ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

In an early-phase study involving patients with advanced non–small-cell lung cancer (NSCLC), the response rate was better with nivolumab plus ipilimumab than with nivolumab monotherapy, particularly among patients with tumors that expressed programmed death ligand 1 (PD-L1). Data are needed to assess the long-term benefit of nivolumab plus ipilimumab in patients with NSCLC.

METHODS

In this open-label, phase 3 trial, we randomly assigned patients with stage IV or recurrent NSCLC and a PD-L1 expression level of 1% or more in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab alone, or chemotherapy. The patients who had a PD-L1 expression level of less than 1% were randomly assigned in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy alone. All the patients had received no previous chemotherapy. The primary end point reported here was overall survival with nivolumab plus ipilimumab as compared with chemotherapy in patients with a PD-L1 expression level of 1% or more.

RESULTS

Among the patients with a PD-L1 expression level of 1% or more, the median duration of overall survival was 17.1 months (95% confidence interval [CI], 15.0 to 20.1) with nivolumab plus ipilimumab and 14.9 months (95% CI, 12.7 to 16.7) with chemotherapy (P=0.007), with 2-year overall survival rates of 40.0% and 32.8%, respectively. The median duration of response was 23.2 months with nivolumab plus ipilimumab and 6.2 months with chemotherapy. The overall survival benefit was also observed in patients with a PD-L1 expression level of less than 1%, with a median duration of 17.2 months (95% CI, 12.8 to 22.0) with nivolumab plus ipilimumab and 12.2 months (95% CI, 9.2 to 14.3) with chemotherapy. Among all the patients in the trial, the median duration of overall survival was 17.1 months (95% CI, 15.2 to 19.9) with nivolumab plus ipilimumab and 13.9 months (95% CI, 12.2 to 15.1) with chemotherapy. The percentage of patients with grade 3 or 4 treatment-related adverse events in the overall population was 32.8% with nivolumab plus ipilimumab and 36.0% with chemotherapy.

CONCLUSIONS

First-line treatment with nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level. No new safety concerns emerged with longer follow-up. (Funded by Bristol-Myers Squibb and Ono Pharmaceutical; CheckMate 227 ClinicalTrials.gov number, NCT02477826.)

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A complete list of the investigators in part 1 of the CheckMate 227 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Substantial progress has been made in the first-line treatment of patients with advanced non–small-cell lung cancer (NSCLC) without driver alterations that can be targeted. These treatments include monotherapy blockade of programmed death 1 (PD-1) in patients with tumors that express programmed death ligand 1 (PD-L1) or such treatment in combination with chemotherapy, regardless of tumor PD-L1 expression.[1-7] Still, current therapies extend long-term survival in only a minority of patients with NSCLC.

Nivolumab, a fully human anti–PD-1 antibody, and ipilimumab, a fully human anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody, are immune checkpoint inhibitors with distinct but complementary mechanisms of action. Combination therapy with nivolumab plus ipilimumab has resulted in longer overall survival than previous standard therapies in patients with melanoma[8] and in those with renal-cell carcinoma.[9] In a phase 1 study involving patients with NSCLC, the response rate was better with nivolumab plus ipilimumab than with nivolumab monotherapy, particularly among patients with PD-L1–expressing tumors.[10] Decreasing the dose and frequency of administration of ipilimumab (1 mg per kilogram of body weight every 6 weeks) when combined with nivolumab resulted in fewer adverse events than other ipilimumab regimens while maintaining improved efficacy in patients with NSCLC.[10]

In CheckMate 227, a randomized, open-label, phase 3 trial, we evaluated nivolumab or nivolumab-based regimens as first-line treatment for advanced NSCLC. Part 1 of the trial has two independent primary end points. We reported the primary end point of progression-free survival with nivolumab plus ipilimumab, as compared with chemotherapy, in patients with a high tumor mutational burden (≥10 mutations per megabase) previously.[11] Here, we report the primary end point of overall survival with nivolumab plus ipilimumab, as compared with chemotherapy, in patients with a tumor PD-L1 expression level of 1% or more.

Methods

Patients

Eligibility criteria for CheckMate 227 have been described previously.[11] Patients were adults with squamous or nonsquamous stage IV or recurrent NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability).[12] None of the patients had received previous systemic anticancer therapy for advanced or metastatic disease. Key exclusion criteria were the presence of *EGFR* mutations or known *ALK* translocations sensitive to targeted therapy, autoimmune disease, or untreated or symptomatic central nervous system metastases. Details regarding the eligibility criteria are provided in the Methods section of the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Design and Treatment

We screened pretreatment tumor tissue (freshly collected or archived ≤6 months before enrollment) for tumor PD-L1 expression.[13] Patients who had PD-L1 expression in 1% or more of tumor cells were enrolled in Part 1a of the trial, and those with a PD-L1 expression level of less than 1% were enrolled in Part 1b. In Part 1a, patients were randomly assigned in a 1:1:1 ratio to receive nivolumab (at a dose of 3 mg per kilogram of body weight every 2 weeks) plus ipilimumab (at a dose of 1 mg per kilogram every 6 weeks), nivolumab monotherapy (240 mg every 2 weeks), or platinum-doublet chemotherapy every 3 weeks for up to four cycles. In Part 1b, patients were randomly assigned in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab (360 mg every 3 weeks) plus platinum-doublet chemotherapy (every 3 weeks for up to four cycles), or platinum-doublet chemotherapy alone (every 3 weeks for up to four cycles). In both portions of the trial, patients were stratified according to tumor histologic features (squamous vs. nonsquamous) (Fig. S1 in the Supplementary Appendix). Details regarding tissue requirements for PD-L1 screening and chemotherapy regimens are provided in the Methods section in the Supplementary Appendix.

Treatment continued until disease progression or unacceptable toxicity or, for the immunotherapy regimens, until 2 years of follow-up. Patients who received immunotherapy regimens could continue to receive treatment beyond disease progression if they met prespecified criteria, as described in the Methods section in the Supplementary Appendix. Crossover between the treatment groups during the trial was not permitted. Subsequent therapy was determined at the physician's discretion.

END POINTS AND ASSESSMENTS

The primary end point reported here is overall survival with nivolumab plus ipilimumab, as compared with chemotherapy, in patients with a PD-L1 expression level of 1% or more. Hierarchical secondary end points were progression-free survival, according to blinded independent central review; overall survival with nivolumab plus chemotherapy, as compared with chemotherapy alone, in patients with a PD-L1 expression level of less than 1%; and overall survival with nivolumab monotherapy, as compared with chemotherapy, in patients with a PD-L1 expression level of 50% or more. Prespecified analyses that were not part of the statistical testing hierarchy are descriptive (Table S1). We determined the PD-L1 expression level[13] and tumor mutational burden[11,14-16] as described previously. Adverse events were assessed by the investigator and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

TRIAL OVERSIGHT

One of the sponsors (Bristol-Myers Squibb) and a steering committee designed the trial and analyzed the data, with the participation of all the authors. The institutional review board or independent ethics committee at each center approved the trial. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. An independent data and safety monitoring committee provided oversight of efficacy and safety. All the authors attest that the trial was conducted in accordance with the protocol (available at NEJM.org) and vouch for the accuracy of the data. The manuscript was developed with medical writing support funded by the sponsor.

STATISTICAL ANALYSIS

We planned to enroll 1200 patients for randomization into the three treatment groups in Part 1a. For the primary end point of overall survival with nivolumab plus ipilimumab, as compared with chemotherapy, among the patients with a PD-L1 expression level of 1% or more, we determined that a sample size of 800 patients (with 553 deaths) would provide a power of 90% to detect a hazard ratio of 0.74 at a two-sided significance level of 2.5%. To account for the prespecified interim analysis, the nominal significance level was 0.023 for the final primary and secondary analyses. (Details are provided in the Methods section in the Supplementary Appendix.) If a hierarchical end point was not met, the remaining end points in the hierarchy were considered to be descriptive only. Analyses of all other end points were also descriptive.

We performed Kaplan–Meier analysis to estimate the duration of overall survival and progression-free survival, along with the duration of response. We used a nonparametric log-rank test to assess the primary and secondary hierarchical end points and a stratified Cox proportional-hazards model, with the treatment group as a single covariate, to calculate hazard ratios for death with associated two-sided confidence intervals (which were 97.72% confidence intervals for end points tested in the statistical hierarchy). If the proportional assumption was not met, hazard ratios were still reported to provide a conventional estimate of overall average effect and supplemented by median and landmark estimates. For objective response rates, we used the Clopper–Pearson method to calculate 95% exact two-sided confidence intervals. This report is based on the final analysis of overall survival with nivolumab plus ipilimumab, as compared with chemotherapy, in patients with a PD-L1 expression level of 1% or more, as of the database lock of July 2, 2019.

RESULTS

PATIENTS AND TREATMENT

From August 2015 through November 2016, a total of 2876 patients were enrolled in CheckMate 227 Part 1; of these patients, 1739 underwent randomization. The main reason for exclusion was not meeting the trial criteria. Of the 1189 patients who had a PD-L1 expression level of 1% or more, 396 were assigned to receive nivolumab plus ipilimumab, 396 to receive nivolumab monotherapy, and 397 to receive chemotherapy. Of the 550 patients with a PD-L1 expression level of less than 1%, 187 were assigned to receive nivolumab plus ipilimumab, 177 to receive nivolumab plus chemotherapy, and 186 to receive chemotherapy. The minimum follow-up for overall survival was 29.3 months. Trial-group assignments are summarized in Figure S2 and Table S3. The characteristics of the patients were balanced across the treatment groups at baseline (Table 1 and Tables S4 and S5).

Among the patients who had disease progression during the trial, subsequent systemic therapy was administered in 44.0% of the patients who had received nivolumab plus ipilimumab and in 56.3% of those who had received chemotherapy; immunotherapy was administered in 42.8% of those in the chemotherapy group. Data regarding treatment duration, number of doses, and subsequent therapies within PD-L1 subgroups and in all patients are provided in Tables S6, S7, and S8.

EFFICACY OF NIVOLUMAB PLUS IPILIMUMAB AS COMPARED WITH CHEMOTHERAPY

In patients with a PD-L1 expression level of 1% or more, the median duration of overall survival was 17.1 months (95% confidence interval [CI], 15.0 to 20.1) with nivolumab plus ipilimumab and 14.9 months (95% CI, 12.7 to 16.7) with chemotherapy (P=0.007) (Fig. 1A). Overall survival rates at 1 year and 2 years were 62.6% and 40.0%, respectively, with nivolumab plus ipilimumab, as compared with 56.2% and 32.8%, respectively, with chemotherapy. The rate of overall survival was significantly higher among the patients who received nivolumab plus ipilimumab than among those who received chemotherapy, but the proportional-hazards assumption was not met. The hazard ratio for death of 0.79 (97.72% confidence interval, 0.65 to 0.96) (Table S2) provides an overall estimate of benefit and should be interpreted in the context of the shape of the curves, which are characterized by transient initial survival benefit with chemotherapy, followed by long-term benefit with nivolumab plus ipilimumab. Overall survival in most subgroups favored nivolumab plus ipilimumab (Fig. 1B); the exceptions were patients with liver metastases and those who had never smoked. The results of the analysis of progression-free survival also favored nivolumab plus ipilimumab over chemotherapy (Fig. S3).

The objective response rate was 35.9% (95% CI, 31.1 to 40.8) with nivolumab plus ipilimumab (with 5.8% of patients having a complete response) versus 30.0% (95% CI, 25.5 to 34.7) with chemotherapy (with 1.8% of patients having a complete response) (Table S9). The median duration of response was 23.2 months (95% CI, 15.2 to 32.2) with nivolumab plus ipilimumab and 6.2 months (95% CI, 5.6 to 7.4) with chemotherapy. The proportion of patients with an ongoing response was also higher with the combination therapy than with chemotherapy (64.2% vs. 27.9% at 1 year and 49.5% vs. 11.0% at 2 years) (Fig. S3).

We further evaluated nivolumab plus ipilimumab, as compared with chemotherapy, in a prespecified descriptive analysis of patients with a PD-L1 expression level of less than 1% and in all the trial patients. In patients with a PD-L1 expression level of less than 1%, the median duration of overall survival was longer with nivolumab plus ipilimumab (17.2 months; 95% CI, 12.8 to 22.0) than with chemotherapy (12.2 months; 95% CI, 9.2 to 14.3), with a hazard ratio for death of 0.62 (95% CI, 0.48 to 0.78) (Fig. 2A). This benefit was observed across most subgroups (Fig. S4). The 2-year overall survival rates were 40.4% for nivolumab plus ipilimumab and 23.0% for chemotherapy.

Among all the trial patients, regardless of the PD-L1 expression level, the median duration and rate of overall survival were higher among the patients who received nivolumab plus ipilimumab than among those who received chemotherapy, with a duration of 17.1 months (95% CI, 15.2 to 19.9) and 13.9 months (95% CI, 12.2 to 15.1), respectively, and a rate of overall survival of 40.1% and 29.7%, respectively, at 2 years (Fig. 2B); the overall survival benefit was consistent across most subgroups (Fig. S5). Benefits for nivolumab plus ipilimumab with respect to progression-free survival, objective response rate, and duration of response were also seen in patients with a PD-L1 expression level of less than 1% and in all the trial patients (Figs. S6 and S7 and Table S9).

SECONDARY END POINTS IN HIERARCHICAL TESTING

Among the patients with a PD-L1 expression level of less than 1%, the rate of progression-free survival was significantly higher with nivolumab plus chemotherapy than with chemotherapy alone (10.5% vs. 4.6% at 2 years; hazard ratio for disease progression or death, 0.73; 97.72% CI, 0.56 to 0.95; P=0.007). The median duration of overall survival was 15.2 months (95% CI, 12.3 to 19.8) with nivolumab plus chemotherapy and 12.2 months (95% CI, 9.2 to 14.3) with chemotherapy alone. However, the between-group difference did not meet the nominal significance level of 0.023 (hazard ratio for death, 0.78; 97.72% CI, 0.60 to 1.02,

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	PD-L1 ≥1%			All Patients	
	Nivolumab plus Ipilimumab (N=396)	Nivolumab Monotherapy (N=396)†	Chemotherapy (N=397)	Nivolumab plus Ipilimumab (N=583)	Chemotherapy (N=583)
Age					
Median (range)	64 (26–84)	64 (27–85)	64 (29–87)	64 (26–87)	64 (29–87)
Category — no. (%)					
<65 yr	199 (50.3)	210 (53.0)	207 (52.1)	306 (52.5)	305 (52.3)
≥65 to <75 yr	157 (39.6)	129 (32.6)	149 (37.5)	219 (37.6)	223 (38.3)
≥75 yr	40 (10.1)	57 (14.4)	41 (10.3)	58 (9.9)	55 (9.4)
Sex — no. (%)					
Male	255 (64.4)	272 (68.7)	260 (65.5)	393 (67.4)	385 (66.0)
Female	141 (35.6)	124 (31.3)	137 (34.5)	190 (32.6)	198 (34.0)
ECOG performance-status score — no. (%)‡					
0	135 (34.1)	142 (35.9)	134 (33.8)	204 (35.0)	191 (32.8)
1	260 (65.7)	252 (63.6)	259 (65.2)	377 (64.7)	386 (66.2)
Other score or missing data	1 (0.3)	2 (0.5)	4 (1.0)	2 (0.3)	6 (1.0)
Smoking status — no. (%)					
Never smoked	56 (14.1)	50 (12.6)	51 (12.8)	79 (13.6)	78 (13.4)
Current or former smoker	334 (84.3)	342 (86.4)	340 (85.6)	497 (85.2)	499 (85.6)
Missing data	6 (1.5)	4 (1.0)	6 (1.5)	7 (1.2)	6 (1.0)
Tumor histologic type — no. (%)					
Squamous	117 (29.5)	117 (29.5)	116 (29.2)	163 (28.0)	162 (27.8)
Nonsquamous	279 (70.5)	279 (70.5)	281 (70.8)	419 (71.9)	421 (72.2)
Missing data	0	0	0	1 (0.2)	0
PD-L1 status — no. (%)§					
<1%	NA	NA	NA	187 (32.1)	186 (31.9)
≥1%	396 (100.0)	396 (100.0)	397 (100.0)	396 (67.9)	397 (68.1)
1–49%	191 (48.2)	182 (46.0)	205 (51.6)	191 (32.8)	205 (35.2)
≥50%	205 (51.8)	214 (54.0)	192 (48.4)	205 (35.2)	192 (32.9)
Tumor mutational burden — no. (%)¶					
Patients evaluated	240 (60.6)	228 (57.6)	242 (61.0)	330 (56.6)	349 (59.9)
≥10 mut/Mb	101 (42.1)	102 (44.7)	112 (46.3)	139 (42.1)	160 (45.8)
<10 mut/Mb	139 (57.9)	126 (55.3)	130 (53.7)	191 (57.9)	189 (54.2)

* NA denotes not applicable because all the patients in this group had a PD-L1 expression level of 1 or more. Percentages may not total 100 because of rounding.

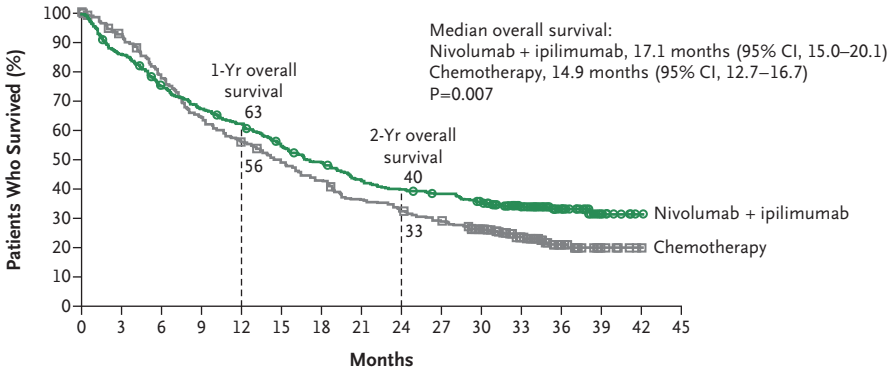
† Nivolumab monotherapy was evaluated only in the primary-analysis population involving patients with a PD-L1 (programmed death ligand 1) tumor expression of 1% or more.

‡ On the performance-status evaluation of the Eastern Cooperative Oncology Group (ECOG), a score of 0 indicates that the patient is fully active, and a score of 1 indicates that the patient is restricted in physically strenuous activity but ambulatory. An ECOG score of 2 or more was reported in 4 patients in the group with PD-L1 expression of 1% or more and in 6 patients in the overall population; data were missing for 3 patients and 2 patients in the two populations, respectively.

§ The status of PD-L1 expression was determined with the use of the PD-L1 IHC 28–8 pharmDx assay (Dako).

¶ The number of mutations (mut) was determined with the use of the FoundationOne CDx assay.

A Overall Survival in Patients with a PD-L1 Expression Level of 1% or More



No. at Risk

Nivolumab + ipilimumab	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
Chemotherapy	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

B Risk of Death in Prespecified Subgroups

Subgroup	No. of Patients	Median Overall Survival		Unstratified Hazard Ratio for Death (95% CI)
		Nivolumab + ipilimumab (N=396)	Chemotherapy (N=397)	
		months		
All patients	793	17.1	14.9	0.79 (0.65–0.96)
Age				
<65 yr	406	19.7	16.0	0.70 (0.55–0.89)
65 to <75 yr	306	16.6	14.5	0.91 (0.70–1.19)
≥75 yr	81	13.5	11.4	0.92 (0.57–1.48)
Sex				
Male	515	18.7	14.0	0.75 (0.61–0.93)
Female	278	16.6	16.2	0.91 (0.69–1.21)
ECOG score				
0	269	24.4	17.5	0.66 (0.48–0.89)
1	519	14.6	12.7	0.89 (0.73–1.09)
Smoking status				
Never smoked	107	15.2	19.6	1.23 (0.76–1.98)
Current or former smoker	674	18.1	14.1	0.77 (0.64–0.92)
Tumor histologic type				
Squamous	236	14.8	9.2	0.69 (0.52–0.92)
Nonsquamous	557	19.4	17.2	0.85 (0.69–1.04)
Liver metastases				
Yes	156	9.5	11.9	1.05 (0.74–1.49)
No	637	19.9	16.3	0.76 (0.63–0.92)
Bone metastases				
Yes	208	13.4	10.0	0.75 (0.55–1.03)
No	585	18.8	16.7	0.81 (0.67–0.99)
CNS metastases				
Yes	81	16.8	13.4	0.68 (0.41–1.11)
No	712	17.1	14.9	0.82 (0.68–0.98)

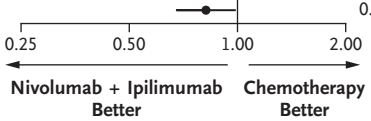


Figure 1 (facing page). Overall Survival in Patients with a Tumor PD-L1 Expression Level of 1% or More and in Prespecified Subgroups.

Panel A shows the primary end point of overall survival in patients in whom 1% or more of tumor cells expressed PD-L1 (programmed death ligand 1) in the group that received nivolumab plus ipilimumab and in the group that received chemotherapy. Also shown are the 1-year and 2-year rates of survival in the two groups. Panel B shows the risk of death according to prespecified subgroups of the patients in Panel A. On the performance-status evaluation of the Eastern Cooperative Oncology Group (ECOG), a score of 0 indicates that the patient is fully active, and a score of 1 indicates that the patient is restricted in physically strenuous activity but ambulatory. The stratified hazard ratio for the overall population is shown with a 97.72% confidence interval (CI). CNS denotes central nervous system.

P=0.035) (Fig. S8). Thus, formal statistical testing of the one remaining secondary end point was not conducted.

EFFICACY OF NIVOLUMAB PLUS IPILIMUMAB AS COMPARED WITH NIVOLUMAB MONOTHERAPY AND NIVOLUMAB PLUS CHEMOTHERAPY

The contribution of ipilimumab was evaluated in an analysis of nivolumab plus ipilimumab, as compared with nivolumab monotherapy, in patients with a PD-L1 expression level of 1% or more (Fig. S3) and in those with a PD-L1 expression level of 50% or more (Fig. S9 and Table S9). In patients with a PD-L1 expression level of 1% or more, the rate of overall survival at 2 years was 40.0% with nivolumab plus ipilimumab and 36.2% with nivolumab monotherapy. In patients with a PD-L1 expression level of 50% or more, the 2-year overall survival rate was 48.1% and 41.9%, respectively. The percentage of patients who had a complete response with nivolumab plus ipilimumab, as compared with nivolumab monotherapy, was 5.8% and 3.0%, respectively, among the patients with a PD-L1 expression level of 1% or more and 8.8% and 4.7%, respectively, among those with a PD-L1 expression level of 50% or more. The median duration of response was 23.2 months (95% CI, 15.2 to 32.2) with nivolumab plus ipilimumab and 15.5 months (95% CI, 12.7 to 23.5) with nivolumab monotherapy among the patients with a PD-L1 expression level of 1% or more; among those with a PD-L1 expression level of 50% or more, the median duration of response was 31.8 months (95% CI, 18.7 to not reached) and 17.5 months (95% CI, 13.5 to 31.0), respectively.

We also evaluated the benefit of nivolumab plus ipilimumab, as compared with nivolumab plus chemotherapy, in patients with a PD-L1 expression level of less than 1% (Fig. S6). The objective response rate was 27.3% with nivolumab plus ipilimumab and 37.9% with nivolumab plus chemotherapy. At 2 years, the overall survival rate was 40.4% and 34.7%, respectively. The median duration of response was longer with nivolumab plus ipilimumab than with nivolumab plus chemotherapy (18.0 months vs. 8.3 months).

EFFECT OF PD-L1 EXPRESSION AND TUMOR MUTATIONAL BURDEN

An overall survival benefit with nivolumab plus ipilimumab, as compared with chemotherapy, was observed regardless of the subgroup of PD-L1 expression level. Exploratory analysis of additional PD-L1 expression thresholds that are currently used for selection of anti–PD-1 monotherapy showed more variable benefit (Fig. 3). Among the 679 patients (58.2%) in whom the tumor mutational burden was evaluated, a similar degree of overall survival benefit was observed in patients who received nivolumab plus ipilimumab, regardless of whether they had a high tumor mutational burden or a low tumor mutational burden (≥10 vs. <10 mutations per megabase, respectively), despite the previous observation of improved progression-free survival in patients with a high tumor mutational burden.[11]

Combining the two key biomarkers (PD-L1 expression level and tumor mutational burden) did not identify a subgroup that had an increased magnitude of benefit with nivolumab plus ipilimumab over chemotherapy, although the sample sizes become more modest in these analyses. For example, the overall survival benefit for nivolumab plus ipilimumab, as compared with chemotherapy, in patients with a high PD-L1 expression level (≥50%) and a high tumor mutational burden was similar to that in patients with a low PD-L1 expression level (<1%) and a low tumor mutational burden (Fig. 3 and Fig. S10).

SAFETY

Data regarding adverse events for all the patients who received nivolumab plus ipilimumab or chemotherapy are provided in Table 2. The frequency of grade 3 or 4 adverse events that were deter-

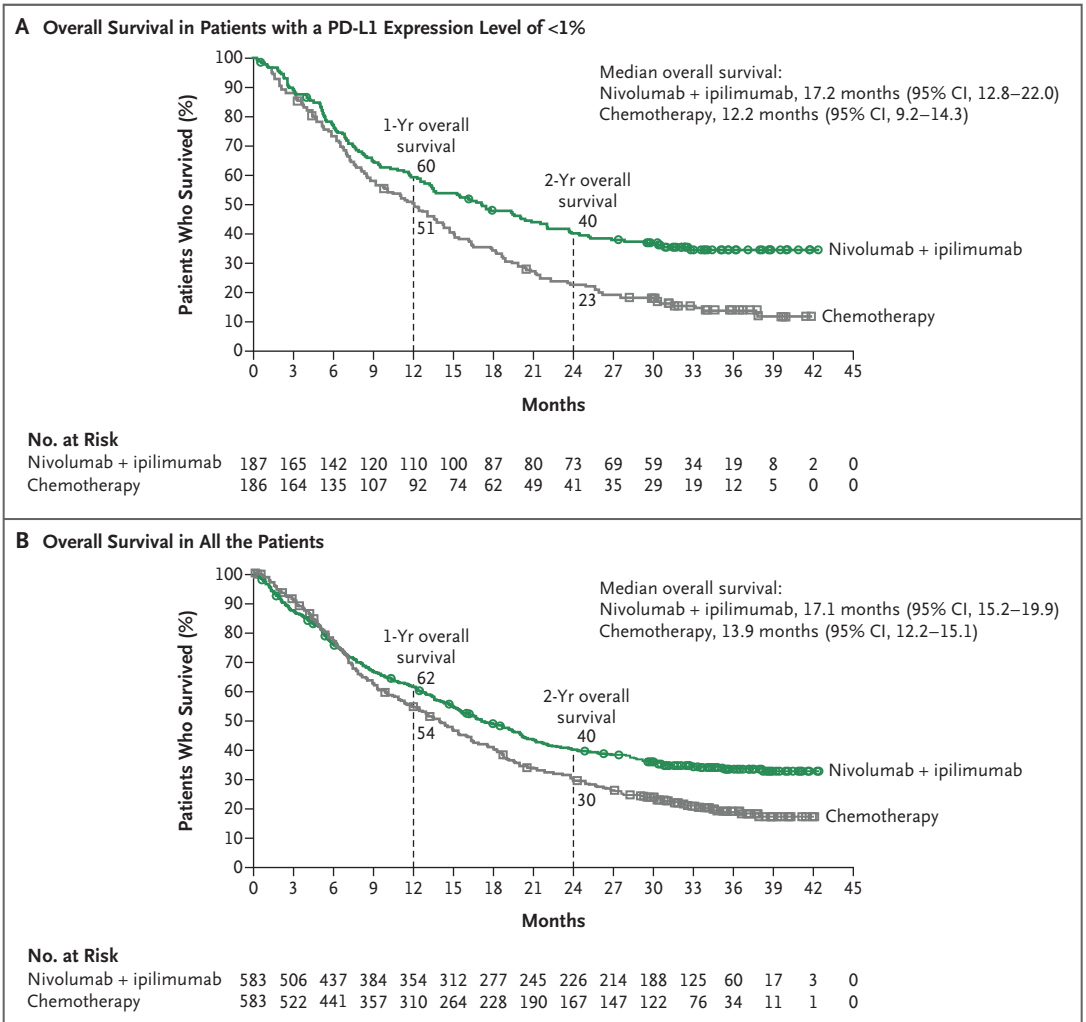


Figure 2. Overall Survival in Patients with a Tumor PD-L1 Expression Level of Less Than 1% and in All the Patients.
Shown is the median duration of overall survival in patients in the group that received nivolumab plus ipilimumab and in the group that received chemotherapy among those who had a tumor PD-L1 expression level of less than 1% (Panel A) and among those in the overall population (Panel B). Also shown are the 1-year and 2-year rates of survival in the two groups.

mined by the investigator to be related to the trial treatment was similar in the group that received nivolumab plus ipilimumab and in the chemotherapy group (32.8% vs. 36.0%). Treatment-related serious adverse events of any grade were more common with nivolumab plus ipilimumab than with chemotherapy (24.5% vs. 13.9%), as were treatment-related adverse events leading to discontinuation (18.1% vs. 9.1%). The most common treatment-related select adverse events of any grade with a potential immunologic cause in the group that received nivolumab plus ipilimumab were skin reactions (in 34.0% of the patients) and endocrine events (in 23.8%) (Table S10). Treatment-related deaths occurred in 8 patients who received nivolumab plus ipilimumab and in 6 patients who received chemotherapy (Table 2). The adverse events that were associated with nivolumab plus ipilimumab and chemotherapy according to PD-L1 expression level were similar to the adverse events in the overall population (Table S11), were consistent with those in previous trials,[10,11] and the incidence did not increase with longer follow-up.[11]

Among the 391 patients who had a PD-L1 expression level of 1% or more who were treated

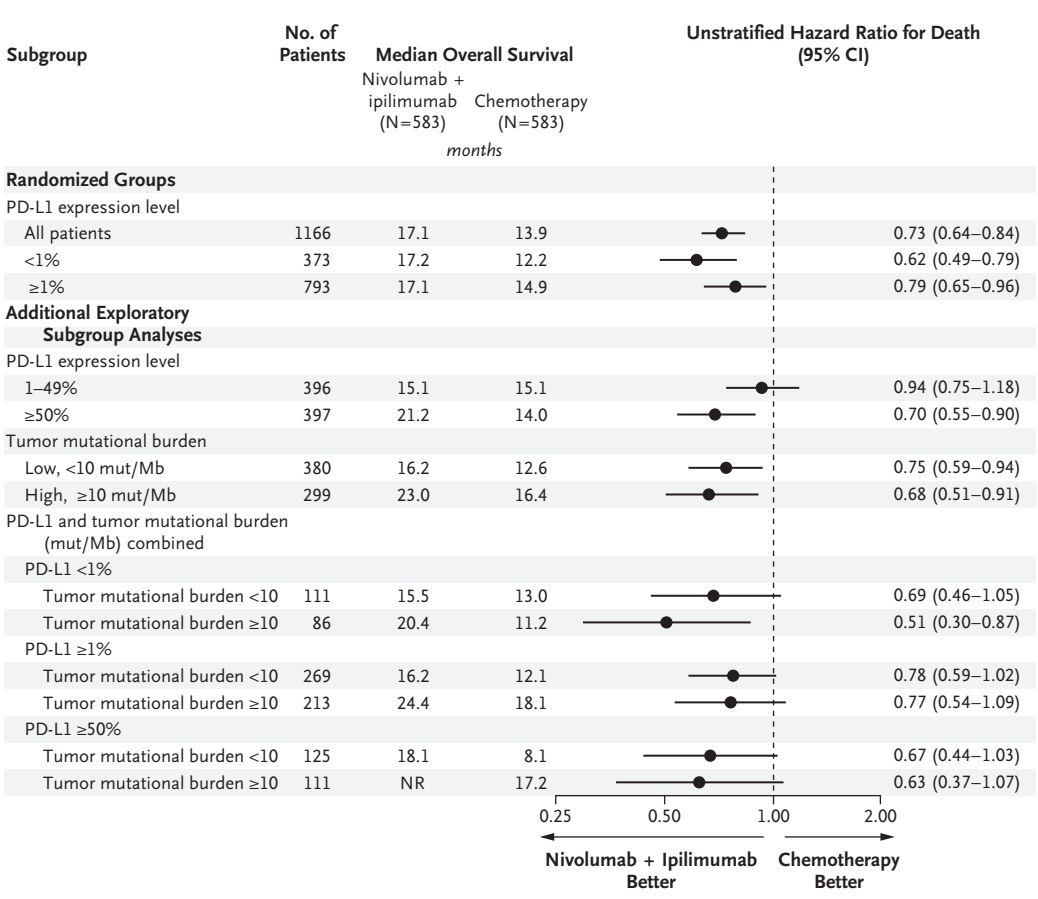


Figure 3. Risk of Death According to Tumor PD-L1 Expression Level and Tumor Mutational Burden.

Shown is the risk of death among the patients who received nivolumab plus ipilimumab and in those who received chemotherapy according to the tumor PD-L1 expression level, tumor mutational (mut) burden, or both in prespecified randomized groups or in exploratory groups. The hazard ratio for the group with a PD-L1 expression level of 1% or more is shown with a 97.72% confidence interval; stratified hazard ratios for all the patients and those with a PD-L1 expression level of 1% or more are shown.

with nivolumab monotherapy, grade 3 or 4 treatment-related adverse events occurred in 76 patients (19.4%), and treatment-related adverse events of any grade resulted in discontinuation in 48 patients (12.3%). Two treatment-related deaths occurred in the nivolumab monotherapy group.

Among the patients with a PD-L1 expression level of less than 1%, fewer grade 3 or 4 treatment-related adverse events or serious adverse events were reported with nivolumab plus ipilimumab (27.0% with adverse events and 16.2% with serious adverse events) than with nivolumab plus chemotherapy (55.8% and 19.2%, respectively). In this subgroup, 3 treatment-related deaths occurred in the group that received nivolumab plus ipilimumab and 4 in the group that received nivolumab plus chemotherapy.

DISCUSSION

In this phase 3, randomized trial, we found that patients with advanced NSCLC and a PD-L1 expression level of 1% or more who received nivolumab plus ipilimumab had a significantly longer duration of overall survival than those who received chemotherapy as first-line treatment. At 2 years, the response rate was 49% with nivolumab plus ipilimumab, as compared with 11% with chemotherapy. The safety of nivolumab plus ipilimumab has been improved in patients with

Table 2. Treatment-Related Adverse Events in All the Recipients of Nivolumab plus Ipilimumab or Chemotherapy.*

Adverse Event	Nivolumab plus Ipilimumab (N=576)		Chemotherapy (N=570)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
	number of patients (percent)			
Treatment-related adverse events				
All events	442 (76.7)	189 (32.8)	467 (81.9)	205 (36.0)
Reported in ≥15% of patients				
Diarrhea	98 (17.0)	10 (1.7)	55 (9.6)	4 (0.7)
Rash	98 (17.0)	9 (1.6)	30 (5.3)	0
Fatigue	83 (14.4)	10 (1.7)	108 (18.9)	8 (1.4)
Decreased appetite	76 (13.2)	4 (0.7)	112 (19.6)	7 (1.2)
Nausea	57 (9.9)	3 (0.5)	206 (36.1)	12 (2.1)
Anemia	22 (3.8)	8 (1.4)	188 (33.0)	66 (11.6)
Neutropenia	1 (0.2)	0	98 (17.2)	54 (9.5)
Treatment-related serious adverse events	141 (24.5)	106 (18.4)	79 (13.9)	61 (10.7)
Treatment-related adverse events leading to discontinuation†	104 (18.1)	71 (12.3)	52 (9.1)	28 (4.9)
Treatment-related death‡	8 (1.4)	—	6 (1.1)	—

* The determination that an adverse event was related to a trial treatment was made by the investigators. The minimum follow-up for safety analyses was 28.3 months, except for treatment-related serious adverse events, which had a minimum follow-up of 29.3 months. All treatment-related adverse events and serious adverse events were reported during the time between the first dose of a trial treatment and 30 days after the last dose.

† For nivolumab plus ipilimumab, these events included treatment-related adverse events leading to the discontinuation of ipilimumab alone or the discontinuation of both nivolumab and ipilimumab; the discontinuation of nivolumab alone was not permitted. Adverse events leading to the discontinuation of ipilimumab earlier than the discontinuation of nivolumab occurred in 18 patients (3.1%).

‡ Treatment-related deaths in the group that received nivolumab plus ipilimumab were from pneumonitis (in 4 patients) and from shock, myocarditis, acute tubular necrosis, and cardiac tamponade (in 1 patient each). Deaths in the chemotherapy group were from sepsis (in 2 patients) and from febrile neutropenia with sepsis, multiple brain infarctions, interstitial lung disease, and thrombocytopenia (in 1 patient each).

NSCLC with the use of a lower dose and frequency of administration of ipilimumab, as was suggested in the phase 1 dose-finding study.[10]

In addition, the duration of overall survival was longer with nivolumab plus ipilimumab than with chemotherapy in all the trial patients, including in those with a PD-L1 expression level of less than 1%, a population for whom anti–PD-1 monotherapy has been insufficient. Although the relative benefit of nivolumab plus ipilimumab, as compared with chemotherapy, was numerically greater in patients with a PD-L1 expression level of less than 1% than in those with a PD-L1 expression level of 1% or more, this result was mostly due to variations in median rates of survival with chemotherapy between the PD-L1 subgroups. The median duration of overall survival and rates of overall survival at 1 year and 2 years with nivolumab plus ipilimumab were nearly identical in these two PD-L1 subgroups. This result is consistent with previous reports involving patients with melanoma and renal-cell carcinoma, which also showed a benefit for nivolumab plus ipilimumab regardless of PD-L1 level.[8,9] The precise underpinnings of the diminished dependence on PD-L1 expression with a combination of PD-1 and CTLA-4 inhibition, as compared with anti–PD-1 monotherapy, are unknown. However, we hypothesize that the differential immune effects of CTLA-4 versus PD-1 inhibition[17,18] may be particularly critical in PD-L1–negative tumors for recruiting effective antitumor immu-

nity from the peripheral compartment, which is increasingly recognized as an important mechanism of response to immunotherapy.[19-21]

Combining nivolumab with ipilimumab has proved to be effective in melanoma and renal-cell carcinoma in previous studies,[8,9,22] yet a key question before this trial was whether the addition of CTLA-4 inhibition to PD-1 blockade contributes to benefit in patients with NSCLC. Although this trial was not powered to compare the two regimens, our findings show better efficacy with nivolumab plus ipilimumab than with nivolumab monotherapy within the same trial. In particular, we observed higher rates of complete response and a longer median duration of response (a difference of >7 months) in the patients who received nivolumab plus ipilimumab. In addition, among the patients with a PD-L1 expression level of less than 1%, those who received nivolumab plus ipilimumab had longer overall survival and a longer duration of response (a difference of nearly 10 months) than did those who received nivolumab plus chemotherapy, although this analysis was not part of the statistical testing hierarchy.

Biomarkers for predicting an enhanced benefit for combination immunotherapy relative to chemotherapy remain elusive. The design of this trial was informed by phase 1 and 2 single-group studies of nivolumab plus ipilimumab that showed increased response rates in patients with PD-L1–expressing tumors or a high tumor mutational burden in patients with NSCLC.[10,23] However, in this large, randomized study, the survival benefit with nivolumab plus ipilimumab over chemotherapy was ultimately similar in the two main PD-L1 subgroups on the basis of a cutoff of 1% of tumor cells. Moreover, based on emerging data related to the tumor mutational burden as a biomarker, CheckMate 227 was amended to add a primary end point of progression-free survival with nivolumab plus ipilimumab versus chemotherapy in patients with a high tumor mutational burden.[11] In the current report, although absolute survival with nivolumab plus ipilimumab was greatest in patients with a high tumor mutational burden, a similar relative benefit of nivolumab plus ipilimumab, as compared with chemotherapy, was seen in patients regardless of tumor mutational burden. The unexpected effect of the tumor mutational burden on the overall survival of patients who received chemotherapy may have contributed to these results. Before we initiated this trial, some[24-27] but not all[28] studies had shown that survival was not affected by tumor mutational burden with chemotherapy treatment. Further understanding of the role of the tumor mutational burden, if any, as a biomarker is warranted before the integration of this factor into clinical practice.

In the primary analysis from this trial, the median duration of overall survival was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with advanced NSCLC who had a PD-L1 expression level of 1% or more. In secondary analyses, the duration of overall survival was also longer with nivolumab plus ipilimumab than with chemotherapy in patients with a PD-L1 expression of less than 1% and in all the trial patients.

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APPENDIX

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