ORIGINAL ARTICLE

Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, C.D. Lao, C.L. Cowey, D. Schadendorf, J. Wagstaff, R. Dummer, P.F. Ferrucci, M. Smylie, D. Hogg, A. Hill, I. Márquez-Rodas, J. Haanen, M. Guidoboni, M. Maio, P. Schöffski, M.S. Carlino, C. Lebbé, G. McArthur, P.A. Ascierto, G.A. Daniels, G.V. Long, L. Bastholt, J.I. Rizzo, A. Balogh, A. Moshyk, F.S. Hodi, and J.D. Wolchok

ABSTRACT

BACKGROUND

Nivolumab plus ipilimumab or nivolumab alone resulted in longer progression-free and overall survival than ipilimumab alone in a trial involving patients with advanced melanoma. We now report 5-year outcomes in the trial.

METHODS

We randomly assigned patients with previously untreated advanced melanoma to receive one of the following regimens: nivolumab (at a dose of 1 mg per kilogram of body weight) plus ipilimumab (3 mg per kilogram) every 3 weeks for four doses, followed by nivolumab (3 mg per kilogram every 2 weeks); nivolumab (3 mg per kilogram every 2 weeks) plus ipilimumab-matched placebo; or ipilimumab (3 mg per kilogram every 3 weeks for four doses) plus nivolumab-matched placebo. The two primary end points were progression-free survival and overall survival in the nivolumab-plus-ipilimumab group and in the nivolumab group, as compared with the ipilimumab group.

RESULTS

At a minimum follow-up of 60 months, the median overall survival was more than 60.0 months (median not reached) in the nivolumab-plus-ipilimumab group and 36.9 months in the nivolumab group, as compared with 19.9 months in the ipilimumab group (hazard ratio for death with nivolumab plus ipilimumab vs. ipilimumab, 0.52; hazard ratio for death with nivolumab vs. ipilimumab, 0.63). Overall survival at 5 years was 52% in the nivolumab-plus-ipilimumab group and 44% in the nivolumab group, as compared with 26% in the ipilimumab group. No sustained deterioration of health-related quality of life was observed during or after treatment with nivolumab plus ipilimumab or with nivolumab alone. No new late toxic effects were noted.

CONCLUSIONS

Among patients with advanced melanoma, sustained long-term overall survival at 5 years was observed in a greater percentage of patients who received nivolumab plus ipilimumab or nivolumab alone than in those who received ipilimumab alone, with no apparent loss of quality of life in the patients who received regimens containing nivolumab. (Funded by Bristol-Myers Squibb and others; CheckMate 067 ClinicalTrials.gov number, NCT01844505.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Larkin at the Royal Marsden NHS Foundation Trust, 203 Fulham Rd., Chelsea, London SW3 6JJ, United Kingdom, or at james.larkin@rmh.nhs.uk.

Drs. Hodi and Wolchok contributed equally to this article.

This article was published on September 28, 2019, and updated on October 11, 2019, at NEJM.org.

N Engl J Med 2019;381:1535-46.
DOI: 10.1056/NEJMoa1910836

In the past decade, progress in the treatment of advanced melanoma has markedly improved survival outcomes.[1] The availability of new systemic therapies — including ipilimumab, an anti–cytotoxic T-lymphocyte–associated antigen 4 monoclonal antibody; anti–programmed death 1 agents (nivolumab and pembrolizumab); nivolumab in combination with ipilimumab; and BRAF and MEK inhibitors (dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib)— has transformed the treatment of this disease.[1]

Initial and follow-up analyses of the phase 3 CheckMate 067 trial, including analyses across clinically relevant subgroups, showed a significantly higher response rate and longer progression-free survival and overall survival with nivolumab plus ipilimumab or nivolumab alone than with ipilimumab alone among patients with advanced melanoma.[2-4] Combination therapy with nivolumab plus ipilimumab has also had clinical efficacy in patients with metastatic melanoma and untreated brain metastases.[5,6] Some patients who have received nivolumab plus ipilimumab have also discontinued therapy without subsequent systemic treatment for melanoma[4,7-9]; this is one aspect of the value of combination nivolumab plus ipilimumab treatment. In this article, we provide an update of survival outcomes from the CheckMate 067 trial with a minimum of 5 years of follow-up as well as an assessment of the long-term benefit of combination nivolumab plus ipilimumab treatment with respect to outcomes in patients who have not received subsequent systemic treatment for melanoma and with respect to health-related quality of life.

Methods

Patients

Adult patients with previously untreated, unresectable or metastatic histologically confirmed stage III or stage IV melanoma, with known *BRAF* V600 mutation status, and with an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability) were included in the trial. The full trial eligibility criteria, design, and assessments have been reported previously.[4]

Trial Design and Treatment

Patients were randomly assigned in a 1:1:1 ratio to receive one of the following regimens: nivolumab at a dose of 1 mg per kilogram of body weight every 3 weeks plus ipilimumab at a dose of 3 mg per kilogram every 3 weeks for four doses, followed by nivolumab at a dose of 3 mg per kilogram every 2 weeks; nivolumab at a dose of 3 mg per kilogram every 2 weeks (plus ipilimumab-matched placebo); or ipilimumab at a dose of 3 mg per kilogram every 3 weeks for four doses (plus nivolumab-matched placebo). Randomization was stratified according to *BRAF* mutation status, metastasis stage defined according to the American Joint Committee on Cancer, and tumor programmed cell death ligand 1 (PD-L1) status.

Treatment was continued until disease progression, the occurrence of unacceptable toxic events, or withdrawal of consent. Patients with clinical benefit and without substantial adverse events could be treated beyond progression according to the investigator's decision. Minimum follow-up was defined as the time from the date on which the last patient underwent randomization to the clinical cutoff date; the extent of follow-up (for which the median is reported) was defined as the time between the randomization date and the last known date alive (for patients who were alive) or death date (for patients who had died).

The two primary end points were progression-free survival and overall survival, as compared between the nivolumab-plus-ipilimumab group or the nivolumab group and the ipilimumab group. Secondary end points included a comparison of the objective response rate between the nivolumab-containing groups and the ipilimumab group and descriptive efficacy evaluations between the nivolumab-plus-ipilimumab group and the nivolumab group. Additional analyses (survival end points according to subgroup and evaluations of the treatment-free interval and treatment-free status) have been published previously[3,4] and are detailed in the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org. Evaluations of health-related quality of life as determined on the basis of the mean change from baseline analyses with the use of the European Quality of Life 5-Dimen-

sions 3-Level (EQ-5D-3L) questionnaire[10,11] are detailed in the Supplementary Methods section.

TRIAL OVERSIGHT

The protocol and amendments for this trial (available at NEJM.org) were reviewed by the institutional review board at each trial site. The trial was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. All the patients provided written informed consent before enrollment.

The trial was designed by the senior academic authors and the sponsor, Bristol-Myers Squibb. Data were collected by the sponsor and analyzed in collaboration with the authors. The authors vouch for the accuracy and completeness of the data reported and also confirm adherence to the protocol. The initial manuscript was written in collaboration with the first author and the last two authors, who provided direct input into all key sections. All the authors contributed to subsequent drafts and provided final approval to submit the manuscript for publication. Professional medical writing and editorial assistance were paid for by the sponsor. A data and safety monitoring committee provided oversight to assess the risk–benefit profile of nivolumab plus ipilimumab, as described previously.[2,3]

STATISTICAL ANALYSIS

Efficacy end points were based on the intention-to-treat population. Formal analyses of the two primary end points were conducted at different prespecified time points according to the trial protocol, as described previously.[2,3] A 60-month follow-up to assess overall survival, progression-free survival, and the objective response rate with confidence intervals at the 95% level was performed, and updated P values were provided for descriptive purposes. The trial was not designed for a formal statistical comparison between the nivolumab-plus-ipilimumab group and the nivolumab group, but descriptive analyses without formal hypothesis testing were performed. Details of the statistical analysis are provided in the Supplementary Methods section and have been published previously.[2-4]

RESULTS

PATIENTS AND TREATMENT

From July 2013 through March 2014, a total of 1296 patients were enrolled and 945 underwent randomization (314 to the nivolumab-plus-ipilimumab group, 316 to the nivolumab group, and 315 to the ipilimumab group) (Fig. S1). The baseline characteristics of the patients have been reported previously (Table S1),[2-4] and information on drug exposure is provided in Table S2.

At database lock on July 2, 2019, the minimum follow-up from the date on which the last patient underwent randomization was 60 months. The median extent of follow-up was 54.6, 36.0, and 18.6 months for the nivolumab-plus-ipilimumab, nivolumab, and ipilimumab groups, respectively. At the current database lock, most patients were no longer receiving trial therapy, and 36 patients were continuing the trial treatment (12 in the nivolumab-plus-ipilimumab group and 24 in the nivolumab group).

SURVIVAL OUTCOMES

Overall survival was longer in the two nivolumab-containing groups than in the ipilimumab group. The median overall survival was more than 60.0 months (median not reached; 95% confidence interval [CI], 38.2 to not reached) in the nivolumab-plus-ipilimumab group, 36.9 months (95% CI, 28.2 to 58.7) in the nivolumab group, and 19.9 months (95% CI, 16.8 to 24.6) in the ipilimumab group (Fig. 1A). Overall survival at 5 years was 52% in the nivolumab-plus-ipilimumab group and 44% in the nivolumab group, as compared with 26% in the ipilimumab group.

The median progression-free survival was 11.5 months (95% CI, 8.7 to 19.3) in the nivolumab-plus-ipilimumab group, 6.9 months (95% CI, 5.1 to 10.2) in the nivolumab group, and 2.9 months (95% CI, 2.8 to 3.2) in the ipilimumab group (Fig. 1B). Five-year progression-free survival was 36%, 29%, and 8% in the nivolumab-plus-ipilimumab, nivolumab, and ipilimumab groups, respectively.

Overall survival and progression-free survival were also evaluated in patient subgroups (Fig. S2). Among patients with tumors with *BRAF* mutations and those with tumors without *BRAF* mutations,

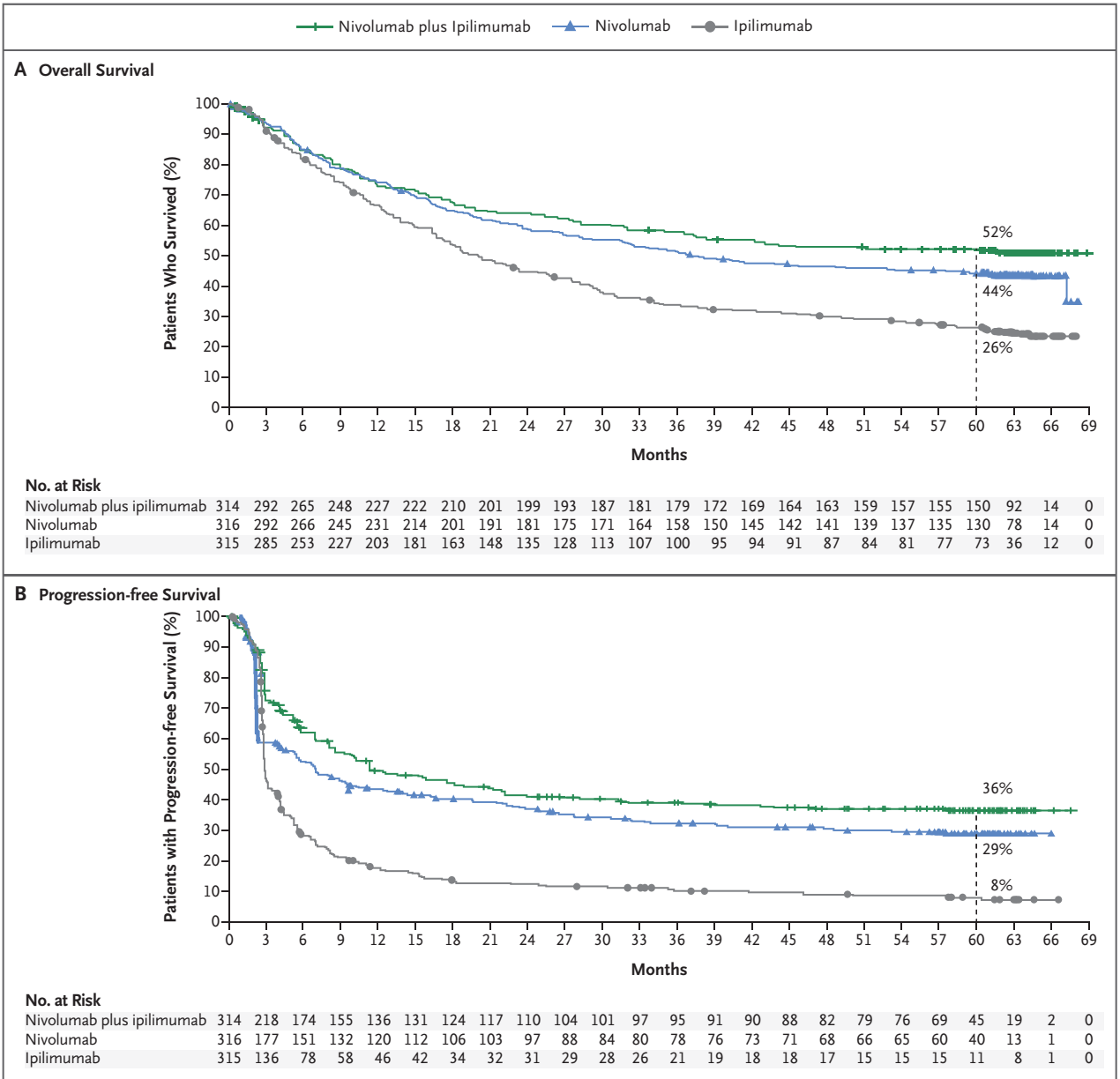

Figure 1. Kaplan–Meier Estimates of Survival in the Overall Population.

Patients were followed for a minimum of 60 months (dashed line). Symbols (tick marks, triangles, and circles) indicate censored data. Panel A shows the Kaplan–Meier estimates of overall survival. The median overall survival was longer than 60.0 months (95% confidence interval [CI], 38.2 to not reached) in the nivolumab-plus-ipilimumab group, 36.9 months (95% CI, 28.2 to 58.7) in the nivolumab group, and 19.9 months (95% CI, 16.8 to 24.6) in the ipilimumab group. The hazard ratio for death was 0.52 (95% CI, 0.42 to 0.64; P<0.001) for nivolumab plus ipilimumab versus ipilimumab, 0.63 (95% CI, 0.52 to 0.76; P<0.001) for nivolumab versus ipilimumab, and 0.83 (95% CI, 0.67 to 1.03) for nivolumab plus ipilimumab versus nivolumab. Overall survival at 5 years was 52% in the nivolumab-plus-ipilimumab group, 44% in the nivolumab group, and 26% in the ipilimumab group. Panel B shows the Kaplan–Meier estimates of progression-free survival as assessed by the investigator. The median progression-free survival was 11.5 months (95% CI, 8.7 to 19.3) in the nivolumab-plus-ipilimumab group, 6.9 months (95% CI, 5.1 to 10.2) in the nivolumab group, and 2.9 months (95% CI, 2.8 to 3.2) in the ipilimumab group. The hazard ratio for disease progression or death was 0.42 (95% CI, 0.35 to 0.51; P<0.001) for nivolumab plus ipilimumab versus ipilimumab, 0.53 (95% CI, 0.44 to 0.64; P<0.001) for nivolumab versus ipilimumab, and 0.79 (95% CI, 0.64 to 0.96) for nivolumab plus ipilimumab versus nivolumab. Progression-free survival at 5 years was 36% in the nivolumab-plus-ipilimumab group, 29% in the nivolumab group, and 8% in the ipilimumab group.

overall survival at 5 years was 60% and 48%, respectively, in the nivolumab-plus-ipilimumab group; 46% and 43% in the nivolumab group; and 30% and 25% in the ipilimumab group (Fig. 2). Five-year overall survival among patients with normal lactate dehydrogenase levels was 60%, 53%, and 34% in the nivolumab-plus-ipilimumab, nivolumab, and ipilimumab groups, respectively; among patients with elevated lactate dehydrogenase levels, these rates were 38%, 28%, and 15% (Fig. S3). Tumor PD-L1 expression alone was not predictive of efficacy outcomes (Figs. S4 and S5 and Table S3); this finding was consistent with previous results.[4]

RESPONSE

The rate of objective response among patients who were receiving trial therapy was 58% in the nivolumab-plus-ipilimumab group, 45% in the nivolumab group, and 19% in the ipilimumab group (Table 1). The rate of complete response was 22%, 19%, and 6%, respectively; all these rates of complete response had increased since the previous analysis.[4] At database lock, the median duration of response had not been reached in the nivolumab-plus-ipilimumab and nivolumab groups and was 14.4 months in the ipilimumab group, with ongoing responses at 5 years in 62%, 61%, and 40% of the patients with a response, respectively. The duration of response was sustained across stratification subgroups (according to *BRAF* mutation status, PD-L1 status, and metastasis stage).

OUTCOMES AFTER TREATMENT

As a part of the subsequent therapy received by patients for the management of progressive disease, 21%, 29%, and 40% of patients who were randomly assigned to nivolumab plus ipilimumab, nivolumab, and ipilimumab, respectively, received radiotherapy and 21%, 23%, and 30% underwent surgery. A total of 46%, 59%, and 75% of all patients who were randomly assigned to nivolumab plus ipilimumab, nivolumab, and ipilimumab, respectively, received subsequent systemic therapy (Table S4). Excluding patients who died and had not received subsequent therapy, the median time from randomization to subsequent systemic therapy was more than 60.0 months (median not reached) in the nivolumab-plus-ipilimumab group, 25.2 months in the nivolumab group, and 8.0 months in the ipilimumab group.

The assessment of the treatment-free interval from the last dose of the trial drug to subsequent systemic therapy or to the last known date alive excluded patients who discontinued trial follow-up or died before receiving subsequent systemic therapy. The median treatment-free interval was 18.1 months in the nivolumab-plus-ipilimumab group, 1.8 months in the nivolumab group, and 1.9 months in the ipilimumab group (Fig. 3A). In addition, of the patients who were alive at the time of the current analysis, the percentage who were not receiving trial treatment or subsequent systemic therapy was 74% in the nivolumab-plus-ipilimumab group, 58% in the nivolumab group, and 45% in the ipilimumab group (Fig. 3B). Survival outcomes at 5 years of follow-up were similar between patients who discontinued nivolumab plus ipilimumab because of treatment-related adverse events during the induction phase (Fig. S6) and the overall population (Fig. 1).

SAFETY

As expected in this long-term follow-up, the results of safety analyses (Tables S5 through S7) were similar to the previously reported results.[4] Grade 3 or 4 treatment-related adverse events occurred in 59%, 23%, and 28% of the patients in the nivolumab-plus-ipilimumab, nivolumab, and ipilimumab groups, respectively. The median time to resolution of treatment-related select adverse events in the various categories was generally less than 12 weeks, with the exception of skin-related adverse events in patients who received nivolumab, which resolved by a median of 40.6 weeks, and some events that had not yet resolved (primarily endocrine events, for which long-term hormonal therapy may be warranted). All treatment-related select adverse events that were unresolved at the time of the current analysis (regardless of time of onset) are listed in Table S8. In addition, no new deaths that were considered by the investigator to be related to a trial drug were reported (Table S9).[3,4] No previously unreported long-term toxic effects were noted.

HEALTH-RELATED QUALITY OF LIFE

The EQ-5D-3L standardized instrument was used to investigate health-related quality of life in the three treatment groups. Baseline rates of EQ-5D-3L completion were similar among the

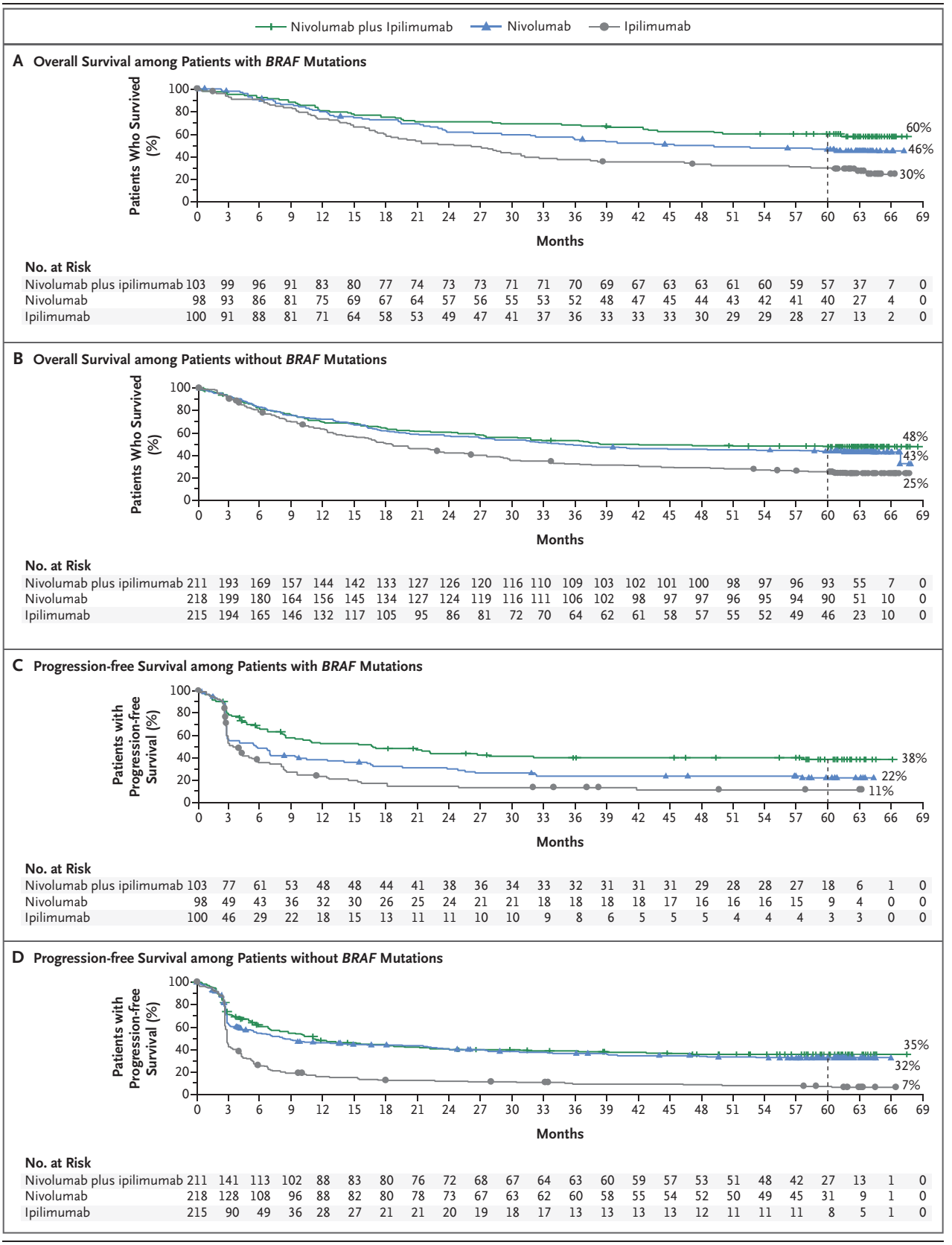

Figure 2 (facing page). Kaplan–Meier Estimates of Overall Survival and Progression-free Survival among Patients with or without *BRAF* Mutations.

Patients were followed for a minimum of 60 months (dashed lines). Symbols (tick marks, triangles, and circles) indicate censored data. The median overall survival among patients with *BRAF* mutations was longer than 60.0 months (95% CI, 50.7 to not reached) in the nivolumab-plus-ipilimumab group, 45.5 months (95% CI, 26.4 to not reached) in the nivolumab group, and 24.6 months (95% CI, 17.9 to 31.0) in the ipilimumab group (Panel A). The median overall survival among patients without *BRAF* mutations was 39.1 months (95% CI, 27.5 to not reached) in the nivolumab-plus-ipilimumab group, 34.4 months (95% CI, 24.1 to 59.2) in the nivolumab group, and 18.5 months (95% CI, 14.1 to 22.7) in the ipilimumab group (Panel B). The median progression-free survival among patients with *BRAF* mutations was 16.8 months (95% CI, 8.3 to 32.0) in the nivolumab-plus-ipilimumab group, 5.6 months (95% CI, 2.8 to 9.5) in the nivolumab group, and 3.4 months (95% CI, 2.8 to 5.2) in the ipilimumab group (Panel C). The median progression-free survival among patients without *BRAF* mutations was 11.2 months (95% CI, 7.0 to 18.1) in the nivolumab-plus-ipilimumab group, 8.2 months (95% CI, 5.1 to 19.6) in the nivolumab group, and 2.8 months (95% CI, 2.8 to 3.1) in the ipilimumab group (Panel D).

treatment groups and ranged from 88% to 92% (Table S10). As would be expected from rates of discontinuation of the trial treatment over time,[2,3] fewer than 10% of patients who underwent randomization were included in the assessment of health-related quality of life while receiving treatment after 3 years of trial follow-up; however, these patients continued to be followed for survival and would have been included in post-treatment assessments of health-related quality of life (after disease progression or discontinuation of the trial treatment).

According to published estimates for the EQ-5D-3L,[11] a change in quality of life was considered to be clinically meaningful if the mean changes from baseline in the index score were above (better) or below (worse) the bounds of 0.08.[10,11] For the duration of treatment, time after discontinuation of treatment for any reason, and the treatment-free interval, changes in the index score were generally within the 0.08 boundary in patients in the nivolumab-plus-ipilimumab and nivolumab treatment groups, indicating no meaningful sustained deterioration of health-related quality of life (Fig. S7). During follow-up for survival, deterioration outside the 0.08 boundary occurred more frequently in the ipilimumab monotherapy group than in the other treatment groups.

DISCUSSION

Historically, 5-year survival rates among patients with metastatic melanoma were dismal. Advances in basic science have produced meaningful therapeutic interventions for this disease in the areas of targeted oncogenic pathway inhibition and immune modulation. The current results of the CheckMate 067 trial set a new foundation on which to make improvements in long-term efficacy outcomes with the combination of nivolumab plus ipilimumab.

At 3 years after treatment initiation, a plateau on the survival curve was evident in the groups that received regimens containing nivolumab.[3,4] The apparent plateau with nivolumab plus ipilimumab has continued with longer follow-up; this indicates sustained long-term survival in approximately half the population of patients who received nivolumab plus ipilimumab, taking into account that subsequent therapies also had an effect on survival outcomes. Nivolumab plus ipilimumab is also currently the only treatment for metastatic melanoma for which median overall survival has not been reached at 5 years. In addition, complete response rates among patients receiving trial therapy have steadily increased across all groups since the original analysis[2]; this indicates that the best response can improve over time with immune checkpoint inhibitors. The treatment-free interval continued to lengthen in the nivolumab-plus-ipilimumab group, and the percentage of patients who were alive and not receiving treatment continued to increase across the groups. No new safety signals were observed, and no meaningful, sustained deterioration (i.e., limited fluctuations outside the 0.08 boundary) of health-related quality of life was observed during treatment or after discontinuation of treatment in the nivolumab-plus-ipilimumab and nivolumab monotherapy groups, although health-related quality of life deteriorated after discontinuation of ipilimumab.

This analysis from the CheckMate 067 trial showed that nivolumab-containing regimens were associated with a benefit with respect to overall survival and progression-free survival across patient subgroups. In addition, the analysis confirmed improved long-term clinical outcomes

Table 1. Response to Treatment.*

Variable	Nivolumab plus Ipilimumab (N=314)	Nivolumab (N=316)	Ipilimumab (N=315)
Best overall response — no. (%)†			
Complete response	69 (22)	60 (19)	18 (6)
Partial response	114 (36)	81 (26)	42 (13)
Stable disease	38 (12)	30 (9)	69 (22)
Progressive disease	74 (24)	121 (38)	159 (50)
Unable to determine	19 (6)	24 (8)	27 (9)
Objective response‡			
Patients with response			
No.	183	141	60
% (95% CI)	58 (53–64)	45 (39–50)	19 (15–24)
Estimated odds ratio (95% CI)§	6.35 (4.38–9.22)	3.54 (2.46–5.10)	—
P value§	<0.001	<0.001	—
Median duration of response (95% CI) — mo			
Intention-to-treat population	NR¶	NR (50.4–NR)	14.4 (8.3–53.6)
BRAF mutation status			
Patients with *BRAF* mutations	NR (21.0–NR)	55.0 (20.6–NR)	14.4 (6.9–NR)
Patients without *BRAF* mutations	NR (42.4–NR)	NR (50.4–NR)	19.2 (6.0–56.4)
Metastasis stage			
M10/M1a/M1b	NR (NR–NR)	NR (36.3–NR)	13.4 (6.0–31.3)
M1c	NR (15.8– NR)	NR (26.2–NR)	47.4 (5.1–NR)
PD-L1 expression level			
<5%	NR (40.1–NR)	NR (50.4–NR)	12.8 (5.3–53.6)
≥5%	NR (18.1–NR)	NR (26.7–NR)	31.3 (6.1–NR)
Lactate dehydrogenase level			
≤ULN	NR (44.0–NR)	NR (45.7–NR)	22.3 (6.9–56.4)
>ULN	NR (25.4–NR)	NR (13.8–NR)	11.6 (1.8–NR)
Patients with complete response	NR (NR–NR)	NR (NR–NR)	NR (13.3–NR)
Continued response — no. of patients/ total no. (%)	57/69 (83)	49/60 (82)	13/18 (72)
Patients with partial response	19.8 (10.2–NR)	25.1 (16.4–NR)	8.3 (4.2–14.4)
Continued response — no. of patients/ total no. (%)	56/114 (49)	37/81 (46)	11/42 (26)

* NR denotes not reached, PD-L1 programmed cell death ligand 1, and ULN upper limit of the normal range.
† The best overall response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
‡ Data included patients with a complete response and those with a partial response. The calculation of the 95% confidence interval was based on the Clopper–Pearson method.
§ The comparison is with the ipilimumab group.
¶ Although a median was reported in the previous analysis,[4] the estimate was immature and greater than the minimum trial follow-up.

with nivolumab plus ipilimumab (median overall survival, >60.0 months [median not reached]; 5-year overall survival, 60%) and nivolumab (median overall survival, 45.5 months; 5-year overall survival, 46%), as compared with ipilimumab, among patients with tumors with *BRAF* mutations.

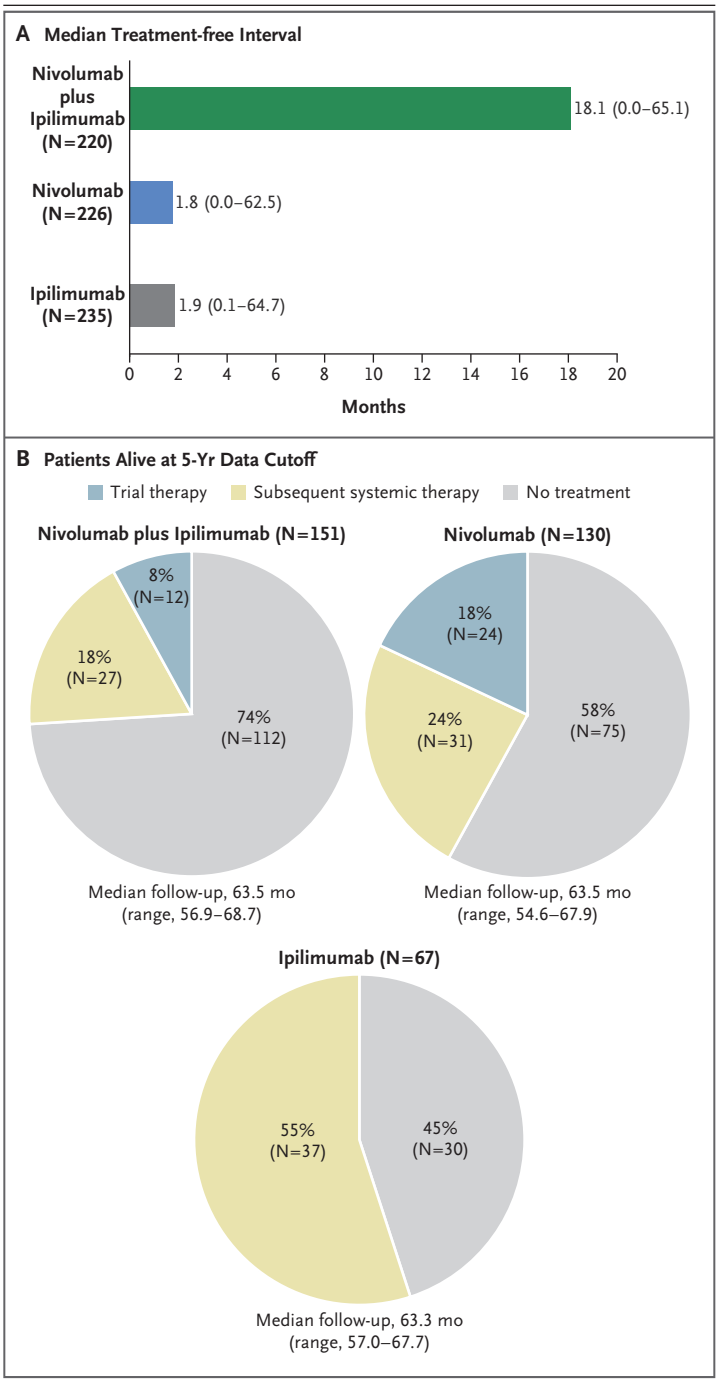

Figure 3. Analyses of the Treatment-free Interval and Outcomes after Treatment.

Panel A shows the median treatment-free interval in each treatment group. Among 313 patients who received treatment in the nivolumab-plus-ipilimumab group, 220 patients were included in the analysis of the treatment-free interval and 93 were excluded (12 were still receiving trial treatment, 53 had died and never received subsequent systemic therapy, and 28 were no longer in follow-up and had never received subsequent therapy). Among 313 patients who received treatment in the nivolumab group, 226 patients were included and 87 were excluded (24 were still receiving trial treatment, 45 had died and never received subsequent systemic therapy, and 18 were no longer in follow-up and had never received subsequent therapy). Among 311 treated patients in the ipilimumab group, 235 patients were included and 76 were excluded (57 had died and never received subsequent systemic therapy, and 19 were no longer in follow-up and had never received subsequent therapy). The duration of treatment was 3.6 months (range, 0.0 to 57.0) in the nivolumab-plus-ipilimumab group, 7.6 months (range, 0.0 to 62.9) in the nivolumab group, and 3.7 months (range, 0.0 to 49.9) in the ipilimumab group. Panel B shows the percentage of patients alive at the 5-year data cutoff date who were still receiving trial therapy, who were receiving subsequent systemic therapy, or who were not receiving trial therapy and had never received subsequent systemic therapy (no treatment).

The results of a pooled analysis of two phase 3 trials of combined BRAF and MEK inhibition with dabrafenib plus trametinib in patients with advanced melanoma and *BRAF* mutations were also reported recently. Those results showed a median overall survival of 25.9 months (95% CI, 22.6 to 31.5) and a 5-year overall survival of 34% (95% CI, 30 to 38).[12] Comparisons between studies of BRAF inhibitors and immune checkpoint inhibitors are not robust because of the many differences in the trial populations. Overall survival outcomes in the current analysis were also favorable for nivolumab plus ipilimumab and nivolumab in patients with normal lactate dehydrogenase levels and in those with elevated lactate dehydrogenase levels.

Consistent with previous analyses,[2-4] both treatments (the nivolumab-plus-ipilimumab combination and nivolumab monotherapy) led to better objective response rates, progression-free survival, and overall survival than ipilimumab, regardless of PD-L1 expression. However, the variations in efficacy results across PD-L1 cutoff values combined with the analysis of the diagnostic usefulness of PD-L1 (i.e., the time-dependent receiver-operating-characteristic analysis) suggest that tumor PD-L1 expression alone is a poor predictive marker of efficacy outcomes in this population, as reported previously.[3,4]

No new safety signals or additional treatment-related deaths were noted at this 5-year

follow-up. As reported previously,[4] the incidences of treatment-related adverse events and treatment-related discontinuation of therapy were higher with nivolumab plus ipilimumab than with either nivolumab or ipilimumab alone. However, overall survival and progression-free survival among patients who discontinued nivolumab plus ipilimumab because of a treatment-related adverse event during the induction phase were similar to the respective survival rates in the overall population; this indicates that early discontinuation due to an adverse event does not negatively affect long-term survival among these patients. The majority of treatment-related adverse events leading to discontinuation of nivolumab plus ipilimumab occurred early in treatment[2-4]; however, given the adoption of checkpoint blockade therapy, long-term follow-up of patients for the appearance of late-onset toxic effects is critical. In addition, studies of alternative dosing regimens involving patients with advanced melanoma are under way[13]; these studies may help to inform the safety profile of nivolumab plus ipilimumab and may also affect global value.

The evaluation of quality of life in patients receiving therapy for melanoma is also an important factor for both physicians and patients to consider. The EQ-5D-3L results from this 5-year analysis showed no sustained deterioration in health-related quality of life in the nivolumab-plus-ipilimumab or nivolumab monotherapy groups during or after treatment; these findings are consistent with those of previous analyses.[14] However, clinically meaningful deterioration was observed more frequently in the ipilimumab group than in the groups receiving nivolumab.

In conclusion, sustained long-term overall survival at 5 years was observed in a greater percentage of patients with advanced melanoma who received nivolumab plus ipilimumab or nivolumab alone than of those who received ipilimumab alone.

Supported by Bristol-Myers Squibb, a grant (P30CA008748, to Dr. Wolchok) from the National Cancer Institute, and a grant (to Dr. Larkin) from the National Institute for Health Research Royal Marsden–Institute of Cancer Research Biomedical Research Centre.

Dr. Larkin reports receiving grant support and consulting fees from Achilles Therapeutics, Bristol-Myers Squibb, Merck Sharp & Dohme, Nektar, Novartis, Pfizer, Roche–Genentech, and Immunocore and consulting fees from AstraZeneca, Boston Biomedical, Eisai, EUSA Pharma, GlaxoSmithKline, Ipsen, Imugen, Incyte, iOnctura, Kymab, Merck Serono, Pierre Fabre, Secama, Vitaccess, Covance, Aveo, and Pharmacyclics; Dr. Chiarion-Sileni, receiving support for meeting expenses from Bristol-Myers Squibb, advisory board fees from Merck Sharp & Dohme, Merck Serono, and Incyte, advisory board fees, lecture fees, and support for meeting expenses from Pierre Fabre, and lecture fees from Novartis; Dr. Gonzalez, receiving grant support and advisory board fees from Bristol-Myers Squibb, Roche–Genentech, Novartis, GlaxoSmithKline, Array BioPharma, Incyte, and NewLink Genetics, grant support from Merck, Takeda, Boston Biomedical, Checkmate Pharmaceuticals, Tesaro, Syndax, and Nektar, and grant support, consulting fees, and advisory board fees from Amgen; Dr. Grob, receiving advisory board fees and travel support from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Pierre Fabre and advisory board fees from Roche, Amgen, Sanofi, and Sun Pharmaceutical Industries; Dr. Rutkowski, receiving grant support, lecture fees, and advisory board fees from Bristol-Myers Squibb, lecture fees and advisory board fees from Merck Sharp & Dohme, Novartis, Pierre Fabre, and Eli Lilly, lecture fees from Roche and Pfizer, and advisory board fees from Blueprint Medicines; Dr. Lao, receiving research funding and travel support from Bristol-Myers Squibb, research funding from Genentech, Merck, Dynavax, and Novartis, and advisory board fees from Immunocore; Dr. Schadendorf, receiving consulting fees, advisory fees, honoraria, and travel support from Roche–Genentech and Merck Serono, grant support, consulting fees, advisory fees, honoraria, fees for serving on a speakers' bureau, and travel support from Novartis and Bristol-Myers Squibb, consulting fees, advisory fees, honoraria, and fees for serving on a speakers' bureau from Merck Sharp & Dohme, Incyte, and Pierre Fabre, consulting fees, advisory fees, honoraria, fees for serving on a speakers' bureau, and travel support from Amgen, consulting fees, advisory fees, and honoraria from Immunocore and 4SC, consulting fees and advisory fees from Mologen and Sanofi–Regeneron, fees for serving on a speakers' bureau from Roche, travel support from Merck, and honoraria from Sysmex, Grünenthal Group, Agenus, Array BioPharma, AstraZeneca, Leo Pharma, Pfizer, Philogen, Regeneron, and Mologen; Dr. Wagstaff, receiving honoraria, paid to his institution, and travel support from Bristol-Myers Squibb; Dr. Dummer, receiving consulting fees from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sun Pharmaceutical Industries, Takeda, and Sanofi; Dr. Ferrucci, receiving grant support, lecture fees, and advisory board fees from Bristol-Myers Squibb, lecture fees and advisory board fees from Merck Sharp & Dohme, Novartis, and Pierre Fabre, and lecture fees from Roche; Dr. Smylie, receiving honoraria from Bristol-Myers Squibb, Merck, Sanofi Genzyme, and Novartis; Dr. Hogg, receiving advisory board fees from Bristol-Myers Squibb, Roche, and Merck, grant support and advisory board fees from EMD Serono, and advisory board fees, lecture fees, and travel support from Novartis; Dr. Márquez-Rodas, receiving grant support, advisory board fees, lecture fees, and travel support from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Roche, grant support, advisory board fees, and lecture fees from Amgen, grant support and advisory board fees from Incyte, grant support, advisory board fees, and travel support from Bioncotech, and advisory board fees from Sanofi and Regeneron; Dr. Haanen, receiving advisory fees, paid to Netherlands Cancer Institute, from AstraZeneca, Celsius Therapeutics, Bayer, Merck Serono, Pfizer, GlaxoSmithKline, Immunocore, Seattle Genetics, Roche–Genentech, and Gadeta, and grant support and advisory fees, paid to Netherlands Cancer Institute, from Bristol-Myers Squibb, Merck Sharp & Dohme, Neon Therapeutics, and Novartis; Dr. Guidoboni, receiving advisory board fees from Bristol-Myers Squibb; Dr. Maio, receiving advisory board fees and lecture fees from Bristol-Myers Squibb, AstraZeneca, Roche, Merck Sharp & Dohme, and Merck Serono and advisory board fees from GlaxoSmithKline, Incyte, and Eli Lilly; Dr. Schöffski, receiving consulting fees, paid to his institution, from Plexxikon, Blueprint Medicines, Ellipses Pharma, Adaptimmune, and Transgene, advisory fees, paid to his institution, from Eisai, Loxo

Oncology, Lilly, Deciphera, Merck, Servier, Genmab, and Intellisphere, grant support from Boehringer Ingelheim, CoBioRes, G1 Therapeutics, and Novartis, grant support and advisory fees, paid to his institution, from Exelixis, and grant support and consulting fees, paid to his institution, from PharmaMar; Dr. Carlino, receiving advisory board fees from Merck Sharp & Dohme, Bristol-Myers Squibb, Pierre Fabre, Roche, and Ideaya; Dr. Lebbé, receiving advisory board fees and travel support from Bristol-Myers Squibb, Roche, and Merck Sharp & Dohme and advisory board fees from Novartis, Sanofi, and Merck Serono; Dr. McArthur, receiving grant support, paid to his institution, from Roche–Genentech, Merck Sharp & Dohme, Bristol-Myers Squibb, Array BioPharma, Amgen, and Pfizer; Dr. Ascierto, receiving grant support and consulting fees from Bristol-Myers Squibb, Roche–Genentech, and Array BioPharma, consulting fees and travel support from Merck Sharp & Dohme, and consulting fees from Novartis, Merck Serono, Pierre Fabre, Incyte, Genmab, NewLink Genetics, MedImmune, AstraZeneca, Syndax, Sun Pharmaceutical Industries, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, and 4SC; Dr. Long, receiving consulting fees from Aduro, Amgen, Array BioPharma, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Oncosec, and Roche; Dr. Bastholt, receiving advisory board fees from Bristol-Myers Squibb, Novartis, Merck Sharp & Dohme, Swedish Orphan, Bayer, and Incyte; Dr. Rizzo, being employed by Bristol-Myers Squibb; Drs. Balogh and Moshyk, being employed by and holding shares in Bristol-Myers Squibb; Dr. Hodi, receiving grant support, paid to his institution, consulting fees, and royalties, paid to his institution, from Bristol-Myers Squibb and Novartis, consulting fees from Merck, EMD Serono, Roche–Genentech, Bayer, Aduro, Partner Therapeutics, Sanofi, Pfizer, and Kairos, advisory board fees from Takeda, Surface Oncology, Compass Therapeutics, Verastem, and Rheos, advisory board fees from and holding equity in Apricity, Pionyr, Torque, and Bicara, advisory fees from 7 Hills Pharma, serving as a consultant for Psioxus Therapeutics, holding and receiving royalties for pending patent 20100111973 on methods for treating *MICA*-related disorders, holding patent 7250291 on tumor antigens and uses, patent 20170248603 on angiopoieten-2 biomarkers predictive of anti-immune checkpoint response, holding patent 20160340407 on compositions and methods for identification, assessment, prevention, and treatment of melanoma using programmed death ligand 1 isoforms, holding patents 20160046716 and 9402905 on therapeutic peptides, holding pending patents 20140004112, 20170022275, and 20170008962 on therapeutic peptides, holding a pending patent on methods of using pembrolizumab and trebananib, holding patent 10279021 on vaccine compositions and methods for restoring NKG2D pathway function against cancers, holding patent 10106611 on antibodies that bind to MHC class I polypeptide-related sequence A, and holding pending patent 20170343552 on antigalectin antibody biomarkers predictive of anti-immune checkpoint and anti-angiogenesis responses; and Dr. Wolchok, receiving consulting fees and holding stock options in Adaptive Biotechnologies, Apricity, Astellas, Beigene, Elucida, Imvaq, Serametrix, and Trieza, consulting fees from Advaxis, Array BioPharma, Bayer, Eli Lilly, F-star, Kleo Pharmaceuticals, Merck, Neon Therapeutics, Polaris Pharmaceuticals, Polynoma, PsiOxus, Puretech, Recepta, Sellas Life Sciences, Syndax, Northern Biologics, Kyowa Hakko Kirin, Syntalogic Pharmaceuticals, and Takara Bio, consulting fees and travel support from Amgen, Ascentage, Celgene, Chugai, Janssen, Ono Pharmaceutical, and Surface Oncology, grant support and consulting fees from Genentech, grant support, consulting fees, and travel support from MedImmune, consulting fees and travel support and holding stock options in Potenza Therapeutics, advisory board fees and travel support and holding stock options in Tizona Therapeutics, and honoraria from Esanex and grant support from Sephora, holding stock options in Linnaeus, holding and receiving royalties for patent 7556805 on xenogeneic DNA vaccines, licensed to Merial, holding pending patent PCT/US2010/030423 on alphavirus replicon particles expressing TRP2, holding patent PCT/US2013/027475 on a myeloid-derived suppressor-cell assay, licensed to Serametrix, holding pending patent PCT/US2014/020299 on Newcastle disease viruses for cancer therapy, holding pending patent PCT/US2014/072125 on a genomic signature to identify patients with a response to ipilimumab in melanoma, licensed to Gritstone, holding pending patent PCT/US2016/019663 on engineered vaccinia viruses for cancer immunotherapy, licensed to Imvaq, holding pending patent PCT/US2017/060064, for an anti-CD40 agonist monoclonal antibody fused to monophosphoryl lipid A for therapy for cancer, holding pending patent PCT/US2017/057098 on CAR+ T cells targeting differentiation antigens as a means to treat cancer, holding patent US 10144779 on anti-CTLA4 antibodies, licensed to Agenus, holding patents US 10155818 and US10280226 on anti–glucocorticoid-induced necrosis factor receptor antibodies and methods of use, licensed to Agenus–Incyte, holding patent US 10,323,091 on anti–programmed death 1 antibody, licensed to Agenus, holding pending patent PCT/US2016/063530 on identifying and treating patients at risk for checkpoint blockade, holding pending patent PCT/US2018/059337 on immunosuppressive follicular helper–like T cells modulated by immune responses, and holding pending patent PCT/US2019/022020 on agents that target phosphatidylserine and their uses. No other potential conflict of interest relevant to this article was reported.

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 investigators who participated in the CheckMate 067 trial; the staff at Ono Pharmaceutical for contributions to nivolumab development; the staff at Dako (an Agilent Technologies company) for collaborative development of the PD-L1 immunohistochemical 28-8 pharmDx assay; Fiona Taylor, Rachel Lawrance, and Alejandro Moreno-Koehler of Adelphi Values for the statistical analysis of patient-reported outcomes; and Melissa Kirk and Michele Salernitano of StemScientific (an Ashfield company) for professional medical writing and editorial assistance with an earlier version of the manuscript.

APPENDIX

The authors' full names and academic degrees are as follows: James Larkin, F.R.C.P., Ph.D., Vanna Chiarion-Sileni, M.D., Rene Gonzalez, M.D., Jean-Jacques Grob, M.D., Piotr Rutkowski, M.D., Ph.D., Christopher D. Lao, M.D., C. Lance Cowey, M.D., M.P.H., Dirk Schadendorf, M.D., John Wagstaff, M.D., Reinhard Dummer, M.D., Pier F. Ferrucci, M.D., Michael Smylie, M.D., David Hogg, M.D., Andrew Hill, M.D., Ivan Márquez-Rodas, M.D., Ph.D., John Haanen, M.D., Massimo Guidoboni, M.D., Michele Maio, M.D., Patrick Schöffski, M.D., Ph.D., Matteo S. Carlino, M.D., Céleste Lebbé, M.D., Ph.D., Grant McArthur, F.R.A.C.P., Ph.D., Paolo A. Ascierto, M.D., Gregory A. Daniels, M.D., Georgina V. Long, M.D., Lars Bastholt, M.D., Jasmine I. Rizzo, M.D., M.P.H., Agnes Balogh, M.Sc., Andriy Moshyk, M.D., F. Stephen Hodi, M.D., and Jedd D. Wolchok, M.D., Ph.D.

The authors' affiliations are as follows: the Royal Marsden NHS Foundation Trust, London (J.L.), and the College of Medicine, Swansea University, Swansea (J.W.) — both in the United Kingdom; the Oncology Institute of Veneto IRCCS, Padua (V.C.-S.), the European Institute of Oncology, IRCCS, Milan (P.F.F.), Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples (P.A.A.), the Immunotherapy and Somatic Cell Therapy Unit, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola (M.G.), and the

Center for Immuno-Oncology, Medical Oncology and Immunotherapy, University Hospital, Siena (M.M.) — all in Italy; the University of Colorado Cancer Center, Aurora (R.G.); Aix-Marseille University, Assistance Publique–Hôpitaux de Marseille Hôpital Timone, Marseille (J.-J.G.), and Université de Paris, INSERM Unité 976, Assistance Publique–Hôpitaux de Paris Dermatology and Centres d'Investigation Clinique, Saint Louis Hospital, Paris (C.L.) — both in France; the Maria Sklodowska-Curie Institute–Oncology Center, Warsaw, Poland (P.R.); the University of Michigan, Ann Arbor (C.D.L.); Texas Oncology–Baylor Charles A. Sammons Cancer Center, Dallas (C.L.C.); the Department of Dermatology, University of Essen, Essen, and the German Cancer Consortium, Heidelberg — both in Germany (D.S.); Universitäts Spital, Zurich, Switzerland (R.D.); Cross Cancer Institute, Edmonton, AB (M.S.), and the Princess Margaret Cancer Centre, Toronto (D.H.) — both in Canada; Tasman Oncology Research, Southport, QLD (A.H.), the Crown Princess Mary Cancer Centre, Melanoma Institute Australia, University of Sydney, Sydney, NSW (M.S.C., G.V.L.), and the Royal North Shore and Mater Hospitals (G.V.L.), Sydney, and the Peter MacCallum Cancer Centre, Melbourne, VIC (G.M.) — all in Australia; General University Hospital Gregorio Marañon and Centro de Investigación Biomédica en Red de Oncología, Madrid (I.M.-R.); the Netherlands Cancer Institute, Amsterdam (J.H.); the Leuven Cancer Institute, Department of General Medical Oncology, University Hospital Leuven, Leuven, Belgium (P.S.); University of California San Diego Health–La Jolla Moores Cancer Center, La Jolla (G.A.D.); the Department of Oncology, Odense University Hospital, Odense, Denmark (L.B.); Bristol-Myers Squibb, Princeton, NJ (J.I.R., A.B., A.M.); Dana–Farber Cancer Institute, Boston (F.S.H.); and the Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York (J.D.W.).

REFERENCES

1. Khair DO, Bax HJ, Mele S, et al. Combining immune checkpoint inhibitors: established and emerging targets and strategies to improve outcomes in melanoma. Front Immunol 2019;10:453.

2. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23-34.

3. 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.

4. 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.

5. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 2018;379:722-30.

6. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol 2018;19:672-81.

7. Regan MM, Werner L, Rao S, et al. Treatment-free survival: a novel outcome measure of the effects of immune checkpoint inhibition — a pooled analysis of patients with advanced melanoma. J Clin Oncol 2019 September 9 (Epub ahead of print).

8. Tarhini A, Benedict A, McDermott D, et al. Sequential treatment approaches in the management of *BRAF* wild-type advanced melanoma: a cost-effectiveness analysis. Immunotherapy 2018;10:1241-52.

9. Tarhini A, McDermott D, Ambavane A, et al. Clinical and economic outcomes associated with treatment sequences in patients with BRAF-mutant advanced melanoma. Immunotherapy 2019;11:283-95.

10. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-108.

11. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:70.

12. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med 2019;381:626-36.

13. Lebbé C, Meyer N, Mortier L, et al. Evaluation of two dosing regimens for nivolumab in combination with ipilimumab in patients with advanced melanoma: results from the phase IIIb/IV CheckMate 511 Trial. J Clin Oncol 2019;37:867-75.

14. Schadendorf D, Larkin JMG, Wolchok JD, et al. Patient-reported quality of life (QoL) of advanced melanoma in a phase 3 study of nivolumab (NIVO) with or without ipilimumab (IPI) versus IPI: CheckMate 067 4-year data. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, May 31–June 4, 2019:9551. abstract.