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ABSTRACT BOOK
PATROCINI
In recent years, the scenario of strategies for the diagnosis and treatment of melanoma and non-melanoma neoplastic skin diseases has profoundly changed. An even greater integration of different clinical and scientific skills is needed, as well as the harmonious sharing of practical experiences within the context of various disciplinary sectors. Over the years it has been shown that melanoma acts as a real “trailblazer” in many aspects related to the systematization and management of oncological diseases. The Italian Melanoma Intergroup (IMI) has been a group operating in a totally multidisciplinary manner since its beginning. Firstly, it developed and supported an integrated and transversal strategy in the professional training, research and management of melanoma, and subsequently also of non-melanoma skin cancers requiring more complex management such as basal cell carcinoma, squamous cell carcinoma and Merkel cell carcinoma. IMI represents a model of interrelatedness and cooperation among diverse scientific activities and focuses on professional training in order to develop harmonious integration and synergy among the various disciplines throughout the country.

Currently IMI’s main objective is to enhance the role of multidisciplinary teams in making the strategies to be implemented in the diagnostic and therapeutic course of our patients increasingly uniform. As a dermatologist and president of the Italian Melanoma Intergroup, I am very proud of this editorial collaboration with ADOI, and I sincerely thank the President of ADOI Francesco Cusano and the Editor-in-Chief of Dermatology Report, Luigi Naldi, for this great opportunity to contribute to developing the area of oncological dermatology together.

Both associations will thereby be able to better promote connection and cooperation in the field of scientific activity and training nationwide. IMI’s main goal in clinical care and applied research is to develop and strengthen synergy among representatives of the various disciplines for the creation and enhancement of multidisciplinary teams.

ADOI and IMI’s common goal in this editorial challenge must be to further quality publications in an area of dermatology that always gives added value to multidisciplinary. IMI represents this ability: “to work together to grow”.

The abstracts published in this issue of Dermatology Reports represent the papers selected and presented at the XXVI National IMI Congress and the First Virtual IMI Congress held on 7-8-9 November 2020.

Ignazio Stanganelli
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FAMILIAL MELANOMA AND MULTIPLE PRIMARY MELANOMA: ANALYSIS OF PREDISPOISING GENETIC MUTATIONS IN 190 PATIENTS

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Introduction: Melanoma develops from a complex interaction between environmental and constitutional risk factors (namely genetic and phenotypic). In addition, familiarity and presence of multiple melanomas in a single patient also play a major role in melanoma onset. Familial melanoma (MF) is a rare hereditary form, characterized by the development of histologically-confirmed melanomas, in two first degree relatives or in 3 or more relatives of the same family.1,2 When 2 synchronous or metachronous melanomas develop in the same individual, a diagnosis of multiple melanoma (MM) can be established. About 10% (8-12%) of patients with melanoma have at least one first-degree family member suffering from this disease; in addiction, history of removal of previous melanomas increases the risk of developing a second melanoma over a lifetime by 5-8%.3

Materials and methods: A retrospective cross-sectional observational study was performed, with clinical and genetic data of 872 patients with melanoma and afferent to the Melanoma Service of the Dermatological Clinic IRCCS Policlinico San Matteo Pavia. Of these, 190 patients were subjected to genetic investigation through molecular analysis NGS (Next Generation Sequencing) of the multigene panel (TruSight Cancer-94 genes) related to eredo-familial neoplasms. The primary objective is to identify the prevalence of patients with MM and/or MF. The secondary objective is to identify the number of patients carrying melanoma-defining mutations and/or newly discovered mutations to correlate the genetic profile with the clinical phenotype and with the histological features of the tumour. The final aim, indeed, is to highlight the huge impact of genetic risk factors on both clinical picture and patient and relative prognosis, as well as to program a more careful clinical and instrumental follow-up.

Results: MF prevalence was calculated at 10% (87 patients out of 872 patients) and MM prevalence was calculated at 7.7% (67 patients out of 872 patients). Of the 190 patients subjected to genetic investigation, 26.8% were mutated. Of the 190 patients, 138 performed the genetic investigation for personal history of MM and/or MM and 52 patients for high eredo-familial cancer risk. Of the first group of 138 patients, 73.2% were wild type and 26.8% mutated, with a higher prevalence for CDKN2A mutations. In the second group of 52 patients, 83% were wild type and 15% mutated, with higher prevalence of MC1R and FANC genes. In patients with CDKN2A mutation, A148T mutation was found in 21 patients and G101W was found in 9 patients. The latter mutation was found to be related to a worse prognosis in terms of Breslow thickness and secondary development. Of the 67 patients out of 190 (35%) who removed a second melanoma during the follow-up, a reduction in the average Breslow thickness of the second melanoma (0.58 mm) was observed compared to the first (1.2 mm); this difference was statistically significant (p=0.0069).

Conclusions: Our study confirm the prevalence of MF (10%) and MM (7.7%) described in the literature. Moreover, it shows the importance of carrying out the genetic investigation in patients with MF and/or MM and suggests extending the genetic investigation to all patients with high eredo-familial oncology risk. The finding the 22% of patients positive to genetic testing of mutations in genes other than CDKN2A and CDK4, which are described to be melanoma-defining lesions, suggests the importance of extending the investigation by complete gene panel compared to targeted research of the mutated gene. Moreover, considering the CDKN2A gene mutations, our data showed a greater aggressiveness of the G101W mutation than the A148T mutation. The diversification of single mutations within the same gene could suggest more careful and targeted prevention programs in case of more aggressive mutations. Finally, the evidence of a statistically significant reduction in the thickness of Breslow in second melanomas compared to the first, confirms the importance of planning a close clinical follow-up supported by genetic data.

References


INFLUENCE OF MC1R GENOTYPE ON MELANOMA RISK IN RELATION TO SUN EXPOSURE


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Background: Melanocortin-1-receptor (MC1R) is one of the major genes that control skin pigmentation and melanomagenesis. MC1R variants play a role in melanoma development both via pigmentary and non-pigmentary pathways.1,2 UVR is a well-established risk factor for melanoma. Data assessing sun exposure measures and the degree to which this variable influences the association between MC1R variants and melanoma risk, apart from phenotypic characteristics, are scarce. The aim of this study was to evaluate whether sun exposure modifies the effect of MC1R variants on melanoma
by analyzing MC1R gene – sun exposure interaction.

**Materials and methods:** Cutaneous melanoma (CM) cases with information on chronic and/or intermittent sun exposure (N=3,365) and the corresponding controls (N=2,793) from nine studies in which the MC1R gene was sequenced were obtained from the Melanocortin 1 receptor, SKin cancer and Phenotypic characteristics (M-SKIP) dataset, described in detail elsewhere.** Sun exposure category was defined as a binary variable. In each study, we calculated estimates for main effects of any MC1R variant, occupational or intermittent sun exposure and for a multiplicative interaction term using a logistic regression model, and considered age, sex, family history of melanoma, sunburn, common and atypical naevi, hair and eye color, freckles, and skin type as potential confounders. A two-stage approach with random effects models was adopted to calculate Summary Odds Ratios (SORs) and 95% Confidence Intervals (CI).

**Results:** No significant interaction of MC1R and sun exposure was observed for either occupational or intermittent sun exposure. SOR and 95% CI for the risk of melanoma for occupationally-exposed subjects with any MC1R variant was 1.60 (1.29-2.00) compared to non-occupationally-exposed subjects without MC1R variants (p-value for interaction: 0.60). SOR (95% CI) for the risk of melanoma for carriers of any MC1R variant with high intermittent sun exposure compared to non-carriers of MC1R with low intermittent exposure was 1.64 (1.22-2.20); p-value for interaction: 0.82.

**Conclusions:** MC1R and sun exposure independently affect melanoma risk, with no synergic or antagonist effect.

**References**

**A03**

**CIRCUITING TUMOUR DNA AND MELANOMA SURVIVAL: A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS**

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**Background:** Melanoma is the most aggressive form of skin cancer and is responsible for nearly 60,000 deaths globally each year. Circulating tumour DNA (ctDNA) corresponds to free fragmented DNA released by tumour cells. Several studies have demonstrated the potential application of ctDNA analysis in clinical management of several solid malignancies such as breast, lung, and gastrointestinal cancers.1,3 In melanoma, ctDNA has drawn a lot of interest because, in addition to having a high mutational burden, somatic mutations of a few key driver genes (e.g. BRAF and NRAS) occur early during tumorigenesis in a large proportion of cases, which outlines an ideal scenario for using mutant ctDNA as a prognostic and monitoring biomarker. We reviewed and meta-analysed the available evidence (until December 2019) about circulating tumour DNA (ctDNA) levels and melanoma patient’s survival.

**Materials and methods:** We included twenty-six studies (>2,000 patients overall), which included mostly stage III-IV cutaneous melanoma patients and differed widely in terms of systemic therapy received and somatic mutations that were searched.

**Results:** Patients with detectable ctDNA before treatment had worse progression-free survival (PFS) (summary hazard ratio (SHR) 2.47, 95% confidence intervals (CI) 1.85-3.29) and overall survival (OS) (SHR 2.98, 95% CI 2.26-3.92), with no difference by tumour stage. ctDNA detectability during follow-up was associated with poorer PFS (SHR 4.27, 95%CI 2.75-6.63) and OS (SHR 3.91, 95%CI 1.97-7.78); in the latter case, the association was stronger (p=0.01) for stage IV vs. III melanomas. Between-estimates heterogeneity was low for all pooled estimates.

**Conclusions:** ctDNA is a strong prognostic biomarker for advanced-stage melanoma patients, robust across tumour (e.g. genomic profile) and patients (e.g. systemic therapy) characteristics.

**References**
Results: CDKN2A pathogenic variants (PV) were detected in 9% of cases, with a higher frequency in familial and multiple melanoma cases; MITF E318K variant was detected in 3 patients, while CDK4 and POT1 PVs were not identified in the studied population. Most of the studied cases displayed MC1R variants (70%). Sporadic melanoma cases and familial/multiple primary melanoma patients displayed significant differences in the frequency rate of CDKN2A PV and MC1R R160W variant; in addition, they differed for hair color, number of nevi, body site of primary melanoma and age at diagnosis. In detail, sporadic cases were younger, infrequently red haired, displayed a lower number of nevi and head/neck melanoma than familial/multiple melanoma cases. CDKN2A common polymorphisms were found associated with nevi and red hair. MC1R variants were associated to primary melanoma body site, Breslow thickness, higher number of nevi in addition to fair skin type and red hair color, thus confirming a role for MC1R variants in melanoma susceptibility in young patients. In children (≤ 12 years) primary melanoma differed from that of the older study population for histotype, being more frequently spitzoid, for higher Breslow thickness and for the more frequent occurrence on the head/neck and upper limbs as compared to trunk and lower limbs. CDKN2A gene PVs were less frequent and MC1R variants V92M and D84E more common in children than in the adolescent group.

Conclusions: Our results confirm the involvement of the major melanoma associated genes in melanoma occurring in children and adolescents. In addition, they suggest the implication of unknown susceptibility genes especially in the children population.

A05

MACHINE LEARNING-BASED EVALUATION OF THE COMPLEX LINKS EXISTING BETWEEN COSTS AND THE CLINICAL AND SOCIO-DEMOGRAPHIC CHARACTERISTICS IN A LARGE ITALIAN COHORT OF MELANOMA PATIENTS

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Background: Melanoma is a menacing public health issue and a cause of rising costs for healthcare systems. Thus, we aimed to cluster patients to predict their healthcare costs from baseline biological characteristics with artificial neural network (ANN), a new statistical tool employing machine learning to understand the connections and complex dynamics of adaptive interactions between melanoma-related clinical, demographic and cost variables.

Materials and methods: A melanoma registry of 590 melanomas was built with the collaboration between Veneto Tumor Registry & Veneto Oncology Network. The registry contained a set of tumor characteristics including: TNM stage at diagnosis; Breslow thickness (mm); Clark’s level of invasion (I-V); presence of ulceration (yes/no); site (trunk, head, limbs); costs categories tertiles (scintigraphic, surgical, medical, instrumental, cyto/histological, biological, blood exams, radio-therapeutic, radiological and total (Hospital Discharge Forms (SDO) based costs), CMM specific mortality. A semantic connectivity map was developed using the AutoCM system (AutoCM, Semeion©, Rome, Italy), a fourth-generation ANN that employ non-linear statistics to solve challenging biological questions (Figure 1).

Results: The item “1-6 mitoses” is the center (main attractor) of our unsupervised analysis, demonstrating its clustering value vis-à-vis the spread of its four main branches (strength ~0.60) depicting four endotypes. The use of radiotherapy, education and marital status were central descriptors in our database. The first one cluster is advance stage patients with nodular melanoma and ulcerated with high risk of death and an heavy economic burden, whilst the second one encloses elderly patients (>60 yoa) with CMM on the trunk or face and high procedural and therapeutic costs. The third endotype clusters only stage Ib patients, whilst the fourth one clusters around the absence of costs for radiotherapy, which includes four main sub-sets, each with their own biological and socioeconomic items.

Conclusions: Our study suggests that machine learning represents a powerful tool to decodify complex biological phenomena and a precious guidance in healthcare management amelioration.

References


A06

INSIGHTS INTO GENETIC SUSCEPTIBILITY TO CDKN2A NEGATIVE MELANOMA BY GENE PANEL TESTING: POTENTIAL PATHOGENIC VARIANTS IN ACD, ATM, BAPI, AND POTI

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Introduction: The contribution of recently established or candidate susceptibility genes to melanoma missing heritability has yet to be determined. Multigene panel testing could increase diagnostic yield and better define the role of candidate genes.

Methods: We characterized 273 CDKN2A/ARF and CDK4-negative probands through a custom-designed targeted gene panel which included CDKN2A/ARF, CDK4, ACD, BAP1, MITF, POT1, TERF2IP, ATM, PALB2. Co-segregation, LOH/protein expression analysis and splicing characterization were performed to improve variant classification. We identified 16 (5.9%) pathogenic and likely pathogenic variants in established high/medium penetrance cutaneous melanoma susceptibility genes (BAP1, POT1, ACD, MITF, and TERF2IP), including 2 novel variants in BAP1 and 4 in POT1. Interestingly, we also found 4 deleterious and 5 likely deleterious variants in ATM (3.3%). Thus, including potentially deleterious variants in ATM increased the diagnostic yield to about 9%. Inclusion of rare variants of uncertain significance would increase the overall detection yield to 14%.

Results: This study shows that, in our population, at least 10% of melanoma missing heritability may be explained through panel testing. To our knowledge, this is the highest frequency of putative ATM deleterious variants reported in melanoma families, suggesting a possible role in melanoma susceptibility which needs further investigation.
A09

**REVERSE TRANSCRIPTASE INHIBITION POTENTIATES TARGET THERAPY IN BRAF-MUTANT MELANOMAS: AN IN VITRO STUDY**

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**Background:** BRAF+MEK inhibitors have become the standard of care for BRAF-mutated melanoma patients. However, drug resistance remains a major clinical hurdle. From here, the need to identify additional therapeutics capable to tackle the onset of drug-resistant clones. Our group has been involved in this topic during last years. Thereby, we reported that anti-ErbB3 receptor monoclonal antibodies are able to delay the emergence of resistance to target therapy in vitro and in vivo. More recently, we have demonstrated that microRNAs are key players of resistance to BRAFi and MEKi in melanoma and that their targeting is able to restore drug sensitivity. Here, we have started to investigate whether reverse transcriptase inhibitors (RTIs) frequently used in the treatment of AIDS can act in combination with target therapy to fight the development of drug resistance.

**Materials and methods:** Human melanoma cells M14 and A375 have been treated with different concentrations of BRAFi, MEKi and/or the non-nucleoside RTI, i.e. SPV122. MTT and colony formation assays have been used to determine cell proliferation. Annexin V assay, cell cycle and mitochondrial membrane depolarization have been tested through FACS analyses. DNA damage have been determined through Western Blot and Immunofluorescence analyses.

**Results:** Our present work has reported for the first time the capability of RTIs to potentiate target therapy in BRAF-mutant melanomas in vitro. We show that SPV122 synergizes with BRAFi+MEKi to: 1) impair BRAF-mutant melanoma cell growth; 2) induce apoptosis; 3) block cell cycle progression and 4) delay the emergence of resistance in vitro. Mechanistically, we also showed that this combination provokes DNA double-strand breaks, mitochondrial membrane depolarization and increased ROS levels.

**Conclusions:** Our in vitro results pave the way for the combinatorial use of RTi+BRAFi+MEKi as a novel therapeutic option for BRAF-mutant melanoma patients and warrant further investigation in vivo.

**References**


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**SURGERY**

**A10**

**THE SURGICAL TREATMENT OF NON-METASTATIC MELANOMA IN A MULTICENTER REGISTRY: A RETROSPECTIVE COHORT QUALITY IMPROVEMENT STUDY TO REDUCE THE MORBIDITY RATES**

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**Background:** Reproducible, high-quality surgery is a key point in the management of cancer patients. Quality indicators for surgical treatment of melanoma has been presented with benchmarks but data on morbidity are still limited. This study presents the quality indicators on morbidity after surgical treatment for non-metastatic skin melanoma in an Italian registry.

**Materials and methods:** Data were extracted from the Central National Melanoma Registry (CNMR) promoted by the Italian Melanoma Intergroup (IMI). All surgical procedures (WE, SLNB or LFND) for non-metastatic skin melanoma between January 2011 and February 2017 were evaluated for inclusion in the study. Only centers with adequate completeness of information (>80%) were included in the study. Short-term complications (wound infection, dehiscence, skin graft failure and seroma) were investigated.

**Results:** Wound infection rate was 1.1% (0.4% to 2.7%) in WE, 1.3% (0.7% to 2.5%) in SLNB and 4.1% (2.1% to 8.0%) in LFND. Wound dehiscence rate was 2.0% (0.8% to 5.1%) in WE, 0.9% (0.2% to 3.0%) in SLNB and 2.8% (0.9% to 8.6%) in LFND. Seroma rate was 4.2% (1.5% to 11.1%) in SLNB and 15.1% (4.6% to 39.9%) in LFND. Unreliable information was found on skin graft failure.

**Conclusions:** Our findings contribute to available literature in setting up the recommended standards for melanoma centers, thus improving the quality of surgery offered to patients. A consensus on the core issues around surgical morbidity is needed to provide practical guidance on morbidity prevention and management.
CIRCULATING LEVELS OF MIR-204-5P PREDICT RESPONSE TO BRAF AND MEK INHIBITORS IN METASTATIC MELANOMA PATIENTS


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Background: Metastatic melanomas harboring BRAF-V600 mutations are currently treated with combinations of BRAF and MEK inhibitors (MAPKi) increasing the objective responses, disease free survival and overall survival over monotherapy with BRAF inhibitors. Unfortunately, several patients suffer from ab initio or acquired resistance to these agents. Several efforts have been directed in recent years to understand mechanisms of resistance to MAPK inhibitors. These studies have shown a prominent involvement of non-mutational adaptive events, among which also deregulation of microRNAs expression. In this regard our laboratory has identified several miRNAs which undergo either up- or down-regulation during the development of drug resistance.1 In this study we have started to assess whether circulating levels of one or more of these miRNAs can act as an early predictor of response to therapy.

Materials and methods: Circulating miRNAs were extracted from the serum of 51 BRAF-mutated melanoma patients before the beginning of therapy through miRNeasy Mini Kit (Qiagen). Real-time PCR for miR-204-5p, miR-199b-5p miR-579-3p, miR-9-5p miR-4433 and miR-4488 was assayed by TaqMan Gene Expression. Data of circulating miRNAs were normalized using Global mean normalization and NormFinder model.2 For analysis purposes, ΔCt miRNA values were dichotomized on the basis of the cut-off established using the receiver operating characteristics (ROC) curve considering OS specific condition (alive/dead within 12 months from MAPKi therapy) as the state variable. Overall Survival (OS) and Progression Free Survival (PFS) analyses were carried out by the Kaplan-Meier product-limit method. The Log Rank test was used to prove if any statistically significant difference between subgroups exists (p-value<0.05).

Results: This retrospective study involved patients with a median age of 45 years. Among them, 27 (53%) were females. All patients were treated with MAPKi therapy in first line except one who received the treatment in second line. Only miR-204-5p emerged to have a role in predicting both OS and PFS. Concerning OS, patients with a ΔCt value under the ROC cut-off show a shorter median time to death in comparison to patients with a ΔCt value over the ROC cut-off (10 months 95% confidence interval (95%CI): (3.9-16.1) vs 34 months 95%CI: (25.7-42.3); p-value=0.013). Concerning PFS analysis, patients with a ΔCt value under the ROC cut-off have a shorter median time to progression in comparison to patients with a ΔCt value over the ROC cut-off (5 months 95%CI: (4.1-5.9) vs 18 months 95%CI: (7.9-28.1); p-value=0.006).

Conclusions: On the basis of these results, miR-204-5p can be a promising predictive biomarker able to discriminate advanced melanoma patients who may benefit of MAPKi treatments. These
data warrants of further validation in an extended cohort of patients as well as in prospective following studies.

References

A13
IRRELEVANCE OF NRAS MUTATION ON FEATURES OF PRIMARY AND METASTATIC MELANOMA OR ON OUTCOMES OF CHECKPOINT INHIBITOR IMMUNOTHERAPY: AN ITALIAN MELANOMA INTERGROUP (IMI) STUDY
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Introduction: It is debated whether the NRAS mutation in melanoma leads to a distinct clinicopathological phenotype and increased aggressiveness compared with NRAS wildtype melanoma. It is equally controversial whether the NRAS mutation is associated with a higher responsiveness to checkpoint inhibitor immunotherapy (CII). Patients and methods: We compared two cohorts of pts with metastatic melanoma (MM) with and without NRAS mutations who were homogeneously treated with CII as the first-line therapy. To avoid the confounding impact of anti-BRAF/anti-MEK-targeted therapy on clinical outcomes, patients harbouring BRAF mutations were excluded. The characteristics of primary and metastatic melanoma, and outcome to CII were analysed.

Results: A total of 331 pts were retrospectively recruited: 162 NRAS mutant/BRAF wild type (mut/wt) and 169 wt/wt. The most common NRAS mutations included Q61K (37%) and Q61R (35%). Iplimonib was given to 45 and 35 pts, anti-PD1 to 114 and 132, and the combination to 3 and 2 pts, in mut/wt and wt/wt, respectively. At melanoma onset, no significant difference was found except for melanoma localization and ulceration more frequent in the wt/wt group (p=0.03). The disease-free interval was identical in the two cohorts: 15.4 months (range 4-36) in mut/wt vs. 15 months (range 3-37) in wt/wt cohort.

In advanced disease, we found no difference in age, LDH level, number of metastatic sites, or EOCOG PS. In contrast, a significant difference was found in the site of metastases, with more frequent lung and brain in the wt/wt group (p=0.01 and p=0.01, respectively) and soft tissue and lymph node in the mut/wt group (p=0.07 and p=0.09, respectively). Additionally, progression to the brain was higher in the wt/wt group (p<0.01). Regarding the outcome to CII, no significant differences were found in ORR, DCR, PFS or OS: 42% vs. 37%, 60% vs. 59%, 12 (95% CI, 7-18) vs. 9 months (95% CI, 6-16) and 32 (95% CI, 23-49) vs. 27 months (95% CI, 16-35) for the mut/wt and wt/wt cohorts, respectively.

A significative longer OS was associated with normal LDH, <3 metastatic sites, lower white blood cell count, lower platelet count, lower N/L ratio. Finally, female sex was found near statistical significance (p=0.06). Conclusions: Our data do not support a higher aggressiveness of NRAS mutant melanoma nor a better responsiveness to CII. The controversy in the published data could be due to different patients’ characteristics and treatment heterogeneity.

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T-WIN: PATTERNS OF RESPONSE TO/PROGRESSION AFTER FIRST-LINE (1L) TREATMENT WITH DABRAFENIB (D) AND TRAMETINIB (T) IN PATIENTS (PTS) WITH UNRESECTABLE/METASTATIC BRAF V600-MUTANT MELANOMA
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**Background:** D+T combination therapy is considered to be the preferred treatment not only for pts with a high tumor burden, but also for the indolent disease. Furthermore, limited data are available on the patterns of disease progression and the impact of the D+T combination on the clinical outcomes of subsequent treatment lines in a real-world setting.

**Materials and methods:** This multicenter, prospective, observational, non-interventional study was conducted in unresectable or metastatic BRAF V600-mutant cutaneous melanoma pts with either limited (cohort A [A]: lactate dehydrogenase [LDH] ≤ upper limit of normal [ULN]) or bulky (cohort B [B]: LDH > ULN) disease burden treated with D+T combination in clinical practice. Pts were analyzed for patterns of 1L treatment response/progression at 17.5 mo (A) and 5.5 mo (B), (this is the median progression-free survival [mPFS] reported in the COMBI-v trial for these subgroups). Response/progression patterns were described according to the number of metastasis per organ, median time to develop new metastases from the treatment start, and ECOG PS. The study also aimed to identify the clinical biomarkers, potentially related to tumor response or disease progression, following 1L and 2L treatments.

**Results:** Of the 205 patients enrolled, at the interim data cutoff (November 15, 2019), 143 pts ([A] n = 72; [B] n = 71) who were treatment naïve for advanced/metastatic disease (median age, 63 y) were analyzed for patterns of 1L treatment response/progression. The median time to develop subsequent new metastases was 19 and 8.6 mo in A and B, respectively. mPFS in 1L treatment was 17.4 and 8.2 mo, respectively. The median overall survival was not estimable in A and 10 mo in B. At least 1 any-grade adverse event (AE) was observed in 67 (93%) and 62 pts (87%) in A and B, respectively. Grade ≥ 3 AEs were higher in B (52%) compared to A (33%). The most common AE was pyrexia in both cohorts (A: 56%; B: 42%), but typically low grade. Serious AEs were observed in 18 (25%) and 26 pts (37%) in A and B, respectively.

**Conclusions:** In this interim analysis of the study, safety and effectiveness of the D+T combination in BRAF-mutant melanoma pts were similar to the clinical phase 3 trials experience, supporting the use of this combination in routine clinical practice, where the patient population is more heterogeneous, and thereby, demonstrating that D+T is an effective treatment for all pts with BRAF V600-mutant melanoma, particularly those with a low disease burden.