ORIGINAL ARTICLE

Final, 10-Year Outcomes with Nivolumab plus Ipilimumab in Advanced Melanoma

J.D. Wolchok, V. Chiarion-Sileni, P. Rutkowski, C.L. Cowey, D. Schadendorf, J. Wagstaff, P. Queirolo, R. Dummer, M.O. Butler, A.G. Hill, M.A. Postow, C. Gaudy-Marqueste, T. Medina, C.D. Lao, J. Walker, I. Márquez-Rodas, J.B.A.G. Haanen, M. Guidoboni, M. Maio, P. Schöffski, M.S. Carlino, S. Sandhu, C. Lebbé, P.A. Ascierto, G.V. Long, C. Ritchings, A. Nassar, M. Askelson, M.P. Benito, W. Wang, F.S. Hodi, and J. Larkin, for the CheckMate 067 Investigators*

ABSTRACT

BACKGROUND

Previous results from this trial showed longer overall survival after treatment with nivolumab plus ipilimumab or with nivolumab monotherapy than with ipilimumab monotherapy in patients with advanced melanoma. Given that patients with advanced melanoma are living longer than 7.5 years, longer-term data were needed to address new clinically relevant questions.

METHODS

We randomly assigned patients with previously untreated advanced melanoma, in a 1:1:1 ratio, to one of the following regimens: nivolumab (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 placebo; or ipilimumab (3 mg per kilogram) every 3 weeks for four doses plus placebo. Treatment was continued until the occurrence of disease progression, unacceptable toxic effects, or withdrawal of consent. Randomization was stratified according to *BRAF* mutation status, metastasis stage, and programmed death ligand 1 expression. Here, we report the final, 10-year results of this trial, including results for overall survival and melanoma-specific survival, as well as durability of response.

RESULTS

With a minimum follow-up of 10 years, median overall survival was 71.9 months with nivolumab plus ipilimumab, 36.9 months with nivolumab, and 19.9 months with ipilimumab. The hazard ratio for death was 0.53 (95% confidence interval [CI], 0.44 to 0.65) for nivolumab plus ipilimumab as compared with ipilimumab and was 0.63 (95% CI, 0.52 to 0.76) for nivolumab as compared with ipilimumab. Median melanoma-specific survival was more than 120 months with nivolumab plus ipilimumab (not reached, with 37% of the patients alive at the end of the trial), 49.4 months with nivolumab, and 21.9 months with ipilimumab. Among patients who had been alive and progression-free at 3 years, 10-year melanoma-specific survival was 96% with nivolumab plus ipilimumab, 97% with nivolumab, and 88% with ipilimumab.

CONCLUSIONS

The final trial results showed a continued, ongoing survival benefit with nivolumab plus ipilimumab and with nivolumab monotherapy, as compared with ipilimumab monotherapy, in patients with advanced melanoma. (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. Dr. Wolchok can be contacted at jwolchok@med.cornell.edu or at the Sandra and Edward Meyer Cancer Center, Weill Cornell Medicine, 413 E. 69th St., Belfer Research Bldg., BRB-1302, New York, NY 10021.

*The CheckMate 067 Investigators are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Hodi and Larkin contributed equally to this article.

This article was published on September 15, 2024, at NEJM.org.

DOI: 10.1056/NEJMoa2407417

For the past 15 years, immune checkpoint inhibitors — such as programmed death 1 (PD-1) inhibitors and anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) antibodies — have had a major effect on the treatment landscape for patients with advanced melanoma, contributing to markedly improved survival outcomes.[1-7] The development of ipilimumab, the only anti–CTLA-4 agent currently approved for the treatment of advanced melanoma, and the two anti–PD-1 antibodies, nivolumab and pembrolizumab, has been especially pivotal.[4-6]

In the phase 3 CheckMate 067 trial, after a minimum follow-up of 7.5 years, median overall survival was 72 months with nivolumab plus ipilimumab,[8] as compared with less than 12 months before 2011, when ipilimumab became commercially available.[9,10] Given that patients with advanced melanoma are living longer, new clinical questions have emerged. Clinically relevant outcomes now include overall survival, melanoma-specific survival, long-term outcomes among patients who had been alive and progression-free at 3 years, and patterns of first progression.

Some of these clinically relevant long-term outcomes have been assessed in the CheckMate 067 trial.[8,11,12] For example, 7.5-year melanoma-specific survival was numerically higher than 7.5-year overall survival in each trial group (55% vs. 48% with nivolumab plus ipilimumab, 47% vs. 42% with nivolumab, and 26% vs. 22% with ipilimumab).[8] In addition, among patients who had been alive and progression-free at 3 years, 7.5-year melanoma-specific survival was 98% with nivolumab plus ipilimumab, 97% with nivolumab, and 95% with ipilimumab.[12] Follow-up data obtained beyond 7.5 years provide a unique opportunity to inform post-treatment surveillance imaging and follow-up schedules, as well as to assess any unexpected effects of immune checkpoint blockade on aging-associated conditions.

Here, we report the final efficacy and safety results from the CheckMate 067 trial, with a minimum follow-up of 10 years. Specifically, this analysis examined overall survival, melanoma-specific survival, outcomes among patients who had been alive and progression-free at 3 years, and patterns of first progression.

METHODS

PATIENTS

We enrolled patients 18 years of age or older who had previously untreated, histologically confirmed, unresectable, advanced, stage III or stage IV melanoma, as well as known *BRAF* mutation status and an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability). Details of the trial design and the full eligibility criteria have been reported previously.[6,11,13-15]

TRIAL DESIGN, TREATMENT, AND END POINTS

In this double-blind, phase 3 trial, patients were randomly assigned, in a 1:1:1 ratio, to one of the following regimens: intravenous nivolumab (1 mg per kilogram of body weight) plus intravenous ipilimumab (3 mg per kilogram) once every 3 weeks for four doses (induction phase), followed by nivolumab (3 mg per kilogram) once every 2 weeks (maintenance phase); nivolumab (3 mg per kilogram) once every 2 weeks plus ipilimumab-matched placebo; or ipilimumab (3 mg per kilogram) once every 3 weeks for four doses plus nivolumab-matched placebo. In all trial groups, treatment was continued until the occurrence of disease progression, unacceptable toxic effects, or withdrawal of consent. After the completion of the primary efficacy analysis, the trial was unblinded and nivolumab-matched placebo was discontinued in the ipilimumab group. Randomization was stratified according to *BRAF* mutation status (wild-type vs. mutation), metastasis stage as classified in the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer (M0, M1a, or M1b vs. M1c), and programmed death ligand 1 (PD-L1) expression in the tumor (<5% or indeterminate vs. ≥5%). Patients with clinical benefit and without unacceptable toxic effects could receive treatment beyond the initial occurrence of disease progression, at the investigator's discretion.

The two primary end points were progression-free survival and overall survival in the nivolumab-plus-ipilimumab group as compared with the ipilimumab group and in the nivolumab group as compared with the ipilimumab group. Secondary end points were investigator-assessed objective response, which was uncon-

firmed; efficacy in the nivolumab-plus-ipilimumab group as compared with the nivolumab group, as assessed in descriptive analyses; and survival outcomes according to prespecified subgroups. The subgroups stratified according to the presence or absence of liver metastases at baseline were not prespecified. Exploratory end points included melanoma-specific survival; confirmed objective response; survival outcomes according to additional subgroups, including patients who had been alive and progression-free at 3 years; and patterns of first progression overall, as well as first progression occurring beyond 3 years and beyond 5 years. Details regarding the assessment of these end points are provided in the Supplementary Appendix (available with the full text of this article NEJM.org).

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 principles of the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Council for 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 and for the fidelity of the trial to the protocol. A data and safety monitoring committee provided oversight to assess the risk–benefit profile of nivolumab plus ipilimumab, as described previously.[6,13] Professional medical writing assistance was paid for by the sponsor.

STATISTICAL ANALYSIS

Efficacy end points were analyzed in the intention-to-treat population, and the formal analyses of the two primary end points were conducted at different prespecified time points, in accordance with the trial protocol.[6,13] The current analysis, performed after a minimum follow-up of 10 years, was conducted to assess long-term overall survival, progression-free survival, melanoma-specific survival (post hoc), and objective response with corresponding 95% confidence intervals; updates for objective response were included when an adequate number of patients at risk allowed. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. The trial was not designed or powered for a formal statistical comparison between the nivolumab-plus-ipilimumab group and the nivolumab group, but descriptive analyses were performed. In the post hoc analysis of melanoma-specific survival, an event was defined as death from melanoma; data for death from other causes were censored. Details regarding the statistical analysis are provided in the Supplementary Methods section of the Supplementary Appendix and have been reported previously.[6,11,13-15]

RESULTS

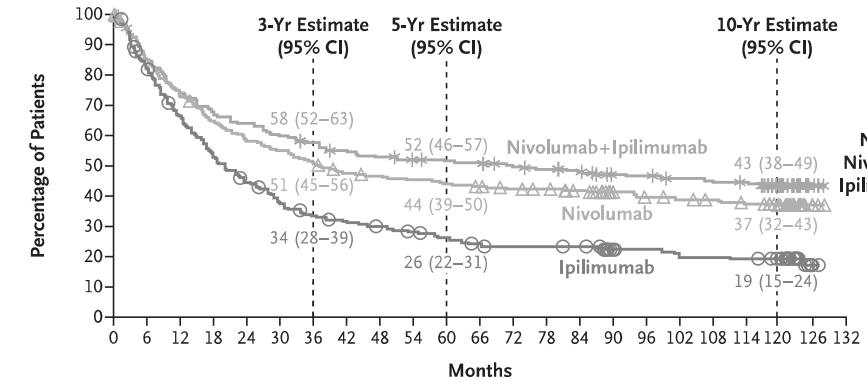
PATIENTS

From July 2013 through March 2014, a total of 1296 patients were enrolled at 137 centers worldwide. Of the 945 patients who underwent randomization, 314 were randomly assigned to the nivolumab-plus-ipilimumab group, 316 to the nivolumab group, and 315 to the ipilimumab group (Fig. S1 in the Supplementary Appendix). The characteristics of the patients at baseline were similar among the trial groups (Table S1). As of the final database lock on May 16, 2024, the minimum follow-up from the date that the last patient had undergone randomization was 120 months, with a median follow-up of 57.5 months (range, 0.1 to 128.1) in the nivolumab-plus-ipilimumab group, 36.0 months (range, 0.0 to 128.1) in the nivolumab group, and 18.6 months (range, 0.0 to 127.2) in the ipilimumab group. No patients were receiving the assigned treatment at the end of the trial (Table S2). The median treatment duration was 2.8 months (95% confidence interval [CI], 2.4 to 3.9; range, 0 to 123.8) in the nivolumab-plus-ipilimumab group, 6.6 months (95% CI, 5.2 to 9.7; range, 0 to 122.3) in the nivolumab group, and 3.0 months (95% CI, 2.6 to 3.7; range, 0 to 49.9) in the ipilimumab group.

SURVIVAL OUTCOMES

Overall survival was longer in the nivolumab-plus-ipilimumab group and in the nivolumab group than in the ipilimumab group (Fig. 1A). Median overall survival was 71.9 months (95% CI, 38.2 to 114.4) with nivolumab plus ipilimumab, 36.9

A Overall Survival



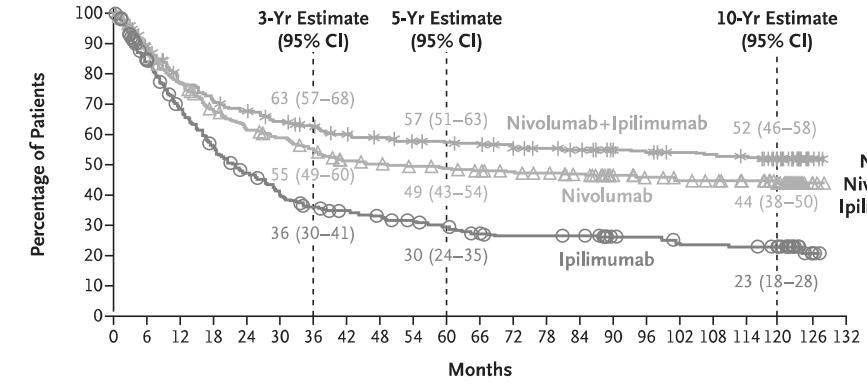
	No. of Patients with Event	Median Overall Survival (95% CI)
		mo
Nivo+Ipi (N=314)	173	71.9 (38.2–114.4)
Nivolumab (N=316)	192	36.9 (28.2–58.7)
Ipilimumab (N=315)	243	19.9 (16.8–24.6)

Hazard ratio for death, nivo+ipi vs. ipilimumab, 0.53 (95% CI, 0.44–0.65)
Hazard ratio for death, nivolumab vs. ipilimumab, 0.63 (95% CI, 0.52–0.76)
Hazard ratio for death, nivo+ipi vs. nivolumab, 0.85 (95% CI, 0.69–1.05)

No. at Risk

Nivo+ipi	314	265	227	210	199	187	179	169	163	158	156	153	147	144	139	126	124	120	117	115	92	10	0
Nivolumab	316	265	231	201	181	171	158	145	141	137	134	130	126	123	118	107	102	98	96	92	77	4	0
Ipilimumab	315	253	203	163	135	113	100	94	87	81	75	68	64	64	63	50	49	44	43	42	35	3	0

B Melanoma-Specific Survival



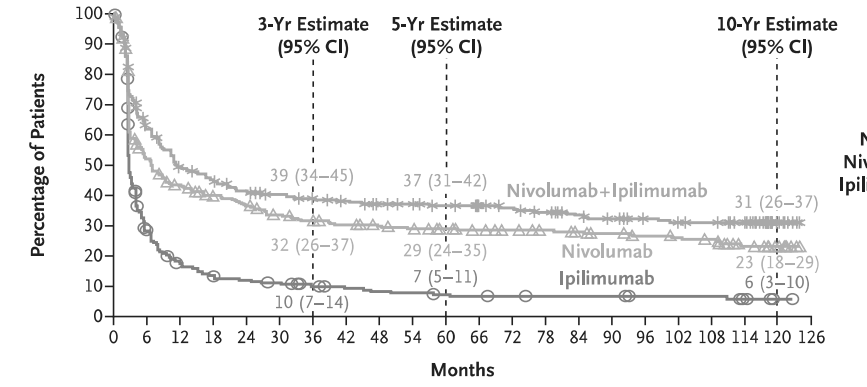
	No. of Patients with Event	Median Melanoma-Specific Survival (95% CI)
		mo
Nivo+Ipi (N=314)	139	NR (71.8–NR)
Nivolumab (N=316)	163	49.4 (35.1–119.4)
Ipilimumab (N=315)	221	21.9 (18.1–27.4)

Hazard ratio for death from melanoma, nivo+ipi vs. ipilimumab, 0.48 (95% CI, 0.39–0.59)
Hazard ratio for death from melanoma, nivolumab vs. ipilimumab, 0.59 (95% CI, 0.49–0.73)
Hazard ratio for death from melanoma, nivo+ipi vs. nivolumab, 0.81 (95% CI, 0.64–1.01)

No. at Risk

Nivo+ipi	314	265	227	210	199	187	179	169	163	158	156	153	147	144	139	126	124	120	117	115	92	10	0
Nivolumab	316	265	231	201	181	171	158	145	141	137	134	130	126	123	118	107	102	98	96	92	77	4	0
Ipilimumab	315	253	203	163	135	113	100	94	87	81	75	68	64	64	63	50	49	44	43	42	35	3	0

C Progression-free Survival



	No. of Patients with Event	Median Progression-free Survival (95% CI)
		mo
Nivo+Ipi (N=314)	192	11.5 (8.9–20.0)
Nivolumab (N=316)	212	6.9 (5.1–10.2)
Ipilimumab (N=315)	262	2.9 (2.8–3.1)

Hazard ratio for disease progression or death, nivo+ipi vs. ipilimumab, 0.42 (95% CI, 0.35–0.51)
Hazard ratio for disease progression or death, nivolumab vs. ipilimumab, 0.54 (95% CI, 0.45–0.65)
Hazard ratio for disease progression or death, nivo+ipi vs. nivolumab, 0.79 (95% CI, 0.65–0.96)

No. at Risk

Nivo+ipi	314	175	138	126	112	104	100	94	88	85	80	78	72	68	62	58	53	51	49	42	15	0
Nivolumab	316	151	120	106	97	84	78	73	69	66	62	58	55	52	49	45	42	40	38	24	12	0
Ipilimumab	315	78	46	34	31	28	21	18	16	15	13	12	11	10	10	10	8	8	8	4	1	0

Figure 1 (facing page). Overall Survival, Melanoma-Specific Survival, and Progression-free Survival in the Intention-to-Treat Population.

Panels A, B, and C show Kaplan–Meier estimates of overall survival, melanoma-specific survival, and progression-free survival, respectively, in the intention-to-treat population. Melanoma-specific survival was an exploratory end point. For progression-free survival, 38 events occurred across all three trial groups beyond 3 years of follow-up (19 new progressions, 2 deaths from melanoma without documented progression, and 17 deaths from nonmelanoma causes without documented progression); of these events, 21 occurred beyond 5 years of follow-up (8 new progressions, 2 deaths from melanoma without documented progression, and 11 deaths from nonmelanoma causes without documented progression). Symbols (tick marks, triangles, and circles) indicate censored data. Dashed lines indicate the minimum follow-up for the estimate. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. For the comparison of nivolumab plus ipilimumab with nivolumab, descriptive analyses were performed. NR denotes not reached.

months (95% CI, 28.2 to 58.7) with nivolumab, and 19.9 months (95% CI, 16.8 to 24.6) with ipilimumab. Overall survival at 10 years was 43% with nivolumab plus ipilimumab, 37% with nivolumab, and 19% with ipilimumab. The hazard ratio for death was 0.53 (95% CI, 0.44 to 0.65) for nivolumab plus ipilimumab as compared with ipilimumab and was 0.63 (95% CI, 0.52 to 0.76) for nivolumab as compared with ipilimumab. In a descriptive analysis, the hazard ratio for death was 0.85 (95% CI, 0.69 to 1.05) for nivolumab plus ipilimumab as compared with nivolumab.

Melanoma-specific survival was numerically longer in the nivolumab-plus-ipilimumab group and in the nivolumab group than in the ipilimumab group (Fig. 1B). Median melanoma-specific survival was more than 120 months (not reached [NR]; 95% CI, 71.8 to NR) with nivolumab plus ipilimumab (with 37% of the patients alive at the end of the trial), 49.4 months (95% CI, 35.1 to 119.4) with nivolumab, and 21.9 months (95% CI, 18.1 to 27.4) with ipilimumab. Melanoma-specific survival at 10 years was 52% with nivolumab plus ipilimumab, 44% with nivolumab, and 23% with ipilimumab. A summary of deaths for the entire trial period, including deaths from melanoma, is shown in Table S3. A total of 61 deaths were reported beyond 5 years of follow-up, with 39 of these deaths attributed to melanoma (13 in the nivolumab-plus-ipilimumab group, 11 in the nivolumab group, and 15 in the ipilimumab group) (Table S4).

Progression-free survival was largely unchanged, with survival curves plateauing after 3 years (Fig. 1C). Among all patients who had undergone randomization, the most common site of first progression was the lymph nodes (in 58 patients [18%] in the nivolumab-plus-ipilimumab group, 79 patients [25%] in the nivolumab group, and 111 patients [35%] in the ipilimumab group) (Table S5). The central nervous system was the site of first progression in 15 patients (5%) in the nivolumab-plus-ipilimumab group, 20 (6%) in the nivolumab group, and 28 (9%) in the ipilimumab group. Beyond 3 years of follow-up, 38 events occurred across all three trial groups (19 new progressions [Table S6], 2 deaths from melanoma without documented progression, and 17 deaths from nonmelanoma causes without documented progression); of these events, 21 occurred beyond 5 years of follow-up (8 new progressions [Table S7], 2 deaths from melanoma without documented progression, and 11 deaths from nonmelanoma causes without documented progression).

SURVIVAL OUTCOMES IN SUBGROUPS

At 10 years, both overall survival and melanoma-specific survival were longer in the nivolumab-plus-ipilimumab group and in the nivolumab group than in the ipilimumab group across subgroups stratified according to *BRAF* mutation status (Fig. 2 and Fig. 3) and PD-L1 expression (Fig. S2), as well as across other prespecified subgroups (Figs. S3A, S3B, S4A, and S4B). Furthermore, the benefits with respect to overall survival and melanoma-specific survival were similar with the two nivolumab-containing therapies but favored nivolumab plus ipilimumab over nivolumab to varying degrees across most subgroups (Figs. S3C and S4C).

Long-term outcomes were assessed among patients who had been alive and progression-free at 3 years (100 patients in the nivolumab-plus-ipilimumab group, 78 patients in the nivolumab group, and 21 patients in the ipilimumab group). The characteristics of these patients at baseline are shown in Table S8. Among these patients, overall survival at 10 years was 86% with

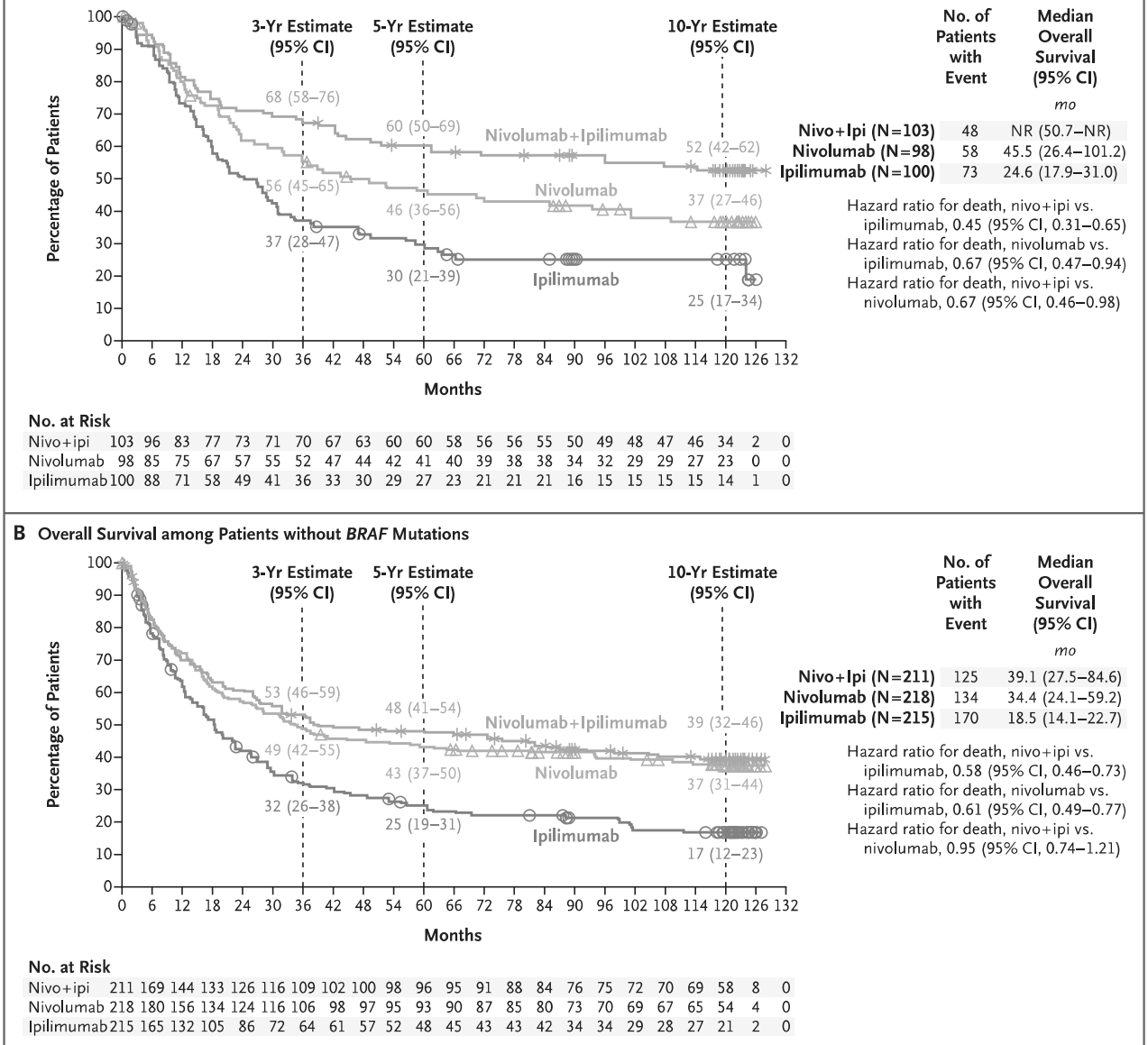


Figure 2. Overall Survival among Patients with or without *BRAF* Mutations.

Panels A and B show Kaplan–Meier estimates of overall survival in the intention-to-treat population among patients with *BRAF* mutations and among patients without *BRAF* mutations, respectively. Symbols (tick marks, triangles, and circles) indicate censored data. Dashed lines indicate the minimum follow-up for the estimate. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. For the comparison of nivolumab plus ipilimumab with nivolumab, descriptive analyses were performed.

nivolumab plus ipilimumab, 85% with nivolumab, and 79% with ipilimumab (Fig. 4A), and melanoma-specific survival at 10 years was 96% with nivolumab plus ipilimumab, 97% with nivolumab, and 88% with ipilimumab (Fig. 4B).

Among patients who had had at least one grade 3 or 4 treatment-related adverse event (an adverse event determined by the physician to be related to treatment) within the first 6 months of follow-up, overall survival from 6 months through 10 years was 49% with nivolumab plus ipilimumab, 62% with nivolumab, and 26% with ipilimumab (Fig. S5). In addition, among patients in the nivolumab-plus-ipilimumab group who had discontin-

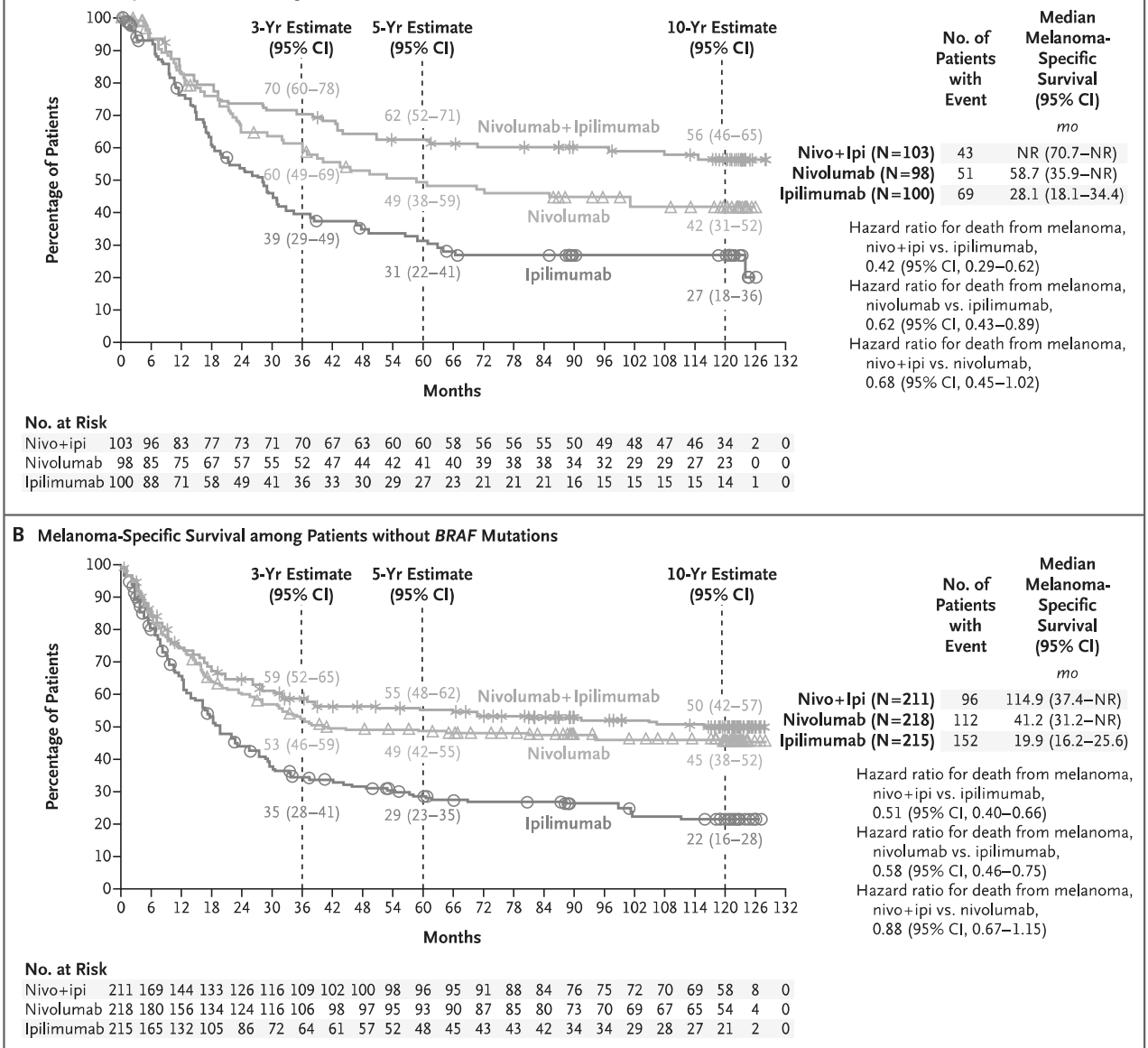


Figure 3. Melanoma-Specific Survival among Patients with or without *BRAF* Mutations.

Panels A and B show Kaplan–Meier estimates of melanoma-specific survival in the intention-to-treat population among patients with *BRAF* mutations and among patients without *BRAF* mutations, respectively. Melanoma-specific survival was an exploratory end point. Symbols (tick marks, triangles, and circles) indicate censored data. Dashed lines indicate the minimum follow-up for the estimate. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. For the comparison of nivolumab plus ipilimumab with nivolumab, descriptive analyses were performed.

ued treatment during the induction phase because of a treatment-related adverse event, overall survival from 6 months through 10 years was 43% and melanoma-specific survival from 6 months through 10 years was 50% (Fig. S6). Among patients who had received immune-modulating medication within the first 6 months of follow-up, melanoma-specific survival from 6 months through 10 years was 59% with nivolumab plus ipilimumab, 53% with nivolumab, and 27% with ipilimumab (Table S9). Among patients who had not received immune-modulating medication within the first 6 months, melanoma-specific survival from 6 months through 10 years was 56%

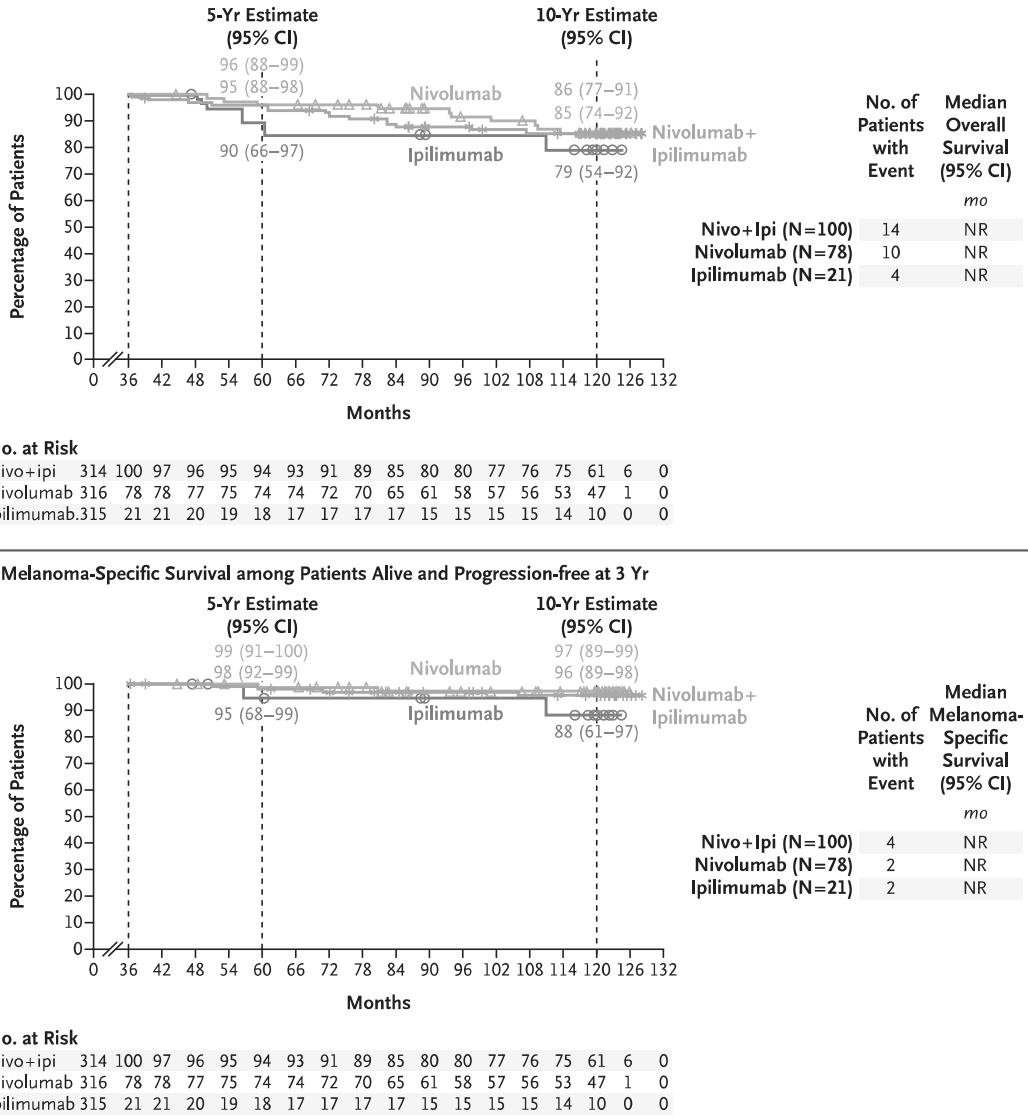


Figure 4. Overall Survival and Melanoma-Specific Survival among Patients Alive and Progression-free at 3 Years.

Panels A and B show Kaplan–Meier estimates of overall survival and melanoma-specific survival, respectively, in the intention-to-treat population among patients who had been alive and progression-free at 3 years. Melanoma-specific survival was an exploratory end point. Symbols (tick marks, triangles, and circles) indicate censored data. Dashed lines indicate the minimum follow-up for the estimate. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

with nivolumab plus ipilimumab, 46% with nivolumab, and 27% with ipilimumab.

RESPONSE

The percentage of patients who had an unconfirmed objective response was higher in the nivolumab-plus-ipilimumab group (58%) and in the nivolumab group (45%) than in the ipilimumab group (19%) (Table S10). The percentage of patients who had a confirmed objective response was also higher in the nivolumab-plus-ipilimumab group (50%) and in the nivolumab group (42%) than in the ipilimumab group (15%). The median duration of response was more than

120 months (NR; 95% CI, 68.2 to NR) in the nivolumab-plus-ipilimumab group, 103.2 months (95% CI, 45.7 to NR) in the nivolumab group, and 19.2 months (95% CI, 8.8 to 47.4) in the ipilimumab group (Fig. S7). In the nivolumab-plus-ipilimumab group, 56% of the patients had an ongoing response at the end of the trial, as compared with 55% of the patients in the nivolumab group and 37% of the patients in the ipilimumab group.

The best reduction in the tumor burden was greater in the nivolumab-plus-ipilimumab group and in the nivolumab group than in the ipilimumab group (Fig. S8A). Among patients across all three trial groups who had a depth of response of at least 80%, both median overall survival and median melanoma-specific survival were more than 120 months (NR) (Fig. S8B and S8C). In the nivolumab-plus-ipilimumab group, melanoma-specific survival at 10 years was 87% among patients with a depth of response of at least 80% and was 72% among patients with a depth of response of 50% to less than 80%; the corresponding results were 88% and 75%, respectively, in the nivolumab group and were 80% and 40% in the ipilimumab group.

SUBSEQUENT TREATMENT

Subsequent systemic therapy was received by 36% of the patients in the nivolumab-plus-ipilimumab group, 50% in the nivolumab group, and 67% in the ipilimumab group (Table S11). Subsequent local therapy (i.e., radiotherapy or surgery) was received by 46% of the patients in the nivolumab-plus-ipilimumab group, 56% in the nivolumab group, and 72% in the ipilimumab group. With the exclusion of patients who had died without receiving subsequent therapy, the median time to the initiation of subsequent systemic therapy was more than 120 months (NR; 95% CI, 45.9 to NR) with nivolumab plus ipilimumab, 23.9 months (95% CI, 12.1 to 34.8) with nivolumab, and 8.0 months (95% CI, 6.3 to 8.7) with ipilimumab. With the same patients excluded, subsequent systemic therapy–free survival at 10 years was 52% with nivolumab plus nivolumab, 37% with nivolumab, and 13% with ipilimumab.

SAFETY

Since the 5-year analysis, no new safety signals have been observed in any of the trial groups, and no new deaths related to treatment have occurred.[15] The final summary of treatment-related adverse events is shown in Table S12, and the time to the resolution of select treatment-related adverse events is shown in Table S13. The incidence of spontaneously reported late treatment-related adverse events (those occurring >100 days after treatment) was low across all trial groups (Table S14).

DISCUSSION

The historically bleak prognosis for patients with advanced melanoma has changed markedly since 2011, thanks to advances such as the availability of immune checkpoint inhibitors and oncogenic signaling pathway inhibitors. Previous analyses of the CheckMate 067 trial have shown the ability of the anti–PD-1 agent nivolumab, whether used alone or in combination with ipilimumab, to induce durable disease control in patients with advanced melanoma. The final, 10-year results of the CheckMate 067 trial continued to show improved survival outcomes with nivolumab plus ipilimumab and with nivolumab monotherapy, as compared with ipilimumab monotherapy, in patients with advanced melanoma. Specifically, 10-year overall survival was 43% with nivolumab plus ipilimumab and was 37% with nivolumab, as compared with 19% with ipilimumab.

With a minimum follow-up of 10 years, plateaus in the survival curves that had been observed 3 years after the initiation of treatment persisted in the nivolumab-plus-ipilimumab group and in the nivolumab group, and both overall survival and melanoma-specific survival were longer with nivolumab plus ipilimumab and with nivolumab monotherapy than with ipilimumab monotherapy. In a descriptive analysis, 10-year melanoma-specific survival was numerically higher with nivolumab plus ipilimumab than with nivolumab alone (52% and 44%, respectively). Both median melanoma-specific survival and the duration of response in the nivolumab-plus-ipilimumab group were more than 120 months (NR, with 37% of the patients alive at the end of the trial), findings that underscore the prolonged clinical benefit with nivolumab-plus-ipilimumab therapy. Furthermore, the nivolumab-plus-ipilimumab group continued to have a high level of control of disease spread to the central nervous system. This finding corroborates observations made in

other studies, including analyses involving patients with tumors that were positive for *BRAF* V600 mutations, thus supporting nivolumab plus ipilimumab as a preferred regimen for the prevention and treatment of brain metastases in melanoma.[16-19]

No new safety signals were observed with the additional follow-up in this trial. The majority of treatment-related adverse events had occurred earlier in the treatment course and had been managed with the use of established algorithms. Nivolumab plus ipilimumab was associated with more frequent and more severe adverse events than either monotherapy. However, a durable survival benefit was seen among patients who had had a grade 3 or 4 treatment-related adverse event within the first 6 months of follow-up, those in the nivolumab-plus-ipilimumab group who had discontinued treatment during the induction phase because of a treatment-related adverse event, and those who had received immune-modulating therapy within the first 6 months of follow-up. These results show that even with a shortened duration of therapy, long-term survival was possible.

Through 10 years, the results for melanoma-specific survival had continued to separate from the results for overall survival, more so in the nivolumab-plus-ipilimumab group (52% vs. 43%) and in the nivolumab group (44% vs. 37%) than in the ipilimumab group (23% vs. 19%). This trend suggests that the patients with advanced melanoma were living long enough to die from other causes, as well as that 10 years of follow-up was adequate for assessing the oncologic survival benefits of immunotherapy while limiting the confounding effects of competing causes of death. In fact, beyond 5 years of follow-up, the number of total deaths (61 in 937 patients; 7%) and the number of melanoma-specific deaths (39 in 937 patients; 4%) were low. Furthermore, among patients who had been alive and progression-free at 3 years, 10-year melanoma-specific survival was 96% with nivolumab plus ipilimumab, 97% with nivolumab, and 88% with ipilimumab. The sustained benefit of immune checkpoint inhibitors observed over the extensive follow-up period in this trial highlights the potential for cure in patients with advanced melanoma who have a response to this type of treatment.

Subsequent systemic therapy was administered less frequently in the nivolumab-plus-ipilimumab group (36%) than in the nivolumab group (50%) or in the ipilimumab group (67%), with a median time to the initiation of subsequent systemic therapy of more than 120 months (NR) with nivolumab plus ipilimumab. With the exclusion of patients who had died and had never received subsequent systemic therapy, 10-year subsequent systemic therapy–free survival was 52% in the nivolumab-plus-nivolumab group, 37% in the nivolumab group, and 13% in the ipilimumab group. It is notable that 26% of the patients in the nivolumab group went on to receive ipilimumab-containing therapy of some form; however, this trial did not assess crossover to ipilimumab-containing therapy at the time of progression among patients receiving first-line nivolumab monotherapy, and thus, the effects of crossover on survival outcomes are difficult to determine.

The percentage of patients who had been alive and progression-free at 3 years was higher in the nivolumab-plus-ipilimumab group (32%) and in the nivolumab group (25%) than in the ipilimumab group (7%). These patients had a remarkably stable clinical benefit with nivolumab-containing therapies, with a 10-year melanoma-specific survival of at least 96%. These results suggest that progression-free survival at 3 years is a surrogate marker of long-term disease-specific survival in patients with advanced melanoma who are treated with immune checkpoint inhibitors. A best reduction in the tumor burden of at least 80% appears to be another surrogate marker of long-term survival; among patients who met this benchmark, 10-year melanoma-specific survival was 87% with nivolumab plus ipilimumab, 88% with nivolumab, and 80% with ipilimumab. These findings may help to inform the appropriate frequency of surveillance imaging for new progression or lesions among such patients.

The survival benefits seen with nivolumab-containing therapies, as compared with ipilimumab monotherapy, persisted across all examined subgroups, including those stratified according to PD-L1 expression and *BRAF* mutation status. Melanoma-specific survival at 10 years favored nivolumab plus ipilimumab over nivolumab monotherapy among patients with PD-L1 expression of at least 5% (59% vs. 54%) and among those with PD-L1 expression of less than 5% (50% vs. 43%). Melanoma-specific survival at 10 years also favored nivolumab plus ipilimumab over nivolu-

mab monotherapy among patients with *BRAF* wild-type tumors (50% vs. 45%); among patients with tumors that were positive for *BRAF* V600 mutations, the difference between the nivolumab-plus-ipilimumab group and the nivolumab group was more pronounced (56% vs. 42%). This clinical observation is supported by translational studies describing an overrepresentation of interleukin-17–expressing helper T-cell gene-expression signatures in *BRAF* V600–mutated tumors, which is associated with clinical benefit from dual CTLA-4 and PD-1 checkpoint inhibition.[20]

Despite the progress made in the treatment of advanced melanoma in the past 15 years, important gaps remain, including the higher incidence of treatment-related adverse events observed with ipilimumab-containing therapies than with nivolumab monotherapy. Emerging treatments, such as combination therapy with anti–PD-1 and anti–lymphocyte-activation gene 3 (LAG-3) agents, may offer efficacy similar to that of ipilimumab-containing therapies but with fewer unacceptable side effects.[7,21] Furthermore, even with available combination therapy with immune checkpoint inhibitors, approximately 40% of patients do not have a response to treatment, and half die from melanoma. Triplet therapy with anti–CTLA-4, anti–PD-1, and anti–LAG-3 agents may be more effective than the available combination therapies, as suggested by the 48-month overall survival of 72% with triplet therapy in the RELATIVITY-048 trial[22]; however, larger studies are needed to confirm these data. The development of new treatments, such as improved targeted therapies, personalized vaccines, and adoptive cell transfer therapy, offers opportunities to enhance long-term outcomes in patients with advanced melanoma.

As compared with ipilimumab monotherapy, nivolumab-containing therapies have continued to show a prolonged survival benefit in patients with advanced melanoma, with no new safety signals. These 10-year data underscore how immune checkpoint inhibitor therapy has helped to change the long-term prognosis for patients with advanced melanoma and highlight the potential for a cure in patients who have a response to this type of treatment.

Supported by Bristol Myers Squibb, a grant from the National Cancer Institute (P30CA008748, to Dr. Postow), and a grant from the National Institute for Health Research Biomedical Research Centre at the Royal Marsden National Health Service Foundation Trust and the Institute of Cancer Research (to Dr. Larkin).

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 who participated in the trial; Ono Pharmaceutical Company (Osaka, Japan) for contributions to the development of nivolumab; Dako (an Agilent Technologies company in Santa Clara, CA) for collaborative development of the PD-L1 immunohistochemical assay 28-8 pharmDx; and Adam J. Santanasto and Michele Salernitano of Ashfield MedComms (an Inizio company) for professional medical writing and editorial assistance with earlier drafts of the article.

We dedicate this article to the memory of our esteemed colleague Dr. Jeffrey Weber, a true leader in the field of melanoma immunotherapy who importantly served on the safety monitoring committee for the phase 1 trial, which led to CheckMate 067.

APPENDIX

The authors' full names and academic degrees are as follows: Jedd D. Wolchok, M.D., Ph.D., Vanna Chiarion-Sileni, M.D., Piotr Rutkowski, M.D., Ph.D., C. Lance Cowey, M.D., M.P.H., Dirk Schadendorf, M.D., John Wagstaff, M.D., Paola Queirolo, M.D., Reinhard Dummer, M.D., Marcus O. Butler, M.D., Andrew G. Hill, M.D., Michael A. Postow, M.D., Caroline Gaudy-Marqueste, M.D., Ph.D., Theresa Medina, M.D., Christopher D. Lao, M.D., John Walker, M.D., Iván Márquez-Rodas, M.D., Ph.D., John B.A.G. Haanen, M.D., Ph.D., Massimo Guidoboni, M.D., Michele Maio, M.D., Ph.D., Patrick Schöffski, M.D., Ph.D., Matteo S. Carlino, M.D., Shahneen Sandhu, M.D., Céleste Lebbé, M.D., Ph.D., Paolo A. Ascierto, M.D., Georgina V. Long, M.D., Ph.D., Corey Ritchings, Pharm.D., Ayman Nassar, M.B., B.S., Margarita Askelson, M.S., Melanie Pe Benito, M.Sc., Wenjia Wang, Ph.D., F. Stephen Hodi, M.D., and James Larkin, F.R.C.P., Ph.D.

The authors' affiliations are as follows: the Sandra and Edward Meyer Cancer Center (J.D.W.) and the Department of Medicine (J.D.W., M.A.P.), Weill Cornell Medicine, and Memorial Sloan Kettering Cancer Center (M.A.P.) — both in New York; Istituto Oncologico Veneto, IRCCS, Padua (V.C.-S.), European Institute of Oncology, IRCCS, Milan (P.Q.), Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, IRCCS, Meldola (M.G.), University of Siena and the Center for Immuno-Oncology, University Hospital of Siena, Siena (M.M.), and Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples (P.A.A.) — all in Italy; Maria Sklodowska-Curie National Institute of Oncology, Warsaw, Poland (P.R.); Texas Oncology–Baylor Charles A. Sammons Cancer Center, Dallas (C.L.C.); University Hospital Essen, the German Cancer Consortium, the National Center for Tumor Diseases–West, the Research Alliance Ruhr, Research Center One Health, and University Duisburg-Essen — all in Essen, Germany (D.S.); the College of Medicine, Swansea University, Swansea (J.W.), Bristol Myers Squibb, Uxbridge (A.N.), and the Royal Marsden Hospital, London (J.L.) — all in the United Kingdom; the Department of Dermatology, University of Zurich, Zurich, Switzerland (R.D.); University Health Network Princess Margaret Cancer Centre, Toronto (M.O.B.), and Cross Cancer Institute, University of Alberta, Edmonton (J.W.) — both in Canada; Tasman Oncology Research, Southport, QLD (A.G.H.), Westmead Hospital, Westmead, NSW (M.S.C.), Blacktown Hospital, Blacktown, NSW (M.S.C.), the Melanoma Institute Australia, University of Sydney (M.S.C., G.V.L.), Royal North Shore Hospital (G.V.L.), and Mater Hospital (G.V.L.), Sydney, and Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, VIC (S.S.) — all in Australia; Aix-Marseille Université, Assistance Publique–Hôpitaux de Marseille, Marseille (C.G.-M.), and Université Paris Cité, Assistance Publique–Hôpitaux de Paris (AP-HP) Dermato-oncology, Clinical Investigation Center, the Cancer Institute, AP-HP Nord Paris Cité, INSERM

Unité 976, and St. Louis Hospital, Paris (C.L.) — all in France; the University of Colorado Cancer Center, Aurora (T.M.); Rogel Cancer Center, University of Michigan, Ann Arbor (C.D.L.); Hospital General Universitario Gregorio Marañon, Madrid (I.M-R.); the Netherlands Cancer Institute, Amsterdam (J.B.A.G.H.); University Hospital Leuven and Leuven Cancer Institute, KU Leuven, Leuven, Belgium (P.S.); Bristol Myers Squibb, Princeton, NJ (C.R., M.A., M.P.B., W.W.); and Dana–Farber Cancer Institute, Boston (F.S.H.).

REFERENCES

1. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.
2. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372:2006-17.
3. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol 2015;33:1889-94.
4. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without *BRAF* mutation. N Engl J Med 2015;372:320-30.
5. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372:2521-32.
6. 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.
7. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med 2022;386:24-34.
8. Hodi FS, Chiarion-Sileni V, Lewis KD, et al. Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. J Clin Oncol 2022;40:Suppl:9522. poster.
9. Agarwala SS. Current systemic therapy for metastatic melanoma. Expert Rev Anticancer Ther 2009;9:587-595.
10. Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. N Engl J Med 2004;351:998-1012.
11. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol 2022; 40:127-37.
12. Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Durable clinical outcomes in patients (pts) with advanced melanoma and progression-free survival (PFS) ≥3y on nivolumab (NIVO) ± ipilimumab (IPI) or IPI in CheckMate 067. J Clin Oncol 2023; 41:Suppl:9542. poster.
13. 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.
14. 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.
15. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2019;381:1535-46.
16. 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.
17. Tawbi HA, Forsyth PA, Hodi FS, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. Lancet Oncol 2021;22:1692-704.
18. Ascierto PA, Casula M, Bulgarelli J, et al. Sequential immunotherapy and targeted therapy for metastatic *BRAF* V600 mutated melanoma: 4-year survival and biomarkers evaluation from the phase II SECOMBIT trial. Nat Commun 2024;15: 146.
19. Atkins MB, Lee SJ, Chmielowski B, et al. Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced *BRAF*-mutant melanoma: the DREAMseq trial — ECOG-ACRIN EA6134. J Clin Oncol 2023;41:186-97.
20. Váraljai R, Zimmer L, Al-Matary Y, et al. Interleukin 17 signaling supports clinical benefit of dual CTLA-4 and PD-1 checkpoint inhibition in melanoma. Nat Cancer 2023;4:1292-308.
21. Schadendorf D, Tawbi HA, Lipson EJ, et al. Efficacy and safety of first-line (1L) nivolumab plus relatlimab (NIVO + RELA) versus NIVO plus ipilimumab (NIVO + IPI) in advanced melanoma: an updated indirect treatment comparison (ITC). J Clin Oncol 2024;42:Suppl:9557. poster.
22. Ascierto PA, Dummer R, Gaudy-Marqueste C, et al. Efficacy and safety of triplet nivolumab, relatlimab, and ipilimumab (NIVO + RELA + IPI) in advanced melanoma: results from RELATIVITY-048. J Clin Oncol 2024;42:Suppl:9504. abstract.