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ORIGINAL RESEARCH

Characteristics of Real-World Patients with High-Risk *BRAF*$^{V600E/K}$-Mutated Melanoma Receiving Adjuvant Treatment with Dabrafenib Plus Trametinib After Surgical Resection, Through the Italian Managed Access Program

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Purpose: Real-world data from patients with *BRAF*^{V600}-mutated, resected, stage III melanoma treated with dabrafenib plus trametinib as adjuvant targeted therapy are limited, and it is important to gain an understanding of the characteristics of this patient population, as well as of the patient journey. Here we aimed to describe the characteristics, dosage reductions and discontinuations in patients with *BRAF*$^{V600E/K}$-mutated melanoma receiving adjuvant dabrafenib plus trametinib after surgical resection through an Italian managed access program (MAP).

Patients and Methods: Eligible patients had completely resected cutaneous melanoma with confirmed *BRAF* V600E or V600K mutation, or initially resectable lymph node recurrence after a diagnosis of stage I or II melanoma. The starting dose of dabrafenib and trametinib was 150 mg twice daily and 2 mg once daily, respectively.

Results: A total of 557 patients received dabrafenib plus trametinib through the MAP (stage III resected disease at inclusion, 554). Median age was 54.0 years, and 40.2% of patients were female. The proportion of all treated patients who required a dose reduction was low (10.8%) as was the proportion of patients who discontinued treatment (13.5%). The main reason for treatment discontinuation was adverse events (36.0%).

Conclusion: New treatments, including BRAF-targeted therapies and immunotherapy, have transformed the natural history of melanoma. This is the largest study to date describing patients treated with dabrafenib plus trametinib in routine clinical practice in Italy between 2018 and 2019. Results highlight the characteristics of the patients treated and their journey, as well as the tolerable safety profile of dabrafenib plus trametinib in a real-world patient population.

Keywords: *BRAF* mutation, dabrafenib, melanoma, real-world, trametinib, managed access program

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Introduction

The incidence of melanoma has increased worldwide in the last decades, although a recent study in the US showed that it appears to have stabilized in recent years.[1–3] In Italy, cutaneous melanoma is the second most frequent cancer diagnosis in men under 50 years of age, and the annual average incidence of new skin melanoma diagnoses is 20.4 per 100,000 for men and 16.6 per 100,000 for women.[4]

Surgical resection associated with sentinel node biopsy is the primary treatment for early-stage (localized or locoregionally advanced) melanoma, whereas treatment for advanced disease involves systemic therapy,[5] including immunotherapy and targeted therapies.

Up to 50% of all melanomas present with *BRAF*^{V600} mutations,[6] which result in constitutive activation of the ERK/MEK signaling pathways.[5] Treatment with the BRAF inhibitor (BRAFi) dabrafenib in combination with the MEK inhibitor trametinib improved progression-free survival (PFS) and overall survival (OS) compared with BRAFi monotherapy in patients with unresectable/metastatic *BRAF*$^{V600E/K}$–mutant melanoma, as demonstrated in the COMBI-d and COMBI-v randomised, phase III trials,[7–9] and led to approval of this combination therapy in this setting.

Before systemic adjuvant therapies were approved for the treatment of stage III melanoma, surgery was the main treatment; the risk of relapse was high, increasing from stage IIIA to stage IIID substages.[10] In the adjuvant setting, the phase III COMBI-AD trial evaluated dabrafenib plus trametinib vs placebo in 870 patients with completely resected, stage III melanoma harboring *BRAF* V600E or V600K mutations.[11,12] The study met its primary endpoint of relapse-free survival (58% vs 39% in the placebo group at 3 years; 52% vs 36% in the placebo group at 5 years) with no new safety signals reported in the adjuvant setting compared with the metastatic setting, laeding to approval of this combination for the adjuvant treatment of melanoma with *BRAF*$^{V600E/K}$ mutations (approval took place in Europe in August 2018 and in Italy in December 2019). However, 26% of patients discontinued the COMBI-AD study due to adverse events (AEs), 9% due to pyrexia.[11] Subsequently, the phase IIIb COMBI-APlus trial explored an adapted pyrexia management algorithm in patients with high-risk, resected stage III *BRAF*$^{V600E/K}$-mutant melanoma treated with adjuvant dabrafenib plus trametinib.[13] This algorithm involved interrupting treatment with dabrafenib plus trametinib at the onset of pyrexia (temperature ≥38°C) and treatment restart at the same dose upon improvement of symptoms if patients remained symptom-free (temperature <38°C) for at least 24 h. Use of this algorithm improved the composite rate of grade 3/4 pyrexia, hospitalization and treatment discontinuation due to pyrexia (8.0% vs 20.0% when not using the algorithm), increasing the numbers of patients on treatment with dabrafenib plus trametinib. Importantly, no significant changes from baseline were observed in patient-reported outcomes from patients enrolled in the COMBI-AD trial receiving adjuvant dabrafenib plus trametinib, suggesting that this treatment did not affect their quality of life.[14]

Historically, clinical trials for adjuvant systemic therapy excluded patients with stage IIIA disease (per American Joint Committee on Cancer [AJCC] 7th edition) who had sentinel node metastases <1 mm (longer diameter)[12,15] as these patients are considered at a lower risk of recurrence compared with patients with stage IIIA disease and larger sentinel node metastases (≥1 mm) or patients with stage IIIB–D disease. Thus, the benefit of adjuvant systemic therapy against its potential toxicity has not yet been established in these patients.[16]

Data from observational studies assessing the characteristics and treatment patterns of patients with *BRAF*$^{V600E/K}$-mutated melanoma receiving adjuvant dabrafenib plus trametinib after surgical resection are limited. Following the European Medicines Agency (EMA) approval of dabrafenib plus trametinib for the adjuvant treatment of patients with *BRAF*^{V600}-mutated stage III melanoma after complete resection, a managed access program (MAP) was set up for eligible patients in Italy to allow access to this combination therapy.

Here we present the characteristics of patients with high-risk, *BRAF*$^{V600E/K}$-mutated melanoma receiving adjuvant dabrafenib plus trametinib after surgical resection through the MAP, as well as describing the patient journey with information on time from diagnosis to treatment start in a new setting for this disease. Separately, we performed an analysis of patients with stage IIIA disease, as this subpopulation was often excluded in the pivotal clinical studies (only patients with stage IIIA and lymph node involvement >1 mm were enrolled in these studies). It should be noted that this is a descriptive analysis of patient characteristics, as collection of efficacy or safety data was not permitted under this program. In line with Italian regulations, certain data can be collected from the MAP application forms in order to expand the available data on this population in clinical practice and to

increase knowledge on this restricted setting. The information collected was only that from the MAP application forms, as the program did not allow for requests for additional information from participating physicians.

Materials and Methods

Patients

In Italy, the MAP cohort was opened between June 2018 and December 2019, at which time dabrafenib plus trametinib was approved for reimbursement. MAP criteria specified that in order for a patient to receive treatment (provided free-of-charge by Novartis), an independent request should be received from the treating physician; the patient to be treated had to be assessed as experiencing a serious or life-threatening disease or condition, and no comparable or satisfactory alternative therapy had to be available to monitor or treat this disease or condition. Furthermore, participating patients were not eligible or able to enrol in a clinical trial.

Eligible patients had completely resected (R0), histologically confirmed, high-risk (stage III according to the AJCC 8th edition)[17] cutaneous melanoma with confirmed *BRAF* V600E or V600K mutation, or initially resectable lymph node recurrence after a diagnosis of stage I or II melanoma. Complete resection (with no residual disease) of stage III cutaneous melanoma must have occurred within 12 weeks of enrollment. Staging was obtained from the MAP application form; it is expected that clinicians used the AJCC 8th edition staging, as this was the one commonly used during the data collection period.

Included patients were not eligible for participation in any available clinical trial evaluating dabrafenib and trametinib, had an Eastern Cooperative Oncology Group (ECOG) performance status ≤3 and agreed to use contraception throughout the treatment period and for 4 months following the last dose. Patients were not eligible for the MAP if they had a diagnosis of uveal or mucosal melanoma, evidence of metastatic disease (including in-transit metastasis), presence of malignancy other than melanoma within 1 year of inclusion, presence of any malignancy with confirmed activating *RAS* mutation, unknown primary melanoma (melanoma with lymph node metastases but no primary melanoma found), or any laboratory abnormalities or AEs/serious AEs (SAEs) greater than Grade 3 (as per CTCAE v5.0). Concomitant treatment with other systemic anti-cancer therapies was not allowed in this program; whole brain radiation and brain radiosurgery were allowed. Patients receiving another systemic anti-cancer therapy (such as chemotherapy, immunotherapy or other targeted therapy) had to discontinue use prior to initiation of treatment with dabrafenib plus trametinib. Patients who received prior therapy with a BRAFi other than dabrafenib were not eligible for inclusion in the program.

Treatment

The starting dose of the combination treatment was dabrafenib 150 mg twice daily (total daily dose 300 mg) and trametinib 2 mg once daily, administered under fasting conditions either 1 hour before or 2 hours after a meal. Dose adjustments for both drugs were allowed in case of intolerance. Dose reductions below 50 mg twice daily for dabrafenib and 1 mg once daily for trametinib were not allowed. Treatment was discontinued if dose reduction below these thresholds was required. If administration of one agent (dabrafenib or trametinib) was interrupted or permanently discontinued, continued administration of the other was permitted.

Guidance provided to attending clinicians for patients in the MAP suggested that dabrafenib and trametinib doses be reduced simultaneously in response to toxicity assessed as treatment-related; exceptions to this guidance were events of pyrexia, uveitis and QT prolongation (likely related to dabrafenib) and reduced left ventricular ejection fraction, retinal vein occlusion, retinal pigment epithelial detachment, pneumonitis and interstitial lung disease (likely related to trametinib). Dose modification guidelines for AEs assessed as treatment-related in this program involved no dose reductions for Grade ≤2 AEs; Grade 2 AEs required dose interruption and restart (without reduction) once the AE had resolved to Grade 1 or baseline. In contrast, Grade ≥3 AEs required dose interruption and restart with a one-level dose reduction at AE resolution.

Patients continued treatment until unacceptable toxicity, disease progression and/or treatment discontinuation (at the discretion of the treating physician), withdrawal of consent, or until the approval of the treatment for reimbursement by the Italian health authorities (December 2019). The period of observation continued until the last dose of dabrafenib or trametinib was administered within the MAP. Data collected from the MAP application and re-supply forms included medical history (including date of surgical resection and type of lymph node resection), drug dosage reduction and reasons for reduction, and treatment after

progression. The data collected through these forms was kept confidential and was managed under the applicable laws and regulations.

Treatment Definitions

Time between initial diagnosis to treatment start was defined as the number of months elapsed from the date of diagnosis to the date of treatment start (ie treatment start date − diagnosis date + 1 divided by 30.4375), whereas time between initial diagnosis to diagnosis of stage III disease was defined as the number of months elapsed from the date of the initial diagnosis of melanoma to the date of the last surgery. When dates of diagnosis were not known, the time was not calculated. For those patients with a missing diagnosis date or date of last surgery, the following imputations were applied: if the full date was missing, no imputation was performed; if only the day was missing, this was imputed as 15; if both day and month were missing, the day was imputed as 1 and the month as July. If these imputation rules led to a date of diagnosis later than the date of last surgery, the date of diagnosis was replaced with the date of last surgery.

Time between treatment start and first reduction was computed as days elapsed between treatment start date and the date of first dose reduction. Time to treatment discontinuation was defined as the number of days elapsed between the treatment start and end date. There were some patients for whom the treatment end date was not known and, consequently, the time was not calculated.

Ethics

This treatment plan was designed, implemented and reported in accordance with applicable local regulations as well as European Directive 2001/83/EC, Regulation (EC) No 726/2004 and US Code of Federal Regulations Title 21, and with the ethical principles laid down in the Declaration of Helsinki. Written patient informed consent was obtained by the treating physician from all patients prior to start of treatment. The treatment plan and the informed consent form were reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC) before treatment start. Confirmation of approval by the IRB/IEC and informed consent were provided to the sponsor (Novartis) using a Treating Physician Attestation Form. Local laws/regulations were followed as applicable. The following IRBs/IECs were consulted: Comitato Etico di Bergamo, Comitato Etico degli IRCCS Istituto Europeo di Oncologia e Centro Cardiologico Monzino, Comitato Etico dell'IDI-IRCCS Lazio, Comitato Etico Interaziendale Piemonte, Comitato Etico Indipendente della Fondazione IRCCS "Istituto Nazionale dei Tumori", Comitato Etico di Area Vasta Emilia Centro, Comitato Etico della Romagna, Comitato Etico Università Federico II Napoli, Comitato Etico per la Sperimentazione Clinica delle Province di Treviso e Belluno, Comitato Etico Indipendente Locale AOUC Policlinico di Bari, Comitato Etico Centrale IRCCS Lazio, Comitato Etico per la Sperimentazione Clinica Veneto, Comitato Etico "Lazio 2", Comitato Etico IRCCS Pascale, Comitato Etico Palermo 1, Comitato Etico Università degli Studi della Campania "Luigi Vanvitelli", Comitato Etico Istituto Tumori Giovanni Paolo II Bari, Comitato Etico Regionale delle Marche, Comitato Etico Area Pavia, Comitato Etico Interaziendale Torino, Comitato Etico Unico Regionale Friuli Venezia Giulia, Comitato Etico dell'Area Vasta Emilia Nord, Comitato Etico Interaziendale AOU Maggiore della Carità Biella, Comitato Etico per le Sperimentazioni Cliniche della Provincia di Vicenza, Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana, Comitato Etico di Brescia, Comitato Etico del Comprensorio Sanitario di Bolzano, Comitato Etico Regionale Liguria, Comitato Etico Fondazione Policlinico Agostino Gemelli, Comitato Etico Indipendente di Etica Medica Brindisi, Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana, Comitato Etico Brianza, Comitato Etico Regionale per la Sperimentazione Clinica della Provincia di Venezia e IRCCS San Camillo, Comitato Etico ASL Lecce, Comitato Etico dell'Area Vasta Emilia Nord, Comitato Etico Milano Area 3, Comitato Etico Lazio 1, Comitato Etico dell'Insubria, Comitato Etico IRCCS di Candiolo, Comitato Etico per le Sperimentazioni Cliniche della Provincia Autonoma di Trento, Comitato Etico Val Padana, Comitato Etico di Area Vasta Nord Ovest, Comitato Etico Milano Area 1, Comitato Etico Catania 2, Comitato Etico Interaziendale AOU Maggiore della Carità, Comitato Etico Indipendente Humanitas Research Center, Comitato Etico per la Sperimentazione Clinica delle Province di Verona e Rovigo, Comitato Etico di Area Vasta Sudest, Comitato Etico Messina, Comitato Etico Brianza, Comitato Etico Indipendente Tor Vergata Roma, Comitato Etico Indipendente di Etica Medica Taranto, Comitato Etico per le Province di

L'Aquila e Teramo, Comitato Etico Regionale dell'Umbria, Comitato Etico AOU di Cagliari, Comitato Etico dell'Università 'Sapienza', Comitato Etico Interprovinciale Area 1, Comitato Etico Indipendente Monserrato, Comitato Etico Sezione Area Centro Calabria, Comitato Etico Area Vasta Nord Ovest Toscana, Comitato Universitario di Bioetica Umbria, Comitato Etico Palermo 2, Comitato Etico della Romagna, Comitato Etico Territoriale Lombardia 1.

Results

Patient Characteristics and Journey

During the period in which the MAP cohort was open (June 2018 to December 2019), there were 629 requests for the treatment, which resulted in 557 (88.5%) patients receiving dabrafenib plus trametinib through the MAP. For the 72/629 (11.5%) patients who did not receive treatment through the MAP, the most common reasons for not receiving treatment were withdrawal of informed consent by the patient, not meeting inclusion and/or exclusion criteria, and reimbursement of treatment after regulatory approval took place in Italy on 16 December 2019 (AIFA, with GU. n°294).

Overall, 557 patients were included in the program. Of these, 110/557 (19.7%) had stage IIIA, 119/557 (21.4%) had stage IIIB, 216/557 (38.8%) had stage IIIC, and 22/557 (3.9%) had stage IIID, while 87/557 (15.6%) of treated patients had stage III disease with no further specification of substage, two patients (2/557, 0.4%) had unknown disease stage and one patient had stage IV disease (1/557, 0.2%). Overall, 116 of the participating patients had stage IIIA disease at program inclusion, of which 110 (94.8%) received treatment.

Patient demographics among all treated patients and patients with stage IIIA disease at inclusion are summarized in Table 1. Patients with stage IIIA disease at inclusion had a median age [Q1–Q3] of 49.0 [43–59] years, whereas all treated patients had a median age of 54.0 [45–65] years. The proportion of female patients was 48.2% among treated patients with stage IIIA disease at inclusion and 40.2% in all treated patients.

The proportion of patients who underwent lymph node resection and sentinel lymph node (SLN) biopsy was similar between groups (treated patients with stage IIIA vs all treated patients: 60.9% vs 69.7% and 66.4% vs 63.4%, respectively) (Table 1). Median time between initial diagnosis to diagnosis of stage III disease was also similar in treated patients with stage IIIA disease at inclusion compared with all treated patients (median time [Q1–Q3]: 2.45 [1.69–3.55] months for stage IIIA at inclusion vs 2.56 [1.51–4.34] months for all treated patients), as was median time between initial disease diagnosis to the start of treatment with dabrafenib plus trametinib (median time [Q1–Q3]: 5.04 [4.17–6.08] months for stage IIIA at inclusion vs 4.93 [3.88–6.93] months for all treated patients). However, median time between last surgery and treatment start was 82.0 days [65.0–90.0] for patients with stage IIIA disease at inclusion and 77.0 days [60.0–88.0] for all treated patients.

Table 1 Patient Demographics and Disease Characteristics

	All Treated Patients (N = 557)	Treated Patients with Stage IIIA Disease (N = 110)
Age (years), median (Q1–Q3)	54.0 (45–65)	49.0 (43–59)
Female patients, n (%)	224 (40.2)	53 (48.2)
Lymph node dissection, n (%)		
Yes	388 (69.7)	67 (60.9)
No	126 (22.6)	31 (28.2)
Unknown	43 (7.7)	12 (10.9)
Positive SLN, n (%)		
Yes	353 (63.4)	73 (66.4)
No	37 (6.6)	3 (2.7)[a]
Unknown[b]	167 (30.0)	34 (30.9)

(*Continued*)

Table 1 (Continued).

	All Treated Patients (N = 557)	Treated Patients with Stage IIIA Disease (N = 110)
Time between initial diagnosis to diagnosis of stage III disease (months), median (Q1–Q3)[c]	2.56 (1.51–4.34)	2.45 (1.69–3.55)
Time between initial diagnosis to treatment start (months), median (Q1–Q3)[c]	4.93 (3.88–6.93)	5.04 (4.17–6.08)
Time between diagnosis of stage III disease (last surgery) and treatment start (days), median (Q1–Q3)	77.0 (60–88)	82.0 (65–90)
Tissue used for *BRAF* mutational testing, n (%)		
Primary tumor	245 (44.0)	54 (49.1)
SLN	40 (7.2)	5 (4.5)
Lymph node	2 (0.4)	–
CLND	43 (7.7)	2 (1.8)
Primary tumor and CLND	8 (1.4)	2 (1.8)
Primary tumor and SLN	41 (7.4)	10 (9.1)
Primary tumor, SLN and CLND	14 (2.5)	3 (2.7)
Unknown[d]	164 (29.44)	34 (30.9)

Notes: [a]Staging was performed by treating physicians; these patients were classified as stage IIIA despite not having a positive SLN. [b]Information on SLNs was not recorded in the application forms, and the MAP did not allow requests for further information from participating physicians. [c]n = 546 for all treated patients and n = 104 for patients with stage IIIA disease. [d]Although the source of tissue used for the *BRAF* mutational testing is unknown, these patients had a confirmed *BRAF* V600E or V600K mutation. Patients who signed the informed consent form were considered enrolled patients. Enrolled patients with a treatment start date reported were considered treated patients.
Abbreviations: CLND, complete lymph node dissection; MAP, managed access program; Q1, first quartile; Q3, third quartile; SLN, sentinel lymph node.

Results from this patient cohort showed that a $BRAF^{V600E/K}$ mutation was detected in the primary tumor in 245/557 (44.0%) of all treated patients and in 54/110 (49.1%) of treated patients with stage IIIA disease at inclusion, while the corresponding proportions for $BRAF^{V600E/K}$ mutation detected in SLN were 4.5% and 7.2%, respectively (Table 1). $BRAF^{V600E/K}$ mutation was detected in complete lymph node dissection (CLND) material in 1.8% of treated patients with stage IIIA disease at inclusion and 7.7% of all treated patients. A small proportion of patients had a $BRAF^{V600E/K}$ mutation detected in both the primary tumor and SLN (9.1% for treated patients with stage IIIA disease at inclusion and 7.4% for all treated patients). The source of tissue used for the *BRAF* mutational testing was unknown in a large proportion of patients (29.4% for treated patients with stage IIIA disease at inclusion and 30.9% for all treated patients).

Treatment Adjustment and Discontinuation

A summary of dose reductions is presented in Table 2. A similar proportion of treated patients with stage IIIA disease at inclusion and of all treated patients required a dose reduction (10.0% vs 10.8%, respectively). The median time between treatment start and first dose reduction was also similar (90.0 vs 89.0 days, respectively). Among patients who required a dose reduction, 36.4% of patients with stage IIIA disease at inclusion and 65.0% of all treated patients required a dose reduction for both dabrafenib and trametinib. After dose reduction, all treated patients with stage IIIA disease at inclusion and almost all treated patients received a new daily dose of 200 mg dabrafenib and a new daily dose of 1.5 mg trametinib.

Patient disposition at the end of treatment and reasons for treatment discontinuation are presented in Table 3. A small proportion of patients discontinued treatment (13.5% for all treated patients and 10.0% for treated patients with stage IIIA at inclusion). Among patients who discontinued treatment, the most common reason for discontinuation was an AE (in 27/75 [36.0%] of all treated patients and 2/11 [18.2%] of treated patients with stage IIIA at inclusion who discontinued treatment). Considering patients who discontinued the treatment due to AEs, the most common AE leading to treatment discontinuation was pyrexia (in 8/27 [29.6%] of all treated patients and 1/2 [50.0%] of treated patients with stage IIIA at inclusion with an AE). The median time to treatment discontinuation was 102.0 (66.0–215.0) days for treated patients with stage IIIA disease at inclusion (n = 10) vs 129.0 (58.5–190.5) days for all treated patients (n = 72).

Table 2 Summary of Dose Reductions

	All Treated Patients (N = 557)	Treated Patients with Stage IIIA Disease (N = 110)
Patients with dose reduction, n (%)	60 (10.8)	11 (10.0)
Time between treatment start and first dose reduction (days), median (Q1–Q3)[a]	89.0 (56–131)	90.0 (48–148)
Treatment with dose reduction[b], n (%)		
Only trametinib	5 (8.3)	2 (18.2)
Only dabrafenib	16 (26.7)	5 (45.4)
Dabrafenib plus trametinib	39 (65.0)	4 (36.4)
Trametinib new total daily dose after reduction[c], n (%)		
1 mg	2 (4.5)	–
1.5 mg	42 (95.5)	6 (100.0)
Dabrafenib new total daily dose after reduction[d], n (%)		
150 mg	2 (3.6)	–
200 mg	53 (96.4)	9 (100.0)

Notes: [a]Time between treatment start and first reduction was computed as days elapsed between treatment start date and the date of first dose reduction. Time calculated for all patients with a dose reduction (n = 60 for all treated patients and n = 11 for treated patients with stage IIIA disease). [b]Percentages were calculated for all treated patients, and for treated patients with stage IIIA disease at enrollment, with first dose reduction. [c]Percentages were calculated for all treated patients, and for treated patients with stage IIIA at enrollment, with trametinib reduction (ie considering both "Only trametinib" and "Dabrafenib plus trametinib"). [d]Percentages were calculated for all treated patients, and for treated patients with stage IIIA at enrollment, with dabrafenib reduction (ie considering both "Only dabrafenib" and "Dabrafenib plus trametinib").
Abbreviations: Q1, first quartile; Q3, third quartile.

Table 3 End of Treatment Disposition and Reasons for Treatment Discontinuation

	All Treated Patients (N = 557)	Treated Patients with Stage IIIA Disease (N = 110)
End of treatment status		
Completed	155 (27.8)	35 (31.8)
Switched to commercially available treatment[a]	243 (43.6)	44 (40.0)
Discontinued	75 (13.5)	11 (10.0)
Unknown	84 (15.1)	20 (18.1)
Reason for treatment discontinuation[b]		
Adverse event	27 (36.0)	2 (18.2)
Progressive disease	13 (17.3)	1 (9.1)
Withdrawal of consent	9 (12.0)	3 (27.3)
Lost to follow-up	2 (2.7)	-
Patient decision	1 (1.3)	1 (9.1)
Unknown	23 (30.7)	4 (36.4)
For patients who discontinued treatment due to adverse events[c] MedDRA System Organ Class/Preferred Term		
Cardiac disorders	3 (11.1)	–
Aortic valve incompetence	1 (3.7)	
Atrial fibrillation	1 (3.7)	
Cardiomyopathy	1 (3.7)	
General disorders and administration site conditions	10 (37.0)	1 (50.0)
Death	1 (3.7)	–
Fatigue	1 (3.7)	–
Pyrexia	8 (29.6)	1 (50.0)

(*Continued*)

Table 3 (Continued).

	All Treated Patients (N = 557)	Treated Patients with Stage IIIA Disease (N = 110)
Skin and subcutaneous tissue disorders	4 (14.8)	1 (50.0)
Dermatitis allergic	1 (3.7)	1 (50.0)
Nodular rash	1 (3.7)	-
Panniculitis	1 (3.7)	-
Rash papular	1 (3.7)	-

Notes: End of treatment status is "Completed" for patient who completed twelve therapy cycles, "Discontinued" for patients who discontinued the treatment and "Unknown" for ongoing patients at the end of Managed Access Program (MAP) for whom no other information is available. [a]Patients who were on treatment within the MAP had to switch to commercially available treatment after approval for reimbursement in Italy, and so it cannot be known whether they completed the treatment or not. [b]Percentages were computed on discontinued patients (ie end of treatment status = "Discontinued"). [c]Percentages were computed on patients who discontinued treatment due to adverse events. Each patient could report more than one adverse event. Terms are coded with MedDRA dictionary version 23.1.

Discussion

Data on the demographic and disease characteristics of patients with melanoma receiving adjuvant treatment are limited. Recent studies have been published that describe the adjuvant treatment of patients with melanoma in Italy;[18,19] however, these studies also include patients who received immunotherapy, and – as is often the case in real-world studies – lack information on treatment dosing and schedule, as well as on dose reductions and interruptions. Our work describes the characteristics and the patient journey of patients with high-risk *BRAF*$^{V600E/K}$-mutated melanoma who were treated with adjuvant dabrafenib plus trametinib after surgical resection as part of an Italian MAP. We also included a detailed analysis of the patient subgroup with stage IIIA disease, since this group was not always included in the pivotal clinical studies of adjuvant therapy for melanoma and is not included in some of the recently published real-world evidence studies either.

Patients with stage III melanoma have regional involvement and are at higher risk of disease recurrence after resection than patients with stage I–II disease.[11] The COMBI-AD trial showed that adjuvant therapy with dabrafenib plus trametinib significantly reduced the risk of recurrence in patients with *BRAF*$^{V600E/K}$-mutant, completely resected, stage III melanoma compared to placebo across all disease stages (including stage IIIA).[11] However, patients with high-risk, resected stage IIIA melanoma treated with adjuvant pembrolizumab in the EORTC 1325-MG/KEYNOTE-054 trial had lower distant metastases-free survival benefit compared with patients with stage IIIB–D disease.[15] It should be noted that patients with stage IIIA disease and lymph-node metastases <1 mm were not eligible for either of these two trials; furthermore, patients with stage IIIA disease were excluded from other adjuvant immunotherapy trials[20,21] and were not included in a recent survival analysis of patients with melanoma receiving adjuvant therapy in a real-world setting.[18]

Patient demographics in the MAP were similar to those of DESCRIBE-AD, an observational retrospective study of 65 patients with histologically confirmed and resected *BRAF*-mutated melanoma previously treated with dabrafenib plus trametinib in the adjuvant setting in Spain,[22] and to those in the COMBI-APlus trial.[13] Moreover, the characteristics of patients enrolled in the MAP were similar to those described in a retrospective analysis of 113 patients with stage III melanoma who received at least one cycle of adjuvant immunotherapy or targeted therapy at two Italian institutions,[19] and an analysis of 787 patients with advanced cutaneous melanoma from the Clinical National Melanoma Registry (CNMR); as previously mentioned, the latter did not include patients with stage IIIA disease.[18] Median age in the MAP was 54.0 years (vs 58 years in DESCRIBE-AD, 53 years in COMBI-APlus, and 54 years in De Falco et al; the majority of patients [55%] were aged >60 years in the CNMR study), with 40.2% female patients (vs 45% in DESCRIBE-AD, 46.2% in COMBI-APlus, 31.9% in De Falco et al, and 39% in the CNMR study).[13,18,19,22] Patients included in the MAP were older than patients in the COMBI-AD study (median age 50.0 years), and there was a smaller proportion of female patients (55% in COMBI-AD).[11] Proportions of patients with stage IIIA, stage IIIB and stage IIIC disease were 19.7%, 21.4% and 38.8%, respectively (vs 29%, 28% and 34% in DESCRIBE-AD and 10.6%, 21.2% and 63.7% in De Falco et al, respectively),[19,22] indicating that the MAP had higher proportions of patients at a more advanced disease stage compared to DESCRIBE-AD, but similar to patients enrolled in the COMBI-AD study (18%, 41% and 40%, respectively)[11] and COMBI-APlus study (10.7%, 31.9% and 55.1%, respectively).[13] Regarding patients with stage IIIA disease at diagnosis, this cohort was younger than the overall patient group in the MAP, with a larger proportion of female patients.

Median time between diagnosis and treatment start in the MAP was very similar to that reported for COMBI-APlus (4.93 vs 5.00 months);[13] it is important to note that the COMBI-APlus study was enrolling patients at the same time the MAP was taking place.

Patients who undergo SLN biopsy have fewer recurrences and increased melanoma-specific survival; however, the MSLT-II trial found that complete lymph node dissection following SLN biopsy was not associated with increased melanoma-specific survival compared to nodal observation.[23] Our results show that a larger proportion of patients with stage IIIA disease did not undergo lymph node dissection compared to all treated patients (28.2% vs 22.6%); this may be due to the limited extent of their disease. However, SLN biopsy status was unknown for approximately one-third of patients in this program, so this result should be interpreted cautiously.

Heterogeneity of *BRAF* mutational status in different samples from the same patient (primary tumor, metastatic site, SLN) has been previously reported,[24,25] prompting testing of *BRAF* mutations at different tumor sites for some patients in the MAP. Almost half of all patients included in the MAP had primary tumor as tissue source for mutation testing.[26] It is important to note that, although the source tissue for the *BRAF* mutational testing was unknown in ~30% of patients, all of these patients had confirmed $BRAF^{V600E/K}$-mutant melanoma. Consistent with their inclusion of patients treated with other therapies as well as BRAF-targeted therapy, a substantial proportion of patients in other Italian real-world studies had wild-type *BRAF*.[18,19]

The proportion of patients requiring dose reductions in the MAP was considerably lower than in COMBI-AD (10.0% vs 38% of patients with AEs leading to dose reduction, respectively).[11] The median time to dabrafenib plus trametinib dose reduction was similar in patients with stage IIIA disease vs all treated patients. However, much smaller proportions of patients with stage IIIA disease required dose reductions for dabrafenib or trametinib only compared to overall treated patients.

The proportion of patients discontinuing treatment with dabrafenib and trametinib due to AEs in the MAP was also lower than in other studies (4.8% patients vs 26% of patients in COMBI-AD and 9% in DESCRIBE-AD).[11,22] It is worth noting that only eight patients in the MAP discontinued treatment due to pyrexia (1.4% vs 2.4% in COMBI-APlus).[13] Management of dabrafenib plus trametinib treatment-related pyrexia has changed following the success of the pyrexia algorithm evaluated in the COMBI-APlus trial,[13] but the MAP was carried out while the trial was ongoing; the small number of patients who discontinued the MAP due to pyrexia even before the pyrexia algorithm management was implemented further highlights the safety of the treatment.

Median time to treatment discontinuation for patients treated in the MAP was 129 days, which is much shorter than that reported in the DESCRIBE-AD study (9 months);[22] this could be explained by the larger proportion of patients at a more advanced stage of disease included in the MAP compared to DESCRIBE-AD. It is also possible that physicians would tend to discontinue adjuvant dabrafenib plus trametinib more frequently given that this was an off-label treatment at the time the MAP took place. Median time to treatment discontinuation was shorter for patients with stage IIIA disease at inclusion than for all treated patients.

As with any observational study, the data collected are limited to the information provided by attending clinicians in the MAP patient form. Details on metastatic involvement, such as diameter of lymph node involvement, number of lymph nodes involved, degree of infiltration and other histological characteristics, were unfortunately unavailable for analysis. Furthermore, information on health services received outside of the MAP setting was not collected. Finally, collection of efficacy data was not permitted in this program. However, efficacy data from patients enrolled in the MAP who received at least one dose of dabrafenib plus trametinib and provided informed consent will be collected every 6 months for 5 years starting from the time of adjuvant treatment completion (eg, completion of the suggested 12-month treatment period) or discontinuation for any reason, as part of the ongoing MADAM study. This study was designed in 2020 in order to collect efficacy data in this patient population. Relapse-free and overall survival will be evaluated, as well as treatment patterns following disease relapse or progression, or treatment discontinuation due to other causes; this analysis will provide information on the effectiveness of adjuvant treatment with dabrafenib plus trametinib in this patient population.

Conclusion

A large number of patients with $BRAF^{V600}$-mutated, stage III melanoma were treated through this MAP with adjuvant dabrafenib plus trametinib before the treatment became available in Italy in this setting. This work reports on the characteristics and patient journey of the largest number of patients treated with this adjuvant therapy in a real-world setting in Italy. A small proportion of

patients required dose reductions and only 27 out of 557 patients discontinued treatment due to AEs; the number of discontinuations due to pyrexia was also very low, supporting the tolerability of this treatment. These results highlight the improvements in the management of patients with melanoma over recent years.

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Disclosure

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