

ORIGINAL ARTICLE

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

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Background: Previous analysis of COMBI-d (NCT01584648) demonstrated improved progression-free survival (PFS) and overall survival (OS) with combination dabrafenib and trametinib versus dabrafenib monotherapy in *BRAF* V600E/K-mutant metastatic melanoma. This study was continued to assess 3-year landmark efficacy and safety after ≥36-month follow-up for all living patients.

Patients and methods: This double-blind, phase 3 study enrolled previously untreated patients with *BRAF* V600E/K-mutant unresectable stage IIIc or stage IV melanoma. Patients were randomized to receive dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily) or dabrafenib plus placebo. The primary endpoint was PFS; secondary endpoints were OS, overall response, duration of response, safety, and pharmacokinetics.

Results: Between 4 May and 30 November 2012, a total of 423 of 947 screened patients were randomly assigned to receive dabrafenib plus trametinib ($n = 211$) or dabrafenib monotherapy ($n = 212$). At data cut-off (15 February 2016), outcomes remained superior with the combination: 3-year PFS was 22% with dabrafenib plus trametinib versus 12% with monotherapy, and 3-year OS was 44% versus 32%, respectively. Twenty-five patients receiving monotherapy crossed over to combination therapy, with continued follow-up under the monotherapy arm (per intent-to-treat principle). Of combination-arm patients alive at

3 years, 58% remained on dabrafenib plus trametinib. Three-year OS with the combination reached 62% in the most favourable subgroup (normal lactate dehydrogenase and <3 organ sites with metastasis) versus only 25% in the unfavourable subgroup (elevated lactate dehydrogenase). The dabrafenib plus trametinib safety profile was consistent with previous clinical trial observations, and no new safety signals were detected with long-term use.

Conclusions: These data demonstrate that durable (≥ 3 years) survival is achievable with dabrafenib plus trametinib in patients with *BRAF* V600-mutant metastatic melanoma and support long-term first-line use of the combination in this setting.

Key words: melanoma, metastatic, BRAF, dabrafenib, trametinib, durable outcomes

Introduction

Before recent therapeutic advances, the prognosis for patients with metastatic melanoma was poor, with a 5-year survival of $\sim 6\%$ and a median overall survival (OS) of 7.5 months [1]. The anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) therapy ipilimumab was the first agent to show durable clinical benefit lasting ≥ 5 years in a subset of patients within molecularly unselected advanced melanoma populations [2]. More recently, BRAF and MEK inhibitor (BRAFi/MEKi) combinations and anti-programmed death-1 (anti-PD-1) checkpoint-inhibitor immunotherapy regimens demonstrated significant improvements in clinical outcomes in phase 3 trials of patients with metastatic melanoma; however, extended follow-up in these studies has been limited to ≤ 2 years [3–9]. Targeted therapies have been purported to be associated with rapid deterioration and death following development of secondary resistance; however, evidence from long-term, large randomized studies is lacking. With multiple treatments now available for *BRAF* V600-mutant melanoma, a better understanding of the proportion and characteristics of patients who can derive durable benefit and maintain tolerability with long-term use of current therapies is needed for optimizing treatment.

Combination dabrafenib and trametinib (D + T) demonstrated improved progression-free survival (PFS) and OS over BRAFi monotherapy in randomized phase 2 and 3 trials in patients with *BRAF* V600E/K-mutant stage IIIC unresectable or stage IV metastatic melanoma [3, 4, 10–13]. The D + T safety profile has been consistent across these studies, in which the combination has been associated with a reduction in hyperproliferative skin lesions [e.g. squamous cell carcinoma (SCC), keratoacanthoma (KA)] compared with BRAFi monotherapy, while the frequency and severity of pyrexia appear higher [3, 4, 10].

In the most recent analysis of COMBI-d, a randomized, double-blind, phase 3 trial of D + T versus dabrafenib monotherapy (dabrafenib plus placebo), with a median follow-up of 20.0 months for the D + T arm and 16.0 months for the monotherapy arm, median PFS was 11.0 versus 8.8 months [HR, 0.67; 95% confidence interval (CI), 0.53–0.84; $P=0.0004$], median OS was 25.1 versus 18.7 months (HR, 0.71; 95% CI, 0.55–0.92; $P=0.0107$), and 2-year OS was 51% versus 42% [3]. These findings confirmed results from the primary analysis of COMBI-d [12] and were consistent with outcomes observed in the randomized phase 3 COMBI-v study of D + T versus vemurafenib [4]. The longest follow-up to date for D + T in a randomized study (median 45.6 months) was reported for the phase 2 BRF113220 study (part C) evaluating D + T ($n=54$) versus dabrafenib monotherapy ($n=54$) [11], in which D + T-treated patients had a 2- and 3-year PFS of 25% and

21%, respectively, and a 2- and 3-year OS of 51% and 38%, respectively. Pooled data across these trials (median follow-up of 20.0 months) showed that normal baseline serum lactate dehydrogenase (LDH) and <3 organ sites containing metastasis were the factors most predictive of durable outcomes; patients with both of these characteristics had a 2-year PFS of 46% and a 2-year OS of 75% [14].

Here, we report an updated 3-year landmark analysis for the phase 3 COMBI-d trial, including updated PFS, OS, best response and safety analyses.

Methods

The COMBI-d study (protocol previously published [3] and further described in the supplementary data, available at *Annals of Oncology* online) was continued after prior primary and OS analyses [3, 12] to provide an updated 3-year landmark analysis of long-term outcomes. Crossover was permitted following the previous OS analysis by patient/physician discretion on the intent-to-treat principle, by which any crossover benefit was applied to the randomized therapy arm estimates. Kaplan–Meier estimations of 2- and 3-year PFS and OS were carried out to describe long-term outcomes. Influences of prognostic factors on patient-derived benefit were explored with descriptive subgroup stratification by baseline factors previously identified as being predictive of outcomes in patients receiving D + T [14].

Results

Baseline characteristics were well balanced across 423 patients randomly assigned to receive D + T ($n=211$) or dabrafenib monotherapy ($n=212$; supplementary Figure S1 and Table S1, available at *Annals of Oncology* online). At data cut-off, 15 February 2016, patients who were alive had ≥ 36 months of follow-up from time of randomization. Forty (19%) D + T-arm patients versus 6 (3%) monotherapy-arm patients remained on randomized treatment.

At data cut-off, 3-year PFS was 22% for the D + T arm and 12% for the monotherapy arm [HR, 0.71 (95% CI, 0.57–0.88)] (Figure 1A), and 3-year OS was 44% and 32%, respectively [HR, 0.75 (95% CI, 0.58–0.96)] (Figure 2A). Notably, 25 (12%) patients in the dabrafenib monotherapy arm crossed over to D + T, of which 6 (24%) had progressed on monotherapy before crossover. Survival outcomes in these crossover patients, all of whom remained on D + T as of data cut-off, continued to be followed up under the monotherapy arm. Of combination-arm patients who were progression free ($n=31$) and alive ($n=76$) at 3 years, 28 (90%) and 44 (58%) remained on D + T, respectively.

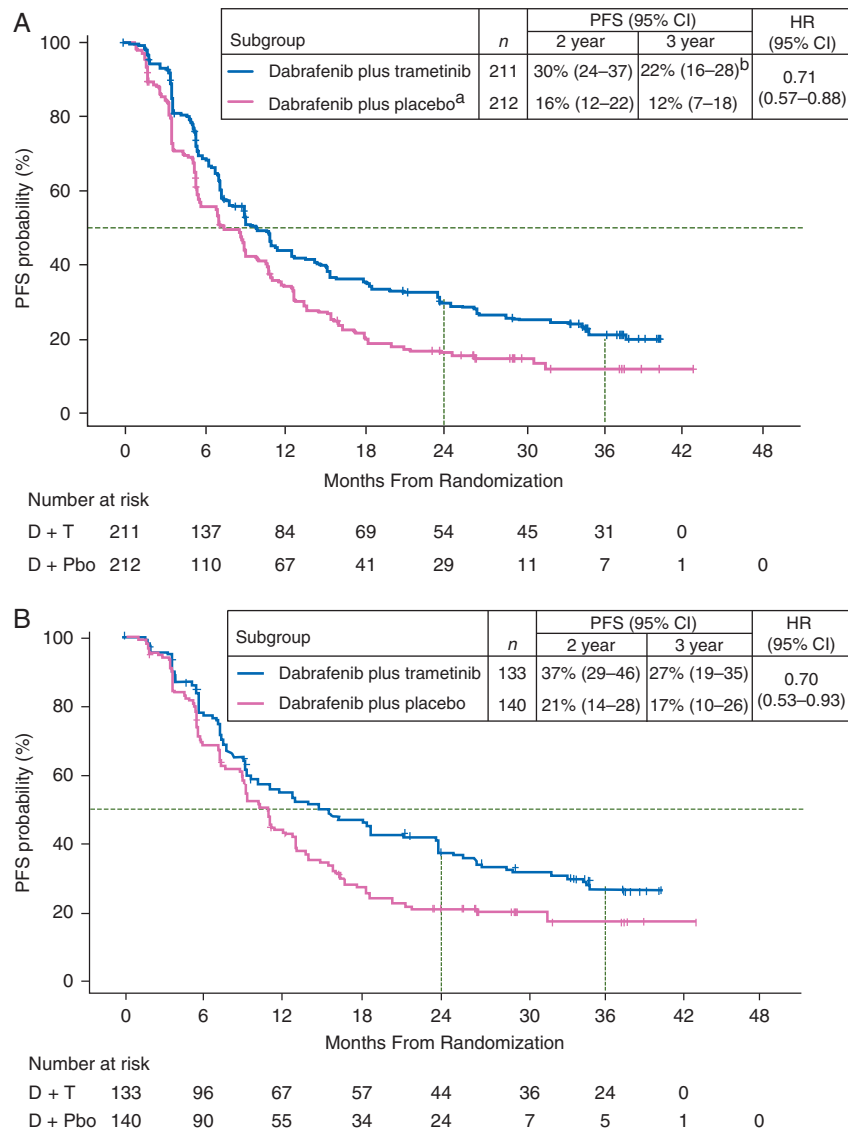


Figure 1. Progression-free survival (PFS) in the dabrafenib and trametinib (D + T) and dabrafenib monotherapy [D + placebo (Pbo)] arms in (A) the intent-to-treat population and patients with (B) normal baseline lactate dehydrogenase (\leq upper limit of normal), (C) normal baseline lactate dehydrogenase and <3 organ sites with metastasis, and (D) elevated baseline lactate dehydrogenase ($>$ upper limit of normal). CI, confidence interval; HR, hazard ratio.

^aIncludes 25 patients who crossed over from monotherapy to the combination.

^bOf D + T patients who were progression free at 3 years, 28 (90%) remained on D + T.

As expected per the progression rate in each arm, more monotherapy-arm patients received post-progression systemic therapy versus D + T-arm patients [130/211 (62%) versus 101/209 (48%); supplementary Table S2, available at *Annals of Oncology* online]. In both the D + T and monotherapy groups, immunotherapy was the most common subsequent anticancer therapy (56% versus 56%, respectively); ipilimumab was the most common immunotherapy (41% versus 50%), with fewer patients receiving nivolumab (7% versus 5%) or pembrolizumab (13% versus 11%).

Long-term PFS and OS consistently favoured D + T over monotherapy, regardless of baseline prognostic factors. Three-year PFS rates in patients with normal baseline LDH levels [\leq upper limit of normal (ULN), $n = 273/423$ (65%)] were 27%

in the D + T arm versus 17% in the monotherapy arm [HR, 0.70 (95% CI, 0.53–0.93)] (Figure 1B), and 3-year OS rates were 54% versus 41%, respectively [HR, 0.74 (95% CI, 0.53–1.03)] (Figure 2B). Of 133 D + T-arm patients with $LDH \leq ULN$, 61 (46%) were alive at 3 years and 34 (26%) remained on D + T. The greatest clinical benefit with D + T was observed in patients with $LDH \leq ULN$ and <3 organ sites with metastasis [$n = 172/423$ (41%)], with 3-year PFS rates of 38% in the combination arm versus 16% in the monotherapy arm [HR, 0.53 (95% CI, 0.38–0.76)] (Figure 1C), and 3-year OS rates of 62% versus 45%, respectively [HR, 0.63 (95% CI, 0.41–0.99)] (Figure 2C). Of 76 combination-arm patients with baseline $LDH \leq ULN$ and <3 organ sites with metastasis, 37 (49%) were alive at 3 years and 23 (30%) remained on D + T. In patients with baseline $LDH > ULN$

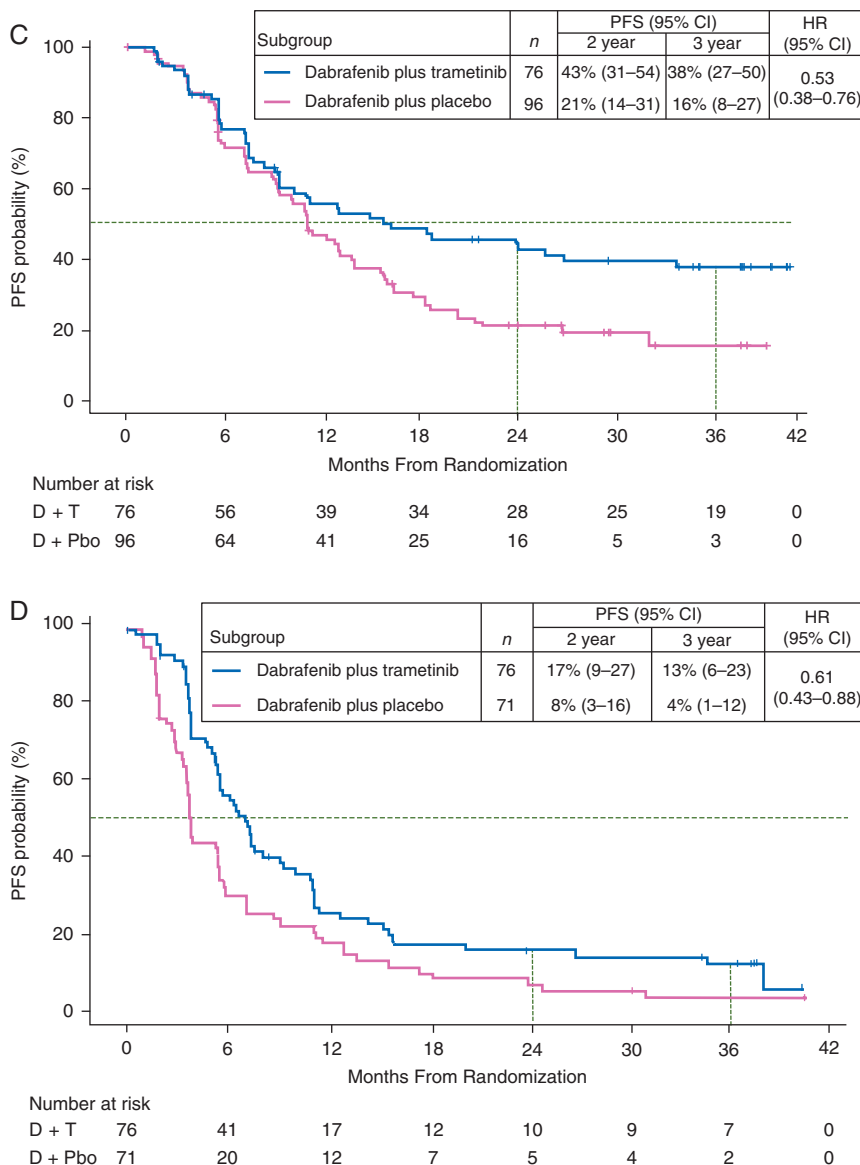


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[*n* = 147/423 (35%)], 3-year PFS rates were 13% in the D + T arm and 4% in the monotherapy arm [HR, 0.61 (95% CI, 0.43–0.88)] (Figure 1D), and 3-year OS rates were 25% versus 14% [HR, 0.61 (95% CI, 0.41–0.89)] (Figure 2D). Of 76 D + T-arm patients with LDH > ULN, 15 (20%) were alive at 3 years and 10 (13%) remained on D + T.

The confirmed response rates per Response Evaluation Criteria In Solid Tumors (RECIST) were 68% in combination-arm patients versus 55% in monotherapy patients (Table 1), with a complete response (CR) rate of 18% versus 15%, respectively. Median duration of response was 12.0 (95% CI, 9.3–17.1) versus 10.6 (95% CI, 8.3–12.9) months.

With a median time on treatment of 11.8 (range, 0.4–43.7) versus 8.3 (range, 0.1–45.3) months in D + T-arm and monotherapy-arm patients, respectively, 49% versus 38% had >12 months of study treatment. Adverse events (AEs) of any grade, regardless of study drug relationship, were observed in 97% of patients (both arms), with 48% of D + T-arm patients

versus 50% of monotherapy patients experiencing ≥1 grade 3/4 AE (supplementary Table S3, available at *Annals of Oncology* online) and 45% versus 38% experiencing serious AEs (supplementary Table S4, available at *Annals of Oncology* online). The incidence of several AEs was higher (>10% difference, any grade) in the D + T versus monotherapy arm: pyrexia (59% versus 33%), chills (32% versus 17%), diarrhoea (31% versus 17%), vomiting (26% versus 15%), and peripheral oedema (22% vs 9%) (supplementary Table S4, available at *Annals of Oncology* online). Conversely, the incidence of hyperkeratosis (35% versus 7%), alopecia (28% versus 9%), and skin papilloma (22% versus 2%) was higher in monotherapy-arm versus combination-arm patients (supplementary Table S3, available at *Annals of Oncology* online). Palmoplantar hyperkeratosis (18% versus 5%), SCC/KA (7% versus 2%), and basal cell carcinoma (7% versus 4%) also occurred more frequently in monotherapy-arm versus D + T-arm patients (supplementary Table S4, available at *Annals of Oncology* online). The incidence of other AEs of special

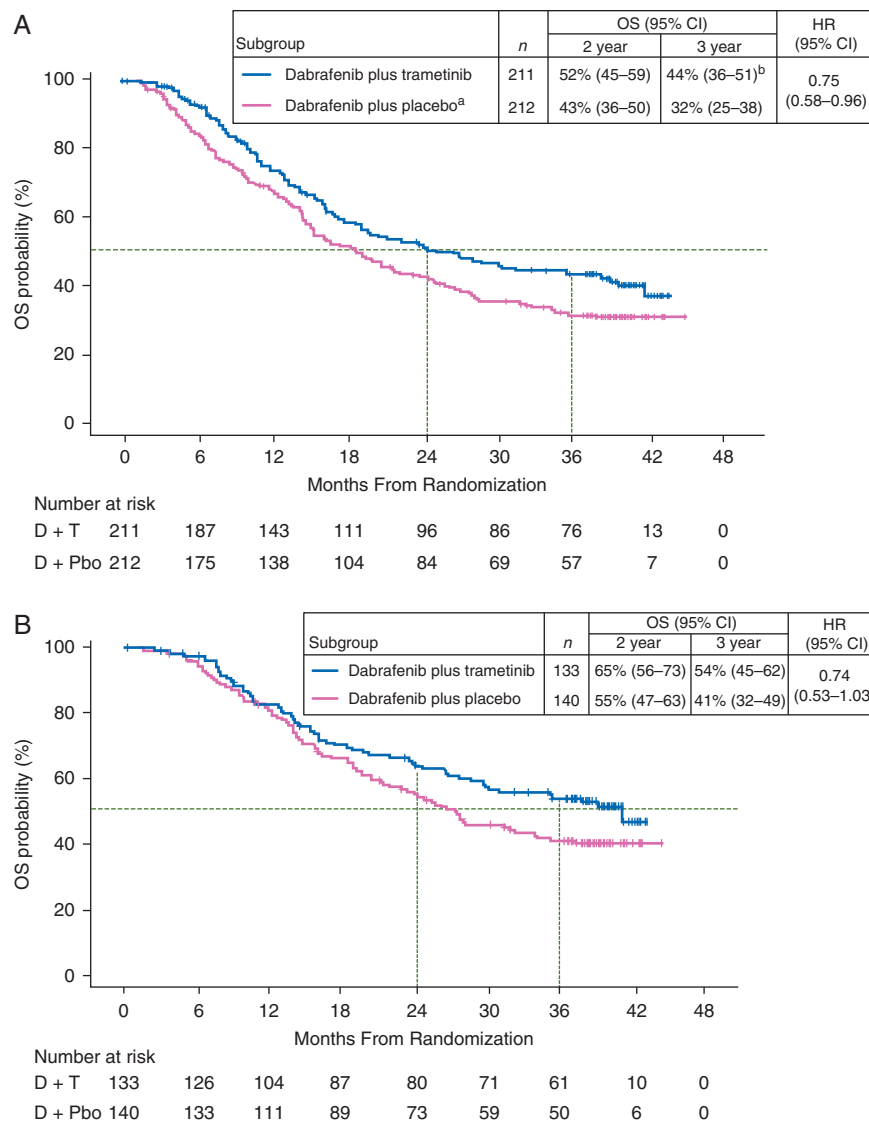


Figure 2. Overall survival (OS) in the dabrafenib and trametinib (D + T) and dabrafenib monotherapy [D + placebo (Pbo)] arms in (A) the intent-to-treat population and patients with (B) normal baseline lactate dehydrogenase (\leq upper limit of normal), (C) normal baseline lactate dehydrogenase and <3 organ sites with metastasis, and (D) elevated baseline lactate dehydrogenase ($>$ upper limit of normal). CI, confidence interval; HR, hazard ratio.

^aIncludes 25 patients who crossed over from monotherapy to the combination.

^bOf patients in the D + T arm alive at 3 years, 44 (58%) remained on D + T.

interest (i.e. cardiotoxicities, ocular events, haemorrhages) was generally similar across the study arms (supplementary Table S5, available at *Annals of Oncology* online).

Notably, the frequency of the most common D + T-associated AEs, including pyrexia, did not increase by $>2\%$ with an additional 13 months of follow-up since the last analysis (supplementary Table S6, available at *Annals of Oncology* online). Similarly, the incidence of key skin-related AEs, including palmoplantar hyperkeratosis, SCC/KA, and basal cell carcinoma, did not increase by $>1\%$ in the combination arm with extended follow-up, and no new primary melanomas were observed. Additionally, occurrence of events leading to dose interruptions ($n=122$; 58%) or permanent discontinuation ($n=29$; 14%) in D + T-arm patients increased by only 2% and 3%, respectively, and no new grade 5 AEs were observed.

Discussion

This 3-year landmark analysis of COMBI-d represents the longest follow-up for any phase 3 BRAFi/MEKi combination therapy trial and provides evidence that long-term clinical benefit and tolerability are achievable with D + T in a subset of patients with previously untreated *BRAF* V600E/K-mutant metastatic melanoma. Importantly, these findings do not support the idea that most patients treated by mitogen-activated protein kinase inhibitors rapidly develop deterioration due to secondary resistance. At the 3-year landmark, D + T continued to demonstrate superior benefit versus dabrafenib monotherapy (PFS, 22% versus 12%; OS, 44% versus 32%), even though 12% of monotherapy patients crossed over to receive D + T. Furthermore, many patients alive at 3 years remained on D + T.

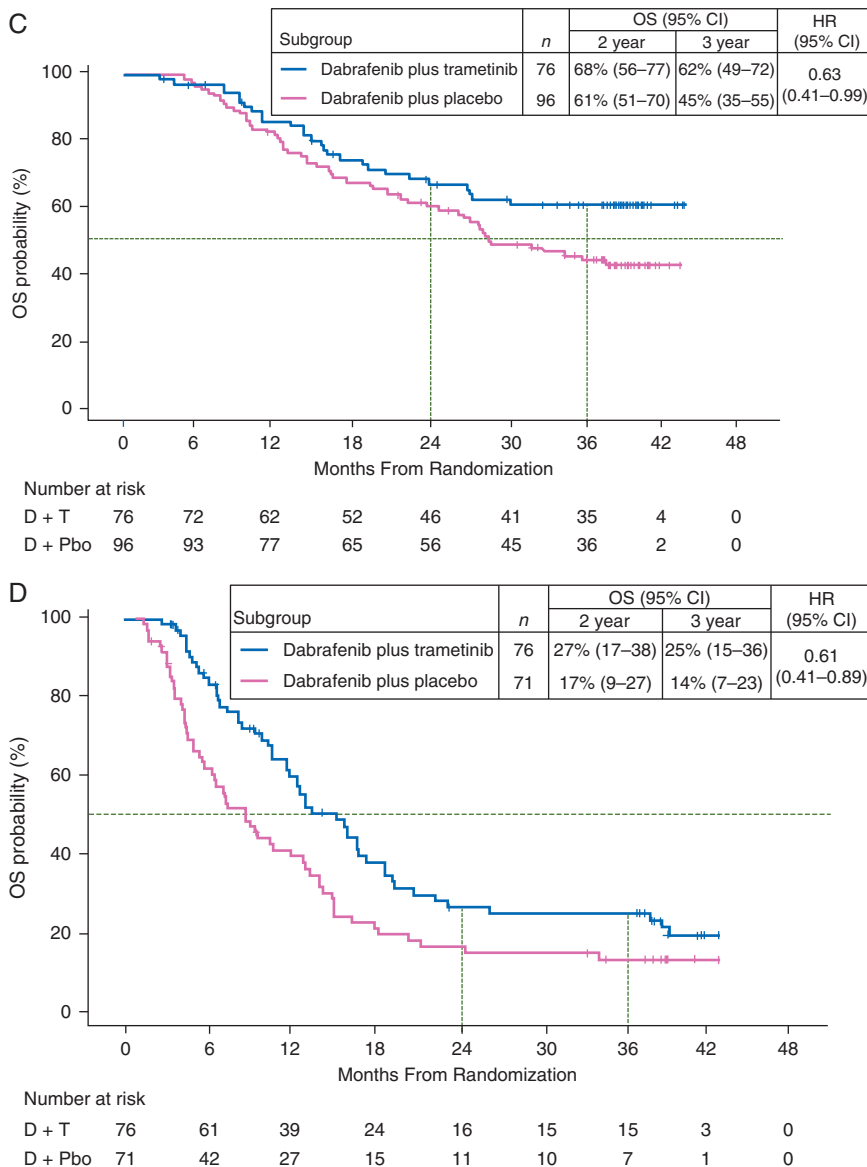


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The 3-year OS reported for D + T in this large phase 3 trial (44%) confirms preliminary results for the smaller corresponding patient subset in the randomized phase 2 BRF113220 trial (3-year OS, 38%) [11]. More generally, survival observed in the current analysis is consistent with previous findings for D + T in *BRAF* V600-mutant melanoma, since the 2-year OS reported here (52%) is similar to that reported in the randomized phase 3 COMBI-v study (51%) and in a pooled analysis across registration trials (53%) [14]. In this era of multiple drugs with significant activity in metastatic melanoma, clinical trial OS results may be confounded by availability of these therapies. In this analysis, of patients who received any post-progression systemic therapy, rates of subsequent anti-PD-1 use were similar between the D + T and monotherapy arms, and the rate of subsequent ipilimumab therapy was numerically higher in the monotherapy arm compared with the D + T arm. Thus, the 3-year OS observed with D + T in this study may be mostly attributed to the combination.

Direct comparisons of survival landmarks across trials of currently available melanoma treatments should be interpreted with caution due to differences in baseline characteristics between study populations, including the requirement for the presence of a *BRAF* V600E or V600K mutation in targeted therapy trials and the period of time during which studies were conducted (e.g. what treatments were available for subsequent therapy). However, in the absence of prospective head-to-head trials evaluating targeted versus checkpoint-inhibitor immunotherapies, pivotal trials to date can be considered to provide outcomes trends for each drug class. Moving forward, it will be important to balance advantages of immunotherapy with anti-PD-1 (\pm anti-CTLA-4) and BRAFi/MEKi combinations.

Follow-up for anti-PD-1 checkpoint-inhibitor immunotherapy regimens has lagged behind targeted therapy; 3-year landmark OS results, as reported here, are currently available only for early-phase trials. In a phase 1 study evaluating nivolumab monotherapy in 107 patients with previously treated melanoma,

Table 1. Confirmed RECIST response

	Dabrafenib plus trametinib (n = 211)	Dabrafenib plus placebo (n = 212)
RECIST response, n (%)		
Complete response (CR)	38 (18)	31 (15)
Partial response (PR)	106 (50)	85 (40)
Stable disease	51 (24)	68 (32)
Progressive disease	12 (6)	18 (8)
Not evaluable	4 (2)	10 (5)
Response rate (CR + PR), n (%) [95% CI]	144 (68) [61.5–74.5]	116 (55) [47.8–61.5]
Duration of response	n = 144	n = 116
Progressed or died, n (%)	100 (69)	84 (72)
Median (95% CI), months	12.0 (9.3–17.1)	10.6 (8.3–12.9)

CI, confidence interval; RECIST, Response Evaluation Criteria In Solid Tumors.

unselected for *BRAF* mutation status and 36% with elevated LDH, the 2-, 3-, and 5-year OS rates were 48%, 42%, and 34%, respectively [15]. In a phase 1 study of combined nivolumab plus ipilimumab, in 53 treatment-naïve (60%) or previously treated (40%) patients with advanced melanoma (38% with elevated LDH), the 3-year OS was 68%; however, it should be noted that these results are preliminary [16] and randomized studies of the combination have shown a consistent 2-year survival of 64% [9, 17], less than this phase 1 landmark. As larger trials evaluating anti-PD-1 regimens in metastatic melanoma continue follow-up, preliminary trends in outcomes in a recent meta-analysis demonstrated no significant difference in OS between first-line BRAFi/MEKi and anti-PD-1 [18].

Altogether, data across trials of currently available therapies suggest that long-term survival profiles, at least up to 3 years, do not seem to confirm the hypothesis that only checkpoint-inhibitor immunotherapy can provide durable benefit in patients with metastatic melanoma. Although initial clinical activity (e.g. response rates) differs between these therapeutic classes [3–9], the proportion of patients with a 3-year benefit may be similar; however this will need to be confirmed by additional analyses of checkpoint-inhibitor immunotherapies specifically in patients with *BRAF*-mutant disease. Furthermore, it is important to note that the plateau survival pattern observed with ipilimumab [2] has not yet been demonstrated with anti-PD-1 therapies and remains a potential survival pattern for BRAFi/MEKi.

It is now well established that efficacy of treatment of metastatic melanoma can differ depending on baseline patient characteristics. Analyses of BRAFi-naïve patients treated with D + T in the phase 2 BRF113220 study and in a pooled analysis across D + T registration trials identified significant associations between baseline LDH and number of organ sites containing metastasis and clinical outcomes [11, 14]. Results from the current analysis support these findings, with the highest 3-year OS observed among patients with LDH < ULN and <3 organ sites containing metastasis (D + T, 62%; monotherapy, 45%). Patients with favourable baseline markers treated with frontline D + T are thus more likely to derive long-term benefit from this combination. Moreover, although

3-year survival was much lower in patients with LDH > ULN, the superiority of D + T over dabrafenib monotherapy was maintained (3-year OS, 25% versus 14%).

With an additional 13 months of follow-up from the previous OS analysis of COMBI-d, CR was achieved by an additional 5 D + T-arm patients, resulting in an updated CR rate of 18% and an overall response rate of 68% with the combination.

The safety profile of D + T with longer follow-up was similar to that observed in previous analyses, in which the combination was associated with a reduction in toxicities related to paradoxical activation of the mitogen-activated protein kinase pathway compared with BRAFi monotherapy [3, 4, 10–13]. Pyrexia remained the most common AE with D + T; however, it has been shown that pyrexia can be managed [19]. The frequency of key AEs did not greatly change with additional follow-up, including pyrexia and secondary malignancies, consistent with a recent report that incidence of D + T-associated AEs is highest during the first 6 months of treatment, declining thereafter [20]. Thus, although patients who remain on and benefit from treatment can become an increasingly biased population due to the disappearance of those with very poor tolerance and/or development of secondary resistance, long-term treatment with D + T appears to be well tolerated in the subgroup of patients who benefit.

This analysis, representing the longest follow-up for any phase 3 trial evaluating BRAFi/MEKi combination therapy, demonstrated that long-term survival is achievable with D + T in a relevant proportion of patients with *BRAF* V600-mutant metastatic melanoma and that long-term treatment with D + T is tolerable, with no new safety signals. These results support long-term use of D + T as a first-line treatment strategy for patients with advanced *BRAF* V600-mutant melanoma. However, a more comprehensive model including clinical factors as described here, along with molecular and/or immune-markers associated with efficacy, is needed to further guide treatment decisions (e.g. BRAFi/MEKi and checkpoint inhibitor immunotherapy sequencing strategies) in this melanoma population. Continued follow-up planned for up to 5 years for COMBI-d will provide further understanding of the extent of benefit achievable with D + T in this setting.

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