The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 21/28, 2025 VOL. 393 NO. 8

Overall Survival with Neoadjuvant Nivolumab plus Chemotherapy in Lung Cancer

Patrick M. Forde, M.B., B.Ch., Ph.D.,[1] Jonathan D. Spicer, M.D., Ph.D.,[2] Mariano Provencio, M.D., Ph.D.,[3] Tetsuya Mitsudomi, M.D., Ph.D.,[4] Mark M. Awad, M.D., Ph.D.,[5] Changli Wang, M.D.,[6] Shun Lu, M.D., Ph.D.,[7] Enriqueta Felip, M.D., Ph.D.,[8] Scott J. Swanson, M.D.,[9] Julie R. Brahmer, M.D.,[10] Keith Kerr, M.B., Ch.B.,[11] Janis M. Taube, M.D.,[12] Tudor-Eliade Ciuleanu, M.D., Ph.D.,[13] Fumihiro Tanaka, M.D., Ph.D.,[14] Gene B. Saylors, M.D.,[15] Ke-Neng Chen, M.D., Ph.D.,[16] Hiroyuki Ito, M.D., Ph.D.,[17] Moishe Liberman, M.D., Ph.D.,[18] Claudio Martin, M.D.,[19] Stephen Broderick, M.D.,[10] Lily Wang, M.D.,[20] Junliang Cai, M.D.,[20] Quyen Duong, Ph.D.,[20] Stephanie Meadows-Shropshire, Ph.D.,[20] Joseph Fiore, Pharm.D.,[20] Sumeena Bhatia, Ph.D.,[20] and Nicolas Girard, M.D., Ph.D.,[21] for the CheckMate 816 Investigators*

ABSTRACT

BACKGROUND

Neoadjuvant nivolumab plus chemotherapy significantly improved pathological complete response and event-free survival in patients with resectable non–small-cell lung cancer (NSCLC) in a phase 3 trial. Data are needed on overall survival.

METHODS

In this open-label, phase 3 trial, patients with stage IB to IIIA resectable NSCLC were randomly assigned to receive nivolumab plus chemotherapy or chemotherapy alone for three cycles, followed by surgery. The primary end points were event-free survival and pathological complete response. Here, we report the results of the planned analysis of overall survival.

RESULTS

A total of 358 patients were concurrently assigned to receive nivolumab plus chemotherapy (179 patients) or chemotherapy alone (179 patients). The final analysis of overall survival significantly favored neoadjuvant nivolumab plus chemotherapy over chemotherapy (hazard ratio for death, 0.72; 95% confidence interval [CI], 0.523 to 0.998; P=0.048). At a median follow-up of 68.4 months, the 5-year overall survival was 65.4% with nivolumab plus chemotherapy and 55.0% with chemotherapy alone, with consistency across most subgroups. In exploratory analyses, the 5-year overall survival in the nivolumab-plus-chemotherapy group was 95.3% (95% CI, 82.7 to 98.8) among the patients with a pathological complete response and 55.7% (95% CI, 46.9 to 63.7) among those without such a response; survival was 75.0% among the patients with presurgery clearance of circulating tumor DNA (ctDNA) and 52.6% among those without such clearance. No new safety signals were observed.

CONCLUSIONS

Three cycles of neoadjuvant nivolumab plus chemotherapy significantly improved overall survival among patients with resectable NSCLC as compared with chemotherapy alone. (Funded by Bristol Myers Squibb; CheckMate 816 ClinicalTrials.gov number, NCT02998528.)

Author affiliations are listed at the end of the article. Dr. Forde can be contacted at fordep1@tcd.ie or at Trinity St. James's Cancer Institute, Trinity College Dublin, Dublin, Ireland.

*A complete list of CheckMate 816 investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 2, 2025, at NEJM.org.

N Engl J Med 2025;393:741-52.
DOI: 10.1056/NEJMoa2502931

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In the phase 3 CheckMate 816 trial[1] involving patients with resectable non–small-cell lung cancer (NSCLC), three cycles (9 weeks) of neoadjuvant nivolumab, a human anti–programmed death 1 (PD-1) antibody, plus platinum-based chemotherapy resulted in a significantly higher percentage of patients with a pathological complete response than platinum-based chemotherapy alone (odds ratio, 13.94; 99% confidence interval [CI], 3.49 to 55.75; P<0.001). The duration of event-free survival was also significantly longer in the nivolumab group (hazard ratio for disease progression, disease recurrence, or death, 0.63; 97.38% CI, 0.43 to 0.91; P=0.005). On the basis of the findings from this phase 3 trial, nivolumab plus chemotherapy is the sole neoadjuvant-only chemoimmunotherapy regimen approved for patients with resectable NSCLC in the United States, European Union, and several other jurisdictions.[2-6]

Subsequently, several clinical trials have shown similar improvements in pathological response or survival outcomes with perioperative immunotherapy–based regimens, which generally included up to four cycles (12 weeks) of neoadjuvant therapy followed by 24 to 52 weeks of adjuvant immunotherapy in patients with resectable NSCLC.[7-14] Overall survival is considered to be the standard end point to assess the clinical benefit of cancer treatments. However, to date no randomized phase 3 trials of neoadjuvant-only immunotherapy-based treatments have reported data regarding overall survival across solid tumors.

Here, we report the prespecified final analysis of overall survival according to status regarding pathological complete response and presurgery clearance of circulating tumor DNA (ctDNA). We also update results regarding event-free survival at 5 years, which provide additional insights into the role of neoadjuvant chemoimmunotherapy in resectable NSCLC.

Methods

Patients

The eligibility criteria for CheckMate 816 have been reported previously.[1] Briefly, enrolled patients had resectable stage IB to IIIA NSCLC (according to the staging criteria of the American Joint Committee on Cancer, 7th edition), an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (assessed on a 5-point scale, with higher scores indicating greater disability), no known *EGFR* mutations or *ALK* translocations, and no previous systemic anticancer treatment.

Trial Design and Treatment

The trial was a phase 3, randomized, open-label, multinational trial (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients underwent concurrent randomization in a 1:1 ratio to receive nivolumab (at a dose of 360 mg) plus platinum-based chemotherapy or platinum-based chemotherapy alone every 3 weeks for three cycles. Surgery was planned to occur within 6 weeks after the last neoadjuvant treatment dose, and patients could receive optional adjuvant chemotherapy, radiotherapy, or both. A third group that received nivolumab (3 mg per kilogram every 2 weeks for three cycles) plus ipilimumab (1 mg per kilogram, cycle 1 only) was closed to enrollment early on the basis of external data reported during the trial.[15,16] Additional details about the trial design, including the chemotherapy regimens, are provided in the Supplementary Appendix.

Outcomes and Assessments

The primary end points, event-free survival and pathological complete response, have been reported previously.[1] Overall survival (the time from randomization until death from any cause) was the key secondary end point. This end point was evaluated in all the patients who had undergone concurrent randomization and in prespecified subgroups, including those defined according to baseline disease stage (IB to II or IIIA), expression of tumor programmed death ligand 1 (PD-L1) (a level of <1%, ≥1%, 1 to 49%, or ≥50%), and findings on histologic analysis (squamous-cell or nonsquamous-cell cancer). Other prespecified end points included major pathological response. As reported previously,[1] event-free survival was also analyzed with the use of a secondary definition. Additional details are provided in the Supplementary Appendix.

Prespecified exploratory analyses included overall survival and event-free survival according to status regarding pathological complete response and major pathological response. Post hoc exploratory analyses of overall survival and event-free survival according to ctDNA clearance and lung-cancer–specific survival (the time from

randomization until death with noted cause of disease according to investigator assessment) were also conducted. As described previously,[1] ctDNA from plasma samples that had been obtained before each treatment administration cycle was analyzed with the use of a tumor-guided personalized ctDNA panel. Clearance was defined as the presurgical change from detectable ctDNA levels before cycle 1 to undetectable levels before cycle 3. Adverse events were assessed at baseline, continuously while the patients were receiving treatment, and within 100 days after the last dose of neoadjuvant therapy, within 90 days after surgery, or up to 30 days after the last dose of adjuvant therapy (whichever period was longest).[1]

OVERSIGHT

The sponsor (Bristol Myers Squibb) and the academic steering committee designed the trial and analyzed the data with participation from all the authors. The trial was conducted according to the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. Independent ethics committees or institutional review boards at each participating center approved the protocol (available at NEJM.org); patients provided written informed consent. Efficacy and safety were monitored by an independent data and safety monitoring committee.

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

STATISTICAL ANALYSIS

Sample-size calculations on the basis of the primary end points of event-free survival and pathological complete response have been described previously.[1] Overall survival was a statistically powered, prespecified secondary end point that was planned to be tested hierarchically if the between-group difference in event-free survival was significant. The final overall survival analysis was planned to be conducted after the occurrence of 185 deaths or at a minimum follow-up of approximately 5 years after randomization of the last patient, whichever occurred first. As of the final database lock (January 23, 2025), 150 deaths had occurred, which resulted in a boundary of 0.0482 for significance according to the Lan–DeMets alpha-spending function with O'Brien–Fleming boundaries.

Efficacy was evaluated in all the patients who had been concurrently assigned to receive nivolumab plus chemotherapy or chemotherapy alone. Event-free survival and overall survival were compared between treatment groups with a stratified log-rank test. Survival curves and rates were estimated by means of the Kaplan–Meier method. Hazard ratios and confidence intervals were estimated with the use of a stratified Cox proportional-hazards model. Confidence intervals for analyses that were not part of hypothesis testing were not adjusted for multiplicity and should be interpreted descriptively. Safety was assessed in all the patients who had received at least one dose of a trial drug. For the analysis of overall survival, the sponsor performed three interim analyses and one final analysis. Missing data were assumed to be missing at random, given the trial design, where missing data probably resulted from identifiable factors present in the observed data set, such as patient characteristics or treatment effects. Additional details are provided in the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENT SUMMARY

From March 2017 through November 2019, a total of 358 patients underwent concurrent randomization to receive nivolumab plus chemotherapy or chemotherapy alone (179 patients in each treatment group). Of these patients, 352 received treatment (176 in each group) (Fig. S2). The characteristics of the patients were similar in the two treatment groups at baseline (Table S1). The demographic characteristics of the patients were representative of the broader population affected by lung cancer, except that Black patients were underrepresented (Tables S1 and S2).

EFFICACY

At the data-cutoff date for the final analysis of overall survival, 150 deaths had occurred (information fraction, 81%; 66 deaths in the nivolumab-plus-chemotherapy group and 84 deaths in the chemotherapy-alone group). The median follow-up was 68.4 months (range, 59.9 to 85.2).

At 5 years, the percentage of patients who were alive was 65.4% (95% CI, 57.8 to 71.9) with nivolumab plus chemotherapy and 55.0% (95% CI,

47.3 to 62.0) with chemotherapy alone (hazard ratio for death, 0.72; 95% CI, 0.523 to 0.998; P=0.048) (Fig. 1A).

Data regarding overall survival with nivolumab plus chemotherapy and chemotherapy alone across prespecified subgroups are provided in Figure 1B; data regarding tumor stage and PD-L1 expression are provided in Figure 2. Additional data regarding overall survival according to PD-L1 expression (1 to 49% or ≥50%), tumor histologic stage (stage II to IIIA with tumor PD-L1 expression of ≥1%), and pathological evidence of lymph-node involvement are shown in Figures S3 to S6.

In an exploratory analysis of lung-cancer–specific survival, investigators determined that the cause of death was NSCLC in 44 patients in the nivolumab-plus-chemotherapy group and in 61 patients in the chemotherapy-alone group. At 5 years, the frequency of lung-cancer–specific survival was 74.9% (95% CI, 67.5 to 80.9) and 65.1% (95% CI, 57.2 to 71.9), respectively (hazard ratio for death from lung cancer, 0.65; 95% CI, 0.44 to 0.96) (Fig. 3).

At 5 years, the percentage of patients who were alive without disease progression or recurrence was 49.2% (95% CI, 40.8 to 57.2) with nivolumab plus chemotherapy and 34.4% (95% CI, 26.8 to 42.1) with chemotherapy (hazard ratio for disease progression or recurrence or death, 0.68; 95% CI, 0.51 to 0.91) (Fig. S7A). Event-free survival with nivolumab plus chemotherapy and with chemotherapy alone across prespecified subgroups is shown in Fig. S7B. Additional data for event-free survival according to stage, PD-L1 expression, tumor histology, and stage II to IIIA with PD-L1 expression of 1% or more are reported in Figures S8 to S11. Event-free survival according to a secondary definition is reported in Figure S12. The percentage of patients with postsurgery disease recurrence was 31.5% in the nivolumab-plus-chemotherapy group and 48.1% in the chemotherapy-alone group. The incidence of locoregional recurrence was 19.5% in the nivolumab-plus-chemotherapy group and 25.2% in the chemotherapy-alone group; the incidence of distant metastases was 11.4% and 20.7%, respectively (Table S3). A similar pattern of recurrence was seen in patients with stage IB to II and stage IIIA NSCLC across the two treatment groups (Table S4). Patterns of recurrence according to the completeness of resection are shown in Table S5.

SUBSEQUENT TREATMENT

At the final analysis of overall survival, subsequent cancer therapy of any type was administered to 31.3% of the patients in the nivolumab-plus-chemotherapy group and 51.4% of those in the chemotherapy-alone group; subsequent systemic therapy was administered to 25.1% and 43.0%, respectively (Table S6). Of the patients who had disease progression or recurrence with nivolumab plus chemotherapy (67 patients) and chemotherapy alone (94 patients), subsequent systemic therapy was administered to 58.2% and 77.7% of the patients, respectively.

EFFICACY ACCORDING TO PATHOLOGICAL RESPONSE AND CTDNA CLEARANCE

The percentage of patients with a pathological complete response was 24.0% (in 43 of 179) in the nivolumab-plus-chemotherapy group and 2.2% (in 4 of 179) in the chemotherapy-alone group.[1] The 5-year overall survival was 95.3% (95% CI, 82.7 to 98.8) among the patients with a pathological complete response and 55.7% (95% CI, 46.9 to 63.7) among those without a pathological complete response in the nivolumab-plus-chemotherapy group (hazard ratio for death, 0.11; 95% CI, 0.04 to 0.36) (Fig. 4A). Overall survival according to status regarding pathological complete response in subgroups that were defined according to PD-L1 expression and stage is shown in Figures S13 and S14.

In the nivolumab-plus-chemotherapy group, there were 3 deaths (7.0%) among the patients who had a pathological complete response and no deaths that were specifically due to lung cancer, as compared with 62 deaths (46.6%) among the patients without a pathological complete response and 44 deaths (33.1%) from lung cancer (Table S7). Baseline characteristics of the patients with or without a pathological complete response are shown in Table S8.

The percentage of patients with a major pathological response was 36.9% (in 66 of 179) in the nivolumab-plus-chemotherapy group and 8.9% (in 16 of 179) in the chemotherapy-alone group.[1] In the nivolumab-plus-chemotherapy group, the 5-year overall survival was 86.3% (95% CI, 75.4 to 92.6) among patients with a major pathological response and 52.8% (95% CI, 43.1 to 61.6) among those without a major pathological response (hazard ratio for death, 0.23; 95% CI, 0.12 to 0.45) (Fig. S15). The baseline characteristics of patients

with or without a major pathological response are shown in Table S9.

The final analysis of event-free survival among patients with a pathological complete response and those without such a response in the nivolumab-plus-chemotherapy group is reported in Figure S16A (hazard ratio for disease progression or recurrence or death, 0.14; 95% CI, 0.06 to 0.33). In the nivolumab-plus-chemotherapy group, disease recurrence was reported in 3 patients (7%) who had a pathological complete response, as compared with 57 patients (42%) who did not have a pathological complete response (Table S7). Similar findings were observed when the data were assessed according to status regarding major pathological response (Fig. S16B).

Among the patients with ctDNA clearance in both the nivolumab-plus-chemotherapy group (in 24 of 43 evaluable patients) and the chemotherapy-alone group (in 15 of evaluable 43 patients), the hazard ratio for overall survival for patients with ctDNA clearance as compared with patients without ctDNA clearance was 0.38 (95% CI, 0.15 to 1.00) in the nivolumab-plus-chemotherapy group and 0.39 (95% CI, 0.14 to 1.11) in the chemotherapy-alone group (Fig. 4B). An association between ctDNA clearance and a pathological complete response was seen, with 46% of patients with ctDNA clearance having a pathological complete response in the nivolumab-plus-chemotherapy group and 13% in the chemotherapy-alone group (Fig. 4C). Event-free survival in patients according to ctDNA clearance in the two treatment groups is shown in Figure S16C. The baseline characteristics of the patients according to ctDNA clearance are shown in Table S10.

SAFETY

Safety outcomes in all treated patients were similar to results that have been reported previously.[1] No new deaths that were determined by the investigator to be related to a trial treatment had occurred. Adverse events of any cause, treatment-related adverse events, and surgery-related adverse events are reported in Table S11; causes of death are reported in Table S12.

DISCUSSION

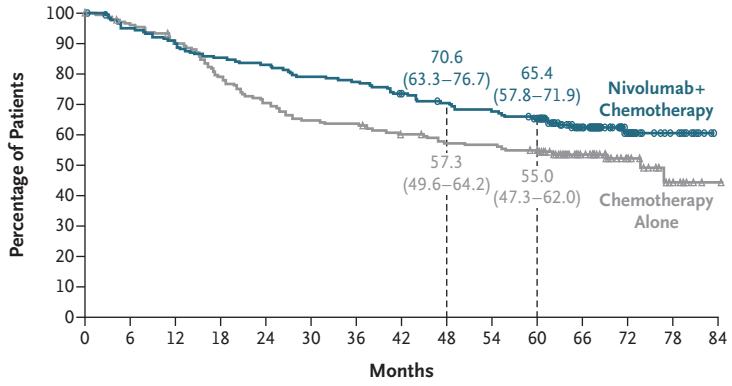
In this preplanned final analysis of overall survival from the CheckMate 816 trial, neoadjuvant nivolumab plus chemotherapy resulted in significantly longer overall survival than chemotherapy alone in patients with resectable NSCLC. Although the statistical significance for overall survival was calculated with a slight margin ($P=0.048$), the separation of the Kaplan–Meier curves for overall survival favoring nivolumab plus chemotherapy over chemotherapy alone began at approximately 16 months after randomization, and an absolute difference of approximately 10 percentage points in overall survival was maintained over 5 years. Neoadjuvant nivolumab plus chemotherapy also maintained an advantage with respect to event-free survival as compared with chemotherapy alone. There were no new safety signals.

A consistent benefit regarding overall survival was apparent in all subgroups, with hazard ratios of less than 1.0, including in patients with stage IB to II or stage IIIA disease and in those with either squamous-cell or nonsquamous-cell histology. Although neoadjuvant therapy has historically been preferred for clinical stage III disease, long-term follow-up in this trial has shown a similar magnitude of benefit from the addition of neoadjuvant nivolumab to chemotherapy among patients with both earlier-stage IB to II disease and more locally advanced stage III disease and regardless of lymph-node status.

Overall survival also favored neoadjuvant nivolumab plus chemotherapy over chemotherapy alone across PD-L1 subgroups; a greater magnitude of benefit regarding overall survival was observed in patients with PD-L1 expression of 1% or more than in those with PD-L1 expression of less than 1%, a finding that was consistent with the results of several previous trials.[8,9,11-13] However, results from the exploratory subgroup analyses should be interpreted with caution because several subgroups were too small for adequate statistical comparison.

Nivolumab was approved in combination with chemotherapy as a neoadjuvant treatment for patients with resectable NSCLC on the basis of significant benefits with respect to event-free survival and pathological complete response.[1] Updated analyses have shown that this benefit regarding event-free survival was maintained at a 5-year follow-up. In addition, the incidence of postsurgery disease recurrence overall, including distant metastases (particularly in the central nervous system), was lower for patients who received nivolumab plus chemotherapy than in

A Overall Survival



	Median Overall Survival (95% CI)
	mo
Nivolumab+Chemotherapy (N=179)	NR (NR–NR)
Chemotherapy Alone (N=179)	73.7 (47.3–NR)

Hazard ratio for death, 0.72 (95% CI, 0.523–0.998)
P=0.048

No. at Risk

Nivolumab+chemotherapy	179	168	159	151	147	140	137	129	122	117	111	67	29	9	0
Chemotherapy alone	179	170	159	139	124	114	112	104	98	97	91	58	29	6	1

B Subgroup Analysis of Overall Survival

Subgroup	No. of Events/ No. of Patients	Median Overall Survival (95% CI)		Unstratified Hazard Ratio for Death (95% CI)
		Nivolumab+ chemotherapy (N=179)	Chemotherapy alone (N=179)	
		mo		
Overall	150/358	NR	73.7 (47.3–NR)	0.71 (0.51–0.98)
Sex				
Male	120/255	NR (61.3–NR)	61.8 (36.8–NR)	0.76 (0.53–1.09)
Female	30/103	NR	NR (55.8–NR)	0.52 (0.25–1.10)
Race				
White	76/169	NR (53.9–NR)	73.7 (45.1–NR)	0.91 (0.58–1.43)
Black	5/7	NR (3.4–NR)	20.9 (20.7–NR)	—
Asian	68/179	NR	76.8 (37.2–NR)	0.52 (0.32–0.85)
Geographic region				
North America	33/91	NR (71.6–NR)	73.7 (55.3–NR)	0.83 (0.41–1.67)
Europe	34/66	NR (44.1–NR)	38.3 (18.4–NR)	0.64 (0.32–1.26)
Asia	67/177	NR	76.8 (37.2–NR)	0.54 (0.33–0.88)
ECOG performance-status score				
0	87/241	NR	76.8 (73.7–NR)	0.70 (0.46–1.07)
1	63/117	71.6 (44.1–NR)	45.3 (22.8–NR)	0.76 (0.46–1.25)
Disease stage at baseline				
IB or II	50/126	NR (64.7–NR)	76.8 (41.6–NR)	0.77 (0.44–1.35)
IIIA	98/229	NR (71.6–NR)	73.7 (39.8–NR)	0.70 (0.47–1.05)
Histologic tumor type				
Squamous	82/182	NR (64.7–NR)	73.7 (28.8–NR)	0.71 (0.46–1.11)
Nonsquamous	68/176	NR (71.6–NR)	NR (47.3–NR)	0.72 (0.45–1.16)
PD-L1 expression level				
<1%	74/155	NR (43.8–NR)	61.8 (31.2–NR)	0.89 (0.57–1.41)
≥1%	64/178	NR	73.7 (47.3–NR)	0.51 (0.31–0.84)
1–49%	39/98	NR (64.7–NR)	73.7 (45.1–NR)	0.66 (0.35–1.24)
≥50%	25/80	NR	76.8 (28.8–NR)	0.33 (0.14–0.78)
Type of platinum therapy				
Cisplatin	112/258	NR (64.7–NR)	76.8 (47.3–NR)	0.81 (0.56–1.18)
Carboplatin	27/72	NR	37.2 (16.8–NR)	0.39 (0.18–0.86)

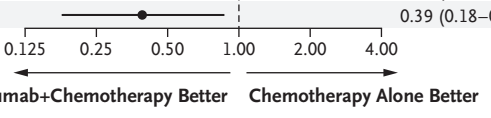


Figure 1 (facing page). Overall Survival in All Patients and According to Prespecified Subgroups.

Panel A shows overall survival among the patients who underwent concurrent randomization. Open circles and open triangles indicate censored data for the nivolumab-plus-chemotherapy group and the chemotherapy-alone group, respectively. The 1-year overall survival was 89.8% (95% confidence interval [CI], 84.3 to 93.5) and 90.4% (95% CI, 85.0 to 93.9) in the two groups, respectively; the 2-year overall survival was 83.1% (95% CI, 76.7 to 87.8) and 70.5% (95% CI, 63.2 to 76.6), respectively; and the 3-year overall survival was 77.4% (95% CI, 70.5 to 82.9) and 63.7% (95% CI, 56.1 to 70.3), respectively. Panel B shows overall survival in prespecified patient subgroups. In Panel B, the confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing; all subgroup analyses were prespecified. ECOG denotes Eastern Cooperative Oncology Group, NR not reached, and PD-L1 programmed death ligand 1.

those who received chemotherapy alone. These findings support nivolumab plus chemotherapy as an effective neoadjuvant treatment with durable local and distant disease control.

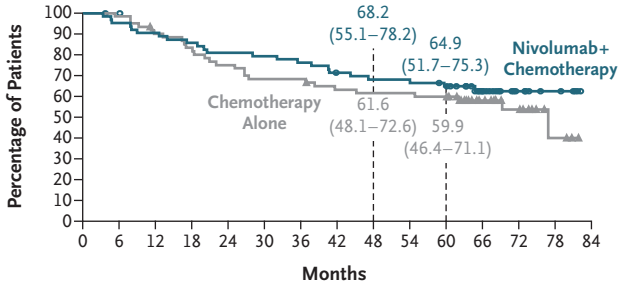
Fewer patients in the nivolumab-plus-chemotherapy group received further systemic treatment for recurrent or progressive cancer than those in the chemotherapy-alone group. In addition, lung-cancer–specific survival, an outcome that is directly related to lung cancer, was also longer with nivolumab plus chemotherapy than with chemotherapy alone. These data collectively inform patient prognosis and guide research to identify patients' risk factors leading to disease-specific death and thus to the tailoring of individual treatment plans.

Surrogate measures of overall survival are needed to better inform treatment choices that can benefit patients before the maturation of longer-term outcomes. In this trial, we found that a pathological complete response was prognostic for overall survival in patients with resectable NSCLC, a finding that was similar to those in a previous report from the CheckMate 816 trial showing that a pathological complete response was prognostic for event-free survival.[17] Patients with a pathological complete response after neoadjuvant nivolumab plus chemotherapy had a nearly 90% lower risk of death at 5 years than those who did not have such a response. Moreover, no deaths from lung cancer occurred in patients who had a pathological complete response. These results were also consistent with the results from the phase 2 NADIM trial,[14] in which investigators found a 5-year overall survival of 95.8% among patients with a pathological complete response as compared with 66.0% among those without such a response. An association between a pathological complete response and survival has been observed in several phase 3 studies of perioperative chemoimmunotherapy, with ongoing efforts to validate the utility of pathological complete response as a surrogate end point in resectable NSCLC.

Furthermore, ctDNA clearance, which has been used to identify patients with resectable NSCLC at risk for relapse,[18] was also prognostic for overall survival in CheckMate 816. Additional research, including longitudinal assessment of ctDNA levels and disease recurrence, is needed to validate these findings, support routine use of surrogate markers, and assess novel markers, such as residual viable tumor, that can guide treatment decisions.[17]

The treatment landscape has evolved since the CheckMate 816 primary analysis report, with several perioperative trials of chemoimmunotherapy showing improved clinical outcomes in patients with resectable NSCLC.[9,11,13,14] The 5-year overall survival with perioperative nivolumab in the NADIM trial was 69.3% (95% CI, 53.7 to 80.6).[14] The phase 3 KEYNOTE-671 trial showed significant benefit regarding overall survival with perioperative pembrolizumab as compared with placebo (hazard ratio, 0.72; 95% CI, 0.56 to 0.93).[13] Data regarding overall survival from the phase 3 CheckMate 77T trial have not yet been published; however, the investigators found significant benefit regarding event-free survival with perioperative nivolumab as compared with placebo (hazard ratio, 0.58; 97.36% CI, 0.42 to 0.81).[11] Trends toward longer overall survival were observed with perioperative toripalimab as compared with placebo (hazard ratio, 0.62; 95% CI, 0.38 to 1.00) and with perioperative durvalumab (hazard ratio, 0.89; 95% CI, 0.70 to 1.14), with data continuing to mature.[10,12] All these perioperative phase 3 trials consisted of more cycles of immunotherapy than the regimen that we evaluated in CheckMate 816.[10-13] Of note, the survival benefits that we report in CheckMate 816 are similar to those in recent trials of perioperative immunotherapy; however, direct comparisons across trials should be interpreted with caution.

A Overall Survival in Patients with Baseline Disease Stage IB to II

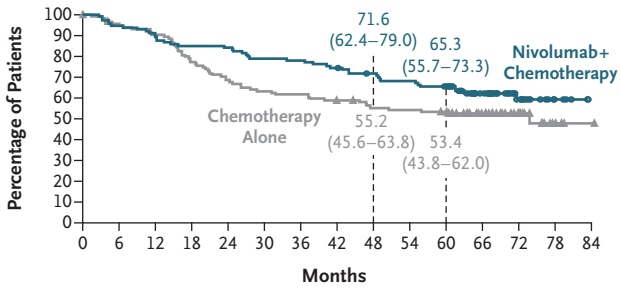


No. at Risk															
Nivolumab+chemotherapy	65	60	57	54	51	50	48	44	42	41	39	21	11	4	0
Chemotherapy alone	61	60	54	50	45	41	41	37	36	36	34	20	12	3	0

	Median Overall Survival (95% CI)
	mo
Nivolumab+Chemotherapy (N=65)	NR (64.7–NR)
Chemotherapy Alone (N=61)	76.8 (41.6–NR)

Hazard ratio for death, 0.77 (95% CI, 0.44–1.35)

B Overall Survival in Patients with Baseline Disease Stage IIIA

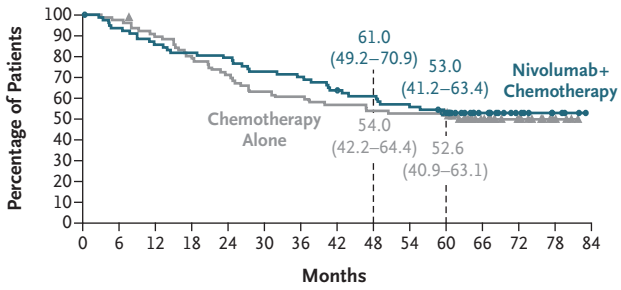


No. at Risk															
Nivolumab+chemotherapy	113	107	101	96	95	89	88	84	79	75	71	46	18	5	0
Chemotherapy alone	116	108	103	88	78	72	70	66	61	60	57	38	17	3	1

	Median Overall Survival (95% CI)
	mo
Nivolumab+Chemotherapy (N=113)	NR (71.6–NR)
Chemotherapy Alone (N=116)	73.7 (39.8–NR)

Hazard ratio for death, 0.70 (95% CI, 0.47–1.05)

C Overall Survival in Patients with Tumor PD-L1 Expression <1%

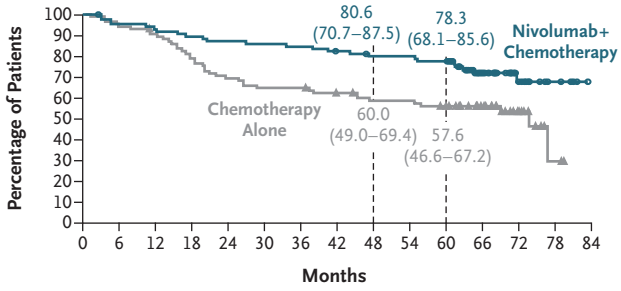


No. at Risk															
Nivolumab+chemotherapy	78	72	66	63	61	56	54	49	46	42	38	23	12	4	0
Chemotherapy alone	77	74	68	61	54	48	46	43	41	40	39	23	13	3	0

	Median Overall Survival (95% CI)
	mo
Nivolumab+Chemotherapy (N=78)	NR (43.8–NR)
Chemotherapy Alone (N=77)	61.8 (31.2–NR)

Hazard ratio for death, 0.89 (95% CI, 0.57–1.41)

D Overall Survival in Patients with Tumor PD-L1 Expression ≥1%



No. at Risk															
Nivolumab+chemotherapy	89	84	82	79	77	76	75	72	69	69	67	40	16	5	0
Chemotherapy alone	89	84	80	70	62	58	58	54	50	50	46	31	15	2	0

	Median Overall Survival (95% CI)
	mo
Nivolumab+Chemotherapy (N=89)	NR (NR–NR)
Chemotherapy Alone (N=89)	73.7 (47.3–NR)

Hazard ratio for death, 0.51 (95% CI, 0.31–0.84)

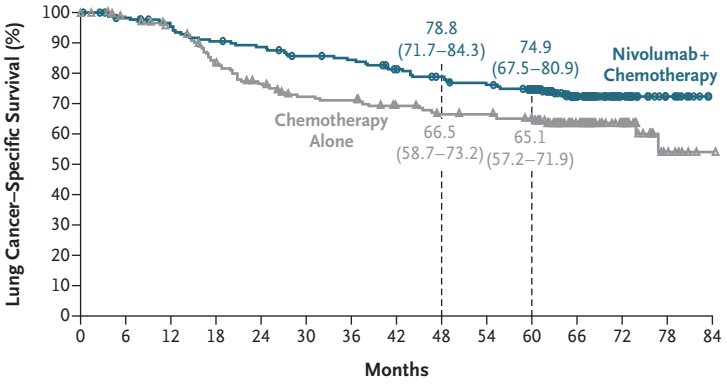
Figure 2 (facing page). Overall Survival According to Disease Stage and Tumor PD-L1 Expression.

Shown are data for overall survival among patients with baseline disease stage IB to II (Panel A) or disease stage IIIA (Panel B) and overall survival among patients with tumor programmed death ligand 1 (PD-L1) expression of less than 1% (Panel C) or expression of 1% or more (Panel D). Open circles and open triangles indicate censored data for patients in the nivolumab-plus-chemotherapy group and the chemotherapy-alone group, respectively. Confidence intervals were not adjusted for multiplicity.

Results from CheckMate 816 also showed that no patients who had a pathological complete response after neoadjuvant nivolumab plus chemotherapy had a reported death from lung cancer at 5 years, results that provide initial support for surveillance rather than further treatment for these patients after neoadjuvant chemoimmunotherapy. Long-term follow-up results from phase 3 perioperative trials are awaited to draw definitive conclusions, since patient-specific factors and preferences need to be considered before measurement of the pathological complete response is used to inform adjuvant treatment. In addition, to the best of our knowledge, none of the phase 3 trials of adjuvant immunotherapy for resectable NSCLC have shown a significant benefit regarding overall survival in the intention-to-treat population. The survival benefit that we found with neoadjuvant-only nivolumab plus chemotherapy in CheckMate 816 highlights the crucial importance of concurrent administration of chemotherapy and immunotherapy before surgery while the tumor is in situ.

Additional prospective investigation is needed to evaluate new treatment regimens that may further improve the frequency of pathological complete response and ultimately long-term survival. An unmet need also exists for more effective treatment options for patients who do not have a pathological complete response. In an analysis of cancer-related mortality in CheckMate 816, patients who did not have a pathological complete response had a higher risk of death than those who had such a response. Initial exploratory analyses of patient-level data regarding those who received neoadjuvant nivolumab plus chemotherapy in our trial as compared with patients who received both adjuvant nivolumab after surgery and neoadjuvant nivolumab plus chemotherapy in CheckMate 77T suggest that patients without a pathological complete response may benefit from the addition of adjuvant immunotherapy after neoadjuvant chemoimmunotherapy and surgery.[19]

In this trial, we found that the use of neoadjuvant nivolumab plus chemotherapy resulted in



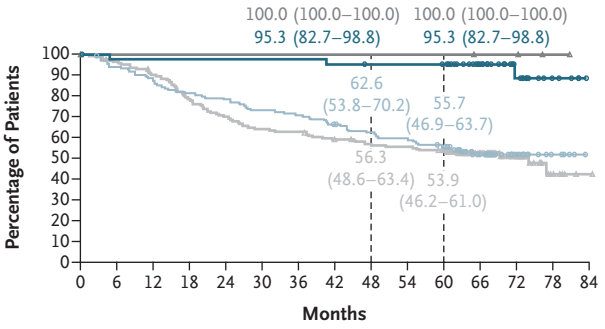
	Median Survival (95% CI)
	mo
Nivolumab+Chemotherapy (N=179)	NR (NR–NR)
Chemotherapy Alone (N=179)	NR (73.7–NR)

Hazard ratio for death from lung cancer, 0.65 (95% CI, 0.44–0.96)

Figure 3. Lung Cancer–Specific Survival.

Listed are events that were determined by the investigator to be specifically related to lung cancer. Open circles and open triangles indicate censored data for patients in the nivolumab-plus-chemotherapy group and the chemotherapy-alone group, respectively. Confidence intervals were not adjusted for multiplicity.

A **Overall Survival in Patients with or without a Pathological Complete Response (pCR)**



Median Overall Survival (95% CI)

mo

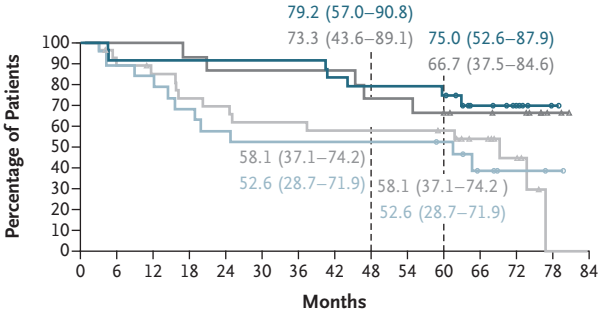
Nivolumab+Chemotherapy
pCR (N=43) NR (NR–NR)
No pCR (N=136) NR (53.9–NR)
Hazard ratio for death, 0.11 (0.04–0.36)

Chemotherapy Alone
pCR (N=4) NR (NR–NR)
No pCR (N=175) 73.7 (46.7–NR)

No. at Risk

Pathological complete response														
Nivolumab+chemotherapy	43	42	42	42	42	42	42	41	40	40	39	25	13	4	0
Chemotherapy alone	4	4	4	4	4	4	4	4	4	4	4	3	3	1	0
No pathological complete response															
Nivolumab+chemotherapy	136	126	117	109	105	98	95	88	82	77	72	42	16	5	0
Chemotherapy alone	175	166	155	135	120	110	108	100	94	93	87	55	26	5	1

B **Overall Survival in Patients with or without Circulating Tumor DNA (ctDNA) Clearance**



Median Overall Survival (95% CI)

mo

Nivolumab+Chemotherapy
ctDNA clearance (N=24) NR (62.9–NR)
No ctDNA clearance (N=19) 61.5 (14.5–NR)
Hazard ratio for death, 0.38 (0.15–1.00)

Chemotherapy Alone
ctDNA clearance (N=15) NR (45.3–NR)
No ctDNA clearance (N=28) 69.2 (20.2–NR)
Hazard ratio for death, 0.39 (0.14–1.11)

No. at Risk

ctDNA clearance														
Nivolumab+chemotherapy	24	22	22	22	22	22	22	20	19	19	18	11	6	1	0
Chemotherapy alone	15	15	15	14	13	13	13	13	11	11	9	8	7	2	0
No ctDNA clearance															
Nivolumab+chemotherapy	19	17	16	13	11	10	10	10	10	10	9	4	2	1	0
Chemotherapy alone	28	24	22	19	18	16	16	15	15	15	14	9	5	0	0

C **Association Between Circluating Tumor DNA Clearance and Pathological Complete Response**

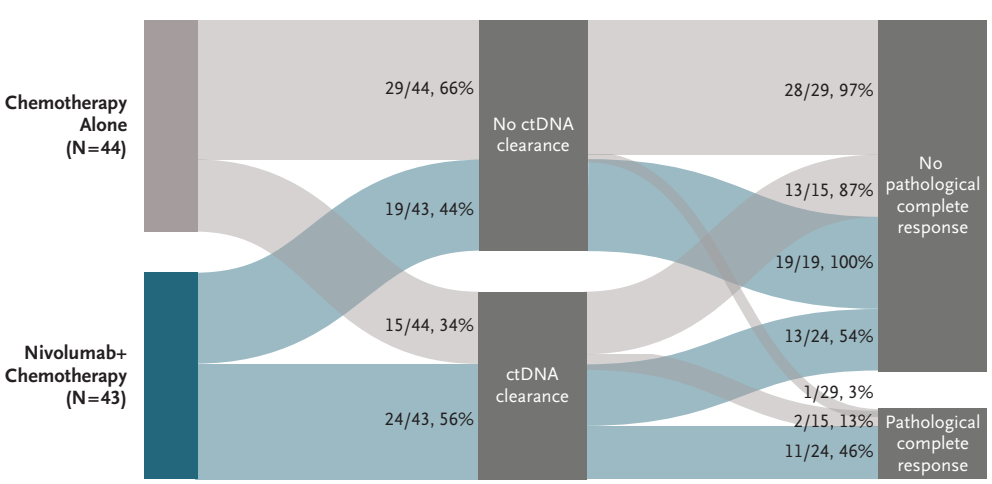


Figure 4 (facing page). Overall Survival According to Pathological Complete Response and Clearance of Circulating Tumor DNA.

Panel A shows overall survival among the patients according to the presence or absence of pathological complete response. Panel B shows overall survival among the patients according to the presence or absence of clearance of circulating tumor DNA (ctDNA) after neoadjuvant treatment. Open circles and open triangles indicate censored data for patients in the nivolumab-plus-chemotherapy group and the chemotherapy-alone group, respectively. Panel C shows the association between ctDNA clearance from cycle 1 to cycle 3 and pathological complete response in patients with detectable ctDNA. Data for patients in China are not included in the analysis of ctDNA because of local regulations. Confidence intervals were not adjusted for multiplicity.

significantly longer overall survival than chemotherapy alone, along with long-term benefit regarding event-free survival. These findings support the hypothesis that neoadjuvant chemoimmunotherapy can have a profound effect on the course of a patient's life when paired with the curative potential of surgical resection.

Supported by Bristol Myers Squibb.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

We thank the patients and their families who made this trial possible; Padma Sathyanarayana, Ph.D., for clinical sciences support; Dako, an Agilent Technologies company, for collaborative development of the PD-L1 IHC 28-8 pharmDx assay; and Zenab Amin, Ph.D., Samantha L. Dwyer, Ph.D., Gráinne Faherty, M.Pharm., and Michele Salernitano, B.A., of Ashfield MedComms, an Inizio company, for their medical-writing and editorial assistance with an earlier version of the manuscript.

AUTHOR INFORMATION

[1] Trinity St. James's Cancer Institute, Trinity College Dublin, Dublin; [2] McGill University Health Centre, Montreal; [3] Hospital Universitario Puerta de Hierro, Madrid; [4] Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; [5] Memorial Sloan Kettering Cancer Center, New York; [6] Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [7] Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [8] Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Universitat Autònoma Barcelona, Barcelona; [9] Brigham and Women's Hospital, Boston; [10] Bloomberg–Kimmel Institute for Cancer Immunotherapy, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medicine, Baltimore; [11] Aberdeen Royal Infirmary, Aberdeen, United Kingdom; [12] Bloomberg–Kimmel Institute for Cancer Immunotherapy, Johns Hopkins University School of Medicine, Baltimore; [13] Institutul Oncologic Prof. Dr. Ion Chiricuţă and University of Medicine and Pharmacy Iuliu Haţieganu, Cluj-Napoca, Romania; [14] University of Occupational and Environmental Health, Kitakyushu, Japan; [15] Charleston Oncology, Charleston, SC; [16] State Key Laboratory of Molecular Oncology, Peking University Cancer Hospital and Institute, Beijing; [17] Kanagawa Cancer Center, Yokohama, Japan; [18] Centre Hospitalier de l'Université de Montréal, Montreal; [19] Instituto Alexander Fleming, Buenos Aires; [20] Bristol Myers Squibb, Princeton, NJ; [21] Institut du Thorax Curie-Montsouris, Institut Curie, Paris.

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