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AUTHOR CONTRIBUTIONS

Dr Hauschild had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hauschild, Mookerjee.

Acquisition, analysis, or interpretation of data: Hauschild, Ascierto, Schadendorf, Grob, Ribas, Kiecker, Demidov, Lebbé, Rutkowski, Blank, Gutzmer, Millward, Kefford, Haas, D'Amelio, Mookerjee, Chapman.

Drafting of the manuscript: Ascierto, Demidov, Mookerjee.

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Statistical analysis: Haas, D'Amelio.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at [doi TBC by the journal].

Conflict of interest statement

Dr Hauschild reported receiving clinical trial support (grant to institution) from Amgen, Bristol-Myers Squibb, Merck Serono, Merck Sharp & Dohme/Merck, Philogen, Pierre Fabre, Provectus, Regeneron, Roche, Sanofi-Genzyme, and Novartis Pharma; personal fees for speaker honoraria from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme/Merck, Pierre Fabre, Provectus, Regeneron, Roche, Sanofi-Genzyme, and Novartis Pharma; and personal fees for consultancy from Amgen, Bristol-Myers Squibb, Merck Serono, Merck Sharp & Dohme/Merck, Philogen, Pierre Fabre, Provectus, Regeneron, Roche, OncoSec, Sanofi Genzyme, Sun Pharma, and Novartis Pharma. 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Long-Term Outcomes in Patients With *BRAF*^{V600}-Mutant Metastatic Melanoma Receiving Dabrafenib Monotherapy: Analysis From Phase 2 and 3 Clinical Trials

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Abstract

Background: Previous analyses of BREAK-2 and BREAK-3 showed that durable outcomes lasting 3 years are achievable with dabrafenib in some patients with *BRAF*^{V600}-mutant metastatic melanoma (MM); however, additional follow-up is needed to fully characterise the long-term impact of dabrafenib in these patients.

Methods: BREAK-2 was a single-arm phase 2 study evaluating dabrafenib in treatment-naïve or previously treated *BRAF*^{V600E/K}-mutant MM. BREAK-3, a randomised (3:1) phase 3 study, assessed dabrafenib vs dacarbazine in previously untreated unresectable or metastatic *BRAF*^{V600E}-mutant melanoma. Five-year landmark analyses were performed.

Results: All BREAK-2 patients (N=92 [V600E, n=76; V600K, n=16]) discontinued treatment by the data cutoff. Median follow-up was 13.0 months. In *BRAF*^{V600E} patients, 5-year PFS and

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overall survival (OS) were 11% and 20%, respectively. Postprogression immunotherapy was received by 22% of patients. In BREAK-3, median follow-up was 17.0 and 12.0 months in the dabrafenib (n=187) and dacarbazine (n=63) arms, respectively. Thirty-seven patients (59%) receiving dacarbazine crossed over to dabrafenib following disease progression. Five-year PFS was 12% in the dabrafenib arm; all dacarbazine-arm patients progressed or were censored by 5 years. Dabrafenib improved PFS vs dacarbazine, regardless of baseline lactate dehydrogenase levels. Five-year OS rates were 24% and 22% in the dabrafenib and dacarbazine arms, respectively. Subsequent therapy in each arm included anti-CTLA-4 (dabrafenib [24%] and dacarbazine [24%]) and/or anti-PD-1 (8% and 2%) treatment. No new safety signals were observed.

Conclusions and Relevance: These data, representing extended follow-up for BRAF inhibitor monotherapy, demonstrate that durable benefit lasting 5 years is achievable in a subset of patients.

Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov) (BREAK-2, [NCT01153763](https://clinicaltrials.gov/ct2/show/study/NCT01153763); BREAK-3, [NCT01227889](https://clinicaltrials.gov/ct2/show/study/NCT01227889)).

Keywords

melanoma; BRAF; dabrafenib; metastatic; long-term outcomes

INTRODUCTION

Targeted therapies and immune checkpoint inhibitors have significantly improved clinical outcomes in metastatic melanoma (MM); however, extended follow-up in randomised studies of these agents has been limited [1–9]. Optimisation of individualised treatment for *BRAF*^{V600}-mutant MM will require a full understanding of the proportion and characteristics of patients most likely to achieve long-term benefit with current therapies.

Clinical activity and tolerability of the BRAF inhibitor (BRAFi) dabrafenib were initially demonstrated in patients with MM, including those with prior treatment, harbouring *BRAF*^{V600E} or *BRAF*^{V600K} mutations in the phase 2 trial BREAK-2 [10]. First-line dabrafenib significantly improved outcomes vs dacarbazine in patients with unresectable or metastatic *BRAF*^{V600E}-mutant melanoma in the randomised phase 3 study BREAK-3 [11]. In both studies, dabrafenib had a manageable safety profile [10,11]. Results from the primary analyses of BREAK-2 and BREAK-3 were confirmed in extended follow-up analyses of these studies, including a 3-year analysis of BREAK-3, demonstrating durable clinical benefit of dabrafenib for 3 years in a substantial proportion of patients (3-year overall survival [OS], 31%) [3]. We report updated 5-year landmark efficacy and safety analyses for BREAK-2 and BREAK-3.

MATERIALS AND METHODS

In BREAK-2, patients with *BRAF*^{V600E/K}-mutant (per central testing) stage IV melanoma received oral dabrafenib 150 mg twice daily. With the exception of BRAF/MEK inhibitors, eligible patients could have received systemic MM treatment prior to enrolment. The primary endpoint was objective response rate (ORR) in *BRAF*^{V600E} patients; secondary

endpoints included ORR in *BRAF*^{V600K} patients, progression-free survival (PFS), OS, duration of response, and safety.

In BREAK-3, patients with previously untreated *BRAF*^{V600E}-mutant (per central testing) unresectable or MM were randomised 3:1 to receive either oral dabrafenib 150 mg twice daily or intravenous dacarbazine 1000 mg/m² every 3 weeks and were stratified according to tumour stage using American Joint Committee on Cancer seventh edition [11]. Patients on the dacarbazine arm with disease progression could cross over to receive dabrafenib. The primary endpoint was investigator-assessed PFS; secondary endpoints included PFS by independent central review, OS, ORR, PFS following crossover, duration of response, quality of life, and safety.

Additional details on study design and statistical analyses can be found in the supplementary material. Full study protocols for BREAK-2 and BREAK-3 were included in previous publications [10,11].

RESULTS

5-Year Efficacy Analysis: BREAK-2

Of 92 BREAK-2 patients (*BRAF*^{V600E}, n=76; *BRAF*^{V600K}, n=16), most (84%) had prior systemic MM therapy, including chemotherapy (80%), interleukin 2 (16%), and ipilimumab (14%), and 31% had elevated lactate dehydrogenase (LDH) (Supplementary Table 1; Supplementary Fig. 1A). All patients discontinued study treatment by the data cutoff (Supplementary Fig. 1A). Median patient follow-up was 13.0 months (interquartile range [IQR], 5.5–37.5 months).

PFS events occurred in 59 *BRAF*^{V600E} patients (78%) and 15 *BRAF*^{V600K} patients (94%) (Fig. 1A). In *BRAF*^{V600E} patients, 5-year PFS was 11%; all *BRAF*^{V600K} patients progressed/died or were lost to follow-up before 3 years. Fifty-eight *BRAF*^{V600E} patients (76%) and 13 *BRAF*^{V600K} patients (81%) died, with 5-year OS rates of 20% and 13%, respectively (Fig. 2A). Across *BRAF* groups, 54 patients (59%) received subsequent therapies, including 22% who received checkpoint inhibitor immunotherapy (Table 1).

5-Year Efficacy Analysis: BREAK-3

Overall, 250 patients were randomised in BREAK-3. Baseline characteristics were balanced between patients in the dabrafenib arm (n=187) and those in the dacarbazine arm (n=63) (Supplementary Table 1; Supplementary Fig. 1B). Median patient follow-up was 17.0 months (IQR, 7.6–39.0 months) and 11.8 months (IQR, 5.7–24.5 months) in the dabrafenib and dacarbazine arms, respectively, with 60 months of follow-up from the time of randomisation to data cutoff. Thirty-seven dacarbazine-arm patients (59%) crossed over to receive dabrafenib (median time to crossover, 3.1 months [IQR, 1.9–5.3 months]; median time from treatment discontinuation to crossover, 1.0 month [IQR, 1.0–1.2 months]), with continued follow-up.

PFS events were observed in 146 dabrafenib-arm (78%) and 54 dacarbazine-arm (86%) patients. Five-year PFS was 12% in the dabrafenib arm (95% CI, 7%–18%; 6 patients at

risk); in the dacarbazine arm, all patients progressed/died or were lost to follow-up before 4 years (Fig. 1B). PFS events occurred in 31 crossover patients (84%); all except 1 progressed/died or were lost to follow-up before 20 months. Median PFS was consistently longer in dabrafenib-arm vs dacarbazine-arm patients, regardless of baseline LDH levels. In the dabrafenib arm, 5-year PFS was 16% in patients with normal LDH and 4% in those with elevated LDH (Fig. 1C and 1D), whereas dacarbazine-arm patients in these subgroups progressed/died or were lost to follow-up before 4 and 3 years, respectively.

A total of 132 dabrafenib-arm (71%) and 43 dacarbazine-arm (68%) patients died, with 5-year OS rates of 24% and 22%, respectively (Fig. 2B). The result in the dacarbazine arm was likely confounded by patients who crossed over to receive dabrafenib. Of 8 patients in the dacarbazine arm alive at 5 years, 4 (50%) were patients who crossed over to receive dabrafenib. Following progression, 129 dabrafenib-arm (69%) and 52 dacarbazine-arm (83%) patients (including 37 of whom crossed over to receive dabrafenib) received subsequent anticancer therapies. Of these, a smaller proportion of patients in the dabrafenib arm received postprogression small molecule-targeted therapy compared with those in the dacarbazine arm; similar proportions received subsequent immunotherapy (Table 1).

Dabrafenib Safety Profile With Extended Follow-Up

The frequency and severity of common adverse events (AEs) in patients treated with dabrafenib were consistent across BREAK-2 and BREAK-3 (Supplementary Table 2), and no new safety signals were observed with extended follow-up. Approximately one-third of patients who received dabrafenib in each study experienced serious AEs (BREAK-2, 36%; BREAK-3, 34%). AEs led to permanent discontinuation in 5 patients (5%) in BREAK-2 and 13 (7%) in BREAK-3. No fatal AEs were observed with dabrafenib in BREAK-2; in BREAK-3, 2 deaths in the dabrafenib arm were attributed to serious AEs possibly related to study treatment.

DISCUSSION

These 5-year landmark analyses of BREAK-2 and BREAK-3 provide extended follow-up for BRAFis in MM. Across studies, 11% to 12% of patients who received first-line single-agent dabrafenib remained progression free at 5 years, with apparent plateaus for PFS and OS after 36 months. These findings are in contrast to previous views that almost all patients treated with BRAFis experience rapid deterioration related to development of secondary resistance [12]. Results from BREAK-3 indicate that previously identified predictors of outcomes with combination targeted therapy in MM (eg, LDH) [5,8] similarly impact the benefit achievable in patients treated with dabrafenib monotherapy (5-year PFS: normal LDH, 16%; elevated LDH, 4%). Thus, patients with favourable baseline clinical features such as normal LDH levels are more likely to derive long-term benefit from dabrafenib therapy. In a 5-year analysis of patients treated with dabrafenib plus trametinib, 5-year PFS and OS rates were 19% and 34%, respectively [13]. Similarly, favourable baseline characteristics were associated with long-term benefit.

The safety profile of dabrafenib with 5-year follow-up was similar to that reported in previous analyses, with no notable change in the frequency of key AEs [2,3]. Long-term

treatment with dabrafenib appears to be well tolerated in patients benefiting from therapy, supporting the use of dabrafenib monotherapy in patients unable to tolerate combination therapy with dabrafenib plus trametinib.

The 95% CIs for 5-year PFS and OS rates were wide, and novel subsequent therapies may have contributed to survival outcomes; however, most patients (70%–78%) did not receive subsequent checkpoint inhibitor therapy. Postprogression treatment with BRAFi was allowed and may support long-term PFS and OS outcomes. Nevertheless, these results provide a robust long-term follow-up data set for BRAFi monotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Progression-free and overall survival with dabrafenib may plateau after 36 months
- Dabrafenib demonstrates benefit 5 years in some patients with *BRAF*-mutant melanoma
- Long-term treatment with dabrafenib monotherapy is well tolerated

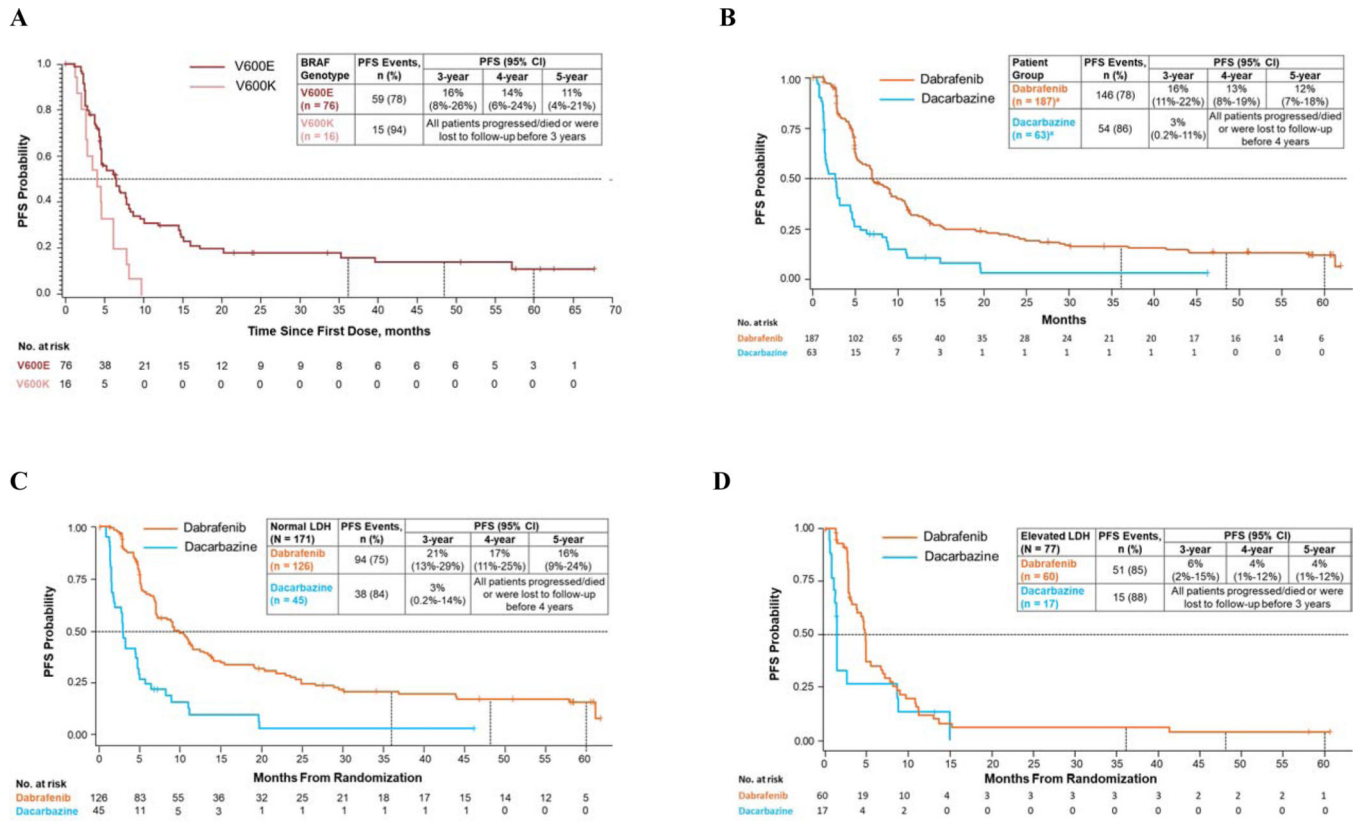


Fig. 1. PFS in intention-to-treat patients in BREAK-2 (A) and BREAK-3 (B) and in patients with normal (C) and elevated (D) baseline LDH levels in BREAK-3. CI, confidence interval; LDH, lactate dehydrogenase; PFS, progression-free survival.

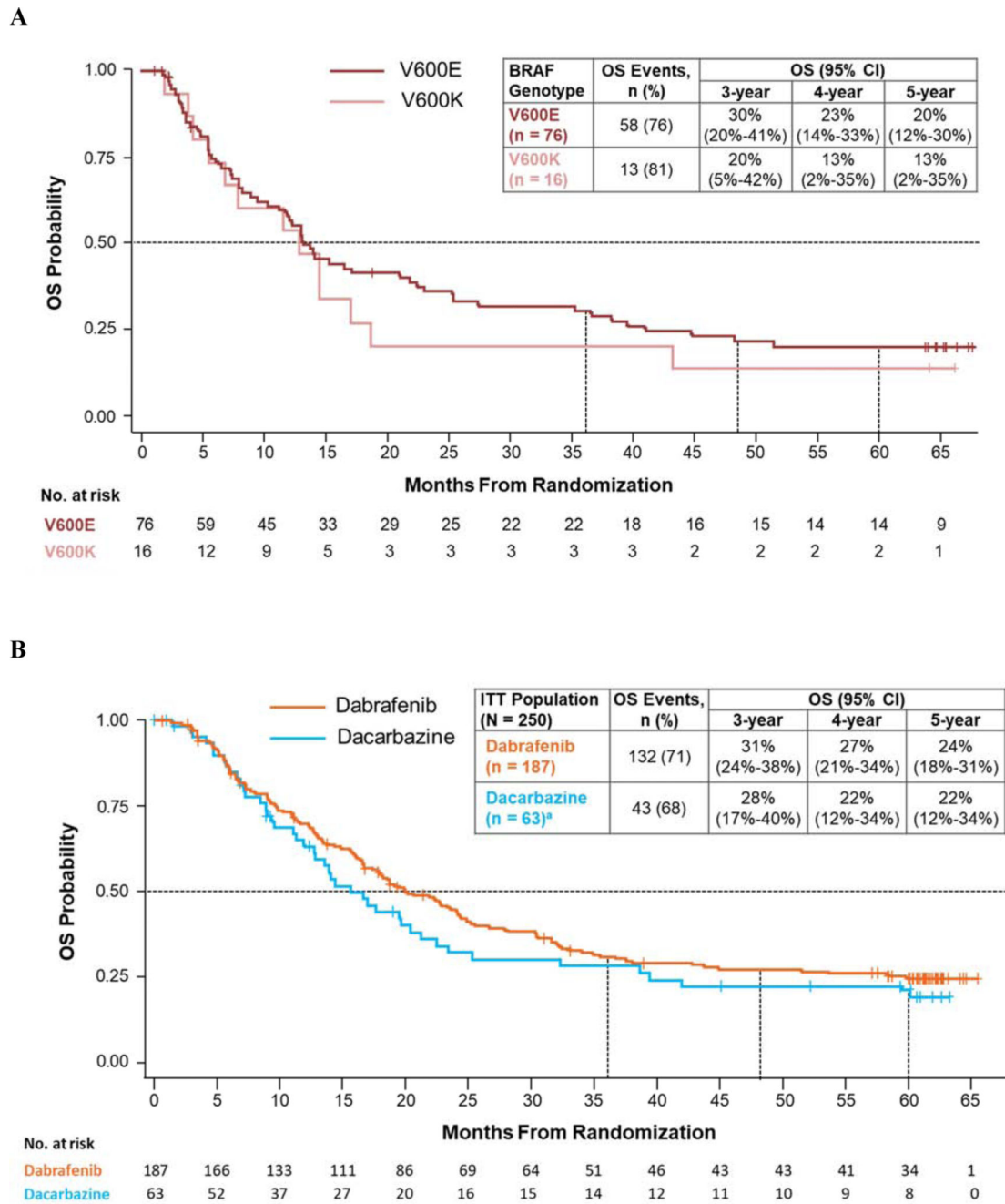


Fig. 2. OS in intention-to-treat patients in BREAK-2 (A) and BREAK-3 (B). CI, confidence interval; ITT, intention-to-treat; OS, overall survival. ^a Thirty-seven patients (59%) receiving dacarbazine crossed over to receive dabrafenib; these patients were analysed for OS in the dacarbazine arm following ITT principle.

Table 1.

Postprogression systemic therapy.

Postprogression Therapy, n (%)	BREAK-2		BREAK-3
	Total (N=92)	Dabrafenib (n=187)	Dacarbazine (n=63)
Any subsequent anticancer therapy ^a	54 (59)	129 (69)	52 (83)
Chemotherapy	22 (24)	55 (29)	18 (45)
Small-molecule-targeted therapy	31 (34)	30 (16)	47 (75) ^b
Vemurafenib	20 (22)	12 (6)	13 (21)
Dabrafenib	10 (11)	9 (5)	39 (62)
Cobimetinib	2 (2)	1 (<1)	0
Checkpoint inhibitor immunotherapy	20 (22)	56 (30)	15 (24)
Anti-CTLA-4	18 (20)	45 (24)	15 (24)
Anti-PD-1	5 (5)	15 (8)	1 (2)
Surgery	16 (17)	37 (20)	15 (24)
Biologic therapy	5 (5)	20 (11)	4 (6)
Other	2 (2) ^c	1 (1) ^d	0
Hormonal therapy	0	1 (1)	0
Radiotherapy	0	67 (36)	27 (43)

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death 1 protein.

^aSome patients received > 1 post-progression systemic therapy.

^bCrossover patients included.

^cIncluded axitinib (n = 1) and an unspecified investigational MEK inhibitor (n = 1).

^dIncluded lenvatinib mesylate (n = 1).