Dabrafenib plus trametinib is effective in the treatment of BRAF V600-mutated metastatic melanoma patients

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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)

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In clinical trials, dabrafenib plus trametinib improved overall survival (OS) compared with single-agent BRAF inhibitors (BRAFi) in patients with *BRAF* V600-mutant unresectable or metastatic melanoma. We investigated dabrafenib plus trametinib therapy in a compassionate-use setting [Named Patient Program (NPP); DESCRIBE II]. A retrospective chart review of patients with *BRAF* V600-mutated unresectable stage III/IV melanoma receiving dabrafenib plus trametinib as compassionate use was conducted. Treatment patterns and duration, clinical outcomes, and tolerability were evaluated. Of 271 patients, 92.6% had stage IV melanoma, including 36.5% with brain metastases. Overall, 162 patients (59.8%) were BRAFi naive and 171 (63.1%) received first-line dabrafenib plus trametinib. Among BRAFi-naive patients, the overall response rate (ORR) was 67.3%, median OS (mOS) was 20.0 months, and median progression-free survival (mPFS) was 7.5 months. In BRAFi-naive patients with known brain metastases ($n = 62$), ORR was 61.3%, mOS was 15.5 months, and mPFS was 6.2 months. Eighty-four patients received BRAFi monotherapy for >30 days and switched to dabrafenib plus trametinib prior to progression. Of these 84 patients, 63 had known disease status at the time of switch, and 22 improved with the combination therapy. No new safety signals were identified, and dabrafenib plus trametinib was well tolerated. Dabrafenib plus trametinib showed substantial clinical activity in NPP patients with *BRAF* V600-mutated unresectable or metastatic melanoma. Analysis of treatment patterns demonstrated the effectiveness of the combination in patients with brain metastases and across lines of therapy with a well tolerated and manageable safety profile. *Melanoma Res* XXX: 000–000 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

An improved understanding of the underlying molecular mechanisms of melanoma has resulted in substantial advances in available treatments, including targeted kinase and immune checkpoint inhibitors [1–7]. Dabrafenib and trametinib are selective inhibitors of mutant BRAF kinase and MEK1/2, respectively. Treatment of patients with advanced *BRAF*-mutant melanoma with dabrafenib plus trametinib has been shown to be superior to treatment with BRAF inhibitor (BRAFi) monotherapy, with significant improvements observed in

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overall response rate (ORR), progression-free survival (PFS), and the overall survival (OS) [6–13].

Prior to the approval of dabrafenib, a compassionate-use Named Patient Program (NPP) for dabrafenib was established to allow access to the drug for patients with unresectable advanced *BRAF* V600-mutant melanoma [14]. As data emerged showing that dabrafenib plus trametinib was superior to single-agent dabrafenib [6–8], an NPP for dabrafenib plus trametinib was initiated [15].

NPPs provide a unique opportunity to evaluate clinical outcomes in patients treated outside a well controlled clinical trial. We previously reported on the single-agent dabrafenib NPP (DESCRIBE I) [14], which demonstrated outcomes comparable with those in randomized clinical trials of dabrafenib. These results were encouraging, considering that the dabrafenib NPP population was generally in poorer health than patients enrolled in the dabrafenib monotherapy studies. At treatment initiation, 39.9% of NPP patients had brain metastases and 13.5% had a known Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or 3 [14]. Treatment of patients with melanoma with brain metastases remains a highly unmet medical need [16–18].

Here we present results from DESCRIBE II, including outcomes in the overall population of patients receiving dabrafenib plus trametinib combination therapy in the NPP and those in additional important and clinically relevant subsets, such as patients with brain metastases and those switched from BRAFi monotherapy to dabrafenib plus trametinib prior to disease progression.

Methods

This was a multicountry, multisite, retrospective chart review of patients enrolled in the dabrafenib plus trametinib NPP. Inclusion and exclusion criteria and other detailed methods are provided in Supplementary Material, Supplemental digital content 1, *http://links.lww.com/MR/A196*.

Primary and secondary objectives

The primary objective was to describe treatment patterns and duration in patients with *BRAF* V600-mutated unresectable or metastatic melanoma who received dabrafenib plus trametinib combination therapy as compassionate use. Secondary objectives were to describe adverse events, serious adverse events (SAEs), adverse events of special interest (AESI), and patterns of progression; and to determine the best overall response, PFS, and OS.

Response criteria

Tumor assessment was performed by treating clinicians as per standard clinical practice, rather than the Response Evaluation Criteria in Solid Tumors, and responses were documented as complete response (CR), partial response (PR), stable disease, and progressive disease (PD).

Patients

The observed population included all patients enrolled in the chart review who had data extracted from their medical charts. Subgroup analyses consisted of patients with brain metastases (who may or may not have had prior local therapy for brain metastases) and patients who were BRAFi naive prior to the initiation of dabrafenib plus trametinib therapy.

Ethical approvals

Approvals were obtained from the appropriate ethics committees in compliance with local country and regulatory guidelines. This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines as applicable to observational research, patient privacy requirements, and ethical principles that are outlined in the Declaration of Helsinki.

Results

Patient characteristics and disposition

The observed population comprised 271 NPP patients whose charts were abstracted. Patients were from 21 sites in six countries [Australia (n = 97), the Netherlands (n = 58), Italy (n = 57), Lithuania (n = 24), Spain (n = 28), and Czech Republic (n = 7)], 19 hospitals (12 university, three community, three oncology specialty, and one research), and two private practices. The median observational period [defined as period from the initiation of dabrafenib plus trametinib to study end (i.e., date when chart abstraction was initiated, the patient died, or the patient was last known to be alive)] was 12.3 months (range, 1–22 months); 20 patients (7.4%) had stage IIIC disease, and 251 patients (92.6%) had stage IV disease. Among patients with a known ECOG PS, 18 patients (10.8%) were classified as 2 or 3 (Table 1). The most common site of metastases was visceral [62.4% (n = 169)], and 36.5% of patients (n = 99) had brain metastases. At the study end, 160 patients (59.0%) were alive; of these, 90 patients (56.3%) continued to receive dabrafenib plus trametinib and the remaining 70 patients (43.8%) discontinued the combination therapy (Supplementary Fig. S1, Supplemental digital content 2, http://links.lww.com/MR/A197).

Clinical treatment patterns

The median treatment duration was 8.5 months [95% confidence interval (CI), 7.3–10.8 months]. Most patients (63.1%) received dabrafenib plus trametinib as first-line treatment (second-line, 29.5%; third-line or higher, 7.4%). The median duration of dabrafenib plus trametinib

Table 1 Patient baseline demographics and disease and treatment characteristics

Parameter	Observed population ($N = 271$)	BRAF inhibitor-naive population[a] ($n = 162$)
Median age, years (range)	56 (22–87)	55.5 (22–87)
Male, *n* (%)	150 (55.4)	90 (55.6)
Melanoma stage, *n* (%)		
IIIC	20 (7.4)	14 (8.6)
IV	251 (92.6)	148 (91.4)
Site of metastasis, *n* (%)[b]		
Brain	99 (36.5)	62 (38.3)
Subcutaneous	88 (32.5)	57 (35.2)
Lymph nodes	136 (50.2)	80 (49.4)
Visceral	169 (62.4)	102 (63.0)
Other	100 (36.9)	54 (33.3)
ECOG PS, *n* (%)[c]	($n = 167$)[d]	($n = 95$)[e]
0	114 (68.3)	64 (67.4)
1	35 (21.0)	18 (18.9)
2	16 (9.6)	11 (11.6)
3	2 (1.2)	2 (2.1)
BRAF V600 mutation status, *n* (%)		
V600E	179 (66.1)	103 (63.6)
V600K	30 (11.1)	19 (11.7)
Other *BRAF* mutation	10 (3.7)	6 (3.7)
V600 mutation detected, unknown subtype	52 (19.2)	34 (21.0)
Treatment line in which dabrafenib plus trametinib was received, *n* (%)		
First line	171 (63.1)	140 (86.4)
Second line	80 (29.5)	17 (10.5)
Third line or higher	20 (7.4)	5 (3.1)
Median treatment duration, months (range)	8.5 (7.3–10.8)	–
With brain metastases	NA	6.9 (6.0–8.4)
Without brain metastases	NA	10.4 (7.9–13.2)
Median treatment duration by line of therapy, months (95% CI)		
First-line ($n = 171$)	10.1 (7.9–12.5)	NA
Second-line ($n = 80$)	7.1 (5.2–8.8)	NA
Third-line or higher ($n = 20$)	7.5 (6.1–not reached)	NA

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, Not available.
[a]Patients who initiated dabrafenib plus trametinib combination therapy without a history of dabrafenib monotherapy or vemurafenib treatment.
[b]Less than 1 site of metastasis could have been reported.
[c]ECOG PS documented in the medical chart within 30 days prior to initiating dabrafenib plus trametinib combination therapy.
[d]Data missing for 104 patients as no documentation was made in the medical chart that ECOG PS was assessed within 30 days prior to initiating dabrafenib plus trametinib combination therapy.
[e]Data missing for 67 patients, as no documentation was made in the medical chart that ECOG PS was assessed within 30 days prior to initiating dabrafenib plus trametinib combination therapy.

therapy as first-, second-, and third-line or higher treatment was 10.1 months (95% CI, 7.9–12.5 months), 7.1 months (95% CI, 5.2–8.8 months), and 7.5 months (95% CI, 6.1 months–not reached), respectively (Table 1).

Of the treatment regimens received by patients in this study (Supplementary Table S1, Supplemental digital content 3, http://links.lww.com/MR/A198), the most common first-line therapies were dabrafenib plus trametinib (63.1%), followed by vemurafenib (18.5%) and chemotherapy [alone or in combination with another agent (11.8%)]. Among 146 patients who received second-line therapy, the most common were dabrafenib plus trametinib (54.8%) and ipilimumab (25.3%). Among 62 patients who received three or more lines of therapy, ipilimumab (37.1%) and dabrafenib plus trametinib (35.5%) were the most common, followed by an anti–programmed death-1 agent (22.6%). Seventy-three of 164 patients (44.5%) who progressed after dabrafenib plus trametinib combination therapy received subsequent therapy, with the most common being ipilimumab [45/73 (61.6%)], dacarbazine [8/73 (11.0%)], and an anti–programmed death-1 agent [6/73 (8.2%)].

Effectiveness outcomes

Total observed population

In the observed population ($N = 271$), the ORR (CR + PR) was 63.5%, median OS (mOS) was 18.4 months, and median PFS was 6.8 months. The mOS in patients who received first- and second-line dabrafenib plus trametinib was 20.0 and 15.1 months, respectively, and the median PFS was 8.1 and 5.0 months, respectively (Supplementary Table S2, Supplemental digital content 4, *http://links.lww.com/MR/A199*).

BRAF inhibitor-naive patients

In BRAFi-naive patients ($n = 162$), the ORR was 67.3%, mOS was 20.0 months, and median PFS was 7.5 months (Table 2; Fig. 1a and b). In BRAFi-naive patients who received dabrafenib plus trametinib as first-line therapy [$n = 140$ (86.4%)], ORR was 66.4%, mOS was 20.0 months, and median PFS was 8.0 months (Supplementary Table S2, Supplemental digital content 4, *http://links.lww.com/MR/A199*). In BRAFi-naive patients who received dabrafenib plus trametinib as second-line therapy or higher [$n = 22$ (13.6%)], ORR was 72.7%, mOS was 15.1 months, and median PFS was 7.1 months (Supplementary Table S2, Supplemental digital content 4, *http://links.lww.com/MR/A199*).

BRAFi-naive patients were analyzed by brain metastases status at treatment initiation. The ORR in BRAFi-naive patients with brain metastases was 61.3 vs. 71.0% in those without brain metastases (Table 2). The mOS and PFS were 15.5 and 6.2 months, respectively, in patients with brain metastases, and 20.0 and 8.0 months, respectively, in patients without brain metastases (Fig. 1c and d).

Patients switched from BRAF inhibitor monotherapy to dabrafenib plus trametinib prior to progression

A total of 84 patients received BRAFi for >30 days [median treatment duration, 6.1 months (range, 0.4–31.3 months)] and were switched to dabrafenib plus trametinib prior to progression. All seven patients with a prior CR maintained a CR after the switch (Supplementary Table S3, Supplemental digital content 5, *http://links.lww.com/MR/A200*). Of the 36 patients with a PR on BRAFi monotherapy, 12 improved to a CR, 12 maintained a PR, four had stable disease, seven had PD, and one was invaluable after

starting dabrafenib plus trametinib. Of the 20 patients with stable disease on BRAFi monotherapy, 10 improved (2 CRs, 8 PRs), three maintained stable disease, and seven had PD after starting dabrafenib plus trametinib. Among patients who switched from BRAFi to dabrafenib plus trametinib, 66.5% had not progressed at 1 year from initiation of BRAFi and 84.2 and 58.1% patients were alive at 1 and 2 years, respectively (Supplementary Table S3, Supplemental digital content 5, *http://links.lww.com/MR/A200*).

Safety

Overall, 415 adverse events occurred in 159 of 271 patients (58.7%). The number of patients with adverse events by the highest grade was as follows: grade 1, n = 39 (14.4%); grade 2, n = 65 (24.0%); grade 3, n = 56

Table 2 Efficacy in the BRAF inhibitor-naive population with and without known brain metastases at baseline ($N = 162$)

Parameter	BRAF inhibitor-naive population ($N = 162$)	Known brain metastases ($n = 62$)	No known brain metastases ($n = 100$)
Median PFS, months, (95% CI)	7.5 (6.3–9.3)	6.2 (5.4–9.5)	8 (6.8–10.0)
Median OS, months (95% CI)	20.0 (14.7–NYR)	15.5 (10.8–NYR)	20 (15.1–NYR)
Best overall response, n (%) (95% CI)[a]			
Overall response rate[b,c]	109 (67.3) (59.5–74.4)	38 (61.3) (48.1–73.4)	71 (71.0) (61.1–79.6)
Complete response	21 (13.0)	5 (8.1)	16 (16.0)
Partial response	88 (54.3)	33 (53.2)	55 (55.0)
Stable disease	20 (12.3)	8 (12.9)	12 (12.0)
Progressive disease	27 (16.7)	12 (19.4)	15 (15.0)

CI, confidence interval; NYR, not yet reached; OS, overall survival; PFS, progression-free survival.
[a]Data missing for six patients in the BRAF inhibitor-naive population.
[b]Best overall response was unknown for four patients with known brain metastases and two patients with no known brain metastases.
[c]Complete response + partial response.

Fig. 1

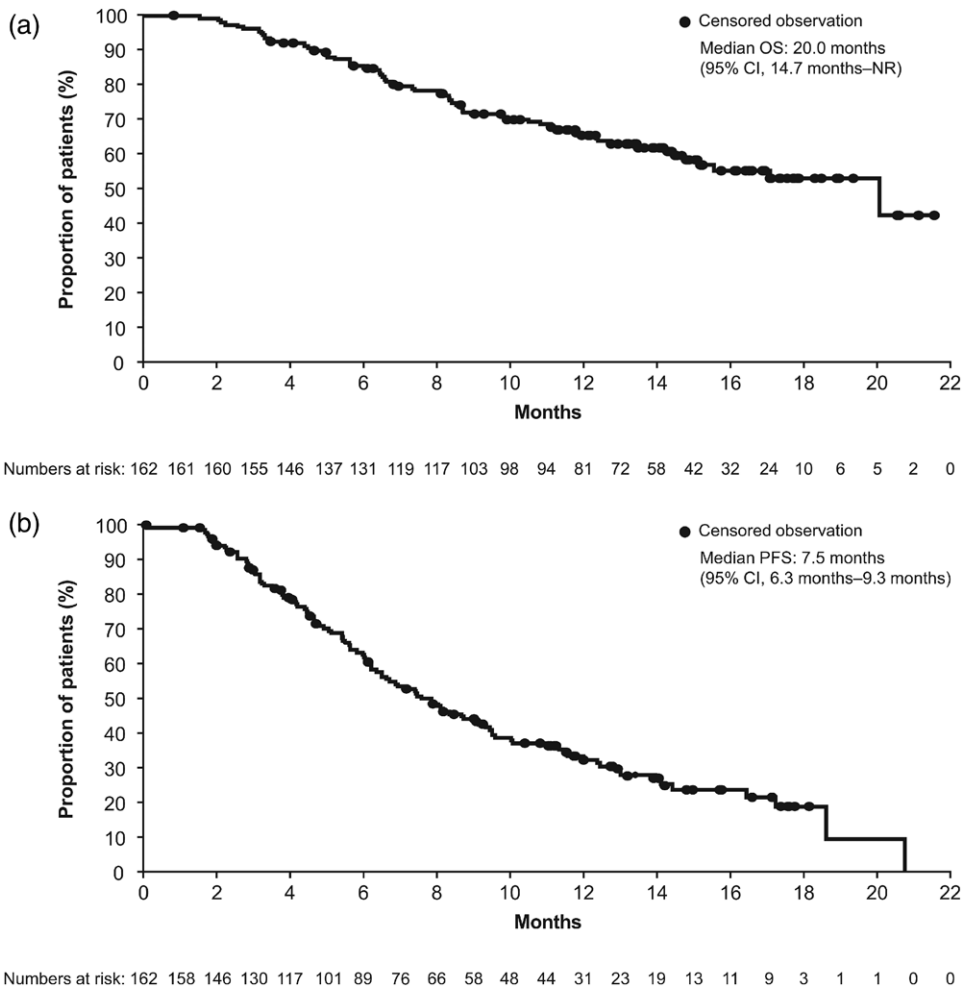

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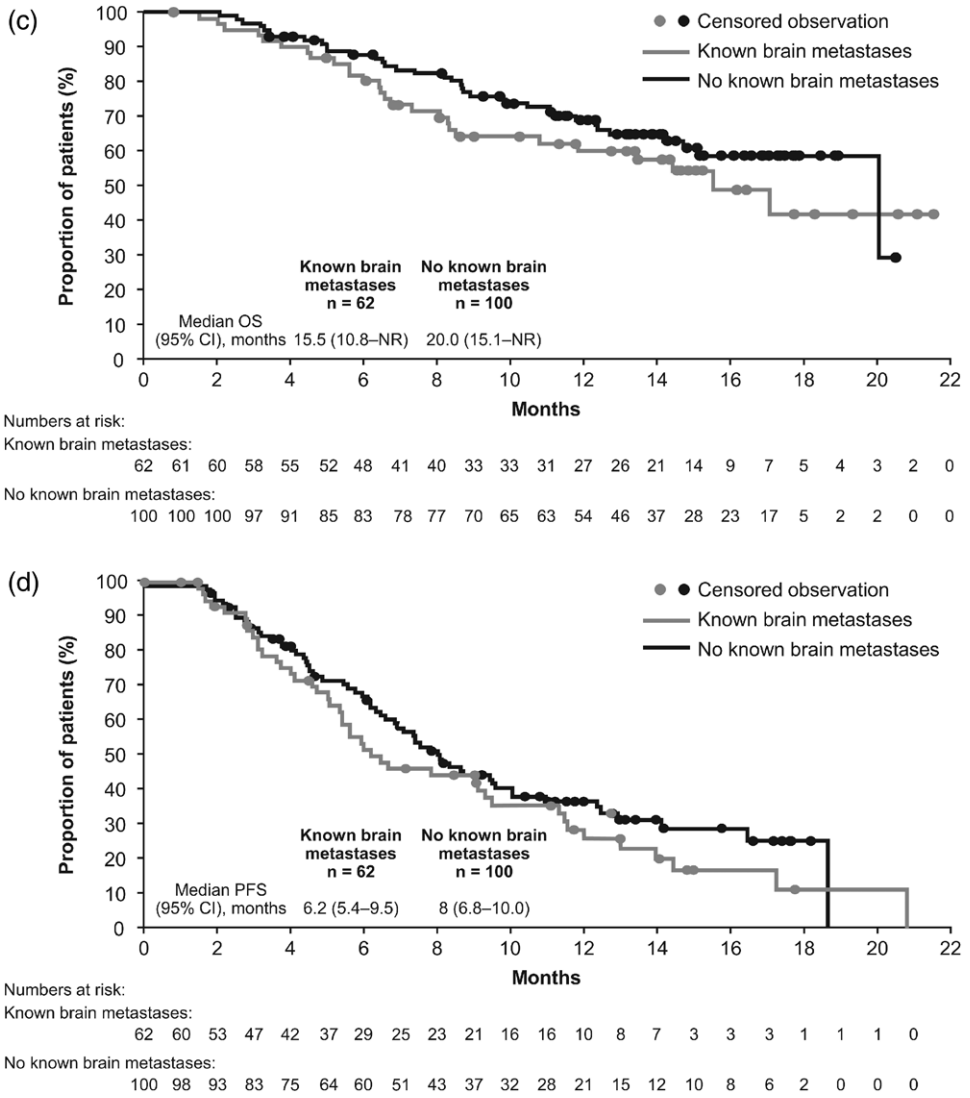
Fig. 1 Continued



Kaplan–Meier estimates of (a) OS and (b) PFS in the BRAF inhibitor-naive subset of patients ($n = 162$), in patients (c) with ($n = 62$), and (d) without ($n = 100$) brain metastases at initiation of dabrafenib treatment. Circles indicate censored observations. CI, confidence interval; NR, not reached; OS, overall survival; PFS, progression-free survival.

(20.7%); grade 4, $n = 3$ (1.1%); grade 5, $n = 3$ (1.1%); and unknown, $n = 18$ (6.6%). The most common adverse events were pyrexia/fever (41.0%), fatigue (17.3%), and nausea (16.2%) (Supplementary Table S4, Supplemental digital content 6, *http://links.lww.com/MR/A201*). The most common AESI were pyrexia/fever (41.0%), rash (24.7%), fatigue (17.3%), and nausea (16.2%) (Supplementary Table S5, Supplemental digital content 7, *http://links.lww.com/MR/A202*). A total of 28 patients (10.3%) discontinued dabrafenib or trametinib owing to an adverse event. Pyrexia was the most frequent adverse event that led to discontinuation of dabrafenib (2.6%) and trametinib (2.2%) (Supplementary Table S6, Supplemental digital content 8, *http://links.lww.com/MR/A203*). Sixty-six (24.4%) and 20 (7.4%) patients had ≥1 adverse event that led to a dose reduction of dabrafenib or trametinib, respectively, with pyrexia being the most common for both [dabrafenib, 15.1%; trametinib, 2.6% (Supplementary Table S7, Supplemental digital content 9, *http://links.lww.com/MR/A204*)].

Sixty-nine patients (25.5%) had ≥1 SAE. SAEs occurring in ≥5 patients were pyrexia [$n = 38$ (14%)], vomiting [$n = 6$ (2.2%)], diarrhea [$n = 5$ (1.8%)], chills [$n = 5$ (1.8%)], and neoplasms [benign, malignant, and unspecified (including cysts and polyps); $n = 5$ (1.8%)]. Most SAEs [31/69 (44.9%)] were grade 3; grade 4 SAEs included pulmonary embolism and neutropenia ($n = 1$ each). Three patients had fatal SAEs: gastritis, sepsis, and pulmonary embolism (none were considered related to dabrafenib or trametinib).

Discussion

Compassionate-use programmes, NPPs, and extended access programmes provide an opportunity to retrospectively evaluate real-world treatment patterns and the effectiveness of treatments. DESCRIBE II is the first evaluation of dabrafenib plus trametinib in patients with *BRAF* V600-mutant unresectable stage III or metastatic melanoma in daily clinical practice. A total of 21 sites from a variety of institution types in six countries participated. Physicians were free to manage patients based on routine practice and clinical judgement. DESCRIBE II included a more diverse patient population than would have been eligible to enroll in prospective clinical trials, and patients were generally in poorer health [6–8]. For example, patients with an ECOG PS >2 are generally excluded from prospective clinical trials, whereas at the initiation of this study, 10.8% of patients had a known ECOG PS of 2 or 3. In addition, previous registration trials required patients with brain metastases to be definitively treated and stable for ≥12 weeks [6–8]; in DESCRIBE II, 36.5% of patients had brain metastases at treatment initiation. Of note, efficacy results observed in the BRAFi-naive subset of DESCRIBE II, which may more closely resemble prospective study populations [6–8], were consistent with those from phase 2 and phase 3 clinical trials of dabrafenib plus trametinib (BRF113220, COMBI-d, and COMBI-v) [7,9–13].

A substantial percentage of patients with brain metastases in DESCRIBE II enabled the evaluation of clinical response in this subgroup. Similar to the findings from DESCRIBE I, patients with brain metastases at treatment initiation (who may or may not have had prior local therapy for brain metastases) had a lower ORR than patients without brain metastases (65.5 vs. 72.4%, respectively), and a separation in the PFS and OS Kaplan–Meier curves were observed at approximately 5 and 6 months, respectively. The inclusion of patients with brain metastases may, in part, account for the shorter PFS observed in this study than what has been observed in prospective clinical trials (median PFS, 7.5 vs. 9.4–11.4 months) [7,9,10]. When patients with brain metastases in DESCRIBE II are excluded from the analyses, the PFS increases to 8 months.

Data for extracranial vs. intracranial ORR were not abstracted from patient charts; thus, it was not possible to determine whether brain metastases were stable or responsive to the combination therapy. Moreover, the proportion of patients with active brain metastases at baseline was not known (i.e., those with no local therapy to the brain or with progression in the brain after local therapy). However, five patients (8.1%) with brain metastases achieved CR and 33 with brain metastases (53.2%) achieved a PR. These rates of overall response were similar to those observed with dabrafenib plus trametinib in patients with *BRAF* V600E-mutant asymptomatic melanoma brain metastases with or without prior local treatment in phase 2 COMBI-MB study (CR, 1 and 0%, respectively; PR, 57 and 56%, respectively) [18]. Furthermore, the median PFS (6.2 months) and OS (15.5 months) observed in this study were consistent with those seen in COMBI-MB across *BRAF* V600-mutant melanoma brain metastases cohorts (median PFS range, 4.2–7.2 months; mOS range, 10.1–24.3 months) [18]. They were also longer than those reported with dabrafenib monotherapy in the phase 2 BREAK-MB study (which included patients with *BRAF* V600E-mutant melanoma with or without prior treatment to the brain [PFS, 3.7 and 3.8 months, respectively; OS, 7.6 and 7.2 months, respectively]) [17] and in DESCRIBE I (PFS, 3.9 months; OS, 9.5 months) [14]. Together, these results suggest that the addition of trametinib improves outcomes in patients with brain metastases.

Better outcomes of median PFS, mOS, and ORR were reported in patients who received dabrafenib plus trametinib combination therapy in the first-line setting (8.1 months, 20.0 months, and 65.5%, respectively) vs. the second-line setting (5.0 months, 15.1 months, and 60%, respectively), suggesting a greater benefit with the combination when used in the first-line setting. In addition, this is the first report of outcomes in patients initially treated with dabrafenib monotherapy who were switched to dabrafenib plus trametinib combination therapy before disease progression (n = 84), and improvement in disease status was observed in 22 of these patients (26.2%). These results differ from those observed in part C of the phase 1/2 BRF113220 study, in which BRAFi-refractory patients could cross over to dabrafenib plus trametinib at progression [8,19]. In that patient group [45/54 patients (83.3%) originally assigned to dabrafenib monotherapy], the activity of dabrafenib plus trametinib was inferior to that observed in patients who were BRAFi naive and received the combination therapy.

Dabrafenib plus trametinib appeared to be well tolerated with a manageable safety profile. Patients received approximately 88 and 95% of the dabrafenib and trametinib-labeled doses, respectively [20,21]. The safety profile was consistent with that observed in pivotal dabrafenib plus trametinib combination trials [7,10]. As expected, pyrexia was the most commonly reported adverse event that resulted in dose reduction or discontinuation in DESCRIBE II, and both the incidence of adverse events related to skin hyperproliferation and the paradoxical activation of the Mitogen-activated protein kinase pathway that is observed with BRAFi monotherapy were lower in DESCRIBE II than in DESCRIBE I. The incidence of adverse events reported is less than documented in previous clinical trials; this could be due to the retrospective nature of this data collection.

Limitations of this study include those that are inherent in chart review analyses. Notably, patients enrolled in this study generally had poorer health compared with

those enrolled in clinical trials (e.g., patients in this analysis may have received dabrafenib plus trametinib beyond the first-line setting). Despite these limitations, results from DESCRIBE II are generally consistent with those from prospective, controlled, randomized trials demonstrating the substantial clinical activity with dabrafenib plus trametinib in patients with *BRAF* V600-mutant unresectable or metastatic melanoma [6–13]. These results provide further evidence for the use of dabrafenib plus trametinib combination therapy in the first-line setting. Robust activity in the second-line setting also supports the potential benefits of switching patients receiving BRAFi monotherapy to BRAFi and MEKi combination therapy prior to disease progression.

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Conflicts of interest

V.A. has received personal fees or travel support from Bristol-Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Merck Serono, Novartis, OncoSec, Pierre Fabre, and Roche. S.S. has received honoraria from Amgen, BMS, Janssen, Merck Serono, and MSD and grant funding from BMS, Merck Serono, and MSD. G.H. has received fees for institution from BMS, MSD, and Roche. G.V.L. has received personal fees from Aduro, Amgen, BMS, Mass-Array, MSD, Novartis, OncoSec, Pierre Fabre, and Roche. M.A. has received personal fees for consulting or advisory role from Bayer, Novartis, BMS, and Merck; research funding from AstraZeneca and PharmaMar; and travel support from Merck, Tesaro, and BMS. P.F.F. has received personal fees for advisory board participation and meeting presentations from BMS, MSD, Novartis, Pierre Fabre, and Roche. S.T. has received personal fees from Roche, Janssen, Eli Lilly (payment for lectures) and travel support from MSD, BMS, Novartis, Janssen, Roche, Amgen, AstraZeneca, and Pfizer. S.A. has received conference sponsorship from GlaxoSmithKline. A.P. has received honoraria for lectures from Bayer, Novartis, Pfizer, and Roche. D.R.-A. has received consulting honoraria, advisory honoraria, and travel grants from AstraZeneca, Roche, MSD, Boehringer, Novartis, Pfizer, and BMS. M.L. and E.dJ. are employees of Novartis. P.L. is a former employee of Novartis. D.S. and B.K. are former employees of United BioSource Corporation (UBC): An Express Script Company. J.V.v.T. has received travel support from Roche and his institution (N.K.I-A.v.L.) has received fees from Novartis and Pfizer for consultancy. There are no conflicts of interest for the remaining authors.

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