ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Nivolumab, a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody, disrupts PD-1–mediated signaling and may restore antitumor immunity.

METHODS

In this randomized, open-label, international phase 3 study, we assigned patients with nonsquamous non–small-cell lung cancer (NSCLC) that had progressed during or after platinum-based doublet chemotherapy to receive nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks or docetaxel at a dose of 75 mg per square meter of body-surface area every 3 weeks. The primary end point was overall survival.

RESULTS

Overall survival was longer with nivolumab than with docetaxel. The median overall survival was 12.2 months (95% confidence interval [CI], 9.7 to 15.0) among 292 patients in the nivolumab group and 9.4 months (95% CI, 8.1 to 10.7) among 290 patients in the docetaxel group (hazard ratio for death, 0.73; 96% CI, 0.59 to 0.89; P=0.002). At 1 year, the overall survival rate was 51% (95% CI, 45 to 56) with nivolumab versus 39% (95% CI, 33 to 45) with docetaxel. With additional follow-up, the overall survival rate at 18 months was 39% (95% CI, 34 to 45) with nivolumab versus 23% (95% CI, 19 to 28) with docetaxel. The response rate was 19% with nivolumab versus 12% with docetaxel (P=0.02). Although progression-free survival did not favor nivolumab over docetaxel (median, 2.3 months and 4.2 months, respectively), the rate of progression-free survival at 1 year was higher with nivolumab than with docetaxel (19% and 8%, respectively). Nivolumab was associated with even greater efficacy than docetaxel across all end points in subgroups defined according to prespecified levels of tumor-membrane expression (≥1%, ≥5%, and ≥10%) of the PD-1 ligand. Treatment-related adverse events of grade 3 or 4 were reported in 10% of the patients in the nivolumab group, as compared with 54% of those in the docetaxel group.

CONCLUSIONS

Among patients with advanced nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy, overall survival was longer with nivolumab than with docetaxel. (Funded by Bristol-Myers Squibb; CheckMate 057 ClinicalTrials.gov number, NCT01673867.)

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Effective options are limited for patients with nonsquamous non–small-cell lung cancer (NSCLC) whose disease progresses after first-line chemotherapy. Docetaxel was approved as a second-line treatment for advanced NSCLC on the basis of longer survival than that with best supportive care.[1-3] Newer agents, such as pemetrexed and erlotinib, which have a better side-effect profile than docetaxel, have either been shown to be noninferior to docetaxel or have failed to show superiority to docetaxel with respect to overall survival when they are used as second-line therapy.[4,5]

The programmed death 1 (PD-1) receptor expressed on activated T cells is engaged by the tumor-expressed ligands PD-L1 and PD-L2 to down-regulate T-cell activation and promote tumor immune escape (i.e., the mechanism by which tumor cells escape recognition and elimination by the immune system).[6] Nivolumab, a fully human IgG4 PD-1 immune-checkpoint–inhibitor antibody, disrupts PD-1–mediated signaling and may restore antitumor immunity.[7-9]

In phase 1 studies, nivolumab monotherapy showed durable antitumor activity and encouraging results on survival in all NSCLC subtypes.[7,9,10] Among heavily pretreated patients with advanced nonsquamous NSCLC, nivolumab was associated with a response rate of 17.6%, overall survival rates of 42% at 1 year, 23% at 2 years, and 16% at 3 years, and a progression-free survival rate of 18% at 1 year.[10] We report the results of a randomized, open-label, international phase 3 study comparing nivolumab with docetaxel in previously treated patients with advanced nonsquamous NSCLC.

METHODS

PATIENTS

Eligible patients had documented stage IIIB or IV or recurrent nonsquamous NSCLC after radiation therapy or surgical resection and had also had disease recurrence or progression during or after one prior platinum-based doublet chemotherapy regimen. Patients with known *EGFR* mutation or *ALK* translocation were allowed to have received or be receiving an additional line of tyrosine kinase inhibitor therapy, and a continuation of or switch to maintenance therapy with pemetrexed, bevacizumab, or erlotinib was allowed in all patients.

Patients had to be 18 years of age or older, have an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a scale from 0 to 5, with higher numbers indicating greater tumor-related disability; a score of 0 indicates no symptoms, and 1 mild symptoms), and have adequate hematologic, hepatic, and renal function; patients with central nervous system metastases were eligible if the metastases had been treated and were stable. Tumor tissue obtained before treatment was required for use in biomarker analyses but was not used in the selection of patients. Exclusion criteria were autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior treatment with immune-stimulatory antitumor agents including checkpoint-targeted agents, and prior use of docetaxel. Complete eligibility criteria are provided in the study protocol, available with the full text of this article at NEJM.org.

STUDY DESIGN AND TREATMENTS

From November 2012 through December 2013, we enrolled 792 patients, of whom 582 underwent randomization; 292 patients were randomly assigned to receive nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks, and 290 were randomly assigned to receive docetaxel at a dose of 75 mg per square meter of body-surface area every 3 weeks (Fig. S1A in the Supplementary Appendix, available at NEJM.org). Both drugs were administered intravenously. Patients were treated until disease progression or discontinuation of treatment owing to toxic effects or for other reasons (Fig. S1B in the Supplementary Appendix).

Randomization was stratified according to prior maintenance treatment (yes vs. no) and line of therapy (second line vs. third line). For patients in the nivolumab group, treatment could continue beyond initial disease progression if the investigator assessed that the patient was having clinical benefit and did not have an unacceptable level of side effects from the study drug. Requirements for treatment delay or discontinuation because of treatment-related adverse events were specified in the protocol, as were requirements regarding reductions in the docetaxel dose owing to toxic effects, which conformed with the prescribing information on the product label. Reductions in the nivolumab dose were not permitted.

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END POINTS AND ASSESSMENTS

The primary end point was overall survival. Patients were followed for survival continuously while they were receiving treatment and every 3 months after the discontinuation of treatment. All the patients who underwent randomization were followed for survival, unless they had withdrawn consent for survival follow-up. For patients who withdrew consent for survival-related follow-up or were lost to follow-up, information regarding survival was obtained by means of a search of publicly available sources.

Secondary efficacy end points included the rate of investigator-assessed confirmed objective response, progression-free survival, efficacy according to tumor PD-L1 expression level, and patient-reported outcomes. All the patients who underwent randomization were followed for disease progression, except those who had withdrawn consent or who were lost to follow-up.

Tumor response was assessed with the use of the Response Evaluation Criteria in Solid Tumors, version 1.1,[11] at week 9 and every 6 weeks thereafter until disease progression. Safety was assessed by an evaluation of the incidence of clinical adverse events and laboratory variables, which were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Select adverse events (those with a potential immunologic cause) were grouped according to prespecified categories. Analyses of patient-reported outcomes are ongoing.

PD-L1 BIOMARKER ANALYSIS

Tumor PD-L1 protein expression was assessed retrospectively in prospectively collected, pretreatment (archival or recent) tumor-biopsy specimens with the use of a validated, automated immunohistochemical assay (Dako North America) that used a rabbit antihuman PD-L1 antibody (clone 28–8, Epitomics). Tumor PD-L1 expression was confirmed when staining of the tumor-cell membrane (at any intensity) was observed at prespecified expression levels of 1% or higher, 5% or higher, and 10% or higher in a section that included at least 100 tumor cells that could be evaluated.

STUDY OVERSIGHT

The study was designed by the academic authors in collaboration with the sponsor (Bristol-Myers Squibb); the sponsor worked jointly with the investigators to collect and analyze data. The study protocol was approved by an institutional review board or ethics committee at each participating center. The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. Written informed consent was collected from all the patients before enrollment.

An independent data and safety monitoring committee provided oversight of safety and efficacy. On April 16, 2015, the committee declared that overall survival among patients receiving nivolumab was superior to that among those receiving docetaxel. We report here the results of the interim analysis, including overall survival, objective response rate, progression-free survival, and safety, which are based on data from a March 18, 2015, database lock. Updated efficacy results with additional follow-up are reported for overall survival only, on the basis of data from a July 2, 2015, database lock.

All the authors attest that the study was conducted in accordance with the protocol and vouch for the accuracy and completeness of the data and analyses. The first draft of the manuscript was written by the first and last authors; all the authors contributed to subsequent drafts and made the decision to submit the manuscript for publication. All the authors signed a confidentiality agreement with the sponsor. Medical-writing support, funded by the sponsor, was provided by StemScientific.

STATISTICAL ANALYSIS

Overall survival and progression-free survival were analyzed with the use of a two-sided log-rank test stratified according to prior maintenance treatment (yes vs. no) and line of therapy (second line vs. third line). Hazard ratios and confidence intervals were estimated with the use of a stratified Cox proportional-hazards model. Survival curves and rates were estimated with the use of the Kaplan–Meier method. The rates of objective response were compared with the use of a stratified, two-sided Cochran–Mantel–Haenszel test. Nonconventional benefit (i.e., a reduction in the size or number [or both] of target lesions with simultaneous appearance of new lesions or initial progression followed by either tumor reduction or no further progression

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for at least two tumor assessments) in patients treated beyond initial progression was not included in response-based analyses (objective response rate or progression-free survival).

Prespecified subgroup analyses were performed for overall survival, objective response rate, and progression-free survival to assess the consistency of treatment effects in patient subgroups. All the prespecified subgroup analyses of survival, including unstratified hazard ratios and 95% confidence intervals, are reported in the Supplementary Appendix. Hazard ratios were not computed for subgroups that had fewer than 10 patients in a treatment group. Additional prespecified analyses were performed to evaluate the prognostic and predictive roles of prestudy status with respect to PD-L1 expression, with an interaction P value of less than 0.20 considered to be a signal of predictive association.

Demographic and efficacy analyses included all the patients who underwent randomization. Safety analyses included all the treated patients (those who received at least one dose of study drug). At the time of the interim analysis, 413 patients had died (93% of the 442 deaths required for the final analysis). The boundary for declaring superiority with respect to overall survival at the interim analysis was a P value of less than 0.0408, on the basis of the O'Brien–Fleming alpha-spending function. The protocol specified that if superiority with respect to overall survival was shown, the response rate and progression-free survival would then be tested hierarchically at the 5% alpha level. Formal testing for the primary end point was based on the interim analysis. An updated P value is provided, which was based on data from the July 2, 2015, database lock.

RESULTS

PATIENTS AND TREATMENT

Of the 582 patients who underwent randomization, 287 were treated with nivolumab and 268 were treated with docetaxel. Five patients in the nivolumab group and 22 in the docetaxel group did not receive the assigned study drug (Fig. S1 in the Supplementary Appendix). The minimum follow-up for overall survival was 13.2 months.

The median age of the patients was 62 years. Most patients had an ECOG performance-status score of 1, had stage IV cancer, and were current or former smokers (Table 1, and Table S1 in the Supplementary Appendix). The baseline characteristics were balanced between the treatment groups, with slight between-group imbalances in the percentages of male patients and patients younger than 65 years of age.

A median of 6 doses (range, 1 to 52) of nivolumab and 4 doses (range, 1 to 23) of docetaxel were administered. Among the patients in the nivolumab group, 83% received at least 90% of the planned dose intensity. Among the patients in the docetaxel group, 66% received at least 90% of the planned dose intensity. At least one dose delay occurred in 39% of the patients in the nivolumab group and in 37% of those in the docetaxel group. Most of the delays in the nivolumab group (117 of 219 cycles [53%]) and in the docetaxel group (99 of 147 cycles [67%]) lasted 7 days or less; 45% of the delays in the nivolumab group and 46% of those in the docetaxel group were due to adverse events. A total of 26% of the patients in the docetaxel group required a dose reduction.

At the time of the interim analysis, 15% of the patients in the nivolumab group and no patients in the docetaxel group were continuing treatment (Table S2 in the Supplementary Appendix). Subsequent systemic cancer therapy was received by 42% of the patients in the nivolumab group and by 50% of those in the docetaxel group. In the nivolumab group, 23% of the patients received subsequent docetaxel; 2% of the patients in the docetaxel group received subsequent immunotherapy (Table S3 in the Supplementary Appendix).

EFFICACY

Overall Survival

Overall survival was significantly longer with nivolumab than with docetaxel (Fig. 1A). At the time of the interim analysis (minimum follow-up for overall survival, 13.2 months), the median overall survival was 12.2 months (95% confidence interval [CI], 9.7 to 15.0) with nivolumab and 9.4 months (95% CI, 8.1 to 10.7) with docetaxel, representing a 27% lower risk of death with nivolumab (hazard ratio, 0.73; 96% CI, 0.59 to 0.89; P=0.002). The overall survival rate at 1 year was 51% (95% CI, 45 to 56) with nivolumab and 39% (95% CI, 33 to 45) with docetaxel.

The hazard ratios in the analysis of overall survival favored nivolumab across most prespecified patient subgroups; the exceptions were

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Table 1. Baseline Characteristics, Stratification Factors, and Prior Therapy.*

Characteristic	Nivolumab (N=292)	Docetaxel (N=290)	Total (N=582)
Age — yr			
Median	61	64	62
Range	37–84	21–85	21–85
Age ≥75 yr — no. (%)	20 (7)	23 (8)	43 (7)
Male sex — no. (%)	151 (52)	168 (58)	319 (55)
Race — no. (%)†			
White	267 (91)	266 (92)	533 (92)
Asian	9 (3)	8 (3)	17 (3)
Black	7 (2)	9 (3)	16 (3)
Other	9 (3)	7 (2)	16 (3)
ECOG performance-status score — no. (%)‡			
0	84 (29)	95 (33)	179 (31)
1	208 (71)	194 (67)	402 (69)
Not reported	0	1 (<1)	1 (<1)
Disease stage — no. (%)			
IIIB	20 (7)	24 (8)	44 (8)
IV	272 (93)	266 (92)	538 (92)
Smoking status — no. (%)			
Current or former smoker	231 (79)	227 (78)	458 (79)
Never smoked	58 (20)	60 (21)	118 (20)
Unknown	3 (1)	3 (1)	6 (1)
Positive *EGFR* mutation status — no. (%)§	44 (15)	38 (13)	82 (14)
Positive *ALK* translocation status — no. (%)§	13 (4)	8 (3)	21 (4)
Positive *KRAS* mutation status — no. (%)§	28 (10)	34 (12)	62 (11)
Prior maintenance therapy — no. (%)	122 (42)	111 (38)	233 (40)
No. of prior systemic regimens — no. (%)¶			
1	256 (88)	259 (89)	515 (88)
2	35 (12)	31 (11)	66 (11)
Other	1 (<1)	0	1 (<1)
Type of prior systemic therapy — no. (%)‖			
Platinum-based therapy	292 (100)	290 (100)	582 (100)
ALK inhibitor	1 (<1)	2 (1)	3 (1)
EGFR tyrosine kinase inhibitor	29 (10)	24 (8)	53 (9)
Best response to most recent prior systemic regimen according to the investigator — no. (%)			
Complete or partial response	73 (25)	68 (23)	141 (24)
Stable disease	103 (35)	96 (33)	199 (34)
Progressive disease	111 (38)	116 (40)	227 (39)
Unknown or not reported	5 (2)	10 (3)	15 (3)

* No formal comparison was performed for the baseline characteristics listed here. *ALK* denotes anaplastic lymphoma kinase, *EGFR* epidermal growth factor receptor, and *KRAS* Kirsten rat sarcoma viral oncogene homologue.

† Race was self-reported. Other race included one patient in the nivolumab group who was American Indian or Alaska Native, eight in the nivolumab group who were of undefined race, one in the docetaxel group who was Native Hawaiian or other Pacific Islander, and six in the docetaxel group who were of undefined race.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating greater disability; a score of 0 indicates no symptoms, and 1 mild symptoms. One patient in the docetaxel group had an ECOG performance-status score of 1 at screening, which met the eligibility criteria, but his score worsened after randomization owing to grade 3 pericardial effusion. On day 1 of treatment, his ECOG performance-status score was 3. This patient was included in our analyses since he had undergone randomization and was part of the intention-to-treat population.

§ Mutation status (*EGFR* or *KRAS*) or *ALK* translocation status was not determined by means of centralized testing. Determination of mutation status was not mandatory per the protocol but was reported by the investigator and collected from case-report forms.

¶ The number of prior lines of therapy was defined as the number of lines of prior therapy received for advanced, metastatic, or recurrent disease. One patient in the nivolumab group had received one prior regimen as neoadjuvant therapy.

‖ Patients may have been treated with more than one type of therapy.

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the subgroups of patients who were receiving third-line therapy (66 patients), those who lived in the rest-of-the-world geographic region, which included South America, Asia, and Australia (98), those with central nervous system metastases (68), those who had never smoked (118), and those with *EGFR* mutation–positive status (82) (Fig. 2, and Fig. S2 in the Supplementary Appendix).

With additional follow-up (minimum, 17.2 months), the median overall survival was 12.2 months (95% CI, 9.7 to 15.1) with nivolumab and 9.4 months (95% CI, 8.1 to 10.7) with docetaxel, representing a 28% lower risk of death with nivolumab (hazard ratio, 0.72; 95% CI, 0.60 to 0.88; P<0.001) (Fig. S3 in the Supplementary Appendix). At 18 months, the rate of overall survival was 39% (95% CI, 34 to 45) with nivolumab and 23% (95% CI, 19 to 28) with docetaxel.

Figure 1 (facing page). Overall Survival, Duration of Response, and Progression-free Survival.

Data are based on a March 18, 2015, database lock. The analyses of overall survival and progression-free survival included all the patients who underwent randomization. Panel A shows the Kaplan–Meier curves for overall survival. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year. Panel B shows the characteristics of response and disease progression as assessed by the investigator, according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Bars indicate progression-free survival. Arrows indicate ongoing response at the time of data censoring. Panel C shows the Kaplan–Meier curves for progression-free survival, which was defined as the time from randomization to the date of the first documented event of tumor progression, death, or last tumor assessment that could be evaluated before subsequent therapy (data-censoring date). Symbols indicate censored observations, and horizontal lines the rates of progression-free survival at 1 year.

Objective Response

The rate of confirmed objective response was significantly higher with nivolumab than with docetaxel (19% [95% CI, 15 to 24] vs. 12% [95% CI, 9 to 17], P=0.02) (Table 2, and Fig. S4 in the Supplementary Appendix). The median time to response was 2.1 months (range, 1.2 to 8.6) in the nivolumab group and 2.6 months (range, 1.4 to 6.3) in the docetaxel group (Table 2 and Fig. 1B). The median duration of response in the nivolumab group was 17.2 months (range, 1.8 to 22.6+ [with the + indicating censored data because of an ongoing response]), and the median duration of response in the docetaxel group was 5.6 months (range, 1.2+ [with the + indicating censored data because the patient discontinued treatment without disease progression] to 15.2+ [with the + indicating censored data because of an ongoing response]).

Progression-free Survival

The median progression-free survival was 2.3 months (95% CI, 2.2 to 3.3) in the nivolumab group and 4.2 months (95% CI, 3.5 to 4.9) in the docetaxel group (Fig. 1C). The rate of progression-free survival at 1 year was 19% (95% CI, 14 to 23) with nivolumab and 8% (95% CI, 5 to 12) with docetaxel, and the hazard ratio for disease progression or death was 0.92 (95% CI, 0.77 to 1.1; P=0.39) (Fig. 1C). The hazard ratios in the analysis of progression-free survival numerically favored nivolumab across most prespecified subgroups, except for the subgroups of patients who were receiving third-line therapy, those in the rest-of-the-world geographic region, those who had never smoked, those with an undetected *KRAS* mutation (123 patients), and those with *EGFR* mutation–positive status (Fig. S5 in the Supplementary Appendix).

A total of 71 patients in the nivolumab group (24%) continued treatment after initial progression, of whom 16 (23%) had a nonconventional pattern of benefit. The characteristics of the patients who were treated after disease progression, including change in tumor burden over time, are provided in Figure S6 and Table S4 in the Supplementary Appendix.

PD-L1 Expression

Among the 582 patients who underwent randomization, 455 (78%) had quantifiable PD-L1 expression. Rates of PD-L1 expression were balanced between the two groups (Table S5 in the Supplementary Appendix). At the time of the interim analysis, a test for interaction suggested a strong predictive association between PD-L1 expression and clinical outcome at all expression levels for all efficacy end points (Table S6 in the Supplementary Appendix).

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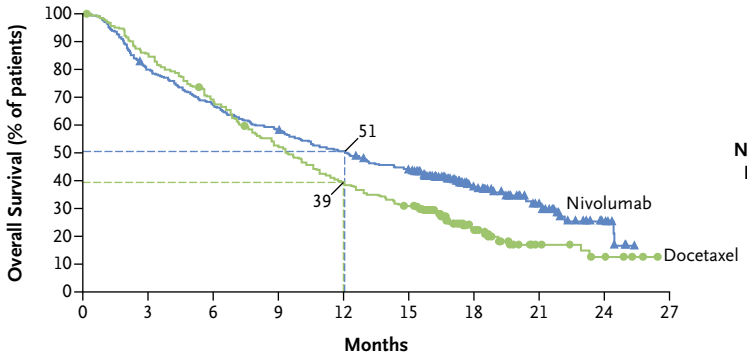
A Overall Survival



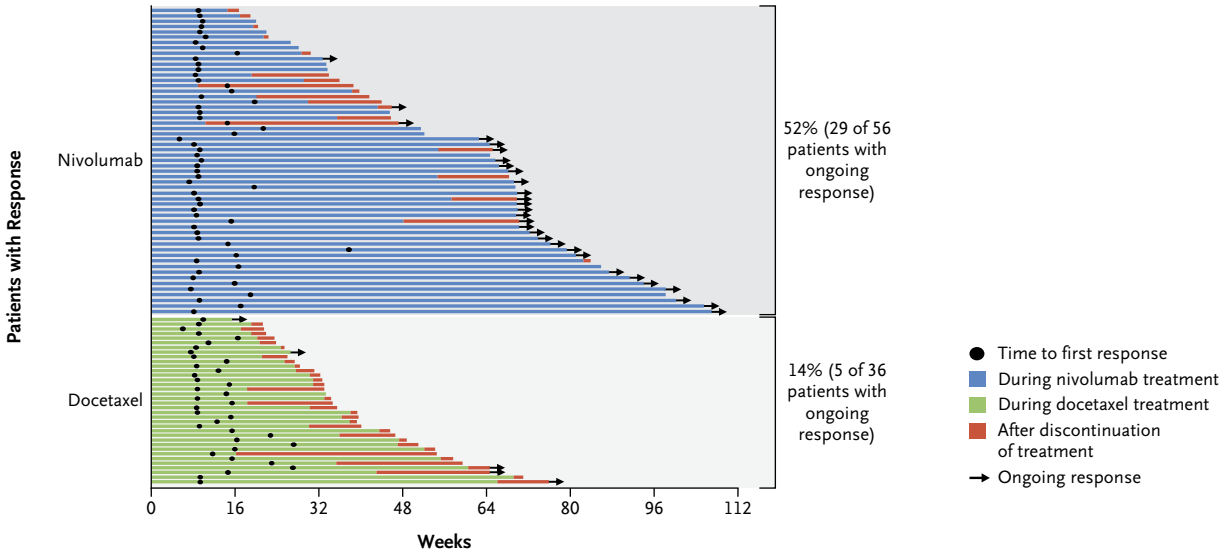
	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

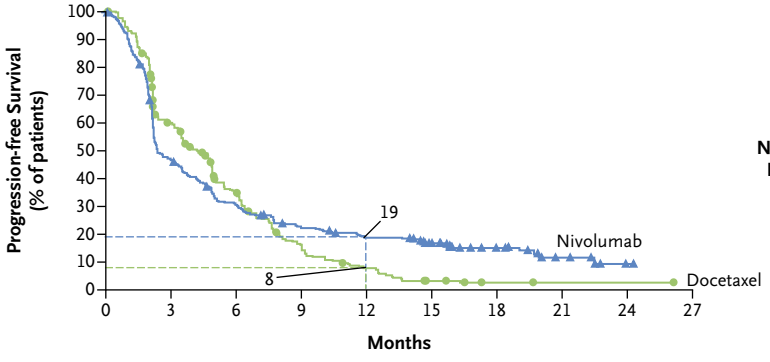
No. at Risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

B Duration of Response



C Progression-free Survival



	No. of Events/ Total No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate (95% CI)
		mo	%
Nivolumab	234/292	2.3 (2.2–3.3)	19 (14–23)
Docetaxel	245/290	4.2 (3.5–4.9)	8 (5–12)

Hazard ratio for disease progression or death, 0.92 (95% CI, 0.77–1.11); P=0.39

No. at Risk

Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

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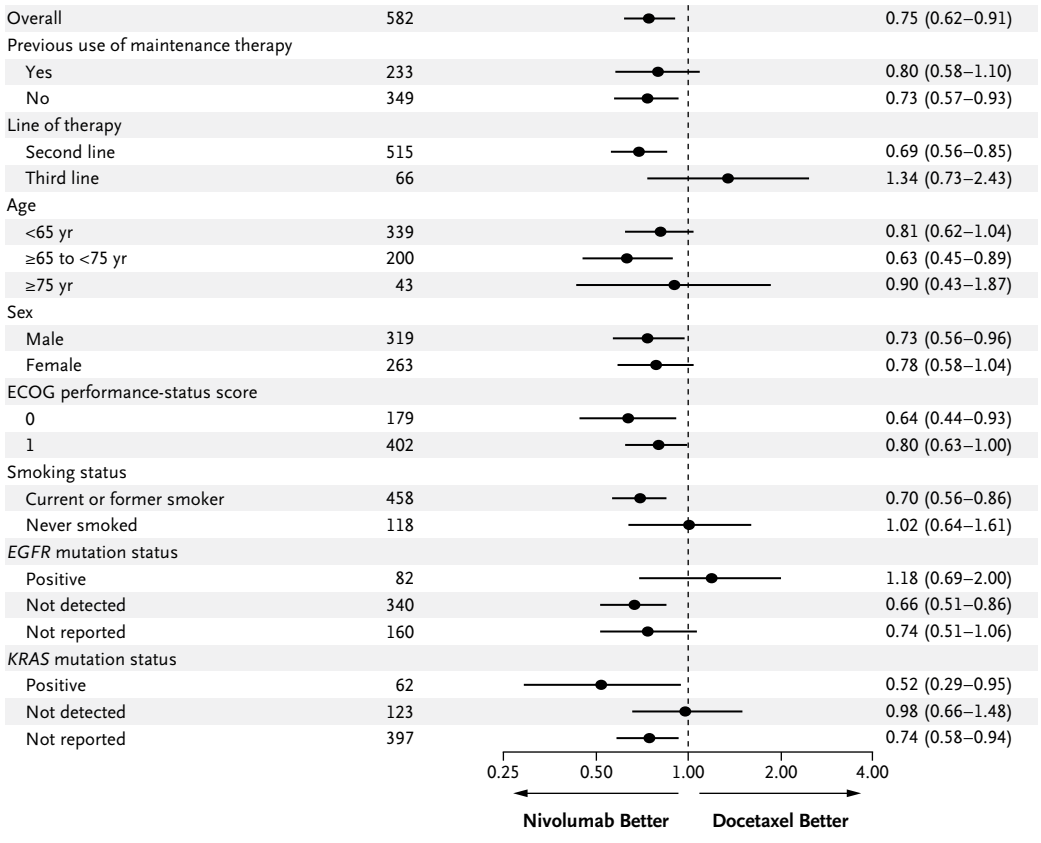

Figure 2. Treatment Effect on Overall Survival, According to Subgroup.

Data are based on a March 18, 2015, database lock. Hazard ratios for death were not computed for subgroups that included a treatment group with fewer than 10 patients, including other line of therapy (1 patient in the nivolumab group), unreported Eastern Cooperative Oncology Group (ECOG) performance-status score (1 in the docetaxel group), and unknown smoking status (3 in the nivolumab group and 3 in the docetaxel group). ECOG performance-status scores range from 0 to 5, with higher numbers indicating greater disability; a score of 0 indicates no symptoms, and 1 mild symptoms. The subgroup of patients with an ECOG performance-status score of 1 included 1 patient in the docetaxel group who had a score of 1 at screening, which met the eligibility criteria, but his score worsened after randomization owing to grade 3 pericardial effusion. On day 1 of treatment, his ECOG performance-status score was 3. This patient was included in our analyses, since he had undergone randomization and was part of the intention-to-treat population. *EGFR* denotes epidermal growth factor receptor, and *KRAS* Kirsten rat sarcoma viral oncogene homologue.

Nivolumab was associated with longer overall survival and progression-free survival (Fig. S7 in the Supplementary Appendix) and higher objective response rates (Table S5 in the Supplementary Appendix) than docetaxel at the prespecified PD-L1 expression levels of 1% or higher, 5% or higher, and 10% or higher. Progression-free survival across all prespecified PD-L1 subgroups, on the basis of data from the database lock for the interim analysis, is provided in Figure S8A in the Supplementary Appendix. Overall survival according to PD-L1 expression level, on the basis of data from the July 2, 2015, database lock, is shown in Figure S8B in the Supplementary Appendix; the difference in overall survival between the two study groups among patients whose tumors expressed PD-L1 was still evident with additional follow-up. The median duration of response was longer with nivolumab than with docetaxel across all the PD-L1 expression levels (Table S5 in the Supplementary Appendix).

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SAFETY

The frequencies of adverse events of any grade and any cause were similar in the two groups, but fewer adverse events of grade 3 or 4 were reported with nivolumab than with docetaxel (Table S7 in the Supplementary Appendix). Treatment-related adverse events were low in severity with nivolumab and were less frequent with nivolumab than with docetaxel (69% vs. 88% of patients had events of any grade, and 10% vs. 54% had events of grade 3 or 4) (Table 3, and Table S8 in the Supplementary Appendix). The most frequently reported treatment-related adverse events of any grade in the nivolumab group were fatigue (in 16% of patients), nausea (in 12%), decreased appetite (in 10%), and asthenia (in 10%). The most frequently reported treatment-related adverse events of any grade in the docetaxel group were neutropenia (in 31% of patients), fatigue (in 29%), nausea (in 26%), and alopecia (in 25%). Treatment-related serious adverse events were less frequent in the nivolumab group than in the docetaxel group (7% vs. 20% of patients had events of any grade, and 5% vs. 18% had events of grade 3 or 4) (Table S9 in the Supplementary Appendix).

The most frequently reported (≥2.5% of patients) treatment-related select adverse events of any grade were rash (in 9% of patients in the nivolumab group and 3% of those in the docetaxel group), pruritus (in 8% and 1%, respectively), erythema (in 1% and 4%, respectively), diarrhea (in 8% and 23%, respectively), hypothyroidism (in 7% of patients in the nivolumab group and none in the docetaxel group), increased alanine aminotransferase level (in 3% and 1%, respectively), increased aspartate aminotransferase level (in 3% and 1%, respectively), infusion-related reaction (in 3% and 3%, respectively), and pneumonitis (in 3% and <1%, respectively) (Table S10 in the Supplementary Appendix). Across categories, the median time to the onset of treatment-related select adverse events of any grade in the nivolumab group ranged from 0.9 to 31.1 weeks (Table S11 in the Supplementary Appendix).

Of the patients who had a treatment-related select adverse event in any category (Table S11 in the Supplementary Appendix), 11 to 70% were treated with immune-modulating agents (generally glucocorticoids), per guidelines specified in the protocol. Across categories, 44 to 100% of the treatment-related select adverse events resolved, with the median time to resolution ranging from 0.1 to 12.1 weeks (Table S11 in the Supplementary Appendix). The median time to resolution of treatment-related select endocrinopathies was not reached, because a proportion of these events were not expected to resolve. The frequencies of treatment-related adverse events, serious adverse events, and adverse events leading to discontinuation of the study drug were similar in the subgroups of patients with a PD-L1

Table 2. Tumor Response with Nivolumab versus Docetaxel in Patients with Advanced Nonsquamous Non–Small-Cell Lung Cancer.*

Variable	Nivolumab (N = 292)	Docetaxel (N = 290)
Objective response†		
No. of patients	56	36
% of patients (95% CI)	19 (15–24)	12 (9–17)
Estimated odds ratio (95% CI)	1.7 (1.1–2.6)	
P value	0.02	
Best overall response — no. (%)		
Complete response	4 (1)	1 (<1)
Partial response	52 (18)	35 (12)
Stable disease	74 (25)	122 (42)
Progressive disease	129 (44)	85 (29)
Could not be determined	33 (11)	47 (16)
Time to response — mo‡§		
Median	2.1	2.6
Range	1.2–8.6	1.4–6.3
Duration of response — mo‡¶		
Median	17.2	5.6
Range	1.8 to 22.6+	1.2+ to 15.2+

* Data are based on a March 18, 2015, database lock.
† Confirmed complete and partial responses were assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1. The 95% confidence interval (CI) is based on the Clopper–Pearson method. The analysis was stratified according to prior maintenance therapy (yes vs. no) and prior line of therapy (second line vs. third line). The strata-adjusted odds ratio (nivolumab vs. docetaxel) and the two-sided P value were calculated with the use of the Cochran–Mantel–Haenszel method.
‡ The analysis was performed with data from all the patients who had a response (56 patients in the nivolumab group and 36 in the docetaxel group).
§ The time to response was defined as the time from randomization to the date of first documented complete or partial response.
¶ Results were calculated with the use of the Kaplan–Meier method. The duration of response was defined as the time between the date of first response and the date of first documented event of progression, death, or last tumor assessment that was evaluated before subsequent therapy (data-censoring date). The + symbol indicates a censored value. The value of 1.2 was censored because the patient discontinued treatment without disease progression, and the other values were censored because the response was ongoing at the time of the analysis.

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Table 3. Treatment-Related Adverse Events Reported in at Least 10% of the Patients Treated with Nivolumab or Docetaxel.*

Event	Nivolumab (N=287)		Docetaxel (N=268)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	199 (69)	30 (10)	236 (88)	144 (54)
Fatigue	46 (16)	3 (1)	78 (29)	13 (5)
Nausea	34 (12)	2 (1)	70 (26)	2 (1)
Decreased appetite	30 (10)	0	42 (16)	3 (1)
Asthenia	29 (10)	1 (<1)	47 (18)	6 (2)
Diarrhea	22 (8)	2 (1)	62 (23)	3 (1)
Peripheral edema	8 (3)	0	28 (10)	1 (<1)
Myalgia	7 (2)	1 (<1)	30 (11)	0
Anemia	6 (2)	1 (<1)	53 (20)	7 (3)
Alopecia	1 (<1)	0	67 (25)	0
Neutropenia	1 (<1)	0	83 (31)	73 (27)
Febrile neutropenia	0	0	27 (10)	26 (10)
Leukopenia	0	0	27 (10)	22 (8)

* Data are based on a March 18, 2015, database lock. Safety analyses included all the patients who received at least one dose of study drug. Some patients had more than one adverse event. No treatment-related grade 5 events (deaths) were reported at the time of the database lock. The association of one death (from encephalitis) in a patient in the nivolumab group was changed from not related to treatment to treatment-related after the database lock. A treatment-related death of a patient in the docetaxel group, which occurred before the database lock, was reported as grade 4 febrile neutropenia.

expression level of 1% or higher and those with a PD-L1 expression level of less than 1% (Table S12 in the Supplementary Appendix).

Discontinuation of the study drug due to treatment-related adverse events occurred less frequently with nivolumab than with docetaxel (in 5% vs. 15% of patients) (Tables S13 and S14 in the Supplementary Appendix). The most common treatment-related adverse event leading to discontinuation was pneumonitis in the nivolumab group (in 1% of patients) and fatigue in the docetaxel group (in 3%).

One death in each of the two treatment groups was assessed by the investigator as being related to treatment. One patient in the nivolumab group died from encephalitis (which was reported before the database lock, but the causality was changed after the database lock), and one patient in the docetaxel group died from febrile neutropenia.

DISCUSSION

Despite the increased number of treatment options for NSCLC, minimal improvement in overall survival has been noted, except among patients with *EGFR* mutations or *ALK* translocations. Docetaxel is regarded as the standard of care for previously treated patients with advanced NSCLC and is an appropriate comparator in this trial. In our phase 3 study involving patients with advanced nonsquamous NSCLC, nivolumab was associated with a significant survival benefit over docetaxel (27% lower risk of death at a minimum follow-up of 13.2 months), which persisted with extended follow-up (28% lower risk of death at a minimum follow-up of 17.2 months). The overall survival curve observed in the nivolumab group in this population is consistent with the results of a prior study of nivolumab.[10] Furthermore, a delay in the separation of overall survival curves with nivolumab and docetaxel is consistent with the results observed with other immune system–modifying agents in patients with advanced melanoma.[12]

In a recent phase 3 study involving patients with nonsquamous NSCLC, the median survival was 1.4 months longer with docetaxel plus ramucirumab, a vascular endothelial growth factor 2 inhibitor, than with docetaxel alone (11.1 months vs. 9.7 months; hazard ratio for death, 0.83).[13] In our study, overall survival was 2.8 months longer

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with nivolumab monotherapy than with docetaxel (median, 12.2 months vs. 9.4 months; hazard ratio for death, 0.73); this benefit persisted with extended follow-up. A total of 22 of 290 patients (8%) who were randomly assigned to receive docetaxel were never treated; however, those patients were followed for overall survival, and the effect on the overall results was minimal. The benefit of nivolumab was further reflected by a significantly higher objective response rate as compared with docetaxel (19% vs. 12%) and a markedly better durability of response (median, 17.2 months vs. 5.6 months). The duration of response with nivolumab is longer than that with other treatment options for patients who have had disease progression during or after prior platinum-based doublet chemotherapy or targeted agents.[4,14,15]

Nivolumab was associated with significantly longer overall survival and a significantly higher response rate than docetaxel but not with longer progression-free survival. A crossing of the progression-free survival curves was noted, with a progression-free survival rate of 19% at 1 year, as compared with 8% with docetaxel, representing a delay in benefit with nivolumab that may be typical with immunotherapy. The numerically lower median progression-free survival observed with nivolumab is not due to underperformance, because the median progression-free survival reported here is consistent with that observed in another study of nivolumab.[10] However, it may be explained in part by the higher median progression-free survival with docetaxel observed in this study (4.2 months), as compared with previously reported data from patients with nonsquamous NSCLC (2.8 months[16] and 3.7 months[13]).

It is also possible that the observed results regarding progression-free survival may be driven by certain subgroups of patients, as suggested by the subgroup analyses for smoking status and *EGFR* mutation. The outcomes observed in patients with *EGFR* mutation–positive tumors may be attributed to better outcomes in this subgroup in the docetaxel group, as compared with patients with *EGFR* wild-type tumors in the docetaxel group. However, the interpretation of these results is limited by the wide confidence intervals for the calculated hazard ratios in a small subgroup of patients and possibly by the incomplete collection of mutation data. A biologic rationale for different outcomes in patients who never smoked and in those with *EGFR* mutation–positive tumors may be related to low levels of mutational heterogeneity, because preliminary data suggest that sensitivity to immune-checkpoint inhibitors may be high in tumors bearing high levels of somatic mutations.[17,18] However, this study was not designed to test this hypothesis.

The current study, which enrolled patients regardless of tumor PD-L1 expression level and included a control group, showed a predictive association between PD-L1 expression and benefit from anti–PD-1 treatment. Analyzed tumor samples included archived tissue, which suggests that the results may be applicable in a real-world context in which fresh tissue may not be available or repeat biopsy may not be feasible. For each of the prespecified expression levels examined, the P value for the descriptive treatment–biomarker interaction met the prespecified threshold, which suggests a predictive association with clinical benefit. Although the benefit of nivolumab was observed in the overall population, the magnitude of benefit across all the efficacy end points appeared to be greater among patients whose tumors expressed PD-L1 than among those whose tumors did not express PD-L1 (Figs. S7 and S8 and Table S5 in the Supplementary Appendix).

Consistent with the results of a recent phase 1 study of pembrolizumab in patients with NSCLC,[19] there was a trend toward a greater response rate as the PD-L1 expression level increased; however, a meaningful separation of the overall survival curves was observed across all prespecified expression levels. Among patients whose tumors expressed PD-L1 (at the ≥1%, ≥5%, and ≥10% expression levels), nivolumab nearly doubled median overall survival as compared with docetaxel. No meaningful differences in overall survival were noted between nivolumab and docetaxel among patients whose tumors did not express PD-L1. These data are in contrast to results in patients with squamous-cell NSCLC, in whom PD-L1 expression did not affect nivolumab clinical activity.[20,21] These observations may imply inherent differences in the immune milieu of the histologic features of squamous-cell cancer versus nonsquamous cancer, suggesting that these may be two distinct diseases.

Although there was no difference in overall survival between nivolumab and docetaxel among patients whose tumors did not express PD-L1, the improved safety profile and durability of responses to nivolumab suggest that it might be a

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reasonable option for patients regardless of PD-L1 expression. Additional research is warranted to characterize subgroups of patients whose disease progresses early and who may benefit from combination therapies.

The safety profile of nivolumab observed in this study is consistent with that in prior studies and was favorable in comparison with docetaxel, with most patients having adverse events of low severity. Only a small percentage of patients in the nivolumab group reported immune-related adverse events, including pneumonitis, and these events were managed with the use of protocol guidelines.

In conclusion, nivolumab led to a statistically superior survival benefit over docetaxel in unselected patients with advanced, previously treated nonsquamous NSCLC.

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APPENDIX

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