

Neoadjuvant Nivolumab Plus Ipilimumab Versus Chemotherapy in Resectable Lung Cancer

Mark M. Awad, MD, PhD¹ ; Patrick M. Forde, PhD, MBBCh² ; Nicolas Girard, MD, PhD³ ; Jonathan Spicer, MD, PhD⁴ ; Changli Wang, MD⁵ ; Shun Lu, MD, PhD⁶ ; Tetsuya Mitsudomi, MD⁷ ; Enriqueta Felip, MD, PhD⁸ ; Stephen R. Broderick, MD²; Scott J. Swanson, MD⁹; Julie Brahmer, MD² ; Keith Kerr, MBChB¹⁰; Gene B. Saylor, MD¹¹ ; Ke-Neng Chen, MD, PhD¹² ; Vishwanath Gharpure, MD¹³; Jaclyn Neely, PhD¹³ ; David Balli, PhD¹³; Nan Hu, PhD¹³; and Mariano Provencio Pulla, MD, PhD¹⁴

DOI <https://doi.org/10.1200/JCO-24-02239>

ABSTRACT

PURPOSE Neoadjuvant immune checkpoint blockade with nivolumab plus ipilimumab improves overall survival (OS) in non–small cell lung cancer (NSCLC); however, randomized data for resectable lung cancer are limited. We report results from the exploratory concurrently randomized nivolumab plus ipilimumab and chemotherapy arms of the international phase III CheckMate 816 trial.

METHODS Adults with stage IB–IIIA (American Joint Committee on Cancer seventh edition) resectable NSCLC received three cycles of nivolumab once every 2 weeks plus one cycle of ipilimumab or three cycles of chemotherapy (on day 1 or days 1 and 8 of each 3-week cycle) followed by surgery. Analyses included event-free survival (EFS), OS, pathologic response, surgical outcomes, biomarker analyses, and safety.

RESULTS A total of 221 patients were concurrently randomly assigned to nivolumab plus ipilimumab ($n = 113$) or chemotherapy ($n = 108$). At a median follow-up of 49.2 months, the median EFS was 54.8 months (95% CI, 24.4 to not reached [NR]) with nivolumab plus ipilimumab versus 20.9 months (95% CI, 14.2 to NR) with chemotherapy (HR, 0.77 [95% CI, 0.51 to 1.15]); 3-year EFS rates were 56% versus 44%. Higher rates of EFS events were initially seen, with later benefit favoring nivolumab plus ipilimumab; 3-year OS rates were 73% versus 61% (HR, 0.73 [95% CI, 0.47 to 1.14]); pathologic complete response rates were 20.4% versus 4.6%, respectively. In the respective arms, 83 (74%) and 82 patients (76%) underwent definitive surgery. Grade 3–4 treatment-related adverse events occurred in 14% and 36% of patients, respectively.

CONCLUSION Neoadjuvant nivolumab plus ipilimumab showed potential long-term clinical benefit versus chemotherapy, despite early crossing of EFS curves in the preoperative phase and a lower rate of high-grade toxicity.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Data Supplement
- Protocol

Accepted October 31, 2024

Published January 8, 2025

J Clin Oncol 43:1453-1462

© 2025 by American Society of Clinical Oncology



[View Online Article](#)

Creative Commons Attribution
Non-Commercial No Derivatives
4.0 License

INTRODUCTION

PD-(L)1 immune checkpoint inhibitor–based regimens have recently expanded neoadjuvant and adjuvant treatment options for resectable non–small cell lung cancer (NSCLC). Nivolumab, a PD-1 antibody, combined with chemotherapy is now a standard neoadjuvant treatment for eligible patients with resectable NSCLC. The international, phase III CheckMate 816 trial demonstrated statistically significant improvement with neoadjuvant nivolumab plus chemotherapy versus neoadjuvant chemotherapy in event-free survival (EFS; hazard ratio [HR], 0.63 [97.38% CI, 0.43 to 0.91]; $P = .005$) and pathologic complete response (pCR; 24.0% v 2.2%; odds ratio [OR], 13.94 [99% CI, 3.49 to 55.75];

$P < .001$).¹ Four-year follow-up results from this trial showed durable and clinically relevant improvement in overall survival (OS; HR, 0.71 [98.36% CI, 0.47 to 1.07]) with neoadjuvant nivolumab plus chemotherapy versus chemotherapy.² Nivolumab plus chemotherapy is recommended by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) as a systemic neoadjuvant treatment option for patients with resectable NSCLC.³

Despite the recent advances with PD-(L)1–based regimens for resectable NSCLC, continued research is warranted for additional treatment options that can further reduce the risk of disease recurrence and improve clinical

CONTEXT

Key Objective

Dual immunotherapy has demonstrated long-term survival benefit in patients with metastatic non–small cell lung cancer (NSCLC) and promising clinical activity as neoadjuvant treatment in patients with resectable disease. This exploratory analysis from the phase III CheckMate 816 trial evaluated the efficacy and safety of neoadjuvant nivolumab plus ipilimumab versus chemotherapy in patients with stage IB–IIIA resectable NSCLC.

Knowledge Generated

Neoadjuvant nivolumab plus ipilimumab showed trends toward improved survival and higher pathologic complete response rates versus chemotherapy. The safety profile of neoadjuvant nivolumab plus ipilimumab was consistent with previous reports in NSCLC, with low rates of high-grade toxicity.

Relevance (T.E. Stinchcombe)

Despite the activity observed with nivolumab and ipilimumab in this exploratory analysis the higher rate of early event-free survival events preclude its use in routine clinical care. Additional studies are needed to refine the patient population.*

*Relevance section written by JCO Associate Editor Thomas E. Stinchcombe, MD.

outcomes.^{4,5} Nivolumab plus ipilimumab (ipilimumab is a CTLA-4 inhibitor with a distinct but complementary mechanism of action from nivolumab)^{6,7} has shown long-term, durable survival benefit in several phase III trials of advanced cancers, including NSCLC.^{8–11} Furthermore, in the phase II NEOSTAR trial, neoadjuvant nivolumab plus ipilimumab with or without concurrent chemotherapy showed promising results in patients with resectable NSCLC.^{12–14} Here, we report exploratory efficacy, surgical outcomes, and biomarker analyses including circulating tumor DNA (ctDNA) levels and four-gene inflammatory score, as well as the nivolumab plus ipilimumab versus chemotherapy safety data from the international phase III CheckMate 816 trial in patients with resectable NSCLC.

METHODS

Patients

The eligibility criteria for patients in the nivolumab plus ipilimumab and chemotherapy arm of CheckMate 816 are the same as those previously reported for nivolumab plus chemotherapy versus chemotherapy¹ and are summarized in the Data Supplement (online only).

Trial Design and Treatments

CheckMate 816 (ClinicalTrials.gov identifier: [NCT02998528](https://clinicaltrials.gov/ct2/show/study/NCT02998528)) is a randomized, open-label, international phase III trial (Data Supplement, Fig S1). Eligible patients were concurrently randomly assigned 1:1 to receive nivolumab (3 mg/kg once every 2 weeks; three cycles) plus ipilimumab (1 mg/kg; one dose at cycle 1 only) or platinum–doublet chemotherapy (every 3 weeks [on day 1 or on days 1 and 8 of each 3-week cycle]; three cycles) as neoadjuvant treatment. Surgery was scheduled

to occur within 6 weeks after the last neoadjuvant treatment; patients could then receive optional adjuvant therapy (up to four cycles of chemotherapy, radiotherapy, or both) per investigator discretion. CheckMate 816 was conducted according to the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. The study protocol and all amendments were approved by an independent ethics committee or institutional review board at each study site. An independent data monitoring committee reviewed/monitored efficacy and safety. All patients provided written informed consent before initiating study procedures.

End Points and Assessments

EFS, EFS on the next line of therapy (EFS2), pCR, major pathologic response (MPR), OS, and time to death or distant metastasis (TTDM) were assessed in all concurrently randomly assigned patients. Biomarker analyses included evaluation of ctDNA levels on day 1 before each of the three treatment cycles and pCR, MPR, and EFS by baseline four-gene inflammatory score (comprising *CD8A*, *STAT1*, *LAG3*, and *CD274* genes¹⁵) in patients with available samples. Safety outcomes were assessed in all treated patients. Additional details are provided in the Data Supplement.

Statistical Analyses

All analyses reported were exploratory, and descriptive statistics were used to report baseline characteristics and associations. Efficacy and surgical outcomes were evaluated in concurrently randomly assigned patients; safety outcomes were evaluated in patients who received ≥one dose of neoadjuvant treatment. Kaplan–Meier methodology was used to estimate EFS, EFS2, OS, and TTDM; HRs and associated 95% CIs were estimated using stratified or unstratified Cox

proportional hazard models. Additional information is provided in the Data Supplement.

RESULTS

Patients and Treatment Summary

From March 2017 to August 2019, 221 patients were concurrently randomly assigned to receive nivolumab plus ipilimumab (n = 113) or chemotherapy (n = 108); 111 (98%) and 104 (96%) patients received at least one dose of study treatment, respectively (Fig 1). Baseline characteristics were generally similar between treatment arms and are presented in Table 1. Patient demographic characteristics were generally representative of the broader population with lung cancer (Data Supplement, Table S1). All patients had completed

treatment at the time of the database lock; 91% and 86% of patients completed their prespecified neoadjuvant treatment in the nivolumab plus ipilimumab and chemotherapy arms, respectively (Fig 1). Adjuvant therapy was received by 34% of patients in the nivolumab plus ipilimumab arm and 32% of patients in the chemotherapy arm. Subsequent anticancer therapy of any kind was received by 32% and 49% of patients, respectively, and subsequent systemic therapy was received by 30% and 41% of patients (Data Supplement, Table S2).

Surgery Summary

Among concurrently randomly assigned patients, 83 (73%) and 82 (76%) patients in the nivolumab plus ipilimumab and chemotherapy arms, respectively, underwent definitive surgery (Data Supplement, Table S3). Surgery was canceled for 29

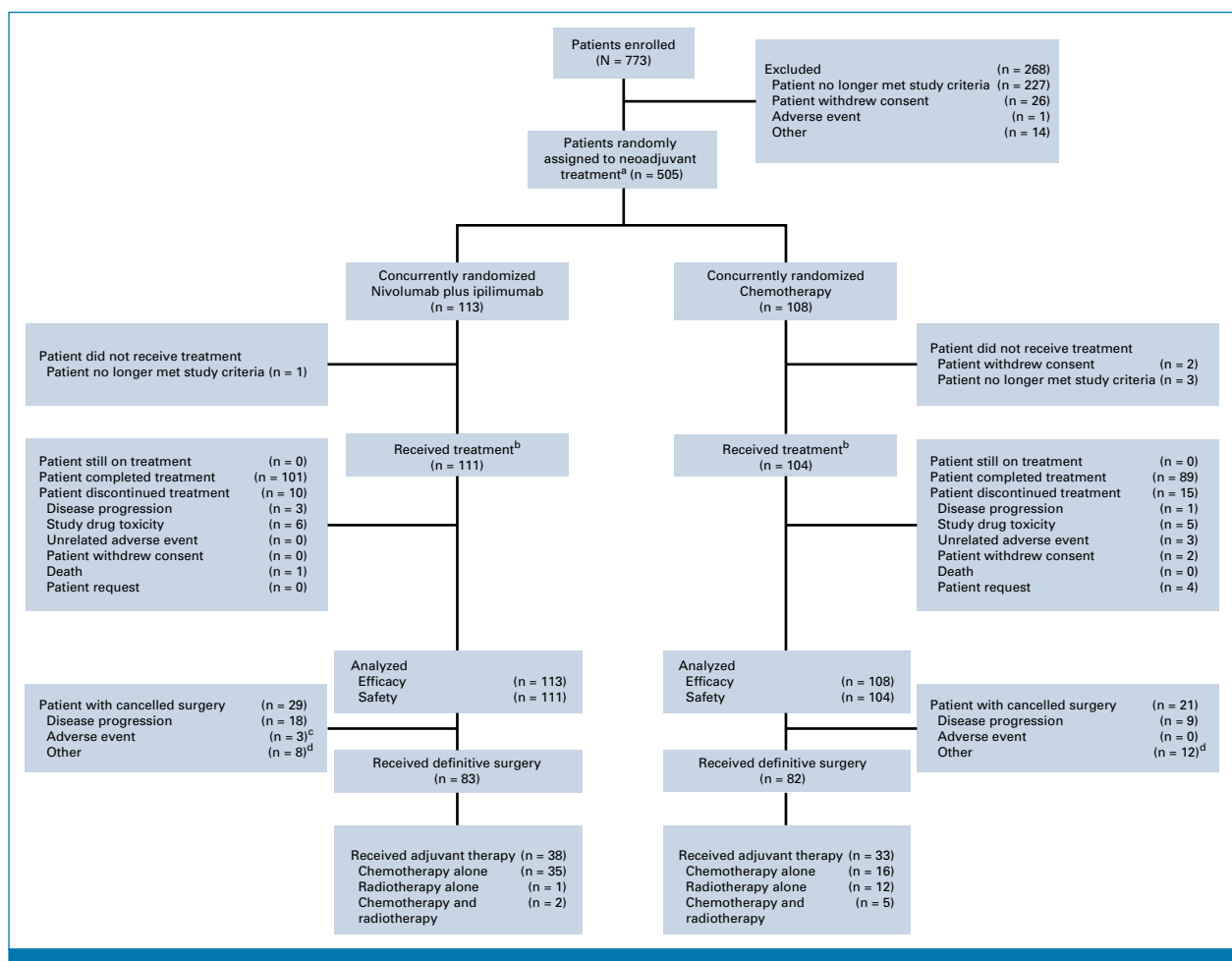


FIG 1. CONSORT diagram of patient disposition. ^aIncludes patients randomly assigned to receive nivolumab plus chemotherapy (n = 179) and chemotherapy (n = 105; these patients were not concurrently randomly assigned to the nivolumab plus ipilimumab arm and are not included in this analysis) in the revised protocol. ^bOne patient randomly assigned to the nivolumab plus ipilimumab arm incorrectly received chemotherapy (this patient is counted in the nivolumab plus ipilimumab arm for baseline and efficacy analyses and in the chemotherapy arm for exposure and safety analyses). ^cIncludes grade 2 pneumonitis, grade 3 pulmonary thromboembolism, and grade 3 diarrhea (n = 1 each). ^dIncludes refusal of surgery or withdrawal of consent (n = 4 per arm), unresectable tumor (n = 1 per arm), patient who was randomly assigned but never treated (n = 1 per arm), patient who was unfit for surgery (nivolumab plus ipilimumab, n = 2; chemotherapy, n = 5), and patient who achieved a complete response (chemotherapy, n = 1).

TABLE 1. Characteristics of the Patients at Baseline

Characteristic	Nivolumab Plus Ipilimumab (n = 113)	Chemotherapy (n = 108)
Age		
Years, median (range)	64 (34-83)	65 (34-86)
<65, No. (%)	62 (55)	49 (45)
≥65, No. (%)	51 (45)	59 (55)
Sex, No. (%)		
Male	73 (65)	70 (65)
Female	40 (35)	38 (35)
Race, No. (%)		
White	64 (57)	65 (60)
Black or African American	4 (4)	3 (3)
Asian	41 (36)	36 (33)
Other	4 (4)	4 (4)
Geographic region, No. (%)		
North America	46 (41)	47 (44)
Europe	15 (13)	16 (15)
Asia	41 (36)	34 (32)
Rest of the world ^a	11 (10)	11 (10)
ECOG PS, No. (%) ^b		
0	73 (65)	68 (63)
1	39 (34)	40 (37)
Disease stage, No. (%) ^c		
IB-II	42 (37)	40 (37)
IIIA	71 (63)	66 (61)
Tumor histology, No. (%)		
Squamous	55 (49)	52 (48)
Nonsquamous	58 (51)	56 (52)
Smoking status, No. (%) ^d		
Current/former	99 (88)	97 (90)
Never	14 (12)	10 (9)
Tumor PD-L1 expression, No. (%) ^e		
Not evaluable	4 (4)	7 (6)
<1%	49 (43)	43 (40)
≥1%	60 (53)	58 (54)
1%-49%	37 (33)	40 (37)
≥50%	23 (20)	18 (17)
Tumor mutational burden, No. (%) ^f		
Not evaluable/not reported	53 (47)	54 (50)
<12.3 mut/Mb	35 (31)	33 (31)
≥12.3 mut/Mb	25 (22)	21 (19)

NOTE. Percentages may not total 100 because of rounding.

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; mut/Mb, mutations per megabase.

^aIncludes Argentina, Brazil, and Turkey.

^bOne (1%) patient in the nivolumab plus ipilimumab arm had ECOG PS >1.

^cDisease stage (per AJCC TNM seventh edition) as reported in case report forms: stage IA and stage IIIB disease: one patient each in the chemotherapy arm. Stage IB, IIA, and IIB disease: nivolumab plus ipilimumab, 5%, 16%, and 16% and chemotherapy, 5%, 23%, and 9%, respectively.

^dUnknown in one patient in the chemotherapy arm.

^eDetermined using the PD-L1 IHC 28-8 pharmDx assay (Dako); patients with tumor tissue that could not be assessed for PD-L1 (<10% of concurrently randomly assigned patients) were stratified to the PD-L1 <1% subgroup at random assignment.

^fEvaluated using the Illumina TSO500 assay; the 12.3-mut/Mb cutoff corresponds with 10 mut/Mb per the FoundationOne assay.¹⁶ Tumor mutational burden was not analyzed in patients in China, who were therefore included in the not evaluable/not reported subgroup.

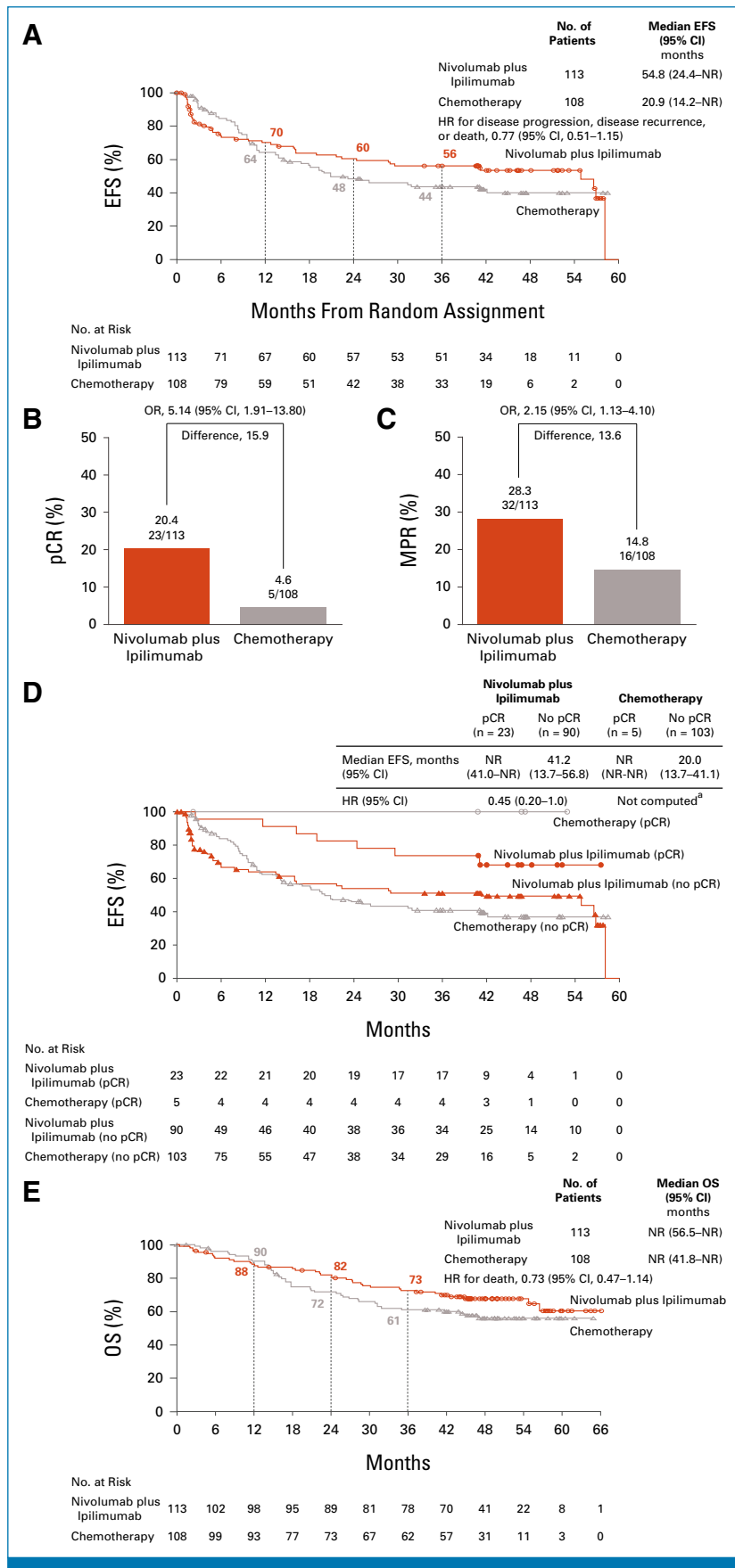


FIG 2. (A) EFS, (B) pCR, (C) MPR, and (D) EFS in patients with or without a pCR and (E) OS with nivolumab plus ipilimumab versus chemotherapy. (continued on following page)

FIG 2. (Continued). EFS per BICR was determined among concurrently randomly assigned patients; patients who received subsequent therapy were censored at the last evaluable tumor assessment on or before the date of subsequent therapy. pCR (0% RVT) and MPR ($\leq 10\%$ RVT) postsurgery in both primary tumor (lung) and sampled lymph nodes per BIPR; patients who did not undergo surgery were classified as nonresponders. The OR was calculated using the stratified Cochran-Mantel-Haenszel method. *Not computed because of the low number of patients with a pCR ($n = 5$). BICR, blinded independent central review; BIPR, blinded independent pathologic review; EFS, event-free survival; HR, hazard ratio; MPR, major pathologic response; NR, not reached; OR, odds ratio; OS, overall survival; pCR, pathologic complete response; RVT, residual viable tumor.

(26%) and 21 (19%) patients and delayed in five (6%) and nine (11%) patients in the respective arms. Reasons for surgery cancellation included disease progression (16% v 8%), adverse events (3% v 0%), and other reasons (7% v 11%). Median (range) duration of surgery was similar between treatment arms (nivolumab plus ipilimumab, 212.0 [152.0–273.0]

minutes; chemotherapy, 217.0 [151.0–307.0] minutes). In the nivolumab plus ipilimumab arm, a minimally invasive approach was more common than in the chemotherapy arm (27% v 21%) and pneumonectomies were less common (11% v 21%). Among patients who underwent surgery, R0 resection (no residual tumor) was achieved in 80% and 71% of patients

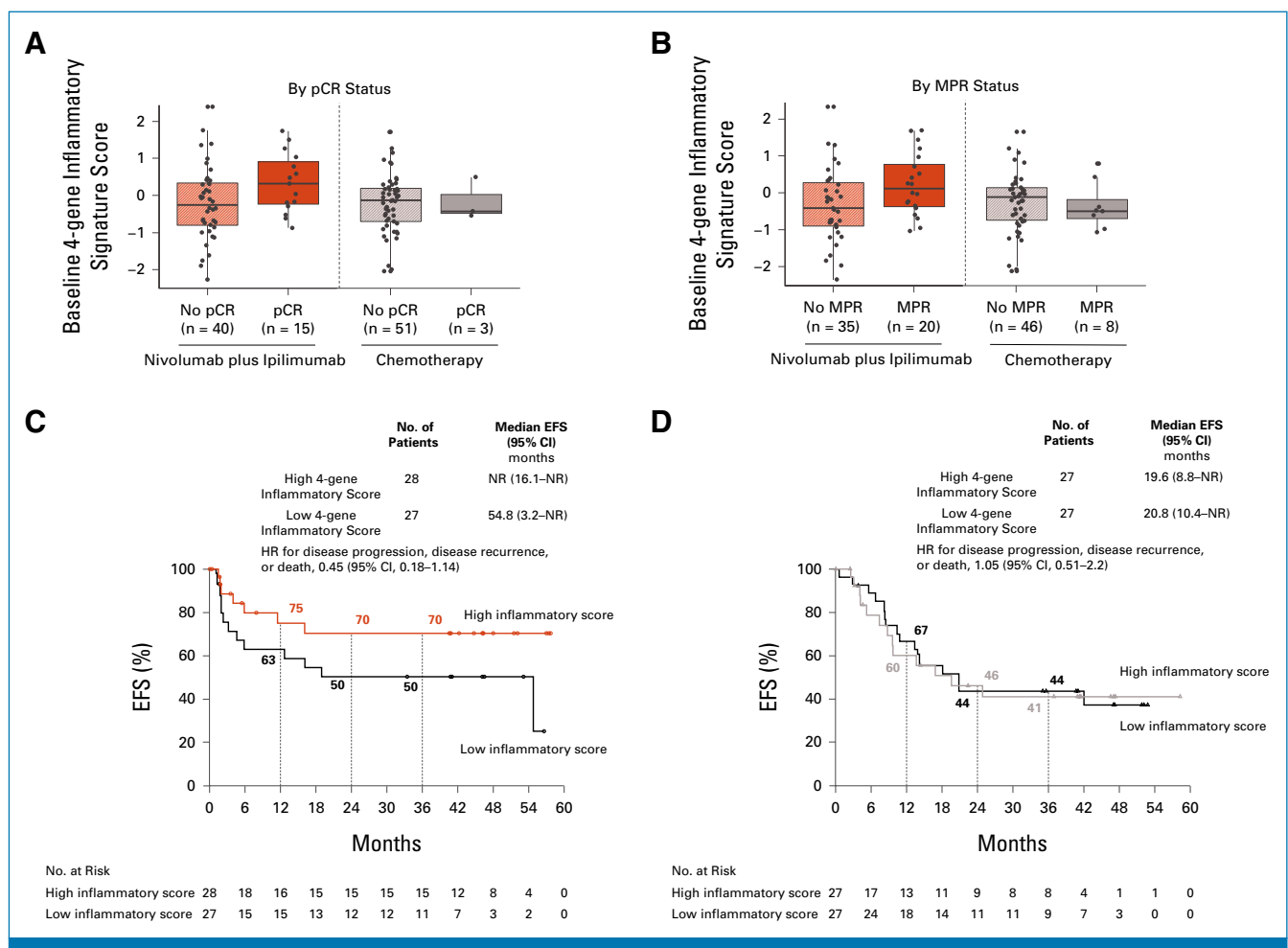


FIG 3. Baseline four-gene inflammatory signature score by (A) pCR, (B) MPR, and (C) EFS in the nivolumab plus ipilimumab arm and (D) EFS in the chemotherapy arm. The four-gene inflammatory signature comprised *CD8A*, *STAT1*, *LAG3*, and *CD274* (encoding PD-L1)¹⁵ and was assessed by RNA sequencing of evaluable tumor samples at baseline; scores were grouped as high or low relative to the median z-score across the data set. pCR (0% RVT) and MPR ($\leq 10\%$ RVT) postsurgery in both primary tumor (lung) and sampled lymph nodes per BIPR. EFS was per BICR. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or before the date of subsequent therapy. BICR, blinded independent central review; BIPR, blinded independent pathologic review; EFS, event-free survival; HR, hazard ratio; MPR, major pathologic response; NR, not reached; pCR, pathologic complete response; RVT, residual viable tumor.

TABLE 2. Summary of Adverse Events

Event	Nivolumab Plus Ipilimumab (n = 111), No. (%)		Chemotherapy (n = 104), No. (%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Adverse event of any cause ^a				
All	97 (87)	22 (20)	103 (99)	47 (45)
Leading to treatment discontinuation	6 (5)	5 (4)	10 (10)	5 (5)
Serious	15 (14)	11 (10)	21 (20)	17 (16)
Treatment-related adverse event ^a				
All	72 (65)	15 (14)	96 (92)	38 (36)
Leading to treatment discontinuation	6 (5)	5 (4)	7 (7)	4 (4)
Serious	10 (9)	6 (5)	15 (14)	13 (12)
Death ^b	0		1	
Surgery-related adverse events ^c	45 (55)	12 (15)	37 (45)	12 (14)

NOTE. Adverse events were assessed in all treated patients and were categorized according to the Medical Dictionary for Regulatory Activities, version 25.0 and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

^aIncludes events reported between the first neoadjuvant dose and 30 days after the last dose of neoadjuvant study treatment.

^bTreatment-related deaths could occur at any time after the first dose of neoadjuvant study treatment. The treatment-related death in the chemotherapy arm occurred at 3.5 months.

^cIncludes events reported within 90 days after definitive surgery. Denominators on the basis of patients who had definitive surgery (n = 82 in the nivolumab plus ipilimumab arm; n = 83 in the chemotherapy arm).

in the nivolumab plus ipilimumab and chemotherapy arms, respectively (Data Supplement, Table S3).

Efficacy

At the database lock (October 14, 2022), the median follow-up time was 49.2 months (range, 37.1–65.2). The median EFS (95% CI) was 54.8 months (24.4 to not reached [NR]) with nivolumab plus ipilimumab versus 20.9 months (14.2 to NR) with chemotherapy (HR for disease progression, disease recurrence, or death, 0.77 [95% CI, 0.51 to 1.15]); 3-year EFS rates were 56% and 44% (Fig 2A). The EFS curves for nivolumab plus ipilimumab and chemotherapy crossed at 9 months, indicating that a higher proportion of patients in the nivolumab plus ipilimumab versus the chemotherapy arm had an EFS event during this time from random assignment (any disease progression or death because of any cause; Fig 2A). Baseline characteristics of these patients with an early progression event are provided in the Data Supplement (Table S4 and Fig S2). EFS favored nivolumab plus ipilimumab in most key subgroups (Data Supplement, Fig S3). Exceptions included the PD-L1 <1% subgroup, which may be confounded by small sample sizes and imbalances in baseline characteristics: for instance, higher rates of female patients, European patients, and those with disease stage IB/II were seen in the PD-L1 <1% subgroup (Data Supplement, Table S5). There was a higher proportion of canceled surgeries in the PD-L1 <1% subgroup in the nivolumab plus ipilimumab arm, the majority of which were due to disease progression.

The percentage of patients with a pCR was 20.4% (95% CI, 13.4 to 29.0) in the nivolumab plus ipilimumab arm versus 4.6% (95% CI, 1.5 to 10.5) in the chemotherapy arm (OR, 5.14 [95%

CI, 1.91 to 13.80]; Fig 2B); the benefit was observed across all key subgroups, including those on the basis of disease stage, tumor PD-L1 expression, and histology (Data Supplement, Fig S4). The percentage of patients with an MPR was 28.3% versus 14.8%, respectively (Fig 2C). The depth of pathologic response was greater with nivolumab plus ipilimumab than with chemotherapy (Data Supplement, Fig S5); median residual viable tumor was 10% (IQR, 0–65) versus 60% (IQR, 0–100), respectively. EFS improvement was seen in patients who had a pCR versus those who did not (Fig 2D); in the nivolumab plus ipilimumab arm, the EFS HR was 0.45 (95% CI, 0.20 to 1.0).

Recurrence rates after definitive surgery in the nivolumab plus ipilimumab and chemotherapy arms were 23% and 44%, respectively (Data Supplement, Table S6), with locoregional recurrence occurring in 16% versus 24% of patients and distant recurrence occurring in 8% versus 23% (CNS recurrence in 2% v 13%).

OS data are immature, and median OS was NR in either treatment arm. However, OS appeared to favor nivolumab plus ipilimumab versus chemotherapy (HR, 0.73 [95% CI, 0.47 to 1.14]); 3-year OS rates were 73% versus 61% (Fig 2E). OS benefit was observed with nivolumab plus ipilimumab in most key subgroups (Data Supplement, Fig S6). In addition, TTDM (HR, 0.61 [95% CI, 0.40 to 0.94]; Data Supplement, Fig S7) and EFS2 (HR, 0.70 [95% CI, 0.45 to 1.08]; Data Supplement, Fig S8) favored nivolumab plus ipilimumab over chemotherapy.

Biomarker Analyses

ctDNA levels were evaluable in 66 patients (nivolumab plus ipilimumab, n = 36; chemotherapy, n = 30). Although

sample sizes were small, a trend toward a decrease in ctDNA levels was observed in both arms before surgery, from treatment cycle 1 to cycle 3; this decrease was more rapid and more pronounced in the chemotherapy arm (Data Supplement, Fig S9A). Of patients who were evaluable for ctDNA clearance, 4 of 36 patients (11%) in the nivolumab plus ipilimumab arm and 10 of 30 patients (33%) in the chemotherapy arm showed ctDNA clearance (Data Supplement, Fig S9B).

A total of 55 patients in the nivolumab plus ipilimumab arm and 54 patients in the chemotherapy arm had RNA-evaluable samples at baseline to assess the four-gene inflammatory signature score. In the nivolumab plus ipilimumab arm, patients with a pCR or an MPR had higher baseline four-gene inflammatory scores than those without (Figs 3A and 3B); no conclusions could be drawn for the chemotherapy arm because of the low number of patients who had a pCR or an MPR. EFS was also evaluated according to the four-gene inflammatory score at baseline. In the nivolumab plus ipilimumab arm, patients appeared to have a better EFS when they had a baseline inflammatory score that was higher than the median value versus lower (HR, 0.45 [95% CI, 0.18 to 1.14]; Fig 3C); this trend was not observed in the chemotherapy arm (HR, 1.05 [95% CI, 0.51 to 2.2]; Fig 3D).

Safety

Adverse events of any cause occurred in 87% of patients in the nivolumab plus ipilimumab group and 99% of patients in the chemotherapy group (Table 2). Grade 3–4 treatment-related adverse events were reported in 14% and 36% of patients, respectively; treatment-related adverse events of any grade leading to treatment discontinuation occurred in 5% and 7% of patients. Grade 3–4 surgery-related adverse events were similar between treatment arms at 15% versus 14%, respectively. The most common immune-mediated adverse events of any grade in the nivolumab plus ipilimumab arm were hypothyroidism/thyroiditis (9%) and rash (8%), and the most common immune-mediated adverse event of grade 3–4 was diarrhea/colitis (3%; Data Supplement, Table S7). No treatment-related death was reported in the nivolumab plus ipilimumab arm, and there was one treatment-related death in the chemotherapy arm (Table 2).

DISCUSSION

In these exploratory analyses of neoadjuvant nivolumab plus ipilimumab versus chemotherapy in CheckMate 816, numerically improved EFS, OS, pCR, and MPR rates and a greater depth of pathologic response were observed with nivolumab plus ipilimumab versus chemotherapy. Neoadjuvant nivolumab plus ipilimumab had a safety profile that was similar to previous reports in NSCLC.^{13,17}

The efficacy and safety data for nivolumab plus ipilimumab should be weighed against the surgical outcomes observed in this trial. Rates of disease progression precluding surgery

were numerically higher in the nivolumab plus ipilimumab arm versus the chemotherapy arm and also higher compared with previous reports of anti-PD-(L)1 agents plus chemotherapy although cross-trial comparisons should be performed with caution.^{1,18,19} Of note, 18 of 29 (62%) patients with canceled surgery in the nivolumab plus ipilimumab arm had disease progression compared with 9 of 21 (43%) in the chemotherapy arm; however, surgery cancellations in the chemotherapy arm were mostly due to reasons other than disease progression. There was a higher R0 resection rate in the nivolumab plus ipilimumab arm (80%) versus the chemotherapy arm (71%) among patients who did undergo surgery, and recurrence rates after surgery were also lower (23% v 44%), including distant recurrence in the CNS (2% v 13%). Therefore, a key consideration for nivolumab plus ipilimumab would be to minimize the risk of disease progression that can potentially preclude surgery for patients with initially resectable disease as surgical resection is necessary to achieve optimal outcomes.

In this trial, the possibility of tumor pseudoprogression from study treatment cannot be ruled out. Early detriment was seen with nivolumab plus ipilimumab for both EFS and OS during the first 9 months, similar to reports of OS with dual immunotherapy versus chemotherapy in metastatic NSCLC⁸ and other advanced solid tumors.^{20,21} However, no early detriment was observed in several studies that evaluated immunotherapy combined with chemotherapy in early-stage¹ or metastatic NSCLC,^{9,22,23} suggesting that immunotherapy plus chemotherapy may help avoid early tumor progression affecting resectability and, moreover, provide long-term survival benefit.

Despite the possibility of early progression, pCR and MPR rates were improved with nivolumab plus ipilimumab, which is consistent with findings from the NEOSTAR trial, where nivolumab plus ipilimumab also demonstrated comparable pCR and MPR rates.¹³ Similarly, the trend toward improved EFS and OS with neoadjuvant nivolumab plus ipilimumab versus chemotherapy in patients with resectable NSCLC was consistent with the long-term clinical benefit seen with nivolumab plus ipilimumab in the treatment of metastatic NSCLC.⁸ However, neoadjuvant nivolumab plus ipilimumab did not prolong EFS for patients with tumor PD-L1 expression <1%, which is in contrast to the results seen with nivolumab plus ipilimumab with or without chemotherapy in patients with metastatic NSCLC, where a greater magnitude of benefit was seen in patients with tumor PD-L1 expression <1% versus ≥1%.^{8,9} It is worth noting that patients in the CheckMate 816 trial received only one dose of ipilimumab per protocol compared with up to 19 doses in studies of metastatic NSCLC.^{8,9}

An association of pCR with prolonged EFS was observed with nivolumab plus ipilimumab, consistent with findings reported previously for other immunotherapy-based regimens for patients with resectable NSCLC,^{1,18,24,25} supporting pathologic response as an emerging surrogate for survival benefit in patients receiving neoadjuvant therapy.

Pre- and post-treatment ctDNA levels have been investigated for the association with long-term outcomes in patients with resectable NSCLC.^{26,27} In CheckMate 816, only 32% of patients in the nivolumab plus ipilimumab arm and 28% in the chemotherapy arm had evaluable ctDNA levels. In both arms, ctDNA levels were reduced after neoadjuvant treatment although the ctDNA clearance rate was surprisingly lower with nivolumab plus ipilimumab versus chemotherapy. By contrast, treatment regimens consisting of anti-PD-(L)1 agents combined with chemotherapy have shown greater ctDNA clearance versus chemotherapy alone across neoadjuvant and perioperative studies.^{1,28} These findings suggest that chemotherapy may be needed to induce ctDNA clearance in most patients with resectable NSCLC, with anti-PD-(L)1 agents enhancing ctDNA clearance once induced. However, in CheckMate 816, ctDNA levels were only evaluated during the neoadjuvant phase. Long-term clinical research is warranted to fully understand the role of ctDNA levels as a predictor of benefit from neoadjuvant immunotherapy.

Biomarkers that can identify patients who will benefit from neoadjuvant immunotherapy are of high clinical interest. In patients treated with nivolumab plus ipilimumab from CheckMate 816, a high baseline four-gene inflammatory score (indicative of an inflamed phenotype in the tumor microenvironment) was associated with higher rates of pCR and MPR and improved EFS compared with patients with a low baseline signature; these results are consistent with clinical studies in advanced cancers where a higher baseline four-gene inflammatory signature score appeared

to be associated with improved response/survival outcomes compared with a lower baseline score.^{21,29,30} By contrast, in patients receiving chemotherapy, there was no association between baseline four-gene inflammatory scores and EFS; the number of patients with a pCR or an MPR was too low to allow for interpretation.

The exploratory analyses reported here are from the nivolumab plus ipilimumab arm of CheckMate 816, which was not powered for comparison with either the nivolumab plus chemotherapy arm or the chemotherapy arm. Some of the analyses included small sample sizes, and the results should be interpreted with caution. Despite these limitations, to our knowledge, this is the first randomized phase III study evaluating neoadjuvant nivolumab plus ipilimumab versus chemotherapy in a large cohort of patients. This report highlights the complexities of neoadjuvant immune checkpoint blockade with not only higher rates of early tumor progression occurring with neoadjuvant nivolumab plus ipilimumab but also high pCR rates, low-grade 3-4 treatment-related adverse events, and evidence of long-term clinical benefit.

Overall, these analyses from CheckMate 816 showed that nivolumab plus ipilimumab can potentially improve long-term survival outcomes and result in increased pCR and MPR rates compared with chemotherapy. Nivolumab plus ipilimumab had a low rate of high-grade toxicity. On the basis of earlier reports from CheckMate 816, nivolumab plus chemotherapy remains the standard neoadjuvant treatment for eligible patients with resectable NSCLC.

AFFILIATIONS

¹Dana-Farber Cancer Institute, Boston, MA

²The Bloomberg-Kimmel Institute for Cancer Immunotherapy, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medicine, Baltimore, MD

³Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France

⁴McGill University Health Centre, Montreal, QC, Canada

⁵Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China

⁶Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

⁷Kindai University Faculty of Medicine, Osaka-Sayama, Japan

⁸Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Universitat Autònoma Barcelona, Barcelona, Spain

⁹Brigham and Women's Hospital, Boston, MA

¹⁰Aberdeen Royal Infirmary, Aberdeen, United Kingdom

¹¹Charleston Oncology, Charleston, SC

¹²Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China

¹³Bristol Myers Squibb, Princeton, NJ

¹⁴Hospital Universitario Puerta de Hierro, Madrid, Spain

CORRESPONDING AUTHOR

Mark M. Awad, MD, PhD; e-mail: awadm3@mskcc.org.

PRIOR PRESENTATION

Presented in part at the European Society for Medical Oncology Congress, Madrid, Spain, October 20-24, 2023.

SUPPORT

Supported by Bristol Myers Squibb and Ono Pharmaceutical Company, Ltd.

CLINICAL TRIAL INFORMATION

NCT02998528

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO-24-02239>.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI <https://doi.org/10.1200/JCO-24-02239>. The Bristol Myers Squibb policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html>.

AUTHOR CONTRIBUTIONS

Conception and design: Nicolas Girard, Jonathan Spicer, Shun Lu, Mariano Provencio Pulla

Administrative support: Shun Lu

Provision of study materials or patients: Nicolas Girard, Shun Lu, Tetsuya Mitsudomi, Enriqueta Felip, Mariano Provencio Pulla

Collection and assembly of data: Nicolas Girard, Jonathan Spicer, Shun Lu, Tetsuya Mitsudomi, Enriqueta Felip, Vishwanath Gharpure, Jaclyn Neely, Mariano Provencio Pulla

Data analysis and interpretation: Nicolas Girard, Jonathan Spicer, Shun Lu, Enriqueta Felip, Vishwanath Gharpure, Jaclyn Neely, Nan Hu, Mariano Provencio Pulla, Mark M. Awad, Patrick M. Forde, Changli Wang, Stephen R. Broderick, Scott J. Swanson, Julie Brahmer, Keith Kerr, Gene B. Saylor, Ke-Neng Chen, David Balli

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank the patients and families who made this trial possible, the investigators and clinical study teams who participated in this trial, and Dako, an Agilent Technologies company, for collaborative development of the PD-L1 IHC 28-8 pharmDx assay. We thank Javed Mahmood, PhD, DDS, for his contributions as a Senior Clinical Scientist. Medical writing and editorial support for the development of this manuscript, under the direction of the authors, was provided by Christine Billecke, PhD, and Michele Salernitano of Ashfield MedComms, an Inizio company, funded by Bristol Myers Squibb. The list of CheckMate 816 investigators can be found in [Appendix 1](#) (online only). The list of CheckMate 816 Central Pathological Reviewers can be found in [Appendix 2](#).

REFERENCES

- Forde PM, Spicer J, Lu S, et al: Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med* 386:1973-1985, 2022
- Spicer J, Girard N, Provencio M, et al: Neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) vs chemo in patients (pts) with resectable NSCLC: 4-year update from CheckMate 816. *J Clin Oncol* 42, 2024 (suppl 17; abstr LBA8010)
- NCCN Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for non-small cell lung cancer. V7.2024. <https://www.nccn.org>
- Taylor MD, Nagji AS, Bhamidipati CM, et al: Tumor recurrence after complete resection for non-small cell lung cancer. *Ann Thorac Surg* 93:1813-1820, 2012
- Uramoto H, Tanaka F: Recurrence after surgery in patients with NSCLC. *Transl Lung Cancer Res* 3:242-249, 2014
- Rotte A: Combination of CTLA-4 and PD-1 blockers for treatment of cancer. *J Exp Clin Cancer Res* 38:255, 2019
- Michielin O, Lalani A-K, Robert C, et al: Defining unique clinical hallmarks for immune checkpoint inhibitor-based therapies. *J Immunother Cancer* 10:e003024, 2022
- Brahmer JR, Lee J-S, Ciuleanu T-E, et al: Five-year survival outcomes with nivolumab plus ipilimumab versus chemotherapy as first-line treatment for metastatic non-small-cell lung cancer in CheckMate 227. *J Clin Oncol* 41:1200-1212, 2023
- Carbone DP, Ciuleanu T-E, Schenker M, et al: Four-year clinical update and treatment switching-adjusted outcomes with first-line nivolumab plus ipilimumab with chemotherapy for metastatic non-small cell lung cancer in the CheckMate 9LA randomized trial. *J Immunother Cancer* 12:e008189, 2024
- Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al: Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. *J Clin Oncol* 40:127-137, 2022
- Motzer RJ, McDermott DF, Escudier B, et al: Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. *Cancer* 128:2085-2097, 2022
- Weissferdt A, Leung CH, Sepesi B, et al: Pathologic patterns following different neoadjuvant therapies in non-small cell lung cancer (NSCLC). *Ann Oncol* 34:S1190-S1201, 2023 (abstr 2334P)
- Cascone T, William WN Jr, Weissferdt A, et al: Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: The phase 2 randomized NEOSTAR trial. *Nat Med* 27:504-514, 2021
- Cascone T, Leung CH, Weissferdt A, et al: Neoadjuvant chemotherapy plus nivolumab with or without ipilimumab in operable non-small cell lung cancer: The phase 2 platform NEOSTAR trial. *Nat Med* 29:593-604, 2023
- Lei M, Siemers NO, Pandya D, et al: Analyses of PD-L1 and Inflammatory Gene Expression Association with efficacy of nivolumab ± ipilimumab in gastric cancer/gastroesophageal junction cancer. *Clin Cancer Res* 27:3926-3935, 2021
- Baden J, Chang H, Greenawalt DM, et al: Comparison of platforms for determining tumor mutational burden (TMB) from blood samples in patients with non-small cell lung cancer (NSCLC). *Ann Oncol* 30:v28, 2019 (suppl 5; abstr 99P)
- Paz-Ares LG, Ciuleanu T-E, Pluzanski A, et al: Safety of first-line nivolumab plus ipilimumab in patients with metastatic NSCLC: A pooled analysis of CheckMate 227, CheckMate 568, and CheckMate 817. *J Thorac Oncol* 18:79-92, 2023
- Wakelee H, Liberman M, Kato T, et al: Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med* 389:491-503, 2023
- Heymach JV, Harpole D, Mitsudomi T, et al: Perioperative durvalumab for resectable non-small-cell lung cancer. *N Engl J Med* 389:1672-1684, 2023
- Rini BI, Signoretti S, Choueiri TK, et al: Long-term outcomes with nivolumab plus ipilimumab versus sunitinib in first-line treatment of patients with advanced sarcomatoid renal cell carcinoma. *J Immunother Cancer* 10:e005445, 2022
- Peters S, Scherpereel A, Cornelissen R, et al: First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743. *Ann Oncol* 33:488-499, 2022
- Garassino MC, Gadgil S, Speranza G, et al: Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. *J Clin Oncol* 41:1992-1998, 2023
- Borghaei H, O'Byrne KJ, Paz-Ares L, et al: Nivolumab plus chemotherapy in first-line metastatic non-small-cell lung cancer: Results of the phase III CheckMate 227 part 2 trial. *ESMO Open* 8:102065, 2023
- Cascone T, Awad MM, Spicer JD, et al: Perioperative nivolumab in resectable lung cancer. *N Engl J Med* 390:1756-1769, 2024
- Lu S, Zhang W, Wu L, et al: Perioperative toripalimab plus chemotherapy for patients with resectable non-small cell lung cancer: The Neotorch randomized clinical trial. *JAMA* 331:201-211, 2024
- Provencio M, Serna-Blasco R, Nadal E, et al: Overall survival and biomarker analysis of neoadjuvant nivolumab plus chemotherapy in operable stage IIIA non-small-cell lung cancer (NADIM phase II trial). *J Clin Oncol* 40:2924-2933, 2022
- Gale D, Heider K, Ruiz-Valdepenas A, et al: Residual ctDNA after treatment predicts early relapse in patients with early-stage non-small cell lung cancer. *Ann Oncol* 33:500-510, 2022
- Reck M, Gale D, Harpole D, et al: Associations of ctDNA clearance and pathological response with neoadjuvant treatment in patients with resectable NSCLC from the phase III AEGEAN trial. *Ann Oncol* 34:S1300, 2023 (abstr LBA59)
- Hodi FS, Wolchok JD, Schadendorf D, et al: TMB and inflammatory gene expression associated with clinical outcomes following immunotherapy in advanced melanoma. *Cancer Immunol Res* 9:1202-1213, 2021
- Sangro B, Melero I, Wadhawan S, et al: Association of inflammatory biomarkers with clinical outcomes in nivolumab-treated patients with advanced hepatocellular carcinoma. *J Hepatol* 73:1460-1469, 2020

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Neoadjuvant Nivolumab Plus Ipilimumab Versus Chemotherapy in Resectable Lung Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Mark M. Awad

Consulting or Advisory Role: Merck, Pfizer, Bristol Myers Squibb, Foundation Medicine, Novartis, Gritstone Bio, Mirati Therapeutics, EMD Serono, AstraZeneca, Instil Bio, Regeneron, Janssen, Affini-T Therapeutics, Coherus Biosciences

Research Funding: Genentech/Roche (Inst), Lilly (Inst), AstraZeneca (Inst), Bristol Myers Squibb (Inst), Amgen (Inst)

Travel, Accommodations, Expenses: Bristol Myers Squibb Foundation

Open Payments Link: <https://openpaymentsdata.cms.gov/physician/1127368>

Patrick M. Forde

Consulting or Advisory Role: AstraZeneca/MedImmune, Bristol Myers Squibb, Janssen, Daiichi Sankyo/UCB Japan, ITeos Therapeutics, Sanofi, Novartis, G1 Therapeutics, F-Star Biotechnology, Merck, Fosun Pharma, Teva, Synthekine, CureVac, Regeneron, Ascendis Pharma, Gilead Sciences, Novocure, Genelux, BioNTech SE, Tavotek BioTherapeutics

Research Funding: Bristol Myers Squibb (Inst), AstraZeneca/MedImmune (Inst), Novartis (Inst), Regeneron, BioNTech SE

Nicolas Girard

Employment: AstraZeneca (I)

Consulting or Advisory Role: Roche, Lilly, AstraZeneca, Novartis, Pfizer, Bristol Myers Squibb, MSD, Takeda, Janssen, Sanofi, Amgen, Gilead Sciences, BeiGene, AbbVie, Daiichi Sankyo/Astra Zeneca, Leo Pharma, Ipsen

Research Funding: Roche (Inst), AstraZeneca (Inst), BMS (Inst), MSDavenir (Inst)

Travel, Accommodations, Expenses: Roche, Janssen Oncology

Jonathan Spicer

Honoraria: Bristol Myers Squibb/Medarex, Merck, AstraZeneca, Amgen, Chemocentryx, Novartis, Pfizer

Consulting or Advisory Role: Bristol Myers Squibb/Medarex, AstraZeneca, Merck, Regeneron, Protalix Biotherapeutics, Xenetic Biosciences

Research Funding: AstraZeneca (Inst), Bristol Myers Squibb/Medarex (Inst), Roche (Inst), CLS-Therapeutics (Inst), Protalix Biotherapeutics (Inst), Merck (Inst)

Travel, Accommodations, Expenses: AstraZeneca, Merck, Bristol Myers Squibb/Medarex

Shun Lu

Leadership: Innovent Biologics, Inc, Simcere Zaiming Pharmaceutical Co, Ltd, Shanghai Fosun Pharmaceutical

Consulting or Advisory Role: AstraZeneca, Pfizer, Boehringer Ingelheim, Hutchison MediPharma, Simcere, Zai Lab, GenomiCare, Yuhan, Roche, Menarini, InventisBio Co Ltd

Speakers' Bureau: AstraZeneca, Roche, Hansoh Pharma, Hengrui Therapeutics

Research Funding: AstraZeneca (Inst), Hutchison MediPharma (Inst), BMS (Inst), Hengrui Therapeutics (Inst), BeiGene (Inst), Roche (Inst), Hansoh (Inst), Lilly Suzhou Pharmaceutical Co (Inst)

Tetsuya Mitsudomi

Honoraria: AstraZeneca, Pfizer, Boehringer Ingelheim, Ono Pharmaceutical, Bristol Myers Squibb, Chugai Pharma, Taiho Pharmaceutical, Lilly, Novartis, MSD K.K, Kyowa Hakko Kirin, Amgen, Guardant Health, Ethicon, Thermofisher Scientific Biomarkers, Merck KGaA, Janssen Oncology, Takeda

Consulting or Advisory Role: AstraZeneca, Ono Pharmaceutical, MSD Oncology, Amgen, Regeneron, Bristol Myers Squibb

Research Funding: Boehringer Ingelheim (Inst), AstraZeneca (Inst), Pfizer (Inst), Chugai Pharma (Inst), Ono Pharmaceutical (Inst), Taiho Pharmaceutical (Inst), MSD K.K (Inst), Bridgebio (Inst)

Enriqueta Felip

Consulting or Advisory Role: AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Lilly, Roche, Gilead Sciences, GlaxoSmithKline, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Peptomyc, Pfizer, Regeneron, Sanofi, Takeda, Genmab

Speakers' Bureau: Amgen, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Lilly, Roche, Genentech, Janssen, Medical Trends, Medscape, Merck Serono, Merck Sharp & Dohme, Peervoice, Pfizer, Sanofi, Takeda, Touch Oncology

Travel, Accommodations, Expenses: AstraZeneca, Janssen, Roche

Other Relationship: Grifols

Uncompensated Relationships: Member of the Scientific Advisory Committee-Hospital Universitari Parc Taulí, SEOM (Sociedad Española de Oncología Médica), President from 2021-2023, "ETOP IBCSG Partners" Member of the Scientific Committee

Stephen R. Broderick

Consulting or Advisory Role: Bristol Myers Squibb, AstraZeneca

Scott J. Swanson

Consulting or Advisory Role: Ethicon, Covidien/Medtronic

Julie Brahmer

Consulting or Advisory Role: Bristol Myers Squibb, Amgen, GlaxoSmithKline, AstraZeneca, Sanofi, Janssen Oncology, Summit Therapeutics, Mestag Therapeutics, RAPT Therapeutics, Genmab
Research Funding: Bristol Myers Squibb (Inst), AstraZeneca (Inst)
Other Relationship: Bristol Myers Squibb, Merck, Regeneron

Keith Kerr

Consulting or Advisory Role: Bristol Myers Squibb, MSD Oncology, Roche/Genentech, AstraZeneca, Lilly, Pfizer, Novartis, Regeneron, Takeda, Sanofi, AbbVie, Amgen, Bayer, Daiichi Sankyo/AstraZeneca, Janssen
Speakers' Bureau: Bristol Myers Squibb, Lilly, Roche/Genentech, AstraZeneca, Pfizer, Novartis, Amgen, AbbVie, Mirati Therapeutics

Jaclyn Neely

Employment: Bristol Myers Squibb
Stock and Other Ownership Interests: Bristol Myers Squibb

David Balli

Employment: Bristol Myers Squibb
Stock and Other Ownership Interests: Bristol Myers Squibb Foundation

Mariano Provencio Pulla

Honoraria: BMS, Roche, MSD, AstraZeneca, Takeda, Lilly, Roche, Janssen, Pfizer
Consulting or Advisory Role: Bristol Myers Squibb, Roche, MSD, AstraZeneca, Takeda, Lilly, Janssen Oncology, Pfizer, Merck, Amgen, Daiichi Sankyo, Johnson & Johnson, Gilead Sciences, Guardant Health, Ipsen, Incyte, Bayer
Speakers' Bureau: BMS, Roche, AstraZeneca, MSD, Takeda, Pfizer, Lilly, Janssen, Amgen
Research Funding: Pierre Fabre (Inst), Roche (Inst), Boehringer Ingelheim (Inst), Bristol Myers Squibb (Inst), MSD (Inst), Takeda (Inst), AstraZeneca (Inst), Pfizer (Inst), Amgen (Inst)
Travel, Accommodations, Expenses: Roche, BMS, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb Company, Lilly, Pierre Fabre, Takeda, MSD, Janssen, Amgen, Pfizer
Other Relationship: Pfizer

No other potential conflicts of interest were reported.

APPENDIX 1. LIST OF CHECKMATE 816 INVESTIGATORS

Argentina: Lorena Lupinacci (Hospital Italiano de Buenos Aires), Claudio Martin (Instituto Alexander Fleming); Brazil: Carlos Barrios (Hospital São Lucas da PUCRS), Fabio Franke (Associação Hospital de Caridade de Ijuí), Rodrigo Medeiros (Hospital Sirio-Libanês), Andre Murad (Personal Oncologia de Precisão e Personalizada); Canada: Moishe Liberman (Centre Hospitalier de l'Université de Montréal), Jonathan Spicer (McGill University Health Center), Shelly Sud (CISSS de l'Outaouais), Sunil Yadav (Saskatoon Cancer Centre); China: Ke-Neng Chen (Beijing Cancer Hospital), Qixun Chen (Zhejiang Cancer Hospital), Junke Fu (The First Affiliated Hospital of Xi'an Jiao Tong University), Yi Hu (Chinese People's Liberation Army [PLA] General Hospital [301 Hospital]), Xiaofei Li (Tangdu Hospital), Jichun Liu (The Second Affiliated Hospital to Nanchang University), Lunxu Liu (Huaxi Hospital of Sichuan University), Shun Lu (Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University), Changli Wang* (Tianjin Medical University Cancer Institute and Hospital), Qun Wang (Zhongshan Hospital, Fudan University), Wenxiang Wang (Hunan Cancer Hospital), Lin Wu (Hunan Cancer Hospital), Kejing Ying (Sir Run Run Shaw Hospital), Chunfang Zhang (Xiangya Hospital of Central South University), Jian Zhao (Cancer Center of Guangzhou Medical University); France: Nicolas Girard (Institut Curie, Institut Mutualiste Montsouris), Hervé Lena (Hôpital Pontchaillou), Julien Mazières (Hôpital Larrey), Bertrand Mennecier (Nouvel Hôpital Civil), Eric Pichon (Hôpital Bretonneau), Pierre Jean Souquet (Centre Hospitalier Lyon-Sud), Gérard Zalcman (Hôpital Bichat-Claude Bernard); Greece: Sofia Baka (Interbalkan European Medical Center); Italy: Elisa Bennicelli (Ospedale Policlinico San Martino), Federico Cappuzzo (Ospedale Santa Maria delle Croci), Manolo D'Arcangelo (Ospedale Santa Maria delle Croci), Domenico Galetta (Istituto Tumori Giovanni Paolo II), Vincenzo Minotti (Azienda Ospedaliera Di Perugia); Japan: Shinji Atagi (National Hospital Organization Kinki-Chuo Chest Medical Center), Norihiko Ikeda (Tokyo Medical University Hospital), Hiroyuki Ito (Kanagawa Cancer Center), Kaoru Kubota (Nippon Medical School Hospital), Tetsuya Mitsudomi (Kindai University Hospital), Yasuhisa Ohde (Shizuoka Cancer Center), Satoshi Oizumi (Hokkaido Cancer Center), Morihito Okada (Hiroshima University Hospital), Jiro Okami (Osaka International Cancer institute), Noriaki Sakakura (Aichi Cancer Center Central Hospital), Yutaka Shio (Fukushima Medical University Hospital), Shunichi Sugawara (Sendai Kosei Hospital), Kazuya Takamochi (Juntendo University Hospital), Fumihito Tanaka (University of Occupational and Environmental Health Hospital), Keisuke Tomii (Shizuoka Cancer Center), Masahiro Tsuboi (National Cancer Center Hospital East); Republic of Korea: Tae Won Jang (Kosin University Gospel Hospital), Young-Chul Kim (Chonnam National University Hwasun Hospital), Sung Yong Lee (Korea University Guro Hospital); Romania: Aurelia Alexandru (Sectia Clinica Oncologie Medicala II), Tudor Ciuleanu (Prof. Dr Ion

Chiricuță Institute of Oncology Day Care Dep); Spain: Enriqueta Felip (H. Univ. Vall d'Hebron), Mariano Provencio Pulla (Hosp. Univ. Puerta De Hierro); Taiwan: Chao-Hua Chiu (Taipei Veterans General Hospital), Kai-Ling Lee (Taipei Medical University Hospital), Kang-Yun Lee (Taipei Medical University, Shuang Ho Hospital), Tsung-Ying Yang (Taichung Veterans General Hospital); Türkiye: Timuçin Cil (Adana Şehir Eğitim ve Araştırma Hastanesi), Ahmet Demirkazık (Ankara Üniversitesi Tıp Fakültesi), Zeynep Turna (Cerrahpaşa Tıp Fakültesi); United States: Wallace Akerley (University of Utah), Warren Alexander (WBAMC Oncology Department), Mark Awad (Dana-Farber Cancer Institute), Hossein Borghaei (Fox Chase Cancer Center), Brian Byrne (Cancer Center of Central Connecticut), Jeremy Cetnar (Oregon Health & Science University), Jason Chesney (University of Louisville), Makenzi Evangelist (New York Oncology Hematology), Patrick Forde (Sidney-Kimmel Comprehensive Cancer Center at Johns Hopkins), Abhimanyu Ghose (Arizona Oncology Associates), Vallathucherry Harish (UNC Regional Physicians Hematology & Oncology), Harry Harper (The Cancer Center at Hackensack University Medical Center), Thomas Harris (Texas Oncology), Leora Horn (Vanderbilt-Ingram Cancer Center), John Hrom (Hattiesburg Clinic), Wade Thomas Iams (Vanderbilt-Ingram Cancer Center), Arielle Lee (HOPE Cancer Center of East Texas), Giberto Lopes (University of Miami), Nisha Mohindra (Northwestern Medicine), Timothy O'Brien (MetroHealth Medical Center), Krishna Pachipala (Millennium Oncology), Andrew Popoff (Henry Ford Health System), Suman Rao (MedStar Franklin Square Medical Center), Ahad Sadiq (Fort Wayne Medical Oncology and Hematology), Gene Saylor (Charleston Hematology Oncology Associates), Lasika Seneviratne (Los Angeles Hematology/Oncology Medical Group), Elaine Shum (Laura & Isaac Perlmutter Cancer Center), David Spigel (Sarah Cannon), Alexander Spira (Virginia Cancer Specialists), James Uyeki (Texas Oncology – South Austin Cancer Center), Christopher Vaughn (Hematology–Oncology Associates of Fredricksburg), John Villano (University of Kentucky), Everett Vokes (University of Chicago Medical Center), Benny Weksler (Allegheny General Hospital), John Wrangle (Medical University of South Carolina).

*Changli Wang is the China national coordinating investigator.

APPENDIX 2. LIST OF CHECKMATE 816 CENTRAL PATHOLOGIC REVIEWERS

Robert A. Anders, Alexander S. Baras, Jonathan D. Cuda, Jaroslaw Jedrych, Ashley Cimino-Mathews, Edward Gabrielson, Peter B. Illei, Julie E. Stein, Janis M. Taube, Elizabeth D. Thompson, and Daphne Wang (all from Johns Hopkins University, Department of Pathology).