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ORIGINAL REPORT

Long-Term Outcomes in Patients With *BRAF* V600–Mutant Metastatic Melanoma Who Received Dabrafenib Combined With Trametinib

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ABSTRACT

Purpose

To report 5-year landmark analysis efficacy and safety outcomes in patients with *BRAF* V600–mutant metastatic melanoma (MM) who received BRAF inhibitor dabrafenib (D) and MEK inhibitor trametinib (T) combination therapy versus D monotherapy in the randomized phase II BRF113220 study part C.

Patients and Methods

BRAF inhibitor–naive patients with *BRAF* V600–mutant MM were randomly assigned 1:1:1 to receive D 150 mg twice a day, D 150 mg twice a day plus T 1 mg once daily, or D 150 mg twice a day plus T 2 mg once daily (D + T 150/2). Patients who received D monotherapy could cross over to D + T 150/2 postprogression. Efficacy and safety were analyzed 4 and 5 years after initiation in patients with ≥ 5 years of follow-up.

Results

As of October 13, 2016, 18 patients who received D + T 150/2 remained in the study (13 [24%] of 54 enrolled at this dose plus five [11%] of 45 initially administered D who crossed over to D + T). With D + T 150/2, overall survival (OS; 4 years, 30%; 5 years, 28%) and progression-free survival (4 and 5 years, both 13%) appeared to stabilize with extended follow-up. Increased OS was observed in patients who received D + T with baseline normal lactate dehydrogenase (5 years, 45%) and normal lactate dehydrogenase with fewer than three organ sites with metastasis (5 years, 51%). With extended follow-up, one additional patient who received D + T 150/2 improved from a partial to a complete response. No new safety signals were observed.

Conclusion

This 5-year analysis represents the longest follow-up to date with BRAF + MEK inhibitor combination therapy in *BRAF* V600–mutant MM. Consistent with trends observed in landmark analyses with shorter follow-up, this therapy elicits durable plateaus of long-term OS and progression-free survival that last ≥ 5 years in some patients with MM.

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INTRODUCTION

Before the recent advances in the treatment of metastatic melanoma (ie, mitogen-activated protein kinase [MAPK] pathway inhibitors, checkpoint inhibitor immunotherapies), disease outcomes were poor, with a median overall survival (OS) of approximately 7.5 months and a 5-year survival rate of approximately 6%.[1,2] The anti–cytotoxic T-lymphocyte–associated protein-4 therapy ipilimumab was the first treatment to demonstrate durable clinical benefit that lasts ≥ 5 years in molecularly unselected patients with advanced melanoma.[3] BRAF inhibitor (BRAFi) therapy with or without MEK inhibitor (MEKi) and anti–programmed death-1 (anti–PD-1) immune checkpoint inhibitor–based regimens also have significantly improved clinical outcomes in patients with metastatic melanoma[4-14]; however, extended follow-up analyses of randomized studies of these therapies typically have been limited to ≤ 3 years.[15-25] A general misconception exists that durable responses with targeted therapies are uncommon, but evidence from long-term randomized studies with survival follow-up > 3 years is lacking. With multiple

ASSOCIATED CONTENT

Appendix
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therapies currently available to treat *BRAF* V600–mutant melanoma, a complete understanding of treatment impact on durable outcomes with extended use is needed to optimize individualized patient treatment strategies.

In a previously reported landmark analysis for the clinical trial BRF113220,[17] BRAFi-naive patients with metastatic melanoma randomly assigned to treatment with the combination of dabrafenib (D) and trametinib (T) at the US Food and Drug Administration–approved dose (n = 54) showed a median progression-free survival (PFS) of 9.4 months, and 41%, 25%, and 21% were progression free after 1, 2, and 3 years, respectively. Median OS in these patients was 25 months, with 1-, 2-, and 3-year OS rates of 80%, 51%, and 38%, respectively. In pooled analyses of data from randomized trials of D + T in previously untreated patients with *BRAF*-mutant metastatic melanoma, median PFS was approximately 11 months and median OS approximately 26 months.[26,27] These findings were consistent with reports from individual randomized phase II and III trials that evaluated these agents in patients with *BRAF* V600E/K–mutant metastatic melanoma.[4,7,8,28-30] In the current study, we report a 5-year landmark efficacy and safety analysis for BRAFi-naive patients with metastatic melanoma treated with D + T.

PATIENTS AND METHODS

Study Design and Participants

This open-label phase I and II study of patients with histologically confirmed unresectable stage IIIC or IV *BRAF* V600E/K–mutant melanoma had four parts (A, B, C, and D) conducted internationally at 16 centers. Patients were age ≥ 18 years and had measurable disease, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function. A detailed study description, including full eligibility criteria, has been previously published.[4,17] The analysis described here includes only patients enrolled in part C because parts A, B, and D did not include patient random assignment to the Food and Drug Administration–approved dose of D 150 mg twice a day plus T 2 mg once daily (D + T 150/2).

All patients in part C were BRAFi and MEKi naive at initial study enrollment. Patients were randomly assigned 1:1:1 to receive D monotherapy twice a day, D 150 mg twice a day plus T 1 mg once daily (D + T 150/1), or D + T 150/2. Patients who progressed in the D monotherapy arm were allowed to cross over to D + T 150/2 treatment.

The protocol was approved by the institutional review board at each study site, and it complied with country-specific regulatory requirements. All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study Assessments

Treatment response, duration of response, PFS, and OS were determined by using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as previously described.[4] Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Statistical Analyses

This 5-year landmark analysis is based on data available as of October 13, 2016. Median PFS and OS were determined by using the Kaplan-Meier method, with 95% CIs estimated using the Brookmeyer-Crowley method. Landmark survival rates were calculated by Kaplan-Meier method. Crossover to D + T 150/2 was permitted for patients in the D monotherapy arm after progression according to the intention-to-treat principle, where any crossover benefit was applied to the randomized therapy arm estimates. The potential influence of previously identified predictive factors for outcomes with D + T (ie, lactate dehydrogenase [LDH] level, number of organ sites that contained metastasis)[17,26] on patient-derived benefit were explored with descriptive subgroup stratification. AEs were summarized by preferred terms.

RESULTS

One hundred sixty-two patients were enrolled in part C, with three groups of 54 patients each randomly assigned to receive D monotherapy, D + T 150/1, or D + T 150/2 (Appendix Fig A1, online only). Patient baseline characteristics were well balanced across treatment groups (Table 1). As of the October 13, 2016, data cutoff, patients still alive had a minimum follow-up of 60 months from time of random assignment (median follow-up, 66.5 months). Thirty-eight patients (70%) who were initiated on D + T 150/2 and 43 (80%) initiated on D monotherapy died (Table 2), with two patients (4%) in the D + T 150/2 arm and one (2%) in the D monotherapy arm still receiving their original study treatment.

At the time of analysis, 43 patients (80%) in the D + T 150/2 arm and 49 (91%) in the D monotherapy arm had experienced progression or died, with stable 4- and 5-year PFS rates of 13% (95% CI, 5% to 25%) with D + T 150/2 (hazard ratio, 0.44; 95% CI,

Table 1. Baseline Characteristics (N = 162)

Characteristic	Treatment Arm, No. (%)		
	D + T 150/2 (n = 54)	D + T 150/1 (n = 54)	D Monotherapy (n = 54)
Median age, years (range)	58 (27-79)	49 (23-85)	50 (18-82)
Sex			
Male	34 (63)	30 (56)	29 (54)
Female	20 (37)	24 (44)	25 (46)
ECOG PS			
0	35 (65)	38 (70)	34 (63)
1	19 (35)	16 (30)	20 (37)
Metastatic status			
M0	0	1 (2)	1 (2)
M1a	6 (11)	9 (17)	11 (20)
M1b	10 (19)	11 (20)	5 (9)
M1c	38 (70)	33 (61)	37 (69)
History of brain metastases	2 (4)	7 (13)	4 (7)
BRAF mutation			
V600E	47 (87)	45 (83)	45 (83)
V600K	7 (13)	9 (17)	9 (17)
LDH			
> ULN	22 (41)	25 (46)	27 (50)
≤ ULN	32 (59)	29 (54)	27 (50)
No. of organ sites with metastasis			
≥ 3	28 (52)	27 (50)	34 (63)
< 3	26 (48)	27 (50)	20 (37)
Previous chemotherapy	7 (13)	15 (28)	12 (22)
Previous immunotherapy	13 (24)	16 (30)	8 (15)

NOTE. As previously reported,[4] except for number of organ sites with metastasis.

Abbreviations: D, dabrafenib; D + T 150/1, dabrafenib 150 mg twice a day plus trametinib 1 mg once daily; D + T 150/2, dabrafenib 150 mg twice a day plus trametinib 2 mg once daily; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Table 2. Study Disposition

Category	Treatment Arm, No. (%)			
			D Monotherapy	
	D + T 150/2 (n = 54)	D + T 150/1 (n = 54)	Total (n = 54)	Crossover to D + T 150/2 (n = 45)*
Died	38 (70)	34 (63)	43 (80)	36 (80)
Ongoing in study	13 (24)	10 (19)	7 (13)	5 (11)
Receiving study treatment	2 (4)	3 (6)	1 (2)	0
In follow-up	11 (20)	7 (13)	6 (11)	5 (11)
Withdrawn from study	3 (6)	10 (19)	4 (7)	4 (9)
Withdrew consent	0	7 (13)	3 (6)	3 (7)
Lost to follow-up	2 (4)	2 (4)	1 (2)	1 (2)
Investigator discretion	1 (2)	1 (2)	0	0

Abbreviations: D, dabrafenib; D + T 150/1, dabrafenib 150 mg twice a day plus trametinib 1 mg once daily; D + T 150/2, dabrafenib 150 mg twice a day plus trametinib 2 mg once daily.
*Percentages calculated by using the total number of crossover patients (n = 45) as the denominator.

0.28 to 0.67) and 3% (95% CI, 0% to 11%) with D monotherapy (Fig 1A). Thirty-eight patients (70%) in the D + T 150/2 arm and 43 (80%) in the D monotherapy arm died, which yielded 4- and 5-year OS rates of 30% (95% CI, 18% to 43%) and 28% (95% CI, 17% to 41%), respectively, with D + T 150/2 (hazard ratio, 0.76; 95% CI, 0.49 to 1.18) and 23% (95% CI, 13% to 35%) and 21% (95% CI, 11% to 33%), respectively, with D monotherapy (Fig 1B). Of note, 45 (83%) of the 54 patients in the D monotherapy arm included in this updated analysis had crossed over to D + T 150/2 (Table 2); the survival outcomes in these crossover patients continued to be followed for the D monotherapy arm.

In line with the observed frequency of disease progression in each treatment arm, more patients who were initiated on D monotherapy than on D + T 150/2 received subsequent anticancer therapy (50 [93%] of 54 *v* 29 [54%] of 54, respectively; Table 3). If patients with disease progression who crossed over from D monotherapy to D + T 150/2 were excluded, 33 (61%) of 54 patients who were initiated on D had subsequent anticancer therapy. Immunotherapy (37% *v* 43% for D + T 150/2 *v* D monotherapy, respectively) and small-molecule targeted therapy (24% *v* 87%, respectively) were the most common subsequent anticancer therapies. The high percentage of patients who received D monotherapy and subsequent targeted therapy reflected the high number of patients who crossed over to the D + T 150/2 treatment arm. Median times from initial study treatment discontinuation to initiation of an alternate anticancer therapy were 37 days (range, 1 to 242 days) in the D + T 150/2 arm and 2 days (range, 1 to 1,022 days [all patients] or 1 to 25 days [which excludes crossover patients]) in the D monotherapy arm.

A RECIST response was confirmed in 41 patients (76%) in the D + T 150/2 arm and 29 (54%) in the D monotherapy arm, with a complete response (CR) observed in nine (17%) and two (4%), respectively (Table 4). Among patients in the D + T 150/2 arm with a best response of CR, PFS was 67% at 3 years and 40% at both 4 and 5 years, and the median PFS was 39.6 months. Among patients with a best response of partial response (PR), 13%, 9%, and 9% remained progression free after 3, 4, and 5 years, respectively, and median PFS was 10.0 months. Among patients in the D + T 150/2 arm with a best response of CR, 3-, 4-, and 5-year OS rates were 67%, 56%, and 44%, respectively, and median OS was 53.4 months. Among patients with a best response of PR, 3-, 4-, and 5-year OS was 31%, 22%, and 22%, respectively, and median OS was 22.9 months. Of note, since the 3-year landmark analysis,[17] best response in one patient in the D + T 150/2 arm improved from a PR to a CR with additional follow-up (PR first documented in May 2011 and continued until CR in October 2015). The median duration of response was 10.5 months (95% CI, 7.4 to 19.2 months) in the D + T 150/2 arm and 5.6 months (95% CI, 4.1 to 7.4 months) in the D monotherapy arm (Table 4). Among patients across all arms who achieved a PR or CR, 50% achieved each response within 1.8 months.

Outcomes also were analyzed in subgroups on the basis of baseline patient characteristics previously associated with clinical benefit.[17,26] Within each treatment arm, patients with more-favorable baseline prognostic factors generally had improved outcomes versus

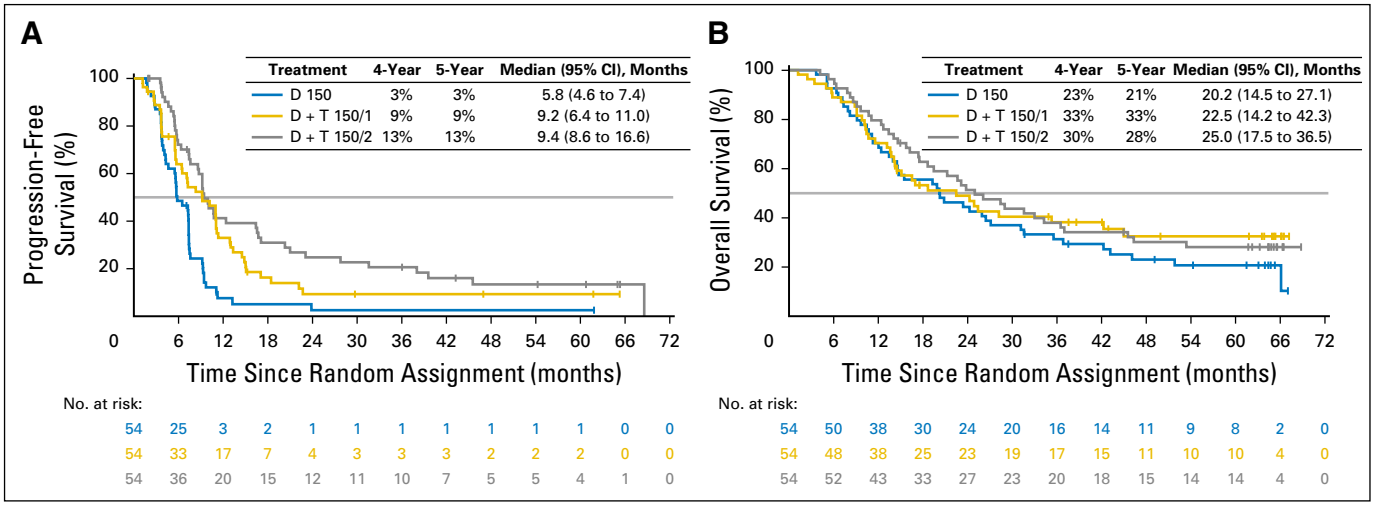

Fig 1. (A) Progression-free survival and (B) overall survival in the intention-to-treat population. D, dabrafenib; D + T 150/1, dabrafenib 150 mg twice a day plus trametinib 1 mg once daily; D + T 150/2, dabrafenib 150 mg twice a day plus trametinib 2 mg once daily.

Table 3. Subsequent Anticancer Therapy

Therapy	Treatment Arm, No. (%)		
	D + T 150/2 (n = 54)	D + T 150/1 (n = 54)	D Monotherapy (n = 54)
Any subsequent anticancer therapy	29 (54)	27 (50)	50 (93)
Subsequent anticancer therapy*			
Immunotherapy†	20 (37)	18 (33)	23 (43)
Small-molecule targeted therapy	13 (24)	11 (20)	47 (87)‡
Radiotherapy	12 (22)	13 (24)	16 (30)
Surgery	11 (20)	8 (15)	14 (26)
Chemotherapy	6 (11)	11 (20)	11 (20)
Biologic therapy	6 (11)	6 (11)	6 (11)
Unknown	0	1 (2)	0
Hormone therapy	0	0	0
Median time from study treatment discontinuation to start of subsequent anticancer therapy, days (range)	37 (1-242)	28 (5-176)	2 (1-1022)

Abbreviations: D, dabrafenib; D + T 150/1, dabrafenib 150 mg twice a day plus trametinib 1 mg once daily; D + T 150/2, dabrafenib 150 mg twice a day plus trametinib 2 mg once daily.
*Some patients received more than one subsequent anticancer therapy.
†Subsequent immunotherapies were identified by medical review.
‡Total includes patients who progressed on D monotherapy and were subsequently initiated on D + T 150/2 combination therapy.

those in poorer prognostic subgroups. Within prognostic subgroups, most comparisons showed longer PFS and OS in patients who received D + T 150/2 than those who received D monotherapy. Among patients with normal baseline serum LDH concentrations (less than or equal to the upper limit of normal [ULN]), PFS remained constant, with rates of 23% (95% CI, 9% to 41%) in the D + T 150/2 arm and 6% (95% CI, 2% to 14%) in the D arm after both 4 and 5 years. Four- and 5-year OS rates in these subgroups in the D + T 150/2 arm were 48% (95% CI, 30% to 64%) and 45% (95% CI, 27% to 61%), respectively, and 31% (95% CI, 15% to 50%) and 26% (95% CI, 11% to 45%) in the D monotherapy arm, respectively (Fig 2). D + T also showed the greatest benefit in patients with serum LDH less than or equal to ULN and fewer than three organ sites with metastasis at baseline, with both 4- and 5-year PFS rates of 25% (95% CI, 7% to 49%) in the D + T 150/2 arm and 8% (95% CI, 1% to 31%) in the D monotherapy arm. Four- and 5-year OS rates were 57% (95% CI, 32% to 76%) and 51% (95% CI, 27% to 71%) with D + T 150/2, respectively, and 42% (95% CI, 15% to 67%) and 31% (95% CI, 8% to 58%) with D monotherapy, respectively (Fig 2). No patients with the previously reported poor prognostic indicator of baseline serum LDH greater than ULN[17,26] were progression free at 5 years, and both 4- and 5-year OS rates in the D + T 150/2 and D monotherapy arms were low at 5% (95% CI, 0% to 19%) and 15% (95% CI, 5% to 30%), respectively (Fig 2). These findings were based on very-low patient numbers and may have been influenced by the type of subsequent anticancer therapy. Five-year OS rates were similar after treatment with D + T 150/1 versus D + T 150/2 (33% *v* 28%, respectively), although the response rate (50% *v* 76%), CR rate (9% *v* 17%), and PFS rate (9% *v* 13%) after extended follow-up were all markedly higher with the D + T 150/2 dose (Table 4; Fig 1).

Table 4. Confirmed Response Rates and Duration

	Treatment Arm, No. (%)		
	D + T 150/2 (n = 54)	D + T 150/1 (n = 54)	D Monotherapy (n = 54)
Best response			
CR	9 (17)	5 (9)	2 (4)
PR	32 (59)	22 (41)	27 (50)
Stable disease	13 (24)	24 (44)	22 (41)
Progressive disease	0	2 (4)	3 (6)
Not evaluable	0	1 (2)	0
Response rate (CR + PR)	41 (76)	27 (50)	29 (54)
95% CI	62 to 87	36 to 64	40 to 67
Duration of response			
No. of patients	41	27	29
Progressed or died	33 (80)	21 (78)	27 (93)
Median months (95% CI)	10.5 (7.4 to 19.2)	11.1 (7.6 to 13.2)	5.6 (4.1 to 7.4)

Abbreviations: CR, complete response; D, dabrafenib; D + T 150/1, dabrafenib 150 mg twice a day plus trametinib 1 mg once daily; D + T 150/2, dabrafenib 150 mg twice a day plus trametinib 2 mg once daily; PR, partial response.

At the time of analysis, median duration of treatment was 10.9 months (range, 1.9 to 68.7 months) for the D + T 150/2 arm and 6.1 months (range, 1.8 to 64.5 months) in the D arm, with 24 (44%) and four (8%) patients in each arm receiving D for > 12 months, respectively, and 22 (40%) in the D + T 150/2 arm receiving T for > 12 months, respectively. All patients in the D + T 150/2 and D monotherapy arms experienced an AE of any grade, with results similar to those previously reported for D + T 150/2[4,17,31,32] and between the D + T 150/1 and D + T 150/2 treatment doses (Appendix Table A1, online only). Serious AEs were more common with the combined therapy regimens than with D monotherapy (Appendix Table A2, online only).

With the additional 21 months of follow-up since the last analysis,[17] the frequency of pyrexia, the most commonly reported AE, in the D + T 150/2 arm remained stable at 69%. Reports of some commonly reported AEs (all grades), such as pyrexia, remained the same, whereas others, such as myalgia (2% increase) and headache (13% increase), changed slightly (Appendix Table A3, online only). After 5 years, nine patients (16%) who received D + T 150/2 discontinued study treatment because of an AE, with pyrexia the most frequent cause (two patients [4%]). Furthermore, with an additional approximately 52.5 months of follow-up since the primary analysis,[4] the number of AEs that led to dose interruptions (40 patients [73%]) or reductions (33 patients [60%]) in the D + T 150/2 arm increased by 6% and 2%, respectively, beyond the rates reported in the original 14-month analysis.

DISCUSSION

To our knowledge, this 5-year landmark analysis represents the longest follow-up for any randomized trial that has evaluated BRAFi plus MEKi combination therapy and provides evidence that long-term clinical benefit and tolerability are achievable with first-line D + T in some patients with *BRAF* V600E/K–mutant metastatic melanoma. These results counter the unsupported notion

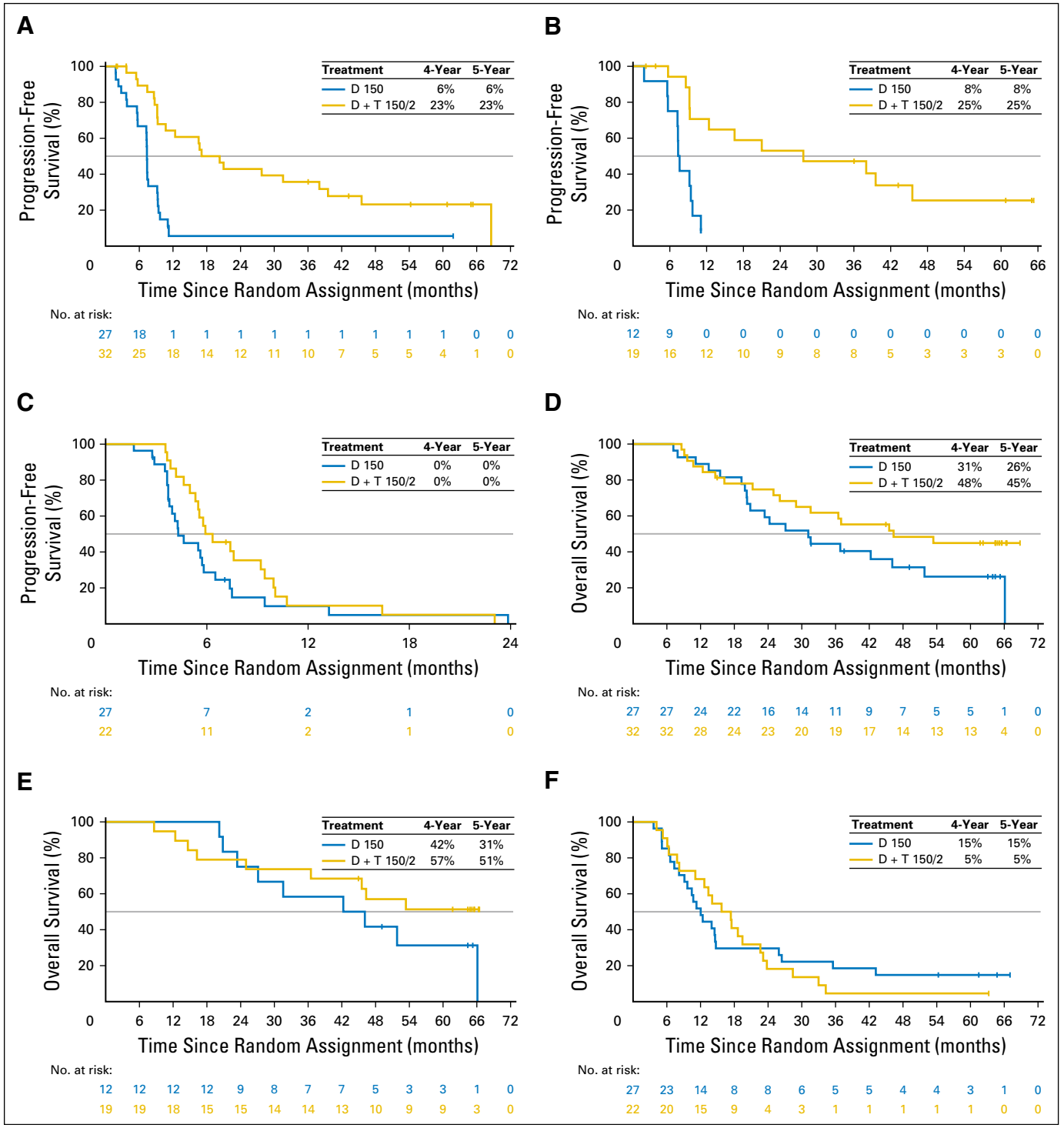

Fig 2. Association of selected patient baseline characteristics on progression-free survival and overall survival in the dabrafenib plus trametinib (D + T) and D monotherapy arms in the intention-to-treat population. (A and D) Patients with normal baseline lactate dehydrogenase (LDH) levels (less than or equal to the upper limit of normal [ULN]). (B and E) Patients with normal baseline LDH levels and fewer than three organ sites with metastasis. (C and F) Patients with elevated baseline LDH (greater than ULN). Patients who progressed on D monotherapy and crossed over to the D 150 mg twice a day plus T 2 mg once daily (D + T 150/2) arm were included and not censored at crossover. D + T 150/1, dabrafenib 150 mg twice a day plus trametinib 1 mg once daily.

that melanoma treatment with targeted therapies is associated with a rapid initial patient response that is inevitably followed by rapid deterioration as a result of the development of secondary tumor resistance.

The current analysis demonstrates long-term benefit and durable treatment responses in some patients. Although this trend must be confirmed in larger phase III studies, these findings suggest that the survival pattern for patients treated with BRAFi

plus MEKi combination therapy that begins at approximately 2 years may mirror the plateau pattern of survival that has been observed with ipilimumab.[3] Individual cases of patients who achieve long-term survival when treated with MAPK inhibitors have been previously associated with unusual autoimmune toxicities, which raises the possibility that immune activation may contribute to long-term disease control in isolated patients who receive these drugs.[33]

Follow-up for anti–PD-1 immune checkpoint inhibitor regimens has generally lagged behind targeted therapy, and 5-year landmark OS results, as reported in this study, are currently available only for a phase I study of nivolumab monotherapy. In patients with melanoma previously treated with one to five lines of prior systemic therapy (n = 107), treatment with nivolumab has resulted in 4- and 5-year OS rates of 35% and 34%, respectively.[34] *BRAF* V600 mutation status and the percentage of patients with stage M1c disease were not reported, but at baseline, 97% of this cohort had an Eastern Cooperative Oncology Group performance status ≤ 1, and 36% showed elevated serum LDH levels. Although cross-trial comparisons are confounded by study differences, such as patient baseline characteristics and the time frame during which studies were conducted, available 5-year landmark data suggest that trends in long-term outcomes are similar between anti–PD-1 and BRAFi plus MEKi combination therapies, although poststudy crossover to the other respective therapy can affect OS.

Because multiple anticancer agents demonstrate significant activity in metastatic melanoma,[35] OS results in clinical trials may be confounded by the availability of these various treatments. Because less than one half of patients received subsequent immunotherapy (37%) or small-molecule targeted therapy (24%), one could infer that the effects of D + T largely accounted for the observed 5-year OS. In addition, the study was not powered to compare efficacy between the D + T 150/1 and D + T 150/2 arms, although the landmark PFS and OS were consistently higher in the D + T 150/2 arm to 4 years. At 5 years, the landmark OS was slightly numerically higher in the D + T 150/1 arm; however, the difference was negligible, and the patient numbers were small.

The efficacy of currently available treatments for metastatic melanoma depends on baseline patient characteristics, such as LDH levels and number of organ sites with metastasis, which are key predictive factors for outcomes with D + T.[17,26] In the current analysis, although interpretation is limited by small patient numbers in these subsets, the highest 5-year OS was observed among patients with normal baseline LDH levels and three or fewer organ sites with metastasis, and patients with favorable baseline markers who were initiated on first-line D + T 150/2 therapy were most likely to derive long-term benefit. Of note, with an additional 21 months of follow-up from the previous 3-year landmark analysis,[17] the RECIST response of one patient who received D + T improved from a PR to a CR, indicating that increased benefit is achievable even after long-term treatment with the combination.

The most commonly reported AE associated with D + T is pyrexia, with fewer instances of the toxicities that are believed to be related to paradoxical MAPK pathway activation with BRAFi monotherapy.[4,7,8,17,28,29] Although extended follow-up can result in a more biased study population that consists of patients who remained on and continued to benefit from treatment, the results of the current analysis of 5-year long-term outcomes indicate that long-term D + T treatment is well tolerated in the subgroup of patients who benefit, with no new AEs associated with long-term use.

Overall, this analysis of BRAFi plus MEKi combination therapy demonstrates that long-term survival is achievable with D + T in a proportion of patients with *BRAF* V600–mutant metastatic melanoma, particularly those with favorable baseline prognostic features. Furthermore, long-term treatment with D + T is tolerable, with no new safety signals. Additional evidence is needed to support optimal treatment strategies for patients with unfavorable prognostic features for melanoma, which remains a great unmet clinical need across the range of current effective melanoma drug therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Appendix

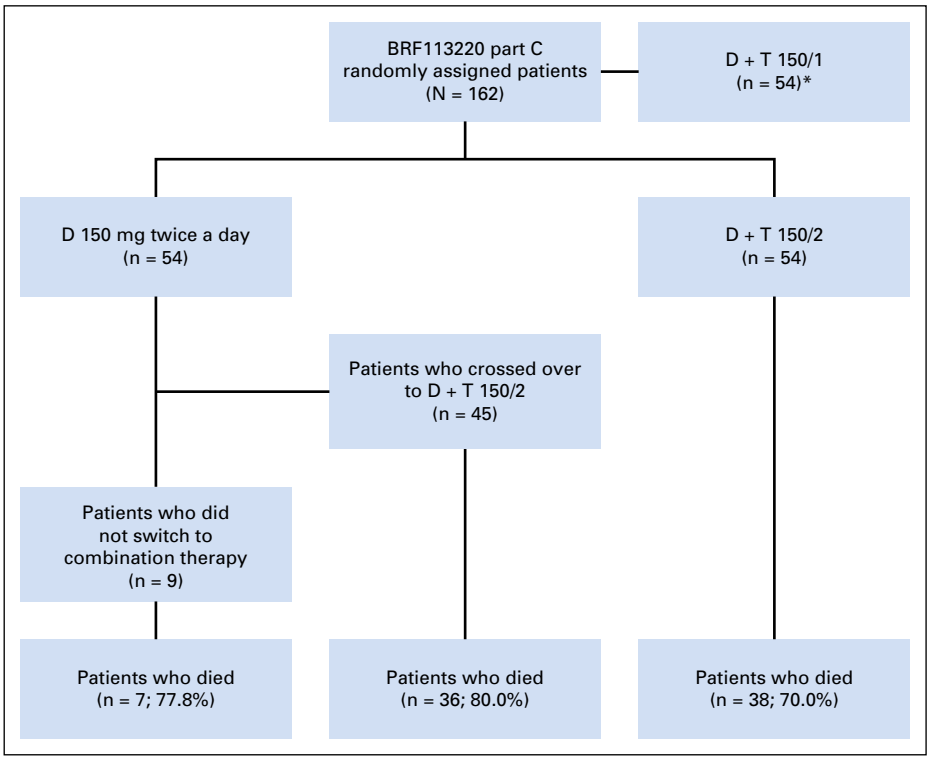

Fig A1. Study schema for part C of the BRF113220 trial. *Randomized arm not included in this analysis. D, dabrafenib; D + T 150/1, dabrafenib 150 mg twice a day plus trametinib 1 mg once daily; D + T 150/2, dabrafenib 150 mg twice a day plus trametinib 2 mg once daily.

Table A1. AEs in the Randomized Phase That Occurred in 20% or More of Patients in Any Treatment Arm

	Treatment Arm, No. (%)					
	D + T 150/2 (n = 55)†		D + T 150/1 (n = 54)		D Monotherapy (n = 53)†	
Preferred Term*	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Any AE	55 (100)	37 (67)	53 (98)	29 (54)	53 (100)	25 (47)
Pyrexia	38 (69)	4 (7)	39 (72)	6 (11)	14 (26)	0
Chills	33 (60)	1 (2)	28 (52)	1 (2)	9 (17)	0
Fatigue	32 (58)	2 (4)	35 (65)	1 (2)	22 (42)	4 (8)
Diarrhea	27 (49)	1 (2)	18 (33)	2 (4)	15 (28)	0
Nausea	26 (47)	2 (4)	30 (56)	4 (7)	11 (21)	0
Vomiting	26 (47)	1 (2)	24 (44)	4 (7)	8 (15)	0
Arthralgia	19 (35)	0	28 (52)	0	18 (34)	0
Cough	19 (35)	0	10 (19)	0	11 (21)	0
Headache	18 (33)	1 (2)	25 (46)	1 (2)	17 (32)	0
Rash	18 (33)	0	13 (24)	0	19 (36)	0
Decreased appetite	16 (29)	0	19 (35)	1 (2)	11 (21)	0
Constipation	15 (27)	0	15 (28)	0	6 (11)	0
Night sweats	15 (27)	0	11 (20)	0	3 (6)	0
Peripheral edema	14 (25)	0	13 (24)	0	9 (17)	0
Back pain	13 (24)	3 (5)	7 (13)	0	6 (11)	1 (2)
Pain in extremity	13 (24)	0	11 (20)	1 (2)	11 (21)	0
Abdominal pain	12 (22)	1 (2)	11 (20)	1 (2)	7 (13)	1 (2)
Actinic keratosis	12 (22)	0	6 (11)	0	7 (13)	1 (2)
Anemia	12 (22)	2 (4)	12 (22)	2 (4)	4 (8)	1 (2)
Myalgia	12 (22)	0	16 (30)	0	12 (23)	1 (2)
Dry skin	11 (20)	0	6 (11)	0	2 (4)	0
Muscle spasms	11 (20)	0	3 (6)	0	2 (4)	0
Dizziness	10 (18)	0	13 (24)	1 (2)	5 (9)	0
Hyperkeratosis	9 (16)	0	4 (7)	0	15 (28)	0
ALT increased	6 (11)	2 (4)	11 (20)	2 (4)	1 (2)	0
Influenza-like illness	6 (11)	0	13 (24)	1 (2)	4 (8)	0
Alkaline phosphatase increased	6 (11)	0	11 (20)	2 (4)	2 (4)	0
γ-Glutamyltransferase increased	6 (11)	3 (5)	11 (20)	6 (11)	1 (2)	0
Alopecia	3 (5)	0	8 (15)	0	19 (36)	0

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; D + T 150/1, dabrafenib 150 mg twice a day plus trametinib 1 mg once daily; D + T 150/2, dabrafenib 150 mg twice a day plus trametinib 2 mg once daily.

*In addition to these events were six grade 5 AEs: one report of sepsis in the D + T 150/1 arm and one report each of pulmonary embolism, cerebral hemorrhage, brain stem hemorrhage, intracranial hemorrhage, and a cerebrovascular accident in the D + T 150/2 arm.

†One patient assigned to the D monotherapy arm received D + T 150/2 and was included in the D + T 150/2 safety analyses.

Table A2. Serious AEs in Two or More Patients Across Treatment Arms

	Treatment Arm, No. (%)		
Preferred Term	D + T 150/2 (n = 55)*	D + T 150/1 (n = 54)	D Monotherapy (n = 53)*
Any serious AE	39 (71)	24 (44)	15 (28)
Pyrexia	16 (29)	10 (19)	1 (2)
Chills	12 (22)	7 (13)	1 (2)
Ejection fraction decreased	4 (7)	3 (6)	0
Pneumonia	3 (5)	1 (2)	1 (2)
Pulmonary embolism	3 (5)	0	0
Acute kidney injury	2 (4)	1 (2)	0
Dehydration	2 (4)	1 (2)	0
GI hemorrhage	2 (4)	0	0
Neutropenia	2 (4)	0	0
Squamous cell carcinoma	2 (4)	1 (2)	0
Squamous cell carcinoma of the skin	2 (4)	0	6 (11)

Abbreviations: AE, adverse event; D, dabrafenib; D + T 150/1, dabrafenib 150 mg twice a day plus trametinib 1 mg once daily; D + T 150/2, dabrafenib 150 mg twice a day plus trametinib 2 mg once daily. GI, gastrointestinal.

*One patient assigned to the D monotherapy arm received D + T 150/2 and was included in the D + T 150/2 safety analyses.

Table A3. Frequency of Common Treatment-Related AEs With Dabrafenib 150 mg Twice a Day Plus Trametinib 2 mg Once Daily Combination Therapy by Data Cutoff (n = 55)

AEs (All Grades)	Analysis, No. (%)	
	January 15, 2015 (Previous Analysis)[17]	October 13, 2016 (Current Analysis)
Pyrexia	38 (69)	38 (69)
Chills	30 (55)	33 (60)
Fatigue	26 (47)	32 (58)
Vomiting	22 (40)	26 (47)
Diarrhea	20 (36)	27 (49)
Nausea	19 (35)	26 (47)
Arthralgia	16 (29)	19 (35)
Rash	14 (25)	18 (33)
Night sweats	13 (24)	15 (27)
Decreased appetite	11 (20)	16 (29)
Headache	11 (20)	18 (33)
Myalgia	11 (20)	12 (22)

Abbreviation: AE, adverse event.