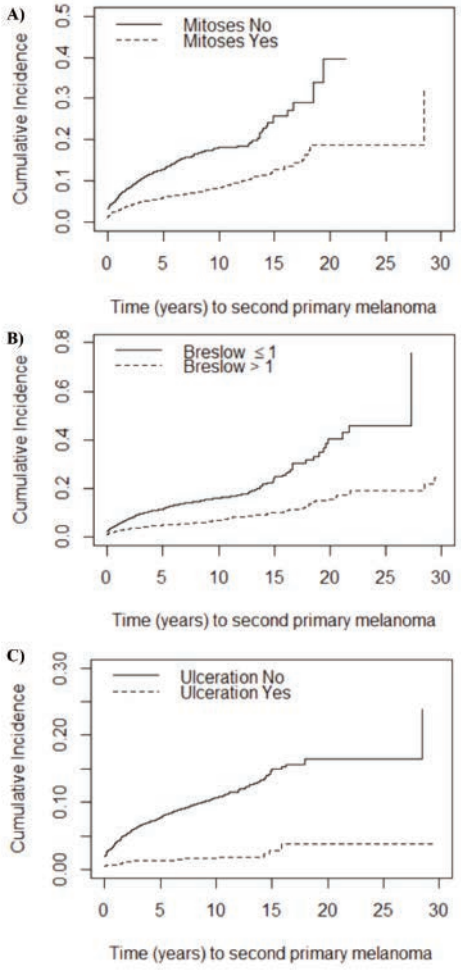


Figure 1. Cumulative incidence function (CIF) of subsequent primary melanoma according to: A) presence of mitoses; B) Breslow thickness; C) presence of ulceration of the first primary melanoma.

TREATMENT AND OUTCOME OF PATIENTS WITH MELANOMA AND POSITIVE SENTINEL LYMPH NODE AFTER MSLT-II, DECOG AND ADJUVANTS TRIAL

Serena Sestini[1], Gianni Gerlini[1], Paola Brandani[1], Annalisa Moccia[1], Raffaella Grifoni[2], Renato Tassi[2], Isabella Ciardetti[3], Emanuele Crocetti[4], Nicola Pimpinelli[3], Lorenzo Borgognoni[1]

[1]SOC Chirurgia Plastica e Ricostruttiva, Melanoma & Skin Cancer Unit, Centro di Riferimento Regionale per il Melanoma, Ospedale S.M. Annunziata, Azienda Toscana Centro, Firenze; [2]SOC Oncologia Medica, Ospedale S.M. Annunziata, Azienda Toscana Centro, Firenze; [3]SOC Dermatologia, Università degli Studi di Firenze, Azienda Toscana Centro; [4]Firenze, Italy

Background: Most sentinel node positive (SN+) melanoma patients have not received complete lymph node dissection (CLND) after MSLT-II and DeCOG trial. During the same time period adjuvant therapies (Adj) were registered for stage III melanoma patients and CLND was mandatory in trial of Adj. In the clinical practice, most SN+ melanoma patients do not currently perform CLND before Adj. However, outcome data of SN+ patients who receive Adj without prior CLND are not known. The aim of this preliminary report is to analyze outcome data of these melanoma patients in the modern melanoma therapheutic era.
Methods: A retrospective analysis of SN+ melanoma patients treated after approval of Adj at Melanoma & Skin Cancer Unit of Florence was performed, with evaluation of recurrence and type of treatment.
Results: 596 patients performed SN biopsy after December 2019. Among these, 127 (21.3%) were SN+ and analyzed for this study. The majority (108 patients) received Adj (74 patients without prior CLND, while 34 underwent CLND). Eighteen patients did neither receive CLND nor Adj. One patient underwent CLND and not Adj. Recurrence was detected in: 11/74 (14.9%) patients who received Adj and no CLND, 8/34 (23.5%) patients who received Adj and CLND, 6/18 (33.3%) patients who did neither receive CLND nor adj. Among 108 patients who received Adj, 64 (59.3%) patients received immuno-therapy and 44 (40.7%) received target-therapy.
Discussion: This pilot study reports outcome data on SN+ melanoma patients who received Adj without prior CLND showing 14.9% of recurrence. Recurrence rate in patients who neither received CLND nor Adj was 33.3%. A limitation of this preliminary report is the low sample size that does not allow enough power for subgroup analysis.
Conclusions: Larger multicenter study is needed to better understand the outcome of SN+ melanoma patients receiving Adj without prior CLND and risk-subgroups evaluation.

ISOLATED LIMB PERFUSION FOR LOCALLY ADVANCED MELANOMA IN THE ERA OF TARGETED THERAPIES AND IMMUNOTHERAPY

Marco Rastrelli[1,2], Paolo Del Fiore[*1], Francesco Cavallin[3], Francesco Russano[1], Claudia Pacilli[4], Jacopo Pigozzo[5], Vanna Chiarion-Sileni[5], Simone Mocellin[1,2]

[1]Soft-Tissue, Peritoneum and Melanoma Surgical Oncology Unit, IOV- IRCCS, Padua; [2]Department of Surgery, Oncology and Gastroenterology (DISCOG), University of Padua, Padua; [3]Independent Statistician, Solagna; [4]Department of Medicine, University of Padua School of Medicine and Surgery, Padua [5]Melanoma Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

Background: Isolated limb hyperthermic-antiblastic perfusion (ILP) was the most effective local treatment for advanced in-transit melanoma, but the advent of modern effective immunotherapy, such as ICI (immune checkpoint inhibitors) has changed the treatment landscape.
Methods: The primary aim of this study is to evaluate the role of ILP in the treatment of locally advanced unresectable melanoma, in particularly in relation to modern systemic therapies. We have analyzed 220 consecutive patients diagnosed with advanced melanoma, treated with ILP (melphalan or melphalan associated with TNF-alpha) at the Istituto Oncologico Veneto (IOV) and at the Padua University Hospital (AOPD), over a period between June 1989 and September 2021. Overall survival (OS), Local disease-free survival (LDFS), distant disease-free survival (DDFS) were evaluated; local toxicities were classified according to the Wieberdink scale and surgical complications according to the Clavien-Dindo classification. The response to locoregional therapy was evaluated during follow-up according to RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumor).
Results: Of the 220 patients treated with ILP, 75 were male (34%), the average age was 61 (52-68). The patients were stratified according to the therapies given in association with perfusion, defining 3 main groups: ILP, ILP + CT/TT, ILP+IT. OS at 36 months was 42% in those who received ILP alone, 11% in those who received ILP+CT/TT, 60% in those who received ILP+IT (p=0.004). LDFS at 36 months was 36% in those who received ILP alone, 12% in those who received ILP+CT/TT, 53% in those who received ILP+IT (p=0.04). DDFS at 36 months was 33% in those who received ILP alone, 0% in those who received ILP+CT/TT, 35% in those who received ILP+IT(p=0.20)
Conclusions: The results confirm the synergy between ILP and immunotherapy, our impression is that the association between ILP and IT determines a better local response than IT/ILP alone, maintaining a comparable OS. ILP remains an effective locoregional treatment option in the era of effective systemic treatments further studies are needed to establish the optimal combination and timing of the high local response rates of locoregional treatments with the systemic effects of immunotherapy.

References

1. Lejeune, F. J., Deloof, T., Ewalenko, P., Fruhling, J., Jabri, M., Mathieu, M., Nogaret, J. M., & Verhest, A. (1983). Objective regression of unexcised melanoma in-transit metastases after hyperthermic isolation perfusion of the limbs with melphalan. Recent results in cancer research. Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer, 86, 268–276.
2. Liénard, D., Eggermont, A. M., Koops, H. S., Kroon, B., Towse,

G., Hiemstra, S., Schmitz, P., Clarke, J., Steinmann, G., Rosenkaimer, F., & Lejeune, F. J. (1999). Isolated limb perfusion with tumour necrosis factor-alpha and melphalan with or without interferon-gamma for the treatment of in-transit melanoma metastases: a multicentre randomized phase II study. Melanoma research, 9(5), 491–502.
3. Di Filippo, F., Calabrò, A., Giannarelli, D., Carlini, S., Cavaliere, F., Moscarelli, F., & Cavaliere, R. (1989). Prognostic variables in recurrent limb melanoma treated with hyperthermic antiblastic perfusion. Cancer, 63(12), 2551–2561.
4. Lienard, D., Ewalenko, P., Delmotte, J. J., Renard, N., & Lejeune, F. J. (1992). High-dose recombinant tumor necrosis factor alpha in combination with interferon gamma and melphalan in isolation perfusion of the limbs for melanoma and sarcoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 10(1), 52–60.
5. Rossi, C. R., Foletto, M., Pilati, P., Mocellin, S., & Lise, M. (2002). Isolated limb perfusion in locally advanced cutaneous melanoma. Seminars in oncology, 29(4), 400–409.
6. Eggermont, A. M., de Wilt, J. H., & ten Hagen, T. L. (2003). Current uses of isolated limb perfusion in the clinic and a model system for new strategies. The Lancet. Oncology, 4(7), 429–437.
7. Rossi, C. R., Mocellin, S., Pilati, P., Foletto, M., Nitti, D., & Lise, M. (2003). TNFalpha-based isolated perfusion for limb-threatening soft tissue sarcomas: state of the art and future trends. Journal of immunotherapy (Hagerstown, Md.: 1997), 26(4), 291–300.
8. Rossi, C. R., Foletto, M., Di Filippo, F., Vaglini, M., Anza', M., Azzarelli, A., Pilati, P., Mocellin, S., & Lise, M. (1999). Soft tissue limb sarcomas: Italian clinical trials with hyperthermic antiblastic perfusion. Cancer, 86(9), 1742–1749.
9. Sevilla-Ortega, L., Ferrándiz-Pulido, L., Palazón-Carrión, N., Álamo de la Gala, M. D. C., de Toro-Salas, R., Garnacho-Montero, J., Marcos-Rodríguez, J. A., Agudo Martínez, A., Araji-Tiliani, O., Calvo-Morón, M. C., Barquero-Aroca, J. M., Fernández-López, A. R., Jaime-Borrego, J. M., Santos-Jiménez, J. C., Moreno-Ramírez, D., & de la Cruz-Merino, L. (2021). Role of Isolated Limb Perfusion in the Era of Targeted Therapies and Immunotherapy in Melanoma. A Systematic Review of The Literature. Cancers, 13(21), 5485.
10. Zaremba, A., Philip, M., Hassel, J. C., Glutsch, V., Fiocco, Z., Loquai, C., Rafei-Shamsabadi, D., Gutzmer, R., Utikal, J., Haferkamp, S., Reinhardt, L., Kähler, K. C., Weishaupt, C., Moreira, A., Thoms, K. M., Wilhelm, T., Pföhler, C., Roesch, A., Ugurel, S., Zimmer, L., … Livingstone, E. (2021). Clinical characteristics and therapy response in unresectable melanoma patients stage IIIB-IIID with in-transit and satellite metastases. European journal of cancer (Oxford, England : 1990), 152, 139–154.
11. Holmberg, C. J., Mattsson, J., & Olofsson Bagge, R. (2023). Effects of the Introduction of Modern Immunotherapy on the Outcome of Isolated Limb Perfusion for Melanoma In-Transit Metastases. Cancers, 15(2), 472.
12. Nan Tie, E., Lai-Kwon, J., Rtshiladze, M. A., Na, L., Bozzi, J., Read, T., Atkinson, V., Au-Yeung, G., Long, G. V., McArthur, G. A., Sandhu, S., Saw, R., Walpole, E., Menzies, A., Smithers, M., & Gyorki, D. E. (2020). Efficacy of immune checkpoint inhibitors for in-transit melanoma. Journal for immunotherapy of cancer, 8(1), e000440.

IDENTIFYING HIGH-RISK FEATURES AND IMPROVING FOLLOW-UP STRATEGIES IN THIN MELANOMA: A RETROSPECTIVE COHORT STUDY

Antonella Vecchiato[1], Paolo Del Fiore[1], Fortunato Cassalia[2], Claudia Cozzolino[1], Pierpaola Vallese[3], Saveria Tropea[1], Marcodomenico Mazza[1], Luisa Piccin[4], Valentina Salizzato[4], Irene Russo[1], Jacopo Pigozzo[4], Vanna Chiarion-Sileni[4], Mauro Alaibac[2], Simone Mocellin[1,3]

[1]Soft-Tissue, Peritoneum and Melanoma Surgical Oncology Unit, IOV-IRCCS, Padua; [2]Unit of Dermatology, Department of Medicine, University of Padua, Padua; [3]Department of Surgery, Oncology and Gastroenterology (DISCOG), University of Padua, Padua; [4]Melanoma Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

Background: The incidence of cutaneous melanoma (MC) is increasing continuously, and a considerable proportion (58 to 81% of cases) of diagnosed melanomas are "thin" in terms of thickness, according to the Breslow index. Although thin melanomas (MS) are associated with a good prognosis (with survival ranging from 85 to 99%) a subset of these may present with recurrence of disease in follow-up and metastasize.
Methods: This is a retrospective cohort study including all patients aged ≥18 years who received diagnosis and/or treatment for thin melanoma in the period between 1998 and 2017 at the UOC Melanoma and Sarcoma of the Veneto Institute of Oncology (IOV) and the Padua Hospital (AOPD). Data regarding patient, disease, treatment and follow-up characteristics were extracted from a purpose-built database. Overall Survival and Melanoma Specific Survival were derived from scheduled visits.
Results: We found statistically significant differences (Table 1) in tumor subtype (0.01566), Breslow thickness (<0.001), T (<0.001), TNM (<0.001), presence of ulceration (<0.001), number of mitoses per mm^2 (<0.001), lymphovascular invasion (0.003468), sentinel lymph node status, number of positive sentinel nodes, mutational test, Overall Survival and Melanoma Specific Survival (<0.001). Survival curves shows the favorable trend in almost all MSs except in those manifesting recurrence of disease where the curves show a drastic decrease (Figures 1-2). Distant metastases account for 42% of recurrences involving the brain in most cases, followed by the lung and liver and extra-regional lymph node stations.
Conclusions: We can conclude by defining a group of patients with high-risk MS characterized by the nodular subtype, Breslow thickness greater than 0.75 mm, T1b, stage IB, presence of ulceration, number of mitoses per mm^2 close to 2, and presence of lymphovascular invasion. In these cases, it would be useful, considering that most recurrences occur at a distance, even after years, to prolong follow-up beyond 5 years.

Table 1. Demographic, clinicopathological characteristics, surgical and medical treatments differences in thin melanoma recurrence and non-recurrence groups.

Variable		Recurrence		p-value
		No (N = 255)	Yes (N = 53)	
Sex	Female	130 (50.98%)	30 (56.60%)	0.5522
	Male	125 (49.02%)	23 (43.40%)	
Age	Min / Max	22.6 / 81.4	20.2 / 79.0	0.8421
	Med [IQR]	47.2 [40.5;58.9]	51.4 [39.3;59.4]	
	Mean (std)	49.7 (13.0)	49.6 (13.0)	
Primary site	Acral	11 (4.31%)	3 (5.66%)	0.2765
	Head and neck	13 (5.10%)	6 (11.32%)	
	Lower limb	57 (22.35%)	15 (28.30%)	
	Trunk	145 (56.86%)	24 (45.28%)	
	Upper limb	29 (11.37%)	5 (9.43%)	
Histology subtype	Acral Lentiginous	5 (1.96%)	0 (0%)	**0.01566**
	Lentigo Maligna	6 (2.35%)	1 (1.89%)	
	Nevoid	1 (0.39%)	1 (1.89%)	
	Nodular	8 (3.14%)	7 (13.21%)	
	Spitzoid	1 (0.39%)	1 (1.89%)	
	Superficial Spreading	234 (91.76%)	43 (81.13%)	
Breslow thickness (mm)	Min / Max	0.1 / 1.0	0.2 / 1.0	**<0.001**
	Med [IQR]	0.4 [0.3;0.6]	0.8 [0.6;0.9]	
	Mean (std)	0.5 (0.2)	0.8 (0.2)	
Ultra Thin Melanoma (Breslow ≤ 0.5 mm)	No	100 (39.22%)	48 (90.57%)	**<0.001**
	Yes	155 (60.78%)	5 (9.43%)	
Breslow ≤ 0.75 mm	No	31 (12.16%)	31 (58.49%)	**<0.001**
	Yes	224 (87.84%)	22 (41.51%)	
Breslow ≤ 0.80 mm	No	20 (7.84%)	28 (52.83%)	**<0.001**
	Yes	235 (92.16%)	25 (47.17%)	
Clark level	II	80 (31.37%)	7 (13.21%)	**0.03477**
	III	119 (46.67%)	27 (50.94%)	
	IV	53 (20.78%)	16 (30.19%)	
	V	3 (1.18%)	1 (1.89%)	
	Unknown	0 (0%)	2 (3.77%)	
T Stage	T1	4 (1.57%)	0 (0%)	**<0.001**
	T1a	220 (86.27%)	20 (37.74%)	
	T1a/b	0 (0%)	1 (1.89%)	
	T1b	31 (12.16%)	32 (60.38%)	
N Stage	N0	253 (99.22%)	36 (67.92%)	**<0.001**
	N1a	0 (0%)	3 (5.66%)	
	N1b	0 (0%)	1 (1.89%)	
	N1c	0 (0%)	8 (15.09%)	
	N2a	2 (0.78%)	4 (7.55%)	
	N3a	0 (0%)	1 (1.89%)	
M Stage	M0	255 (100.00%)	53 (100.00%)	1.000
pTNM Stage	IA	221 (86.67%)	17 (32.08%)	**<0.001**
	IB	32 (12.55%)	19 (35.85%)	
	IIIA	2 (0.78%)	7 (13.21%)	
	IIIB	0 (0%)	9 (16.98%)	
	IIIC	0 (0%)	1 (1.89%)	
Ulceration	Absent	244 (95.69%)	44 (83.02%)	**<0.001**
	Present	7 (2.75%)	9 (16.98%)	
	Unknown	4 (1.57%)	0 (0%)	
Mitoses per mm²	Min / Max	0 / 5.0	0 / 9.0	**<0.001**
	Med [IQR]	0 [0;1.0]	2.0 [1.0;2.0]	
	Mean (std)	0.6 (0.9)	2.1 (2.0)	
Lymphovascular invasion	Absent	254 (99.61%)	49 (92.45%)	**0.003468**
	Present	1 (0.39%)	2 (3.77%)	
	Unknown	0 (0%)	2 (3.77%)	
Regression	Absent	141 (55.29%)	26 (49.06%)	0.1253
	Present	106 (41.57%)	22 (41.51%)	
	Unknown	8 (3.14%)	5 (9.43%)	
TIL	Absent	25 (9.80%)	4 (7.55%)	0.05707
	Brisk	82 (32.16%)	27 (50.94%)	
	Non-brisk	115 (45.10%)	15 (28.30%)	
	Unknown	33 (12.94%)	7 (13.21%)	
Wide excision	Conducted	255 (100.00%)	53 (100.00%)	1.000
Final margin	Involved	0 (0%)	1 (1.89%)	0.1786
	Uninvolved	247 (96.86%)	50 (94.34%)	
	Unknown	8 (3.14%)	2 (3.77%)	
SLNB status	Negative	91 (35.69%)	25 (47.17%)	**<0.001**
	Not Conducted	162 (63.53%)	20 (37.74%)	
	Positive	2 (0.78%)	8 (15.09%)	
N. Excised sentinel LNs	Min / Max	1.0 / 10.0	0 / 4.0	0.8418
	Med [IQR]	2.0 [1.0;2.0]	2.0 [1.0;2.8]	
	Mean (std)	2.2 (1.6)	1.9 (1.1)	
N. Positive sentinel LNs	0	91 (97.85%)	25 (75.76%)	**<0.001**
	1	2 (2.15%)	6 (18.18%)	
	2	0 (0%)	2 (6.06%)	
Mutation Test	Not Conducted	231 (90.59%)	32 (60.38%)	**<0.001**
	Conducted	0 (0%)	21 (39.62%)	
	Unknown	24 (9.41%)	0 (0%)	
Mutation	BRAF T599_V600insT	-	1 (4.76%)	-
	BRAF V600E	-	13 (61.90%)	
	NRAS p.Gln61Lys	-	1 (4.76%)	
	NRAS Q61K	-	2 (9.52%)	
	NRAS Q61R	-	2 (9.52%)	
	No	-	2 (9.52%)	
Overall Survival	No	20 (7.84%)	27 (50.94%)	**<0.001**
	Yes	235 (92.16%)	26 (49.06%)	
Melanoma Specific Survival	No	3 (1.18%)	26 (49.06%)	**<0.001**
	Yes	252 (98.82%)	27 (50.94%)	

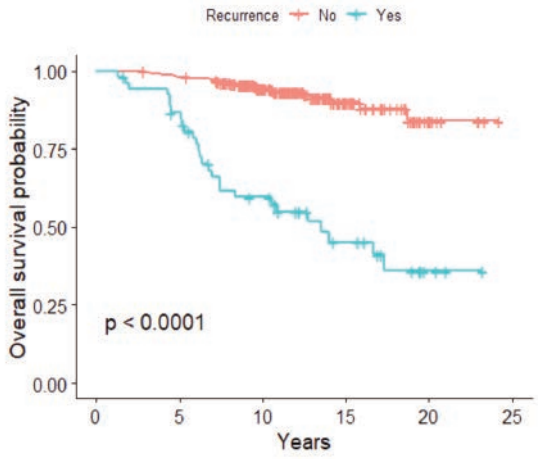


Figure 1. Overall survival probability for all thin melanomas with recurrence and without recurrence.

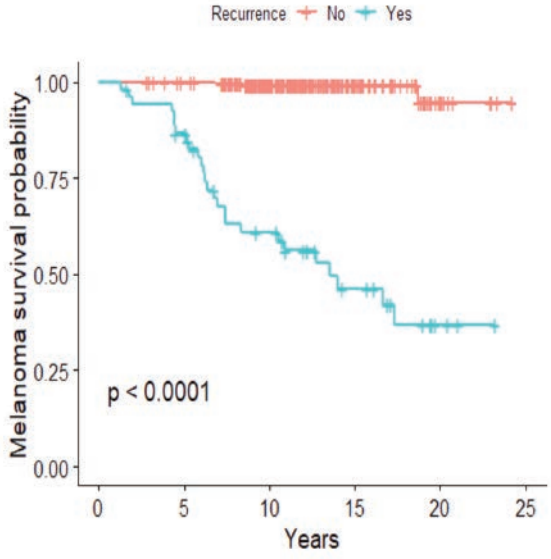


Figure 2. Melanoma survival probability for all thin melanomas with recurrence and without recurrence

THERAPY

COMBOIMMUNOTHERAPY IN MELANOMA PATIENTS WITH BRAIN METASTASES: A MULTICENTER INTERNATIONAL STUDY

Maria Chiara Sergi[1], Paul Lorigan[2], Maria Grazia Vitale[3], Diana Giannarelli[4], Ana Maria Arance[5], Eva Munoz Couselo[6], Bart Neyns[7], Marco Tucci[1], Michele Guida[8], Francesco Spagnolo[9], Ernesto Rossi[10], Paola Queirolo[11], Pietro Quaglino[12], Roberta Depenni[13], Barbara Merelli[14], Anna Maria Di Giacomo[15], Michele del Vecchio[16], Alice Indini[16], Georgina Long[17], Joanna Placzke[18], Piotr Rutkowski[18], Paolo A. Ascierto[3], Mario Mandalà[19], on behalf of the Italian Melanoma Intergroup (IMI)

[1]Medical Oncology Unit, Azienda Ospedaliero Universitaria Policlinico di Bari, Bari, Italy; [2]The University of Manchester, Oxford Rd, Manchester, UK; [3]Department of Melanoma, Cancer Immunotherapy and Development Therapeutics, I.N.T. IRCCS Fondazione "G. Pascale" Naples, Naples, Italy; [4]Regina Elena National Cancer Institute, IRCCS-Biostatistical Unit, Rome, Italy [5]Hospital Clínic Barcelona, 08036, Barcelona, Spain; [6]Vall d'Hebron University, Barcelona, Spain; [7]Department of Medical Oncology, UZ Brussel, Brussels, Belgium; [8]Rare Tumors and Melanoma Unit, IRCCS Istituto dei Tumori "Giovanni Paolo II," Bari, Italy; [9]IRCCS Ospedale Policlinico San Martino, Skin Cancer Unit, Genova, Italy; [10]Medical Oncology, Fondazione Policlinico Universitario, A. Gemelli IRCCS, Rome, Italy; [11]IEO European Institute of Oncology, IRCCS, Milan, Italy; [12]Department of Dermatology, University of Turin, Turin, Italy; [13]Università degli Studi di Modena e Reggio Emilia, Department of Oncology, Hematology, Modena, Emilia-Romagna, Italy; [14]Oncology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; [15]Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [16]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [17] Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, New South Wales, Australia; [18]Maria Sklodowska-Curie National Institute of Oncology, Warsaw, Poland; [19]Unit of Medical Oncology, University of Perugia, Perugia, Italy

Background: Ipilimumab plus Nivolumab (COMBO) is the standard treatment in asymptomatic patients with melanoma brain metastases (MBM) (1-3). We report an international study aiming to evaluate the outcome of patients (pts) with MBM treated with COMBO outside clinical trials.

Methods: Consecutive pts treated with COMBO have been included. Demographic characteristics, use of steroids, brain-related symptoms, treatment with radiotherapy or surgery, BRAF status, reponse rate, PFS and OS have been analysed.

Results: 376 pts were included, 247 were male, median age was 57.4, 174 patients were BRAF wild-type; 262 and 115 patients received COMBO as first or subsequent line of therapy, respectively. Overall, 161 asymptomatic pts didn't receive steroids (mOS 35 months), 74 had either symptoms or received steroids (mOS 19.5 months), whilst 139 were symptomatic and received steroids (mOS 12 months). At multivariate analysis, the following variables were associated with OS: ECOG (0 *vs.* ≥1) (1.97 [1.46-2.66]), extracerebral metastases (1.92 [1.09-3.40]), steroide use (1.59 [1.08-2.38]), neurological symptoms (1.59 [1.08-2.34]), SRS (0.63 [0.45-0.88]), surgery (0.63 [0.43-0.91]) (Figure 1). At a median follow-up of 38 months the mOS was not reached in pts treated with COMBO at first line without steroids (n=102). Pts receiving COMBO after BRAFi failure (n=107) had poor outcome regardless of steroid use (p=0.36). Dose of steroids (dexamethasone < *vs.* >4 mg) was not associated with OS. Median OS was 26.8, 17.1 and 5 months, in pts with PR, SD and PD, respectively, but not reached in those with CR. Toxicities were in line with previous studies.

Conclusions: Our results show a remarkable long-term survival in pts with MBM without steroids and symptoms and in those achieving a CR at first line. Pts receiving COMBO after BRAFi show a poor prognosis regardless steroids and symptoms. The role of SRS is worthy of further investigation

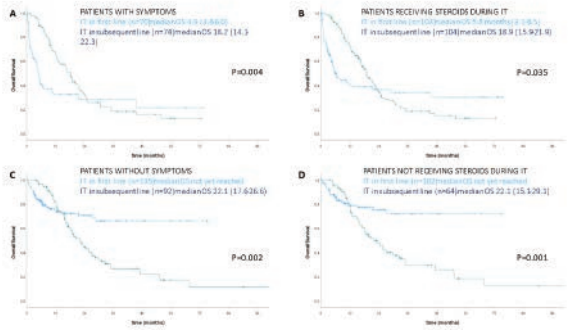


Figure 1. Overal Survival of asymptomatic and symptomatic patients with or without steroids.

References

1. Tawbi HA, Forsyth PA, Hodi FS, Algazi AP, Hamid O, Lao CD, Moschos SJ, Atkins MB, Lewis K, Postow MA, Thomas RP, Glaspy J, Jang S, Khushalani NI, Pavlick AC, Ernstoff MS, Reardon DA, Kudchadkar R, Tarhini A, Chung C, Ritchings C, Durani P, Askelson M, Puzanov I, Margolin KA. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. Lancet Oncol. 2021 Dec;22(12):1692-1704. doi: 10.1016/S1470-2045(21)00545-3.
2. Long GV, Atkinson V, Lo S, et al. Five-year overall survival from anti-PD1 brain collaboration (ABC study): randomised phase 2 study of nivolumab or nivolumab+ipilimumab in patients 23 with melanoma brain metastases. Presented at the 2021 American Society of Clinical Oncology (ASCO) Virtual Congress; June 8–12, 2021; Abstract 9508.
3. Di Giacomo AM, Chiarian-Sileni V, Del Vecchio M, et al. Primary analysis and 4-year follow-up of the phase III NIBIT-M2 trial in melanoma patients with brain metastases. Clin Cancer Res 2021. doi: 10.1158/1078-0432.CCR-21-1046.

DISCONTINUATION OF ANTI-PD1 IN ADVANCED MELANOMA: LONGER FOLLOW UP OF A REAL-WORLD STUDY FROM THE ITALIAN MELANOMA INTERGROUP

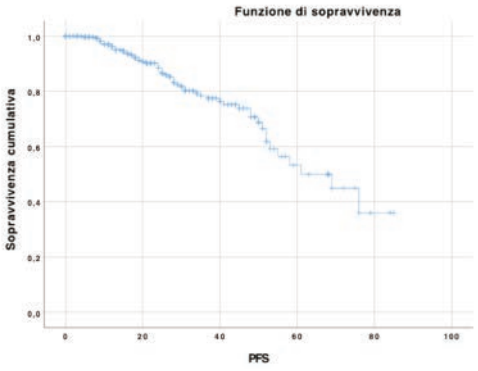
Marco Rubatto[1,2], Paolo Fava[1], Nicole Macagno[1], Ignazio Stanganelli[3], Simone Ribero[1], Jacopo Pigozzo[4], Anna Maria Di Giacomo[5], Laura Ridolfi[6], Maria Chiara Tronconi[7], Claudia Trojaniello[8], Perrone Fabiana[9], Mattia Garutti[10], Alice Indini[11], Ivana De Risi[12], Michele De Tursi[13], Barbara Merelli[14], Francesca Morgese[15], Marcella Occelli[2], Gian Carlo Antonini Cappellini[16], Stefano Poletto[17], Dahlia Fedele[18], Sonia Brugnara[19], Luigi Formisano[20], Raffele Conca[21], Giacomo Triggiano[22], Virginia Ferraresi[23], Leonardo Brunetti[24], Andrea Boutros[25], Alessandro Marco Minisini[26],Mario Mandalà[27,28], Martina Ubaldi[27,28], Nicole Cipressi[27,28], Sabino Strippoli[12], Mario Mandalà[27,28], Michele Guida[12], Pietro Quaglino[1]

[1]Department of Medical Sciences, Section of Dermatology, University of Turin, Torino; [2]Department of Medicine, Clinical Oncology and Translational Research, Azienda Ospedaliera Santa Croce and Carle University Teaching Hospital, Cuneo; [3]Skin Cancer Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Meldola; [4]Veneto Institute of Oncology-Istituto di Ricovero e Cura a Carattere Scientifico, Padua; [5]Center for Immuno-Oncology, University Hospital of Siena, Siena; [6]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola; [7]Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center, IRCCS; [8]Department of Melanoma and Cancer Immunotherapy, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples; [9]Medical Oncology Unit, University Hospital of Parma, Parma; [10]CRO Aviano National Cancer Institute IRCCS, Aviano; [11]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [12]Rare Tumors and Melanoma Unit, IRCCS Istituto Tumori Giovanni Paolo II, Bari; [13]Department of Medical, Oral and Biotechnological Sciences, Gabriele d'Annunzio University of Chieti and Pescara, Chieti; [14]Unit of Medical Oncology, Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo; [15]Clinica Oncologica, Università Politecnica delle Marche, AOU Ospedali Riuniti Di Ancona, Ancona; [16]UOC Oncologia Interpresidio, Ospedale Sandro Pertini, ASL Roma2; [17]Istituto di Candiolo, FPO-IRCCS, Candiolo; [18]Skin Cancer Unit, Department of Medical Oncology, Maggiore Hospital of Trieste, Trieste; [19]Department of Medical Oncology, Santa Chiara Hospital, Trento; [20]Department of Clinical Medicine and Surgery, Federico II University, Naples; [21]Division of Medical Oncology, Department of Onco-Hematology , IRCCS-CROB, Referral Cancer Center of Basilicata, Rionero, Vulture; [22]Department of Biomedical Sciences and Clinical Oncology, Section of Internal Medicine and Oncology, University of Bari 'Aldo Moro', Bari; [23]Department of Cancer Medicine, Istituto Regina Elena, Rome; [24]Policlinico Universitario Campus Bio-Medico di Roma; [25]U.O. Oncologia Medica 2, IRCCS Ospedale Policlinico San Martino, Genova; [26]Academic Hospital "Santa Maria della Misericordia", Udine; [27]University of Perugia, Perugia; [28]Ospedale Papa Giovanni XXIII, Bergamo, Italy

Background: Immunotherapy has improved the survival of patients with stage IV melanoma. In responding subjects, clinical benefits may be long-lasting and persist even after treatment discontinuation. The optimal treatment duration of immunotherapy with anti-PD1 antibodies in responding patients with metastatic melanoma has not yet been determined. However, a few data are available on clinical outcomes of patients that discontinued anti-PD1 immunotherapy in a real-life setting. The aim of this study was to evaluate the progression free survival (PFS) in patients with metastatic melanoma who interrupted anti PD-1 treatment in complete response (CR) or due to limiting toxicity.

Methods: We retrospectively reviewed patients with advanced/metastatic melanoma treated with anti-PD1 at 27 Italian medical centers belonging to the Italian Melanoma Intergroup (IMI). The study investigated the relapse risk in patients who stopped anti-PD1 therapy due to CR, treatment-related toxicity, or by their own choice after a long period of treatment. Clinical and biological factors associated with recurrence were studied.

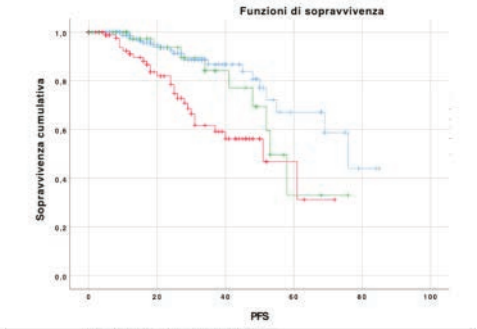
Results: The study population included 342 patients. The median age of patients was 69.5 years (standard deviation: 13; range 34-95). The median time on treatment was 33 months (standard deviation: 20,1; range 1-117). Among 342 patients, 193 (56.4%) interrupted anti-PD1 for CR, 101 patients (29.5%) for adverse events (54 patients in CR, 38 patients in partial response (PR), 9 patients in stable disease (SD)), and 48 patients (14%) by their own choice (24 patients in CR, 17 in PR and 7 patients in SD) (Figure 1).



		N° of Patients at Risk					
Months		0	20	40	60	80	100
N° of Events	56	342	178	70	16	2	0

Mean Event	Median Event
60,30	61

Figure 1. Kaplan–Meier probability curves for progression-free survival from discontinuation of anti-PD-1.



	N° of Events	N° of Patients at Risk					
Months		0	20	40	60	80	100
CR	20	193	101	38	11	2	0
Toxicity	27	101	50	19	2	0	0
Patient's choice	9	48	26	11	2	0	0

	Mean Event	Median Event	Log Rank pValue
CR	67,30	76	
Toxicity	46,83	51	<0.01
Patient's choice	55,66	53	

Figure 2. Kaplan–Meier probability curves for progression-free survival from discontinuation of anti-PD-1 according to the reason of drug interruption.

After a mean follow-up of 25 months (range 1-85), the progression free survival (PFS) after anti-PD1 discontinuation was 83.6%. Fifty-six patients (16.4%) developed disease progression after a median of 60 months (range 44-77): 20 patients (35.7%) after discontinuation in CR, 27 patients (48.2%), 27 after discontinuation for treatment-related toxicity (9 in CR, 11 in PR, 7 in SD) and 9 patients (16.0%) after discontinuation due to the patient's decision (2 in CR, 4 in PR, 3 in SD). Only 10.2% of patients who interrupted in CR (20/195), 27% of patients who interrupted for limiting toxicity (27/101) and 18.8% of patients who interrupted by their own choice (9/48) developed recurrence (Figure 2). A subpopulation called "super-responders", who achieved CR within 3 months after the start of immunotherapy treatment, was studied. Hematochemical parameters such as blood count, systemic immune-inflammatory index (SII), prognostic nutritional index (PNI) and high neutrophil-to-lymphocyte ratio (NLR) were evaluated. Super-responders had statistically lower PNI at the beginning of anti PD-1 treatment (standard error CR 9077, super-responders 4596, p=0.05) than patients who obtained CR and statistically higher PNI at the end of treatment (standard error CR 13577, super-responder 36669 p=0.049). Finally, super-responders have higher platelet counts than other patients with complete response. The blood count at the beginning of treatment with anti PD1 then at 3 and 6 months has shown a higher number of about 17 x10^9/l platelet units. (p=0.013)
Conclusions: This study confirms in a real life setting that immunotherapy can achieve long-lasting responses that can be maintained after anti-PD1 interruption. With more experience regarding patients responsive to anti PD-1 new hematochemical parameters may be supportive in identifying patients who may benefit from immunotherapy treatment.

INTERIM ANALYSIS OF NISSO: NON-INTERVENTIONAL, MULTI-NATIONAL, MULTI-CENTER POST AUTHORIZATION SAFETY STUDY (PASS) TO ASSESS THE LONG-TERM SAFETY AND TOLERABILITY OF ODOMZO® (SONIDEGIB) ADMINISTERED IN PATIENTS WITH LOCALLY ADVANCED BASAL CELL CARCINOMA

Luigi Scarpato[1], Gabriele Madonna[1], Mirella D'Andrea[1], Rossella Di Trolio[1], Claudio Marasca[2], Claudia Costa[3], Benedetta Alfano[1], Miriam Paone[1], Paolo A. Ascierto[1], Marco Palla[1]

[1]Complex Operating Unit, Medical Oncology, Oncology Immunotherapy and Innovative Therapies, Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale", Naples; [2]Departmental Simple Operational Unit of Dermatology, Multi-specialty Medical Department, Azienda Ospedaliera di Rilievo Nazionale "Antonio Cardarelli", Naples; [3]Dermatology Clinic, University of Naples "Federico II", Naples, Italy

Background: It is estimated that approximately 1 in 3 Caucasians will develop basal cell carcinoma (BCC) in their life. BCC is typically associated with considerable morbidity. There is still an unmet medical need for systemic treatments for locally advanced (la) BCC that has failed primary therapy or for untreated patients for whom primary treatment modalities are contraindicated due to the anatomic location and/or the nature of the tumour. The inhibition of the Hedgehog (Hh) signaling pathway has become a therapeutic area of research. The approval of sonidegib was based on a Phase II, multicenter, double-blind, and multiple cohort clinical trial conducted in patients with laBCC or mBCC. Sonidegib is associated with an acceptable and manageable safety profile.
Methods: Non-interventional, multinational, multi-center post-authorization safety study (PASS), in patients aged 18 years or older with laBCC who are not amendable to curative surgery or radiation therapy, treated with sonidegib 200 mg taken orally, once daily, according to the EU prescribing information as long as clinical benefit is observed or until unacceptable toxicity develops. This study will observe patients for 3 years after enrolment.
Results: 89 patients were included in this interim analysis. The patients 'status is described in Table 1. The mean duration time relating to "successful treatment" observed (also a PR or even CR) was 10 months. Patients with ongoing treatment showed a maximum duration of 28 months. 221 adverse events (AEs) were recorded, with 71% of patients experiencing at least one AE: the grade and the most common AEs are reported in Table 2.
Conclusions: In this PASS, called "NISSO", organized to characterize the long-term safety and tolerability profile of sonidegib under real-world conditions, the number and severity grading of the AEs registered is lower than could be expected based on registration studies. The relevance of these findings needs further studies to provide conclusive evidence.

Table 1. Patients' status.

Ongoing	**55**	**62%**
END of TREATMENT	**19**	**21%**
Patient/guardian decision	8	9%
Treatment success	7	8%
Physician decision	2	2%
Toxicity	1	1%
Disease progression	1	1%
END of STUDY	**15**	**17%**
Lost to follow-up	8	9%
Death	2	2%
Patient withdrawn consent	2	2%
Patient/guardian decision	2	2%
Physician decision	1	1%
Total	***89***	***100%***

Table 2. Grade and the most common AEs.

Grade 1	169	76.5%
Grade 2	46	20.8%
Grade 3	5	2.3%
Grade 4	1	0.5%
Total	*221*	*100%*
Muscle cramp	42	19%
Dysgeusia	38	17%
Fatigue	24	11%
Alopecia	15	7%
Weight loss	13	6%
Nausea	12	5%
CPK increased	8	4%
Other adverse events	69	31%
Total	*221*	*100%*

NEUROLOGICAL ADVERSE EVENTS OF ICI THERAPY IN SKIN CANCER PATIENTS: THE TEN-YEAR EXPERIENCE AT THE UNIVERSITY HOSPITAL OF SIENA

Vincenzo D'Alonzo[1], Sabina Bartalini[2], Serena Cutarella[1], Alfonso Cerase[3], Eleonora Carbonari[1], Valentina Croce[1], Maura Colucci[1], Monica Valente[4], Matteo Ravara[1], Federica Santangelo[1], Elena Simonetti[1], Tommaso Sani[1], Federica Ginanneschi[2], Nila Volpi[2], Michele Maio[1,4], Anna Maria Di Giacomo[1,4]

[1]University of Siena, Siena; [2]Neurology Unit, University Hospital of Siena, Siena; [3]Neuroradiology Unit, University Hospital of Siena, Siena; [4]Center for Immuno-Oncology, Medical Oncology and Immunotherapy, Department of Oncology, University Hospital of Siena, Siena, Italy

Background: The unique immune-activating mechanism of action of immune checkpoint inhibitors (ICI) can lead to auto-inflammatory/auto-reactive events, potentially involving any organ. Among these, different rare immune related adverse events (irAEs) have been also identified, and Neurological irAEs (NirAEs) account for about 2% of them. Due to their rarity and insidious onset, NirAEs may result in potentially life-threatening toxicity. In this scenario, we here report the decennial experience of the multidisciplinary team at the University Hospital of Siena (UHS), Italy, in the diagnosis and clinical management of NirAEs.
Methods: We collected a case series of consecutive patients (pts) with metastatic skin cancer treated with ICI who received a diagnosis of Nir-AEs. Onconeural and neuronal surface antibodies, or myositis-specific/associated and myasthenia gravis antibodies were tested in central, neural-peripheral, and in muscular-peripheral toxicities, respectively. In the event of laboratory and CNS imaging suspicious for NirAEs, lumbar puncture was utilized to exclude infectious and/or paraneoplastic causes.
Results: From Jan 2012 to Dec 2022, 604 cancer pts with melanoma (MM) and squamous cell carcinoma (SCC) were treated with ICI. Of those, 17 (2,8%) developed clinical, bio-humoral and/or radiologic signs suggestive for NirAEs. Pts [13 males, 4 females; median age 66 years (range 38-85)], were affected by MM (16) and SCC (1) and were treated with anti-PD-1 (11), anti-CTLA-4 (2) or their combination (4). Among the observed NirAEs, 1, 15 and 1 case were diagnosed as central, peripheral neurotoxicity or both, respectively. NirAEs were Grade (G) 1 (2), G2 (6), G3 (3), G4 (3), or G5 (3), with a median time to onset from the beginning of ICI therapy of 14 weeks (range: 1-52). NirAEs were treated with high doses steroids, immunoglobulins and/or plasma exchange. Treatment led to complete or partial recovery of NirAEs in 8 (57%) and 3 pts (21,5%), respectively. In 3 cases (21,5%) NirAEs progressively worsened, and pts died thereafter.
Conclusions: Though rare, NirAEs are potentially life-threatening toxicities. However, our long-term experience indicates that a prompt and multidisciplinary approach, avoided more severe complications, and led to a clinical recovery from NirAEs in a large proportion of pts.

EFFECTIVENESS OF DABRAFENIB PLUS TRAMETINIB IN MELANOMA STAGE III ADJUVANT SETTING: RESULTS FROM THE FIRST INTERIM ANALYSIS OF THE OBSERVATIONAL ITALIAN STUDY MADAM

Pietro Quaglino[1], Francesca Consoli[2], Marco Tucci[3], Jacopo Pigozzo[4], Ester Simeone[5], Francesco Spagnolo[6,7], Teresa Troiani[8], Francesca Morgese[9], Michele Del Vecchio[10], Barbara Melotti[11], Maria Chiara Tronconi[12], Maria Francesca Morelli[13], Federica Grosso[14], Barbara Merelli[15], Ilaria Gioia Marcon[16], Diletta Valsecchi[16]

[1]Dermatology Clinic, Department of Medical Sciences, University of Turin, Turin; [2]Medical Oncology, ASST Spedali Civili, Brescia; [3]Medical Oncology Unit, University of Bari 'Aldo Moro'-Policlinico Hospital of Bari, Bari; [4]Veneto Institute of Oncology IOV-IRCCS, Padua; [5]Unit of Melanoma, Cancer Immunotherapy and Innovative Therapy, National Cancer Institute "G. Pascale", Naples; [6]Department of Medical Oncology, Oncologia Medica 2, IRCCS Ospedale Policlinico San Martino, Genoa; [7]Department of Surgical Sciences and Integrated Diagnostics (DISC), Plastic Surgery, University of Genova, Genoa; [8]Medical Oncology Unit, Department of Precision Medicine, University of Campania Luigi Vanvitelli, Naples; [9]Oncology Clinic, Polytechnic University of Marche, United Hospitals of Ancona, Ancona; [10]S.S. Oncologia Medica Melanomi, S.C. Oncologia Medica 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [11]Divisione di Oncologia Medica, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna; [12]IRCCS Humanitas Research Hospital, Rozzano, Milan; [13]Oncologia e Oncologia Dermatologica, Istituto Dermopatico dell'Immacolata IDI-IRCCS, Rome; [14]Mesothelioma and Rare Cancers Unit, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria; [15]Unit of Medical Oncology, ASST Papa Giovanni XXIII, Bergamo; [16]Novartis Farma S.p.A, Milan, Italy

Background: Adjuvant therapy has shown improvement in the outcome of patients (pts) with resected stage III melanoma, reducing the risk of recurrence by elimination of residual disease after surgery. Considerable experience in the use of dabrafenib plus trametinib (D+T) for the treatment of pts with BRAF mutant disease was acquired from clinical trials, that demonstrated the efficacy in reducing relapse and in increasing overall survival. Limited data are available on the impact of the D+T in a real-world setting.
Methods: This multicenter retrospective-prospective, observational study enrolled pts treated with at least one dose of D+T within the melanoma adjuvant MAP run in Italy. Relapse free survival (RFS) and overall survival (OS), estimated using the Kaplan-Meier product-limit method, were the primary endpoints.

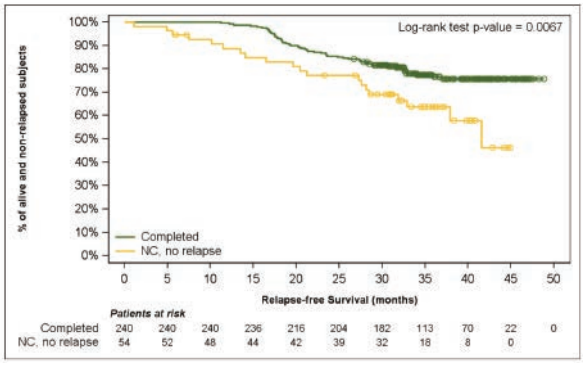


Figure 1. Relapse free survival, 2 subgroups: completed the adjuvant combination and not completed for other reasons than relapse. Dots represent censors. NC= Not Completed. Subjects at risk are patients who have no censored observation and do not experience the event *(i.e.*, the first tumour relapse or death) at the considered timepoint yet. Subgroups are defined comparing patients who completed the adjuvant combination *vs.* patients who did not complete the adjuvant combination due to other reasons than relapse. Only patients for which the category is defined are displayed. P-value is obtained from stratified two-sided log-rank test. Log-rank test is used instead of Wilcoxon test as specified in the SAP to give equal weight to all time points. The p-value refers to the comparison between the two subgroups.

Results: 310 pts were included in the interim analysis (IA) with data cut-off September 30, 2022, with a 35,4 months median follow up from start of D+T. AJCC 8 stage at time of start of D+T is mostly represented by stage IIIC (41.61%), followed by IIIB (24.5%), IIIA (24.19%) and IIID (4.84%). 240 pts completed 12 months of adjuvant treatment (C) and 70 not (NC), of whom 54 pts for other reasons than relapse (NC no relapse). Median (95% CI) RFS was not reached overall and in C subgroup. RFS in subgroup NC no relapse was 41.56 months (32.89, NE) (Figure 1). The estimated 2-year rate of RFS was 80.0% in overall population, 85.4% in the C group and 77.1% in the NC no relapse group. Median (95% CI) RFS was reached only in subgroup IIID, 16.82 months (4.93, 21.26) (Figure 2).

Conclusions: The results of this IA consolidate the efficacy results in term of RFS in an uncontrolled setting in all stage III subpopulations, including IIIA. The completion of the 12 months of treatment with D+T brings a further benefit.

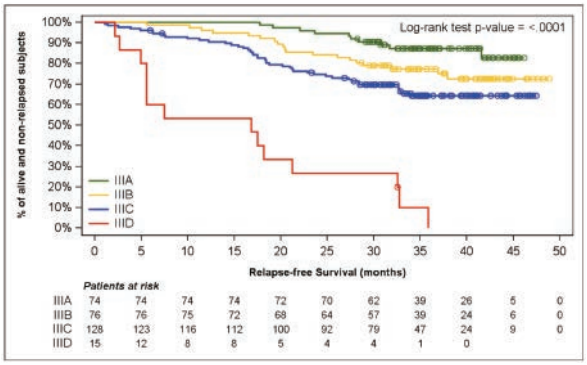


Figure 2. Relapse free survival by stage at time of start of combination therapy. Dots represent censors. Subjects at risk are patients who have no censored observation and do not experience the event (*i.e.,* the first tumour relapse or death) at the considered timepoint yet. P-value is obtained from stratified two-sided log-rank test. Log-rank test is used instead of Wilcoxon test as specified in the SAP to give equal weight to all time points.

TEBENTAFUSP IN METASTATIC UVEAL MELANOMA PATIENTS (MUM): VENETO INSTITUTE OF ONCOLOGY EXPERIENCE

Luisa Piccin[1], Valentina Salizzato[1], Jacopo Pigozzo[1], Francesca Di Sarra[2], Elisabetta Di Liso[1], Alice Menichetti[1], Francesca Porra[3], Valentina Guarneri[1,3], Vanna Chiarion Sileni[1]

[1]UOC Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padua; [2]Pharmacy Unit, Veneto Institute of Oncology IOV-IRCCS, Padua; [3]Department of Surgery, Oncology and Gastroenterology, University of Padua, Italy

Background: Real world data about Tebentafusp, the first agent improving 1-year survival in mUM are currently limited.
Methods: We retrospectively collected clinical data concerning mUM patients treated with Tebentafusp after HLA haplotyping, between May 2022 and July 2023 at our Institute.
Results: HLA-A*02:01 was found in 11/32 (34%) mUM cases tested. Ten (10) HLA-A*02:01+ patients (M:F 5:5, median age 67) were included in this analysis while one was referred to another center. At data cut-off (01 Aug 2023) 8 subjects were alive and 5 recorded progressive disease (PD). Median follow up was 5.4 months. Baseline characteristics were as follows: 4(40%) patients had exclusive liver mets and 6 (60%) patients also extrahepatic involvement, 1(10%) subject was pretreated with systemic treatment and 3(30%) with loco-regional therapy (2 hepatic transarterial chemoembolization and 1 decompressive laminectomy), 9 (90%) patients showed serum LDH above ULN and 5 (50%) above 2xULN. All subjects reported drug related adverse events: 8(80%) cytokine release syndrome (CRS), 4(40%) cutaneous toxicity and 6 (60%) transaminases increased. At data cut-off, 8 patients had performed at least one radiologic assessment: 1(10%) obtained partial response (PR), 2(20%) stable disease (SD) and 5(50%) PD according to RECIST 1.1 Median progression free survival (PFS) was 3.6 months; overall survival (OS) not yet reached. The partial responding patient has been receiving treatment for 14 months, experiencing G2 CRS, (early) skin toxicity and, recently, diarrhea. At baseline intra- and extrahepatic lesions were present, LDH was >2xULN and the largest metastasis diameter was 7 cm (liver).
Conclusions: In this rare and until now treatment orphan tumor we confirmed safety, response rate and PFS profile of Tebentafusp of published studies. A longer follow-up is necessary for OS evaluation. Although the limited number of patients, we often observed an early clinical benefit, that seemed to be independent from tumor burden and LDH levels.

OBESITY AND IMMUNE-CHECKPOINT INHIBITORS IN ADVANCED MELANOMA: A META-ANALYSIS OF SURVIVAL OUTCOMES FROM CLINICAL STUDIES

Gabriele Roccuzzo[1], Giovenale Moirano[2,3], Paolo Fava[1], Milena Maule[2], Simone Ribero[1], Pietro Quaglino[1]

[1]Section of Dermatology, Department of Medical Sciences, University of Turin, Turin; [2]Cancer Epidemiology Unit and CPO-Piemonte, Department of Medical Sciences, University of Torino, Turin; [3]Postgraduate School in Biostatistics, Department of Public Health and Pediatrics, University of Turin, Torino, Italy

Background: The role of obesity in melanoma incidence, progression, and response to immune-checkpoint-inhibitors (ICI) is still controversial. On the one hand, increased levels of lipids/adipokines can promote tumor proliferation and several genes associated with fatty acid metabolism have been found to be upregulated in melanomas. On the other hand, immunotherapy seems to be more effective in obese animal models, presumably due to an increase in CD8+ and subsequent decrease in PD-1+ T-cells in the tumor microenvironment.
Methods: The aim of this research has been to systematically review the scientific literature on studies evaluating the relationship between increased BMI and survival outcomes (*i.e.*, OS-PFS) in melanoma patients treated with ICI and to perform a meta-analysis on those sharing common characteristics. A sensitivity analysis using the "leave-one-out" method was performed. Heterogeneity among studies was measured through the I^2 statistic.
Results: After screening 1070 records, 18 articles assessing the role of BMI-related exposure in relation to survival outcomes in ICI-treated melanoma patients were included in our review. In the meta-analysis of the association between overweight (defined as BMI>25 or BMI 25–30), overall survival (OS), and progression free survival (PFS), 7 studies were included, yielding a summary HR of 0.87 (95% CI: 0.74–1.03) and 0.96 (95% CI: 0.86–1.08), respectively (Figures 1-2).

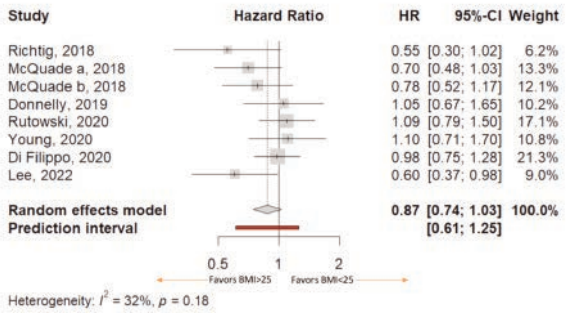


Figure 1. Forest plot of the association between BMI >25 or BMI 25-30 and overall survival in patients with advanced melanoma treated with ICI.

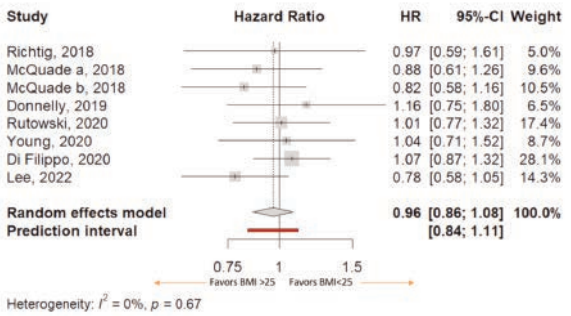


Figure 2. Forest plot of the association between BMI >25 or BMI 25-30 and progression-free survival in patients with advanced melanoma treated with ICI.

Conclusions: The potential protective role of BMI >25 at first suggested by McQuade *et al.* has not been replicated by the following studies, except for Lee *et al.*, with meta-analytic estimates close to the null (HR: 1.00) in terms of both OS and PFS. Our results show that, despite few suggestive findings, the use of BMI as a valuable predictor of melanoma patients' survival in terms of PFS and OS should not be currently recommended, due to the limited evidence available.

A RETROSPECTIVE OBSERVATIONAL MULTICENTER STUDY ON CUTANEOUS ADVERSE EVENTS INDUCED BY CEMIPLIMAB

Matelda Medri[1], Francesco Savoia[1,2], Ilaria Proietti[3], Concetta Potenza[3], Pietro Quaglino[4], Marco Rubatto[4], Gabriella Brancaccio[5], Stefania Napolitano[6], Gabriella Saurato[6], Giulio Tosti[7], Flavia Foca[8], Anna Miserocchi[8], Laura Mazzoni[1], Serena Magi[1], Michele De Tursi[9], Pietro Di Marino[9], Rosalba Buquicchio[10], Raffaele Filotico[10], Laura Ridolfi[11], Ignazio Stanganelli[1,12]

[1]Skin Cancer Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola; [2]Unit of Dermatology, Bufalini Hospital, Cesena (FC); [3]Dermatology Unit "Daniele Innocenzi", Department of Medical-Surgical Sciences and Bio-Technologies, Sapienza University of Rome, Fiorini Hospital, Polo Pontino, Terracina; [4]Department of Medical Sciences, Dermatologic Clinic, University of Turin Medical School; [5]Dermatology Unit, University of Campania Luigi Vanvitelli, Naples; [6]Oncology Unit, University of Campania Luigi Vanvitelli, Naple; [7]Unità di Dermatoncologia, IRCCS, IEO, Milan; [8]Unit of Biostatistics and Clinical Trials, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola; [9]Department of Innovative Technologies in Medicine and Dentistry, University G. D'Annunzio, Chieti-Pescara; [10]Dermato-Oncology Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Tumori "Giovanni Paolo II", Bari; [11]Oncology Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola; [12]Dermatology Unit, Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy

Background: Cemiplimab is an anti-PD1 drug approved for locally advanced and metastatic cutaneous squamous cell carcinoma.
Methods: We report here the results of a retrospective observational study collecting the data of 120 patients affected by locally advanced cutaneous squamous cell carcinomas treated with cemiplimab. All possible cutaneous adverse events were recorded according to the Common Terminology Criteria for Adverse Events version 5.0. Data on clinical outcome were also collected. Univariable and multivariate models were carried out for overall survival and progression-free survival.
Results: Of the 120 enrolled patients, 107 (90.8%) did not present any cutaneous adverse event during treatment, while 11 patients (9.2%) presented a cutaneous adverse event. The list of these adverse events, that occurred after a time that was variable from 1 to 24 months, included macular rash, alopecia areata, pruritus, autoimmune bullous disease, psoriasis, nummular eczema. All the cutaneous adverse events observed were grade 1 or 2, except 1 bullous pemphigoid, that was reported as grade 4. In most of these patients, the treatments of choice were oral antihistamines, topical or systemic corticosteroid therapy and the use of emollients, with resolution, improvement or stable disease (Table 1). The best objective response was calculated and disease control rate (complete response + partial response + stable disease) was observed in 78 patients (65.0%), of which 10 had at least one cutaneous adverse event. The median progression free survival was 21.9 months (95%CI: 11.7-Not estimable), while the 12-months overall survival was 69.0% (95%CI:58.4-77.4).
Conclusions: Cutaneous adverse events are uncommon in patients receiving cemiplimab and in our study pruritus was the most frequent one, followed by psoriasis and autoimmune bullous disease. Our study suggests that the presence of a cutaneous adverse event is not an independent predictor associated to overall survival and progression-free survival, at a multivariate level.

Table 1. Cutaneous AE reported in 11/120 patients treated with cemiplimab.

Patient	Type	Grade	Therapy for the cutaneous AE	Months from start	Outcome
1	Rash	1	Oral corticosteroid therapy	1	Resolution
2	Alopecia	1	None	1	Stable
3	Autoimmune bullous disease	2	Oral and topical corticosteroid therapy	10	Improvement
4	Autoimmune bullous disease	4	Intravenous and topical corticosteroid therapy	5	Resolution
5	Nummular eczema	1	Oral and topical corticosteroid therapy	4	Improvement
6	Itch	1	Oral antihistamines, emollients	5	Improvement
7	Itch	1	Oral antihistamines, emollients	3	Stable
8	Itch	1	Oral antihistamines, topical corticosteroid therapy, emollients	4	Stable
9	Itch	2	Oral antihistamines, topical corticosteroid therapy, emollients	4	Improvement
10	Itch and psoriasis	2	Oral antihistamines, topical corticosteroid therapy	1	Resolution
11	Psoriasis	2	Topical corticosteroid therapy	24	Stable

REAL-LIFE OUTCOMES OF ADJUVANT THERAPY IN MELANOMA: A SINGLE-CENTER EXPERIENCE

Gabriele Roccuzzo, Giulia Carpentieri, Eleonora Bongiovanni, Umberto Santaniello, Valentina Pala, Paolo Fava, Simone Ribero, Pietro Quaglino

Section of Dermatology, Department of Medical Sciences, University of Turin, Turin, Italy

Background: Adjuvant therapy, encompassing immune checkpoint inhibitors (ICI) and targeted therapies (TT), has demonstrated enhanced prognosis for stage III and IV-NED melanoma patients in numerous clinical trials. Nevertheless, the evaluation of real-world outcomes and the impact of prognostic factors on patient outcomes remains essential. This study aims to assess the real-world effectiveness of adjuvant therapy in terms of relapse-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS).

Methods: This retrospective analysis encompassed 163 disease-free stage III/IV-NED melanoma patients who received targeted therapy (dabrafenib/trametinib) or immunotherapy (nivolumab, pembrolizumab) for up to 12 months at the University of Turin. TT and pembrolizumab were administered for stage III, while nivolumab was suitable for stage III and IV-NED.
Results: Of the patients, 82 (50.3%) underwent TT, and 81 (49.7%) received ICI. At the 45-month assessment, the overall RFS was 59%, with figures of 57.6% for TT and 63.9% for nivolumab. Pembrolizumab exhibited a 38-month RFS of 27.1% (p=0,628). In terms of DMFS at 45 months, the overall rate stood at 76.2%, split between 75.6% for TT and 78.9% for nivolumab. Pembrolizumab demonstrated a 38-month DMFS of 50.2% (p=0,960). The overall OS at 45 months was 63.9%, with 68.3% for TT and 75.3% for nivolumab. Pembrolizumab displayed a 38-month OS of 46.7% (p=0,724) (Figure 1). Multivariate Cox models underscored the influence of ulceration (p=0,048), stage (p=0.018), and metastasis size (p=0,021) on recurrence probability. Ulceration also exerted significant influence on distant metastasis development (p=0,031) and mortality probability (p=0.021).
Conclusions: Both ICI and TT validate in real-life the enhancements seen within clinical trials, without notable disparities between the two classes. The study brings to light differences in recurrence patterns and locations influenced by various prognostic factors. These findings offer novel insights into adjuvant treatments, warranting confirmation through multicentric real-world investigations with a larger patient cohort.

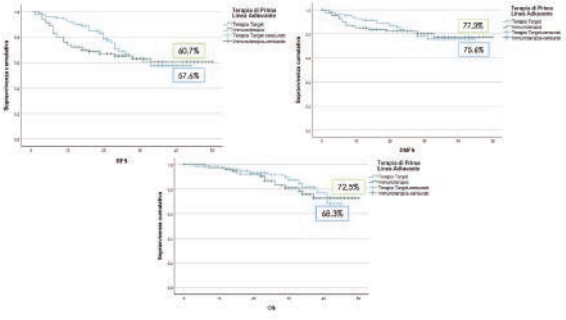


Figure 1. Recurrence-free survival (RFS), Distant-metastasis-free survival (DMFS), Overall Survival (OS) according to adjuvant therapy type (TT or ICI). Time expressed in months. Statistical analysis was conducted using SPSS.

REGULATION OF IMMUNE SYSTEM GENE EXPRESSION IN CSCC TREATED WITH IMMUNOTHERAPY: REAL LIFE DATA OF RESPONDERS/NON-RESPONDERS PATIENTS

Gabriella Suarato[1], Vincenzo De Falco[2], Rossella Napolitano[1], Eleonora Cioli[1], Alfonso Esposito[1], Vincenzo Terrano[1], Cristina Giugliano[1], Francesco Caraglia[1], Giuseppe Argenziano[3], Renato Franco[4], Andrea Ronchi[4], Federica Zito Marino[4], Valerio Nardone[5], Angelo Sangiovanni[5], Emma D'Ippolito[5], Roberta Grassi[5], Luigi Formisano[6], Francesco Iovino[7], Teresa Troiani[1]

[1]Medical Oncology, Department of Precision Medicine, Università degli Studi della Campania "Luigi Vanvitelli", Naples; [2]Department of Experimental Medicine, Section of Biotechnology, Molecular Medicine and Medical Histology, University of Campania "L. Vanvitelli", Naples; [3]Dermatology Unit, Department of Mental and Physical Health and Preventive Medicine, Università degli Studi della Campania "Luigi Vanvitelli", Naples; [4]Pathology Unit, Department of Mental and Physical Health and Preventive Medicine, Università degli Studi della Campania "Luigi Vanvitelli", Naples; [5]Department of Precision Medicine, University of Campania "L. Vanvitelli", Naples; [6]Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples; [7]Department of Translational Medical Science, School of Medicine, University of Campania Luigi Vanvitelli, Italy

Background: Cemiplimab significantly modified outcomes of patients with metastatic or locally advanced squamous cell carcinoma no longer amenable to radiotherapy or curative surgery. Recent real-life data confirms the good results demonstrated in the pivotal Empower cSCC1 clinical trial. However 1/3 of patients did not respond to treatment and progressed rapidly. This is a problem considering the limited therapeutic opportunities and unsatisfactory results.

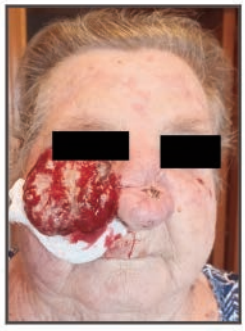


Figure 1. Patient female,73 years old, two cSCC sites, nose and cheek, bleeding lesion at baseline.

xs

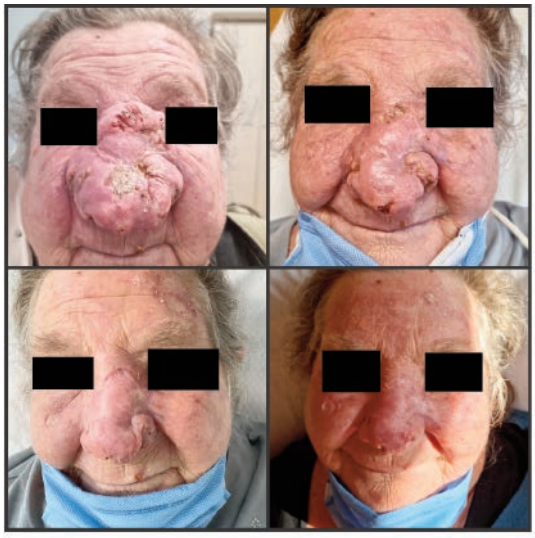


Figure 2. During the treatment, cheek lesion responded rapidly to Cemiplimab, nose lesion was in progression disease. We treated nose lesion with immunotherapy and after restart Cemiplimab obtaining ad amazing partial response.

Methods: Our retrospective analysis enrolled 81 patients >18yr with LAcSCC or McSCC, who received at least one cycle with Cemiplimab. 71 patients had already received at least one prior

loco-regional treatment, radiotherapy or surgery. 9 patients received concomitant radiotherapy (Figures 1-2) to improve response or manage local progression maintaining systemic treatment. To understand the possible link between treatment response and an alteration in the expression of genes regulating immune system, we selected 20 pre-treatment tissue samples, of which 9 responders, 11 non-responders and 3 healthy controls. The paraffin-coated tissues were processed for gene expression profiling using Nanostring Technologies, measuring 770 cancer and immune system-related genes to identify specific genetic signatures associated with treatment response or resistance.**Results:** At data cut off, 41 patients progressed or died, 33 are still on treatment. PFS at 24 months was 42%. ORR was 58% (Figures 1-2), of which 14 CR (17.3%). DOR has not been reached. Median time to response was 3 months. DCR was 77.8%. OS at 24 months was 61%. Analysis of 770 mRNA levels identified a different immune system activation status between responders and non responders/healty control and overexpression of chemokines CCL20 and CXCL8 in non-responder patients promoting invasion, migration, EMT, recruitment and migration of Tregs.
Conclusions: our Real Life results confirm the efficacy and safeness of Cemiplimab. The peculiar gene expression highlighted in non-responders patients could explain treatment resistance and constitute the basis for subsequent analysis to overcome primary resistance to immunotherapy.

ADJUVANT TREATMENT IN MELANOMA STAGE III PATIENTS: EFFECTS ON DISEASE RELAPSE AND PROGNOSIS. A REAL WORLD STUDIO/DATA

Jacopo Pigozzo[1], Luisa Piccin[1], Valentina Salizzato[1], Tommaso Berton[2], Paolo Del Fiore[3], Saveria Tropea[3], Marcodomenico Mazza[3], Francesco Cavallin[4], Simone Mocellin[3,5], Vanna Chiarion-Sileni[1]

[1]Melanoma Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua [2]Department of Medicine, University of Padua School of Medicine and Surgery, Padua; [3]Soft-Tissue, Peritoneum and Melanoma Surgical Oncology Unit, IOV- IRCCS, Padua; [4]Independent Statistician, Solagna; [5]Department of Surgery, Oncology and Gastroenterology (DISCOG), University of Padua, Padua, Italy

Background: Stage III melanoma management has changed in the last years. Lymphadenectomy (LA) is no more indicated after a positive sentinel node biopsy (SNB), and adjuvant (adj) therapy with anti-PD-1 agents or BRAF/MEK inhibitors has become part of the standard treatment of these patients in all guidelines. However, studies on the *real-world* effectiveness and toxicity are scarce. In this retrospective analysis we evaluated the outcomes of the adj-treatment in the standard clinical practice.
Methods: In this retrospective study, we analyzed resected stage III melanoma patients (resected stage IV patients have been excluded), who received adj-treatment with anti-PD-1 immunotherapy (IT) or target therapy (TT). The primary endpoints were 3-years overall survival (OS), relapse-free survival (RFS) and distant metastasis-free survival (DMFS); safety evaluation is ongoing.
Results: A total of 170 patients were analyzed: 96 treated with SNB, 54 with SNB + LA and 20 with complete LA due to macroscopic nodes presentation or recurrence. Median age 54 years (range: 23-82), 60/40% male/female, 95% had an ECOG PS = 0. At a median follow-up of 3 years there was no statistically significant difference between patients who did not undergo LA and those who underwent LA after SNB in term of OS, RFS and DMFS (89% *vs.* 83%, p=0.60; 57% *vs.* 54%, p=0.40; 82% *vs.* 86%, p=0.20; respectively) confirming that LA does not improve the prognosis of patients with loco-regional positive lymph-nodes. All patients received adj-treatment: 73 pts IT and 97 TT. While the difference between the use of IT *vs.* TT in was not statistically significant in subjects who did not undergo LA after SNB term of OS, RFS and DMFS, in the group that underwent LA, TT showed a 3y-OS of 77% *vs.* 93% of IT (p=0.03); at variance, no statistically significant association was documented for RFS and DMFS. An exploratory analysis of IT *vs.* TT outcomes, according to AJCC 8th ed. stage subgroups, highlighted 3y-RFS of 48% *vs.* 85% (p =0.01) in stage IIIA and 55% *vs.* 76% (p=0.10) in stage IIIB while it was 51% *vs.* 43% (p=0.90) in stage IIIC.
Conclusions: We confirmed that LA does not improve the prognosis of stage III patients treated with adjuvant therapy. Our preliminary data support that TT effectiveness in no lower than IT in this setting, above all in early stages where the cost-effectiveness, also due to long-term toxicities, should be carefully taken into account. However, a larger sample size and a longer follow-up are needed. Safety evaluation and discontinuation rate are under evaluation.

References

1. Morton, D. L., Thompson, J. F., Cochran, A. J., Mozzillo, N., Nieweg, O. E., Roses, D. F., Hoekstra, H. J., Karakousis, C. P., Puleo, C. A., Coventry, B. J., Kashani-Sabet, M., Smithers, B. M., Paul, E., Kraybill, W. G., McKinnon, J. G., Wang, H. J., Elashoff, R., Faries, M. B., & MSLT Group (2014). Final trial report of sentinel-node biopsy versus nodal observation in melanoma. The New England journal of medicine, 370(7), 599–609.
2. Leiter, U., Stadler, R., Mauch, C., Hohenberger, W., Brockmeyer, N., Berking, C., Sunderkötter, C., Kaatz, M., Schulte, K. W., Lehmann, P., Vogt, T., Ulrich, J., Herbst, R., Gehring, W., Simon, J. C., Keim, U., Martus, P., Garbe, C., & German Dermatologic Cooperative Oncology Group (DeCOG) (2016). Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. The Lancet. Oncology, 17(6), 757–767.
3. Faries, M. B., Thompson, J. F., Cochran, A. J., Andtbacka, R. H., Mozzillo, N., Zager, J. S., Jahkola, T., Bowles, T. L., Testori, A., Beitsch, P. D., Hoekstra, H. J., Moncrieff, M., Ingvar, C., Wouters, M. W. J. M., Sabel, M. S., Levine, E. A., Agnese, D., Henderson, M., Dummer, R., Rossi, C. R., … Elashoff, R. M. (2017). Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. The New England journal of medicine, 376(23), 2211–2222.
4. Eggermont, A. M. M., Blank, C. U., Mandala, M., Long, G. V., Atkinson, V., Dalle, S., Haydon, A., Lichinitser, M., Khattak, A., Carlino, M. S., Sandhu, S., Larkin, J., Puig, S., Ascierto, P. A., Rutkowski, P., Schadendorf, D., Koornstra, R., Hernandez-Aya, L., Maio, M., van den Eertwegh, A. J. M., … Robert, C. (2018). Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. The New England journal of medicine, 378(19), 1789–1801.
5. Eggermont, A. M. M., Blank, C. U., Mandalà, M., Long, G. V., Atkinson, V. G., Dalle, S., Haydon, A. M., Meshcheryakov, A., Khattak, A., Carlino, M. S., Sandhu, S., Larkin, J., Puig, S., Ascierto, P. A., Rutkowski, P., Schadendorf, D., Koornstra, R., Hernandez-Aya, L., Di Giacomo, A. M., van den Eertwegh, A. J. M., … EORTC Melanoma Group (2021). Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free

survival results from a double-blind, randomised, controlled, phase 3 trial. The Lancet. Oncology, 22(5), 643–654.
6. Weber, J., Mandala, M., Del Vecchio, M., Gogas, H. J., Arance, A. M., Cowey, C. L., Dalle, S., Schenker, M., Chiarion-Sileni, V., Marquez-Rodas, I., Grob, J. J., Butler, M. O., Middleton, M. R., Maio, M., Atkinson, V., Queirolo, P., Gonzalez, R., Kudchadkar, R. R., Smylie, M., Meyer, N., … CheckMate 238 Collaborators (2017). Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. The New England journal of medicine, 377(19), 1824–1835.
7. Ascierto, P. A., Del Vecchio, M., Mandalá, M., Gogas, H., Arance, A. M., Dalle, S., Cowey, C. L., Schenker, M., Grob, J. J., Chiarion-Sileni, V., Márquez-Rodas, I., Butler, M. O., Maio, M., Middleton, M. R., de la Cruz-Merino, L., Arenberger, P., Atkinson, V., Hill, A., Fecher, L. A., Millward, M., … Weber, J. (2020). Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. The Lancet. Oncology, 21(11), 1465–1477.
8. Long, G. V., Hauschild, A., Santinami, M., Atkinson, V., Mandalà, M., Chiarion-Sileni, V., Larkin, J., Nyakas, M., Dutriaux, C., Haydon, A., Robert, C., Mortier, L., Schachter, J., Schadendorf, D., Lesimple, T., Plummer, R., Ji, R., Zhang, P., Mookerjee, B., Legos, J., … Kirkwood, J. M. (2017). Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. The New England journal of medicine, 377(19), 1813–1823.
9. Dummer, R., Hauschild, A., Santinami, M., Atkinson, V., Mandalà, M., Kirkwood, J. M., Chiarion Sileni, V., Larkin, J., Nyakas, M., Dutriaux, C., Haydon, A., Robert, C., Mortier, L., Schachter, J., Lesimple, T., Plummer, R., Dasgupta, K., Gasal, E., Tan, M., Long, G. V., … Schadendorf, D. (2020). Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma. The New England journal of medicine, 383(12), 1139–1148.
10. Broman, K. K., Bettampadi, D., Pérez-Morales, J., Sun, J., Kirichenko, D., Carr, M. J., Eroglu, Z., Tarhini, A. A., Khushalani, N., Schabath, M. B., Sarnaik, A., Sondak, V. K., & Zager, J. S. (2021). Surveillance of Sentinel Node-Positive Melanoma Patients Who Receive Adjuvant Therapy Without Undergoing Completion Lymph Node Dissection. Annals of surgical oncology, 28(12), 6978–6985.
11. Mitra, D., Ologun, G., Keung, E. Z., Goepfert, R. P., Amaria, R. N., Ross, M. I., Gershenwald, J. E., Lucci, A., Fisher, S. B., Davies, M. A., Lee, J. E., Bishop, A. J., Farooqi, A. S., Wargo, J., & Guadagnolo, B. A. (2021). Nodal Recurrence is a Primary Driver of Early Relapse for Patients with Sentinel Lymph Node-Positive Melanoma in the Modern Therapeutic Era. Annals of surgical oncology, 28(7), 3480–3489.
12. R Core Team (2023). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.
13. Eggermont, A. M. M., Blank, C. U., Mandala, M., Long, G. V., Atkinson, V. G., Dalle, S., Haydon, A. M., Meshcheryakov, A., Khattak, A., Carlino, M. S., Sandhu, S., Larkin, J., Puig, S., Ascierto, P. A., Rutkowski, P., Schadendorf, D., Koornstra, R., Hernandez-Aya, L., Di Giacomo, A. M., van den Eertwegh, A. J. M., … Robert, C. (2020). Longer Follow-Up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results From the EORTC 1325-MG/KEYNOTE-054 Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 38(33), 3925–3936.
14. Grover, P., Li, I., Kuijpers, A., Kreidieh, F. Y., Williamson, A., Amaral, T. M. S., Dimitriou, F., Placzke, J., Olino, K., Vitale, M. G., Saiag, P., Gutzmer, R., Allayous, C., Olofsson Bagge, R., Asher, N., Meniawy, T., Lawless, A., Warburton, L., Menzies, A. M., & Long, G. V. (2023, June 1). Efficacy of adjuvant therapy in patients (pts) with AJCC v8 stage IIIA cutaneous melanoma. Journal of Clinical Oncology, 41(16_suppl), 9518–9518.

AUTOIMMUNE BULLOUS DERMATOSES IN CANCER PATIENTS TREATED BY IMMUNOTHERAPY: A LITERATURE REVIEW AND ITALIAN MULTICENTRIC EXPERIENCE

Martina Merli[1], Martina Accorinti[1], Maurizio Romagnuolo[2,3], Angelo Marzano[2,3], Giovanni Di Zenzo[4], Francesco Moro[4], Emiliano Antiga[5], Roberto Maglie[5], Emanuele Cozzani[6,7], Aurora Parodi[6,7], Giulia Gasparini[6,7], Pietro Sollena[8], Clara De Simone[8,9], Marzia Caproni[10], Luigi Pisano[11], Davide Fattore[12], Riccardo Balestri[13], Paolo Sena[14], Pamela Vezzoli[14], Miriam Teoli[15], Marco Ardigò[15], Camilla Vassallo[16], Andrea Michelerio[17,18], Rosanna Rita Satta[19], Emi Dika[20,21], Barbara Melotti[22], Simone Ribero[1], Pietro Quaglino[1]

[1]Dermatology Clinic, Department of Medical Sciences, University of Turin, Turin; [2]Dermatology Unit, Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan; [3]Department of Pathophysiology and Transplantation, Università Degli Studi di Milano, Milan; [4]Laboratory of Molecular and Cell Biology, Istituto Dermopatico dell'Immacolata (IDI)IRCCS, Rome; [5]Section of Dermatology, Department of Health Sciences, University of Florence, Florence; [6]Section of Dermatology, Department of Health Sciences (DISSAL), University of Genoa, Genoa; [7]Dermatology Unit, IRCCS Ospedale Policlinico San Martino, Genoa; [8]Dermatology Unit, Department of Surgical and Medical Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome; [9]Dermatology Unit, University Department of Medicine and Translational Surgery, Sacred Heart Catholic University, Rome; [10]Immunopathology and Rare Skin Diseases Unit, Section of Dermatology, Department of Health Sciences, Azienda Unità Sanitaria Locale Toscana Centro, University of Florence, Florence; [11]Section of Dermatology, Department of Health Sciences, Azienda Unità Sanitaria Locale Toscana Centro, University of Florence, Florence; [12]Section of Dermatology, Department of Clinical Medicine and Surgery, Università Degli Studi di Napoli Federico II, Naples; [13]Division of Dermatology, Outpatient Consultation for Rare Diseases, APSS, Trento; [14]Dermatology Unit ASST-Papa Giovanni XXIII, Bergamo; [15]Porphyria and Rare Diseases, San Gallicano Dermatological Institute IRCCS, Rome; [16]Dermatology Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia; [17]Dermatology Unit, Ospedale Cardinal Massaia, Asti; [18]Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia; [19]Department of Medical, Surgical, and Experimental Sciences, University of Sassari, Sassari; [20]Melanoma Center, Dermatology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna; [21]Unit of Dermatology, Department of Medical and Surgical Sciences, DIMEC, Alma Mater Studiorum, University of Bologna, Bologna; [22]Oncology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Background: Immune checkpoint inhibitors (ICIs) have introduced a significant innovation in the treatment of various malignancies, including melanoma, as their mechanism of action enhances the

immune system's response against cancer. However, this immune activation is not specific and can impact numerous organ systems, resulting in immune-related adverse events (irAEs). Among cutaneous irAEs, autoimmune blistering diseases have also been documented, with the bullous pemphigoid (BP)-like eruption being the predominant phenotype. Additionally, cases of lichen planus pemphigoides (LPP), pemphigus vulgaris (PV), and mucous membrane pemphigoid (MMP) have been reported anecdotally.

Methods: We conducted a case series based on a national multicentre, retrospective, observational cohort including all patients treated with ICIs and who developed an immunobullous irAE during treatment. Furthermore, we conducted an exhaustive review of the English-language medical literature concerning immunobullous irAEs.

Table 1. Characteristics of the 45 patients collected in our national multicenter cohort. All patients developed ICI-induced BP. The information reported are about patients' demographics, primary cancer, immunotherapy, and ICI-induced BP.

Characteristics	All patients (N=45)	Characteristics	All patients (N=45)
Demographics		**ICI-BP diagnosis**	
Sex, No. (%) male / female	41 (91) / 4 (9)	**Histopathologic examination**	**No. (%)**
Age (years), median (range)	74 (46 - 90)	Yes	28 (62)
Tumour type	**No. (%)**	No	17 (38)
NSCLC	18 (40)	**DIF**	**No. (%)**
Melanoma	12 (27)	Yes	31 (69)
Colorectal adenocarcinoma	5 (11)	No	14 (31)
Renal clear cell carcinoma	5 (11)	**IIF**	**No. (%)**
HNSCC	4 (9)	Yes	26 (58)
Urothelial carcinoma	1 (2)	No	19 (42)
Tumour stage	**No. (%)**	**BP180 autoantibodies**	**No. (%)**
Stage IV	33 (73)	Positive	30 (66)
Stage III	9 (20)	Negative	12 (27)
Other or NR	3 (7)	Not performed	3 (7)
Immunotherapy	**No. (%)**	**BP230 autoantibodies**	**No. (%)**
Nivolumab	28 (62)	Positive	15 (33)
Pembrolizumab	11 (24)	Negative	26 (58)
Nivolumab + ipilimumab	2 (5)	Not performed	4 (9)
Cemiplimab	2 (5)	**ICI management**	No. (%)
Spartalizumab	1 (2)	ICI temporarily held	16 (36)
Atezolizumab	1 (2)	BP flare after rechallenged with the same ICI	7 (16)
ICI-BP features	**Median (range)**	ICI permanently discontinued	17 (38)
Time to symptoms onset after ICI initiation (weeks)	35 (4 - 260)	**ICI-BP management**	
Time to BP diagnosis after ICI initiation (weeks)	48 (5 - 286)	**First line therapy**	**No. (%)**
First manifestations	**No. (%)**	Topical costicosteroid	4 (9)
Pruritus without other manifestations	19 (42)	Topical corticosteroid + systemic corticosteroid	41 (91)
Eczematous eruption	11 (24)	**Second line therapy**	**No. (%)**
Bullous lesions	9 (20)	Doxycycline	5 (11)
Urticarial eruption	7 (16)	Dapsone	3 (7)
Mucositis	3 (7)	**Third line therapy**	**No. (%)**
Papular lesions	1 (2)	Dupilumab	1 (2)
Mucosal membrane involvement	**No. (%)**	**ICI-BP response**	**No. (%)**
No	37 (82)	Partial to complete resolution	38 (84)
Yes	8 (18)	Refractory symptoms	7 (16)
CTCAE grade	**No. (%)**	**Tumour response**	**No. (%)**
1	12 (27)	CR or PR	9 (20)
2	15 (33)	SD	16 (36)
3	17 (38)	PD	11 (24)
4	1 (2)	NR	9 (20)

ICI, immune checkpoint inhibitor; BP, bullous pemphigoid; NSCLC, non-small-cell lung cancer; HNSCC, head and neck squamous cell carcinoma; NR, not reported; CTCAE, Common Terminology Criteria for Adverse Events; DIF, direct immunofluorescence; IIF, indirect immunofluorescence; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease.

Results: The multicentre cohort included 45 patients who developed ICI-induced BP during treatment (Table 1). Nivolumab was identified as the causative drug in 62% of cases. Among these patients, immunotherapy was administered for the treatment of melanoma in 27% of cases. The median time from ICI initiation to the onset of cutaneous symptoms was 35 weeks, and BP affected more than 30% of the body surface area in 40% of patients. Immunotherapy was permanently discontinued for 17 patients (38%). Additionally, our literature review has provided data about 373 patients affected by ICI-induced BP, 10 patients affected by ICI-induced MMP, and 23 patients affected by ICI-induced LPP.

Conclusions: Bullous autoimmune dermatoses have gained increasing attention as cirAEs. Various theories have been proposed to elucidate their underlying pathogenesis without a complete success. Their clinical presentation can vary, potentially leading to diagnostic delays. For this reason, immunosuppressive therapy and/or discontinuation of immunotherapy are often necessary for their management. Therefore, prompt recognition is essential to establish appropriate treatment, thereby avoiding a negative impact on cancer outcomes.

UNVEILING THE IMMUNOLOGICAL LANDSCAPE OF RESECTED STAGE III/IV MELANOMA PATIENTS TREATED WITH PERSONALIZED DENDRITIC CELLS VACCINATION IN A PHASE II RANDOMIZED TRIAL

Laura Ridolfi[1], Francesco De Rosa[1], Massimo Guidoboni[1], Claudia Piccinini[1], Anna Maria Granato[1], Elena Pancisi[1], Emanuela Scarpi[2], Laura Renzi[3], Silvia Carloni[1], Marcella Tazzari[1], Valentina Ancarani[1], Francesco Limarzi[4], Massimiliano Petrini[1], Jenny Bulgarelli[1]

[1]Immunotherapy Cell Therapy and Biobank (ITCB), IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola (FC); [2]Unit of Biostatistics and Clinical Trials, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola (FC); [3]Medical Genetics Unit, AUSL Romagna, Cesena; [4]Pathology Unit, Morgagni-Pierantoni Hospital, AUSL Romagna, Forlì, Italy

Background: In the last 20 years we have treated more than 80 advanced melanoma patients (pts) with a tumor lysate-loaded autologous DC vaccine, observing a clinical benefit of 54.1%. Additionally, the analysis of post-vaccine biopsies highlighted the vaccine ability to induce intratumoral CD8+ up-regulation.

Methods: This was a randomized phase II trial of adjuvant autologous DC vaccination in resected stage III/IV melanoma patients (pts). Primary endpoint was relapse free survival (RFS) and secondary endpoints were both clinical (OS) and biological.

Results: After the introduction in the clinical practice of adjuvant therapies for melanoma, the study was closed as being no longer ethical. Eighteen pts (10 DC-ARM, 8 FU-ARM) have been enrolled between 2015 and 2019 with a median age of 60 years (33-79). DC-Arm pts had better RFS and favorable trends in DC-Arm were observed for females, pts younger than 60 years and pts with wild-type BRAF status (Table 1). No grade 3-4 toxicities were observed. Not relapsed (NR) DC-Arm pts (n=3) presented a maximal heterozygosity at HLA class I, carried an HLA-A*02 profile and two of them had the HLA-B*35 supertype. An increased number of specific anti-survivin and anti-NY-ESO1 spot forming cells was observed along treatment. In NR pts we observed an increase of INFα and IL-8, while in relapsed (R) pts we found increment of IL-4 and IL-9. Conversely, any modulation of circulating cytokines was observed in FU-ARM. Finally we observed an increase of the percentage of total lymphocytes after DC vaccination, increase of the Lymphocyte to Monocyte Ratio, and a decrease of the Neutrophil to Lymphocyte Ratio.

Conclusions: Overall our data show the safety profile of DC vaccination and highlight peculiar traits of immunomodulation, especially in NR pts, that will be further explored to guide the design of new immunotherapy combinations.

Table 1. Univariate analysis of RFS and OS according to gender, BRAF and arm.

	N. events / N. patients	Median RFS (months) (95% CI)	p-value	N. events / N. patients	Median OS (months) (95% CI)	p-value
All cases	13/18	5.3 (3.2-22.5)	-	4/18	40.8 (20.7-nr)	-
DC-Arm	7/10	**6.6 (2.3-nr)**	0.928	3/10	40.8 (9.4-nr)	0.871
FU-Arm	6/8	5.2 (2.5-nr)		1/8	nr	
Age (years)						
<60	5/8	**14.2 (2.6-nr)**	0.253	0/8	nr	0.151
≥60	8/10	4.6 (2.3-9.1)		3/10	40.8 (20.7-nr)	
Gender						
Male	6/8	3.2 (2.3.nr)	0.148	2/8	22.1 (20.7-nr)	0.017
Female	7/10	**8.9 (2.6-nr)**		1/10	nr	
BRAF status						
Wild type	4/6	**15.5 (3.2-nr)**	0.343	2/6	nr	0.857
Mutated	9/12	4.2 (2.5-nr)		1/12	nr	
Male						
DC-Arm	3/4	3.3 (2.3-nr)	0.927	1/4	22.1 (-)	0.479
FU-Arm	3/4	3.2 (2.5-nr)		1/4	nr	
Female						
DC-Arm	4/6	**15.5 (2.6-nr)**	0.927	1/6	nr	ne
FU-Arm	3/4	7.5 (4.5-nr)		0/4	nr	
Age <60						
DC-Arm	3/5	**22.5 (2.6-nr)**	0.973	0/5	nr	ne
FU-Arm	2/3	5.9 (3.2-nr)		0/3	nr	
Age ≥60						
DC-Arm	4/5	4.7 (2.3-nr)	0.890	2/5	40.8 (22.1-nr)	0.221
FU-Arm	4/5	4.5 (2.5-nr)		1/5	nr	
BRAF WT						
DC-Arm	2/3	**22.5 (8.6-nr)**	0.302	1/3	nr	0.221
FU-Arm	2/3	5.9 (3.2-nr)		1/3	nr	
BRAF mut						
DC-Arm	5/7	3.8 (2.3-nr)	0.976	1/7	nr	0.479
FU-Arm	4/5	4.5 (2.5-nr)		0/5	nr	

A MULTIDISCIPLINARY CHARACTERIZATION OF IMMUNE-CHECKPOINT INHIBITOR-RELATED PNEUMONITIS TO IMPROVE ITS CLINICAL MANAGEMENT

Maura Colucci[1], Monica Valente[2], Virginia Vegni[3], Valentina Croce[1], Cristiana Bellan[4], Giulia Rossi[2], Giulia Gibilisco[1], Francesco Frongia[1], Riccardo Danielli[2], Raffaella Guazzo[4], Claudia Ghiribelli[5], Tommaso Sani[1], Elena Simonetti[1], Michele Maio[1,2], Anna Maria Di Giacomo[1,2]

[1]University of Siena, Siena; [2]Center for Immuno-Oncology, Medical Oncology and Immunotherapy, Department of Oncology, University Hospital of Siena, Siena; [3]Rugani Hospital, Siena; [4]Department of Medical Biotechnology, University Hospital of Siena; [5]Interventional and Diagnostic Bronchoscopy, Cardio-Thoracic-Vascular Department, University Hospital of Siena, Siena, Italy

Background: Treatment with immune checkpoint inhibitors (ICI) can associate with a wide spectrum of immune-related adverse events (irAEs). Among irAEs is immune-mediated pneumonitis (im-PN), a rare but potentially life-threatening side effect; thus, prompt diagnosis and effective management of im-PN is essential to avoid severe complications.
Methods: We collected a case series of skin cancer patients (pts) treated with ICI at the Center for Immuno-Oncology of the University Hospital of Siena, Italy, diagnosed with im-PN. Clinical and radiologic data were collected, as well as bronchoalveolar lavage (BAL) samples; im-PN were graded using CTCAE v. 5.0.
Results: From January 2014 to February 2023, 564 pts with melanoma (n=522) and SCC (n=42) were treated with ICI (349 anti-PD-1 monotherapy, 215 combination). Among treated pts, 18 (5%) developed an im-PN, and 10 (55%) were symptomatic. Im-PN was classified as grade (G) 1 in 8 pts and as G2 in 10 pts. Steroid treatment was carried out in 16 pts, leading to complete resolution of im-PN in all pts [median 8.9 weeks (wks), range 3-24 wks]. Eight pts resumed ICI therapy once fully-recovered from im-PN, and 2 experienced im-PN recurrence that completely resolved with steroids treatment (median 18 wks, range 3-51 wks). According to the Fleischner Society classification of drug-related pneumonitis, we identified 3 main radiologic patterns: organizational pneumonia-like in 10 (55%) pts, pulmonary eosinophilia in 7 (39%) pts, and hypersensitivity pneumonitis in 1 (6%) patient. BAL sample analysis performed in 5 (29%) symptomatic pts showed an inflammatory lymphocytic infiltrate, predominantly consisting in a foam cell-like macrophage infiltrate in 3 cases. Notably, Transmission Electron Microscopy evaluation performed in 2 out of these 3 pts, revealed the presence of multilamellar bodies, lysososomes, and lipid vacuoles into the alveolar macrophages, suggestive for a drug-mediated toxicity.
Conclusions: Im-PN associated with ICI therapy was found to be a rare and challenging side effect, with variable onset and heterogenous clinical presentation. A multidisciplinary characterization of im-PN may help optimizing its clinical management to resume ICI therapy.

EVALUATION OF PREDICTIVE FACTORS IN PATIENTS WITH ADVANCED MELANOMA TREATED WITH IMMUNE CHECKPOINT INHIBITORS IN A REAL-WORLD POPULATION

Stefano Poletto[1], Luca Paruzzo[2], Alessandro Nepote[1], Daniela Caravelli[3], Pio Manlio Mirko Frascione[3], Dario Sangiolo[2], Fabrizio Carnevale Schianca[3]

[1]Department of Oncology, University of Turin, A.O.U. S. Luigi Gonzaga, Orbassano (TO); [2]Department of Oncology, University of Turin; [3]Medical Oncology Division, Candiolo Cancer Institute, FPO-IRCCs, Candiolo (TO), Italy

Background: Immune checkpoint inhibitors (ICIs) significantly improved outcomes of metastatic melanoma, however less than 50% of patients achieve a long-term benefit. Identification of predictive factors of response to ICIs a priority to permit an early detection of poor-responder patients.
Methods: We retrospectively analysed 124 adult patients with advanced melanoma treated with ICIs from 1st January 2014 to 31st December 2020 at the Candiolo Cancer Institute. We evaluated gender, age, performance status, body mass index, BRAF and NRAS mutational status, stage, presence of liver metastases, LDH, C-reactive-protein (CRP), complete blood count values and concomitant steroid at baseline. Median progression free survival (mPFS) and overall survival (mOS) were evaluated with the Kaplan-Meier method. Comparison between groups was performed with log-rank test. Multivariate analysis was performed considering factors that showed a significant difference in the subgroup analysis. Results with a p-value <0.05 were considered statistically significant.
Results: In the whole cohort most patients (72.6%) received ICI as first line therapy. 37 patients (29.8%) received initially Ipilimumab, while 87 patients (70.2%) received anti-PD1. In the overall population the mPFS was 4.4 months and the mOS 28.4 months. In

the subgroup analysis patients with BRAF wild-type (p=0.011), stage M1a-b (p<0.001), absence of liver metastases (p=0.01), normal LDH (p=0.024) and PCR (p=0.022) had significantly prolonged PFS, while patients with stage M1a-b (p=0.01), normal PCR (p=0.038) and lower monocyte to lymphocyte ratio (MLR) (p=0.04) (Figure 1) had better OS. At multivariate analysis stage (p=0.005), class of ICI (p=0.036) and MLR (p=0.026) were independently correlated with PFS, while stage (p=0.002), PCR (p=0.038) and MLR (p=0.022) were correlated with OS.

Conclusions: MLR, PCR and stage are significantly correlated with outcomes in advanced melanoma patients treated with ICIs. The described results suggest considering the incorporation of these predictive factors in future clinical trials.

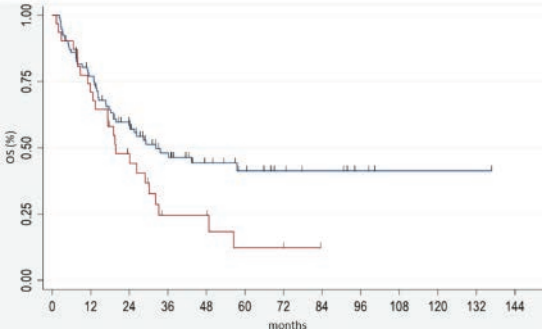


Figure 1. Analysis of overall survival stratified by monocyte to lymphocyte ratio (red line: higher; blue line: lower).