Targeted Oncology (2021) 16:789–799
https://doi.org/10.1007/s11523-021-00850-1

ORIGINAL RESEARCH ARTICLE

# Retrospective Chart Review of Dabrafenib Plus Trametinib in Patients with Metastatic *BRAF* V600-Mutant Melanoma Treated in the Individual Patient Program (DESCRIBE Italy)

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Accepted: 11 October 2021 / Published online: 10 November 2021


## Abstract

**Background** Real-world data on extended follow-up of patients with *BRAF* V600-mutant metastatic melanoma are limited. We investigated dabrafenib plus trametinib (dab + tram) outside of a clinical trial setting (Individual Patient Program; DESCRIBE Italy).

**Objective** To describe the baseline features, treatment patterns, efficacy, and safety outcomes in patients with *BRAF* V600-mutant unresectable or metastatic melanoma who had received dab + tram as part of the Managed Access Program (MAP) in Italy.

**Patients and methods** An observational, retrospective chart review was conducted in Italian patients with *BRAF* V600-mutant unresectable stage III/IV melanoma receiving dab + tram as part of the MAP. Baseline features, treatment patterns, efficacy, and safety outcomes were evaluated.

**Results** Overall, 499 patients were included in this analysis. *BRAF* V600E mutation was seen in 81.4% of patients. Overall response rate achieved in 243 of the 390 evaluable patients was 62.3% (95% CI 57.5–67.1). Median progression-free survival (PFS) was 9.3 months (95% CI 8.6–10.6). Subgroup analyses revealed that patients with normal lactate dehydrogenase (LDH) and ≤ three metastatic sites without brain metastases at baseline had better outcomes. With normal LDH at baseline, median PFS for patients with one or two metastatic sites other than cerebral was 18 months. No new safety signals were observed. Treatment was permanently discontinued because of treatment-emergent adverse events (TEAEs) in 9.2% of patients, and pyrexia (27.3%) was the most common TEAE, with a lower incidence than that in the phase 3 studies of dab + tram.

**Conclusion** Treatment of *BRAF* V600E-mutant metastatic melanoma with dab + tram in the real-world setting was effective and safe, including the unselected population with several patients having a high tumor burden – concordant with the results of the pivotal phase 3 studies of dab + tram.

## 1 Introduction

The COMBI-d and COMBI-v studies established the superior efficacy of dabrafenib (dab) in combination with trametinib (tram) compared with BRAF inhibitor monotherapy in patients with *BRAF* V600-mutant metastatic melanoma [1, 2]. In the 5-year pooled analysis of the COMBI-d and COMBI-v studies, the progression-free survival (PFS)

**Key Points**

The findings of this retrospective analysis are consistent with those from the pivotal phase 3 studies of dabrafenib plus trametinib (COMBI-d and COMBI-v).

The results confirm the risk/benefit balance of using the dabrafenib plus trametinib combination in the real-world setting.

The clinical benefit achieved supports the use of dabrafenib plus trametinib combination therapy in patients with metastatic melanoma in routine clinical practice.

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rate was 19% and the overall survival (OS) rate was 34%, demonstrating the long-term clinical benefit of dab + tram in patients with *BRAF* V600-mutant metastatic melanoma. In the same analysis, a subgroup of patients with a normal lactate dehydrogenase (LDH) level and fewer than three metastatic sites at baseline reported a PFS rate of 31% and an OS rate of 55% at 5 years [3]. Overall, these outcomes suggest that patients having a lower initial tumor and disease burden are more likely to achieve long-term benefits from dab + tram combination therapy. However, the extended follow-up data supporting these observations are limited to highly controlled clinical trial settings.

Analyses from large population-based studies help extend and confirm the results from randomized controlled clinical trials. Three real-world studies (DESCRIBE I ($N = 331$), DESCRIBE II ($N = 271$), and DESCRIBE III ($N = 509$)) evaluated the treatment patterns and clinical outcomes in patients with *BRAF* V600-mutant unresectable or metastatic melanoma enrolled in the Named Patient Program who were treated with dab monotherapy and/or dab + tram combination therapy. The efficacy and safety outcomes in these studies were consistent with those reported in the randomized controlled clinical trials [4–6].

The DESCRIBE Italy study was designed to retrospectively evaluate the use of dab + tram combination therapy in a real-world setting in patients with *BRAF* V600-mutant unresectable or metastatic melanoma in Italy.

## 2 Materials and Methods

### 2.1 Study Design

The DESCRIBE Italy study was an observational, retrospective chart review conducted in adult patients (aged ≥ 18 years) with *BRAF* V600-mutant unresectable or metastatic melanoma who had received at least one dose of dab + tram as part of the Managed Access Program (MAP) and had signed the written informed consent (not applicable for deceased patients). Patients who had not participated in the MAP; who were part of a dab + tram investigational trial; or whose medical chart was missing, empty, or not retrievable were excluded from the study.

The objective of the study was to describe the baseline features, treatment patterns, efficacy, and safety outcomes in patients with *BRAF* V600-mutant unresectable or metastatic melanoma who had received dab + tram combination therapy as part of the MAP in Italy.

The patients enrolled in this study were part of the MAP in Italy during 2013–2017. Pseudonymized retrospective data of baseline characteristics, treatment patterns, disease progression, survival status, and safety were retrieved from the medical charts of all patients and entered in electronic case report forms from 21 March 2018 to 31 December 2018. Data were collected from the first dose of dab + tram until discontinuation, death, last clinical encounter, or 31 October 2017, whichever occurred first.

The MAP did not impose visit schedules, assessments, or therapeutic interventions. Assessments were performed according to the investigator's judgment and in accordance with the local clinical practice.

### 2.2 Disease Progression and Survival Assessment

Disease progression was documented by the treating physician based on radiographic imaging, symptoms, and performance status. Tumor evaluation constituted the basis for determining the objectives, such as overall response rate (ORR), PFS, duration of response (DOR), clinical benefit rate (CBR), and OS.

ORR was defined as the proportion of enrolled patients with complete response (CR) or partial response (PR) according to the treating physician/radiological evaluation per the local clinical practice. PFS was defined as the time from initiation of treatment to the date of the first documented disease progression or death from any cause, whichever occurred first. DOR was defined as the time from the first documented tumor response (CR/PR) until the first documented disease progression or death, whichever occurred first. CBR was defined as the percentage of patients achieving CR, PR, or stable disease for > 24 weeks. OS was defined as the time from initiation of treatment to the date of death from any cause. The pattern of progression was described by evaluating the number of sites with new lesions in patients with disease progression.

Subgroup analyses consisted of patients with a normal LDH level at baseline versus patients with an LDH level greater than the upper limit of normal (ULN) at baseline and patients with three or fewer metastatic sites without brain metastases (BM) at baseline versus patients with more than three metastatic sites and/or BM at baseline. Additionally, PFS estimates were evaluated in various subgroups of patients as part of a post hoc analysis.

### 2.3 Safety Assessment

Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and treatment-emergent adverse events of special interest (TEAESIs) occurring from treatment initiation to 30 days after treatment discontinuation were analyzed and coded using the Medical Dictionary for Regulatory Activities (MedDRA) along with their severity.

### 2.4 Statistical Analysis

No statistical sample size calculation was performed. The statistical analyses were descriptive for all endpoints. Demographic and baseline disease characteristics were summarized descriptively. DOR, PFS, and OS were estimated using the Kaplan-Meier product-limit method, and two-sided 95% confidence intervals (CIs) were calculated. ORR and CBR were summarized and presented with 95% CIs computed referring to the binomial distribution, and the standard Wald asymptotic confidence limits were calculated. All statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA).

## 3 Results

### 3.1 Baseline Demographics and Clinical Characteristics

Of the 499 patients enrolled, 390 were considered evaluable. The excluded patients (109) had at least one non-protocol deviation, including initiation of tram > 90 days after the initiation of dab (71 patients), lack of any post-baseline tumor evaluation (42 patients), prior dab monotherapy ending < 32 days before the initiation of dab + tram combination therapy (32 patients), lack of a comparable baseline metastatic evaluation (five patients), and initiation of dab after the initiation of tram (two patients). Among the enrolled patients, 144 did not definitively interrupt the study therapy before 31 October 2017, and continued the treatment later (Fig. 1). Data were collected from 35 Italian centers.

The median age of the patients was 59 years (range 23–90 years). More than half of the patients (54.3%) had a baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 0. A majority of the patients (81.4%) had *BRAF* V600E mutations, whereas 10.6% had *BRAF* V600K mutations and 7.2% had other *BRAF* V600 mutations (D, R, and others). Among the enrolled patients, 48.1% had three or fewer metastatic sites without BM and 38.7% had more than three metastatic sites and/or BM. Elevated LDH levels (≥ ULN) at baseline were observed in 28.7% of the patients (Table 1).

Most patients (81.4%) were on first-line therapy. Notably, 15% of patients had received prior adjuvant therapy (Table 1). Among patients on a subsequent line of therapy (17.4%), the most common prior antineoplastic medications in the therapeutic setting were ipilimumab (43.7%), vemurafenib monotherapy (32.2%), dacarbazine (14.9%), and temozolomide (12.6%). Prior radiotherapy was received by 98 patients (19.6%). The most common site of prior radiotherapy was the brain (8.8%). Forty-eight patients (88.2%) underwent prior antineoplastic surgery or local regional therapy. The most frequent surgical and medical procedures were skin neoplasm excision (45.5%) and lymphadenectomy (39.3%).

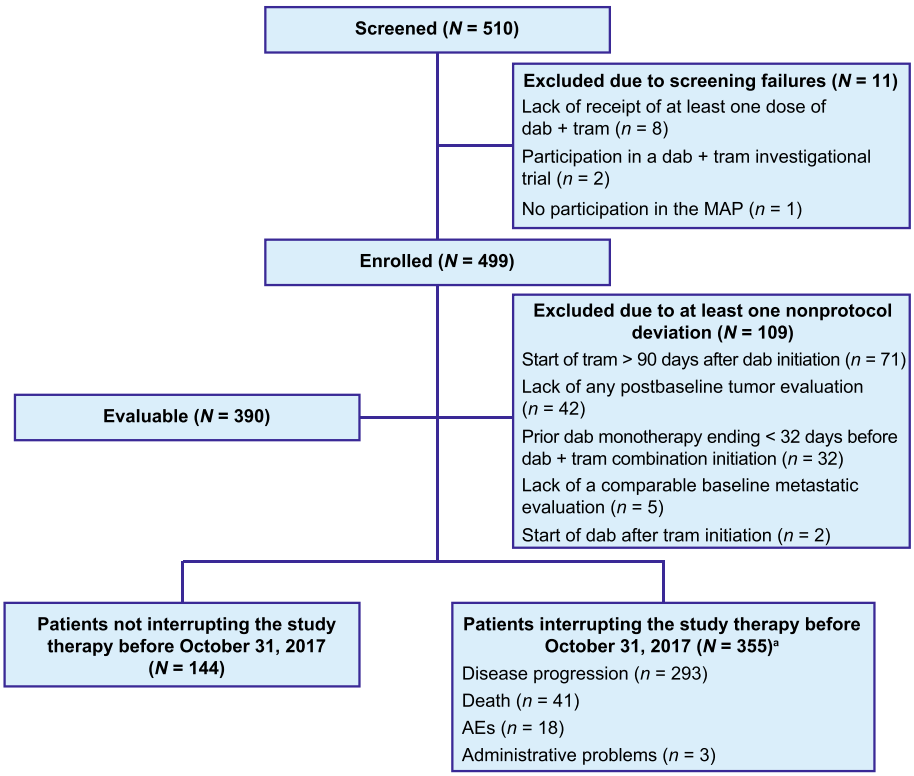


**Fig. 1** Patient disposition. *AE* adverse event, *dab* dabrafenib, *eCRF* electronic case report form, *MAP* Managed Access Program, *tram* trametinib. [a]Only 355 patients who definitively interrupted the study therapy before 31 October 2017 are shown here because three patients were considered to not have completely discontinued the study therapy in the "End of treatment" page of the eCRF

### 3.2 Disease Status and Survival

Overall response rate was achieved in 243 of the 390 evaluable patients (62.3%; 95% CI 57.5–67.1). The median DOR was 9.9 months (95% CI 8.1–12.4) and CBR was 52.6% (95% CI 47.0–58.2; Table 2).

The median PFS was 9.3 months (95% CI 8.6–10.6) and the PFS rate at 1, 2, and 3 years was 41%, 24%, and 14%, respectively (Fig. 2). The median OS could not be estimated because the cutoff for the follow-up was 31 October 2017. The OS rate at 1, 2, and 3 years was 95%, 90%, and 87%, respectively (Online Supplementary Material (OSM), Resource 1).

Among patients who had disease progression, the median number of sites with new lesions was 1 (range 0–11) in 240 patients. Notably, 169 patients (70.4%) had one or more new metastatic site (OSM, Resource 2).

### 3.3 Patients with Normal Lactate Dehydrogenase (LDH) ($n = 178$) and LDH Greater than the Upper Limit of Normal ($n = 115$) at Baseline

The ORR was higher among patients with normal LDH versus LDH > ULN at baseline: 67.4% (95% CI 60.5–74.3) versus 58.3% (95% CI 49.3–67.3). The median DOR and CBR were higher in the normal LDH subgroup compared with the LDH > ULN subgroup: 13.1 months (95% CI 9.5–23.7) versus 5.8 months (95% CI 3.5–8.5) and 58.7% (95% CI 50.8–66.6) versus 38.8% (95% CI 28.1–49.4), respectively (Table 2).

The median PFS in patients with normal LDH at baseline was approximately twice the median PFS in patients with LDH > ULN at baseline: 12.8 months (95% CI 9.3–16.2) versus 5.8 months (95% CI 5.0–7.4) (OSM, Resource 3).

Among patients with disease progression, the median number of sites with new lesions was similar between the normal LDH and LDH > ULN subgroups: 1 (range 0–11) and 1 (range 0–9), respectively. Notably, one or more new metastatic site was noted in 73 (75.3%) and 59 (67.8%) patients in the normal LDH and LDH > ULN subgroups, respectively (OSM, Resource 2).

### 3.4 Post Hoc Analysis (Progression-Free Survival Estimates)

In the subgroup with LDH > ULN at baseline, the median PFS in patients with more than three metastatic sites and/or BM versus three or fewer metastatic sites without BM was 5.1 months (95% CI 3.8–5.8) versus 7.5 months (95% CI 5.4–10.5), respectively. In the subgroup with normal LDH at baseline, the median PFS in patients with one or two metastatic sites versus three or more metastatic sites was 17.8 months (95% CI 12.9–29.7) versus 7.4 months (95% CI 6.0–9.2), respectively (Table 3).

The median PFS in patients on first-line therapy (no prior antineoplastic therapy at baseline) was 9.3 months (95% CI 8.3–10.3). Tumor burden in terms of the number of metastatic sites had a remarkable impact on the median PFS. Notably, in patients on first-line therapy and with normal LDH at baseline, the median PFS with one or two metastatic sites versus three or more metastatic sites was 16.7 months (95% CI 12.9–29.7) versus 9.1 months (95% CI 6.2–13.4), respectively. The median PFS in patients on first-line therapy and with LDH > ULN at baseline was 5.8 months (95% CI 4.7–7.3; Table 3).

Among patients with one or two metastatic sites other than cerebral and normal LDH at baseline, the median PFS was 18.0 months (95% CI 13.0–32.0) and the PFS rate at 1, 2, and 3 years was 67%, 49%, and 18%, respectively (Table 3).

### 3.5 Patients with Three or Fewer Metastatic Sites without Brain Metastases (BM) ($n = 198$) and Those with More Than Three Metastatic Sites and/or BM ($n = 146$) at Baseline

The ORR was 65.7% (95% CI 59.0–72.3) in patients with three or fewer metastatic sites without BM at baseline, whereas in patients with more than three metastatic sites and/or BM at baseline, the ORR was 61.6% (95% CI 53.8–69.5). The median DOR and CBR were higher in patients with three or fewer metastatic sites without BM versus more than three metastatic sites and/or BM: 13.4 months (95% CI 9.0–23.7) versus 7.2 months (95% CI 4.7–9.5) and 58% (95% CI 50.4–65.6) versus 46% (95% CI 36.7–55.2), respectively (Table 2).

Moreover, the median PFS was remarkably higher in patients with three or fewer metastatic sites without BM at baseline versus patients with more than three metastatic sites and/or BM at baseline: 13 months (95% CI 10.1–16.2) versus 6.9 months (95% CI 5.9–8.8; OSM, Resource 4).

### 3.6 Treatment Patterns

The median duration of exposure to dab + tram combination was 9.4 months (range 0–48.8 months). The median average daily dose of dab was 300 mg (range 86–300 mg) and of tram was 2 mg (range 1–2 mg). Dab + tram was permanently discontinued in 358 patients (71.7%), and the median time to discontinuation was 10.3 months (95% CI 9.1–11.5). Disease progression (58.7%) was the most common reason for treatment discontinuation, followed by death (8.2%), adverse events (3.6%), and administrative problems (< 1%; Fig. 1). Dose adjustments were observed in 101 patients (20.2%) receiving dab, 41 patients (8.2%) receiving tram, and 31

**Table 1** Baseline demographics and disease characteristics of patients

| Parameter | Overall enrolled ($N = 499$) |
|---|---|
| Age, median (range), years | 59 (23–90) |
| Sex, *n* (%) | |
| Male | 269 (53.9) |
| Female | 230 (46.1) |
| ECOG PS, *n* (%) | |
| 0 | 271 (54.3) |
| 1 | 91 (18.2) |
| 2 | 25 (5.0) |
| 3 | 2 (0.4) |
| 4 | 1 (0.2) |
| Missing | 109 (21.8) |
| *BRAF* V600 mutation status, *n* (%) | |
| V600E | 406 (81.4) |
| V600K | 53 (10.6) |
| Other *BRAF* V600 mutations | 36 (7.2) |
| Missing | 4 (0.8) |
| AJCC 7 stage at initial diagnosis, *n* (%) | |
| Stage I (IA and IB) | 68 (13.6) |
| Stage II (IIA, IIB, and IIC) | 123 (24.6) |
| Stage III | 176 (35.3) |
| Stage IV | 110 (22.0) |
| Not evaluable | 2 (0.4) |
| Missing | 20 (4.0) |
| No. of metastatic sites, *n* (%) | |
| ≤ 3 (without BM) | 240[a] (48.1) |
| > 3 (and/or BM) | 193[b] (38.7) |
| Patients with BM, *n* (%) | 115 (23.0) |
| ≤ 3 metastatic sites | 67 (13.4) |
| > 3 metastatic sites | 48 (9.6) |
| Patients without BM, *n* (%) | 318 (63.7) |
| ≤ 3 metastatic sites | 240 (48.1) |
| > 3 metastatic sites | 78 (15.6) |
| LDH at baseline, median (range), U/L | 318 (76–4471) |
| < ULN, *n* (%) | 226 (45.3) |
| ≥ ULN, *n* (%) | 143 (28.7) |
| Missing, *n* (%) | 130 (26.1) |
| Time to first recurrence, median (range), months | 17.9 (0–298) |
| Time to the most recent relapse, median (range), months | 28.2 (0–301) |
| Patients on first line of therapy in a metastatic setting | 406 (81.4) |
| Patients on subsequent line of therapy in a metastatic setting | 87 (17.4) |
| Patients with ≥ 1 prior adjuvant therapy | 75 (15.0) |
| Patients on first line of therapy with ≥ 1 prior adjuvant therapy | 58 (11.6) |
| Patients on subsequent line of therapy with ≥ 1 prior adjuvant therapy | 12 (2.4) |

*AJCC* American Joint Committee on Cancer, *BM* brain metastases, *ECOG PS* Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *ULN* upper limit of normal

[a]Excluding patients with > 3 metastatic sites (without BM; $n = 78$)

[b]Including patients with > 3 metastatic sites (without BM; $n = 78$)

**Table 2** Best overall response rate, duration of response, and clinical benefit rate in evaluable patients and subgroups

| Parameter | Evaluable patients | | Normal LDH level at baseline | | LDH > ULN at baseline | | ≤ 3 metastatic sites without BM at baseline | | > 3 metastatic sites and/or BM at baseline | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | Value | *n* | Value | *n* | Value | *n* | Value | *n* | Value |
| ORR, % (Wald 95% CI) | 390 | 62.3 (57.5–67.1) | 178 | 67.4 (60.5–74.3) | 115 | 58.3 (49.3–67.3) | 198 | 65.7 (59.0–72.3) | 146 | 61.6 (53.8–69.5) |
| Median DOR,[a] months (95% CI) | 243 | 9.9 (8.1–12.4) | 120 | 13.1 (9.5–23.7) | 67 | 5.8 (3.5–8.5) | 130 | 13.1 (9.0–23.7) | 90 | 7.2 (4.7–9.5) |
| CBR,[b] % (Wald 95% CI) | 306 | 52.6 (47.0–58.2) | 150 | 58.7 (50.8–66.6) | 80 | 38.8 (28.1–49.4) | 162 | 58.0 (50.4–65.6) | 111 | 46.0 (36.7–55.2) |

*BM* brain metastases, *CI* confidence interval, *CBR* clinical benefit rate, *CR* complete response, *DOR* duration of response, *LDH* lactate dehydrogenase, *ORR* overall response rate, *PR* partial response, *SD* stable disease, *ULN* upper limit of normal

[a]DOR was evaluated in patients achieving CR or PR

[b]CBR was evaluated in patients achieving CR, PR, or SD

patients (6.2%) receiving the dab + tram combination. Dab was temporarily interrupted in 158 patients (31.7%); tram in 137 patients (27.5%); and the dab + tram combination in 121 patients (24.3%; OSM, Resource 5).

### 3.7 Safety

Overall, 320 patients (64.1%) reported one or more TEAE. Of these, 233 patients (46.7%) had drug-related TEAEs. Treatment was permanently discontinued because of TEAEs in 46 patients (9.2%). The most commonly reported TEAEs were pyrexia (27.3%), asthenia (7.4%), rash (7.2%), and nausea (7.2%). The most commonly reported drug-related TEAEs were pyrexia (22.7%), rash (6.0%), and asthenia (5.0%). Most of the TEAEs were either grade 1 or 2. TESAEs were observed in 110 patients (22.0%), of whom 36 (7.2%) had drug-related TESAEs. The most frequent TESAE was pyrexia (2.6%; Table 4; OSM, Resource 6). Overall, 41 patients (8.2%) died during the study, and melanoma ($n$ = 24) was the most common cause. None of the deaths were related to the study treatment.

## 4 Discussion

Compassionate-use programs provide an opportunity to retrospectively evaluate the treatment patterns and clinical outcomes in a real-world setting and are critical tools in extending and confirming the results derived from randomized controlled clinical trials. Three real-world studies (DESCRIBE I, DESCRIBE II, and DESCRIBE III) assessed the treatment patterns and clinical outcomes of the therapies evaluated in the BREAK trials (dab monotherapy) and the COMBI-d and COMBI-v trials (dab + tram combination therapy) and demonstrated consistency with these previous pivotal clinical trials [4–6].

Similarly, the DESCRIBE Italy study retrospectively evaluated the real-world treatment patterns and effectiveness of treatments as well as gathered real-life evidence of patients with metastatic *BRAF* V600-mutant melanoma treated with the dab + tram combination in the MAP initiated in Italy after the approval of the combination by the European Medicines Agency. This study analyzed the data of a more diverse patient population from 35 Italian centers. The availability of data from an unselected patient population treated in the MAP provided an opportunity to gather real-life data and insights from the medical practice setting in Italy.

The results of this retrospective chart review were consistent with the efficacy and safety data described in the registration trials (COMBI-d and COMBI-v) [1, 2], substantiating the evidence that clinical benefit and tolerability with

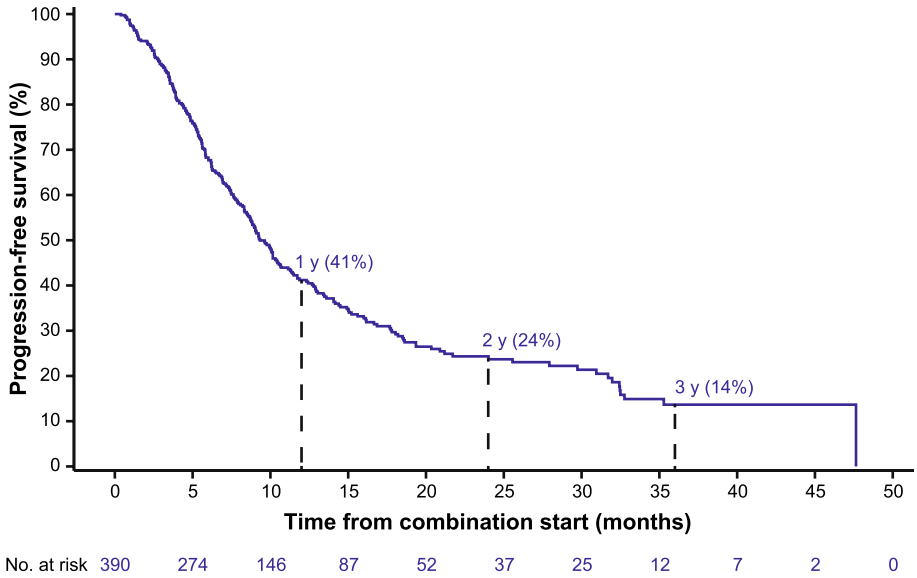


**Fig. 2** Progression-free survival. *No.* number, *y* years

**Table 3** Progression-free survival estimates for subgroups of patients

| Subgroups | No. of patients | No. (%) of patients with PFS events | Median PFS (95% CI) | 1-Year PFS rate, % | 2-Year PFS rate, % | 3-Year PFS rate, % |
|---|---|---|---|---|---|---|
| Normal LDH with > 3 metastatic sites and/or BM | 57 | 36 (63.2) | 9.1 (6.7–12.8) | 39 | 25 | 0 |
| Normal LDH with ≤ 3 metastatic sites without BM | 102 | 54 (52.9) | 16.7 (12.9–27.9) | 62 | 42 | 14 |
| LDH > ULN with > 3 metastatic sites and/or BM | 56 | 49 (87.5) | 5.1 (3.8–5.8) | 13 | 6 | 3 |
| LDH > ULN with ≤ 3 metastatic sites without BM | 48 | 38 (79.2) | 7.5 (5.4–10.5) | 30 | – | – |
| Normal LDH with 1 or 2 metastatic sites | 93 | 47 (50.5) | 17.8 (12.9–29.7) | 64 | 46 | 10 |
| Normal LDH with ≥ 3 metastatic sites | 159 | 119 (74.8) | 7.4 (6.0–9.2) | 32 | 15 | 3 |
| First line of therapy | 325 | 214 (65.9) | 9.3 (8.3–10.3) | 40 | 24 | 10 |
| First line of therapy, normal LDH, and 1 or 2 metastatic sites | 85 | 44 (51.8) | 16.7 (12.9–29.7) | 65 | 44 | 8 |
| First line of therapy, normal LDH, and ≥ 3 metastatic sites | 60 | 39 (65.0) | 9.1 (6.2–13.4) | 39 | 23 | 0 |
| First line of therapy with LDH > ULN | 91 | 77 (84.6) | 5.8 (4.7–7.3) | 17 | 6 | 3 |
| Metastatic sites different than cerebral | 256 | 163 (63.7) | 10.2 (8.7–13.0) | 46 | 27 | 14 |
| Normal LDH with 1 or 2 metastatic sites different than cerebral | 80 | 39 (48.8) | 18.0 (13.0–32.0) | 67 | 49 | 18 |

*BM* brain metastases, *CI* confidence interval, *LDH* lactate dehydrogenase, *PFS* progression-free survival, *ULN* upper limit of normal

the dab + tram combination are achievable in patients with *BRAF* V600-mutant metastatic melanoma. In addition, this study showed the effectiveness of this combination outside of a randomized controlled clinical trial setting. Unlike the registration trials, the population analyzed in this study was not entirely treatment naïve; however, the percentage of patients in subsequent lines of therapy was low, and the two populations were not comparable. Nevertheless, the clinical benefit achieved in these patients further supports the efficacy of this combination therapy and its use in routine clinical practice.

The ORR (62%) was comparable to the findings reported in the COMBI-d (67%) and COMBI-v (64%) trials [1, 2], considering the real-word setting of this study. Furthermore, the DESCRIBE II study, a retrospective chart review study whose design was analogous to this study, reported an ORR of 67% in BRAF inhibitor-naïve patients treated with dab + tram [5]. Moreover, the 3- and 5-year pooled analyses data

**Table 4** Safety summary

| Adverse events | Overall ($N = 499$) | |
|---|---|---|
| | Any grade | Grade ≥ 3 |
| TEAEs | 320 (64.1) | – |
| TEAEs (≥ 5%) | | |
| Pyrexia | 136 (27.3) | 11 (2.2) |
| Asthenia | 37 (7.4) | 1 (0.2) |
| Rash | 36 (7.2) | 2 (0.4) |
| Nausea | 36 (7.2) | 3 (0.6) |
| Diarrhea | 30 (6.0) | 4 (0.8) |
| Vomiting | 29 (5.8) | 6 (1.2) |
| Suspected drug-related TEAEs | 233 (46.7) | – |
| Suspected drug-related TEAEs (≥ 3%) | | |
| Pyrexia | 113 (22.7) | 9 (1.8) |
| Rash | 30 (6.0) | 2 (0.4) |
| Asthenia | 25 (5.0) | 1 (0.2) |
| Nausea | 20 (4.0) | 2 (0.4) |
| Diarrhea | 16 (3.2) | 3 (0.6) |
| Vomiting | 16 (3.2) | 2 (0.4) |
| TESAEs | 110 (22.0) | – |
| TESAEs (≥ 2%) | | |
| Pyrexia | 13 (2.6) | 5 (1.0) |
| Suspected drug-related TESAEs | 36 (7.2) | – |
| Suspected drug-related TESAEs (≥ 2%) | | |
| Pyrexia | 11 (2.2) | 3 (0.6) |
| TEAESIs | 171 (34.3) | – |
| TEAESIs (≥ 2%) | | |
| Rash | 36 (7.2) | 2 (0.4) |
| Diarrhea | 30 (6.0) | 4 (0.8) |
| Erythema | 18 (3.6) | 0 |
| Neutropenia | 15 (3.0) | 7 (1.4) |
| Edema peripheral | 14 (2.8) | 0 |
| Pyrexia | 11 (2.2) | 11 (2.2) |
| Suspected drug-related TEAESIs | 124 (24.9) | – |
| Suspected drug-related TEAESIs (≥ 2%) | | |
| Rash | 30 (6.0) | 2 (0.4) |
| Diarrhea | 16 (3.2) | 3 (0.6) |
| Neutropenia | 12 (2.4) | 5 (1.0) |
| Erythema | 12 (2.4) | 0 |

*TEAE* treatment-emergent adverse event, *TEAESI* treatment-emergent adverse event of special interest, *TESAE* treatment-emergent serious adverse event

from the COMBI-d and COMBI-v trials showed ORRs of 67% and 68%, respectively [3, 7].

The median PFS was 9.3 months (95% CI 8.6–10.6). The OS estimates (95%, 90%, and 87% at 1, 2, and 3 years, respectively) were much higher than those noted in the previous BRF112330, COMBI-d, and COMBI-v studies [2, 7–10]. However, as most patients were censored, the OS probability curves should be interpreted with caution.

Serum LDH levels and the number of metastatic sites at baseline were identified as the most predictive factors for durable response and survival, and are indicators of poor prognosis in patients with cancer [11]. In the COMBI-d and COMBI-v studies, patients with normal LDH levels and fewer than three metastatic sites had the longest survival outcomes, whereas patients with LDH levels two or more times the ULN had the shortest survival outcomes [7, 8]. In the 5-year pooled analysis of COMBI-d and COMBI-v, patients with normal LDH levels and fewer than three metastatic sites at baseline with a PFS of 31% and OS of 55% were identified as the most favorable subgroup [3]. This finding was consistent with the current study, where the subgroup analyses revealed that patients in the most favorable subgroups had better outcomes than patients in the corresponding unfavorable subgroups, with patients with normal LDH levels and three or fewer metastatic sites achieving the greatest benefit with dab + tram. The ORR was higher among patients with normal LDH levels (67.4%) and in patients with three or fewer metastatic sites without BM (65.7%) at baseline. The same was true for median PFS as well, with the two subgroups of patients with normal LDH levels or three or fewer metastatic sites without BM showing a longer PFS (12.8 and 13 months, respectively). These results are consistent with those from the previous studies, where patients with the most favorable baseline characteristics had a better prognosis [3, 5, 7, 8, 10, 12].

A post hoc analysis revealed that patients with normal LDH levels and one or two metastatic sites at baseline and patients with normal LDH levels and three or fewer metastatic sites without BM at baseline had a longer median PFS (17.8 months and 16.7 months, respectively). On the other hand, patients with normal LDH levels and three or more metastatic sites at baseline and patients with normal LDH levels and more than three metastatic sites and/or BM at baseline had a shorter median PFS (7.4 months and 9.1 months, respectively). Similarly, patients with LDH > ULN and three or fewer metastatic sites without BM at baseline and patients with LDH > ULN and more than three metastatic sites and/or BM at baseline had a shorter median PFS (7.5 months and 5.1 months, respectively). These data further confirm that patients with three or fewer metastatic sites along with normal LDH levels at baseline are likely to achieve better outcomes than patients with an aggressive disease and dab + tram combination therapy is also effective in patients with BM.

PFS was similar between patients on first and subsequent lines of treatment (median PFS, 9.3 and 10.4 months, respectively). The number of patients who received subsequent lines of therapy was lower ($n = 61$) compared with the number of patients who received first-line therapy ($n = 325$). Hence, direct intergroup comparisons cannot be made. The median PFS in the subgroup of patients on

first-line therapy with normal LDH levels and one or two metastatic sites at baseline was 16.7 months compared with 9.1 months in patients with three or more metastatic sites. A notable observation from this analysis was that the subgroup of patients with one or two metastatic sites different than cerebral and normal LDH levels at baseline had the longest median PFS of 18.0 months. All these findings confirm that patients having a lower initial tumor and disease burden are more likely to achieve a benefit from dab + tram combination therapy.

The safety data in this study were similar to those described in previous clinical studies of dab + tram. Notably, treatment was permanently discontinued because of TEAEs in 9.2% of patients, and pyrexia (27.3%) was the most common TEAE, with a lower incidence compared with that in the phase 3 studies of dab + tram (AEs leading to discontinuation of treatment, 18%; pyrexia, 58%) [3]. This finding is noteworthy and suggests that these drugs have good handling and tolerance that are growing with clinical experience. Besides, the rules for treatment discontinuation are less rigorous in real-world practice compared with the clinical studies, which in turn favors the maintenance of treatment in responding patients when AEs are not life-threatening. The most frequent AEs reported in this study, such as pyrexia, asthenia, rash, nausea, diarrhea, and vomiting, were consistent with the AEs reported in the summary of product characteristics and previous clinical studies of dab + tram. No new findings related to the safety of dab + tram combination therapy were reported. Therefore, the results of this study are in line with the risk/benefit ratio of this combination treatment, making this combination therapy a safe option for use in the real-world population in a compassionate-use setting.

As this was a retrospective observational study, potential limitations need to be considered while interpreting the results. The information captured in the electronic case report form was limited to that available in the medical records held by physicians at the participating centers and did not include data related to health-care services received outside the physician's care setting. The response criteria not being dictated by an interventional protocol and assessments (such as imaging studies) not being necessarily performed on a uniform schedule were additional limitations of this study. The physicians performed the assessments and used response criteria per the local clinical practice. There is also a possibility that the physicians from the practice settings may have used varying and possibly subjective criteria to assess clinical responses. Additionally, the patient population in this study differed in their baseline characteristics from those in the clinical trials. For example, fewer patients in this study had favorable characteristics at baseline compared with the pooled analysis of COMBI-d and COMBI-v studies: ECOG PS 0 (54% vs. 72%) and normal LDH level (45% vs. 65%) [3]. This variation is expected as this unselected patient population was from the real-world clinical practice setting with aggressive disease compared with the patients selected based on predefined eligibility criteria in the controlled clinical trial setting. Most patients were censored in the OS estimates; hence, the OS results should be interpreted cautiously, and there would be no further follow-up. However, these limitations are inherent and expected of retrospective chart reviews but did not impact the overall findings of this study.

## 5 Conclusions

Treatment of *BRAF* V600E-mutant metastatic melanoma with a dab + tram combination in the real-world setting was effective and safe, including the unselected population, with several patients having a high tumor burden and BM. The real-world data from this retrospective analysis are concordant with the results of the pivotal phase 3 studies of dab + tram and confirm the efficacy and safety of this combination in patients with metastatic melanoma. It is noteworthy that even though the analyzed population was not entirely treatment naïve, a clinical benefit was achieved. Therefore, the results confirm the risk/benefit balance of using the dab + tram combination and further support the use of this combination therapy in patients with metastatic melanoma in routine clinical practice.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s11523-021-00850-1.

**Acknowledgements** The authors thank the patients and their families for participation in the study and Sharol Janice Rodrigues (Novartis Healthcare Pvt Ltd) and Paola Amore (Novartis Farma S.p.A) for providing medical writing and editorial support, which was funded by Novartis Farma S.p.A in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

## Declarations

**Funding** This study was sponsored by Novartis Farma S.p.A. As of 2 March 2015, dabrafenib and trametinib have become assets of Novartis AG. Financial support for medical editorial assistance was provided by Novartis Farma S.p.A.

**Conflict of interest** Vanna Chiarion-Sileni reports participation as a consultant for Bristol Myers Squibb (BMS), Merck Serono, Novartis, and Pierre Fabre; participation as an invited speaker for Merck Serono, Merck Sharp & Dohme (MSD), Novartis, Pierre Fabre, and Sanofi; and travel and accommodation support from BMS and Pierre Fabre outside the submitted work. Massimo Guidoboni received personal fees for participation in advisory boards from BMS and Novartis; travel support and consultation fees from Pierre Fabre; and a grant from MSD outside the submitted work. Roberta Depenni received grants from BMS, MSD, Novartis, and Sanofi outside the submitted work. Alessandro Minisini reports personal fees from Merck, MSD,

Novartis, Pierre Fabre, Sanofi, and Sun Pharma outside the submitted work. Francesca Consoli reports personal fees for advisory board and consultancy from BMS, MSD, Novartis, and Pierre Fabre outside the submitted work. Paolo Ascierto received grants/research funds from Array, BMS, Roche-Genentech, and Sanofi; personal fees for a consultant/advisory role from Alkermes, Array, AstraZeneca, BMS, Boehringer Ingelheim, Daiichi Sankyo, Eisai, Idera, Immunocore, Incyte, Italfarmaco, Lunaphore, MedImmune, Merck, MSD, Nektar, Nouscom, Novartis, Oncosec, Pfizer, Pierre Fabre, Regeneron, Roche-Genentech, Sandoz, Sanofi, Seagen, Sun Pharma, Syndax, Takis, Ultimovacs, and 4SC; and travel support from MSD outside the submitted work. Riccardo Marconcini reports consulting fees from Incyte, La Roche, MSD, Novartis, and Pierre Fabre; honoraria from BMS, Ipsen, La Roche, MSD, Novartis, and Pierre Fabre; travel support from BMS, Ipsen, La Roche, MSD, Novartis, and Pierre Fabre; and participation in advisory boards for BMS, Ipsen, MSD, Novartis, and Pierre Fabre outside the submitted work. Michele Guida reports an advisory role for BMS, MSD, Novartis, and Pierre Fabre outside the submitted work. Michele Del Vecchio reports an advisory and consultant role for BMS, MSD, Novartis, Pierre Fabre, and Sanofi. Ilaria Gioia Marcon is an employee of Novartis Farma S.p.A. Paola Queirolo reports participation in advisory boards of BMS, Merck, MSD, Novartis, Pierre Fabre, Roche, Sanofi, and Sun Pharma. Massimo Aglietta, Paolo Fava, Gaetana Rinaldi, Maria Banzi, Rossana Gueli, Virginia Ferraresi, Marco Tucci, Giuseppe Tonini, and Giovanni Lo Re have declared no conflicts of interest.

**Ethics approval** This study was designed, implemented, and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and ethical principles that are outlined in the Declaration of Helsinki.

**Consent to participate** All patients provided written informed consent (not applicable for deceased patients).

**Consent for publication** Not applicable.

**Availability of data and material** Not applicable.

**Code availability** Not applicable.

**Authors' contributions** This study was designed and sponsored by Novartis Farma S.p.A. Data were collected and analyzed by the funder. All the authors were involved in the investigation, critically reviewed and drafted the manuscript, provided final approval, and agreed to be accountable for all aspects of the work. All the authors had full access to the study data and share final responsibility for the content of the report and the decision to submit for publication.



## References

1. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371:1877–88. https://doi.org/10.1056/NEJMoa1406037.
2. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372:30–9. https://doi.org/10.1056/NEJMoa1412690.
3. Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med. 2019;381:626–36. https://doi.org/10.1056/NEJMoa1904059.
4. Martin-Algarra S, Hinshelwood R, Mesnage S, Cebon J, Ferrucci PF, Aglietta M, et al. Effectiveness of dabrafenib in the treatment of patients with BRAF V600-mutated metastatic melanoma in a Named Patient Program. Melanoma Res. 2019;29:527–32. https://doi.org/10.1097/CMR.0000000000000608.
5. Atkinson V, Sandhu S, Hospers G, Long GV, Aglietta M, Ferrucci PF, et al. Dabrafenib plus trametinib is effective in the treatment of BRAF V600-mutated metastatic melanoma patients: analysis of patients from the dabrafenib plus trametinib Named Patient Program (DESCRIBE II). Melanoma Res. 2020;30:261–7. https://doi.org/10.1097/CMR.0000000000000654.
6. Atkinson VG, Quaglino P, Aglietta M, Del Vecchio M, Depenni R, Consoli F, et al. A retrospective analysis of dabrafenib and/or dabrafenib plus trametinib combination in patients with metastatic melanoma to characterize patients with long-term benefit in the Individual Patient Program (DESCRIBE III). Cancers (Basel). 2021;13:2466. https://doi.org/10.3390/cancers13102466.
7. Schadendorf D, Long GV, Stroiakovski D, Karaszewska B, Hauschild A, Levchenko E, et al. Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials. Eur J Cancer. 2017;82:45–55. https://doi.org/10.1016/j.ejca.2017.05.033.
8. Long GV, Grob JJ, Nathan P, Ribas A, Robert C, Schadendorf D, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. Lancet Oncol. 2016;17:1743–54. https://doi.org/10.1016/S1470-2045(16)30578-2.
9. Long GV, Weber JS, Infante JR, Kim KB, Daud A, Gonzalez R, et al. Overall survival and durable responses in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. J Clin Oncol. 2016;34:871–8. https://doi.org/10.1200/JCO.2015.62.9345.
10. Long GV, Flaherty KT, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol. 2017;28:1631–9. https://doi.org/10.1093/annonc/mdx176.
11. Zhang J, Yao YH, Li BG, Yang Q, Zhang PY, Wang HT. Prognostic value of pretreatment serum lactate dehydrogenase level in patients with solid tumors: a systematic review and meta-analysis. Sci Rep. 2015;5:9800. https://doi.org/10.1038/srep09800.
12. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroyakovskiy D, et al. LBA40—three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K–mutant cutaneous melanoma. Ann Oncol. 2016;27:vi575. https://doi.org/10.1093/annonc/mdw435.37.

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