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ORIGINAL REPORT

Overall Survival and Durable Responses in Patients With *BRAF* V600–Mutant Metastatic Melanoma Receiving Dabrafenib Combined With Trametinib

Georgina V. Long, Jeffrey S. Weber, Jeffrey R. Infante, Kevin B. Kim, Adil Daud, Rene Gonzalez, Jeffrey A. Sosman, Omid Hamid, Lynn Schuchter, Jonathan Cebon, Richard F. Kefford, Donald Lawrence, Ragini Kudchadkar, Howard A. Burris III, Gerald S. Falchook, Alain Algazi, Karl Lewis, Igor Puzanov, Nageatte Ibrahim, Peng Sun, Elizabeth Cunningham, Amy S. Kline, Heather Del Buono, Diane Opatt McDowell, Kiran Patel, and Keith T. Flaherty

Author affiliations appear at the end of this article.

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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Corresponding author: Georgina V. Long, MD, PhD, Melanoma Institute Australia and The University of Sydney, 40 Rocklands Rd, North Sydney 2060, New South Wales, Australia; e-mail: georgina.long@sydney.edu.au.

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ABSTRACT

Purpose
To report the overall survival (OS) and clinical characteristics of BRAF inhibitor–naive long-term responders and survivors treated with dabrafenib plus trametinib in a phase I and II study of patients with *BRAF* V600 mutation–positive metastatic melanoma.

Methods
BRAF inhibitor–naive patients treated with dabrafenib 150 mg twice daily plus trametinib 2 mg daily (the 150/2 group) from the non–randomly assigned (part B) and randomly assigned (part C) cohorts of the study were analyzed for progression-free and OS separately. Baseline characteristics and factors on treatment were analyzed for associations with durable responses and OS.

Results
For BRAF inhibitor–naive patients in the 150/2 groups (n = 78), the progression-free survival at 1, 2, and 3 years was 44%, 22%, and 18%, respectively, for part B (n = 24) and 41%, 25%, and 21%, respectively, for part C (n = 54). Median OS was 27.4 months in part B and 25 months in part C. OS at 1, 2, and 3 years was 72%, 60%, and 47%, respectively, for part B and 80%, 51%, and 38%, respectively, for part C. Prolonged survival was associated with metastases in fewer than three organ sites and lower baseline lactate dehydrogenase. OS at 3 years was 62% in patients with normal baseline lactate dehydrogenase and 63% in patients with a complete response.

Conclusion
Dabrafenib plus trametinib results in a median OS of more than 2 years in BRAF inhibitor–naive patients with *BRAF* V600 mutation–positive metastatic melanoma, and approximately 20% were progression free at 3 years. Durable responses occurred in patients with good prognostic features at baseline, which may be predictive.

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INTRODUCTION

Inhibition of the MAPK (mitogen-activated protein kinase) pathway using BRAF or MEK inhibitors as single agents improves the survival of patients with *BRAF* V600E–mutant metastatic melanoma compared with chemotherapy.[1-3] Concurrent BRAF and MEK inhibition improved clinical outcomes further over single-agent BRAF inhibitors, with decreased toxicities related to paradoxical activation of the MAPK pathway in *BRAF* wild-type cells.[4-7]

More than 95% of patients experience tumor reduction when treated with dabrafenib and trametinib in combination, and, although 50% of patients progress after 12 months,[7a] a proportion of patients experience long-term benefit without progression. Because durable responses have been observed in a subset of patients treated with immunotherapies for this disease (cytotoxic T-lymphocyte–associated protein 4-blocking[8] and programmed death 1 [PD-1]/programmed death ligand 1 [PD-L1]–blocking[9-11b] antibodies, in particular), there is a need to understand the characteristics of patients who derive the greatest benefit from each mode of therapy. The future selection of patients for combined BRAF and MEK inhibition, and the rational design of clinical trials for those who fail it, may be assisted by an

analysis of the clinicopathological features of those experiencing long-term benefit and those who progress.

The extended duration of follow-up afforded by this, the first study of combined MAPK inhibition, provided a unique opportunity to report on overall survival (OS) and to analyze the clinical correlates of those who sustained prolonged survival when treated with these drugs. Here we report the updated OS results for BRAF inhibitor–naive patients treated with dabrafenib plus trametinib in optimal doses from the study. We also report the clinical factors associated with long-term survival.

METHODS

Study Population and Study Design

This open-label phase I and II study of combination therapy with dabrafenib and trametinib had four parts (parts A, B, C, and D) and was conducted at 16 international centers, as previously reported.[4]

The analysis described here includes patients enrolled in parts B and C who received the phase III dose of oral dabrafenib 150 mg twice daily combined with oral trametinib 2 mg once daily and were BRAF inhibitor naive. The remaining cohorts in parts B and C and all cohorts in parts A and D are not described here because these patients did not receive the phase III dose and formulation of the combination. Details of the study design for parts B and C are in the Data Supplement.

For all parts of the trial, patients with histologically confirmed unresectable stage IIIC or IV V600E or V600K *BRAF*-mutant melanoma were enrolled, and eligibility criteria are outlined in the Data Supplement.

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

Study Assessments

All patients were treated until PD, death, or unacceptable adverse events. Patients with radiographically confirmed PD who continued to have clinical benefit as assessed by the investigators were allowed to remain on treatment.

Demographic and disease characteristics were recorded at baseline. All patients underwent a physical examination, ECG, echocardiogram, dermatologic skin assessment, and assessment of vital signs and Eastern Cooperative Oncology Group (ECOG) performance status. Radiologic disease assessment was performed at baseline and every 8 weeks according to RECIST (Response Evaluation Criteria in Solid Tumors), version 1.1.[12] Toxicities were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. *BRAF* mutations were detected by Clinical Laboratory Improvement Amendment–approved tests or equivalent country-specific regulatory approved tests at local laboratories.

The primary and secondary end points for this phase I and II study of dabrafenib plus trametinib were previously reported.[4] For the part of the study reported here, we analyzed the proportion of patients who had achieved an investigator-assessed objective response and progression-free survival (PFS), which were secondary end points for part B and primary end points for part C, as well as OS (secondary end point for part C only).

PFS and OS were measured from the first dose of study treatment of part B and from random assignment for part C; time of first progression was used to calculate PFS. The duration of response was calculated in patients with a complete response (CR) or partial response. All responses were confirmed by a second scan. Dose modifications and interruptions of dabrafenib and/or trametinib were recommended for treatment-related toxic effects of grade 2 or worse, according to the severity of the event. Dose modifications for toxicities were managed as previously reported.[4]

Statistical Analysis

This report is based on data as of January 15, 2015. Sample size justification for part C was previously reported and was not informed by the current analysis of duration of response or OS.[4] All analyses in this report are post hoc explorations. PFS and OS were summarized using the Kaplan-Meier method as medians and 95% CIs (estimated using the Brookmeyer Crowley method). Landmark survival rates were calculated using the Kaplan-Meier method. Cox proportional hazards regression analysis was performed to evaluate factors associated with OS. Patients were categorized as treated with dabrafenib plus trametinib beyond progression if therapy was continued for $\geq$ 28 days after RECIST progression. Baseline characteristics were compared between patients with RECIST progression and patients still on study treatment with no RECIST progression. For categorical covariates such as sex, the two-sided Fisher's exact test was used for the comparison; for continuous covariates such as the baseline sum of lesion diameters, a *t* test was used to compare the two groups.

RESULTS

Patient Characteristics

Between March 26, 2010, and July 7, 2011, 443 patients at 16 centers were screened; 103 patients enrolled in part B and 162 in part C (Data Supplement). In part B, 24 BRAF inhibitor–naive

Table 1. Baseline Characteristics of BRAF Inhibitor–Naive Patients in Parts B and C Treated With a Combination of Dabrafenib 150 mg Twice Daily and Trametinib 2 mg Once Daily (150/2)

Characteristic	150/2	
	Part B (n = 24), No. (%)	Part C (n = 54), No. (%)
Median age (range), years	54.5 (25-74)	57.5 (27-79)
Sex		
Male	17 (71)	34 (63)
Female	7 (29)	20 (37)
Baseline ECOG PS		
0	11 (46)	35 (65)
1	13 (54)	19 (35)
Baseline *BRAF* mutation		
V600E	22 (92)	47 (87)
V600K	2 (8)	7 (13)
Baseline LDH		
> ULN	13 (54)	22 (41)
≤ ULN	11 (46)	32 (59)
History of brain metastases		
No	17 (71)	52 (96)
Yes	7 (29)	2 (4)
No. of disease sites at baseline		
≥ 3	18 (75)	28 (52)
< 3	6 (25)	26 (48)
Prior immunotherapy*		
Interferon, adjuvant, stage 3	11 (46)	14 (26)
Ipilimumab	8 (33)	1 (2)
IL-2	5 (21)	4 (4)
Anti–PD-1/PD-L1	0 (0)	0 (0)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IL-2, interleukin 2; LDH, lactate dehydrogenase; PD-1, programmed death 1; PD-L1, programmed death ligand 1; ULN, upper limit of normal.
*Some patients received several immunotherapies.

patients (23%) received dabrafenib 150 mg twice daily plus trametinib 2 mg once daily (the 150/2 group). In part C, all patients were BRAF inhibitor naive; 54 patients were randomly assigned to each of the three treatment groups: dabrafenib monotherapy, dabrafenib plus trametinib 1 mg once daily, and dabrafenib plus trametinib 2 mg once daily (the 150/2 group). Only the BRAF inhibitor–naive, 150/2 groups from parts B and C were analyzed here (n = 78). One patient randomly assigned to the monotherapy group received the 150/2 combination because of a dispensing error and was analyzed in the monotherapy group for efficacy, as is standard for an intention-to-treat analysis. Baseline characteristics for BRAF inhibitor–naive patients treated with 150/2 in parts B and C are shown in Table 1.

At the time of data cut, the median follow-up for patients was 47.11 months (range, 45.4 to 51.4 months) and 45.59 months (range, 42.8 to 48.8 months) in parts B and C, respectively. The proportions of patients who had progressed, died, or remained on study treatment of parts B and C were similar (Data Supplement). Best RECIST response rates with 150/2 in part C were reanalyzed for correlation with OS only.

Updated PFS and OS Analyses

For the 24 BRAF inhibitor–naive patients treated with 150/2 in part B, the median PFS was 10.8 months (95% CI, 5.3 to 18.6), and 44%, 22%, and 18% of patients were progression free at 1, 2, and 3 years, respectively (Fig 1). The median OS was 27.4 months (95% CI, 12.9 to not reached), and the OS at 1, 2, and 3 years was 72%, 60%, and 47%, respectively (Fig 2).

For the 54 BRAF inhibitor–naive patients treated with 150/2 in part C, the median PFS was 9.4 months (95% CI, 8.6 to 16.6; Fig 1), and 41%, 25%, and 21% of patients were progression free at 1, 2, and 3 years, respectively. The median OS was 25 months (95% CI, 17.5 to 36.5), and the OS at 1, 2, and 3 years was 80%, 51%, and 38%, respectively (Table 2 and Fig 2).

Baseline Characteristics of Patients Who Had Not Progressed

Of the 78 BRAF inhibitor–naive patients treated with 150/2 in parts B and C, 61 (78%) progressed (54 had RECIST progression and seven died without radiologic progression but were recorded as a progression event), nine (12%) ceased study treatment before progression (because of adverse events, withdrawal of consent, or clinical progression without radiologic evidence), and eight (10%) had not progressed and remained on treatment at the time of data cut. In total, 11 patients (14%) remained on study treatment at data cut (three had progressed and eight had not). Baseline characteristics of patients with RECIST progression (n = 54) were compared with those with no progression (n = 8; Table 2). The only baseline characteristic associated with a continued long-term response without progression was normal lactate dehydrogenase (LDH) versus elevated LDH (P = .024). Other baseline factors indicative of a good prognosis were more frequent in the nonprogressing group, including fewer than three metastatic organ sites, lower median sum of diameters, lower melanoma stage, lower ECOG performance status, and no history of brain metastases (Table 2). Results were similar when all patients who had RECIST progression, died before radiologic progression, or commenced a new drug therapy before radiologic progression (n = 66) were compared with those on treatment who had not progressed (n = 8; Data Supplement).

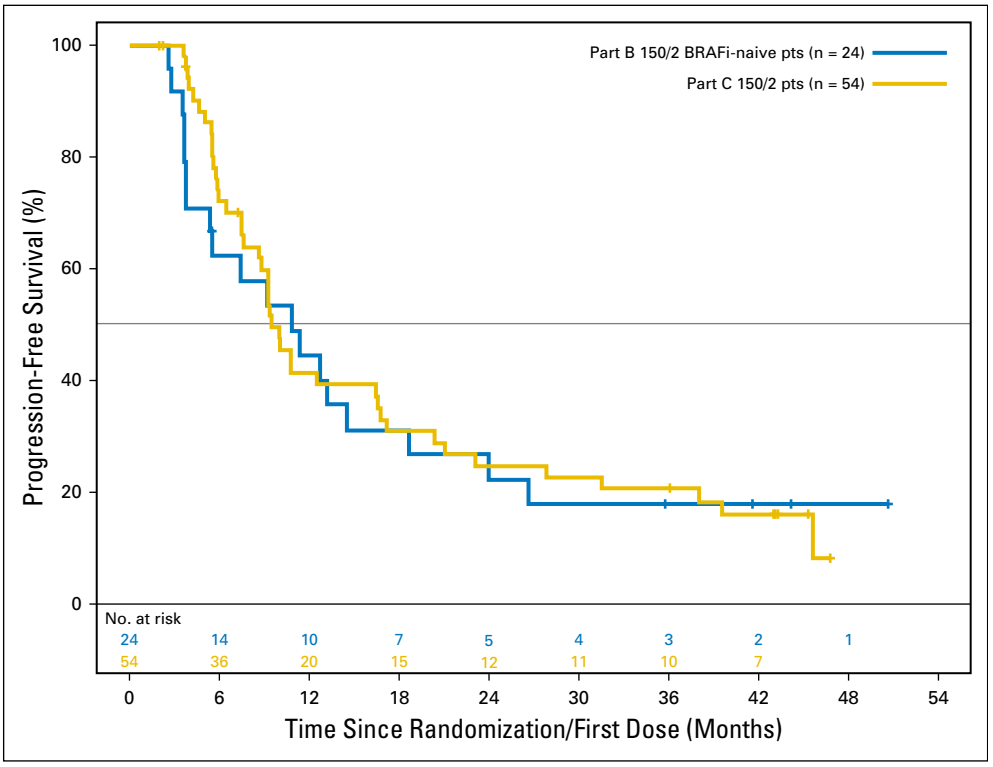

Fig 1. Progression-free survival of BRAF inhibitor (BRAFi)–naive patients (pts) from part B (blue) and part C (gold) treated with a combination of dabrafenib 150 mg twice daily and trametinib 2 mg once daily (150/2). Tick marks indicate censored patients.

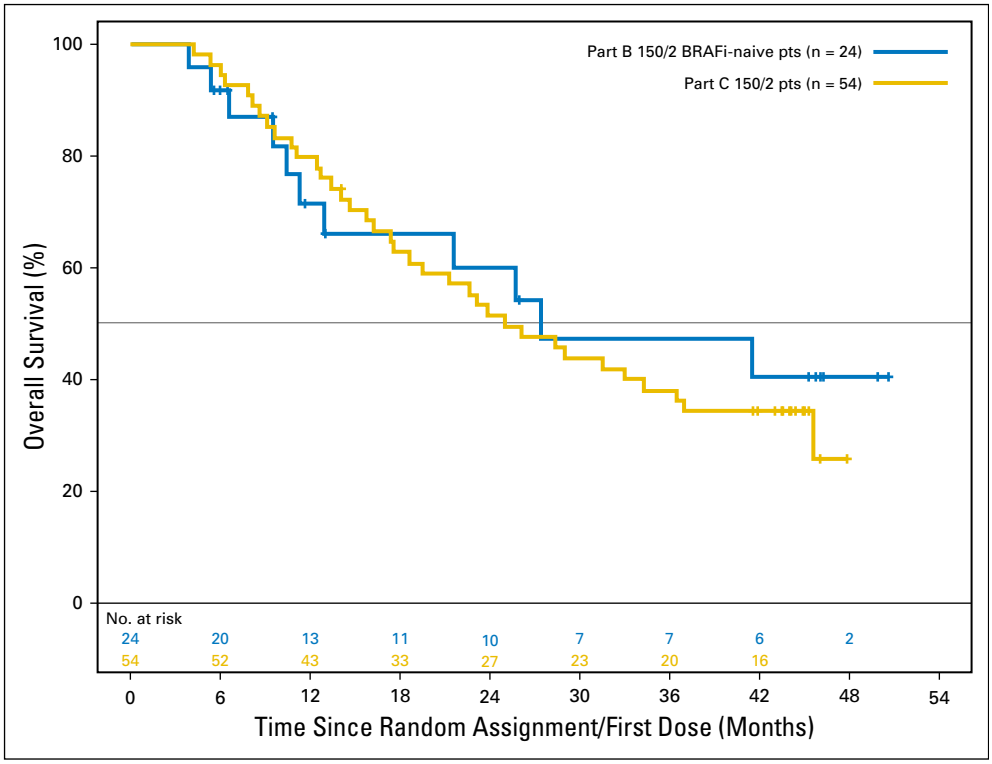

Fig 2. Overall survival (OS) of BRAF inhibitor (BRAFi)–naive patients (pts) from part B (blue) and part C (gold) treated with a combination of dabrafenib 150 mg twice daily and trametinib 2 mg once daily (150/2). Tick marks indicate censored patients.

Baseline and On-Treatment Factors Associated With Prolonged Survival

Baseline characteristics associated with a prolonged OS were analyzed for the 150/2 group in part C only, because OS was not an end point for part B initially, and survival follow-up was incomplete after the protocol amendment to include it.

Baseline characteristics associated with a prolonged OS were similar to those associated with a lack of progression at data cut and included a normal LDH, earlier-stage disease, and fewer organ disease sites of metastases (Table 2). Other factors analyzed included age, sex, sum of target lesion diameters, ECOG performance status, and prior immunotherapy (Table 2). In a Cox proportional hazards regression analysis, only lower LDH and a lower number of disease sites were significantly associated with prolonged survival (Table 4). The median OS for patients with a normal LDH at baseline was 45.5 months (95% CI, 45.5 to not reached) and was 16.6 months (95% CI, 11.1 to 22.6) for patients with an elevated LDH. The 1-, 2-, and 3-year OS values, respectively, were 88%, 75%, and 62% for patients with a normal LDH and were 68%, 18%, and 5% for those with an elevated LDH (Table 2). Five patients had an LDH greater than two times the upper limit of normal, and their survival ranged from 5.3 to 17.5 months.

The best RECIST response of CR was associated with a prolonged OS, although it was not significant because of small patient numbers (Table 2). The 1-, 2-, and 3-year OS rates, respectively, were 69%, 35%, and 35% for patients with stable disease; 79%, 48%, and 33% for patients with partial response; and 100%, 88%, and 63% for patients with CR as their best response (Table 2). For all subsets of patients examined, those with a CR or normal baseline LDH had the highest 3-year survival rates: 63% and 62%, respectively.

Patterns of Progression, Therapy After Progression, and Survival After Progression

Of the 61 BRAF inhibitor–naive patients treated with 150/2 in parts B and C who had progressed at data cut, 54 had RECIST progression and therefore could be analyzed for patterns of progression. Thirty-five of the 54 patients (65%) had new metastases at RECIST progression, and 19 (35%) progressed in existing metastases only. Of those with new metastases, eight (15%) patients had concurrent progressing existing metastases and 27 (50%) had new metastases only, of whom 12 (22%) had new brain metastases for which the brain was the sole site of progression (Data Supplement).

Of the 54 patients with RECIST progression, analysis of survival and treatment after progression was possible only in the 36 BRAF inhibitor–naive patients treated with 150/2 in part C, as these data were not collected for the 18 patients with RECIST progression in part B 150/2. ECOG performance status, LDH, and RECIST target lesion sum of diameters at progression influenced survival from progression, although it was not statistically significant because of the small numbers of patients (Data Supplement). Furthermore, 27 of the 36 progressing patients (75%) treated with 150/2 in part C received subsequent systemic therapy, including those treated with dabrafenib plus trametinib beyond progression. Nine patients (25%) did not receive post-progression systemic therapy. Patient characteristics at progression associated with no further systemic therapy compared with those who received post-progression systemic therapy were as follows: higher ECOG performance status, higher LDH, larger sum of diameters of RECIST target lesions at progression, greater absolute change in the RECIST sum of diameters from nadir, progression in the brain, and female sex (Data Supplement).

Table 2. Baseline Characteristics, Best Response, and OS in Patients Treated With a Combination of Dabrafenib 150 mg Twice Daily and Trametinib 2 mg Once Daily: Part C (n = 54)

Factor	No.	HR	Median OS, Months	1-Year OS, %	2-Year OS, %	3-Year OS, %
Overall population	54		25 (17.5 to 36.5)	80 (66 to 88)	51 (37 to 64)	38 (25 to 51)
LDH						
> ULN	22		16.6 (11.1 to 22.6)	68 (44.6 to 83.4)	18 (5.7 to 36.3)	5 (0.3 to 18.9)
≤ ULN	32	0.25 (0.12 to 0.53)	45.5 (29.0 to not reached)	88 (70.0 to 95.1)	75 (55.6 to 86.4)	62 (42.4 to 76.1)
No. of disease sites						
≥ 3	28		17.5 (12.7 to 23.8)	68 (47.3 to 81.8)	30 (14.5 to 47.9)	19 (7.0 to 35.5)
< 3	26	0.36 (0.18 to 0.69)	45.5 (28.4 to not reached)	92 (72.6 to 98.0)	73 (51.7 to 86.2)	58 (36.8 to 73.9)
Sex						
Male	34	1.13 (0.57 to 2.23)	23.8 (17.5 to 36.5)	88 (71.6 to 95.4)	49 (31.1 to 64.3)	37 (20.8 to 52.6)
Female	20		25.5 (9.1 to not reached)	65 (40.3 to 81.5)	55 (31.3 to 73.5)	40 (19.3 to 60.0)
Stage						
IIIC/M1a/M1b	16	0.36 (0.18 to 0.72)	— (34.3 to not reached)	88 (58.6 to 96.7)	74 (45.4 to 89.6)	68 (38.8 to 85.2)
M1c	38		21.9 (15.7 to 28.4)	76 (59.4 to 86.9)	42 (26.4 to 57.0)	26 (13.7 to 40.8)
Sum of diameters						
≥ Median	27		17.4 (10.7 to 29.0)	63 (42.1 to 78.1)	37 (19.6 to 54.6)	30 (14.1 to 47.0)
< Median	27	0.61 (0.31 to 1.18)	34.3 (22.6 to 45.5)	96 (76.5 to 99.5)	66 (44.2 to 80.4)	46 (26.8 to 63.8)
Age, years						
≥ 65	11		21.3 (12.4 to not reached)	82 (44.7 to 95.1)	36 (11.2 to 62.7)	27 (6.5 to 53.9)
< 65	43	0.81 (0.35 to 1.88)	28.4 (17.5 to 45.5)	79 (63.6 to 88.5)	55 (39.1 to 68.7)	41 (26.0 to 55.1)
Baseline ECOG PS						
≥ 1	19		22.6 (12.7 to not reached)	74 (47.9 to 88.1)	42 (20.4 to 62.5)	37 (16.5 to 57.5)
< 1	35	0.92 (0.46 to 1.86)	29.0 (18.6 to 37.0)	83 (65.8 to 91.9)	56 (38.3 to 70.9)	39 (22.5 to 54.3)
Prior immunotherapy						
No	34	1.27 (0.64 to 2.48)	24.0 (17.4 to 36.5)	79 (61.6 to 89.6)	50 (32.4 to 65.3)	35 (19.9 to 51.0)
Yes	20		31.6 (14.6 to not reached)	80 (55.1 to 92.0)	53 (29.4 to 72.4)	43 (20.8 to 63.0)
RECIST best response						
Stable disease	13		21.3 (8.6 to not reached)	69 (37.3 to 87.2)	35 (10.9 to 60.2)	35 (10.9 to 60.2)
Partial response	33	0.98 (0.44 to 2.19)	23.1 (16.2 to 34.3)	79 (60.6 to 89.3)	48 (30.8 to 64.1)	33 (18.2 to 49.3)
Complete response	8	0.38 (0.12 to 1.25)	— (29.0 to not reached)	100	88 (38.7 to 98.1)	63 (22.9 to 86.1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

Of the 27 patients who received systemic therapy after progression in the 150/2 group in part C, 17 (63%) patients were treated with continued dabrafenib plus trametinib, and 15 (56%) were treated with immunotherapy at any time after progression. Patients who received immunotherapy at any time had a median OS of 36.5 months (95% CI, 23.1 to not reached) with 1-, 2-, and 3-year OS values of 100%, 65%, and 53%, respectively, from the start of study treatment (ie, combined dabrafenib and trametinib). Immunotherapies included ipilimumab (n = 15), PD-1/PD-L1 inhibitors (n = 6), interleukin 2 (n = 4), and tumor-infiltrating lymphocyte transfer (n = 1). Seven patients received more than one immunotherapy in sequence. Patients who received continued dabrafenib plus trametinib after progression had a median OS of 25.0 months (95% CI, 18.6 to 37.0) from the start of study treatment with 1-, 2-, and 3-year OS values of 100%, 53%, and 29%, respectively.

Updated Safety

There were no unexpected adverse events compared with those reported previously,[4] and toxicities were manageable. The most common adverse event in patients treated with 150/2 in part C was pyrexia; hyponatremia and neutropenia/leukopenia were the most common grade 3 and grade 4 adverse events, respectively (Data Supplement). Skin toxicities were fewer relative to dabrafenib monotherapy,[4] including cutaneous squamous cell carcinoma (Data Supplement).

Details regarding study treatment discontinuation and fatal serious adverse events (all not considered related to study treatment) are reported in the Data Supplement.

DISCUSSION

This study suggests that a prolonged OS may be achieved in metastatic melanoma with combined MAPK inhibitors when compared with that reported in historical comparators,[13-15] and a subset of patients (approximately 20%) may remain progression free at 3 years. The median OS for BRAF inhibitor–naive patients who received dabrafenib plus trametinib (150/2) in the randomized phase II part of this study was more than 2 years, and the 2- and 3-year survival rates were 51% and 38%, respectively. Consistently, good prognostic features at baseline were associated with both durable ongoing responses and prolonged OS and included normal LDH, earlier-stage melanoma, and fewer metastatic sites. A normal baseline LDH and a RECIST CR were associated with the highest 3-year OS rates of 62% and 63%, respectively. Additionally, good prognostic features at progression seemed to prolong survival from the time of progression but were also associated with receiving subsequent systemic therapy. Although this analysis is limited, as it is post hoc and in small numbers of patients, these findings are consistent with those from studies of other systemic drug therapies, which have shown that good prognostic features are associated with better clinical outcomes and may be predictive.[16,17]

Table 3. Baseline Characteristics of BRAF Inhibitor–Naive Patients Who Had RECIST Progression Versus Patients Who Had Not Progressed and Remained on Combination of Dabrafenib 150 mg Twice Daily and Trametinib 2 mg Once Daily From Parts B and C

Factor	RECIST Progression (n = 54), No. (%)	Not Progressed, Remain on Treatment (n = 8), No. (%)	*P*
LDH			
> ULN	31 (57)	1 (13)	.024
≤ ULN	23 (43)	7 (88)	
No. of disease sites			
≥ 3	34 (63)	3 (38)	.250
< 3	20 (37)	5 (63)	
Sum of diameters, mm*	92	36	.149
Stage			
IIIC/M1a/M1b	9 (17)	3 (38)	.176
M1c	45 (83)	5 (63)	
Baseline ECOG PS			
0	27 (50)	5 (63)	.708
1	27 (50)	3 (38)	
History of brain metastases			
No	45 (83)	8 (100)	.590
Yes	9 (17)	0	
Age, years			
≥ 65	10 (19)	1 (13)	1.00
< 65	44 (81)	7 (88)	
Sex			
Male	36 (67)	6 (75)	1.00
Female	18 (33)	2 (25)	

NOTE. Nine patients ceased study treatment before progression, and seven patients died without radiologic progression. These patients were not included in this analysis.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

*Median of RECIST sum of diameters (mm).

Correlative tissue studies are needed to examine the molecular phenotype of these patients with durable responses and prolonged survival. Much work has been conducted using tissue taken from patients at progression on MAPK inhibitors,[18-23] in the hope of designing clinical trials of drug combinations to delay progression. Currently, little information is available about the relative contribution of each mechanism of resistance in relation to time on therapy. As data mature, there is an opportunity to determine molecular predictors of prolonged response to combined BRAF and MEK inhibition, and comparison with biopsies taken from patients who progress early may identify drivers of response that assist with future clinical trial designs.

Many effective targeted and immune therapies are approved for use in metastatic melanoma in the United States, Europe, and Australia, including some or all of the following: the combination of dabrafenib and trametinib (and the respective monotherapies), vemurafenib, ipilimumab, and most recently the anti–PD-1 therapies pembrolizumab[11] and nivolumab.[9,10] Indeed, the use of immunotherapies after cessation of dabrafenib and trametinib in this study may have impacted the OS; 28% and 11% of patients received ipilimumab and/or PD-1/PD-L1 inhibitors after progression, respectively, in part C at time of analysis. The paradigm for selection of systemic therapy is evolving, as drivers of long-term clinical benefit are determined for each therapy. On the basis of longer-term survival data from the current study and other studies,[9,16,24] it would not be possible to use baseline features to select one therapy over another. Specifically, this study showed that long-term survival and durable responses with dabrafenib plus trametinib are associated with good prognostic features at baseline, including factors associated with low-volume disease—classically considered a hallmark for front-line immunotherapy. Furthermore, those with a CR also had prolonged survival rates, although a CR does not preclude recurrence.[24a] It should be noted that although this study reports the longest follow-up data for patients treated with targeted therapies, the analyses were limited by small numbers of patients; thus, phase III trials of targeted therapies and newer immunotherapies (eg, PD-1/PD-L1 axis inhibitors) will help clarify the predictive versus prognostic nature of the baseline factors. The need to develop specific predictive molecular markers for each therapy is now even more compelling.

This study demonstrates that the combination of dabrafenib and trametinib is associated with a median OS of more than 2 years, and a subset of patients has prolonged durable responses. The combination has an acceptable long-term safety profile and is a standard of care for patients with *BRAF* mutation–positive metastatic melanoma, particularly given the recent publications demonstrating a significant improvement in the PFS and OS in phase III trials of combination versus single-agent BRAF inhibitors.[5,6]

Table 4. Cox Regression Analysis for Overall Survival Using Baseline Characteristics in Patients Treated With a Combination of Dabrafenib 150 mg Twice Daily and Trametinib 2 mg Once Daily: Part C (n = 54)

Covariate	Effect Tested	HR (95% CI)	*P*
Baseline LDH	≤ ULN *v* > ULN	0.21 (0.10 to 0.44)	< .001
No. of disease sites	< 3 *v* ≥ 3	0.34 (0.17 to 0.70)	.004

Abbreviations: HR, hazard ratio; LDH, lactate dehydrogenase; ULN, upper limit of normal.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception and design: Georgina V. Long, Jeffrey R. Infante, Adil Daud, Rene Gonzalez, Omid Hamid, Richard F. Kefford, Donald Lawrence, Igor Puzanov, Peng Sun, Elizabeth Cunningham, Kiran Patel, Keith T. Flaherty
Collection and assembly of data: Georgina V. Long, Jeffrey S. Weber, Jeffrey R. Infante, Kevin B. Kim, Rene Gonzalez, Omid Hamid, Jonathan Cebon, Richard F. Kefford, Donald Lawrence, Ragini Kudchadkar, Howard A. Burris III, Gerald S. Falchook, Alain Algazi, Karl Lewis, Igor Puzanov, Peng Sun, Elizabeth Cunningham, Amy S. Kline, Diane Opatt McDowell, Kiran Patel, Keith T. Flaherty
Data analysis and interpretation: Georgina V. Long, Jeffrey S. Weber, Jeffrey R. Infante, Kevin B. Kim, Adil Daud, Rene Gonzalez, Jeffrey A. Sosman, Omid Hamid, Lynn Schuchter, Richard F. Kefford, Donald Lawrence, Ragini Kudchadkar, Howard A. Burris III, Gerald S. Falchook, Alain Algazi, Karl Lewis, Igor Puzanov, Nageatte Ibrahim, Peng Sun, Elizabeth Cunningham, Heather Del Buono, Diane Opatt McDowell, Kiran Patel, Keith T. Flaherty
Manuscript writing: All authors
Final approval of manuscript: All authors

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Affiliations

Georgina V. Long, Melanoma Institute Australia; The University of Sydney; Richard F. Kefford, Melanoma Institute Australia; The University of Sydney; Macquarie University, Sydney; Westmead Hospital, Westmead; Jonathan Cebon, Austin Health, Melbourne, Victoria, Australia; Jeffrey S. Weber and Ragini Kudchadkar, Moffitt Cancer Center, Tampa, FL; Jeffrey R. Infante and Howard A. Burris III, Sarah Cannon Research Institute/Tennessee Oncology; Kevin B. Kim, California Pacific Medical Center; Adil Daud, Alain Algazi, University of California, San Francisco, San Francisco; Omid Hamid, The Angeles Clinic and Research Institute, Los Angeles, CA; Rene Gonzalez, Karl Lewis, University of Colorado; Gerald S. Falchook, Sarah Cannon Research Institute at HealthONE, Denver, CO; Jeffrey A. Sosman, Igor Puzanov, Vanderbilt University Medical Center, Nashville, TN; Lynn Schuchter, University of Pennsylvania Abramson Cancer Center; Nageatte Ibrahim, Elizabeth Cunningham, Merck; Peng Sun, Amy S. Kline, Heather Del Buono, Diane Opatt McDowell, GlaxoSmithKline, Philadelphia, PA; Donald Lawrence and Kiran Patel, Incyte Corporation, Wilmington, DE; and Keith T. Flaherty, Massachusetts General Hospital Cancer Center, Boston, MA.

GLOSSARY TERMS

BRAF: an isoform of RAF.

***BRAF* V600E:** the most common oncogenic mutation of *BRAF* in cancer. The V600E amino acid change results in constitutive activation of the BRAF kinase and promotes cell transformation.

Eastern Cooperative Oncology Group performance status: criteria used by doctors and researchers to define the progression of a patient's disease, assessing how the disease affects daily living habits, and to assist in the determination of the appropriate treatment and prognosis.

lactate dehydrogenase (LDH): an enzyme found in the blood and other body tissues and involved in energy production in cells. High levels of lactate dehydrogenase in the blood may indicate tissue damage, cancer, or another disease.

MAPK (mitogen-activated protein kinase): a family of enzymes that form an integrated network influencing cellular functions such as differentiation, proliferation, and cell death. These cytoplasmic proteins modulate the activities of other intracellular proteins by adding phosphate groups to their serine/threonine amino acids.

overall survival: the duration between random assignment and death.

progression-free survival: time from random assignment until death or first documented relapse, categorized as either locoregional (primary site or regional nodes) failure or distant metastasis or death.

RECIST (Response Evaluation Criteria in Solid Tumors): a model proposed by the Response Evaluation Criteria Group by which a combined assessment of all existing lesions, characterized by target lesions (to be measured) and nontarget lesions, is used to extrapolate an overall response to treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Overall Survival and Durable Responses in Patients With *BRAF* V600–Mutant Metastatic Melanoma Receiving Dabrafenib Combined With Trametinib

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Georgina V. Long
Consulting or Advisory Role: GlaxoSmithKline, Bristol-Myers Squibb, Novartis, Genentech, Amgen, Merck, Provectus Pharmaceuticals

Jeffrey S. Weber
Honoraria: GlaxoSmithKline
Consulting or Advisory Role: GlaxoSmithKline
Research Funding: GlaxoSmithKline (Inst)

Jeffrey R. Infante
No relationship to disclose

Kevin B. Kim
Research Funding: GlaxoSmithKline

Adil Daud
Leadership: OncoSec Medical
Stock or Other Ownership: OncoSec Medical
Consulting or Advisory Role: Novartis, Merck, Amgen
Research Funding: Novartis, Merck, Amgen, Incyte, Bristol-Myers Squibb

Rene Gonzalez
Honoraria: Genentech, GlaxoSmithKline, Novartis, Bristol-Myers Squibb, Merck, Piramal, Millenium Pharmaceuticals
Research Funding: GlaxoSmithKline, Genentech, Bristol-Myers Squibb, Merck, Piramal, Millennium Pharmaceuticals, Plexxikon, Novartis
Travel, Accommodations, Expenses: GlaxoSmithKline, Genentech, Bristol-Myers Squibb, Merck, Piramal, Millennium Pharmaceuticals, Plexxikon, Novartis

Jeffrey A. Sosman
Research Funding: GlaxoSmithKline (Inst)

Omid Hamid
Research Funding: GlaxoSmithKline

Lynn Schuchter
No relationship to disclose.

Jonathan Cebon
Consulting or Advisory Role: Amgen (Inst), Bionomics (Inst), Bristol-Myers Squibb (Inst), Merck Sharp & Dohme (Inst), GlaxoSmithKline (Inst)
Research Funding: GlaxoSmithKline (Inst), CSL (Inst), Merck Sharp & Dohme (Inst)

Richard F. Kefford
Honoraria: Merck
Consulting or Advisory Role: Roche (Inst), Bristol-Myers Squibb (Inst), Merck (Inst), Novartis (Inst)
Speakers' Bureau: Merck

Donald Lawrence
No relationship to disclose

Ragini Kudchadkar
Honoraria: Bristol-Myers Squibb, Genentech

Howard A. Burris III
No relationship to disclose

Gerald S. Falchook
Research Funding: GlaxoSmithKline

Alain Algazi
Research Funding: GlaxoSmithKline (Inst)

Karl Lewis
Research Funding: GlaxoSmithKline

Igor Puzanov
Consulting or Advisory Role: GlaxoSmithKline, Roche

Nageatte Ibrahim
No relationship to disclose

Peng Sun
Employment: GlaxoSmithKline
Stock or Other Ownership: GlaxoSmithKline

Elizabeth Cunningham
Employment: GlaxoSmithKline, Merck

Amy S. Kline
No relationship to disclose

Heather Del Buono
No relationship to disclose

Diane Opatt McDowell
Employment: GlaxoSmithKline
Stock or Other Ownership: GlaxoSmithKline

Kiran Patel
Employment: GlaxoSmithKline

Keith T. Flaherty
Consulting or Advisory Role: GlaxoSmithKline
Research Funding: GlaxoSmithKline

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