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

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, MS.,

Jedd D. Wolchok, M.D., Ph.D, FAACR, FASCO, Sandra and Edward Meyer Cancer Center and Weill Cornell Medicine, 413 East 69th St (Belfer Research Building), BRB-1302, New York, NY, 10021, jwolchok@med.cornell.edu.
Stephen Hodi and James Larkin contributed equally to this work.
*Affiliation at the time of the study.

We dedicate this manuscript 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 I trial which led to CheckMate-067

Melanie Pe Benito, MSc.,

Wenjia Wang, Ph.D,

F. Stephen Hodi, M.D.,

James Larkin, FRCP, Ph.D.,

CheckMate 067 investigators.

The Sandra and Edward Meyer Cancer Center and Weill Cornell Medicine, New York (J.D.W.); Veneto Institute of Oncology IOV-IRCCS, Padua, Italy (V.C.-S.); 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 (NCT-West), the Research Alliance Ruhr, Research Center One Health, and University Duisburg-Essen, all Essen, Germany (D.S.); the College of Medicine, Swansea University, Swansea, United Kingdom (J.W.); European Institute of Oncology, IRCCS, Milan, Italy (P.Q.); Department of Dermatology, University of Zurich, Zurich, Switzerland (R.D.); University Health Network Princess Margaret Cancer Centre, Toronto, Canada (M.O.B.); Tasman Oncology Research, Southport, Australia (A.G.H.); Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York (M.A.P.); Aix-Marseille Université, AP-HM, Marseille, France (C.G.-M.); University of Colorado Cancer Center, Aurora (T.M.); University of Michigan, Rogel Cancer Center, Ann Arbor (C.D.L.)*; University of Alberta, Cross Cancer Institute, Alberta, Canada (J.W.); Hospital General Universitario Gregorio Marañon, Madrid, Spain (I.M-R.); the Netherlands Cancer Institute, Amsterdam (J.B.A.G.H.); Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, IRCCS, Meldola, Italy (M.G.); University of Siena, Center for Immuno-Oncology, University Hospital, Siena, Italy (M.M.); University Hospital Leuven, Leuven Cancer Institute, KU Leuven, Leuven, Belgium (P.S.); Westmead Hospital, Blacktown Hospital, University of Sydney, Melanoma Institute Australia, Sydney, Australia (M.S.C.); Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Australia (S.S.); Université Paris Cite, AP-HP Dermato-oncology and CIC, Cancer institute APHP.nord Paris cité, INSERM U976, Saint Louis Hospital, Paris, France (C.L.); Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy (P.A.A.); Melanoma Institute Australia, the University of Sydney, Royal North Shore Hospital, and Mater Hospital, all Sydney, Australia (G.V.L.); Bristol Myers Squibb, Princeton (C.R.); Bristol Myers Squibb, Uxbridge, United Kingdom (A.N.); Bristol Myers Squibb, Princeton (M.A., M.P.B., W.W.); Dana-Farber Cancer Institute, Boston (F.S.H.); and The Royal Marsden Hospital, London, United Kingdom (J.L.).

Abstract

Background: The phase 3 CheckMate 067 trial has demonstrated improved survival with nivolumab-plus-ipilimumab or nivolumab monotherapy compared with ipilimumab monotherapy in patients with advanced melanoma. Here, we report the final, 10-year results from the trial.

Methods: Patients with previously untreated advanced melanoma (N=945) were randomized 1:1:1, stratified by PD-L1 expression status, *BRAF* mutation status, and metastasis stage, to receive nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) Q3W for four doses, followed by nivolumab (3 mg/kg) Q2W; nivolumab (3 mg/kg) Q2W plus placebo; or ipilimumab (3 mg/kg) plus placebo Q3W for four doses. Treatment continued until disease progression, unacceptable

toxicity, or consent withdrawal. Here, we report overall and melanoma-specific survival, as well as durability of response.

Results: After a minimum of 10-years of follow-up, 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 (95% CI) for death was 0.53 (0.44 to 0.65) with nivolumab-plus-ipilimumab versus ipilimumab and 0.63 (0.52 to 0.76) for nivolumab versus ipilimumab. Median melanoma-specific survival was >120 months (not reached, with 37.1% of patients alive at study closeout [May 16, 2024 – minimum 120-month follow-up]) with nivolumab-plus-ipilimumab, 49.4 months with nivolumab, and 21.9 months with ipilimumab. In patients who were progression-free at 3-years, 10-year melanoma-specific survival rates were 96% with nivolumab-plus-ipilimumab, 97% with nivolumab, and 88% with ipilimumab.

Conclusions: Final results from CheckMate 067 demonstrated a continued, ongoing survival benefit with nivolumab-containing therapies versus ipilimumab monotherapy. (Funded by Bristol Myers Squibb, and others. ClinicalTrials.gov number, NCT01844505.)

Introduction

Over the past 15-years, immune checkpoint inhibitors (such as anti-programmed death 1 [PD-1] inhibitors and anti–cytotoxic T-lymphocyte–associated antigen 4 [CTLA-4] antibodies) have had a major impact on the treatment landscape for patients with advanced melanoma, contributing to markedly improved survival outcomes.[1–7] In particular, 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, have been especially pivotal.[4–6] In the phase 3 CheckMate 067 trial, after a minimum of 7.5 years of follow-up, the overall survival rate of patients randomized to receive nivolumab-plus-ipilimumab was 48%.[8] Because patients with advanced melanoma are demonstrating longer survival times, compared with data before 2011 (when ipilimumab became commercially available), new clinical questions have emerged. Clinically relevant outcomes now include overall survival, melanoma-specific survival, long-term outcomes in patients who were progression-free at 3-years, and patterns of early versus delayed first progressions.

Analyses from CheckMate 067 have begun to examine some of these clinically relevant long-term outcomes.[8–10] For example, 90-month melanoma-specific survival rates were numerically higher than overall survival rates within each treatment group (55% vs. 48% with nivolumab-plus-ipilimumab; 47% vs. 42% with nivolumab; 26% vs. 22% with ipilimumab).[8] Additionally, in patients who were progression-free at 3-years, 7.5-year melanoma-specific survival rates were 98% with nivolumab-plus-ipilimumab, 97% with nivolumab, and 95% with ipilimumab.[10] Follow-up beyond 7.5 years is a unique opportunity to inform post-treatment surveillance imaging and follow-up schedules as well as to any unexpected effects of immune checkpoint blockade on aging-associated conditions.

Here, we report the final efficacy, post-treatment, and safety results from CheckMate 067 after a minimum of 10 years of follow-up. Specifically, these analyses examined melanoma-

specific survival, outcomes in those who were progression-free at 3-years, and patterns of early versus late first progressions.

Methods

Patients

Eligible patients were aged ≥18 years; had previously untreated, histologically confirmed, unresectable, advanced, stage III or stage IV melanoma; known *BRAF* V600 mutation status; and an Eastern Cooperative Oncology Group performance status of 0 or 1 (a 5-point scale where higher numbers reflect greater disability). Full study design and eligibility criteria have been described previously.[6, 9,11–13]

Trial Design, Treatment, and Assessments

CheckMate 067 was a double-blind, phase 3 study in which patients were randomized 1:1:1 to receive intravenous nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks (Q3W) for four doses (induction phase), followed by nivolumab 3 mg/kg once every 2 weeks (Q2W, maintenance phase); nivolumab 3 mg/kg Q2W (plus ipilimumab-matched placebo); or ipilimumab 3 mg/kg Q3W for four doses (plus nivolumab-matched placebo). Treatment in all arms continued until disease progression, development of unacceptable toxicity, or consent withdrawal. Following completion of the primary efficacy analysis, the study was unblinded and nivolumab placebo was stopped in the ipilimumab arm. Randomization was stratified by *BRAF* mutation status, American Joint Committee on Cancer 7th edition metastatic stage (M0, M1a, or M1b vs. M1c), and tumor programmed cell death ligand 1 (PD-L1) status (<5% or indeterminate vs. ≥5%). At the investigator's discretion, based on clinical benefit and treatment tolerance, treatment may have been continued beyond initial disease progression.

Co-primary end points were investigator-assessed progression-free survival and overall survival, comparing the nivolumab-containing groups versus the ipilimumab group. Secondary endpoints included investigator-assessed objective response rate (unconfirmed), descriptive evaluations of efficacy between the nivolumab-containing groups and efficacy by prespecified subgroups shown in forest plots (except baseline liver metastases, which was a post-hoc analysis). Exploratory post hoc analyses included melanoma-specific survival; confirmed objective response rate; efficacy according to additional subgroups; and patterns of first progressions overall and after 36 and 60 months. Details regarding these assessments are in the Supplementary Appendix.

Study Oversight

The protocol and amendments for this trial (available at NEJM.org) were reviewed by the institutional review board at each trial site. All patients provided written informed consent before enrollment, and the trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice as defined by the International Conference on Harmonization. CheckMate 067 was designed by the senior academic authors and Bristol Myers Squibb (the sponsor). Data were collected by the sponsor and analyzed in collaboration with the authors, and the authors confirm adherence to the protocol and

vouch for the completeness and accuracy of the data and analyses. A data and safety monitoring committee provided oversight to assess the risk–benefit profile of nivolumab-plus-ipilimumab, as described previously.[6,11] Professional medical writing assistance were paid for by the sponsor, and the initial manuscript was written with direct contributions from the lead and co-senior authors. All authors contributed to subsequent drafts.

Statistical Analysis

Efficacy end points were based on the intention-to-treat population, and formal co-primary end point analyses were conducted at different prespecified time points per the study protocol.[6,11] The current analyses, with a minimum of 10 years of follow-up, were performed to assess long-term overall, progression-free, and melanoma-specific survival, as well as objective response rates with corresponding 95% confidence intervals (CIs); updated rates are also included, where an adequate number of patients at risk allowed. Confidence interval widths 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 versus the nivolumab group, but descriptive analyses were performed. In a post hoc analysis of melanoma-specific survival, events were defined as deaths due to melanoma (deaths due to other causes were censored). Additional details regarding statistical analysis are provided in the Supplementary Methods section of the Supplementary Appendix and have been described previously.[6,9,11–13]

Results

Patients

Between July 2013 and March 2014, a total of 1296 patients were enrolled at 137 centers globally. A total of 945 were randomized: 314 to nivolumab-plus-ipilimumab, 316 to nivolumab, and 315 to ipilimumab (Fig. S1). Baseline characteristics were similar between treatment groups (Table S1). As of the final database lock (May 16, 2024), the minimum follow-up from the date the last patient was randomized was 120 months, with a median follow-up of 57.5 months (range, 0.1 to 128.1) with nivolumab-plus-ipilimumab, 36.0 months (range, 0.0 to 128.1) with nivolumab, and 18.6 months (range, 0.0 to 127.2) with ipilimumab. No patients were continuing treatment on study (Fig. S1, Table S2), and median treatment duration was 2.8 months (95% CI, 2.4 to 3.9, range: 0 to 123.8 months) with nivolumab-plus-ipilimumab, 6.6 months (95% CI, 5.2 to 9.7, range: 0 to 122.3 months) with nivolumab, and 3.0 months (95% CI, 2.6 to 3.7, range: 0 to 49.9 months) with ipilimumab.

Survival Outcomes

Overall survival was longer in the nivolumab-containing groups compared with the ipilimumab group (Figure 1A). Median overall survival was 71.9 months (95% CI, 38.2 to 114.4) with nivolumab-plus-ipilimumab, 36.9 months (95% CI, 28.2 to 58.7) with nivolumab, and 19.9 months (95% CI, 16.8 to 24.6) with ipilimumab, with 10-year overall survival rates of 43%, 37%, and 19% in these groups, respectively. The hazard ratio for death was 0.53 (95% CI, 0.44 to 0.65) with nivolumab-plus-ipilimumab versus ipilimumab and 0.63 (95% CI, 0.52 to 0.76) for nivolumab versus ipilimumab. In a descriptive analysis,

the hazard ratio for death with nivolumab-plus-ipilimumab versus nivolumab was 0.85 (95% CI, 0.69 to 1.05).

Similar to overall survival, melanoma-specific survival was numerically longer in the nivolumab-containing groups compared with ipilimumab (Figure 1B). Median melanoma-specific survival was >120 months (not reached; 95% CI, 71.8 to not reached; 37.1% of patients were alive at study closeout [May 16, 2024 – minimum 120-month follow-up]) with nivolumab-plus-ipilimumab, 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 rates at 10-years were 52% with nivolumab-plus-ipilimumab, 44% with nivolumab, and 23% with ipilimumab. A summary of deaths for the entire study period, including the numbers of deaths due to melanoma, is shown in Table S3. After 60 months, a total of 61 deaths were reported, with 39 of these attributed to melanoma (13 in the nivolumab-plus-ipilimumab group, 11 in the nivolumab group, and 15 in the ipilimumab group; Table S4).

The co-primary endpoint of progression-free survival was largely unchanged, with survival curves plateauing after 3 years (Figure. 1C). Among all randomized patients, the most frequent site of first progression was the lymph nodes (58 [18.5%] patients in the nivolumab-plus-ipilimumab group, 79 [25.0%] in the nivolumab group, and 111 [35.2%] in the ipilimumab group; Table S5). The central nervous system was the site of first progression in 15 patients (4.8%) in the nivolumab-plus-ipilimumab group, 20 (6.3%) in the nivolumab group, and 28 (8.9%) in the ipilimumab group (Table S5). After 36-months, 38 events were noted across all 3 treatment arms (19 new progressions, 2 deaths due to melanoma without documented progression, and 17 deaths due to non-melanoma causes without progression); of those, 21 occurred after 60 months (8 new progressions, 2 deaths due to melanoma without documented progression, and 11 deaths due to non-melanoma causes without documented progression).

Survival Outcomes in Subgroups

At 120-months, both overall and melanoma-specific survival were longer in the nivolumab-containing groups compared with ipilimumab, regardless of *BRAF* mutation status or PD-L1 expression level (Figure 2A–D and Fig. S2A–D), as well as across other prespecified subgroups (Figure 3A–B and Fig. S3A–B; note presence of baseline liver metastasis was a post-hoc analysis). Further, the overall and melanoma-specific survival benefits were similar but favored nivolumab-plus-ipilimumab over nivolumab to varying degrees across most subgroups (Fig. S3C and Figure 3C).

In a post-hoc analysis, baseline characteristics of patients who were progression-free at 3-years (nivolumab-plus-ipilimumab, n=100; nivolumab, n=78; ipilimumab, n=21) are shown in Table S8. Among these patients, 10-year overall survival rates were 86% with nivolumab-plus-ipilimumab, 85% with nivolumab, and 79% with ipilimumab (Figure 3A), and 10-year melanoma-specific survival rates were 96% with nivolumab-plus-ipilimumab, 97% with nivolumab, and 88% with ipilimumab (Figure 3B).

The following were descriptive post-hoc survival analyses starting at a 6-month landmark. In patients who experienced ≥1 grade 3–4 treatment-related adverse event(s) within the

first 6-months of follow-up, 10-year overall survival rates were 49% with nivolumab-plus-ipilimumab, 62% with nivolumab, and 26% with ipilimumab (Fig. S4 and Table S9). Additionally, in those who discontinued treatment due to a treatment-related adverse event during induction in the nivolumab-plus-ipilimumab group, the 10-year overall survival rate was 43% and the 10-year melanoma specific survival rate was 50% (Fig. S5). Patients who received immune-modulating medication within the first 6-months of follow-up had 10-year melanoma-specific survival rates of 59% with nivolumab-plus-ipilimumab, 53% with nivolumab and 27% with ipilimumab (Table S9). Patients who did not receive immune-modulating medication within the first 6-months had 10-year melanoma-specific survival rates of 56% with nivolumab-plus-ipilimumab, 46% with nivolumab and 27% with ipilimumab (Table S9).

Response

Objective response rate (unconfirmed) was higher in the nivolumab-plus-ipilimumab group (58.3%) and in the nivolumab group (44.9%) compared with the ipilimumab group (19.0%; Table S10). Similarly, confirmed objective response rate was higher in the nivolumab-plus-ipilimumab group (50.0%) and in the nivolumab group (41.8%) compared with the ipilimumab group (14.6%; Table S10). Median duration of response was >120 months (not reached; 95% CI, 68.2 to not reached) in the nivolumab-plus-ipilimumab group, 103.2 months (95% CI, 45.7 to not reached) in the nivolumab group, and 19.2 months (95% CI, 8.8 to 47.4) in the ipilimumab group (Fig. S6). In the nivolumab-plus-ipilimumab group, 56.3% of patients had an ongoing response at study closure, compared with and 54.9% of patients in the nivolumab group, and 36.7% of patients in the ipilimumab group (Table S10).

Tumor burden reduction was greater in the nivolumab-containing groups compared with ipilimumab (Figure 4A). In post-hoc analyses, median overall and melanoma-specific survival was >120 months (not reached) in patients with a depth of response ≥80% with any treatment (Figure 5B & Fig. S7). In the nivolumab-plus-ipilimumab group, 10-year melanoma-specific survival was 87% in patients with a depth of response ≥80% and 72% in those with a depth of response of 50% to <80%; with nivolumab, 10-year melanoma-specific survival was 88% and 75% in those two groups, respectively, and with ipilimumab, 80% and 40% (Fig. S7).

Outcomes After Treatment

Subsequent systemic therapy was received by 36.0% of patients in the nivolumab-plus-ipilimumab group, 49.7% of patients in the nivolumab group, and 66.7% of patients in the ipilimumab group (Table S11). Subsequent local therapy (i.e. radiotherapy or surgery) was received by 46.2% of patients in the nivolumab-plus-ipilimumab arm, 56.0% in the nivolumab arm and 72.4% in the ipilimumab arm. Excluding patients who died without receiving subsequent therapy, median time to subsequent systemic therapy was >120 months (not reached; 95% CI, 45.9 to not reached) 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 (Table S11). In these patients, 52% of patients in the nivolumab-plus-nivolumab arm and 37% in the nivolumab arm had subsequent systemic therapy-free survival at 10-years, compared with 13% in the ipilimumab arm.

Safety

Since the 5-year analysis, no new safety signals were observed in any of the treatment groups, including no new deaths due to treatment.[13] The final summary of treatment-related adverse events is reported in Table S12, and time to resolution of select treatment-related adverse events is presented in Table S13. The incidence of spontaneously reported late-emergent treatment-related adverse events (occurring >100 days after treatment) was low across all treatment arms (Table S14).

Discussion

Since 2010, the historically bleak prognosis for patients with advanced melanoma has markedly changed thanks to advances in checkpoint inhibition and oncogenic signaling pathway inhibitors. Results from the CheckMate 067 trial have demonstrated the ability of nivolumab, an anti–PD-1 agent, alone or in combination with ipilimumab to induce durable disease control in patients with advanced melanoma.

This final, 10-year analysis continues to demonstrate unprecedented survival length in patients with advanced melanoma. Specifically, 10-year overall survival rates were 43% with nivolumab-plus-ipilimumab, 37% with nivolumab, and 19% with ipilimumab.

The plateaus in survival curves observed 3 years after treatment initiation persisted in the nivolumab-containing groups after a minimum of 120 months of follow-up, and this analysis has continued to show that nivolumab-plus-ipilimumab and nivolumab alone improve overall and melanoma-specific survival compared with ipilimumab monotherapy. In a descriptive analysis, the combination also demonstrated a numerically higher 10-year melanoma-specific survival rate versus nivolumab alone (52% and 44%, respectively). Median melanoma-specific survival and duration of response in the combination group were >120 months (not reached, with 37.1% of patients alive at study closeout), underscoring the prolonged clinical benefit with nivolumab-plus-ipilimumab therapy. Further, nivolumab-plus-ipilimumab continued to demonstrate high rates of control of CNS spread of disease. This corroborates observations made in other settings, including in patients with tumors that are *BRAF* V600 mutation-positive, supporting nivolumab-plus-ipilimumab as a preferred treatment to prevent and treat melanoma brain metastases.[14–17]

No new safety signals were observed with the additional follow-up. The majority of treatment-related adverse events in CheckMate 067 occurred earlier in the treatment course and were managed through established algorithms. Nivolumab-plus-ipilimumab was associated with more frequent and more severe adverse events relative to either monotherapy, but patients who experienced a grade 3 or 4 adverse event within the first 6-months of follow-up, those who discontinued treatment during induction due to a treatment-related adverse event, and those who received immune-modulating therapy within the first 6-months of follow-up experienced a durable survival benefit. These results demonstrate that even with a shortened duration of therapy, long-term survival was possible.

At 10-years, melanoma-specific survival rates continued to separate from overall survival rates, especially in the nivolumab-containing groups (overall vs. melanoma-specific survival

rates: 43% vs. 52% with nivolumab-plus-ipilimumab; 37% vs. 44% with nivolumab; 19% vs. 23% with ipilimumab). This suggests that patients with advanced melanoma are living long enough to experience mortality from other causes, and that 10-years of follow-up is long enough to adequately assess the oncologic survival benefits of immunotherapy, while limiting the confounding effects of competing causes of death. In fact, after 60 months, numbers of both total (61/937; 6.5%) and melanoma-specific (39/937; 4.2%) deaths were low. Further, in patients who had progression-free survival at 3-years, 10-year melanoma-specific survival rates were 96% with nivolumab-plus-ipilimumab, 97% with nivolumab, and 88% with ipilimumab. The sustained benefit of immune checkpoint inhibitors observed over the extensive length of follow-up in CheckMate 067 highlights the potential for cure in patients with advanced melanoma who are responsive to this type of treatment.

Patients treated with nivolumab-plus-ipilimumab required subsequent systemic therapy less frequently than patients treated with nivolumab or ipilimumab monotherapy (36.0% vs. 49.7% and 66.7%), with a median time to subsequent systemic therapy initiation of >120 months (not reached). Excluding those who died and never received subsequent systemic therapy, at 10 years – 52% of patients in the nivolumab-plus-nivolumab arm and 37% in the nivolumab arm had subsequent systemic therapy-free survival, compared with 13% in the ipilimumab arm. Of note, 26.3% of patients treated with nivolumab monotherapy went on to receive ipilimumab-containing therapy in some form; however, since this study did not include crossover to ipilimumab-containing regimens at the time of progression on first-line nivolumab, the effects of crossover on survival are difficult to determine.

Larger proportions of patients randomized to the nivolumab-plus-ipilimumab (31.8%) and nivolumab monotherapy (24.7%) groups were progression-free at 3-years compared with those randomized to the ipilimumab monotherapy group (6.7%); as mentioned, these patients experienced a remarkably stable clinical benefit, with 10-year melanoma-specific survival rates ≥96% in the nivolumab-containing groups. These results suggest that progression-free survival at 3-years is a powerful surrogate marker of long-term disease-specific survival in patients with advanced melanoma treated with immune checkpoint inhibitors. Similarly, best overall tumor burden reduction of ≥80% appears to be another surrogate marker of long-term survival, as these patients had 10-year melanoma-specific survival rates of 87% with nivolumab-plus-ipilimumab, 88% with nivolumab, and 80% with ipilimumab. These results also have important clinical implications for helping determine the frequency at which patients who reach these benchmarks should undergo imaging for the surveillance of new progressions or lesions.

The survival benefits seen in the nivolumab-containing groups versus the ipilimumab group persisted across all examined subgroups, including those stratified by PD-L1 expression and *BRAF* mutation status. When comparing the combination vs. nivolumab monotherapy groups, 10-year melanoma-specific-survival rates favored nivolumab-plus-ipilimumab over nivolumab in those with PD-L1 expression ≥ 5% (59% vs. 54%), and with PD-L1 expression <5% (50% vs. 43%). While melanoma-specific survival also favored nivolumab-plus-ipilimumab over nivolumab monotherapy in patients with *BRAF* wild-type tumors (10-year rates: 50% vs. 45%), in patients with *BRAF* V600 mutation-positive melanoma, the difference between the nivolumab-plus-ipilimumab vs. the nivolumab group was more

pronounced (56% vs. 42%). This clinical observation is supported by translational studies describing an over-representation of interleukin-17–expressing T-helper cell gene expression signatures in *BRAF* V600–mutated tumors, which is associated with clinical benefit from dual CTLA-4 and PD-1 checkpoint inhibition.[18]

Despite unprecedented improvements made in the treatment of advanced melanoma over the past 15 years, important gaps remain – including the higher incidence of treatment-related adverse events observed in the ipilimumab-containing treatment arms compared with nivolumab monotherapy. Emerging treatments, such as anti–PD-1 plus anti–lymphocyte-activation gene 3 (LAG-3) combination therapy, may offer similar efficacy with improved tolerability compared with ipilimumab containing regimens.[7,19] Further, even with available immune checkpoint inhibitor combinations, ~40% of patients do not respond to treatment, and half die from melanoma. Triplet therapy (anti–CTLA-4 plus anti–PD-L1 plus anti–LAG-3 agents) may be more effective than combination therapies (48-month overall survival rate of 72% in NCT03459222);[20] however, larger studies are needed to confirm these data. The development of new treatment regimens, such as improved targeted therapies, personalized vaccines, and adoptive cell transfer therapy, offer opportunities to optimize long-term outcomes in patients with advanced melanoma.

In conclusion, in patients with advanced melanoma, nivolumab-containing therapy has continued to show prolonged clinical benefit compared with ipilimumab monotherapy, 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 are responsive to this type of treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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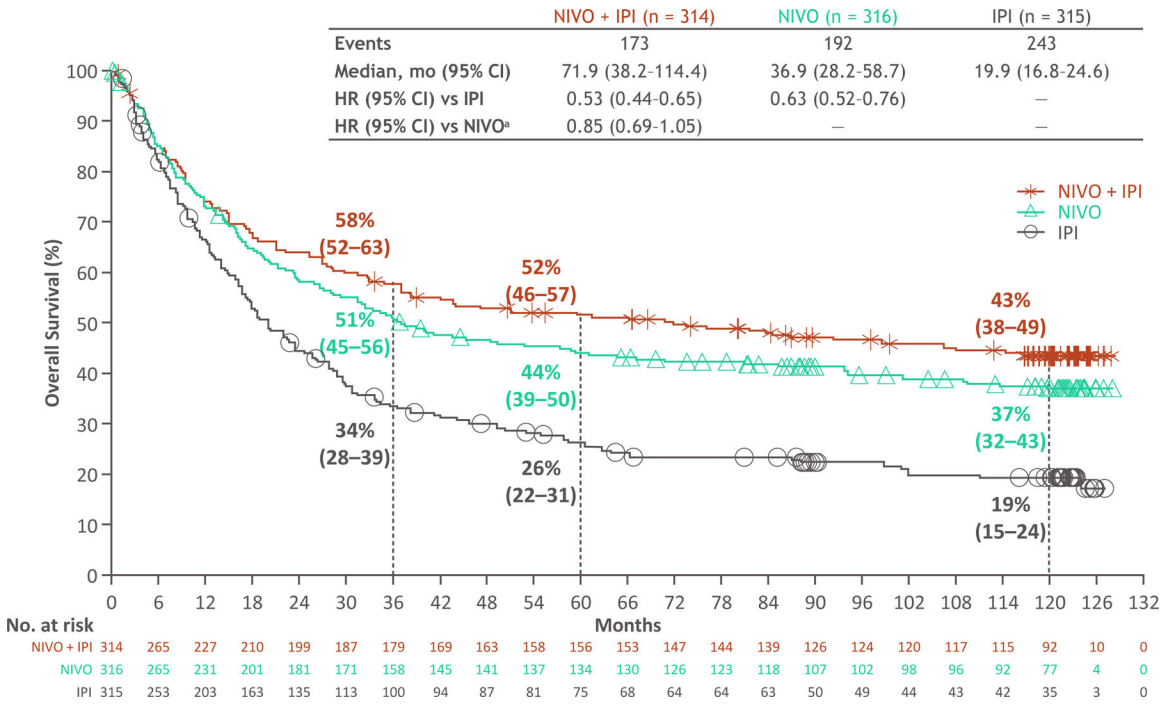
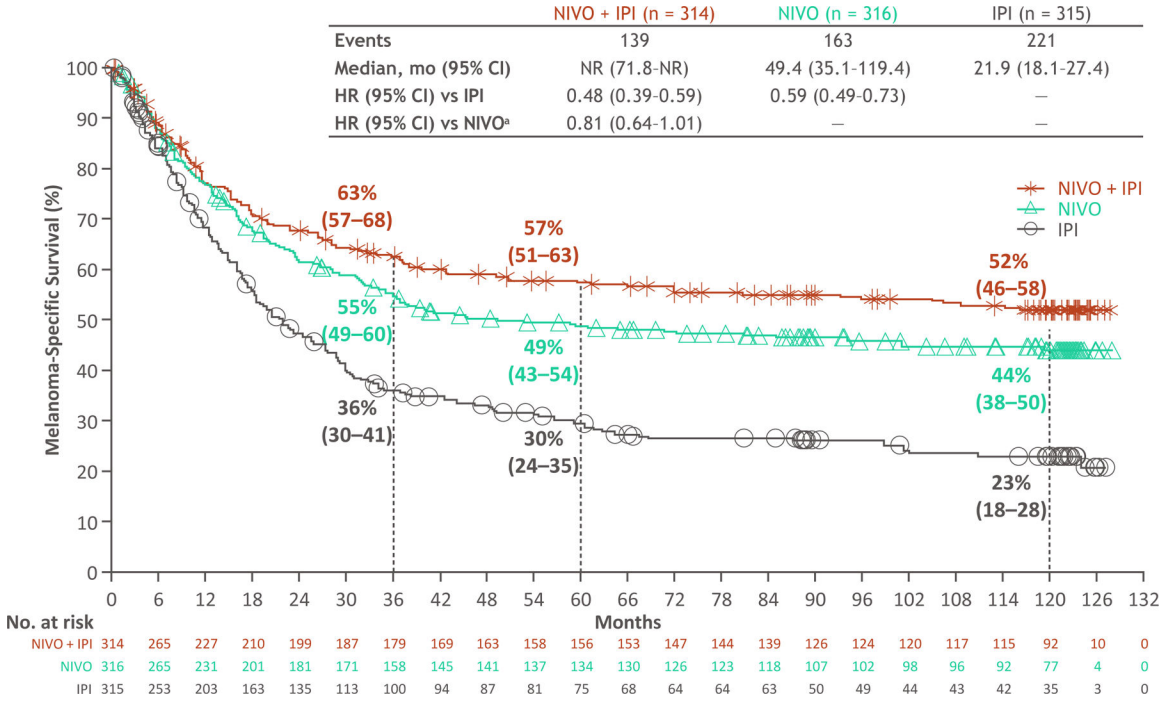




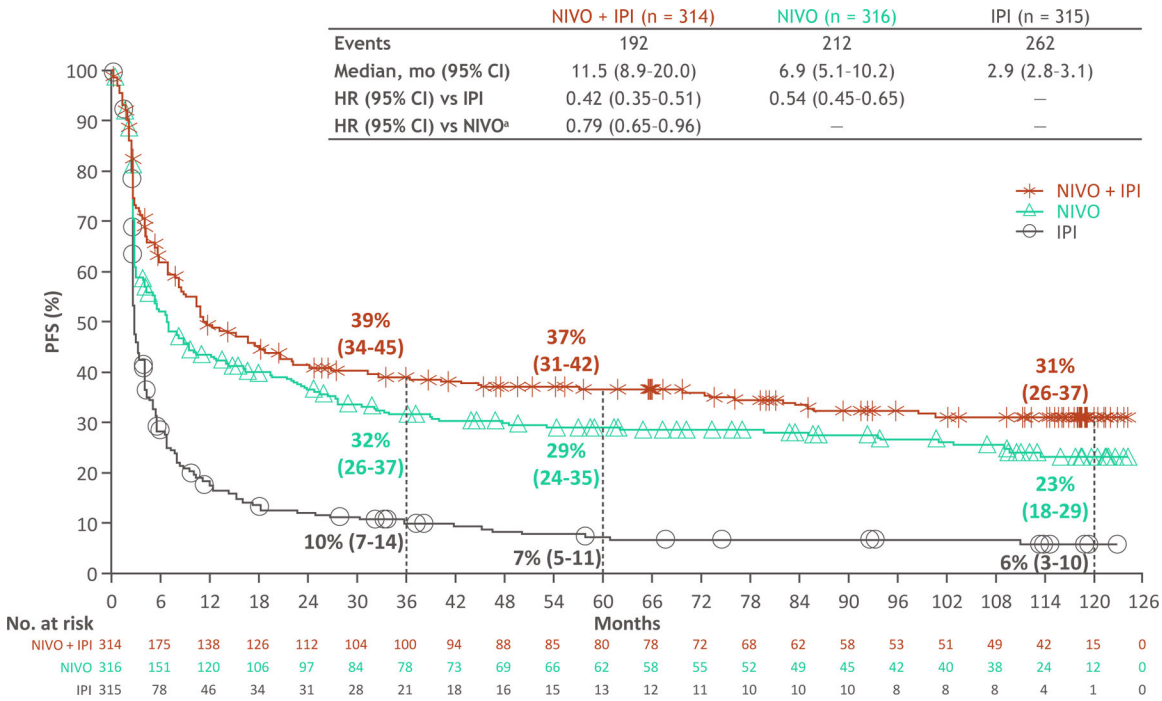


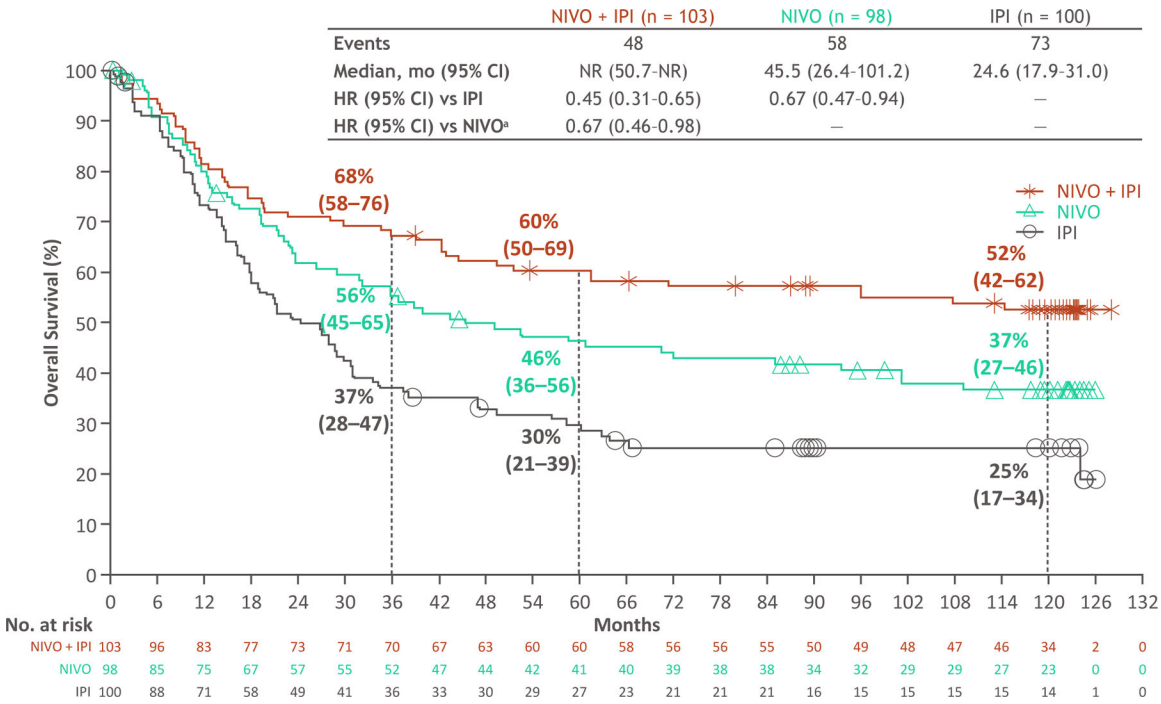
FIGURE 1. Overall Survival, Melanoma-Specific Survival and Progression-Free Survival in the Intention-to-Treat Population.

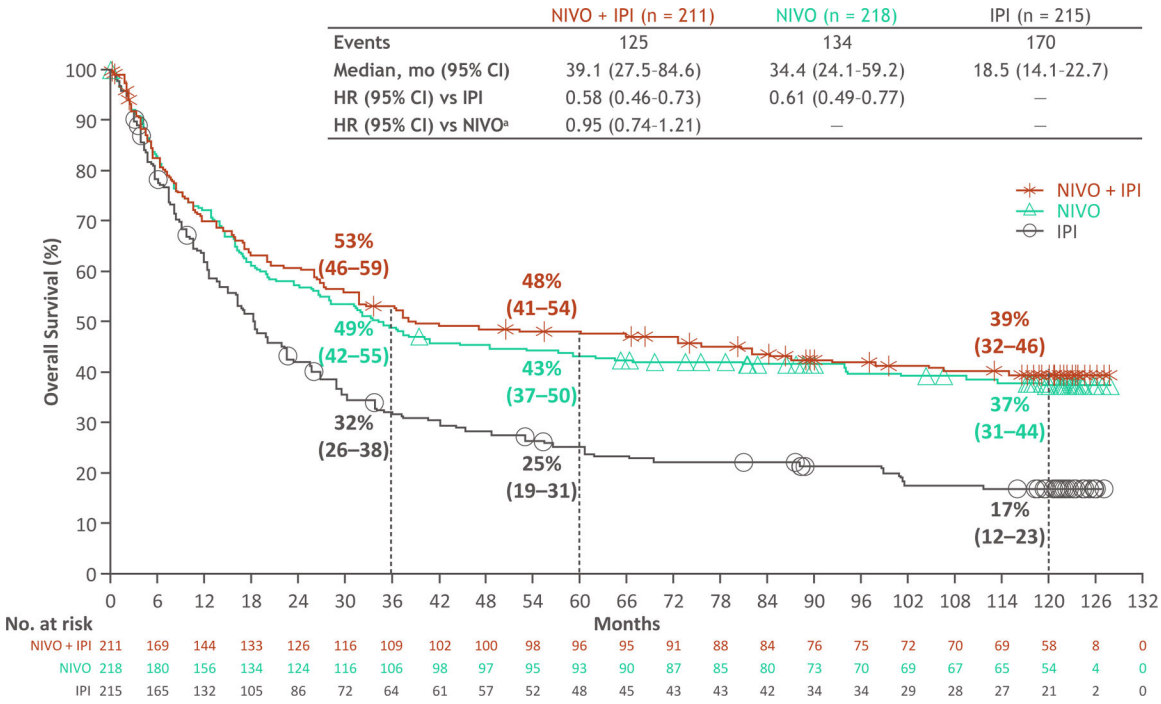
Panel A shows overall survival among the intention-to-treat population. Panel B shows melanoma-specific survival among the intention-to-treat population. Melanoma-specific survival was a post-hoc analysis. Panel C shows progression-free survival among the intention-to-treat population. After 36-months, there were 38 total reported events for the progression-free survival analysis - 19 new progressions, 2 deaths due to melanoma without documented progression, and 17 deaths due to non-melanoma causes without progression; of those, 21 occurred after 60 months (8 new progressions, 2 deaths due to melanoma without documented progression, and 11 deaths due to non-melanoma causes without documented progression). Confidence interval widths have not been adjusted for multiplicity and should not be used in place of hypothesis testing. NIVO denotes nivolumab, IPI ipilimumab, and HR hazard ratio. *Descriptive comparison

A. Overall Survival Among Intention-to-Treat Population

B. Melanoma-Specific Survival Among Intention-to-Treat Population

C. Progression-Free Survival Among Intention-to-Treat Population





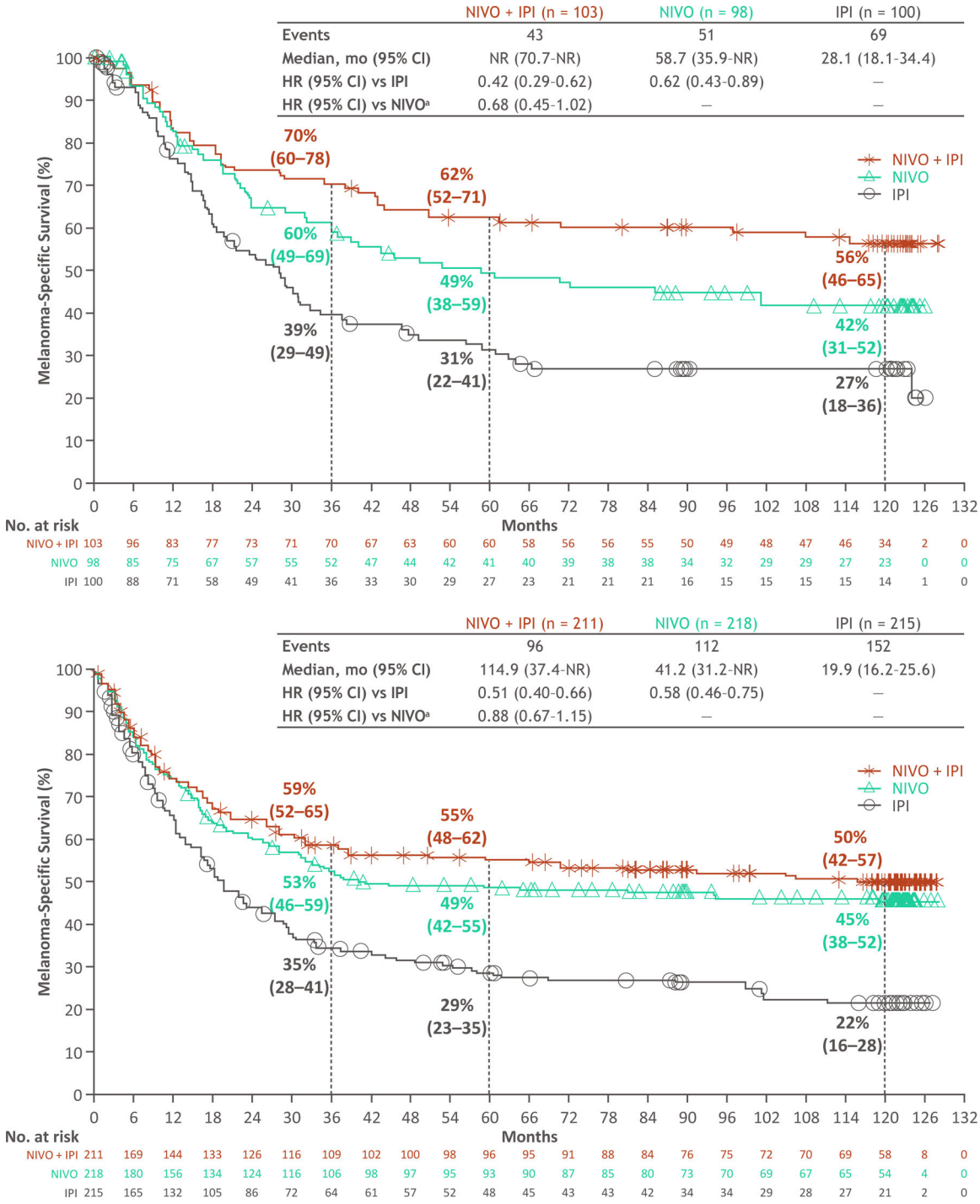


FIGURE 2. Overall Survival and Melanoma-Specific Survival by *BRAF* Mutation Status

Panels A and B show overall survival in the intention-to-treat population among patients with *BRAF* mutations and among patients without *BRAF* mutations, respectively. Panels C and D show 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 a post-hoc analysis. Confidence interval widths have not

been adjusted for multiplicity and should not be used in place of hypothesis testing. NIVO denotes nivolumab, IPI ipilimumab, HR hazard ratio, and NR not reached. *Descriptive comparison

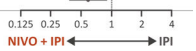
A. Overall Survival Among Intention-to-Treat Population with *BRAF* Mutations

B. Overall Survival Among Intention-to-Treat Population without *BRAF* Mutations

C. Melanoma-Specific Survival Among Intention-to-Treat Population with *BRAF* Mutations

D. Melanoma-Specific Survival Among Intention-to-Treat Population without *BRAF* Mutations

Subgroup	No. of patients		120-Month OS Rates, %		Unstratified Hazard Ratio (95% CI)
	NIVO + IPI	IPI	NIVO + IPI	IPI	
Overall	314	315	43	19	0.53 (0.44-0.65)
BRAF mutant	103	100	52	25	0.45 (0.31-0.65)
BRAF wild-type	211	215	39	17	0.58 (0.46-0.73)
M0/M1A/M1B	129	127	50	24	0.49 (0.35-0.68)
M1C	185	188	39	16	0.56 (0.44-0.71)
Age <65 years	185	182	47	22	0.50 (0.38-0.65)
Age ≥65 years	129	133	38	16	0.59 (0.44-0.79)
Male	206	202	43	20	0.52 (0.41-0.67)
Female	108	113	45	17	0.57 (0.41-0.79)
US	64	75	50	18	0.45 (0.29-0.71)
EU	177	170	40	16	0.52 (0.41-0.68)
Australia	40	37	61	37	0.46 (0.24-0.88)
Rest of world	33	33	30	18	0.86 (0.49-1.50)
ECOG PS 0	230	224	48	23	0.52 (0.41-0.65)
ECOG PS ≥1	83	91	31	10	0.59 (0.42-0.84)
With Liver Metastases	93	92	36	17	0.63 (0.45-0.89)
Without Liver Metastases	221	223	47	20	0.49 (0.39-0.62)
LDH ≤ULN	199	194	50	25	0.51 (0.39-0.66)
LDH >ULN	114	115	33	10	0.57 (0.42-0.77)
AJCC Stage III	16	22	46	20	0.41 (0.18-0.96)
AJCC Stage IV	298	293	43	19	0.54 (0.44-0.66)
PD-L1 <1%	123	113	39	19	0.59 (0.43-0.81)
PD-L1 ≥1%	155	164	47	20	0.50 (0.38-0.67)
PD-L1 <5%	210	202	42	17	0.52 (0.41-0.66)
PD-L1 ≥5%	68	75	48	26	0.59 (0.38-0.91)



Subgroup	No. of patients		120-Month OS Rates, %		Unstratified Hazard Ratio (95% CI)
	NIVO	IPI	NIVO	IPI	
Overall	316	315	37	19	0.63 (0.52-0.76)
BRAF mutant	98	100	37	25	0.67 (0.47-0.94)
BRAF wild-type	218	215	37	17	0.61 (0.49-0.77)
M0/M1A/M1B	132	127	48	24	0.54 (0.39-0.75)
M1C	184	188	30	16	0.68 (0.53-0.86)
Age <65 years	198	182	42	22	0.58 (0.45-0.75)
Age ≥65 years	118	133	28	16	0.72 (0.54-0.96)
Male	202	202	40	20	0.57 (0.45-0.73)
Female	114	113	32	17	0.76 (0.55-1.03)
US	68	75	42	18	0.64 (0.42-0.97)
EU	170	170	33	16	0.60 (0.47-0.78)
Australia	38	37	47	37	0.59 (0.32-1.09)
Rest of world	40	33	35	18	0.76 (0.44-1.30)
ECOG PS 0	237	224	42	23	0.60 (0.47-0.75)
ECOG PS ≥1	79	91	21	10	0.76 (0.54-1.06)
With Liver Metastases	90	92	30	17	0.78 (0.55-1.09)
Without Liver Metastases	226	223	40	20	0.57 (0.46-0.72)
LDH ≤ULN	197	194	46	25	0.57 (0.44-0.74)
LDH >ULN	112	115	21	10	0.73 (0.54-0.97)
AJCC Stage III	25	22	47	20	0.44 (0.21-0.93)
AJCC Stage IV	291	293	36	19	0.65 (0.53-0.79)
PD-L1 <1%	117	113	31	19	0.78 (0.57-1.05)
PD-L1 ≥1%	171	164	44	20	0.52 (0.39-0.68)
PD-L1 <5%	208	202	36	17	0.62 (0.49-0.78)
PD-L1 ≥5%	80	75	46	26	0.61 (0.41-0.91)

Subgroup	No. of patients		120-Month OS Rates, %		Unstratified Hazard Ratio (95% CI)
	NIVO + IPI	NIVO	NIVO + IPI	NIVO	
Overall	314	316	43	37	0.85 (0.69-1.04)
BRAF mutant	103	98	52	37	0.67 (0.46-0.98)
BRAF wild-type	211	218	39	37	0.95 (0.74-1.21)
M0/M1A/M1B	129	132	50	48	0.90 (0.64-1.28)
M1C	185	184	39	30	0.82 (0.64-1.06)
Age <65 years	185	198	47	42	0.85 (0.65-1.12)
Age ≥65 years	129	118	38	28	0.82 (0.60-1.12)
Male	206	202	43	40	0.92 (0.71-1.19)
Female	108	114	45	32	0.75 (0.53-1.06)
US	64	68	50	42	0.71 (0.44-1.15)
EU	177	170	40	33	0.87 (0.66-1.13)
Australia	40	38	61	47	0.77 (0.39-1.53)
Rest of world	33	40	30	35	1.13 (0.65-1.99)
ECOG PS 0	230	237	48	42	0.86 (0.67-1.11)
ECOG PS ≥1	83	79	31	21	0.78 (0.54-1.13)
With Liver Metastases	93	90	36	30	0.82 (0.57-1.17)
Without Liver Metastases	221	226	47	40	0.86 (0.67-1.10)
LDH ≤ULN	199	197	50	46	0.89 (0.68-1.18)
LDH >ULN	114	112	33	21	0.79 (0.58-1.07)
AJCC Stage III	16	25	46	47	0.93 (0.38-2.28)
AJCC Stage IV	298	291	43	36	0.84 (0.68-1.03)
PD-L1 <1%	123	117	39	31	0.76 (0.55-1.04)
PD-L1 ≥1%	155	171	47	44	0.97 (0.72-1.31)
PD-L1 <5%	210	208	42	36	0.84 (0.66-1.08)
PD-L1 ≥5%	68	80	48	46	0.97 (0.62-1.53)

FIGURE 3. Forest Plot of Overall Survival in Subgroups.

Panel A shows overall survival with nivolumab plus ipilimumab versus ipilimumab monotherapy. Panel B shows overall survival with nivolumab monotherapy versus ipilimumab monotherapy. Panel C shows overall survival with nivolumab plus ipilimumab versus nivolumab monotherapy (descriptive comparison). The x-axes are shown on a logarithmic scale. Confidence interval widths have not been adjusted for multiplicity and should not be used in place of hypothesis testing. All of these subgroups were prespecified, with the exception of baseline liver metastasis, which was a post-hoc analysis. OS denotes overall survival, NIVO nivolumab, IPI ipilimumab, M metastasis, US United States, EU European Union, ECOG Eastern Cooperative Oncology Group, LDH lactate dehydrogenase, AJCC American Joint Committee on Cancer (7^{th} edition), PD-L1 programmed cell death ligand 1, and ULN upper limit of normal.

A. Nivolumab plus Ipilimumab Versus Ipilimumab

B. Nivolumab Versus Ipilimumab

C. Nivolumab plus Ipilimumab Versus Nivolumab

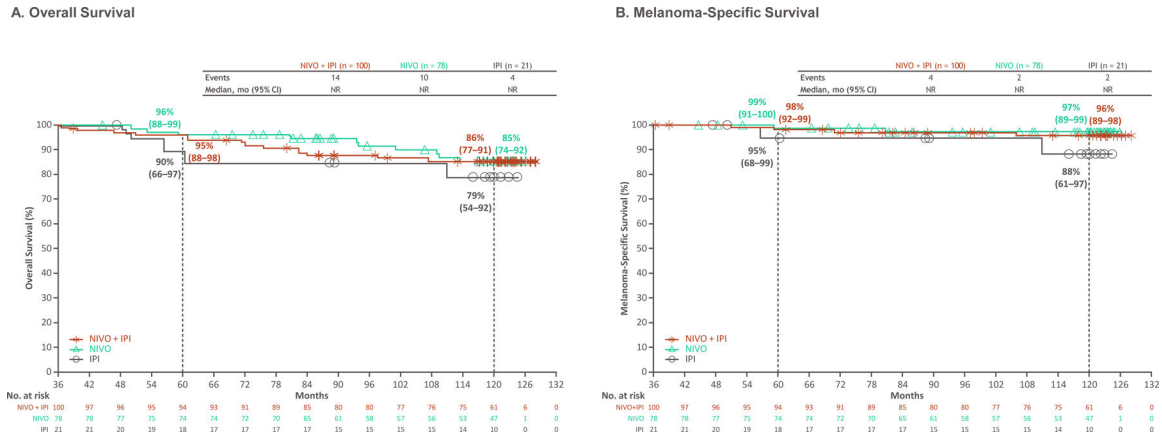


FIGURE 4. Overall Survival and Melanoma-Specific Survival in Patients with Progression-Free Survival at 3-Years.

Panels A and B show overall and melanoma-specific survival in patients who were progression-free at 3-years, respectively. Melanoma-specific survival was a post-hoc analysis. Confidence interval widths have not been adjusted for multiplicity and should not be used in place of hypothesis testing. NIVO denotes nivolumab, IPI ipilimumab, and NR not reached.

A. Overall Survival

B. Melanoma-Specific Survival

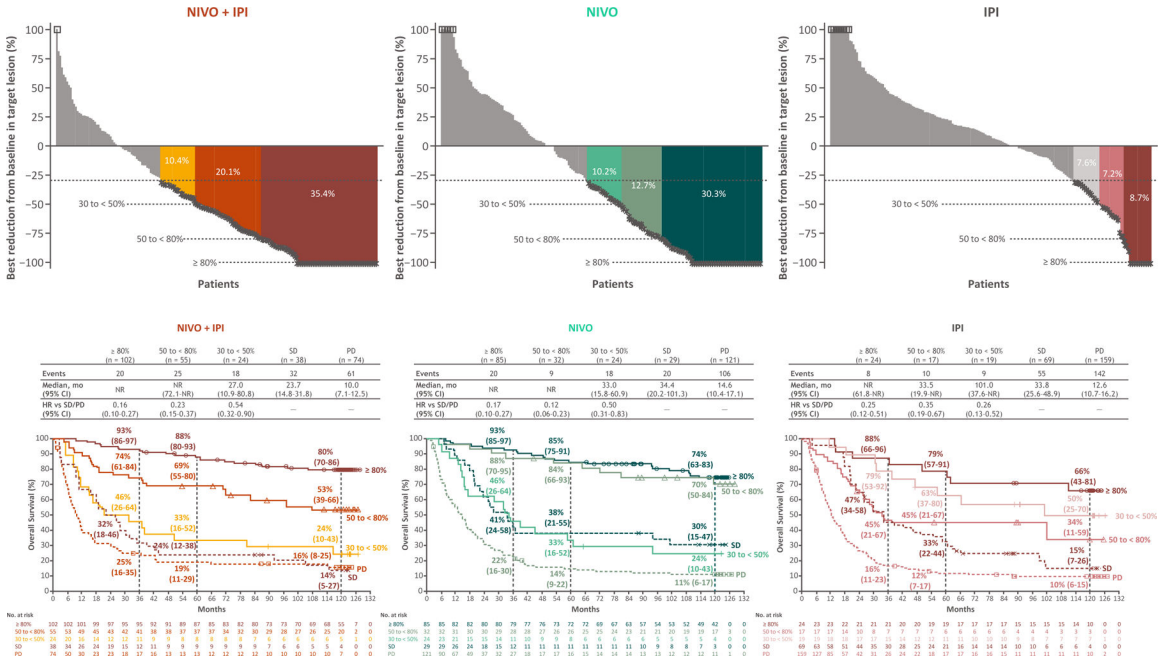


FIGURE 5. Best Tumor Burden Reduction, and Overall Survival by Best Depth of Response.

Panels A depicts waterfall plots showing best tumor burden reduction by treatment group where each vertical bar represents one patient. Panel B shows overall survival by best tumor burden reduction within each treatment arm. The analysis included patients with target lesion(s) at baseline and at least one on-treatment tumor assessment up to progression or start of subsequent therapy. Best tumor burden reduction is maximum reduction in sum of diameters of evaluable target lesions (negative value means true reduction, positive value means increase only observed over time). First horizontal reference line indicates the 30% reduction consistent with a RECIST 1.1 response. Asterisk symbol represents responders. Square symbol represents % change truncated to 100%. Two patients with best overall response of “partial response” and best reduction in target lesions per investigator <30% were excluded from the analysis. Confidence interval widths have not been adjusted for multiplicity and should not be used in place of hypothesis testing. NIVO denotes nivolumab, IPI ipilimumab, HR hazard ratio, NR not reached, CR complete response, PR partial response, SD stable disease, and PD progressive disease.

A. Best Tumor Burden Reduction

B. Overall Survival by Best Depth of Response