ORIGINAL ARTICLE

Perioperative Nivolumab in Resectable Lung Cancer

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ABSTRACT

BACKGROUND

Standard treatment with neoadjuvant nivolumab plus chemotherapy significantly improves outcomes in patients with resectable non–small-cell lung cancer (NSCLC). Perioperative treatment (i.e., neoadjuvant therapy followed by surgery and adjuvant therapy) with nivolumab may further improve clinical outcomes.

METHODS

In this phase 3, randomized, double-blind trial, we assigned adults with resectable stage IIA to IIIB NSCLC to receive neoadjuvant nivolumab plus chemotherapy or neoadjuvant chemotherapy plus placebo every 3 weeks for 4 cycles, followed by surgery and adjuvant nivolumab or placebo every 4 weeks for 1 year. The primary outcome was event-free survival according to blinded independent review. Secondary outcomes were pathological complete response and major pathological response according to blinded independent review, overall survival, and safety.

RESULTS

At this prespecified interim analysis (median follow-up, 25.4 months), the percentage of patients with 18-month event-free survival was 70.2% in the nivolumab group and 50.0% in the chemotherapy group (hazard ratio for disease progression or recurrence, abandoned surgery, or death, 0.58; 97.36% confidence interval [CI], 0.42 to 0.81; P<0.001). A pathological complete response occurred in 25.3% of the patients in the nivolumab group and in 4.7% of those in the chemotherapy group (odds ratio, 6.64; 95% CI, 3.40 to 12.97); a major pathological response occurred in 35.4% and 12.1%, respectively (odds ratio, 4.01; 95% CI, 2.48 to 6.49). Grade 3 or 4 treatment-related adverse events occurred in 32.5% of the patients in the nivolumab group and in 25.2% of those in the chemotherapy group.

CONCLUSIONS

Perioperative treatment with nivolumab resulted in significantly longer event-free survival than chemotherapy in patients with resectable NSCLC. No new safety signals were observed. (Funded by Bristol Myers Squibb; CheckMate 77T ClinicalTrials.gov number, NCT04025879.)

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CME

Nivolumab, a fully human antibody against programmed death 1 (PD-1), in combination with platinum-doublet chemotherapy is now a standard neoadjuvant treatment for eligible patients with resectable non–small-cell lung cancer (NSCLC). The clinical benefit of this regimen in patients with resectable NSCLC was initially observed in several phase 2 trials[1-3] and subsequently confirmed in the landmark phase 3 CheckMate 816 trial, which showed significant improvements in event-free survival (hazard ratio for disease progression or recurrence or death, 0.63; 97.38% confidence interval [CI], 0.43 to 0.91; P=0.005) and in pathological complete response (odds ratio, 13.94; 99% CI, 3.49 to 55.75; P<0.001) with neoadjuvant nivolumab plus chemotherapy as compared with chemotherapy alone.[4] Furthermore, at an interim analysis from the CheckMate 816 trial, overall survival appeared to favor neoadjuvant nivolumab plus chemotherapy over chemotherapy alone (hazard ratio for death, 0.62; 99.34% CI, 0.36 to 1.05), with data continuing to mature.[5]

On the basis of these findings, neoadjuvant nivolumab plus chemotherapy was approved in the United States, the European Union, and several other countries for eligible patients with resectable NSCLC.[6-10] Adjuvant immunotherapy has also shown benefit with respect to disease-free survival as compared with best supportive care or placebo in patients with resectable NSCLC.[11,12]

A perioperative approach (which involves treatment with neoadjuvant therapy followed by surgery and adjuvant therapy) with immunotherapy-based treatments may further reduce the risk of disease relapse, which is typically observed in 30 to 55% of patients who undergo surgery with curative intent.[13,14] This approach may also improve clinical outcomes by enhancing antitumor immunity and promoting the elimination of micrometastasis and residual tumor cells.[15-17] Recently, perioperative durvalumab and pembrolizumab in combination with neoadjuvant chemotherapy resulted in significant improvements in event-free survival and pathological response, with perioperative pembrolizumab also showing significant overall survival benefit as compared with perioperative placebo added to neoadjuvant chemotherapy in patients with resectable stage IIA to IIIB (N2 node stage) NSCLC (according to the American Joint Committee on Cancer [AJCC] *Cancer Staging Manual*, 8th edition) in the phase 3 AEGEAN and KEYNOTE-671 trials, respectively.[18-20] In the phase 2 NADIM II trial, perioperative nivolumab also resulted in significant improvements in pathological complete response, as well as in substantial improvements in progression-free and overall survival, as compared with chemotherapy alone, in patients with stage IIIA or IIIB resectable NSCLC.[21] Here, we report efficacy and safety results from the prespecified interim analysis of the phase 3, randomized, double-blind, international CheckMate 77T trial that evaluated neoadjuvant nivolumab plus chemotherapy followed by adjuvant nivolumab (i.e., perioperative nivolumab) as compared with neoadjuvant placebo plus chemotherapy followed by adjuvant placebo (i.e., chemotherapy) in patients with resectable NSCLC.

A Quick Take is available at NEJM.org

Methods

Patients

Adults with resectable stage IIA (>4 cm) to IIIB (N2 node stage, single- or multistation) NSCLC (according to the AJCC *Cancer Staging Manual*, 8th edition) were eligible to enroll in the trial if they had an Eastern Cooperative Oncology Group performance-status score of 0 or 1, had no *EGFR* mutations or known *ALK* translocations, and had not received previous systemic anticancer treatment. Additional eligibility criteria are described in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Design and Treatments

Patients were randomly assigned in a 1:1 ratio with the use of a computerized interactive response technology system to receive either perioperative nivolumab or chemotherapy (Fig. S1 in the Supplementary Appendix). Randomization was stratified according to disease stage (II or III), tumor histology (squamous-cell or nonsquamous-cell), and tumor expression of programmed death ligand 1 (PD-L1) (<1%, ≥1%, or not evaluable or indeterminate), as determined with the use of the PD-L1 IHC 28-8 pharmDx assay (Dako).

During the neoadjuvant period, patients received either nivolumab (at a dose of 360 mg) plus platinum-doublet chemotherapy or placebo plus platinum-doublet chemotherapy every 3 weeks for 4 cycles. Within 6 weeks after the last neoadjuvant treatment dose and subsequent radiologic restaging, patients underwent definitive surgery. During the adjuvant period, which began within 90 days after surgery, patients received either nivolumab (at a dose of 480 mg) or placebo every 4 weeks for 1 year. Additional treatment information is provided in the Supplementary Appendix.

OUTCOMES AND ASSESSMENTS

The primary outcome was event-free survival, which was assessed in a time-to-event analysis from randomization to disease progression or death from any cause. Disease progression included progression that precluded surgery, abandoned surgery owing to unresectability, and progression or recurrence with or without surgery. Data for the primary analysis were evaluated by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Data for patients who had received subsequent therapy before event-free survival review were censored at the last evaluable tumor assessment on or before the date that subsequent therapy had been initiated.

Secondary outcomes were pathological complete response (no residual viable tumor cells after surgery in the primary tumor and sampled lymph nodes) and major pathological response (≤10% residual viable tumor cells after surgery in the primary tumor and sampled lymph nodes) as assessed by blinded independent pathological review according to the pan-tumor immune-related pathological response criteria,[22,23] along with overall survival and safety.

Prespecified exploratory analyses included the objective response as assessed by blinded independent central review, event-free survival according to the type of pathological response, and patient-reported outcomes measuring disease-related symptoms and health-related quality of life (according to the NSCLC Symptom Assessment Questionnaire [NSCLC-SAQ] and other assessments). Analysis of event-free survival according to adjuvant treatment status was performed post hoc. Additional information is provided in the Supplementary Appendix.

TRIAL OVERSIGHT

CheckMate 77T was designed by the sponsor (Bristol Myers Squibb) and members of the trial steering committee. Data were collected by investigators and analyzed in collaboration with the sponsor, with an independent data-monitoring committee providing oversight. The trial was performed in accordance with the provisions of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The protocol was approved by the independent ethics committee or institutional review board at each trial site. Patients provided written informed consent to participate.

The manuscript was prepared with medical writing support funded by the sponsor and under the direction of the authors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

We determined that the enrollment of 452 patients in the two treatment groups would provide the trial with 90% power to detect a hazard ratio of 0.65 with a two-sided type I error of 0.05, according to the observation of approximately 231 patients with disease progression or recurrence, abandoned surgery, or death. According to the protocol, the current interim analysis was to be performed when 185 such events had occurred. We used the Lan–DeMets alpha-spending function with O'Brien–Fleming boundaries to determine the significance boundary (0.0264) for this interim analysis on the basis of the actual number of events. A hierarchical analysis of overall survival was planned if a prespecified number of patients had died and the between-group difference in event-free survival was significant.

Efficacy was evaluated in all the patients who had undergone randomization, with stratified analyses performed for main and supportive analyses of the efficacy outcomes and unstratified analyses performed for supplementary and subgroup analyses of the efficacy outcomes. Safety was evaluated in patients who had received at least one dose of a trial treatment. A stratified two-sided log-rank test was used to compare differences in event-free survival between the treatment groups. We used the stratified Cochran–Mantel–Haenszel method to assess the pathological response, with confidence inter-

vals calculated by means of the Clopper–Pearson method. A 97.36% confidence interval was estimated for the primary analysis on the basis of the boundary for statistical significance (P value, <0.0264). Because the other outcomes were not formally compared, standard 95% confidence intervals are reported. Confidence intervals for outcomes that were not part of the hypothesis testing were not adjusted for multiplicity and were descriptive in nature. Additional statistical information is provided in the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENT SUMMARY

Between November 2019 and April 2022, a total of 735 patients were enrolled; of these patients, 461 underwent randomization (229 to the nivolumab group and 232 to the chemotherapy group) (Fig. S2). The characteristics of the patients at baseline were generally balanced between the treatment groups and were largely representative of those observed in the overall population of patients with NSCLC, except for Black patients, who were underrepresented (Table 1 and Table S1).

Neoadjuvant treatment was administered to 228 patients (99.6%) in the nivolumab group and 230 patients (99.1%) in the chemotherapy group; all four treatment cycles were completed in 194 patients (84.7%) and 205 patients (88.4%), respectively (Fig. S3). Three cycles of neoadjuvant nivolumab or placebo were completed in 9 patients (3.9%) in each group. A summary of exposure during the neoadjuvant period is provided in Table S2.

After neoadjuvant treatment, definitive surgery (defined as completed surgery with curative intent) was performed in 178 patients (77.7%) in the nivolumab group and in 178 patients (76.7%) in the chemotherapy group. Among the patients who underwent definitive surgery, lobectomy was performed in 79.8% in the nivolumab group and in 71.9% in the chemotherapy group; pneumonectomy was performed in 9.0% and 13.5%, respectively; R0 resection (i.e., resection with no residual tumor cells visible on the margin) was achieved in 89.3% and 90.4% of the patients, respectively. Table S3 summarizes surgical outcomes, including resection type, reasons for canceled or delayed surgery, and operative times.

Adjuvant treatment was administered to 142 patients (62.0%) in the nivolumab group and 152 patients (65.5%) in the chemotherapy group; 1 year of treatment was completed in 85 patients (37.1%) and 92 patients (39.7%), respectively. In each treatment group, 8 patients (3.5% and 3.4%, respectively) were continuing treatment. Data regarding the discontinuation of treatment or cancellation of surgery because of disease progression or other reasons are provided in Figure S3. Adjuvant treatment exposure is summarized in Table S4. Any subsequent anticancer therapy was received by 23.1% of patients in the nivolumab group and 37.5% of those in the chemotherapy group, with 17.5% and 31.5%, respectively, receiving subsequent systemic therapy (Table S5).

EFFICACY

As of the database lock date (median follow-up, 25.4 months; range, 15.7 to 44.2), the percentage of patients with 18-month event-free survival (the primary outcome) was 70.2% in the nivolumab group and 50.0% in the chemotherapy group (hazard ratio for disease progression or recurrence, abandoned surgery, or death, 0.58; 97.36% CI, 0.42 to 0.81; P<0.001) (Fig. 1A). Similar benefit was observed with perioperative nivolumab over chemotherapy for investigator-assessed event-free survival (hazard ratio, 0.56; 95% CI, 0.41 to 0.76) (Fig. S4).

Subgroup analysis of the primary outcome is shown in Figure 1B. Event-free survival appeared to be improved with perioperative nivolumab across subgroups of tumor PD-L1 expression, albeit with different magnitudes. There was an apparent event-free survival benefit in patients with tumor PD-L1 expression of 1% or more (hazard ratio, 0.52; 95% CI, 0.35 to 0.78); in the subgroup with tumor PD-L1 expression of less than 1%, the hazard ratio was 0.73 (95% CI, 0.47 to 1.15). Additional data regarding tumor PD-L1 expression — along with disease stage at baseline, tumor histology, and neoadjuvant platinum chemotherapy agent — are provided in Figures S5 to S8.

Outcomes with respect to pathological response appeared to be better among patients in the nivolumab group than among those in the chemotherapy group. A pathological complete response occurred in 25.3% of the patients (95% CI, 19.8 to 31.5) in the nivolumab group and in

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Nivolumab (N=229)	Chemotherapy (N=232)
Age		
Median (range) — yr	66 (37–83)	66 (35–86)
Distribution — no. (%)		
<65 yr	102 (44.5)	100 (43.1)
≥65 yr	127 (55.5)	132 (56.9)
Sex — no. (%)		
Male	167 (72.9)	160 (69.0)
Female	62 (27.1)	72 (31.0)
Race — no. (%)†		
White	155 (67.7)	175 (75.4)
Black	4 (1.7)	4 (1.7)
Asian	66 (28.8)	50 (21.6)
Other	4 (1.7)	3 (1.3)
Geographic region — no. (%)		
North America	23 (10.0)	21 (9.1)
Europe	123 (53.7)	127 (54.7)
Asia	65 (28.4)	50 (21.6)
Other‡	18 (7.9)	34 (14.7)
ECOG performance-status score — no. (%)§		
0	147 (64.2)	141 (60.8)
1	82 (35.8)	91 (39.2)
Disease stage — no. (%)¶		
IIA to IIB	81 (35.4)	81 (34.9)
IIIA to IIIB	146 (63.8)	149 (64.2)
Node stage — no. (%)‖		
N0	80 (34.9)	87 (37.5)
N1	56 (24.5)	52 (22.4)
N2	91 (39.7)	91 (39.2)
Single-station	59 (25.8)	53 (22.8)
Multistation	31 (13.5)	38 (16.4)
Tumor histology — no. (%)		
Squamous	116 (50.7)	118 (50.9)**
Nonsquamous	113 (49.3)	114 (49.1)
Smoking status — no. (%)		
Current or former smoker	212 (92.6)	205 (88.4)
Never smoked	17 (7.4)	27 (11.6)
Tumor PD-L1 expression — no. (%)		
Could not be evaluated	8 (3.5)	11 (4.7)
<1%	93 (40.6)	93 (40.1)
≥1%	128 (55.9)	128 (55.2)
1 to 49%	83 (36.2)	76 (32.8)

Table 1. (Continued.)

Characteristic	Nivolumab (N=229)	Chemotherapy (N=232)
≥50%	45 (19.7)	52 (22.4)
Neoadjuvant platinum chemotherapy — no. (%)††		
Cisplatin	55 (24.0)	42 (18.1)
Carboplatin	167 (72.9)	180 (77.6)

* PD-L1 denotes programmed death ligand 1.
† Race was reported by the patients.
‡ This category includes Argentina, Australia, Brazil, and Mexico.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
¶ Data for disease stage are from case-report forms, with staging criteria of the American Joint Committee on Cancer *Cancer Staging Manual*, 8th edition, used for classification. Stage IIIC disease was reported in 2 patients (0.9%) in the nivolumab group, and stage IV disease was reported in 2 patients (0.9%) in the chemotherapy group. Stage IIA disease was reported in 15 patients (6.6%) in the nivolumab group and in 18 patients (7.8%) in the chemotherapy group; stage IIB disease was reported in 66 patients (28.8%) and 63 patients (27.2%), respectively. Stage IIIA disease was reported in 103 patients (45.0%) in the nivolumab group and in 114 patients (49.1%) in the chemotherapy group; stage IIIB disease was reported in 43 patients (18.8%) and 35 patients (15.1%), respectively.
‖ N3 node stage was reported in 2 patients (0.9%) in each treatment group.
** One patient (0.4%) in the chemotherapy group with a squamous tumor had a reported *EGFR* mutation; this finding was tested locally and could not be confirmed because of site closure interval.
†† Five patients (2.2%) in the nivolumab group and six patients (2.6%) in the chemotherapy group switched from cisplatin to carboplatin. Neoadjuvant platinum chemotherapy was not reported in two patients (0.9%) in the nivolumab group and four patients (1.7%) in the chemotherapy group.

4.7% of those (95% CI, 2.4 to 8.3) in the chemotherapy group (between-group difference, 20.5 percentage points; 95% CI, 14.3 to 26.6), for an odds ratio of 6.64 (95% CI, 3.40 to 12.97) (Fig. 2A). A major pathological response occurred in more patients in the nivolumab group (35.4%; 95% CI, 29.2 to 41.9) than in the chemotherapy group (12.1%; 95% CI, 8.2 to 17.0), for a between-group difference of 23.2 percentage points (95% CI, 15.8 to 30.6) and an odds ratio of 4.01 (95% CI, 2.48 to 6.49) (Fig. 2B). Subgroup analyses of pathological complete response and major pathological response are shown in Figure 2C and Figure S9. Objective response data are provided in Table S6.

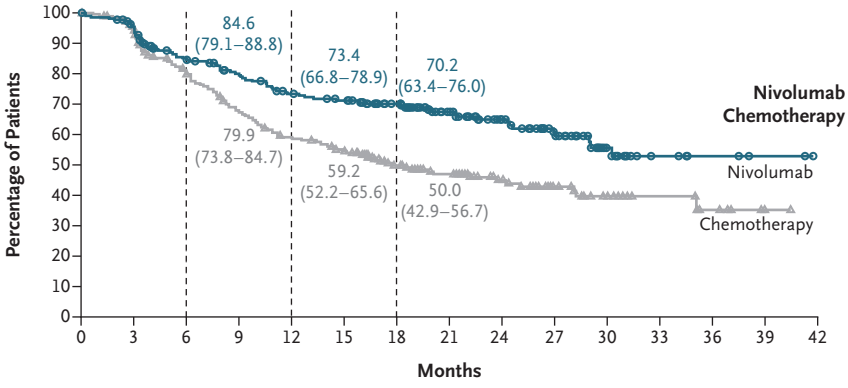
In an exploratory landmark analysis, event-free survival from definitive surgery appeared to favor nivolumab over chemotherapy both in patients who had a pathological complete response and in those who did not (Fig. 3A). Landmark analysis of event-free survival from definitive surgery in patients who had or did not have a major pathological response is shown in Figure S10A.

In a post hoc landmark analysis of efficacy according to adjuvant treatment status, apparent improvement in event-free survival from definitive surgery was observed among patients who had received adjuvant therapy in the nivolumab group as compared with those in the chemotherapy group (Fig. S10B). Among the patients who could not receive adjuvant therapy, event-free survival from definitive surgery also appeared to be longer in the nivolumab group than in the chemotherapy group (Fig. S10C). Event-free survival from definitive surgery in patients who had received adjuvant therapy regardless of their pathological complete response is shown in Figure S11.

PATIENT-REPORTED OUTCOMES

At baseline, patients were assessed as having a generally low symptom burden, as shown by a mean (±SD) total NSCLC-SAQ score of 4.98±3.26 in the nivolumab group and 5.07±3.34 in the chemotherapy group (on a scale ranging from 0 to 20, with higher scores indicating a greater symptom burden). The percentage of patients who completed their outcome assessments during treatment was generally more than 90%, except at visits before and after surgery. According to total scores on the NSCLC-SAQ, patients in the nivolumab group had a longer time until definitive deterioration in disease-related symptoms than did those in the chemotherapy group, with a median time of 40.0 months (95% CI, 33.6 to not reached) in the nivolumab group and

A Event-free Survival



	No. of Patients	Median Event-free Survival (95% CI)
		mo
Nivolumab	229	NR (28.9–NR)
Chemotherapy	232	18.4 (13.6–28.1)

Hazard ratio for disease progression or death, 0.58 (97.36% CI, 0.42–0.81)
P<0.001

No. at Risk

Nivolumab	229	208	173	157	141	134	115	89	69	46	20	7	4	2	0
Chemotherapy	232	204	165	138	118	106	78	59	44	29	19	10	6	1	0

B Subgroup Analyses for Event-free Survival

Subgroup	No. of Patients	Median Event-free Survival		Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
		Nivolumab (N=229)	Chemotherapy (N=232)	
		mo		
Overall	461	NR (28.9–NR)	18.4 (13.6–28.1)	0.59 (0.44–0.79)
Age				
<65 yr	202	NR (24.4–NR)	16.7 (11.0–28.2)	0.55 (0.36–0.85)
≥65 yr	259	NR (28.9–NR)	20.1 (11.2–NR)	0.61 (0.41–0.91)
Sex				
Male	327	NR (28.9–NR)	16.7 (10.2–NR)	0.53 (0.37–0.75)
Female	134	30.2 (19.7–NR)	18.8 (14.7–35.1)	0.71 (0.41–1.20)
Geographic region				
North America	44	30.2 (7.9–NR)	9.4 (6.2–22.0)	0.59 (0.25–1.38)
Europe	250	NR (27.0–NR)	23.7 (15.1–NR)	0.61 (0.40–0.92)
Asia	115	NR (24.2–NR)	13.9 (8.1–NR)	0.47 (0.26–0.86)
ECOG performance-status score				
0	288	NR (27.0–NR)	20.1 (12.6–NR)	0.57 (0.39–0.83)
1	173	29.0 (22.6–NR)	17.3 (10.6–35.1)	0.61 (0.39–0.97)
Baseline disease stage				
II	162	NR (22.6–NR)	NR (24.2–NR)	0.81 (0.46–1.43)
III	297	30.2 (26.9–NR)	13.4 (9.8–17.7)	0.51 (0.36–0.72)
Node stage				
N0	167	NR (24.2–NR)	NR (15.8–NR)	0.80 (0.48–1.32)
N1	108	NR (24.4–NR)	28.1 (17.0–NR)	0.58 (0.29–1.16)
N2	182	30.2 (26.9–NR)	10.0 (8.1–15.1)	0.46 (0.30–0.70)
Single-station	112	30.2 (18.2–NR)	10.0 (6.5–18.4)	0.49 (0.29–0.84)
Multistation	69	NR (13.2–NR)	10.0 (8.0–18.8)	0.43 (0.21–0.88)
Tumor histology				
Squamous	234	NR (NR–NR)	17.0 (10.2–NR)	0.46 (0.30–0.72)
Nonsquamous	227	28.9 (21.4–NR)	18.4 (13.6–28.1)	0.72 (0.49–1.07)
Smoking status				
Current or former smoker	417	NR (29.0–NR)	17.0 (11.4–28.1)	0.54 (0.40–0.74)
Never smoked	44	19.7 (3.7–NR)	25.0 (13.9–NR)	1.32 (0.54–3.20)
Tumor PD-L1 expression				
<1%	186	29.0 (21.4–NR)	19.8 (13.9–NR)	0.73 (0.47–1.15)
≥1%	256	NR (28.9–NR)	15.8 (9.3–35.1)	0.52 (0.35–0.78)
1–49%	159	30.2 (20.0–NR)	28.1 (11.0–NR)	0.76 (0.46–1.25)
≥50%	97	NR (NR–NR)	8.0 (6.3–23.7)	0.26 (0.12–0.55)
Neoadjuvant platinum chemotherapy				
Cisplatin	97	27.0 (21.3–NR)	15.8 (8.8–28.1)	0.61 (0.35–1.08)
Carboplatin	347	NR (29.0–NR)	17.3 (12.6–35.1)	0.53 (0.37–0.75)

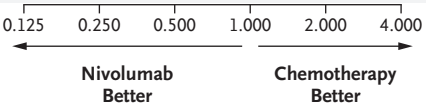


Figure 1 (facing page). Event-free Survival.
Shown is event-free survival as assessed by blinded independent central review in the intention-to-treat population (Panel A) and in patient subgroups (Panel B). Disease progression included progression that precluded surgery, resulted in abandoned surgery owing to unresectability, and progression or recurrence that occurred with or without surgery. In Panel A, the P value was calculated by means of a stratified two-sided log-rank test, with the hazard ratio and confidence intervals estimated according to a stratified Cox proportional-hazards model with the treatment group as a covariate. In Panel B, the randomization stratification was not applied to the analysis of the subgroup population, so unstratified data are reported. Confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing; all subgroup analyses were prespecified except for analyses according to node stage, which were performed post hoc. ECOG denotes Eastern Cooperative Oncology Group, NR not reached, and PD-L1 programmed death ligand 1.

a median of 31.1 months (95% CI, 25.0 to not reached) in the chemotherapy group (hazard ratio, 0.66; 95% CI, 0.45 to 0.98) (Fig. 3B). The overall change from baseline in the NSCLC-SAQ score as assessed by a mixed model of repeated measures was not considered to be clinically meaningful in either group (Table S7).

SAFETY AND SURGICAL COMPLICATIONS

Among treated patients, an adverse event was reported in 97.4% of those in the nivolumab group and in 97.8% in the chemotherapy group (Table 2). Adverse events of any grade that were determined by the investigator to be related to the trial treatment occurred in 89.0% of the patients in the nivolumab group and in 87.0% of those in the chemotherapy group, with grade 3 or 4 treatment-related adverse events occurring in 32.5% and 25.2% of the patients, respectively. The most common grade 3 or 4 treatment-related adverse event in the nivolumab and chemotherapy groups was a decreased neutrophil count (in 10.1% and 6.5%, respectively) (Table S8). Treatment-related adverse events of any grade that led to treatment discontinuation occurred in 19.3% of the patients in the nivolumab group and in 7.4% of those in the chemotherapy group; grade 3 or 4 treatment-related adverse events leading to treatment discontinuation occurred in 11.0% and 4.8% of the patients, respectively (Table 2).

As compared with the incidence of treatment-related adverse events overall, the incidence of such events was generally similar during the neoadjuvant period and was lower during the adjuvant period in the two treatment groups. Immune-mediated adverse events occurred infrequently and were typically of grade 1 or 2; the most common immune-mediated adverse event was hypothyroidism or thyroiditis, which was reported in 11.0% of the patients in the nivolumab group and in 1.7% of those in the chemotherapy group (Table S9). Death that was deemed by investigators to be related to a trial treatment was reported in 2 patients (both from pneumonitis) in the nivolumab group and in no patients in the chemotherapy group (Table 2).

Of patients who underwent surgery, surgery-related adverse events occurred in 41.0% of those in the nivolumab group and in 38.8% of those in the chemotherapy group; 11.8% in each group had grade 3 or 4 events (Table 2). The most frequent surgery-related adverse events in the nivolumab and chemotherapy groups were incision-site pain (in 6.2% and 6.7%, respectively), procedural pain (in 5.6% and 1.7%, respectively), and dyspnea (in 5.1% and 6.2%, respectively) (Table S10). Grade 5 surgery-related adverse events (i.e., events that led to death ≤24 hours after onset) occurred in three patients (1.7%) in the nivolumab group and in one patient (0.6%) in the chemotherapy group; all events were deemed to be unrelated to the trial treatment according to investigator assessment (Table 2). Adverse events that delayed definitive surgery occurred in 3.5% of patients in the nivolumab group and in 2.2% of those in the chemotherapy group; adverse events leading to the cancellation of definitive surgery occurred in 3.1% and 1.7% of the patients, respectively.

DISCUSSION

In the CheckMate 77T trial, we found that the addition of perioperative nivolumab to neoadjuvant chemotherapy resulted in significantly longer event-free survival than perioperative placebo added to neoadjuvant chemotherapy in patients with resectable NSCLC (hazard ratio, 0.58; P<0.001). We also observed that a higher percentage of patients in the nivolumab group than in the chemotherapy group had a pathological complete response (25.3% vs. 4.7%) and a major

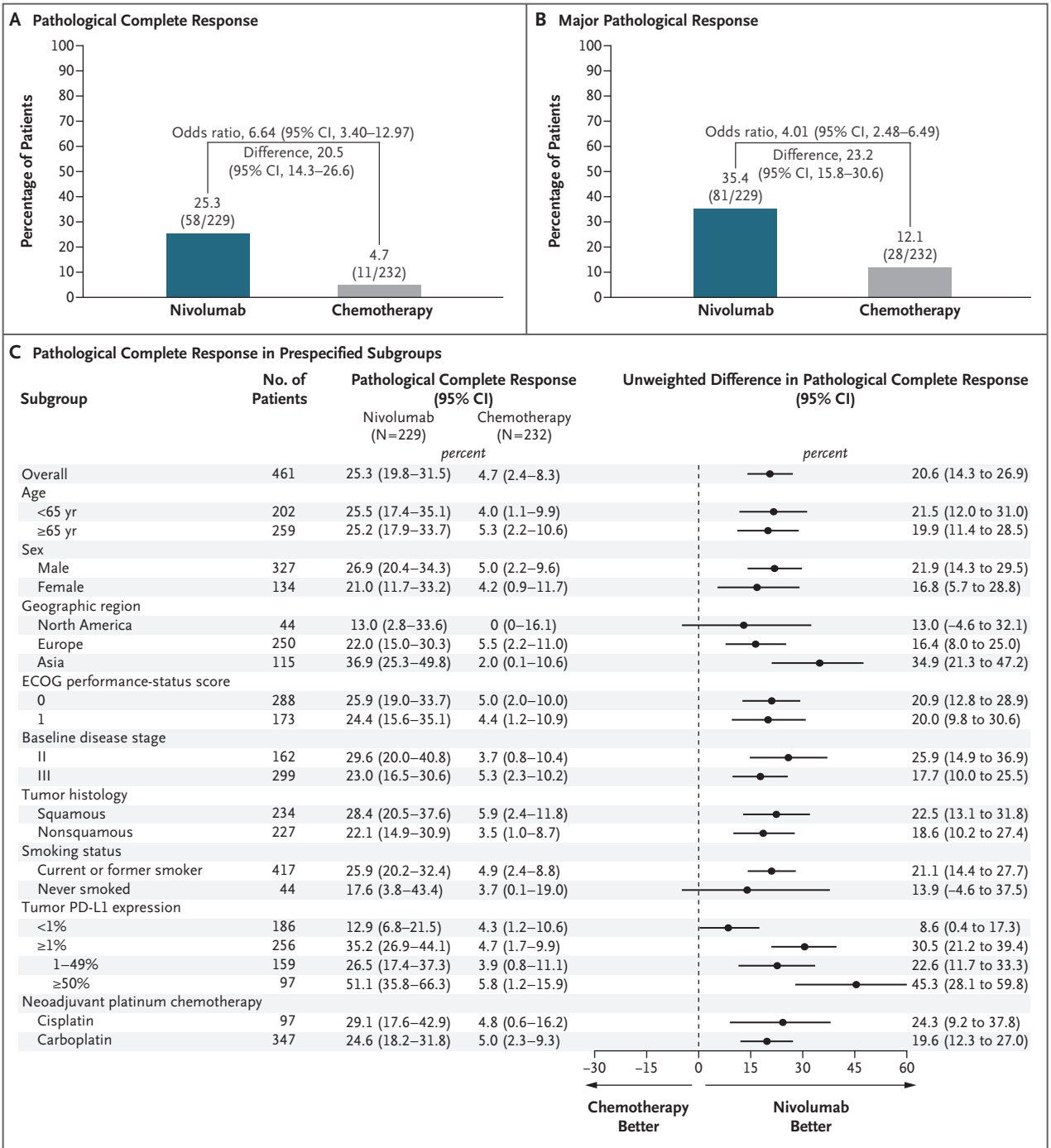
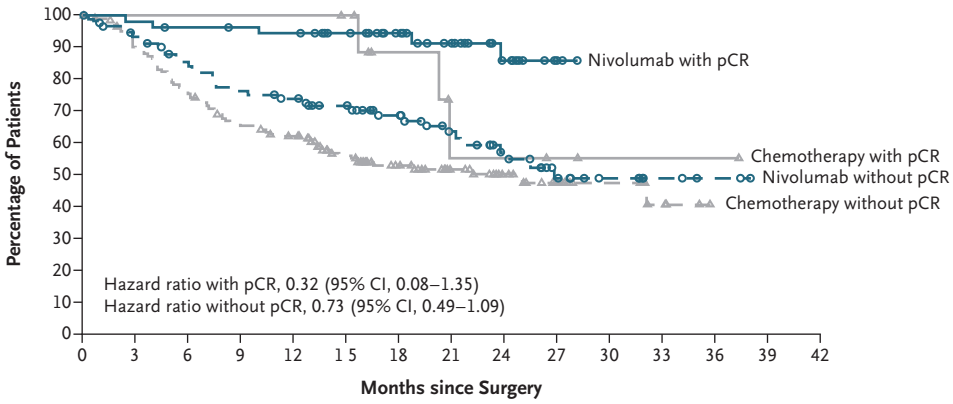


Figure 2. Pathological Response as Assessed by Central Review.

Shown is the pathological complete response in the intention-to-treat population (Panel A), the major pathological response in the intention-to-treat population (Panel B), and the pathological complete response in prespecified patient subgroups (Panel C). The pathological response was measured as the number of residual viable tumor cells after surgery in the primary tumor and sampled lymph nodes; the response was defined as complete if there were no residual viable tumor cells and as major if there were no more than 10% residual viable tumor cells. The confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. In Panel C, the unweighted difference between the treatment groups for subgroup analyses is shown according to the statistical analysis plan. Two patients in the chemotherapy group with stage IV disease at baseline were included in the stage III subgroup.

A Analysis of Event-free Survival from Definitive Surgery, According to Pathological Complete Response

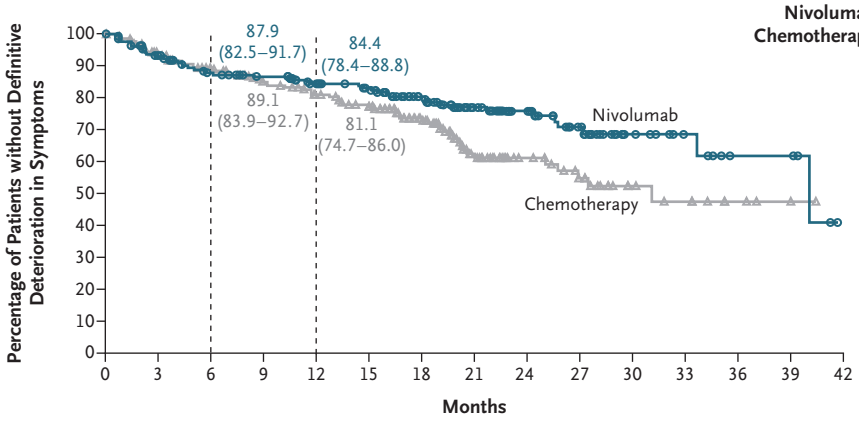


No. at Risk															
With pCR															
Nivolumab	58	56	54	53	52	45	35	25	14	2	0	0	0	0	0
Chemotherapy	11	11	11	11	11	10	6	3	3	2	1	1	1	0	0
Without pCR															
Nivolumab	98	85	74	67	62	54	45	33	23	14	7	4	2	0	0
Chemotherapy	148	129	109	93	84	61	45	33	22	14	9	5	0	0	0

B TTDD in Disease-Related Symptoms, According to NSCLC-SAQ Total Scores

	No. of Patients	Median TTDD (95% CI)
		mo
Nivolumab	229	40.0 (33.6–NR)
Chemotherapy	232	31.1 (25.0–NR)

Hazard ratio for TTDD, 0.66 (95% CI, 0.45–0.98)



No. at Risk															
Nivolumab	229	182	159	150	137	129	105	72	52	36	16	10	5	5	0
Chemotherapy	232	188	163	148	135	124	90	48	33	24	12	9	4	1	0

Figure 3. Exploratory Landmark Analysis of Event-free Survival According to Pathological Complete Response and Analysis of Time to Definitive Deterioration (TTDD) in Disease-Related Symptoms.

Panel A shows the landmark analysis of event-free survival from definitive surgery according to the pathological complete response (pCR). Panel B shows the percentage of patients without definitive deterioration in disease-related symptoms on the basis of total scores on the Non–Small-Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) in the intention-to-treat population. In Panel A, the landmark time point was the date of definitive surgery; an unstratified Cox proportional-hazards model with the treatment group as a covariate was used to estimate hazard ratios and confidence intervals. The hazard ratio for the comparison between patients with a pathological complete response and those without such a response was 0.20 (95% CI, 0.08 to 0.50) in the nivolumab group and 0.41 (95% CI, 0.13 to 1.30) in the chemotherapy group. In Panel B, a stratified Cox proportional-hazards model with the treatment group and baseline NSCLC-SAQ total score as covariates was used to estimate hazard ratios and confidence intervals; the threshold for definitive deterioration in the NSCLC-SAQ total score was 3 points.

Table 2. Summary of Adverse Events.*

Event	Overall				Neoadjuvant Period				Adjuvant Period			
	Nivolumab (N=228)		Chemotherapy (N=230)		Nivolumab (N=228)		Chemotherapy (N=230)		Nivolumab (N=142)		Chemotherapy (N=152)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Adverse event of any cause — no. (%)†												
Any	222 (97.4)	108 (47.4)	225 (97.8)	99 (43.0)	216 (94.7)	78 (34.2)	221 (96.1)	63 (27.4)	124 (87.3)	28 (19.7)	121 (79.6)	23 (15.1)
Leading to treatment discontinuation	56 (24.6)	32 (14.0)	25 (10.9)	14 (6.1)	30 (13.2)	20 (8.8)	16 (7.0)	10 (4.3)	20 (14.1)	7 (4.9)	7 (4.6)	1 (0.7)
Serious	96 (42.1)	65 (28.5)	71 (30.9)	46 (20.0)	48 (21.1)	33 (14.5)	34 (14.8)	19 (8.3)	31 (21.8)	19 (13.4)	23 (15.1)	14 (9.2)
Treatment-related adverse event — no. (%)†‡												
Any	203 (89.0)	74 (32.5)	200 (87.0)	58 (25.2)	197 (86.4)	62 (27.2)	195 (84.8)	52 (22.6)	71 (50.0)	12 (8.5)	45 (29.6)	4 (2.6)
Leading to treatment discontinuation	44 (19.3)	25 (11.0)	17 (7.4)	11 (4.8)	26 (11.4)	17 (7.5)	12 (5.2)	9 (3.9)	14 (9.9)	6 (4.2)	4 (2.6)	0
Serious	44 (19.3)	31 (13.6)	22 (9.6)	13 (5.7)	32 (14.0)	23 (10.1)	19 (8.3)	11 (4.8)	10 (7.0)	5 (3.5)	2 (1.3)	1 (0.7)
Death§	2 (0.9)	0	0	0	2 (0.9)	0	0	0	0	0	0	0
Surgery-related adverse event — no./total no. (%)¶	73/178 (41.0)	21/178 (11.8)	69/178 (38.8)	21/178 (11.8)	0	0	0	0	0	0	0	0

* Adverse events were categorized according to the *Medical Dictionary for Regulatory Activities*, version 26.0, and graded according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.0.

† Events in this category were reported between the receipt of the first dose of a trial treatment and 30 days after the last dose, with the exception of treatment-related deaths, which may have occurred at any point after receipt of the first dose of a trial treatment.

‡ The determination that an adverse event was related to a trial treatment was made by the investigators.

§ In the nivolumab group, the two treatment-related deaths were from grade 5 pneumonitis (with grade 5 indicating that the event led to death ≤24 hours after the onset of illness) and grade 4 pneumonitis; both events occurred after neoadjuvant treatment, and curative-intent surgery was not performed in either patient.

¶ The denominators in this category were the number of patients who had undergone definitive surgery (178 patients in each treatment group). Events that were reported within 90 days after definitive surgery were included. Grade 5 surgery-related adverse events occurred in 3 patients (1.7%) in the nivolumab group (1 each due to acute myocardial infarction, post-procedural hemorrhage, and septic shock) and 1 patient (0.6%) in the chemotherapy group (from pneumonia); all three events were deemed to be unrelated to a trial treatment as assessed by investigators.

pathological response (35.4% vs. 12.1%). Furthermore, the perioperative use of nivolumab resulted in a lower risk of definitive deterioration of disease-related symptoms than chemotherapy. No new safety signals were reported with perioperative nivolumab; surgical outcomes were similar in the two treatment groups.

The benefit of perioperative nivolumab over chemotherapy was evident with respect to event-free survival in patients with stage III disease, including those with single-station and multistation nodal involvement, who represented nearly two thirds of the population in the trial. These findings are consistent with other reports of perioperative immunotherapy in patients with resectable NSCLC.[18,19]

Event-free survival was also longer in the nivolumab group across PD-L1 subgroups. Although cross-trial comparisons must be made with caution because of differences in trial design, patient population, and sample size (with the associated differences in statistical power), it is interesting to note that a hazard ratio of 0.85 (95% CI, 0.54 to 1.32) was observed with neoadjuvant nivolumab plus chemotherapy in patients with tumor PD-L1 expression of less than 1% in CheckMate 816.[4] Recent trials of perioperative immunotherapy have also shown hazard ratios for analyses of event-free survival in patients with tumor PD-L1 expression of less than 1%.[18,19] These comparisons were similar to the findings in CheckMate 77T, although the 95% confidence intervals crossed 1 in all such subgroups.

In CheckMate 77T, a pathological complete response occurred in approximately 5 times as many patients in the nivolumab group as in the chemotherapy group (25.3% and 4.7%, respectively). Of note, the percentage of patients with a pathological complete response in the nivolumab group was almost identical to that observed in CheckMate 816 for neoadjuvant nivolumab plus chemotherapy (24.0%; 95% CI, 18.0 to 31.0).[4] In the phase 3 AEGEAN, KEYNOTE-671, and Neotorch trials, the percentage of patients with a pathological complete response ranged from 17.2 to 24.8% (with data from the Neotorch trial that included only patients with resectable stage III NSCLC) in the perioperative durvalumab, pembrolizumab, and toripalimab groups, respectively.[18,19,24]

The association of pathological response with event-free survival benefit was also confirmed in CheckMate 77T and was consistent with the findings from other trials of perioperative immunotherapy.[19,21] In a post hoc landmark analysis of data from CheckMate 77T in which we assessed event-free survival from definitive surgery according to adjuvant treatment status, perioperative nivolumab resulted in longer event-free survival than chemotherapy in patients who had received adjuvant treatment (hazard ratio, 0.43; 95% CI, 0.28 to 0.67); among the patients who could not receive adjuvant treatment, neoadjuvant nivolumab plus chemotherapy continued to provide event-free survival benefit (hazard ratio, 0.44; 95% CI, 0.22 to 0.87). Furthermore, in a similar post hoc landmark analysis of event-free survival from definitive surgery, event-free survival favored perioperative nivolumab regardless of status with respect to pathological complete response among the patients who had received adjuvant treatment. Among the patients who had received adjuvant treatment and did not have a pathological complete response, the hazard ratio for the analysis of event-free survival from definitive surgery was 0.70 (95% CI, 0.43 to 1.13), whereas the corresponding hazard ratios were 0.84 (95% CI, 0.61 to 1.17) in CheckMate 816 and 0.69 (95% CI, 0.55 to 0.85) in KEYNOTE-671 among all patients without a pathological complete response.[4,19] Although heterogeneous populations limit cross-trial comparisons and the CheckMate 77T trial was not designed to directly evaluate the role of adjuvant immunotherapy after neoadjuvant chemoimmunotherapy, findings from our trial suggest benefit with a perioperative approach of including adjuvant nivolumab after neoadjuvant nivolumab plus chemotherapy and surgery in patients with resectable NSCLC.

The overall safety profile and surgical outcomes in CheckMate 77T were similar in the two treatment groups and correspond to the findings in previous studies.[18,19,21,24] Safety outcomes with neoadjuvant therapy were also similar in the two groups; adverse events were less common during the adjuvant period in both groups. The incidence of treatment-related adverse events resulting in treatment discontinuation or death with perioperative nivolumab was similar to that observed previously with neoadjuvant chemoimmunotherapy or perioperative immunotherapy.[4,18,19,21,24] Surgical outcomes were similar in the two treatment groups, with fewer

surgery cancellations and pneumonectomies noted with perioperative nivolumab; findings were consistent with results for neoadjuvant nivolumab plus chemotherapy in CheckMate 816 and for perioperative durvalumab in AEGEAN.[4,18] Overall, long-term clinical benefit in CheckMate 77T with four cycles of neoadjuvant nivolumab plus chemotherapy followed by adjuvant nivolumab will be ascertained as the trial data mature.

A limitation of our trial is the underrepresentation of Black patients, which also occurred in other trials that have evaluated perioperative immunotherapy in patients with resectable NSCLC.[18,19]

In the CheckMate 77T trial, we found that neoadjuvant nivolumab plus chemotherapy followed by surgery and adjuvant nivolumab resulted in significantly longer event-free survival than neoadjuvant placebo plus chemotherapy followed by surgery and adjuvant placebo in patients with resectable stage IIA to IIIB NSCLC. A higher percentage of patients in the nivolumab group also had a pathological response than those in the chemotherapy group. Patient-reported outcomes with respect to disease-related symptoms were better with perioperative nivolumab than with chemotherapy as well. The safety profile of perioperative nivolumab revealed no unexpected safety signals.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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