ORIGINAL ARTICLE

Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma

C. Robert, J.J. Grob, D. Stroyakovskiy, B. Karaszewska, A. Hauschild, E. Levchenko, V. Chiarion Sileni, J. Schachter, C. Garbe, I. Bondarenko, H. Gogas, M. Mandalá, J.B.A.G. Haanen, C. Lebbé, A. Mackiewicz, P. Rutkowski, P.D. Nathan, A. Ribas, M.A. Davies, K.T. Flaherty, P. Burgess, M. Tan, E. Gasal, M. Voi, D. Schadendorf, and G.V. Long

ABSTRACT

BACKGROUND

Patients who have unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation have prolonged progression-free survival and overall survival when receiving treatment with BRAF inhibitors plus MEK inhibitors. However, long-term clinical outcomes in these patients remain undefined. To determine 5-year survival rates and clinical characteristics of the patients with durable benefit, we sought to review long-term data from randomized trials of combination therapy with BRAF and MEK inhibitors.

METHODS

We analyzed pooled extended-survival data from two trials involving previously untreated patients who had received BRAF inhibitor dabrafenib (at a dose of 150 mg twice daily) plus MEK inhibitor trametinib (2 mg once daily) in the COMBI-d and COMBI-v trials. The median duration of follow-up was 22 months (range, 0 to 76). The primary end points in the COMBI-d and COMBI-v trials were progression-free survival and overall survival, respectively.

RESULTS

A total of 563 patients were randomly assigned to receive dabrafenib plus trametinib (211 in the COMBI-d trial and 352 in the COMBI-v trial). The progression-free survival rates were 21% (95% confidence interval [CI], 17 to 24) at 4 years and 19% (95% CI, 15 to 22) at 5 years. The overall survival rates were 37% (95% CI, 33 to 42) at 4 years and 34% (95% CI, 30 to 38) at 5 years. In multivariate analysis, several baseline factors (e.g., performance status, age, sex, number of organ sites with metastasis, and lactate dehydrogenase level) were significantly associated with both progression-free survival and overall survival. A complete response occurred in 109 patients (19%) and was associated with an improved long-term outcome, with an overall survival rate of 71% (95% CI, 62 to 79) at 5 years.

CONCLUSIONS

First-line treatment with dabrafenib plus trametinib led to long-term benefit in approximately one third of the patients who had unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation. (Funded by GlaxoSmithKline and Novartis; COMBI-d ClinicalTrials.gov number, NCT01584648; COMBI-v ClinicalTrials.gov number, NCT01597908.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Robert at Institut Gustave Roussy, 114 Rue Edouard Vaillant, 94800 Villejuif, France, or at caroline.robert@gustaveroussy.fr.

Drs. Robert and Grob and Drs. Schadendorf and Long contributed equally to this article.

This article was published on June 4, 2019, at NEJM.org.

N Engl J Med 2019;381:626-36.
DOI: 10.1056/NEJMoa1904059

Historically, metastatic melanoma has been associated with a poor prognosis, but the introduction of BRAF- and MEK-targeted therapies and immune checkpoint inhibitors has substantially improved outcomes in these patients.[1] Each of these therapies — including drugs that target programmed cell death 1 (PD-1) with or without inhibitors of cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) — has resulted in a durable survival benefit in a subgroup of patients.[2-7] However, resistance (either primary or acquired) develops in many patients, which ultimately results in death from the underlying disease. Among patients who have received no previous treatment, those who received anti–PD-1 therapies (pembrolizumab or nivolumab) in phase 3 trials had progression-free survival rates of 27 to 31% and an overall survival rate of 46% at 4 years[6,7]; the 5-year overall survival rate among patients receiving pembrolizumab was 43%.[6] In patients treated with a combination of nivolumab plus ipilimumab, 4-year progression-free survival and overall survival rates were 37% and 53%, respectively.[7] To date, 5-year survival data from randomized phase 3 trials of other BRAF-targeted therapies have not been reported. These data will be critical to assess the potential of therapy to exert long-term disease control through analysis of survival plateaus and to understand factors predictive of long-term survival.

Two previously reported randomized phase 3 trials (COMBI-d and COMBI-v) evaluated the efficacy and safety of dabrafenib plus trametinib, as compared with BRAF inhibitor monotherapy, in patients who had unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation.[8-10] In a previous pooled analysis of patients treated with dabrafenib plus trametinib in the COMBI-d and COMBI-v trials, 3-year rates of progression-free survival and overall survival were 23% (95% confidence interval [CI], 20 to 27) and 44% (95% CI, 40 to 49), respectively.[3] Univariate and multivariate analyses showed a significant association between several baseline factors (e.g., performance status, age, sex, number of organ sites with metastasis, and lactate dehydrogenase level) and both progression-free survival and overall survival.[3,11]

Here, we report findings from a 5-year analysis of patients treated with dabrafenib plus trametinib in the COMBI-d and COMBI-v trials, including progression-free survival and overall survival. We also provide an analysis of factors that appear to be associated with patients who derived long-term benefit from this treatment.

METHODS

PATIENTS, TRIAL DESIGN, AND TREATMENT

We performed a pooled analysis of data from the intention-to-treat population of previously untreated patients who had metastatic melanoma with a *BRAF* V600E or V600K mutation in the COMBI-d trial[8] (with enrollment from May 2012 through January 2013) and the COMBI-v trial[10] (with enrollment from June 2012 through September 2013). In the two trials, the patients had to be at least 18 years of age. The age ranges for patients were 22 to 89 years in the COMBI-d trial and 18 to 91 years in the COMBI-v trial. The patients in the two trials had been randomly assigned to receive dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The COMBI-d trial was a double-blind, randomized, phase 3 trial comparing dabrafenib plus trametinib with dabrafenib plus placebo. The COMBI-v trial was an open-label, randomized, phase 3 trial comparing dabrafenib plus trametinib with vemurafenib. In the two trials, patients were stratified according to *BRAF* genotype and baseline lactate dehydrogenase level and were treated until the occurrence of disease progression or unacceptable toxic effects. Complete eligibility criteria for the COMBI-d and COMBI-v trials have been reported previously.[8,10] Additional trial design methods and statistical analyses are described in the Supplementary Appendix.

PRIMARY AND SECONDARY END POINTS

In the COMBI-d trial, the primary end point was investigator-assessed progression-free survival. Secondary end points were overall survival, response rate, duration of response, safety, and pharmacokinetic features. The primary end point in the COMBI-v trial was overall survival. Secondary end points were investigator-assessed progression-free survival, response rate, duration of response, and safety. End-point definitions have been published previously.[8,10]

OVERSIGHT

The two trials were sponsored by GlaxoSmithKline; dabrafenib and trametinib were designated as assets of Novartis on March 2, 2015, after which Novartis took over sponsorship of the trials. The trials were conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocols for the COMBI-d trial and the COMBI-v trial were approved by the institutional review board or human research ethics committee at each site and are available at NEJM.org.

The present study was designed by the authors and representatives of Novartis. The data were collected by staff members at each study site and monitored by the sponsor and independent data and safety monitoring committees. The sponsor was also involved in the analysis and interpretation of the data and in the writing of the report. All the authors had full access to all the data in the study. Editorial support was provided by ArticulateScience and was funded by Novartis. All the original patients provided written informed consent before enrolling in the trials.

RESULTS

POOLED POPULATION

A total of 563 patients underwent randomization to receive dabrafenib plus trametinib (211 in the COMBI-d trial and 352 in the COMBI-v trial). At the time of data cutoff for the COMBI-v trial (October 8, 2018), 38 patients (11%) were continuing to receive dabrafenib and 35 (10%) were continuing to receive trametinib in the dabrafenib-plus-trametinib group (Table S1 in the Supplementary Appendix). The COMBI-d trial was closing at the data cutoff (December 10, 2018). At that time, the 19 patients who were continuing to receive a trial agent were offered a commercial drug (i.e., no longer provided as part of the trial), except for 1 patient who was unable to access the medication and thus continued to receive the trial agent after the cutoff date. Of the 563 patients at baseline, 363 (64%) had stage IV M1c disease and 194 (34%) had an elevated lactate dehydrogenase level (Table S2 in the Supplementary Appendix). The median follow-up was 22 months (range, 0 to 76).

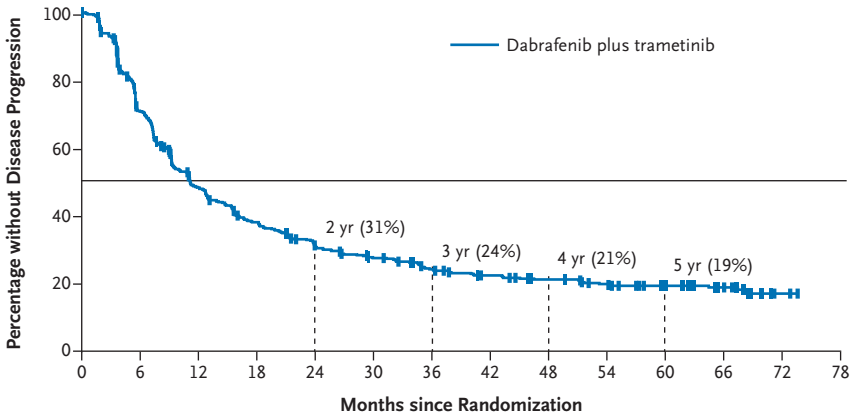
PROGRESSION-FREE SURVIVAL

Disease progression or death had occurred in 417 of 563 patients (74%) at the time of data cutoff. The median duration of progression-free survival was 11.1 months (95% CI, 9.5 to 12.8). The progression-free survival rates were 21% (95% CI, 17 to 24) at 4 years and 19% (95% CI, 15 to 22) at 5 years (Fig. 1A). Patients with a normal baseline lactate dehydrogenase level (at or below the upper limit of the normal range) had a 5-year progression-free survival rate of 25% (95% CI, 20 to 30), as compared with 8% (95% CI, 4 to 13) in patients with an elevated lactate dehydrogenase level at baseline (Fig. 1B). Previous regression-tree analysis identified a subgroup of 216 patients (38%) who had a particularly prolonged duration of progression-free survival that was characterized by a normal lactate dehydrogenase level and fewer than three disease sites at baseline.[11] Among the patients in this subgroup, the 5-year progression-free survival rate was 31% (95% CI, 24 to 38) (Fig. 1C).

Of the 59 patients who remained in the trial and were progression-free 5 years after randomization, 52 (88%) continued to receive dabrafenib, trametinib, or both. A multivariate analysis identified several baseline factors that were significantly associated with a prolonged duration of progression-free survival ($P<0.05$): older age, female sex, *BRAF* V600E genotype, better performance status, normal lactate dehydrogenase level, and fewer than three disease sites (Table 1). These findings were corroborated by analyzing baseline characteristics in patients who were progression-free 5 years after randomization (as compared with the overall population) and in those who had disease progression after the median duration of progression-free survival (as compared with those who had progression before the median duration). The association with progression-free survival was particularly evident with respect to factors associated with tumor kinetic features and disease

Figure 1 (facing page). Progression-free Survival.
Panel A shows progression-free survival in the overall pool of patients with unresectable or metastatic melanoma who received dabrafenib plus trametinib in either the COMBI-d or COMBI-v trial. Panel B shows progression-free survival in patients who had a normal lactate dehydrogenase (LDH) level and in those with an elevated level at baseline. Panel C shows progression-free survival in patients with a normal lactate dehydrogenase level and fewer than three disease sites at baseline. The solid horizontal line indicates the median value.

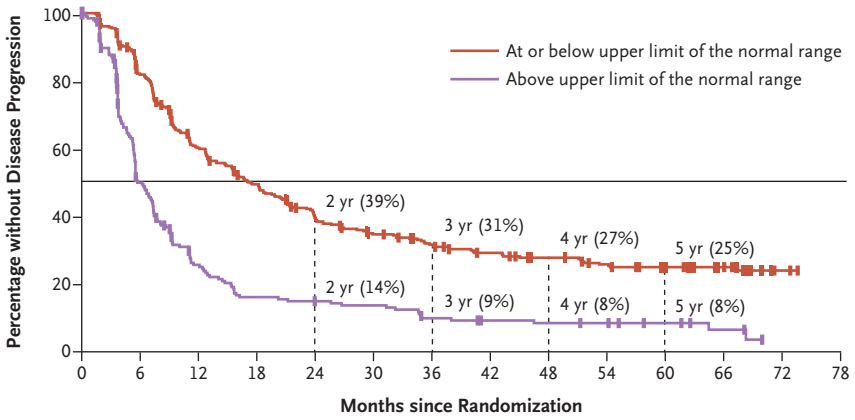
A Progression-free Survival in All Patients



No. at Risk

Dabrafenib plus trametinib	563	371	243	188	148	126	105	91	81	71	59	31	2	0

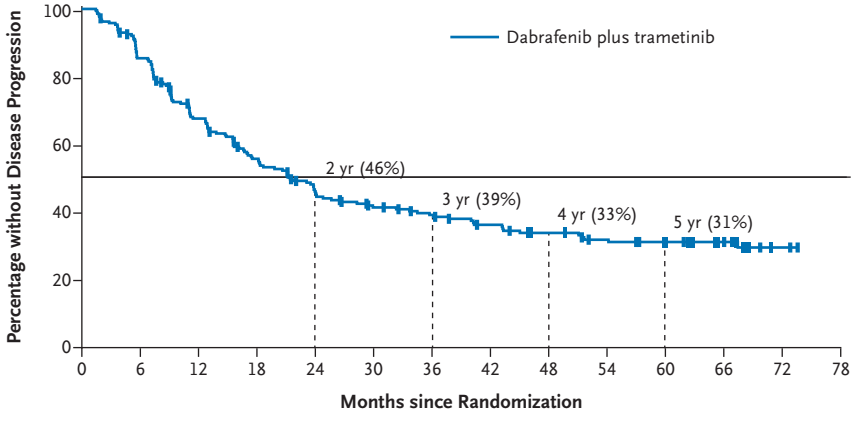
B Progression-free Survival, According to LDH Level



No. at Risk

At or below upper limit of the normal range	366	281	201	162	125	105	91	80	71	62	53	28	2	0
Above upper limit of the normal range	196	90	42	26	23	21	14	11	10	9	6	3	0	0

C Progression-free Survival with Normal LDH Level and <3 Disease Sites



No. at Risk

Dabrafenib plus trametinib	216	179	137	110	88	75	68	60	52	45	40	23	2	0

Table 1. Multivariate Analysis of Baseline Factors Associated with Progression-free Survival and Overall Survival.*

Variable	Effect Tested (no. of patients)	Progression-free Survival		Overall Survival	
		Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Age†	10-year increment	0.92 (0.85–0.99)	0.02	0.92 (0.85–1.00)	0.04
Sex	Female (238) vs. male (313)	0.74 (0.61–0.90)	0.003	0.68 (0.55–0.84)	<0.001
Disease stage	III, IVM1a, or IVM1b (195) vs. IVM1c (356)	0.82 (0.64–1.06)	0.13	0.76 (0.58–1.00)	0.05
BRAF genotype	V600E (482) vs. V600K or V600E plus V600K (69)	0.65 (0.49–0.87)	0.004	0.77 (0.55–1.06)	0.11
ECOG performance status score‡	0 (398) vs. ≥1 (153)	0.68 (0.55–0.85)	<0.001	0.49 (0.39–0.62)	<0.001
Lactate dehydrogenase level	Normal (359) vs. elevated (192)	0.50 (0.40–0.64)	<0.001	0.47 (0.37–0.61)	<0.001
No. of organ sites with metastasis	<3 sites (282) vs. ≥3 sites (269)	0.72 (0.58–0.91)	0.005	0.58 (0.46–0.74)	<0.001
Sum of lesion diameters§	<Median value (270) vs. ≥median value (281)	0.97 (0.77–1.23)	0.80	1.01 (0.79–1.30)	0.93

* Data are for 551 patients for whom information regarding the listed covariates was available. CI denotes confidence interval.
† In these patients, an increase in a 10-year increment of age was associated with a decreased risk of disease progression or death.
‡ The Eastern Cooperative Oncology Group (ECOG) performance status scale ranges from 0 to 5, with higher numbers indicating greater disability.
§ The median sum of lesion diameters at baseline was 57 mm in the intention-to-treat population.

burden (e.g., performance status, lactate dehydrogenase level, and number of disease sites) (Tables S2 and S3 in the Supplementary Appendix).

POST-TREATMENT ANTICANCER THERAPY

After the discontinuation of the trial agent, subsequent anticancer therapy was administered to 299 of 563 patients (53%) treated with dabrafenib plus trametinib (Table 2). Among the patients who received subsequent anticancer therapy, immunotherapy was most common and was administered to 196 of 299 patients (66%), including 151 (51%) who received anti–CTLA-4 therapy and 102 (34%) who received anti–PD-1 therapy. Table S4 in the Supplementary Appendix provides an overview of the best response and duration of second-line therapy.

Of note, an assessment of response with the use of the Response Evaluation Criteria in Solid Tumors (RECIST) was not performed beyond treatment discontinuation, and data were not collected with respect to the method of response assessment (i.e., clinical criteria or RECIST), dose or regimen, and reason for discontinuation of subsequent therapy. Furthermore, it is unknown whether the responses shown in Table S4 were confirmed. Because of these factors, these data should be interpreted cautiously.

OVERALL SURVIVAL

At the time of this analysis, 351 of 563 patients (62%) had died. The median overall survival duration was 25.9 months (95% CI, 22.6 to 31.5). The overall survival rates were 37% (95% CI, 33 to 42) at 4 years and 34% (95% CI, 30 to 38) at 5 years (Fig. 2A). The 5-year overall survival rate was higher among the patients who had a normal lactate dehydrogenase level at baseline (43%; 95% CI, 38 to 49) than among those with an elevated level (16%; 95% CI, 11 to 22) (Fig. 2B). Among the patients with a normal lactate dehydrogenase level and fewer than three organ sites with metastasis at baseline, the estimated 5-year rate of overall survival was 55% (95% CI, 48 to 61) (Fig. 2C). The baseline factors that were associated with overall survival by multivariate analysis were generally consistent with those associated with progression-free survival (Table 1).

The baseline characteristics of the patients who were alive 5 years after randomization were similar to those of the patients who did not have disease progression (Table S2 in the Supplemen-

tary Appendix). Among the 161 surviving patients who were continuing in the trial, 69 (43%) were receiving dabrafenib, trametinib, or both. Post-treatment anticancer therapy was given to 72 of 161 patients (45%); immunotherapy was most common (in 56 of 72 patients [78%]), including anti–PD-1 therapy (in 48 of 72 [67%]) and anti–CTLA-4 therapy (in 30 of 72 [42%]). The remaining 89 patients (55%) did not report receiving any subsequent anticancer therapy at any time during the trial (Table S5 in the Supplementary Appendix).

Table 2. Summary of Post-Treatment Anticancer Therapy.*

Variable	COMBI-d Trial (N=211)	COMBI-v Trial (N=352)
Any anticancer therapy — no. (%)		
Yes	113 (54)	186 (53)
No	98 (46)	166 (47)
Type of anticancer therapy — no./total no. (%)†		
Chemotherapy	37/113 (33)	48/186 (26)
Immunotherapy	67/113 (59)	129/186 (69)
Anti–PD-1	32/113 (28)	70/186 (38)
Anti–CTLA-4	51/113 (45)	100/186 (54)
Hormone therapy	0	1/186 (1)
Biologic therapy	3/113 (3)	4/186 (2)
Small molecule–targeted therapy	36/113 (32)	71/186 (38)
Surgery	0	33/186 (18)
Radiotherapy	55/113 (49)	97/186 (52)

* CTLA-4 denotes cytotoxic T-lymphocyte protein 4, and PD-1 programmed death 1.
† Patients could have received more than one type of anticancer therapy and are counted once under each category that applies.

RATES OF RESPONSE

An objective response to treatment with dabrafenib plus trametinib occurred in 383 of 563 patients (68%), with a complete response in 109 (19%) (Table S6 in the Supplementary Appendix). The 5-year progression-free survival rate was 49% (95% CI, 39 to 58) among patients with a complete response, 16% (95% CI, 12 to 22) among those with a partial response, and 1% (95% CI, 0 to 6) among those with stable disease (Fig. 3A).

Of the 59 patients who were progression-free 5 years after randomization, a confirmed objective response occurred in 58 (98%; 95% CI, 91 to 100), including 37 of 59 patients (63%) with a complete response (Table S7 in the Supplementary Appendix). Five-year overall survival rates were 71% (95% CI, 62 to 79) among patients with a complete response, 32% (95% CI, 26 to 37) among those with a partial response, and 16% (95% CI, 10 to 24) among those with stable disease (Fig. 3B). Most patients who were alive 5 years after randomization had a confirmed objective response (90%; 95% CI, 84 to 94), including 72 of 161 patients (45%) with a complete response (Table S7 in the Supplementary Appendix). The median duration of complete response was 36.7 months (95% CI, 24.1 to not reached).

The baseline characteristics of the patients who had a complete response were similar to those of the patients who were progression-free at 5 years (Table S8 in the Supplementary Appendix). There were no substantial differences in baseline characteristics between the patients who had a complete response and did not have disease progression (or were withdrawn from the trial before progression) and all the patients who had a complete response.

Of the 383 patients with a complete or partial response, 88 (23%) discontinued a trial agent before disease progression. Of these 88 patients, 48 (55%) underwent additional scans after discontinuation. Data regarding disease progression, which are available for 15 patients, showed that the median time until disease progression was 3.7 months.

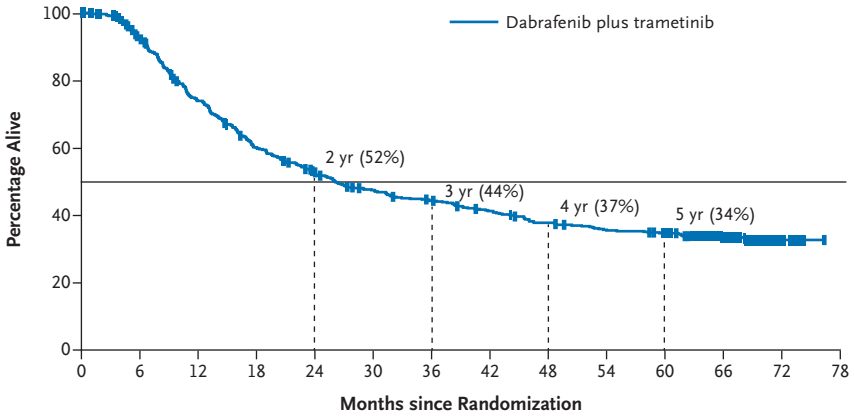
ADVERSE EVENTS

Adverse events (regardless of cause) were reported in 548 of 559 patients (98%); no unexpected adverse events were reported with extended follow-up (Table S9 in the Supplementary Appendix). Adverse events led to permanent discontinuation of a trial agent in 99 of 559 patients (18%). The most common events that led to permanent discontinuation were pyrexia (in 23 patients [4%]), decreased ejection fraction (in 21 [4%]), and an increased alanine aminotransferase level (in 7 [1%]). No deaths that were deemed by the investigators to be related to a trial agent were reported in the patients who received dabrafenib plus trametinib.

PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL IN THE INDIVIDUAL TRIALS

When data from the COMBI-d and COMBI-v trials were analyzed individually, results for progression-free survival and overall survival in patients treated with dabrafenib plus trametinib

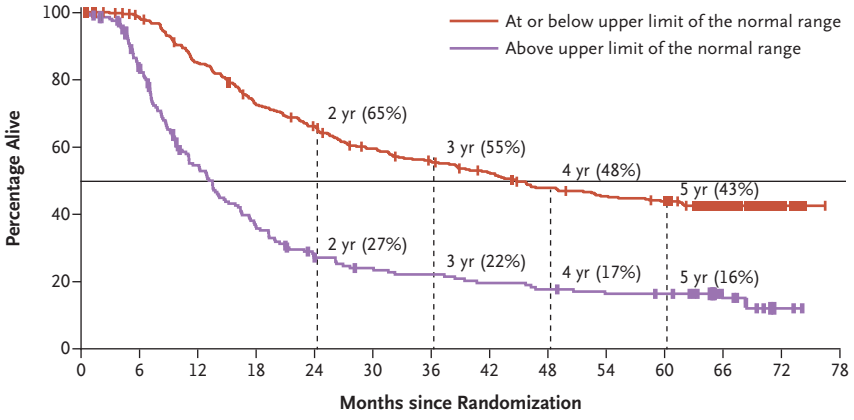
A Overall Survival in All Patients



No. at Risk

Dabrafenib plus trametinib	563	499	391	314	269	237	219	201	181	169	161	103	16	0

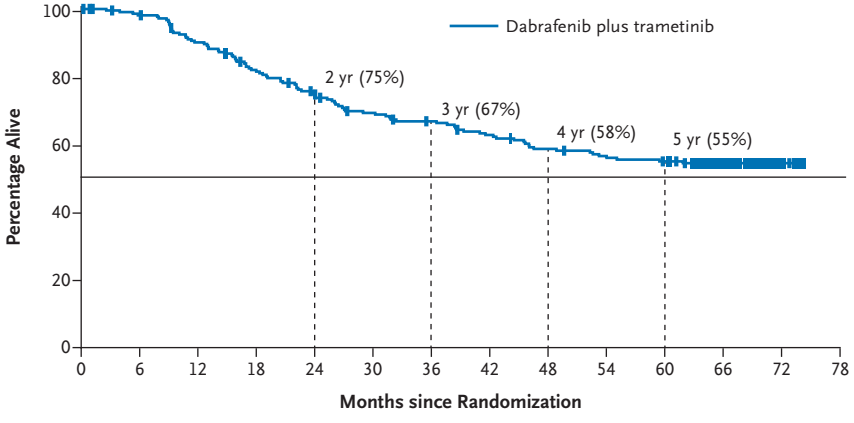
B Overall Survival, According to LDH Level



No. at Risk

At or below upper limit of the normal range	366	348	299	252	226	201	185	171	154	145	138	91	14	0
Above upper limit of the normal range	196	151	92	62	43	36	34	30	27	24	23	12	2	0

C Overall Survival with Normal LDH Level and <3 Disease Sites



No. at Risk

Dabrafenib plus trametinib	216	208	189	169	152	138	131	122	112	107	103	68	11	0

Figure 2 (facing page). Overall Survival.
Shown is overall survival in the pooled population of patients in the COMBI-d and COMBI-v trials (Panel A), in those with a normal baseline lactate dehydrogenase (LDH) level and in those with an elevated level (Panel B), and in those with a normal lactate dehydrogenase level and fewer than three disease sites at baseline (Panel C).

were similar to those in the pooled population (Figs. S2 and S3 in the Supplementary Appendix). In the dabrafenib-plus-placebo group (in the COMBI-d trial) and in the vemurafenib group (in the COMBI-v trial), the 5-year progression-free survival rate was 13% and 9%, respectively; the 5-year overall survival rate was 27% and 23%, respectively.

DISCUSSION

Results from this analysis show that in patients who had unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation, an estimated 34% were alive and 19% were progression-free at 5 years after first-line treatment with dabrafenib plus trametinib. Furthermore, the 5-year overall survival rate was 71% among patients who had a complete response and 55% among those who had a normal lactate dehydrogenase level plus fewer than three metastatic organ sites at baseline; at 5 years, the progression-free survival rate was 49% and 31% in each subgroup, respectively.

Of note, the survival curves appear to plateau from 3 to 5 years. This finding suggests stabilization of rates of progression-free survival and overall survival over time in this population. Results from 5-year analyses of other first-line targeted therapy combinations have not yet been reported.

For anti–PD-1 checkpoint inhibitors, the 5-year progression-free survival results are currently limited to large phase 1 trials (involving 107 patients who were treated with nivolumab and 655 treated with pembrolizumab) and appear to be similar to the findings reported here.[12,13] The rate of 5-year progression-free survival among patients who were treated with anti–PD-1 therapies ranged from 26% among previously treated patients to 29% among those with no previous treatment.[12,13] A 5-year overall survival analysis was recently reported for patients receiving pembrolizumab in the phase 3 KEYNOTE-006 trial.[6] In this analysis, the 5-year overall survival rate was 43% among patients who received pembrolizumab as first-line therapy. Among the patients who received ipilimumab, the rate of long-term survival was inferior to what has been observed with dabrafenib plus trametinib or with anti–PD-1 therapies. Although patients were not followed for 5-year survival analysis in the phase 3 MDX-010-20 trial, in which ipilimumab with or without a glycoprotein 100 (gp100) peptide vaccine was compared with gp100 alone in patients with previously treated metastatic melanoma, 5-year overall survival rates were 13 to 25% in phase 1/2 trials evaluating ipilimumab and 18% in a phase 3 trial evaluating ipilimumab plus dacarbazine.[14,15]

Multivariate analysis of baseline factors that were associated with progression-free survival and overall survival confirmed findings from previous analyses, which identified a significant association with age, sex, performance status, lactate dehydrogenase level, and number of disease sites.[3,11] The similarity in factors that were identified at 3 years and 5 years suggests that the baseline predictive markers may not depend on the timing of the evaluation (i.e., markers defining risk between 1 and 3 years and between 3 and 5 years are similar).

A higher proportion of patients who remained progression-free or alive 5 years after randomization had baseline characteristics that were associated with a lower tumor burden and less aggressive tumor kinetics than those in the overall population. Patients who had a complete response had particularly good outcomes, with 5-year rates of progression-free survival and overall survival of 49% and 71%, respectively, as compared with 19% and 34% in the overall population. Patients who had a complete response and those with long-term survival had baseline factors that were associated with a favorable prognosis, which suggests that patients with a lower initial disease burden may be more likely to have a response and have a greater depth of response, which may ultimately drive long-term survival.

The evaluation of biomarkers according to the category of response, which appears to be associated with long-term outcomes, may constitute a surrogate end point for earlier assessment in future studies. Our analysis also showed an association between female sex and improved long-term outcomes, which is common in historical

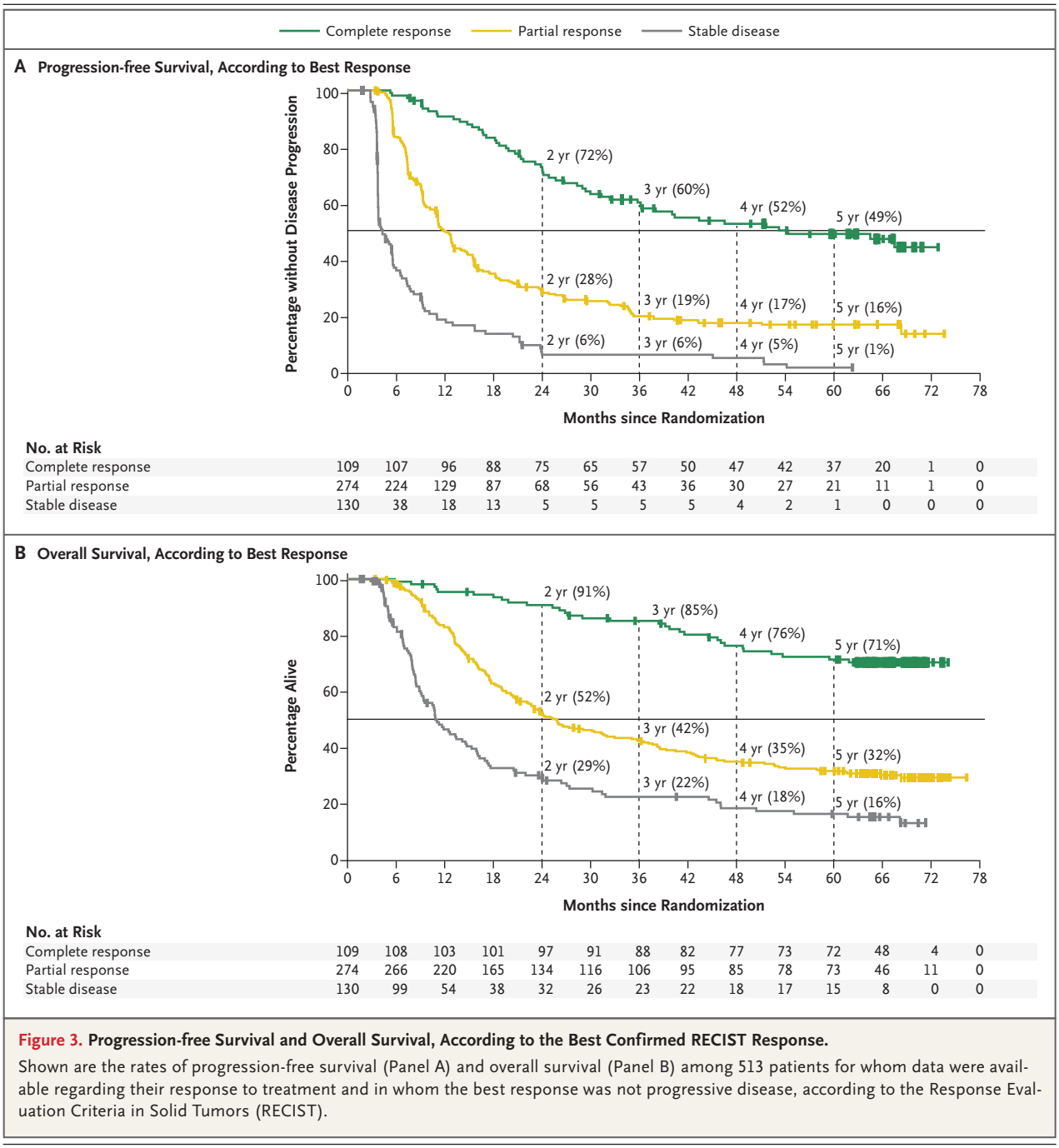


Figure 3. Progression-free Survival and Overall Survival, According to the Best Confirmed RECIST Response.

Shown are the rates of progression-free survival (Panel A) and overall survival (Panel B) among 513 patients for whom data were available regarding their response to treatment and in whom the best response was not progressive disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST).

melanoma studies. In comparison, a recent meta-analysis of 20 randomized trials of immune checkpoint inhibitors, in which 7 of the trials involved patients with melanoma, showed a significant difference in relative efficacy, with an increased benefit in men.[16]

Across trials evaluating available therapeutic options, including trials of immune checkpoint inhibitors, substantially worse outcomes have been observed in patients who had an elevated lactate dehydrogenase level at baseline.[5,17,18] These patients with more aggressive tumor kinetics need new therapeutic options. One potential option under evaluation is the combination of targeted therapy and immune checkpoint inhibitors. Such combination strategies are being evaluated in the

ongoing phase 3 COMBI-i trial (ClinicalTrials.gov number, NCT02967692), in which a regimen of spartalizumab (an anti–PD-1 antibody) plus dabrafenib and trametinib is being compared with placebo plus dabrafenib and trametinib, and in the phase 3 TRILOGY trial (NCT02908672), in which a regimen of atezolizumab (an anti–PD-L1 antibody) plus vemurafenib and cobimetinib is being compared with placebo plus vemurafenib and cobimetinib.

In our study, immunotherapy was the most common post-treatment anticancer therapy overall and in the patients who were alive 5 years after randomization. Among the patients who had disease progression after receiving dabrafenib plus trametinib, responses (including a complete response) were observed in those who received subsequent immune checkpoint inhibitors. The clinical use of targeted therapy and immune checkpoint inhibitors in patients with metastatic melanoma remains an open clinical question. However, several ongoing trials (NCT02631447, NCT02224781, NCT02902029, and NCT02858921) are evaluating the most effective sequencing of treatment.

In conclusion, we found that first-line treatment with dabrafenib plus trametinib led to 5-year survival in approximately one third of patients who had unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation. Having a complete response to the combined treatment appears to be a strong and early predictor of prolonged benefit. However, no biomarkers are currently available to determine which patients who discontinue therapy are likely to have disease progression.

Supported by GlaxoSmithKline and Novartis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families for participating in these trials; Jorge J. Moreno-Cantu, Ph.D., of Novartis Pharmaceuticals, for editorial assistance; and Michael Demars, Ph.D., of ArticulateScience, for medical writing assistance.

APPENDIX

The authors' full names and academic degrees are as follows: Caroline Robert, M.D., Ph.D., Jean J. Grob, M.D., Ph.D., Daniil Stroyakovskiy, M.D., Boguslawa Karaszewska, M.D., Axel Hauschild, M.D., Evgeny Levchenko, M.D., Vanna Chiarion Sileni, M.D., Jacob Schachter, M.D., Claus Garbe, M.D., Igor Bondarenko, M.D., Ph.D., Helen Gogas, M.D., Mario Mandalá, M.D., John B.A.G. Haanen, M.D., Ph.D., Celeste Lebbé, M.D., Andrzej Mackiewicz, M.D., Ph.D., Piotr Rutkowski, M.D., Ph.D., Paul D. Nathan, M.D., Antoni Ribas, M.D., Ph.D., Michael A. Davies, M.D., Ph.D., Keith T. Flaherty, M.D., Paul Burgess, M.Sci., Monique Tan, M.D., Eduard Gasal, M.D., Maurizio Voi, M.D., Dirk Schadendorf, M.D., and Georgina V. Long, M.B., B.S., Ph.D.

The authors' affiliations are as follows: Institut Gustave Roussy and Paris-Sud-Paris-Saclay University, Villejuif (C.R.), Aix-Marseille University, Marseille (J.J.G.), and Assistance Publique–Hôpitaux de Paris Dermatology and Clinical Investigation Center, Unité 976, Université de Paris, Hôpital Saint-Louis, Paris (C.L.) — all in France; Moscow City Oncology Hospital, Moscow (D. Stroyakovskiy), and the Petrov Research Institute of Oncology, St. Petersburg (E.L.) — both in Russia; Przychodnia Lekarska Komed, Konin (B.K.), the University of Medical Sciences, Poznań (A.M.), and the Maria Skłodowska-Curie Institute–Oncology Center, Warsaw (P.R.) — all in Poland; the University Hospital Schleswig-Holstein, Kiel (A.H.), the Department of Dermatology, University of Tübingen, Tübingen (C.G.), University Hospital Essen, Essen (D. Schadendorf), and the German Cancer Consortium, Heidelberg (D. Schadendorf) — all in Germany; the Veneto Institute of Oncology, Padua (V.C.S.), and Papa Giovanni XXIII Hospital, Bergamo (M.M.) — both in Italy; the Ella Lemelbaum Institute for Immuno-Oncology and Melanoma, Sheba Medical Center, Tel Hashomer (J.S.), and Sackler Medical School, Tel Aviv University, Tel Aviv (J.S.) — both in Israel; Dnipropetrovsk State Medical Academy, Dnipropetrovsk, Ukraine (I.B.); Laiko General Hospital, National and Kapodistrian University of Athens School of Medicine, Athens (H.G.); the Netherlands Cancer Institute, Amsterdam (J.B.A.G.H.); Mount Vernon Cancer Centre, Northwood, United Kingdom (P.D.N.); the University of California, Los Angeles, Los Angeles (A.R.); the University of Texas M.D. Anderson Cancer Center, Houston (M.A.D.); Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston (K.T.F.); Novartis Pharma, Basel, Switzerland (P.B.); Novartis Pharmaceuticals, East Hanover, NJ (M.T., E.G., M.V.); and the Melanoma Institute Australia, the University of Sydney, and Royal North Shore and Mater Hospitals, Sydney (G.V.L.).

REFERENCES

1. Ugurel S, Röhmel J, Ascierto PA, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. Eur J Cancer 2017;83:247-57.
2. Long GV, Eroglu Z, Infante J, et al. Long-term outcomes in patients with BRAF V600-mutant metastatic melanoma who received dabrafenib combined with trametinib. J Clin Oncol 2018;36:667-73.
3. Schadendorf D, Long GV, Stroiakovski D, et al. Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials. Eur J Cancer 2017;82:45-55.
4. McArthur GA, Dréno B, Atkinson V, et al. Efficacy of long-term cobimetinib combined with vemurafenib in advanced BRAFV600-mutated melanoma: 3-year follow-up of the phase 3 coBRIM study and 4-year follow-up of the phase 1b BRIM7 study. Presented at the 13th International Congress of the Society for Melanoma Research, Boston, November 6–9, 2016. poster.
5. Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018;19:1315-27.
6. Robert C, Schachter J, Long GV, et al. 5-Year survival and other long-term outcomes from KEYNOTE-006 study of pem-

brolizumab (pembro) for ipilimumab (ipi)-naive advanced melanoma. Presented at the American Association for Cancer Research Annual Meeting, Atlanta, March 29–April 3, 2019. abstract (https://www.abstractsonline.com/pp8/#!/6812/presentation/9957).
7. Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:1480-92.
8. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371:1877-88.
9. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015;386:444-51.
10. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30-9.
11. Long GV, Grob JJ, Nathan P, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. Lancet Oncol 2016;17:1743-54.
12. Hamid O, Robert C, Daud A, et al. 5-Year survival outcomes in patients (pts) with advanced melanoma treated with pembrolizumab (pembro) in KEYNOTE-001. J Clin Oncol 2018;36:9516. abstract.
13. Hodi FS, Kluger H, Sznol M, et al. Durable, long-term survival in previously treated patients with advanced melanoma (MEL) who received nivolumab (NIVO) monotherapy in a phase I trial. Proc Am Assoc Cancer Res 2016;76:Suppl:CT001. abstract.
14. Prieto PA, Yang JC, Sherry RM, et al. CTLA-4 blockade with ipilimumab: long-term follow-up of 177 patients with metastatic melanoma. Clin Cancer Res 2012;18:2039-47.
15. Maio M, Grob JJ, Aamdal S, et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol 2015;33:1191-6.
16. Conforti F, Pala L, Bagnardi V, et al. Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol 2018;19:737-46.
17. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017;377:1345-56.
18. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17:1248-60.