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Combined Nivolumab and Ipilimumab or Monotherapy in Previously Untreated Melanoma

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Abstract

Background—The results of phase 1 and phase 2 studies suggest that nivolumab (a PD-1 checkpoint inhibitor) and ipilimumab (a CTLA-4 checkpoint inhibitor) have complementary activity in metastatic melanoma. In this randomized, double-blind, phase 3 study, nivolumab alone or nivolumab combined with ipilimumab versus ipilimumab alone were evaluated in patients with metastatic melanoma.

Methods—We randomly assigned 945 previously untreated patients with unresectable stage III or IV melanoma, in 1:1:1 ratio, to nivolumab alone (3 mg per kilogram of body weight every 2 weeks), or to nivolumab (at a dose of 1 mg per kilogram) plus ipilimumab (at a dose of 3 mg per kilogram) every 3 weeks for 4 doses followed by nivolumab (3 mg per kilogram every 2 weeks), or to ipilimumab alone (3 mg per kilogram every 3 weeks for 4 doses). Progression-free and overall survival were co-primary end points. Patients continue to be followed for overall survival.

Results—Median progression-free survival was 11.5 months (95% confidence interval [CI], 8.9 to 16.7) for nivolumab plus ipilimumab as compared with 2.9 months (95% CI, 2.8 to 3.4) for ipilimumab alone (hazard ratio, 0.42; 95% CI, 0.31 to 0.57; P<0.00001), and was 6.9 months (95% CI, 4.3 to 9.5) for nivolumab alone (hazard ratio in the comparison with ipilimumab alone, 0.57; 95% CI, 0.43 to 0.76; P<0.00001). In PD-L1-positive patients, median progression-free survival was 14.0 months in both the nivolumab plus ipilimumab and nivolumab alone groups, but in PD-L1-negative patients, progression-free survival was longer with the combination as compared with nivolumab alone (11.2 months [95% CI, 8.0 to not reached] versus 5.3 months [95% CI, 2.8 to 7.1]). Grade 3–4 drug-related adverse events occurred in 16.3%, 55.0%, and 27.3% of patients in the nivolumab, nivolumab plus ipilimumab, and ipilimumab alone groups, with 1, 0, and 1 drug-related deaths, respectively.

Conclusions—Nivolumab alone or combined with ipilimumab significantly improved progression-free survival, as compared with ipilimumab, among previously untreated patients with metastatic melanoma. Results with the combination versus either agent alone suggest complementary activity between PD-1 and CTLA-4 blockade, particularly for patients with PD-L1-negative tumors. (Funded by Bristol-Myers Squibb; CheckMate 067, ClinicalTrials.gov number, NCT01844505.)

Introduction

Historically, metastatic melanoma has been considered relatively refractory to systemic therapy. Significant progress has been made in the past 5 years, with the approval of agents targeting aberrant signalling in the 40–50% of melanomas with BRAF mutations.[1–4] In parallel, immunologic checkpoint blocking antibodies have been developed, which have similarly transformed the melanoma treatment landscape.[5,6] Ipilimumab, an anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) antibody, acts to upregulate antitumor immunity and was the first agent to show an improvement in overall survival in a phase 3 study of patients with metastatic melanoma.[5,6] Ipilimumab is associated with radiographic

responses in 10–15% of patients and produces long-term survival in approximately 20% of patients.[7,8]

Two anti-programmed death-1 (PD-1) antibodies, nivolumab and pembrolizumab, were approved by the US FDA in 2014 for the treatment of metastatic melanoma after progression on ipilimumab and, in patients with BRAF-mutant melanoma, a BRAF inhibitor. These anti-PD-1 antibodies have been shown to produce objective response in 30–40% of patients, with the majority of responses being durable. Two phase 3 trials have reported superior efficacy for nivolumab in comparison with cytotoxic chemotherapy in treatment-naïve patients with BRAF wild-type tumors[9] or in patients with either mutant or wild-type BRAF tumors following progression on ipilimumab and, if BRAF-mutation-positive, a BRAF inhibitor.[10] Similar results have been observed in a phase 2 trial of pembrolizumab versus chemotherapy.[11] Recently, pembrolizumab demonstrated an improvement in progression-free survival, overall survival, and response rates as compared with ipilimumab in patients with advanced melanoma.[12]

Tumor immunity is negatively regulated by both CTLA-4 and PD-1, but these pathways are distinct and complementary, and preclinical data suggest additional antitumor activity with simultaneous blockade of both targets.[13,14] In support of this hypothesis, a phase 1 trial of combined nivolumab and ipilimumab in advanced melanoma demonstrated an objective response rate of over 50% and a complete response rate of over 17% in select dose cohorts,[15] higher than previously reported with either agent alone. Recently, the results of a phase 2 study with combined nivolumab and ipilimumab versus ipilimumab alone showed objective response rates of 61% and 11%, with complete responses in 22% and 0% of patients, respectively.[16] Grade 3 or 4 treatment-related adverse events were reported in 54% of patients in the combination group and 24% of patients in the ipilimumab group. Importantly, adverse events were similar to previous experience with each agent alone and were generally manageable with established guidelines, including use of corticosteroids for grade 3 or 4 events. Expression of the PD-1 ligand (PD-L1) has been reported to result in greater benefit for anti-PD-1 monotherapy,[9,10] but not for the combination of anti-PD-1 and anti-CTLA-4 therapy.[15,16] However, the optimal cutoff for defining PD-L1 expression and clinical utility have not yet been established.

To confirm and extend these findings, we report one of the co-primary end points (progression-free survival) of a randomized, double-blind, multicenter, phase 3 trial (CheckMate 067) conducted to evaluate the safety and efficacy of nivolumab alone or nivolumab combined with ipilimumab in comparison with ipilimumab alone in previously untreated metastatic melanoma.

Methods

Patients

Eligible patients had histologically confirmed stage III (unresectable) or stage IV melanoma, and no prior systemic treatment for unresectable or metastatic melanoma. Other eligibility criteria included an age of at least 18 years, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 (indicating no symptoms) or 1 (indicating mild

symptoms), measurable disease by computed tomography or magnetic resonance imaging per RECIST v1.1, availability of tissue collected from metastatic or unresectable tumors for the assessment of PD-L1 status, and known BRAF V600 mutation status (or consent to BRAF V600 mutation testing per local standards). Key exclusion criteria were presence of active brain metastases, ocular melanoma, or autoimmune disease, and any prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody. Patients who required systemic corticosteroid treatment or other immunosuppressive medications within 14 days of study drug administration were excluded.

Study Design and Treatment

In this double-blind, phase 3 study, enrolled patients were randomly assigned in a 1:1:1 ratio to receive 3 mg of nivolumab per kilogram of body weight every 2 weeks (plus ipilimumab-matched placebo), or 1 mg of nivolumab per kilogram every 3 weeks plus 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses (plus nivolumab-matched placebo), followed by 3 mg of nivolumab per kilogram every 2 weeks for cycle 3 and beyond, or 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses (plus nivolumab-matched placebo).

Both nivolumab and ipilimumab were administered by intravenous infusion. Randomization was stratified according to tumor PD-L1 status (positive vs. negative or indeterminate), BRAF mutation status (V600 mutation positive vs. wild-type), and American Joint Committee on Cancer metastasis stage (M0, M1a, or M1b vs. M1c). Treatment continued until RECIST v1.1-defined disease progression, unacceptable toxicity, or withdrawal of consent. Patients could be treated beyond progression provided they had a clinical benefit without clinical deterioration, and did not have substantial adverse effects, as assessed by the investigator (further details are provided in the study protocol, available at NEJM.org).

Progression-free survival and overall survival were co-primary end points. Secondary end points included objective response rate, tumor PD-L1 expression as a predictive biomarker for progression-free and overall survival, and health-related quality of life. Exploratory end points include duration of objective response and safety/tolerability of study drug therapy.

Assessments

Patients were assessed for tumor response, according to RECIST v1.1,[17] at 12 weeks after randomization and continuing every 6 weeks for 49 weeks, and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Progression-free survival was defined as the time between the date of randomization and the first date of documented progression or death, whichever occurred first. Patients treated beyond progression were considered to have progressive disease at the time of the initial progression event, as assessed by the investigator, regardless of subsequent tumor responses. Expression of PD-L1 on the surface of the tumor cells was assessed in a central laboratory by immunohistochemistry in formalin-fixed, paraffin-embedded tumor specimens using a rabbit monoclonal anti-human PD-L1 antibody (clone 28-8) and an analytically validated automated assay developed by Dako (Carpinteria, CA). PD-L1 positivity was defined as at least 5% of tumor cells showing cell surface PD-L1 staining of any intensity in a section containing at least 100 tumor cells that could be evaluated. Indeterminate status was

attributed to samples for which tumor cell–surface expression could not be discerned because of melanin content or strong cytoplasmic staining.

Any patient who received at least one dose of study drug in each of the 3 treatment groups was included in the assessment of safety. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[18] Safety assessments were made continuously during the treatment phase, and up to 100 days after the last dose of study drug. Guidelines for the management of adverse events were provided by the sponsor and have been published previously.[9,10,16]

Study Oversight

The study protocol and all amendments were approved by the institutional review boards of all participating study sites, and are available (along with the statistical analysis plan) at NEJM.org. The study was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference on Harmonization. All patients (or their legal representatives) gave written informed consent before enrollment. The trial was designed through a collaboration between the senior academic authors and the sponsor, Bristol-Myers Squibb. Data were collected by the sponsor and analyzed in collaboration with all authors. All authors vouch for the accuracy and completeness of the data and analyses reported and for the fidelity of the study to the protocol. The first draft of the manuscript was prepared by the first and last authors. All authors contributed to subsequent drafts and provided final approval to submit for publication. Medical-writing support, funded by the sponsor, was provided by StemScientific.

A data and safety monitoring committee was established to provide oversight of safety and efficacy considerations, in order to assess the benefit-risk profile of nivolumab combined with ipilimumab. On March 17, 2015, the monitoring committee recommended that the study be analyzed for the co-primary end point of progression-free survival, the results of which are reported here. The study remains blinded for overall survival as follow-up of the patients continues until the planned number of events have occurred.

Statistical Analysis

A study sample size of approximately 915 patients, randomized to the 3 treatment arms in a 1:1:1 ratio, was planned. For the comparison of progression-free survival, the number of events projected to be observed at a follow-up of at least 9 months provided approximately 83% power to detect an average hazard ratio of 0.71 with a type I error of 0.005 (two-sided). Progression-free survival was compared between nivolumab plus ipilimumab and ipilimumab alone, and between nivolumab alone and ipilimumab alone with the use of a two-sided log-rank test stratified according to PD-L1 status, BRAF mutation status, and metastasis stage (as described above). The study was not designed for a formal statistical comparison between the nivolumab alone and nivolumab plus ipilimumab groups. Hazard ratios and corresponding two-sided 99.5% confidence intervals (CIs) were estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. Progression-free survival curves, medians with 95% CIs, and progression-free survival rates at 6, 12, and 18 months with 95% CIs were estimated using Kaplan-Meier

methodology. Overall survival will be analyzed when all patients have a minimum follow-up of 22 months.

Results

Patients and Treatment

From July 2013 through March 2014, a total of 1296 patients were enrolled at 137 centers in Australia, Europe, Israel, New Zealand, and North America. A total of 945 patients underwent randomization: 316 patients were assigned to the nivolumab group, 314 to the nivolumab plus ipilimumab group, and 315 to the ipilimumab group (Fig. S1 in the Supplementary Appendix). Baseline characteristics were balanced across the three groups. A total of 58.0% had stage M1c disease, 36.1% had an elevated lactate dehydrogenase level, 31.5% had a BRAF mutation, and 26.5% had positive PD-L1 status (Table 1).

All randomized patients had been followed for a minimum of 9 months at the time of database lock (February 17, 2015); 117 of 313 patients (37.4%) in the nivolumab group, 93 of 313 patients (29.7%) in the nivolumab plus ipilimumab group, and 50 of 311 patients (16.1%) in the ipilimumab group were continuing study treatment (Table S1 in the Supplementary Appendix). The most frequent reason for discontinuation was disease progression in the nivolumab and ipilimumab monotherapy groups (154 of 313 patients [49.2%] and 202 of 311 patients [65.0%], respectively), versus study drug toxicity in the nivolumab plus ipilimumab group (120 of 313 patients [38.3%]). The number of patients who had died was 85 (27.2%) in the nivolumab group, 86 (27.5%) in the nivolumab plus ipilimumab group, and 114 (36.7%) in the ipilimumab group.

The median number of doses in patients who received nivolumab alone or ipilimumab alone was 15 (range 1–38) and 4 (1–4), respectively. In the combination group, the median number of doses was 4 (range 1–39) for nivolumab and 4 (range 1–4) for ipilimumab; 147 of 313 patients (47%) received four or more doses of nivolumab monotherapy after combination treatment.

Efficacy

The median progression-free survival was 6.5 months (95% confidence interval [CI], 4.3 to 9.5) in the nivolumab group, 11.5 months (95% CI, 8.9 to 16.5) in the nivolumab plus ipilimumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group. A significant improvement in progression-free survival was observed in the nivolumab plus ipilimumab group as compared with the ipilimumab group (hazard ratio, 0.42; 95% CI, 0.31 to 0.57; $P<0.0001$) (Fig 1A). A significant improvement in progression-free survival was also observed in the nivolumab group as compared with the ipilimumab group (hazard ratio, 0.57; 95% CI, 0.43 to 0.76; $P<0.00001$) (Fig. 1A). The hazard ratio for the comparison between nivolumab plus ipilimumab and nivolumab groups was 0.74 (95% CI, 0.60 to 0.92).

Analyses of progression-free survival among prespecified patient subgroups showed a consistent improvement with nivolumab or nivolumab plus ipilimumab as compared with ipilimumab, including subgroups defined by PD-L1 status, BRAF mutation status, and metastasis stage (Fig. S2 in the Supplementary Appendix). In the combination group,

median PFS was 11.7 months (95% CI, 8.0 to not reached) among patients with a BRAF mutation and was 11.2 months (95% CI, 8.3 to not reached) in patients with wild-type BRAF. For patients with a positive PD-L1 tumor status, median progression-free survival in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups was 14.0 months (95% CI, 9.1 to not reached), 14.0 months (95% CI, 9.7 to not reached), and 3.9 months (95% CI, 2.8 to 4.2), respectively (Fig. 1B). For patients with a negative PD-L1 tumor status, median progression-free survival in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups was 5.3 months (95% CI, 2.8 to 7.1 months), 11.2 months (95% CI, 8.0 to not reached) and 2.8 months (95% CI, 2.8 to 3.1), respectively (Fig. 1C).

Investigator-assessed objective response rates were 43.7% (95% CI, 38.1 to 49.3%), 57.6% (95% CI, 52.0 to 63.2), and 19.0% (95% CI, 14.9 to 23.8) in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively (Table 2). The percentage of patients with a complete response was higher in the nivolumab plus ipilimumab group than in either the nivolumab or ipilimumab alone groups (11.5% vs. 8.9% and 2.2%) (Table 2). Time to objective response was similar in each group (Table 2), and the median duration of response was not reached in any of the groups.

Median reduction in the sum of the longest diameters of tumor target lesions was −34.5% (interquartile range: −75.4 to 15.4), −51.2% (−75.8 to −10.2), and 5.8% (−28.0 to 33.3) in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively (Fig. 2). Among patients with PD-L1-positive tumors, the objective response rates were 57.5% (95% CI, 45.9 to 68.5), 72.1% (95% CI, 59.9 to 82.3), and 21.3% (95% CI, 12.7 to 32.3) for the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively; in patients with PD-L1-negative tumors, the objective response rates were 41.3% (95% CI, 34.6 to 48.4), 54.8% (95% CI, 47.8 to 61.6), and 17.8% (95% CI, 12.8 to 23.8) (Table S2 in the Supplementary Appendix).

Adverse Events

Treatment-related adverse events of any grade occurred in 82.1%, 95.5%, and 86.2% of patients in the nivolumab, nivolumab plus ipilimumab groups, and ipilimumab groups, respectively (Table 3). The most common adverse events in the nivolumab group were fatigue (in 34.2% of patients), rash (in 21.7%), and diarrhea (in 19.2%). In the nivolumab plus ipilimumab and ipilimumab groups, diarrhea (in 44.1% and 33.1% of patients, respectively), fatigue (in 35.1% and 28.0%), and pruritus (in 33.2% and 35.4%) were most common. The incidence of treatment-related adverse events of grade 3 or 4 was also higher in the nivolumab plus ipilimumab group than in either the nivolumab or ipilimumab groups (55.0% vs. 16.3% and 27.3%), with diarrhea being the most common (2.2%, 9.3%, and 6.1% in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively). Treatment-related adverse events of any grade leading to discontinuation occurred in 7.7%, 36.4%, and 14.8% of patients in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively, with the most common being diarrhea (in 1.9%, 8.3%, and 4.5%, respectively) and colitis (in 0.6%, 8.3%, and 7.7%, respectively). One death due to study-drug toxicity was reported in the nivolumab group (neutropenia) and one in the ipilimumab

group (cardiac arrest), although such adverse events have not been associated with these drugs in prior studies. No treatment-related deaths were reported in the combination group.

Select adverse events — defined as those with a potential immunologic etiology — were analyzed according to organ category as in previous studies.[9,10] The most frequent grade 3 or 4 treatment-related select adverse events were diarrhea (2.2%, 9.3%, and 6.1% of patients in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively), colitis (in 0.6%, 7.7%, and 8.7%, respectively), increased alanine aminotransferase (in 1.3%, 8.3%, and 1.6%, respectively), and increased aspartate aminotransferase (in 1.0%, 6.1%, and 0.6%, respectively) (Table S3 in the Supplementary Appendix). With the use of immune modulatory agents, resolution rates for grade 3 or 4 select adverse events were generally similar across treatment groups, and were between 85–100% across organ categories in the nivolumab plus ipilumumab group. As observed in prior studies, most endocrine events in all treatment groups did not resolve (Table S4 in the Supplementary Appendix).

Discussion

In this randomized, double-blind, phase 3 study, both nivolumab alone and the combination of nivolumab and ipilimumab significantly increased progression-free survival and objective response rates, as compared with ipilimumab alone, in previously untreated advanced melanoma. These results were observed independently of PD-L1 tumor status, BRAF mutation status, or metastasis stage. Baseline characteristics of study participants were typical of patients with advanced melanoma, although the BRAF mutation rate (31.5%) was lower than the 40–50% generally reported for advanced disease.[19] While not a primary end point of the study, the combination of nivolumab and ipilimumab resulted in numerically longer progression-free survival and a higher response rate as compared with nivolumab alone in the overall study population. While time to response was similar between groups, the first tumor assessment was done at week 12 and thus the possibility that responses may have occurred earlier with the combination remains unknown.

The median progression-free survival reported for the combination of nivolumab and ipilimumab in this study (11.7 months in BRAF-mutant patients) is similar to that recently reported for the combination of BRAF and MEK inhibition in BRAF-mutant metastatic melanoma (9.9 months for vemurafenib and cobimetinib;[2] 9.3 to 11.4 months for dabrafenib and trametinib[3,4]). Resistance to such targeted therapies is almost inevitable when used as monotherapy and in many cases is very rapid. The confirmed rate of objective response for combined nivolumab and ipilimumab (57.6%) is numerically higher than observed with PD-1 blockade alone in advanced melanoma (nivolumab [40%] in treatment-naïve patients with wild-type BRAF[9] or pembrolizumab [37%] in ipilimumab-naïve patients[20]). The results are also consistent with those of previous studies evaluating the combination.[15,16] It is hoped that based on the mechanism of action of nivolumab and ipilimumab, which in a phase 1 trial resulted in a 2-year overall survival rate of 88%,[21] as well as the long-term survival data reported for ipilimumab,[7,8] the efficacy results reported here will be reflected in an overall survival benefit.

The results of subgroup analyses suggest that the greatest benefit for the combination of nivolumab and ipilimumab versus nivolumab alone may occur in the setting of negative PD-L1 tumor expression. In the PD-L1-positive group, both nivolumab alone and nivolumab plus ipilimumab resulted in a similar prolongation of progression-free survival as compared with ipilimumab alone, although objective response rates were numerically higher in the combination group versus either nivolumab or ipilimumab alone. Thus, the use of PD-L1 as a biomarker may allow clinicians to make more informed decisions about the risk-benefit of combination therapy versus monotherapy. However, caution is warranted in interpreting these data as (1) the effects on overall survival are not yet known, and (2) the optimal method and cut-off for assaying PD-L1 expression remains to be determined. Nonetheless, the observation of at least additive activity of the combination of ipilimumab and nivolumab in the setting of negative PD-L1 expression is of interest in melanoma as well as in other tumor types in which PD-1 checkpoint inhibitors are under evaluation.

The incidence of adverse events in this study was, in general, lowest in the nivolumab group and highest in the combination group. The overall incidence of grade 3 or 4 drug-related adverse events was higher in the combination group as compared with ipilimumab alone (39.6% versus 18.6%), as a result of a slightly higher incidence in most adverse events, particularly hepatic toxicity, where the rates of grade 3 or 4 ALT/AST elevations were 6–8% for the combination and approximately 1% for ipilimumab alone. One drug-related death was reported in each of the nivolumab and ipilimumab groups but none in the combination group. Overall, the safety profile of the combination of nivolumab and ipilimumab was consistent with previous experience with nivolumab or ipilimumab alone.[15,16] No new safety signals were identified, and adverse events were manageable with established treatment guidelines as most select adverse events resolved with immune modulatory agents. These data suggest that the combination of nivolumab and ipilimumab can be used safely in a broad range of clinical settings.

In summary, we report increased progression-free survival and objective response rates for nivolumab alone and the combination of nivolumab and ipilimumab, as compared with ipilimumab alone, in previously untreated advanced melanoma. Adverse events with the combination were managed with established algorithms, with no study drug-related deaths. The combination of nivolumab and ipilimumab may represent a means to improve outcomes with either agent as monotherapy, particularly for patients having PD-L1-negative tumors. Overall, nivolumab alone and the combination of nivolumab and ipilimumab are promising treatment options for previously untreated advanced melanoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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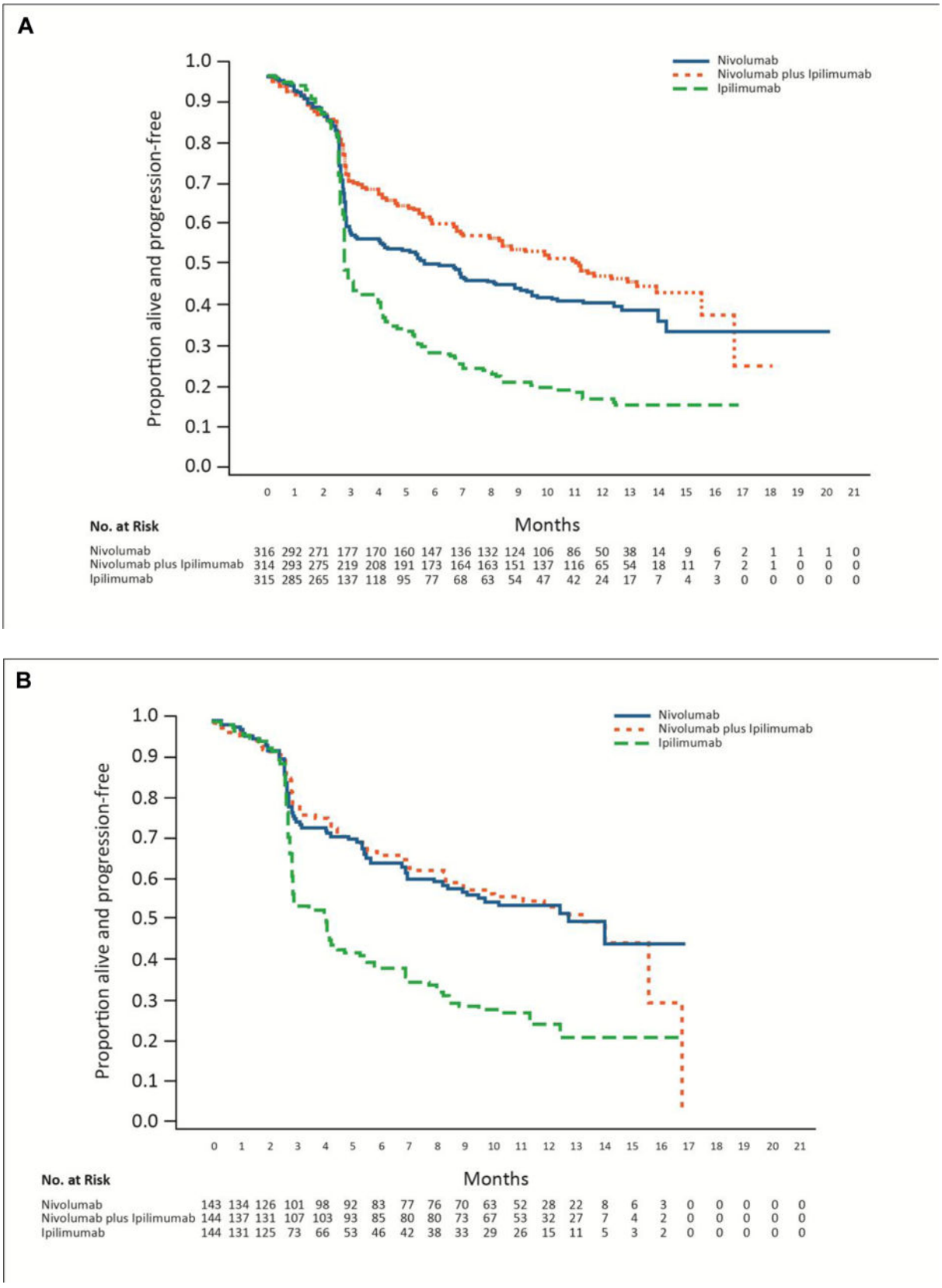

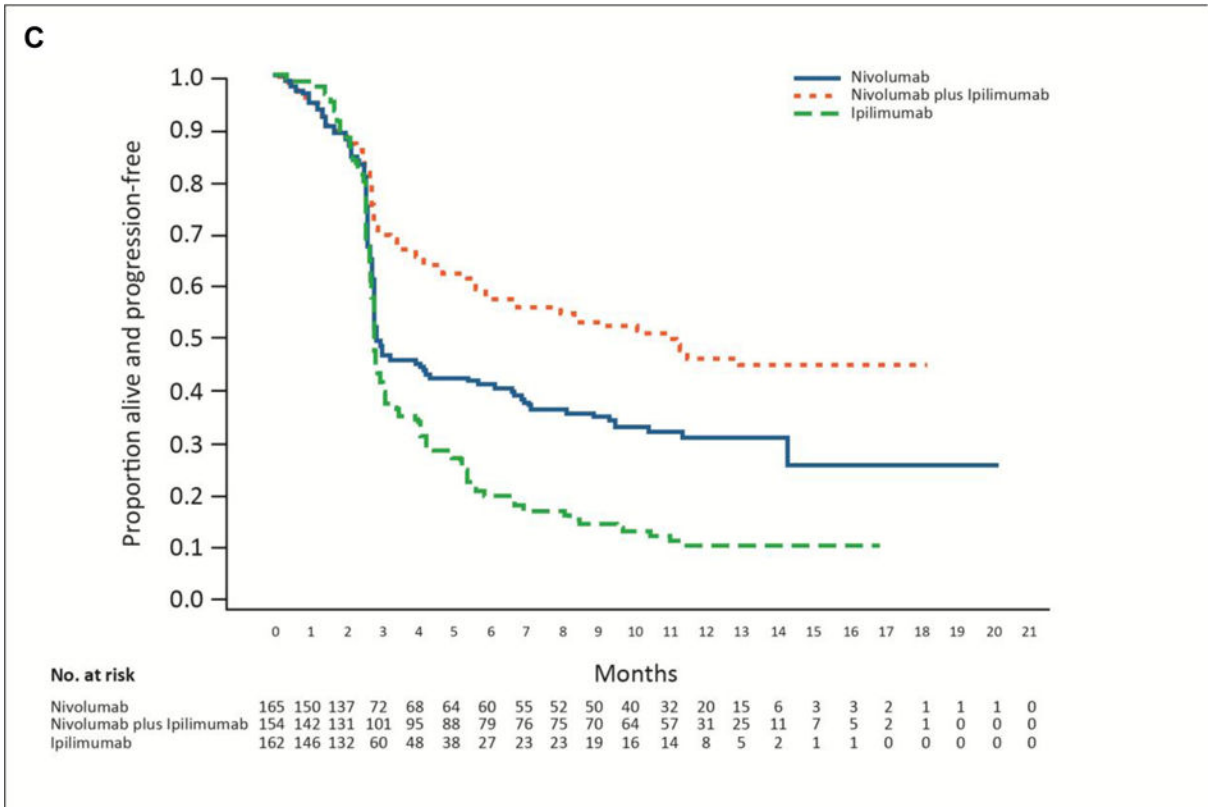

Figure 1. Progression-free Survival

Panel A shows the Kaplan–Meier curves for progression-free survival in the intention-to-treat population. Patients were followed for a minimum of 9 months. Panels B and C show the Kaplan–Meier curves for progression-free survival in patients with PD-L1-positive and PD-L1-negative tumors, respectively.

[Please note: the KM curves shown in the graph below are based on verified PD-L1 assay data. The graphs will be updated based on validated PD-L1 data, although it is expected that there will be little difference between the verified and validated graphs.]

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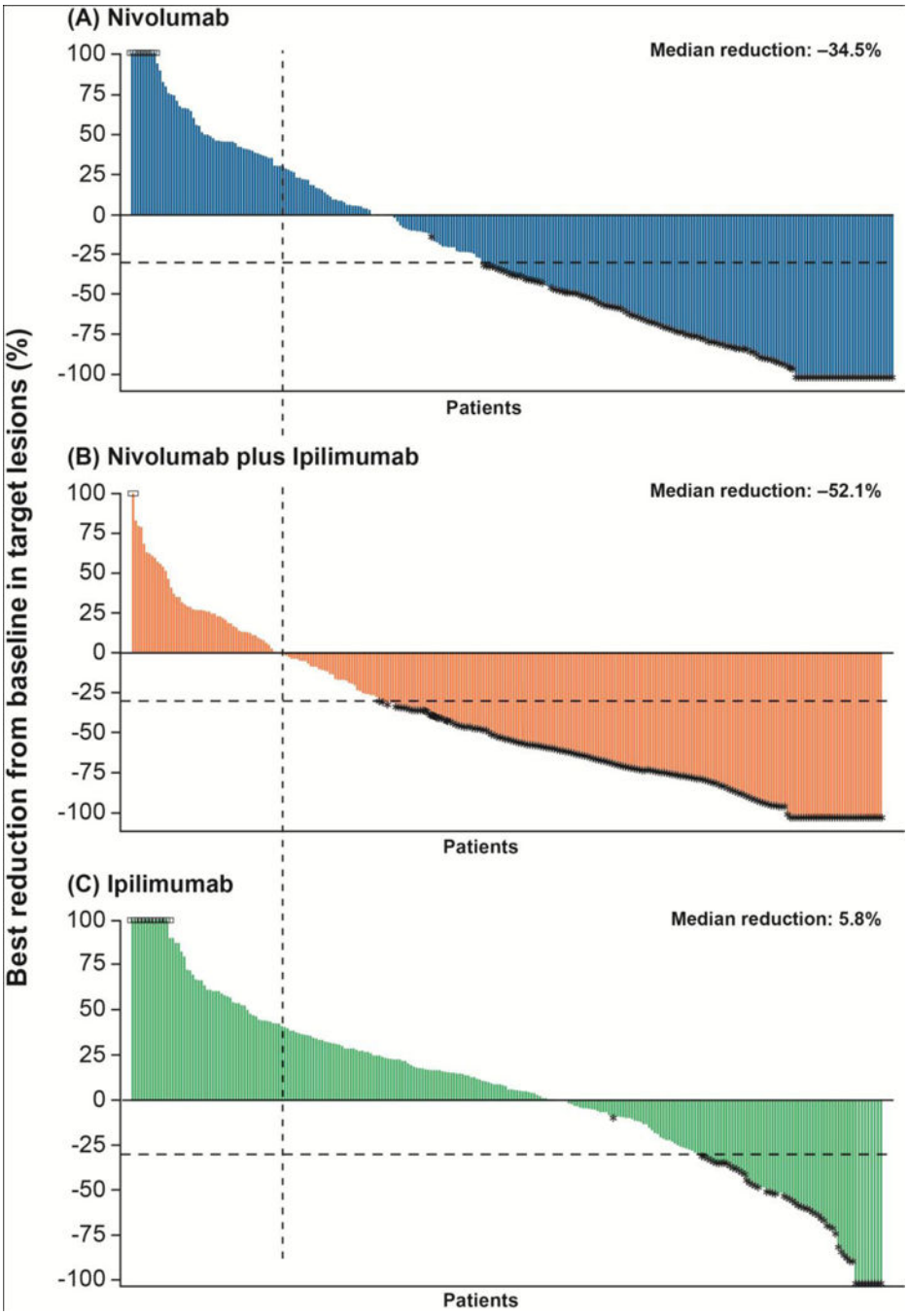

Figure 2. Tumor Burden Change in Target Lesions

The waterfall plots show the maximum change from baseline in the sum of the reference diameters of the target lesion in patients receiving nivolumab (Panel A), nivolumab plus ipilimumab (Panel B), and ipilimumab (Panel C). Data are shown for all the patients who had a response that could be evaluated in the target lesion at baseline and who underwent at least one tumor assessment during treatment. The percentage increase was truncated at 100% (rectangles). Symbols indicate patients who had a response to treatment according to the Response Evaluation Criteria in Solid Tumors, version 1.1. The vertical dashed lines

indicate a 30% reduction in the tumor burden in the target lesion, and the horizontal dashed line indicates the inflexion point for the nivolumab plus ipilimumab group.

Table 1

Baseline Characteristics of the Patients.

Characteristic	Nivolumab alone (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab alone (N=315)	Total (N=945)
Age — yr				
Mean	58.7	59.3	60.8	59.6
Range	25–90	18–88	18–89	18–90
Age groups — no. (%)				
<65 yr	198 (62.7)	185 (58.9)	182 (57.8)	565 (59.8)
≥ 65, < 75 yr	79 (25.0)	94 (29.9)	89 (28.3)	262 (27.7)
≥ 75 yr	39 (12.3)	35 (11.1)	44 (14.0)	118 (12.5)
Sex — no. (%)				
Male	202 (63.9)	206 (65.6)	202 (64.1)	610 (64.6)
Female	114 (36.1)	108 (34.4)	113 (35.9)	335 (35.4)
ECOG performance status — no. (%)				
0	238 (75.3)	230 (73.2)	224 (71.1)	692 (73.2)
1	77 (24.4)	83 (26.4)	91 (28.9)	251 (26.6)
2	1 (0.3)	0	0	1 (0.1)
Not reported	0	1 (0.3)	0	1 (0.1)
M stage — no. (%)				
M1c	184 (58.2)	181 (57.6)	183 (58.1)	548 (58.0)
M0, M1a, or M1b	132 (41.8)	133 (42.4)	132 (41.9)	397 (42.0)
Lactate dehydrogenase — no. (%) *				
≤ ULN	196 (62.0)	199 (63.4)	194 (61.6)	589 (62.3)
>ULN	112 (35.4)	114 (36.3)	115 (36.5)	341 (36.1)
≤2× ULN	271 (85.8)	276 (87.9)	279 (88.6)	826 (87.4)
>2× ULN	37 (11.7)	37 (11.8)	30 (9.5)	104 (11.0)
Unknown	8 (2.5)	1 (0.3)	6 (1.9)	15 (1.6)
Brain metastases at baseline — no. (%)				
Yes	8 (2.5)	11 (3.5)	15 (4.8)	34 (3.6)
No	308 (37.5)	303 (96.5)	300 (95.2)	911 (96.4)
PD-L1 status — no. (%)				
Positive	80 (27.8)	68 (24.5)	75 (27.1)	223(26.4)
Negative	208 (72.2)	210 (75.5)	202 (72.9)	620 (73.5)
BRAF status — no. (%)				
Mutation	100 (31.6)	101 (32.2)	97 (30.8)	298 (31.5)
No mutation	216 (68.4)	213 (67.8)	218 (69.2)	647 (68.5)

* ULN denotes upper limit of normal.

Table 2

Response to Treatment.

Response	Nivolumab alone (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab alone (N=315)
Best overall response — no. (%)[†]			
Complete response	28 (8.9)	36 (11.5)	7 (2.2)
Partial response	110 (34.8)	145 (46.2)	53 (16.8)
Stable disease	34 (10.8)	41 (13.1)	69 (21.9)
Progressive disease	119 (37.7)	71 (22.6)	154 (48.9)
Could not be determined	25 (7.9)	21 (6.7)	32 (10.2)
Objective response[‡]			
No. of patients (% [95% CI])	138 (43.7 [38.1–49.3])	181 (57.6 [52.0–63.2])	60 (19.0 [14.9–23.8])
Estimated odds ratio (95% CI)[§]	3.40 (2.02–5.72)	6.11 (3.59–10.38)	—
Two-sided P value	<0.00001	<0.00001	—
Time to objective response — mo			
No. of responders	138	181	60
Median	2.78	2.76	2.79
Range	2.3–12.5	1.1–11.6	2.5–12.4

[†]Best overall response was assessed by the investigator with the use of RECIST v1.1.

[‡]Data include patients with a complete response and those with a partial response. The calculation of the confidence interval was based on the Clopper–Pearson method. These analyses were conducted using a two-sided Cochran-Mantel-Haenszel test stratified by PD-L1 status, BRAF mutation status, and metastasis stage.

[§]Relative to ipilimumab alone.

Table 3

Adverse Events (Safety Population).*

Event	Nivolumab alone (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab alone (N=311)	
	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4
	no. of patients with event (%)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine aminotransferase	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate aminotransferase	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

*The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

†The treatment-related adverse events listed here were reported in at least 10% of the patients in any of the three study groups.