
XXX
CONGRESSO NAZIONALE IMI
RIMINI
27-28-29 SETTEMBRE 2024
PALACONGRESSI DI RIMINI
Via della Fiera, 23
intergruppo melanoma italiano
imi

ADOI
ASSOCIAZIONE DERMATOLOGI-VENEREOLOGI OSPEDALIERI ITALIANI e della SANITÀ PUBBLICA

AIDNID

A.I.L.M.A.G.
SENTINELLA ATTIVA CONTRO IL MELANOMA

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

Aiom
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AIRO
LA CURA DI PRECISIONE
Associazione Italiana Radioterapia e Oncologia clinica

Melanoma Associazione Pazienti Italia
APaIM

CAROLINA ZANI
MELANOMA FOUNDATION

EMME ROSSE
M
IN RICORDO DI MARA NAHUM

fondazione melanoma
ONLUS

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MELANOMA ONLUS

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vicino a chi soffre, insieme a chi cura

MELANOMA DAY

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LETTERA DEI PRESIDENTI

Care colleghe, cari colleghi

Siamo molto lieti di annunciare la XXX edizione del Congresso annuale della nostra società scientifica che si terrà a Rimini dal 27 Settembre al 29 Settembre 2024.

Seguendo una consolidata tradizione il Congresso si articola in sedute plenarie, con esperti nazionali che affronteranno argomenti scientifici di particolare interesse quali la prevenzione, la telemedicina, le strategie diagnostiche innovative, l'inquadramento del melanoma ad alto rischio, i consolidati e nuovi approcci terapeutici sia chirurgici che farmacologici (adiuvante e neoadiuvante) nelle varie fasi della malattia, avanzata e localmente avanzata. Una specifica enfasi verrà data alla immunoterapia e terapie a bersaglio molecolare, con l'illustrazione del profilo di efficacia e sicurezza delle varie strategie prescrittive (somministrazione in sequenza o combinazione). Si incontreranno i colleghi esperti e si conosceranno le nuove leve, che rappresentano il futuro di questa nostra Società.
Quest'anno abbiamo introdotto tre novità importanti per la nostra società: 1) Apriremo il congresso con una sessione dedicata alla gestione dei tumori cutanei nell'era della comunicazione mediante i social media. Questo tema verrà discusso con un esperto del settore e con le associazioni dei pazienti. La centralità del paziente, ancora una volta, nel nostro operato, viene pertanto ad aprire le sessioni scientifiche e ne diventa idealmente il presupposto etico, relazionale e umano; 2) diverse 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 sostenibilità dei nuovi farmaci e della governance sanitaria sarà ospitato nella sessione dedicata all'area IMI incontra AIOM

Il congresso IMI di Rimini ospiterà anche un esperto tedesco, il prof Dirk Schedendorf, che ci parlerà del ruolo dei nuovi biomarcatori nella gestione dei pazienti con melanoma. IMI incontra l'Europa nella collaborazione scientifica e della 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) per discutere l'elaborazione di documenti di consensus, per monitorare e ottimizzare le varie attività relative alla qualità dell'assistenza ed all'adesione alle linee guida, in base alle recenti innovazioni 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, Melanoma Italia Onlus e l'Istituto Oncologico Romagnolo, socio fondatore dell'IRCCS IRST "Dino Amadori", che ci ha accolto e supportato nel suo territorio.

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

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

Mario Mandalà
Presidente IMI

Ignazio Stanganelli
Presidente del Congresso

EPIDEMIOLOGY, GENETICS AND PATHOGENESIS

IMPACT OF PARTICULATE MATTER EXPOSURE ON MELANOMA RISK: A MULTICENTRE CASE-CONTROL STUDY

Francesco Bellinato,[1] Giovanni Adami,[2] Maria Antonietta Reatini,[3] Giorgio Cattani,[3] Maria Vittoria Cannizzaro,[4,5] Laura Del Regno,[4,5] Ketty Peris,[4,5] Paolo Gisondi,[1] Giampiero Girolomoni[1]

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Background: The relationship between particulate matter (PM) exposure and melanoma risk remains largely unexplored. This study aims to investigate the association between PM10 and PM2.5 long-term exposure and melanoma risk.

Methods: Case-control study involving 2,575 participants, comprising 1,473 melanoma patients and 1,102 healthy controls attending Departments of Dermatology of University Hospital in North and Central Italy. Demographic data, smoking status, history of sunburns, and skin type were collected. PM10 and PM2.5 exposure levels were estimated for each participant's residential address using a Bayesian hierarchical model, providing daily concentrations at a 1 km^2 spatial resolution from 2013 to 2021. Logistic regression analyses were performed to evaluate the association between PM exposure and melanoma risk, adjusting for potential confounders.

Figure 1.

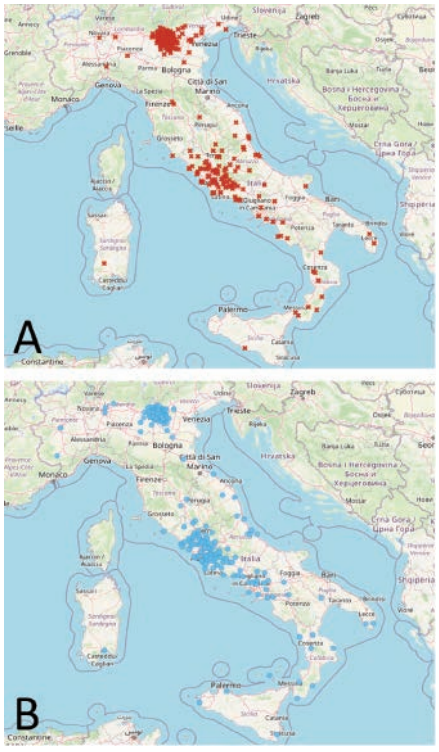

Table 1. Univariate and multivariate logistic regression assessing the risk of developing melanoma

	Univariate logistic regression			Multivariate logistic regression		
	OR	95%CI	p	OR	95%CI	p
PM10 (continuous var)	1.03	1.02-1.05	0.001	0.89	0.86-0.92	0.001
PM25 (continuous var)	1.06	1.04-1.08	0.001	0.72	0.68-0.76	0.001
Fitzpatrick phototype						
1	Ref			Ref		
2	1.05	0.54-2.08	0.869	0.65	0.28-1.49	0.300
3	0.66	0.34-1.31	0.237	0.33	0.17-1.67	0.277
4	0.91	0.36-2.28	0.839	0.53	0.14-0.77	0.010
5						
Gender (male)	1.41	1.21-1.66	0.005	1.13	0.85-1.50	0.402
Age						
1st quartile	Ref			Ref		
2nd quartile	3.59	2.85-4.53	0.001	3.27	2.21-4.83	0.001
3rd quartile	4.68	3.70-5.93	0.001	4.24	2.83-6.37	0.001
4th quartile	6.77	5.30-8.66	0.001	6.44	4.22-9.84	0.001
Cigarette smoking	0.38	0.29-0.50	0.001	0.28	0.20-0.38	0.001
History of sun burns	6.65	5.17-8.55	0.001	8.50	6.38-11.59	0.001

OR odds ratio, CI confidence interval

Results: Melanoma patients and controls were 52% males and had a mean age of 63.89 and 61.66 years, respectively. There were no significant differences in the geographical distribution of cases and controls based on ZIP codes (p=0.894) (Figure 1). The average melanoma Breslow thickness was 1.01 mm, with 68.15% of cases diagnosed at stage 0 and IA. The multivariate logistic regression revealed a protective effect for higher PM10 (OR=0.89, 95%CI: 0.86-0.92, p<0.001) and PM2.5 levels (OR=0.72, 95%CI: 0.68-0.76, p<0.001). Darker skin phototypes (Fitzpatrick 4) and cigarette smoking were also associated with a reduced risk of melanoma (Table 1).
Conclusions: Higher levels of PM10 and PM2.5 may have a protective effect against melanoma, potentially due to the reduction in ultraviolet radiation exposure. Further research to understand the complex interactions between environmental factors and melanoma risk are needed.

IMPACT OF COVID-19 PANDEMIC ON DELAY OF MELANOMA DIAGNOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Gaeta Aurora,[1,2] Cristina Pellegrini,[3] Saverio Caini,[4] Eleonora Lucantonio,[3] Mirco Mastrangelo,[3] Manfredo Bruni,[3] Maria Esposito,[3,5] Chiara Doccioli,[6] Paola Queirolo,[7] Giulio Tosti,[8] Sara Raimondi,[2] Sara Gandini,[2]* Maria Concetta Fargnoli[3,5]*
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Background. Several studies described how the restrictive measures due to COVID-19 have led to a delay in melanoma diagnosis, with a consequent increase in the proportion of more severe cases. Summarising the sparse findings in this context could help to understand the real impact of COVID-19 pandemic on melanoma. We performed a systematic review and meta-analysis to investigate how clinical and prognostic factors of new melanoma diagnosis changed after the COVID-19, intending to observe the consequence of a possible diagnostic delay.
Methods: A literature search in MEDLINE, EMBASE, and Scopus was conducted until September 2023. We included studies reporting data on new diagnoses of cutaneous melanoma in adult patients during and/or after lockdown compared to those diagnosed before the COVID-19 pandemic. Meta-analysis was conducted utilizing a random effects model to synthesize the summary results. The between-study heterogeneity was assessed via Higgins's I^2 statistic. Publication bias was assessed with Begg and Egger test. The estimated Odds Ratios (ORs) and 95% Confidence Interval (CI) were estimated from crude data where possible, or the adjusted ORs were extracted.
Results. A total of 44 studies were included. We found a significantly higher proportion of all factors indicating worse prognosis in the post-lockdown period compared to the preCOVID-19 phase, such as invasiveness Summary OR (SOR)=1.31, 95%CI 1.14-1.50), thickness (SOR =1.14, 95%CI 1.08-1.20 for 1-2 mm; SOR =1.62, 95%CI 1.08-2.40, for > 2 mm), nodular subtype (SOR= 1.19, 95%CI 1.07-1.32), presence of ulceration (SOR= 1.35, 95% 1.18-1.54) and of mitosis ((SOR = 1.57, 95% CI 1.17-2.11), stage III (SOR= 1.39, 95%CI 1.19 -1.52) and IV (SOR= 1.44, 95%CI 1.26-1.63).
Conclusions. Some limitations can involve the limited geographical distribution of the studies and the moderate heterogeneity that affects most meta-analysis estimates. Our meta-analysis provided evidence of more advanced melanomas diagnosed in the postCOVID-19 pandemic period, emphasizing the importance of creating and updating pandemic preparedness plans, to be able to contain as much as possible the impact of any future event on oncological care.

SEX AND GENDER INFLUENCE ON ADVERSE EVENTS FOR MELANOMA PATIENTS: A COMPREHENSIVE REVIEW AND META-ANALYSIS

Aurora Gaeta[1,2], Luca Nuvoli[3], Federico Cattò[1], Maristella Saponara[4], Carolina Cimminiello[4], Claudia Cosma[5], Palmieri Giuseppe[6], Saverio Caini[7], Antonio Cossu [8], Luca Mazzarella[9,10], Vicini Francesco[9], Giulio Tosti [11], Paola Queirolo[4], Sara Gandini[1]

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Background. Immunotherapy and target therapy have revolutionized melanoma treatment. However, adverse events (AEs) are still frequent and might impact treatment adherence. Female sex was demonstrated to be associated with a higher risk of AEs from cytotoxic therapy related to cancer treatment. This study aims to conduct a systematic review and meta-analysis to investigate Sex and Gender (S/G) effect on adverse events.
Methods. We extracted data from independent studies published until April 2024 with information regarding toxicity by S/G. Only studies that involved patients with melanoma as a primary disease were included. Summary Odds ratios OR (sOR) estimates were obtained through random-effects models, and 95% Confidence Intervals (CI) were estimated. I^2 was used to evaluate the between-study heterogeneity. Publication bias was investigated using Begg and Egger tests.
Results. Information regarding toxicity and gender were extracted from seventy articles. A significant increase in AE related to the thyroid was observed in women (sOR=2.00, 95%CI [1.41-2.85], I^2=29). S/G did not affect Grade III-IV, Dermatological, Gastrointestinal, Hypophyses, Kidney, Liver, or Ocular toxicities.

The increased risk of AE related to the thyroid was mainly seen for those undergoing first-line treatments, sOR=2.17, 95%CI [1.42-3.32], I^2=44. Women undergoing TT (target therapy) had an increased risk of dermatological AE (sOR= 1.99, 95%CI 1.55-2.55, I^2=64) and grade III-IV AE (sOR = 1.6, 95%CI 1.08-2.38, I^2=64).
Conclusions. This study supports and extends the discussion on the impact of S/G on the development of toxicities. Women have an increased risk of AE related to the thyroid, mainly seen during first-line treatment, and showed an increased risk of dermatological and severe AE when treated with TT. Women should be monitored closely for precursor signs of thyroid-related AE and dermatological and generally severe AE to preserve good treatment adherence.

INNOVATIVE APPROACH TO ENRICH AND RECOVER VIABLE CIRCULATING MELANOMA CELLS FOR DOWNSTREAM CUSTOMIZED GENETIC ANALYSIS

Cristina Poggiana[1], Cristina Catoni[1], Ilaria Gallingani[1], Alessandro Francesco Piazza[1], Jacopo Pigozzo[2], Luisa Piccin[2], Antonella Facchinetti[1,3], Chiara Menin[1], Stefania Pellegrini[1], Valentina Salizzato[2], Paolo Del Fiore[4], Simone Mocellin[3,4], Alessio Fabozzi[5], Vanna Chiarion-Sileni[2], Antonio Rosato[1,3], Maria Chiara Scaini[1]

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Background. Circulating melanoma cells (CMCs) are responsible for the haematogenous spread of melanoma and, ultimately, metastasis. However, their in-depth study has been limited by their low abundance in patient blood and the heterogeneous surface marker expression. The FDA-approved CellSearch platform enriches CD146-positive CMCs, whose number correlates with PFS and OS, but a single marker may not be sufficient to identify them all. A newly developed instrument, the Parsortix system, allows the CMC enrichment based solely on their size and deformability, keeping them viable and suitable for downstream molecular analyses. In this study, we tested the strengths, weaknesses and possible convergences of both platforms to integrate CMC counting with an efficient protocol for downstream genetic analysis.
Methods. The CellSearch and Parsortix systems were used to enrich tumor cells from 14 spike-in and 4 metastatic melanoma samples. Parsortix samples were also labelled with a customized antibody cocktail. Finally, enriched CMCs from a paradigmatic uveal melanoma patient were subjected to lysis and whole genome amplification followed by custom NGS, ddPCR and MLPA analyses.
Results. The customized antibody cocktail efficiently labeled and distinguished CMCs from endothelial cells/leukocytes. The capture rate of the two platforms was comparable for cell lines, but the Parsortix had a higher recovery rate in real-life samples. Downstream genetic analysis of the CMCs from a metastatic uveal melanoma patient revealed multiple genetic variants (SNV, indel, and copy number variation). The driver GNAQ p.Q209L was identified as homozygous, while a deletion in BAP1 exon 9, heterozygous at baseline, was found hemizygous at progression, but in a copy number neutral manner, suggesting the amplification of the mutated copy. Moreover, an isochromosome 8 and a homozygous deletion of the CDKN2A gene were detected.
Conclusions. We optimized and validated an approach to successfully enrich and retrieve viable CMCs from patients with metastatic melanoma. This study provides proof-of-principle for the feasibility of this type of enrichment and genetic analysis, adding complementary and/or overlapping information to that derived from circulating tumor DNA analysis, useful for assessing the disease landscape in real time.

EXPLORING THE INTERPLAY OF B3-ADRENERGIC RECEPTOR, HIF-1A AND CD31 IN THE MICROENVIRONMENT OF ATYPICAL MELANOCYTIC LESIONS

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Background. Melanoma has swiftly increased worldwide in recent years and stands out due to its high lethality. Despite advances in clinical treatment, melanoma-sensitive genes and molecular pathogenesis understanding, the focus is shifting to the connection between stress-related β-adrenergic receptors (ARs), hypoxia, and neovascularization in melanoma tumor progression.
Methods. The study aimed to evaluate β3-AR, HIF-1α and CD31 expression in several cellular subsets of atypical melanocytic lesions and to investigate their interplay in promoting melanoma malignancy. Twenty-seven patients with melanocytic lesions at different stages, surgically removed, were retrospectively selected; clinical-pathological and dermoscopic data were collected.
Results. The immunohistochemical and digital evaluation revealed a significant upregulation of β3-AR in malignant melanoma melanocytes and invasive >pT1a melanomas macrophages compared to the dysplastic nevi. Increased HIF-1α expression in malignant melanocytes and CD31 expression levels in >pT1a melanomas was observed. Ulcerated lesions exhibited higher percentage of β3-AR, HIF-1α and CD31. A positive Pearson correlation supported a strong relationship between these markers in human malignant melanoma, reinforcing the tight connection between hypoxia, adrenergic response and tumor vascularization.
Conclusions. This investigation contributes to broader research, emphasizing the significance of predictive markers in assessing tumor aggressiveness. Unraveling melanoma's interactions with β3-AR, HIF-1α, and CD31 may pave the way for innovative therapies and deepen comprehension of melanoma pathogenesis.

COULD GERMLINE VARIANTS IN HEDGEHOG SIGNALING PATHWAY GENES IMPACT ON MELANOMA PREDISPOSITION?

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Background. Germline variants in the Hedgehog signaling (SHH) pathway (PTCH1, PTCH2 and SUFU genes) predispose to Nevoid Basal-Cell Carcinoma Syndrome (NBCCS)/Gorlin Syndrome (GS) with high penetrance and variable expressivity. NBCCS/GS is a rare autosomal dominant disease characterized by a wide range of abnormalities and tumor predisposition, mainly multiple basal cell carcinomas (BCCs), medulloblastoma, cardiac and gonadal tumors. Here, we assume that germline SHH variants could also promote melanoma predisposition.
Methods. SHH genes were evaluated in 233 cases with suspected melanoma predisposition but with a non-informative genetic test for high-penetrant melanoma genes. The DNA extracted from blood samples was genotyped by NGS sequencing on the Illumina MiSeq platform, using a customized multi-gene panel. Data were analyzed using SOPHiA_DDM™ software. Pathogenic variants were then confirmed by Sanger sequencing.
Results. Among our melanoma patients, we identified 12 probands with rare variants in SHH genes: five in PTCH1, six in PTCH2 and one in SUFU. We found a nonsense PTCH2 variant (p.Cys559*), classified as "likely pathogenic", in a 40-year-old woman with two melanomas. Her family's clinical features did not fulfill the GS diagnostic criteria, except for a maternal aunt with an early onset medulloblastoma. It is noteworthy that also the patient's mother (hypothetical carrier) had a melanoma. All the other variants were missense variants with unknown significance. Two PTCH2 variants have never been reported before, while one PTCH1 variant, found in a multiple melanoma case with also 4 BCCs, was located in a codon that has already been described in a previous NBCCS study.
Conclusions. Although further evidence (i.e. co-segregation analysis and functional studies) is needed to validate the association between SHH variants and melanoma, we suggest that the inclusion of SHH genes in genetic testing for melanoma predisposition could be appropriate and useful in a context of Syndromic Familial Melanoma and Gorlin-like Syndrome.

GENETIC TELECOUNSELING: EVALUATION OF EFFICACY AND OUTCOMES THROUGH THE GENETIC COUNSELING OUTCOME SCALE (GCOS) QUESTIONNAIRE IN A COHORT OF PATIENTS WITH A SUSPECTED MELANOMA SUSCEPTIBILITY SYNDROME

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Since 2019, the Italian Melanoma Intergroup (IMI) provided a genetic telecounseling (GTC) service to identify patients with criteria for genetic testing for melanoma-associated syndromes who did not have easy access to a genetic counselor and could benefit from centralized testing through a standardized gene panel. As of 2023, 640 GTC requests had been received from 32 specialists (8 different regions) and 559 genetic tests had been offered. The implementation of quality assessment tools for genetic counseling may provide feedback to measure its effectiveness and outcomes in terms of clinical benefit and patient and family awareness. In 2018, a shortened version of the Genetic Counseling Outcome Scale (GCOS) questionnaire, comprising only 6 items, was statistically validated (Grant *et al*., EJMG, 2019) to retain the ability of the original 24-item version to capture patient empowerment (cognitive, decisional and behavioral control, emotional regulation, hope), while providing a patient-reported outcome measure specific to clinical genetics services. A total of 278 patients, followed up in three of the major centers, were administered by the referring clinicians the shortened GCOS, adapted to our language and cultural context, also ensuring anonymity. A pilot study including 30 patients who underwent in-presence counseling (IPGC) was conducted at the Genoa Cancer Genetics Unit to assess its feasibility and validate it, though on a non-homogeneous cohort of patients. From 31 to 80% of the patients replied, for a total of 177. The results allowed us to quantify the level of understanding and processing of the test results, including which family members were at risk, acceptance of the proposed surveillance measures, and the psychological impact of GTC. Over 85% of the patients declared that GTC offered useful and understandable information and clinical benefits to their families, in line with the emerging evidence that the GTC efficacy is comparable to that of IPGC.

FOUR YEARS OF ACTIVITY OF THE MELANOMA UNIT OF SASSARI ACROSS NORTH SARDINIA

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The aim of this hospital-based study was to analyze and describe the epidemiological features and the molecular characteristics of cutaneous melanoma in North Sardinia, through the activity reports of the multidisciplinary team constituted in 2019 in Sassari, Italy. From January 2021 to June 2024, 468 patients with melanoma were taken into care, equally distributed between the two sexes [241 (51%) females and 227 (49%) males. Regarding the origin, 276 (59%) were referred to the AOU of Sassari, 192 (41%) from other centers in Sardinia; for the geographical origin, 85% of the patients (N = 397) are Sardinian. Here is the histological distribution of cutaneous melanoma cases.Regarding the AJCC stage at disease onset, 84/468 (17.9%) patients were diagnosed with *in situ* melanoma (pTis), whereas the infiltrating melanomas (N=384) were distributed as follows: **IA** [pT1a, 163; pT1aN0, 24; pT1bN0, 44], **231** (*49.4%*); **IB** (pT2aN0), **21** (*4.5%*); **IIA** [pT2bN0, 11; pT3aN0, 9], **20** (*4.3%*); **IIB** [pT3bN0, 16; pT4aN0, 6], **22** (*4.7%*); **IIC**, **16** (*3.4%*); **IIIA**, **4** (*0.9%*); **IIIB**, **7** (*1.5%*); **IIIC**, **34** (*7,2%*); **IIID**, **6** (*1.3%*); **IV**, **23** (*4.9%*). Mutational analyses were performed on 147 patients using NGS assays: 112 cases at the time of diagnosis (from stage IIB to stage IV) and 35 cases after metastatic progression of the disease from other stages. *BRAF* gene was found mutated in 65

(44%) patients [V600E, 47/65 (71%); V600K, 13 (20%); V600D, 2 (3%); the remaining 3 (5%) were non-canonical mutations (D594N, T470P, T599dup). *NRAS* gene mutations were identified in 31 (21%) patients [13/31 (42%) cases presented a Q61R mutation, 10 (32%) Q61K, 4 (13%) Q61L, and remaining 4 (13%) cases the Q61H, G12A, and G12V variants]. Three melanomas (one NM and two AM subtypes) were found to carry a pathogenic mutation in *KIT*: E554G, H708R e W557R. With the exception of one case with coexistence of mutated *NRAS* and *KIT* genes, all driver mutations were mutually exclusive. According to the melanoma subtypes, *BRAF*/*NRAS* mutations were found in 40/63 (63.5%) NM, 25/266 (9.4%) SSM, 5/31 (16.1%) EM, 7/16 (43.8%) AM. Among 98 advanced cases, tests for PD-L1 immunohistochemical expression showed a percentage of positive tumor cells >1% in 15 (15%) patients; the remaining ones were negative for PD-L1 expression [negative, 55 (56%) cases; <1%, 28 (29%)]. Adjuvant therapy was administered in 50 stage III patients: among the 23 (46%) *BRAF*-mutated cases, 17 (74%) were treated with dabrafenib/trametinib combination and 6 (26%) with anti-PD-1 immunotherapy; the remaining 27 (54%) cases with *BRAF* wild-type gene received immunotherapy. Among 58 metastatic patients, first line treatment was constituted by BRAF/MEK inhibitors in 17/25 (68%) *BRAF*-mutated cases, while immunotherapy was carried out in remaining *BRAF*-mutated and all wild-type cases. Relapse-free and overall survivals are being evaluated.

Table 1. SAMPUS, Superficial Atypical Melanocytic Proliferation of Uncertain Significance.

Primary melanoma subtype	Patients (%)	Primary melanoma subtype	Patients (%)
Superficial spreading melanoma (SSM)	266 (56.9)	Nevoid melanoma	9 (1.9)
Nodular melanoma (NM)	63 (13.5)	Desmoplastic melanoma	4 (0.9)
Lentigo maligna melanoma (LMM)	52 (11.1)	Polypoid melanoma	3 (0.6)
Epithelioid melanoma (EM)	31 (6.6)	Spitz melanoma	3 (0.6)
Acral melanoma (AM)	16 (3.4)	Others (5 cases with SAMPUS)	21 (4.5)

CLINICAL CHARACTERIZATION AND PREVALENCE OF BRAIN METASTASES IN UVEAL MELANOMA PATIENTS

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Background. Metastatic uveal melanoma (mUM) is a rare cancer characterized by a strong hepatotropism and a life expectancy of approximately 12-17 months. Brain metastases (BMs) have been rarely described (6.3%), but data on their prevalence is probably underestimated considering that brain imaging is performed only in symptomatic patients.

Methods. Our single-center retrospective chart review aimed at characterizing UM BMs and their prevalence. We collected clinical data including demographics, tumor characteristics, treatment history and disease outcomes. Distant metastasis free-survival and overall survival (OS) from primary, first distant metastasis or BM diagnosis were calculated.

Results. From 1993 to 2024, 300 mUM patients were referred to our center and 16 (5.3%) developed BMs. Median age of BM patients was 61y (45-70), 9 (56.3%) were female, 8 (50%) had neurologic symptoms and 7 (43.8%) ECOG-PS ≥ 2. Serum LDH levels, measured in 13/16 patients, were elevated in 9 (56.3%). At initial diagnosis of BMs 11 patients (68.8%) had multiple brain lesions with a median number of organs involved of 4 (0-7) and 1 previous systemic treatment (0-3). The median time to develop any distant metastasis or BMs was 52.4 and 71.8 months (95%CI 4.77-100.03; 64.35-79.24), respectively. At the time of analysis 11 patients were dead, 4 lost to FUP and 1 alive. mOS from primary, any distant localization or BM diagnosis was 80.8, 15.1 and 5.1 months (95%CI 66.14-95.45; 4.9-25.3; 2.16-8.04), respectively.

Conclusions. BMs in UM patients mostly occur late during the clinical evolution of the disease. We suggest brain surveillance in patients with a long history of systemic metastases to treat them before the appearance of neurologic complications, especially now that new therapies could prolong OS.

PREVENTION AND DIAGNOSIS

EVALUATION OF THE DIAGNOSTIC UTILITY OF PRAME (PREFERENTIALLYEXPRESSED ANTIGEN IN MELANOMA) IN CHALLENGING MELANOCYTIC LESIONS

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Background. The PReferentially expressed Antigen in Melanoma (PRAME) is a tumor-associated antigen overexpressed in cutaneous and ocular melanomas. Most melanocytic lesions can be readily classified as benign or malignant, but frequently, ambiguous microscopic features make interpretation difficult. The aim of this study is to demonstrate the utility of PRAME as support tool in the differential diagnosis of challenging melanocytic lesions, allowing the distinction between benign nevi and malignant melanocytic neoplasms.
Materials: PRAME immunohistochemical investigations were performed on a total of 160 melanocytic lesions divided in 4 categories. The antibody expression was evaluated as percentage of positive cells and the intensity of immunoreactivity.
Results. Considering a conventional PRAME-score cut-off of 4+, an aggregated sensitivity and specificity of 49% and 96%, respectively, and an aggregated diagnostic accuracy of 76% were observed. Using a PRAME-score cutoff >3+, aggregated sensitivity and specificity values of 66% and 94%, respectively, and an aggregated diagnostic accuracy of 80% were achieved. Comparing the positive predictive value and negative predictive value of the PRAME-score test yields respective results of 0.93 (cutoff 4+) and 0.80 (cutoff >3+), and 0.35 (cutoff 4+) and 0.26 (cutoff >3+).
Conclusions. Our results are concordant with the literature, demonstrating that the diffuse PRAME reactivity is a feature of malignancy. Conversely, marker negativity does not necessarily define a lesion as benign. Caution is advised in interpreting PRAME reactivity in melanocytic tumors of uncertain classification because they may show focal or incomplete PRAME staining.

IMPACT OF MELANOMA MULTIMEDIA EDUCATION (MELAMED) PROGRAM IN PRIMARY CARE: A MULTICENTER E-HEALTH IMI STUDY

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Table 1. Effect of training on theoretical knowledge of melanoma. Numbers and percentages of correct answers pre- and post-training. All percentages are based on the 161 participants who completed both the pre- and the post-training questionnaire.

Theoretical question	Pre-training N(%)	Post-training N(%)	P-value*	Correct answer
Question 1	160 (99.4%)	161 (100%)	1	Ultraviolet radiation
Question 2	149 (92.5%)	154 (95.7%)	0.228	Live evaluation of the entire skin area in optimal lighting conditions and with the use of a magnifying glass
Question 3	153 (95.0%)	159 (98.8%)	0.114	Asymmetry, Irregular edges, Uneven colour, Dimensions >6 mm, rapid Evolution
Question 4	120 (74.5%)	156 (96.9%)	<0.001	Elevation, Firm, Growth
Question 5	145 (90.1%)	161 (100%)	<0.001	Different nevus that "stands out" compared to other nevus due to its shape, colour and/or rapid evolution
Question 6	99 (61.5%)	111 (68.9%)	0.097	Dermoscopy is a non-invasive technique that allows the in vivo evaluation of skin colours and structures not visible to the naked eye
Question 7	56 (34.8%)	77 (47.8%)	0.007	It indicates the thickness of the melanoma from the granular layer of the skin (or from the base of the ulcer if the lesion is ulcerated) to the point of maximum infiltration into the dermis. It is measured in mm

Abbreviations: mm, millimetres
*P-value for McNemar test

Table 2. Effect of training on diagnostic skill and on melanoma management. Numbers and percentages of correctly identified lesions between benign and malignant, of correct diagnoses and of correct referrals, pre- and post-training. All percentages are based on the 161 participants who completed both the pre- and the post-training questionnaire

Image	Question								
	Correct answer if benignant/malignant			Correct diagnosis			Referral to a dermatologist		
	Pre-training N(%)	Post-training N(%)	P-value*	Pre-training N(%)	Post-training N(%)	P-value*	Pre-training N(%)	Post-training N(%)	P-value*
Thin melanoma	101 (62.7%)	123 (76.4%)	0.002	72 (44.7%)	106 (65.8%)	<0.001	151 (93.8%)	142 (88.2%)	0.110
Congenital melanocytic nevus	93 (57.8%)	135 (83.9%)	<0.001	56 (34.8%)	103 (64.0%)	<0.001	107 (66.5%)	64 (39.8%)	<0.001
Seborrheic keratosis	101 (62.7%)	125 (77.6%)	0.001	123 (76.4%)	133 (82.6%)	0.123	100 (62.1%)	69 (42.9%)	<0.001
Nodular melanoma	99 (61.5%)	142 (88.2%)	<0.001	114 (70.8%)	140 (87.0%)	<0.001	151 (93.8%)	153 (95.0%)	0.814
Thick melanoma	130 (80.7%)	156 (96.9%)	<0.001	80 (49.7%)	125 (77.6%)	<0.001	158 (98.1%)	160 (99.4%)	0.480
Melanocytic nevus	86 (53.4%)	96 (59.6%)	0.212	133 (82.6%)	114 (70.8%)	0.009	98 (60.9%)	84 (52.2%)	0.077
Congenital melanocytic nevus	133 (82.6%)	143 (88.8%)	0.123	132 (82.0%)	136 (84.5%)	0.607	65 (40.4%)	41 (25.5%)	0.003
Melanoma with regression	101 (62.7%)	152 (94.4%)	<0.001	95 (59.0%)	141 (87.6%)	<0.001	159 (98.8%)	156 (96.9%)	0.371
Malignant lentigo	36 (22.4%)	99 (61.5%)	<0.001	65 (40.4%)	107 (66.5%)	<0.001	112 (69.6%)	134 (83.2%)	0.006
Basal cell carcinoma	131 (81.4%)	157 (97.5%)	<0.001	138 (85.7%)	134 (83.2%)	0.617	156 (96.9%)	160 (99.4%)	0.221

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Background: The Melanoma Multimedia Education (MelaMEd) is an innovative e-learning program developed for physicians, particularly general practitioners (GPs) due to their pivotal role in in triaging patients to dermatologists. The project is characterized by an asynchronous e-learning course, on the behalf of FNOMCeO, switching to a web platform that includes a multimedia and multidimensional library. It provides GPs with a comprehensive understanding of the primary and secondary prevention of cutaneous melanoma and an overview of diagnostic and therapeutic pathways. A study evaluating its clinical impact on the diagnosis and management of melanoma by GPs has been conducted.

Methods: This study, planned completely *online* in 2023, included presenting the synopsis, kick-off meetings with centres, pre- and post-training questionnaires with theoretical questions and diagnostic images. The training's impact on diagnostic accuracy and management of melanoma in primary care setting was evaluated. The clinical impact was assessed by statistically comparing pre- and post-training questionnaire responses.

Results: Ten IMI centres participated, involving 1531 participants. Of these, 461 completed the pre-training questionnaire, and 161 (35%) also completed the post-training questionnaire. The study focused on the responses of the 161 participants who completed both questionnaires. There was an increase in correct answers for each of the seven theoretical questions (Table 1). Positive Predictive Value, Negative Predictive Value, Sensitivity, Specificity, and Accuracy were computed to evaluate diagnostic abilities pre- and post-training. All indicators showed an increase post-training, reaching values between 77.5% and 85.8%, indicating improved diagnostic abilities and better discrimination of non-malignant lesions. There was significant improvement in diagnostic accuracy for both benign and malignant melanocytic proliferations, especially in the setting of malignant lentigo (pre-training 40.4%, post-training 66.5%), nodular melanoma (pre-training 70.8%, post-training 87.0%) and the related EFG rule (pre-training 74.5%, post-training 96.9%), see Table 2. Moreover, there was a decrease of referral of benign melanocytic and non-melanocytic lesions to dermatologists. The main critical point was the low knowledge of Breslow thickness, but there was a post-training significant improvement (pre-training 34.8%, post-training 47.8%). Furthermore, a sufficient comprehension of the value of dermoscopy was demonstrated.

Conclusions: The MelaMEd program has significantly enhanced GPs' capabilities, improving diagnostic accuracy and melanoma management. It represents a unique e-learning program in the national and international panorama of e-health education on melanoma. Moreover, it can be considered the largest e-learning program in terms of number of GPs involved in evaluating the program's effect.

PREDICTING BRAIN METASTASIS AS PRIMARY SITE OF RECURRENCE IN PRIMARY CUTANEOUS MELANOMA: A LARGE MULTICENTER INTERNATIONAL STUDY ON BEHALF OF ITALIAN MELANOMA INTERGROUP

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Background. Predicting of brain metastasis (BM) as primary site of recurrence in primary cutaneous melanoma (PCM) is clinically relevant in order to identify asymptomatic patients with BM during follow-up, and to save low-risk patients from exposure to ionizing radiation. Clinical predicting nomograms are lacking and represent an unmet medical need.

Objective: The primary endpoint was to investigate clinical and pathological biomarkers predicting BM as primary site of recurrence in PCM melanoma patients included in prospectively collected database. Secondary endpoints included prediction of disease-free survival (DFS), and overall survival (OS).

Methods. The study included consecutive patients with PCM treated and followed up in referral melanoma centers. Logistic regression and Cox regression models were used to identify independent clinical and pathological biomarkers predicting BM as primary site of recurrence, as well DFS, and OS. Cox, Fine and Gray models were stratified by center. A nomogram for clinical use was developed.

Results. From 1998 to 2022, 11432 PCM (median age 55 years) cases were diagnosed in four Institutions of the Italian Melanoma Intergroup and 1 Polish cancer center. Median follow-up was 10 years. Overall, 305 patients (11.9%) developed BM as primary site of recurrence. By multivariate analysis, BM occurrence was associated with SLN positivity (OR 1.79, 95% CI 1.18-2.70, p =0 .006), Breslow thickness (OR 2.74 95% CI 1.63-4.59, P =0.0001), ulceration (OR 2.22 95% CI 1.69-2.91, p =0.0001), primary site of melanoma (Trunk vs other OR 1.77 95% CI 1.11-2.83, p =0.01) and gender (male versus female OR 1.69 95% CI 1.28-2.23, p=0.0002). These covariates have been included in a nomogram, that is able to predict BM at following category risk: < 5%, 6-10%, 11-20%, 21-30%, > 30%. The same covariates independently predict DFS and OS (data will be shown at the meeting)

Conclusion: The risk of BM as primary site of recurrence can be predicted through simple clinical and pathological biomarkers. A nomogram for clinical use can be adopted to tailor imaging and schedule of follow-up according to the clinical risk.

PATHOLOGICAL AND MOLECULAR CLASSIFICATION

MONITORING CIRCULATING TUMOR DNA LIQUID BIOPSY IN STAGE III BRAF-MUTANT MELANOMA PATIENTS UNDERGOING ADJUVANT TREATMENT

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Backgroung: The field of melanoma biomarker has been sprouting of growing interest, with special regard to circulating tumor DNA (ctDNA). However, uncertainties persist regarding its relevance for prognostic assessments.
Materials and Methods. A cohort of 32 stage III BRAF+ melanoma patients, treated with either adjuvant anti-PD1 or dabrafenib/trametinib, was collected from 2019 to 2021. The detection and quantification of the most common mutations in codon 600 (V600E, V600R, V600K) of the BRAF gene in circulating free DNA were performed with a sensitive multiplexed digital droplet-PCR. Blood samples were retrieved monthly, starting from the initial administration of treatment until therapy completion or relapse. Samples were classified as mutated when the number of copies exceeded the limit of blank (LOB = meanblank + 1.645*SDblank).
Results. The negative baseline ctDNA patients exhibited a significantly higher 36-month recurrence-free survival (RFS) of 75.0% (95% CI 50.0-88.8) compared to 36.4% (95% CI 11.2-62.7) of the positive group (p=0.014). In-transit metastasis (HR 4.20, 95% CI 1.11-15.87, p=0.034) and positive basal ctDNA status (HR 3.79, 95% CI 1.20-12.00, p=0.023) emerged as significant risk factors for RFS. A significantly higher OS of 95.0% (95% CI 69.5-99.3) was described in patients with negative basal ctDNA compared to the 54.6% (95% CI 22.9-77.9) in the positive group (p=0.004). Age (HR 1.07, 95% CI 1.01-1.14, p=0.015), stage IIID (HR 8.81, 95% CI 1.68-46.21, p=0.010), in-transit metastasis (HR 9.44, 95% CI 1.89-47.16, p=0.006), relapse during adjuvant therapy (HR 24.58, 95% CI 2.65-228.08, p=0.005), brain relapse (HR 100.69, 95% CI 1.14-100.80, p=0.039), and positive basal ctDNA (HR 7.92, 95% CI 1.56-40.36, p=0.013) were identified as significant variables for OS.
Conclusions: Basal ctDNA status can hold potential in predicting relapse and survival outcomes in stage-III melanoma patients, overcoming the traditionally recognized prognostic factors. A wider comprehensive evaluation across a broader cohort of patients in essential to deeply understand its clinical value.

CLINICO-PATHOLOGICAL CHARACTERISTICS IN BRAF V600K-MUTANT MELANOMA PATIENTS: A SINGLE-INSTITUTION EXPERIENCE

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Background. More than 50% of primary cutaneous melanoma show a BRAF gene mutation, most frequently found at codon V600E. However, up to 20% of patients display a V600K mutation. Although literature data have reported that BRAF V600K-mutant melanomas have their own biological features, large series focusing In this scenario, we aimed to describe the clinico-pathological traits of the BRAF V600K-mutant melanomas in a large series of primary cutaneous melanomas and to compare them with the BRAF V600E.
Methods: A retrospective and consecutive case series of 317 patients with primary cutaneous melanoma who underwent BRAF mutational analysis at the Molecular Pathology Unit of the Città della Salute e della Scienza of Turin between 2015-2021 was collected. Mutational analysis was performed by Mass Spectrometry combined with Single Base Extension technology using the Sequenom Myriapod Diatech Pharmacogenetics system. Clinical and follow-up data were collected and histology was revised as well.
Results. BRAF mutations were distributed as follows: 248/317 cases (78%) V600E, 62/317 (20%) V600K and 7/317 (2%) V600R/D. The median age at diagnosis was 54for BRAF V600E *vs* 71 years for BRAF V600K-mutant patients (p<0.001). Higher lesion diameter (20 *vs* 14 mm; p=0.010) and more frequent head/neck district involvement (*p*=0.010) were observed in BRAF V600K-mutant. In addition, BRAF V600K-mutant melanomas showed a prevalent nodular histotype (54 *vs* 27%; p<0.001), ulceration (74 *vs* 52%; p=0.01) and higher Breslow thickness (5.29±4.58 *vs* 4.30±5.00 mm; p=0.005). No differences regarding disease progression in the two groups were observed. On the contrary, in BRAF V600K-mutant patients, the Time to Disease progression was significantly shorter (1.10 *vs* 2.46; p=0.007; 1.30 *vs* 3.18 years in negative-SLNB patients; 2.08 *vs* 0.3 in positive-SLNB patients).
Conclusions. In conclusion, patients with BRAF V600K-mutant melanoma show peculiar clinico-pathological parameters associated to more aggressiveness.

IDENTIFICATION OF PROGNOSTIC AND PREDICTIVE LIQUID BIOPSY BIOMARKERS IN PATIENTS WITH CUTANEOUS SQUAMOUS CELL CARCINOMA TREATED WITH CEMIPLIMAB

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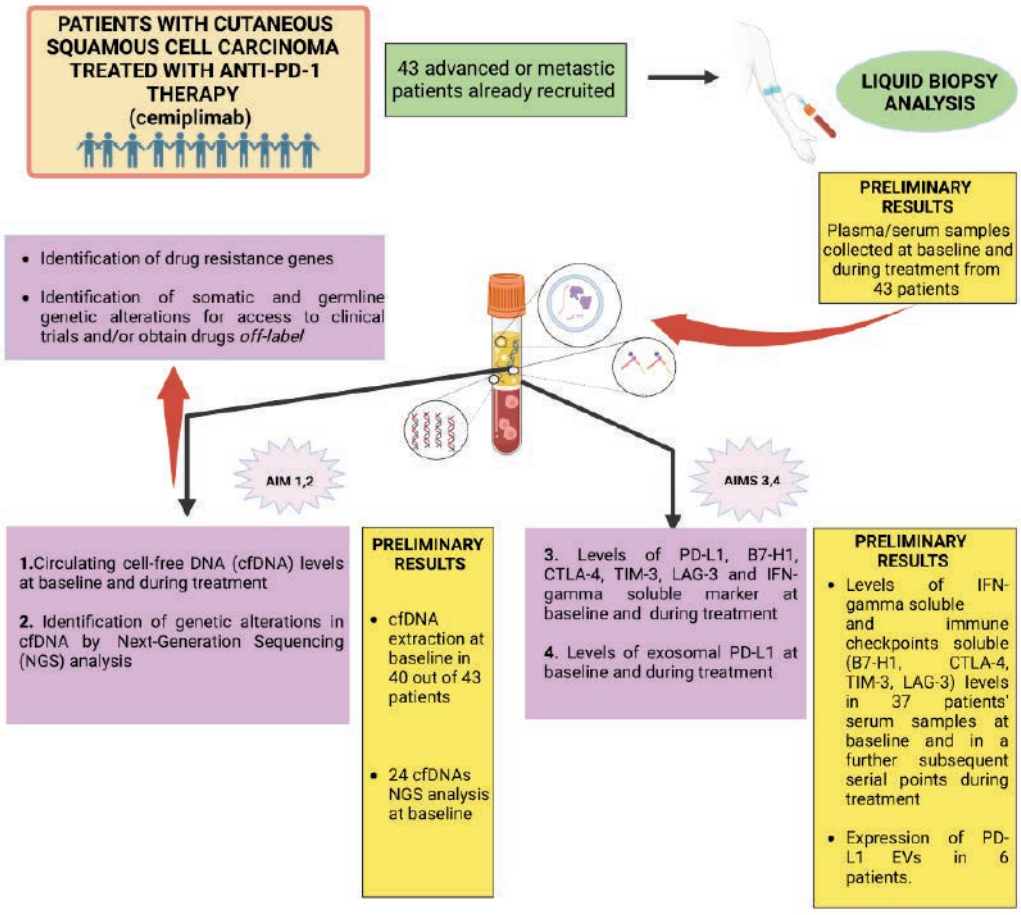
Background. A small percentage of patients with cutaneous squamous cell carcinoma (CSCC) develop locally advanced or metastatic disease. These patients are candidate for anti-PD-1 agent Cemiplimab, with an overall response rate of about 50%. However, there are as yet no predictive biomarkers to select the patients most likely to benefit of the treatment.

Methods. A cohort of 43 patients with unresectable and/or metastatic CSCC, treated with Cemiplimab, was enrolled between August 2019 and March 2024. IFN-gamma soluble cytokine and 4 immune checkpoints soluble markers (B7-H1, CTLA-4, TIM-3, LAG-3) levels were evaluated in the patients' serum samples at baseline and in a further subsequent serial point during treatment. cfDNA at baseline was sequenced using the TruSight Oncology 500 ctDNA (Illumina; 523 cancer-related genes). Plasma extracellular vesicles (EVs) were isolated and characterized from a subgroup of 6 patients at baseline and at the time of response. Study design, aims and preliminary results are reported in Figure 1.

Results. No difference between males (60.5%) and females (39.5%) age at onset was observed (81 years). The tumors were located in head-neck (81.4%), arms (7%), trunk (9.3%) and genitals (2.3%). Twenty-seven patients (62.8%) and 16 (37.2%) had a locally advanced and metastatic disease, respectively. Ten cases presented an history of immunosuppression. An average of 7.7ng/mL of cfDNA at baseline was obtained from 40/43 patients. PD patients showed a higher average amount of cfDNA at baseline compared to patients with DCR (15.7 *vs* 5.8ng/mL). The sIFN-gamma level at baseline was significant lower in patients with DCR compared to patients with PD ($P<.005$). The concentrations of PD-L1 EVs correlate with response in 2 out 6 patients analyzed.

Conclusions. Although based on small numbers, and with several analyses still ongoing, preliminary results shows promise combined approaches to identify biomarkers of response.



Study design, aims and preliminary results: Aims and preliminary results are reported in violet and yellow, respectively.

SURGERY

SENTINEL LYMPH NODE BIOPSY IN MALIGNANT MELANOMA OF THE SKIN, COMPARATIVE ANALYSIS BETWEEN STANDARD TECHNIQUE WITH TECHNETIUM99M AND INDOCYANINES GREEN. EXPERIENCE OF A HIGH-FLOW REGIONAL REFERENCE CENTER

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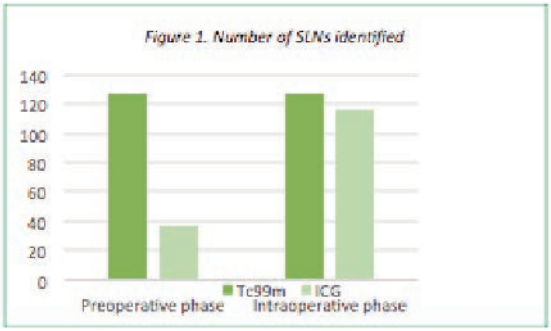
Background. In cutaneous melanoma lymphatic spread is an essential prognostic factor. Sentinel lymph node biopsy (SLNB) with preoperative lymphoscintigraphy and technetium99m (Tc99m) is currently the gold standard. Recent studies, however, describe the use of indocyanine green (ICG) as a second tracer in combination with Tc99m as a promising option to reduce the number of false negatives. The main aim of our study is to compare the concordance of radiotracer and fluorescent dye ICG in a consecutive series of patients.
Methods. We conducted a prospective observational study at San Salvatore Hospital in L'Aquila in a period between March 2017 and May 2023. All procedures were performed by a single operator with standard technique in association with the ICG. All patients diagnosed with no-metastatic melanoma with Breslow thickness >0.8 mm were consecutively included in the study. The comparative statistical analysis between the Tc99m vs ICG procedure was obtained through Concordance Rates Analysis. The impact of some covariates related to ICG use was assessed with multivariable statistical models.
Results. 127 lymph nodes were removed in 113 patients, 77 located in the groin and 50 in the axillary cavity (Table 1). Research with fluorescence probe before skin incision of SLNs was possible in 37 of 127 cases (29%). Identification of SLNs using fluorescence in intraoperative navigation was possible in 116 of 127 cases (92%) (Figure 1). In the multivariate analysis the inguinal location and low BMI in the preoperative phase and BMI alone in the intraoperative phase were statistically related a correct response with ICG.

Table 1. Demographic characteristics.

Patients (n)	113
Lymph nodes (n)	127
Age (mean)	59,33
Sex (n)	
F	48
M	75
BMI (mean)	25,85
Primary melanoma site (n)	
Trunk	58
Limbs	55
Lymph node basin (n)	
Axilla	50
Groin	77

Conclusions. SLNB with Tc99m in melanoma remains the gold standard at present. The use of ICG has limitations, including the difficult identification of deep SLNs due to low tissue penetration and the limited ability to perform preoperative lymphatic imaging for surgical planning. However, the undoubted advantages of the fluorescence technique, such as the speed of execution, the lower costs and the absence of radiation, shouldn't be overlooked even considering the development of improved dyes and new fluorescence detection technologies.

Figure 1.



SHOULD WE RETHINK THE WAY WE TREAT MELANOMA *IN SITU*?

Taglione Bianca[1], Mercurio Simona[1], Patuzzo Roberto[1], Mercurio Giuseppe[2], Valeri Barbara[3], Cossa Mara[3], Cortese Domenico[1], Spadola Giuseppe[1], Gallino Gianfrancesco[1], Mattavelli Ilaria[1], Petrella Mattia[1], Maurichi Andrea[1].

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Background. Current guidelines for surgical treatment of histologically confirmed melanoma in situ (MIS) recommend a wide local excision with a 5 mm margin. However, we have found a considerable number of patients who refused to undergo a wide excision after the diagnosis and instead opted for close follow-up. This study aims to determine whether recurrence occurred in patients who did not undergo wide local excision following a diagnosis of MIS.
Methods.A retrospective monoinstitutional study including 747 patients diagnosed with MIS was conducted between 2001 and 2024. Clinicopathological and follow-up data were recorded.
Results. Out of 747 patients with MIS, 22 (3%) were lentigo maligna (LMM) subtype. The presence of residual disease after the first excision was 27 (4%) of which 5 (19%) LMM. Patients who did not undergo a 5-mm wide local excision were 114 (15%); none of them developed a recurrence at the excision site. Totally, 743/747 (99%) patients did not develop a recurrence at the excision site over a median of 48-months follow-up period.
Conclusions. Based on this study, we suggest a re-evaluation of the current guidelines to critically assess the necessity of a 5-mm margin excision for all cases of MIS and, in particular, for LMM and for acral subtype, allowing a clinical judgement on a case-by-case basis. The possibility of achieving a single, histologically clear excision could alleviate the burden on patients to undergo a second surgery. This approach could also mitigate the overload of surgical interventions, thereby reducing the number of negative histological samples for pathologists. We hope that our monoinstitutional experience inspires similar data analyses at other institutions, ultimately fostering a national consensus on the management of suspicious melanocytic lesions and MIS.

WINDOW-OF-OPPORTUNITY STUDY OF CHEMO-IMMUNOTHERAPY IN PATIENTS WITH RESECTABLE MERKEL CELL CARCINOMA PRIOR TO SURGERY: THE MERCURY TRIAL - PRELIMINAR RESULTS.

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Background. Merkel cell carcinoma (MCC) is a rare and highly aggressive type of skin cancer. Despite aggressive surgical interventions and multidisciplinary treatments, MCC has a high relapse rate and a notably poor prognosis, with survival rates significantly lower than those of melanoma and other skin cancers. We present in this session the preliminar findings of the Mercury trial.

Methods. This multicenter, single-arm, open-label, phase 2 trial evaluates the efficacy of a single cycle of preoperative retifanlimab (500 mg intravenously on day 1) combined with Cisplatin (25 mg/sqm intravenously on days 1 and 2) and Etoposide (100 mg/sqm intravenously on days 1, 2, and 3) in patients with resectable MCC (stage IIA-III). After completing preoperative chemo-immunotherapy, patients will undergo radical surgery on day 35 ± 7. If necessary, adjuvant radiation therapy will be given after-surgery, followed by standard follow-up care. Tumor reassessments will be conducted immediately before surgery on day 28 ± 5.

Results. The study involved 8 patients (Table 1), of whom 6 with MCC in the gluteal region with or without inguino-iliac lymphadenopathy, 1 with carcinoma on the face with submandibular lymphadenopathy and 1 with carcinoma on the arm with axillary lymphadenopathy. Radiological follow-up after therapy showed a disease reduction in 5 patients and disease stability in 3 patients. Surgery was not performed in one case, due to the complete disappearance of the mass, indicating a full response. Histological examination of the surgical specimens showed no further evidence of disease in 2 patients.

Conclusions. This trial differs from others neoadjuvant trials because it focuses on evaluating the independent activity and pharmacodynamic effects of the experimental treatment rather than demostrating improved disease outcomes or survival. These findings may inspire significant hypotheses to enhance treatment efficacy, improve the treatment approach for early-stage MCC and identify specific biomarkers for further personalized cancer therapy.

Table 1. Preliminary results of MERCURY trial for eight patients.

Case	Primary tumor Site	Adenopathy Site	Clinical – Radiological response	Histological residual	Preliminary result
1	Superior Limb	Axillary	Yes	No	CR
2	Inferior Limb	Inguinal - Iliac	No	Yes	SD
3	Inferior Limb	Inguinal - Iliac	Yes	No	CR
4	Face	submandibolar	Yes	No	CR
5	Inferior Limb	Inguinal - Iliac	No	Yes	PR
6	Inferior Limb	Inguinal - Iliac	No	Yes	PR
7	Inferior Limb	none	No	Yes	SD
8	Inferior Limb	none	No	Yes	SD

CR: complete response; SD: stability of disease, PR: partial response.

SURVIVAL OUTCOMES FOR DIFFERENT METHODS OF SURGICAL MANAGEMENT OF PATIENTS WITH SENTINEL LYMPH NODE POSITIVE MELANOMA: A POPULATION BASED COHORT STUDY

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Background. Surgical resection, with wide excision and lymph node biopsy, remains the main treatment in locoregional metastases of cutaneous malignant melanoma (CMM). The true therapeutic value and applicability of complete lymph-node dissection (CLND) for clinical nodal disease remains uncertain. The aim of the study was to investigate in a real-world situation the survival benefit of CLND in positive lymph node patients and the association with clinicopathologic factors.

Methods. This retrospective population-based cohort study included 288 incident cases of TNM I-III CMM with a positive sentinel lymph node biopsy (SLNB) as recorded in 2015, 2017 and 2019 by the Regional Veneto Cancer Registry (Northeast Italy). Kaplan-Meier analysis and Fine-Gray models were used to estimate the association between the performance of lymphadenectomy and overall or melanoma-specific survival.

Results. A lymphadenectomy was performed on 199 (71.1%) patients with a SLNB. 14 (5.3%) subjects with positive axillary or inguinal SLNB had an inadequate number of lymph nodes removed. The patients who underwent lymphadenectomy were the younger (p=0.017), prevalently with superficial spreading melanoma (p=0.28) and higher N stages (p=0.029). The multivariate analyses confirmed the associations between lymphadenectomy and old age and high stage N (p<0.001). Overall and Melanoma-specific survival did not differ according to lymphadenectomy.

Conclusions. Our real-world data confirm the absence of survival benefit of CLND.

TREATMENT PATTERNS AND OUTCOMES OF STAGE-III MELANOMA PATIENTS WITH POSITIVE SENTINEL LYMPH NODE BIOPSY: A REAL-LIFE EXPERIENCE ON THE ROLE OF NODAL DISSECTION

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Background. Advancements in managing stage III melanoma have involved the implementation of adjuvant therapies alongside a simultaneous decrease in the utilization of completion lymph node

dissection (CLND) following positive sentinel node biopsy (SLNB).
Methods. This retrospective study from the University of Turin's Dermatology Clinic analyzed relapse-free survival (RFS) and overall survival (OS) among 157 stage III melanoma patients who underwent CLND after positive SLNB versus those who did not (study time range: 2017-2022). A propensity scores for CLND to estimate the marginal hazard ratios (HR) for CLND and marginal survival curves using an inverse-probability-of-treatment weights (IPTW) were used to control for baseline covariates potentially leading to imbalances between the two groups (stage, age, sex, Breslow thickness, ulceration, adjuvant therapy).
Results. Patients without CLND (n=69) had a median RFS of 49 months (95% CI 42-NA), while CLND recipients (n=88) showed 51 months (95% CI 31-NA) (p=0.139). The 48-month OS for non-CLND patients was 79.8% (95% CI 58.2-91.0) versus 79.2% (95% CI 67.5-87.0) for CLND recipients (p=0.463). Adjusted HR through IPTW revealed the impact of CLND to be insignificant on RFS (aHR 0.90, 95% CI 0.37-2.22) and marginal on OS (aHR 0.41, 95% CI 0.13-1.21) (Figures 1-2). Conversely, adjuvant therapy, administered to 86.6% of patients (63 dabrafenib+trametinib, 60 anti-PD1), significantly reduced the risk of relapse (aHR 0.46, 95% CI 0.25-0.84), irrespective of CLND and BRAF status. This benefit in risk of relapse reduction did not translate into an appreciable difference in OS between patients receiving adjuvant therapy and those who did not (aHR for adjuvant therapy: 1.00, 95% CI 0.39-2.69).
Conclusion: This study corroborates the growing evidence that CLND after positive SLNB does not significantly enhance RFS or OS, while emphasizes the crucial role of adjuvant therapy, be it immunotherapy or targeted therapy, in reducing the risk of relapse in melanoma patients with positive SLNB.

Figure 1. Relapse free survival according to the IPTW model of the no-CLND *vs* the CLND cohort.

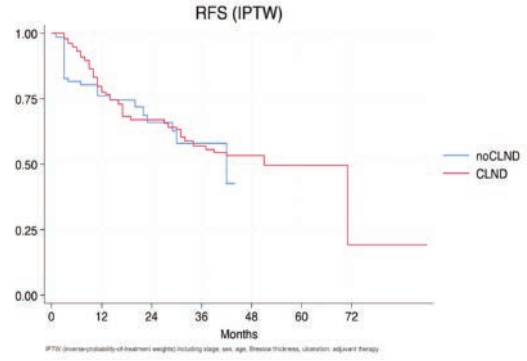
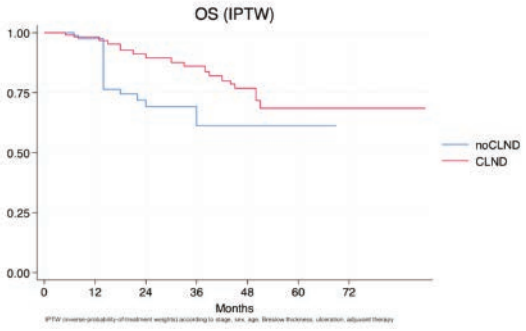


Figure 2. Overall survival according to the IPTW model of the no-CLND *vs* the CLND cohort.



MICROSURGICAL RECONSTRUCTION IN SKIN CANCER PATIENTS: REAL-LIFE DATA FROM A TERTIARY HOSPITAL AND REVIEW OF LITERATURE

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Background. Melanoma skin cancers (MSCs) and non-melanoma skin cancers (NMSCs) are the most common types of cancer, significantly impacting both quality and duration of life. Surgery may have a role in different steps of skin cancer treatment, but wide resections to obtain oncological radicality may lead to wide defects or functional or aesthetic impairment, affecting the quality of life. Once histopathological examination confirms radicality, reconstruction must restore function and guarantee adequate soft tissue coverage and a pleasant appearance. When adequate coverage or optimal functional and aesthetic results are not achievable through other techniques microsurgical reconstruction should be considered.
Methods. This is a systematic review of the literature, a retrospective study of our cases, and a comparative analysis
Results. Two databases have been created: one containing literature works and the other with our cases. Regarding the recording of "oncological" data (neoadjuvant/adjuvant therapies, type of surgery/flap, survival, disease-free period, etc.), the literature provides limited or incomplete results. The studies predominantly focus on the reconstructive aspect, lacking data and correlation with the oncological aspect. The aim is to establish a more comprehensive case series.
Conclusions. There is no evidence that microsurgery is a contraindication or obstacle to oncological therapies. Since it is primarily used in advanced cases, this demonstrates its utility and, in many cases, its indispensability in achieving disease-free margins (through wide excisions), better restoration of form and function and faster healing times.

INTRAOPERATIVE ELECTROCHEMOTHERAPY FOR THE TREATMENT OF THE CANCERIZATION FIELD OF SKIN METASTASES FROM MELANOMA AND NON-MELANOMA SKIN CANCER

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Background. The treatment of skin metastases (SM) from melanoma and non-melanoma skin cancer involves a combination of local/loco-regional and systemic therapies. Responses are variable, with high risk of relapse and progression. Recently, Electrochemotherapy (ECT) has been proposed as a local treatment of SM. Objective and complete responses are documented in 85% and 70% of cases, regardless of tumor histotypes. We report a new application of intraoperative ECT (IECT) for the treatment of the bottom and excision margins after removal of SM. IECT targets the

perilesional cancerization field, possible site of sub-clinical micrometastatic deposits.
Methods. A retrospective study was conducted on patients who underwent IECT at the Plastic and Reconstructive Surgery, Melanoma & Skin Cancer Unit, Azienda Toscana Centro, Firenze. Response rates and outcomes were assessed within the area treated with ECT and outside the treated field, evaluating the Local Clearance (LC: absence of recurrence within the treatment field); Local Progression (LP: one or more new lesions within the treatment field); in-Transit Progression (i-TP: one or more new metastases in transit); Nodal Progression (NP: one or more new lymph node metastases) and Systemic Progression (SP: one or more new distant metastases).
Results. IECT was performed on 28 patients (25 with melanoma and 3 with squamous cell carcinoma SM). After IECT, no recurrence occurred within the area of treatment field, while i-TP, NP and SP were 8%, 8% and 40%, respectively. The treatment was well tolerated, only grade 1 adverse events were observed.
Conclusions. ECT is a promising combination treatment with surgery on the bottom and margins of the residual tissues after SM excision. ECT acts on the peri-lesional cancerization field, possible site of micrometastatic deposits, in order to prevent future local recurrences. The treatment is well tolerated and can be associated with systemic adjuvant immunological therapies with possible synergistic effects.

THERAPY

THE ACTION OF IMMUNE CHECKPOINT INHIBITORY ANTIBODIES IMPAIRS THE MOTILITY FUNCTION OF HUMAN SPERM *IN VITRO*

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Background: The use of immune checkpoint inhibitors (ICIs) such as Ipilimumab (anti-CTLA-4), Nivolumab, and Pembrolizumab (both anti-PD-1), have significantly improved treatment outcomes for Melanoma and many other cancers. However, the impact of these therapies on male fertility, especially sperm function, remains under-explored.
Methods: This study investigates the direct effects of ICIs on human sperm cells, focusing on motility, viability, and apoptotic events. Sperm samples from ten normo-zoospermic donors were exposed to varying concentrations (1-100 ng/mL) of Ipilimumab, Nivolumab, and Pembrolizumab. Sperm motility was assessed through standard parameters, while viability and apoptosis were evaluated using Annexin V-FITC and TUNEL assays. Additionally, purified therapeutic antibodies were isolated to discern their specific impacts.
Results: The phenotypic characterization of sperm cells revealed high PD-1 expression (>99%), with negligible CTLA-4 expression. Upon exposure to ICIs, there was a significant, concentration-dependent decrease in sperm motility, noticeable from 10 ng/mL for Pembrolizumab and Ipilimumab, and at 100 ng/mL for Nivolumab. Despite the motility impairment, ICIs did not induce significant apoptotic changes or affect cell viability. Purified ICIs continued to show motility impairment without affecting viability, suggesting a specific motility disruption mechanism independent of cell apoptosis.
Conclusion: ICIs, specifically Pembrolizumab, Nivolumab, and Ipilimumab, adversely affect sperm motility in vitro without triggering apoptosis. These findings raise concerns about the reproductive side effects of ICIs and highlight the need for further research to understand the underlying mechanisms and clinical implications.

LINKING EARLY IMMUNITY CHANGES TO CLINICAL OUTCOMES IN CUTANEOUS SQUAMOUS CELL CARCINOMA FOLLOWING ANTI-PD1 TREATMENT

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The anti-Program Death 1 (PD1) Cemiplimab is the first-choice treatment in patients with advanced cutaneous squamous cell carcinoma (cSCC), when curative options are unavailable. However, reliable biomarkers for patient selection are still lacking. In this translational study, clinical annotations, tissue and liquid biopsies were acquired to investigate the association between early and sustained objective responses with transcriptional profiles, immune cell dynamics in tumor tissue and peripheral blood, as well as circulating cytokine levels. We transcriptionally investigated early changes in immune-related gene sets associated with response to cemiplimab treatment. We observed that treatment induced increase of B cells and $CD8^+$T cells in responders, while their abundance decreased in non-responder patients. Moreover, IL1β and IL8 exhibited early downregulation in samples acquired from responder patients. Next, we assessed whether changes in the local tumor microenvironment were mirrored in peripheral blood. Similar to tissue findings, no changes were observed in the whole Treg population, albeit PD1+ Tregs that were downregulated in responder patients (vs T0), whereas showed a rebound enrichment in non-responders after three cycles of cemiplimab. Finally, we determined that unlike IL1β, IL8 mirrored the tissue results, with early (T1) and then sustained (T3) downregulation of its levels in responder patients, while increased in non-responders. Taken together, these findings shed light on the significance of early transcriptomic alterations and immune cell population modifications in predicting response to cemiplimab therapy. Additionally, our data suggest that IL8 levels in peripheral blood offer promising avenues for personalized treatment selection and response assessment in cSCC patients receiving cemiplimab, while PD1+ Tregs can be followed longitudinally to monitor response to therapy.

ITALIAN INTERIM ANALYSIS OF THE MULTINATIONAL, POST-AUTHORISATION SAFETY STUDY (NISSO) TO ASSESS THE LONG-TERM SAFETY OF SONIDEGIB IN PATIENTS WITH LOCALLY ADVANCED BASAL CELL CARCINOMA: FOCUS ON TIME TO ONSET OF ADVERSE EVENTS

Alessia Villani[1], Paolo Antonio Ascierto[2], Luigi Scarpato[2], Massimilano Scalvenzi[1], Paolo Bossi[3], Andrea Alberti[4], Vincenzo De Giorgi[5], Lisa Licitra[6], Maria Concetta Fargnoli[7], Paola Savoia[8], Michele Guida[9], Francesco Spagnolo[10], Federica De Galitiis[11], Ignazio Stanganelli[12], Ketty Peris[13]

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Background. Sonidegib is an orally inhibitor of the hedgehog signalling pathway, approved by EMA in 2015, following the pivotal BOLT study, for the treatment of adult patients with locally advanced BCC (laBCC) not amenable to curative surgery or radiation therapy. This interim analysis presents Italian data from the post-authorization safety NISSO study.

Methods. The non-interventional, multinational, multi-center, long-term observational post-authorization safety NISSO study (NCT04066504) collected real-world safety data in laBCC patients aged 18 years or older, treated with sonidegib 200 mg orally once daily. and followed for 3 years. Dose modifications were allowed according to the local Prescribing Information.

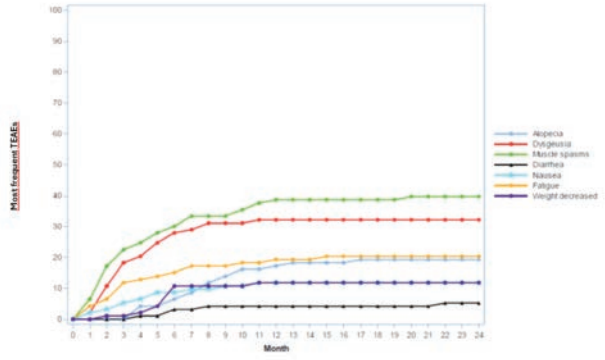
Results. In Italy 12 centres participated in the study and screened 93 patients. The median age was 79 years and 66% of patients were male. At the time of the analysis 32 patients (34.4%) were still on study, while treatment ended in 61 (65.6%) patients, among which the main reasons were patient/guardian decision (n=21, 22.6%), treatment success (n=14, 15.1%) and physician decision (n=8, 8.6%). The median duration of sonidegib exposure was 8.9 months. The safety profile is described in Table 1. Overall, 73 (78.5%) patients had ≥1 treatment-emergent adverse event (TEAE). Most TEAEs were Grade 1 and the most reported were muscle spasms (n = 37, 39.8%), dysgeusia (n = 30, 32.3%), fatigue (n=20, 21.5%) and alopecia (n = 18, 19.4%). The onset of most common TEAEs over time is described in Figure 1.

Table 1. Safety overall summary.

	n	%
Patients with AE	73	78.5
Patients with SAE	12	12.9
Patients with TEAE	73	78.5
Patients with drug-related TEAE	70	75.2
Patients with TEAE leading to discontinuation of sonidegib	12	12.9
Patients with serious TEAE	11	11.8
Patients with serious drug-related TEAE	2	2.1
Patients with at least 1 dose interruption	44	47.3
Patients who interrupted therapy for AE	36	38.7
Patients who interrupted therapy for SAE	1	1.0

(Adverse Events with missing start data are classified as TEAE)

Figure 1. Cumulative incidence of the most frequent TEAE in the first 24 months. It can be appreciated a plateau effect after the first 5-10 months



Conclusions. The Italian interim analysis of NISSO indicates that, under real-world conditions, sonidegib has a better safety profile compared to pivotal BOLT trial. Most patients experienced the onset of common AEs after 3 months of treatment. All the above supports the use of sonidegib as a manageable first-line systemic treatment in patients with laBCC allowing a favourable impact on patients' compliance.

SEX-DRIVEN RESPONSE TO A DENDRITIC CELL VACCINE FOR METASTATIC MELANOMA

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Background. Epidemiological studies provide strong evidence for sex differences in immune responses toward self-antigens (i.e., autoimmunity), viruses, and cancer. Men with advanced melanoma show a significantly better response to immunotherapy with ICIs in the short- and in the long-term than women, on the contrary a Bayesian network meta-analysis of comparison of cancer therapeutic vaccines for melanoma showed that female patients who received vaccination had better survival outcomes. In the last 20 years we treated more than 80 advanced melanoma patients (pts) with a tumor lysate-loaded autologous DC vaccine, observing an overall clinical benefit (OCB) of 54.1%. Based on the literature data we reviewed our database in order to understand if there might be any differences in outcomes due to sex.
Methods. In 2017 we published (De Rosa F. et al Melanoma Research) the results of a retrospective pooled analysis on all the patients treated with immature DC vaccine (14 patients) or mature dendritic cells vaccine (mDC; 28 patients) in a phase I–II study, with low-dose temozolomide plus mDC vaccine (18 patients) and in a compassionate use program (21 patients). We re-analyzed these data by gender point of view in order to discover any differences that could provide suggestions for designing new prospective clinical and translational studies
Results. The database included 30 females (F) and 50 males (M) with median age of respectively 48.5 and 55.5 years. All patients were stage IV and pre-treated for metastatic disease with a median number of sites of metastases of 2 for both M and F and a median number of previous lines of treatment of 2 (range 0-3) for F and 1 (range 0-5) for M. Median number of vaccine cycles was 5.5 for F (1-16) and 5 for M (1-18). We observed an OCB (CR+PR+SD) of 44.4% for the 27 evaluable F and 33.3% for the 42 evaluable M. For the same patients median PFS was 4.7 and 3.3 months, and median OS was 16.2 and 12.3 months for F and M, respectively. Previous overall data showed a statistically OS benefit for patients who developed a positive DTH skin test (in vivo immune response test), so we analyzed these data also in F and M separately and we found the same OS benefit between negative (NF) or positive (PF) F and negative (NM) or positive (PM) M. In particular, median OS was 10.0 and 19.0 months for NF and PF, and 7.1 and 18.3 months for NM and PM, respectively. No toxicity differences were registered between M and F.
Conclusions. Even with the bias of a retrospective study and the numerical imbalance of the two groups of males and females, it seems that even for our cell vaccine there may be an advantage in both DCR and OS for females over males. The advantage seems even more pronounced when the DTH-negative subgroups are considered.

IDENTIFICATION OF IMMUNE PROFILE IN ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA PREDICTING IMMUNOTHERAPY RESPONSE

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Background. Cutaneous squamous cell carcinoma (cSCC) is the second most common form of skin cancer, characterized by malignant proliferation of epidermal keratinocytes. If treated at an early stage with surgical excision, the 5-year cure rate is over 90%. However, in a minority of cases, they are diagnosed at locally advanced(lacSCC) or metastatic(mcSCC) stages, not amenable to surgery, radiotherapy, or a combination of both. Cemiplimab, a monoclonal antibody anti-PD-1, is the first drug approved for the treatment of mcSCC and lacSCC. Here we show how the expression levels of cytokines and chemokines in patiens undergoing treatment vary compared to baseline, and how these variations correlate with treatment response.
Methods. Cytokine profiling is the objective of this study, in the research of potential parameters that specifically respond to Cemiplimab treatment. PBMCs from the blood of lacSCC patients or healthy donors were collected. The expression levels of genes encoding for immune checkpoint (*PD-L1, CTLA4*) and of several proinflammatory cytokines, such as *CXCL8 IL-6, IL-1β, IL12, TNFα, IFNγ* and anti-inflammatory ones (*IL4, IL-10*) were analysed by RT-qPCR. We performed a baseline sample at the start of treatment on both populations, then we conducted sample every 2 cycles on patients in treatment.

Results. Increase of CXCL8 expression was found in patients in treatment, and specifically, the increase in CXCL8 was linked with the timing of clinical response.
Patients in clinical response showed a subsequent reduction in CXCL8 that persists and correlates with the maintenance of clinical response.
Conclusions. CXCL8 appears to be a predictive marker of response in the early stages of treatment in patients who respond to Cemiplimab.

COAGULOME-BASED SIGNATURE PREDICTS CLINICAL RESPONSE IN MELANOMA PATIENTS TREATED WITH CHECKPOINT INHIBITORS IMMUNOTHERAPY

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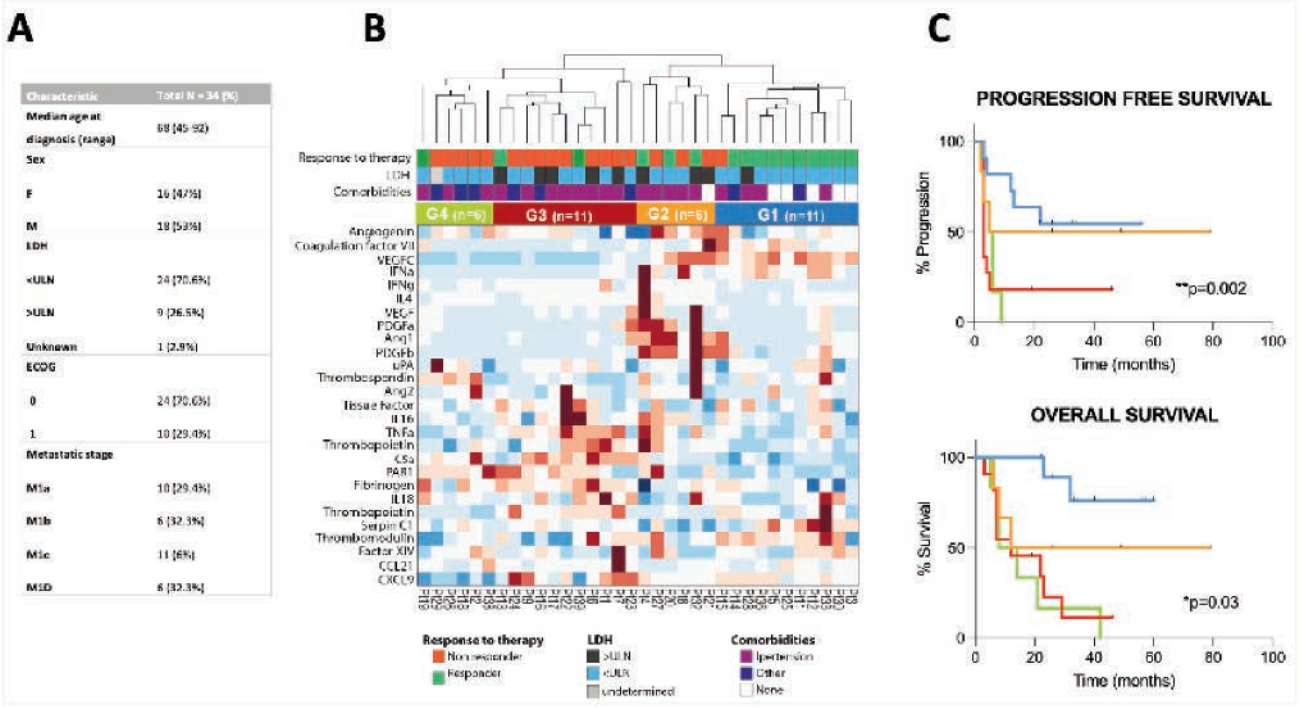
Background. Tumors often exhibit features of chronic wound healing, including activation of the coagulation system. This process is implicated in cancer metastasis, immune evasion, and angiogenesis. While previous studies have highlighted the potential role of coagulation factors in cancer progression, neoangiogenesis, and immune escape, the impact of anticoagulant therapies on checkpoint inhibitors (ICIs) efficacy remains unclear. We aim at elucidating the interplay between coagulation, immunity, and angiogenesis in shaping clinical outcomes for melanoma patients receiving first-line ICIs immunotherapy.
Patients and Methods. We retrospectively assessed the concentration of coagulation, immune, and angiogenic factors (n=33) in the plasma of 34 melanoma patients treated with first-line ICIs (Figure 1A). Plasma was collected at baseline (before starting ICI treatment). The amount of each factor was measured using multiplex ELISA and conventional ELISA assays.
Results. Unsupervised hierarchical clustering (Figure 1B) revealed the presence of 4 groups of patients characterized by specific signatures of soluble factors. Group 1 (G1) was characterized by increased levels of pro-inflammatory cytokines, upstream mediators of coagulation, and VEGFC. G2 was enriched in pro-angiogenic factors, while G3 and G4 showed high expression of PAR1 and Fibrinogen, directly associated with blood clot formation. Remarkably, patients from G3 and G4 showed a higher proportion of non-responding patients to ICIs compared to G1 and G2 (82% and 83% *vs* 9% and 50%, respectively). G3 and G4 also showed shorter PFS (median 3 and 5.5 months) and OS (median 12 and 11 months) compared to G1 and G2 (median PFS: G1 not-reached, G2 42 months; OS: G1 not-reached, G2 45.5 months, Figure 1C).
Conclusions. Our data demonstrate that specific coagulome-based signatures were associated with different melanoma patient responses and survival to ICIs treatment. To understand the precise role of individual coagulation factors in modulating anti-tumor immunity, further functional studies will be performed. These insights could help to understand if the use of anticoagulant therapies could influence anti-tumor immunity and enhance immunotherapy efficacy.

Figure 1. A) Summary table with the general features of the analyzed patients cohort. B) Unsupervised hierarchical clustering of the 34 melanoma patients based on quantification of the listed markers (left side of the heatmap). C) Progression free survival (PFS) and Overall Survival (OS) for each group of patients identified in (B).



EXTREMELY RARE IMMUNE-RELATED ADVERSE EVENTS IN THE COURSE OF IMMUNE-CHECKPOINT BLOCKADE THERAPY

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Background. Immunotherapy with immune checkpoint inhibitors (ICI) has emerged as a pillar of cancer treatment; however, ICI therapy can associate with a variety of common cutaneous, gastrointestinal, hepatic and endocrine immune-related adverse events (irAEs), occurring in about 50-70% of patients.[1,2] The majority of these irAEs occurs in the first 3 months of therapy, while 5-15% may develop even 2 years after treatment initiation.[2] Instead, rare irAEs (*e.g.*, myocarditis, encephalitis, myositis, pneumonitis) occur in <2% of ICI-treated patients[7]. In addition, extremely rare irAEs (ERirAEs), inducing potentially life threatening complications, should also be considered in the course of ICI therapy.

Methods. We collected a case series of metastatic melanoma (MM) patients, treated with ICI at the Center for Immuno-Oncology of the University Hospital of Siena, Italy, who developed ERirAEs. Clinical, radiological and histopathological features of ERirAEs were thoroughly collected. ERirAES were graded according to the CTCAE v. 5.0.

Results. From January 2008 to March 2024, among 915 ICI-treated MM patients, 5 (0,5%) developed ERirAEs including eosinophilic fasciitis, Miescher's granulomatous cheilitis (MGC), hemolytic anemia, macrophage activation syndrome (MAS), and sarcoidosis-like reaction (SLR). Patients [4 males; median age 63 years (range 49-74)] had unresectable stage III (1)/IV (4) MM, and had received ICI monotherapy (2) or in combination (3). ERirAEs were classified as grade (G) 1, G2 (2), G3 (1), and G5 (1). One patient developed MGC 5 years after ICI discontinuation, for the remaining patients the median time to onset and to resolution of ERirAEs was 96 weeks (range 7-327) and 19 weeks (range 2-39), respectively. Treatment with steroids (80%) and additional immunosuppressive drugs (40%), including mycophenolate and immunoglobulins, were required to treat ERirAEs. One patient resumed ICI therapy after ERirAEs resolution.

Conclusions. ERirAEs could be fatal events with an insidious onset and unpredictable evolution during ICI therapy. Raising awareness among oncologists about the potential occurrence of ERirAEs is crucial to optimize their clinical management and to avoid fatal complications.

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TACKLING THE INVASIVE PROPERTIES OF DRUG RESISTANT MELANOMAS USING LOCKED NUCLEIC ACID (LNA) TO INHIBIT THE ONCOMIRS MIR-4443 AND MIR-4488

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Metastatic melanoma is a devasting disease and its incidence is rapidly increasing worldwide. The combinatorial treatments with BRAF and MEK inhibitors has improved the survival of BRAF-mutant melanoma patients. However, acquired resistance to targeted therapy still limits the efficacy of these treatments in time. Recently, many findings have underscored the involvement of microRNAs in this process. In our laboratory we have identified a subset of miRNAs divided into oncosuppressors and oncomiRs strongly deregulated in drug resistant melanomas. Among them, we discovered that two novel oncomiRs, namely miR-4443 and miR-4488 govern the migratory and invasive phenotypes, that are a hallmark of drug resistant melanoma cells. This occurs through their ability to target the intermediate filament nestin. Given these results, we decided to exploit the targeting of miR-4443 and miR-4488 as a novel therapeutic strategy to tackle the metastatic potential of drug resistant melanomas. This has been accomplished using locked nucleic acid (LNA)-modified antimiRs, which are highly resistant to nuclease degradation *in vitro* and *in vivo*. Exploiting a different set of biological assays, we have demonstrated that LNA-miR-4443/miR-4488 reduce migration and invasion of different drug-resistant melanoma cell lines. Molecularly, the treatment with LNA-oncomiRs is able to restore the levels of nestin in drug resistant cells as demonstrated by western blotting and confocal analyses. Finally, we deepened the kinetics of intracellular uptake of LNAs by flow cytometry analyses, since these molecules are modified with 5'FAM fluorescent dye. Results demonstrated that melanoma cells are effectively targeted by LNAs until 5 days post treatment. These promising results will be validated on *in vivo* metastatic melanoma models recently established in our lab. Altogether, these data pave the way to further deepen the therapeutic potential of LNA-miR-4443/miR-4488 for melanoma treatment.

A SINGLE CENTER, REAL WORLD EXPERIENCE OF CEMIPLIMAB IN ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA

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Background. Cutaneous Squamous Cell Carcinoma (CSCC) is the second most frequent non melanocytic skin cancer, with an increasing incidence predominantly in elderly subjects. The anti-PD-1 monoclonal antibody cemiplimab has significantly improved the outcome of CSCC patients, with an objective response rate (ORR) of 47 % and a median duration of response of 41.3 months (95% CI 38.8-46.3).[1] Based on these impressive results, cemiplimab is currently the standard of care for CSCC patients, and real-world data can help the daily practice.
Methods. This single-Center experience included adult patients with locally advanced (la) or metastatic (m) CSCC treated with cemiplimab (350 mg) at the Center for Immuno-Oncology, University Hospital of Siena, Italy, within an Expanded Access Program or as standard of care. Clinical outcome and adverse events (AEs) are reported.
Results. Between December 2019 and December 2023, 27 patients (24 male; median age 76 years [range 41-90]) diagnosed with laCSCC (n=20 [74.0 %]) and mCSCC (n=7 [25.9 %]) were treated with cemiplimab as first line therapy. The most common primary tumor location was head and neck (88.8 %), followed by trunk (7.4 %), and lower extremities (3.7 %). All patients had comorbidities including 6 patients (22.2%) with hematologic malignancies.
As of June 2024, with a median follow-up of 22.8 months, the ORR was 66.6% (CR 22.2%) with a DCR of 77.7%. Median progression free survival (mPFS) and overall survival (mOS) were not reached, while 1-year OS and -PFS rates were 74% and 70%, respectively. Treatment was well tolerated with 3 (11.1%) patients experiencing grade ≥ 3 treatment-related adverse events, and 2 (7%) patients discontinuing treatment due to AEs.
Conclusion: Our real-world experience in elderly patients with CSSC, confirms the high rate of objective responses and the good tolerability of cemiplimab.

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SEVERE TREATMENT-RELATED ADVERSE EVENTS (TRAES) WITH ADJUVANT ANTI-PD1 THERAPY: A REAL-LIFE ANALYSIS FROM A MELANOMA REFERRAL CENTER

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Background. Anti-PD1 treatments (tx) have improved recurrence-free survival (RFS) and overall survival (OS) in resected stage III/IV melanoma patients (pts). However, grade 3–4 (G3-4) treatment-related adverse events (trAEs) are challenging. This study provides a descriptive analysis of G3-4 trAEs in adjuvant anti-PD1 therapy.
Methods. We conducted a real-life observational retrospective analysis of 192 pts receiving adjuvant anti-PD1 tx between 2019 and 2024 at IRCCS Regina Elena National Cancer Institute. Clinical data and treatment outcomes were extracted from clinical records.
Results. 192 pts were analyzed, 21 (10.9%) experiencing G3-4 trAEs. Pts characteristics: 16 males/5 females, median age 71 years (range 49-86) at tx start. Stages: IIIA 2 pts (10%), IIIB 6 (28%), IIIC 6 (28%), and IV NED 7 (34%). Eight pts (38%) had multiple concurrent/sequential G3-4 trAEs, primarily gastrointestinal (hepatitis 19%, pancreatitis 28%, colitis 10%), arthritis (28%), and peripheral neurological toxicities (24%). Less common trAEs: skin toxicity (14%), central neurological toxicity (10%), polymyalgia-like syndrome (10%), pneumonia (4.7%), nephritis (4.7%), and endocrine toxicities (4.7%). Median toxicity duration was 2 months (range 1-15), with definitive tx discontinuation in 17 pts (81%). Most pts (58%) received intravenous corticosteroids: two (10%) required immunosuppressive therapy due to worsening despite intravenous tx. Nine pts (42%) received oral corticosteroids per international guidelines: 5 cases of arthritis, 1 of polymyalgia-like syndrome, and 3 of pancreatitis were reported. Rheumatologic immunosuppressants were required in 3 cases of steroid-refractory arthritis. At median FUP of 26.5 months (range 8-60), 19 pts (91%) were alive and recurrence-free; one pt's status was unknown and one pt died due to myasthenic-like syndrome. Two pts needed chronic toxicity management (1 replacement, 1 immunosuppressive).
Conclusions. Chronic toxicity in potentially cured pts poses a significant challenge in using immunotherapy. Further research is needed to identify biomarkers for risk stratification to tailor adjuvant therapy and reduce severe toxicities.

FLASH RADIOTHERAPY: A NEW POSSIBLE ARM AGAINST SKIN CANCERS?

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Background. Flash Radiotherapy is a new technique that has been shown to improve the therapeutic ratio of radiotherapy by reducing toxicities in healthy tissues while preserving the same efficacy in cancer tissues. Our knowledge of Flash Radiotherapy is largely based on very limited data and mainly on low-energy electrons. The aims of this research are: to compare the effect of FLASH and conventional irradiation on human skin tissue at increasing doses of radiation; to assess the correlation between beam parameters (ADR, DPP, PR) and the dose that provides better sparing; and to evaluate the dependence of the FLASH effect on adjacent fields, volume, and dose fractionation.
Methods. We used skin samples from cadaveric donors. Eight samples measuring 2 cm by 2 cm were irradiated with conventional and ultra-high dose rate (UHDR) at doses of 10, 20, 30, and 40 Gy. Ultra-high-frequency ultrasound was performed before and after irradiation. Furthermore, RNA extraction was carried out after irradiation to study the expression of specific genes at different time points (6-72 hours) related to cell death, inflammation, senescence, and cell cycle control. The tests were conducted using a system of current transformer, ionization chamber, calorimeter, and flashDiamond detector to verify the dose delivered.
Results. Qualitative analysis of the ultrasound images showed edematous and hypoechoic changes in the irradiated samples (signs of tissue damage), which were more evident with conventional irradiation. Quantitative analyses of images and gene expression are still ongoing.
Conclusions. Human tissue provides a more relevant way of studying human biology than in vitro assays or animal models. This study will be useful in understanding if adjacent fields, volume, and dose fractionation influence the degree of the Flash effect. This knowledge will be fundamental for the use of UHDR electrons with very high energy in the treatment of skin cancers.

SYSTEMIC ADJUVANT TREATMENT IN RESECTED STAGE III AND IV MELANOMA: A SINGLE INSTITUTION EXPERIENCE

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Background. Almost a third of melanoma patients is diagnosed with a radically operable stage III and IV melanoma, but a large part of these patients inevitably relapses. Systemic adjuvant treatments such as anti PD1 immunotherapy (nivolumab and pembrolizumab) and dabrafenib plus trametinib (D+T) significantly reduced the risk of relapse. We report the survival outcomes of patients treated with either adjuvant antiPD1 or D+T at a single institution.
Methods. We performed a survival analysis in patients treated with adjuvant treatment for completely resected stage III and IV melanoma. Patients included in this study gave informed consent and are followed in the ambispective observational protocol Melabase.
Results. From June 2019, 76 patients received adjuvant treatment for stage III and IV melanoma. Patients were mostly male (n=47; 62%), median age was 62.3 years (IQR 52.1-73.4), had an ulcerated primary tumor (n=50; 66%), were stage IIIC (n=41; 55%), a BRAF mutation (n=44; 55%), Breslow thickness was 2.95 mm (IQR 1.9-4.8), median number of mitosis was 4/mmq (IQR 2-11). All other relevant variables are listed in Table 1.

Variable	
Age median (IQR)	62.4 (52.1-73.2)
Sex (%)	M= 47 (61.8%) F= 29 (38.2%)
Familiar melanoma (%)	Yes=3 (3.1%) No= 73 (96.9 %)
Breslow thickness mm (IQR)	2.9 (1.9-4.8)
N mitosis (IQR)	4 (2-11)
Primary site (%)	Trunk= 40 (52.6%) Upper limb= 9 (11.8%) Lower limb= 17 (22.4%) Foot= 3 (3.9%) Head= 5 (6.6%) Neck= 2 (2.6%)
Ulceration (%)	Yes=50 (65.8%) No=26 (34.2%)
BRAF mutation (%)	No=32 (42.1%) V600E=42 (55.3%) V600K=2 (2.6%)
pT (%)	1a=1 (1.3%) 1b=7 (9.2%) 2a=11 (14.5%) 2b=6 (7.9%) 3a=6 (7.9%) 3b=22 (28.9%) 4a=3 (3.9%) 4b=19 (25)% TX=1 (1.3%)
Stage at adjuvant treatment (%)	IIIA=9 (12%) IIIB=15 (20%) IIIC=41 (54.7%) IIID=1 (1.3%) IV=9 (12%)

Most patients received D+T (n=39; 51.3%) and concluded adjuvant therapy (n=57; 75%). Nine patients each discontinued adjuvant treatment for G3-4 toxicity or PD (11.8%). Most frequent G3 AEs were adrenal toxicity (n=5 6%), liver toxicity (3 3.9%), musculoskeletal toxicity (3; 3.9%). With a median follow-up time of 35 months, median DFS was 38.9 months (95%CI 21.7-74.5), and DFS was comparable according to the type of adjuvant treatment (p=0.62). mOS was 56.7 months (95%CI 46.6-66.6). There was no significant statistical difference between adjuvant treatments (p=0.57).
Conclusion. In this observational study immunotherapy and D+T treatment yielded comparable survival and toxicity outcomes in a real-life cohort of patients. Our results are comparable to registrative clinical trials and support the use of adjuvant treatment in these patients.

SELF-ASSEMBLING NANOPARTICLES FOR MIRNA DELIVERY TOWARDS PRECISION MEDICINE AGAINST MELANOMA

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Background. Target therapy for BRAF mutated tumors and immunotherapy with checkpoint inhibitors, have significantly improved survival of patients with metastatic melanoma. However, the development of *ab initio* or *de novo* drug resistance remains a big deal. We have previously identified a set of microRNAs (miRNAs) involved in the development of drug resistance. Some of these behave as oncosuppressors and are downregulated in drug resistant tumors. Here we evaluated the therapeutic potential of three of them, namely miR-199b-5p, miR-204-5p and miR-579-3p, delivered by self-assembling lipid nanoparticles (SANP). SANPs consist of a calcium phosphate core enclosed by a lipid shell and can be generated immediately before the use.

Methods: BRAF-mutant A375 cells and BRAF-mutant ME4686 primary cells were subjected to treatments with miRNA-loaded SANPs, MAPKi or their combinations. Crystal violet staining and CellTiter-Glo assay were used to assess proliferation and vitality. qRT-PCR, Western Blot assay and ELISA assay were used to evaluate genes expression.

Results. First we observed that SANPs loaded with miR-199b-5p and miR-204-5p (SANPs bis) induced a high level of miRNA intracellular uptake accompanied by a strong enhancement of the cell growth inhibitory activity of MAPKi. SANPs bis inhibited the release of soluble tumor-promoting factors such as VEGFA and TGFβ1, target genes of the two miRNAs. Subsequently we showed that SANPs delivering the third miRNA, *i.e.* miR-579-3p alone, which targets BRAF and MDM2 oncogenes, were able to further enhance the growth inhibitory effect of MAPKi when combined with SANPs bis and gave rise to the most powerful inhibition of cell growth. Surprisingly, SANPs carrying the three miRNAs together showed a paradoxical loss of biological activity.

Conclusions. SANPs are a powerful delivery strategy for oncosuppressor miRNAs in melanoma. However, significant efforts must be directed to identify the best formulations and to avoid unwanted interfering effects played by the different cargos, before starting *in vivo* studies.

"CORRELATION BETWEEN CLINICAL CHARACTERISTICS AND RELAPSE FREE SURVIVAL IN RESECTED STAGE III MELANOMA TREATED WITH ADJUVANT DABRAFENIB AND TRAMETINIB: A REAL WORLD EXPERIENCE FROM A SINGLE CENTER"

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Background. In the phase 3 COMBI-AD trial, 12 months of adjuvant dabrafenib plus trametinib in resected, stage III, BRAF mutated melanoma, resulted in longer relapse-free survival (RFS) than placebo. However, the prognostic relevance of specific clinical characteristics, such as baseline LDH values, and of the omission of lymphadenectomy after primary tumor resection and sentinel lymph node biopsy, is still unclear in this setting. Our analysis aims at assessing the results of adjuvant treatment in a real-world cohort of patients from IDI-IRCCS in Rome, Italy.

Figure 1. Multivariable analysis on the correlation between RFS and baseline characteristics of stage III melanoma patients.

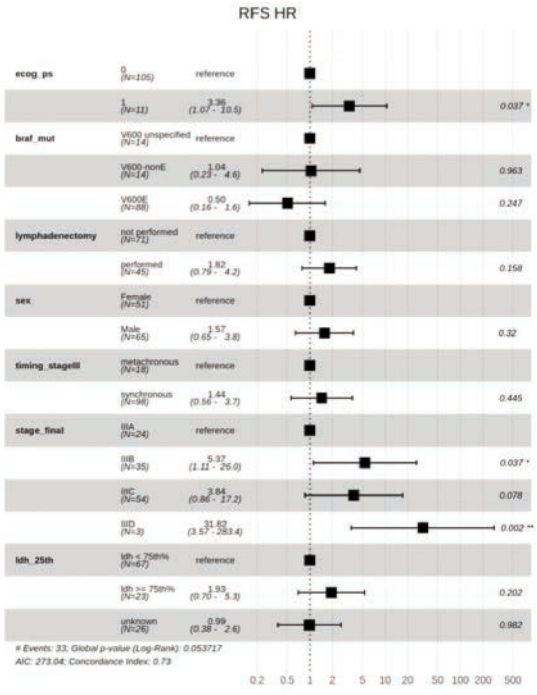

Figure 2. RFS in patients with resected stage III melanoma treated with adjuvant dabrafenib trametinib according to baseline LDH level.