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Neoadjuvant nivolumab plus chemotherapy in resectable non-small-cell lung cancer in Japanese patients from CheckMate 816

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Abstract

In the open-label, phase III CheckMate 816 study (NCT02998528), neoadjuvant nivolumab plus chemotherapy demonstrated statistically significant improvements in event-free survival (EFS) and pathological complete response (pCR) versus chemotherapy alone in patients with resectable non-small-cell lung cancer (NSCLC). Here we report efficacy and safety outcomes in the Japanese subpopulation. Patients with stage IB–IIIA, resectable NSCLC were randomized 1:1 to nivolumab plus chemotherapy or chemotherapy alone for three cycles before undergoing definitive surgery within 6 weeks of completing neoadjuvant treatment. The primary end-points (EFS and pCR) and safety were assessed in patients enrolled at 16 centers in Japan. Of the Japanese patients randomized, 93.9% (31/33) in the nivolumab plus chemotherapy arm and 82.9% (29/35) in the chemotherapy arm underwent surgery. At 21.5 months' minimum follow-up, median EFS was 30.6 months (95% confidence interval [CI], 16.8–not reached [NR]) with nivolumab plus chemotherapy versus 19.6 months (95% CI, 8.5–NR) with chemotherapy; hazard ratio, 0.60 (95% CI, 0.30–1.24). The pCR rate was 30.3% (95% CI, 15.6–48.7) versus 5.7% (95% CI, 0.7–19.2), respectively; odds ratio, 7.17 (95% CI, 1.44–35.85). Grade 3/4 treatment-related adverse events were reported in 59.4% versus 42.9% of patients, respectively, with no new safety signals identified. Neoadjuvant nivolumab plus

Abbreviations: AE, adverse event; AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; BIPR, blinded independent pathological review; CI, confidence interval; DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; IHC, immunohistochemistry; IMAE, immune-mediated adverse event; IQR, interquartile range; MPR, major pathological response; NR, not reached; NSCLC, non-small-cell lung cancer; OR, odds ratio; ORR, objective response rate; pCR, pathological complete response; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PS, performance status; TRAE, treatment-related adverse event; TTDM, time to distant metastases or death.

The trial is registered with ClinicalTrials.gov: NCT02998528.

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chemotherapy resulted in longer EFS and a higher pCR rate versus chemotherapy alone in Japanese patients, consistent with findings in the global population. These data support nivolumab plus chemotherapy as a neoadjuvant treatment option in Japanese patients with resectable NSCLC.

KEYWORDS
Japanese, minimally invasive surgical procedure, non-small-cell lung carcinoma, neoadjuvant therapy, nivolumab

1 | INTRODUCTION

Curative surgery remains the standard of care for patients with resectable NSCLC.[1,2] However, despite complete surgical resection, 25%–70% of patients experience recurrence,[2,3] with estimated 5-year survival rates ranging from 71% for stage IB disease to 36% for stage IIIA disease (per pathological staging criteria of the AJCC Cancer Staging Manual, 7th edition) based on multinational data from the International Association for the Study of Lung Cancer (IASLC) International Staging Project.[4]

Systemic therapy postresection has been shown to be beneficial in some patients with early-stage and locally advanced NSCLC.[5] International guidelines recommend adjuvant chemotherapy for patients with resected stage II–III NSCLC,[5–7] which is associated with 4%–5% absolute improvement in 5-year survival.[8] Currently, effective adjuvant therapies for resectable NSCLC include *EGFR*-targeted therapies[9,10] and immunotherapy.[11,12]

Until recently, effective neoadjuvant treatments were an unmet need for patients with resectable NSCLC.[5] Neoadjuvant therapy has several advantages over adjuvant therapy, including potentially increasing the likelihood of pCR by reducing tumor volume.[1] Neoadjuvant platinum-based chemotherapy followed by surgery is a treatment option for patients with early-stage resectable NSCLC who would have been candidates for adjuvant chemotherapy after surgery[7]; however, only 5% and 6% absolute improvements in 5-year survival and recurrence-free survival, respectively, have been reported with neoadjuvant chemotherapy versus surgery alone.[13]

Nivolumab is a fully human anti-PD-1 immune checkpoint inhibitor that restores the function of antitumor T cells.[14] Immunotherapy could be beneficial in the neoadjuvant setting because it potentially provides an early opportunity to treat micrometastatic disease and enhances the immune response when bulk tumor and tumor antigens are still present intratumorally.[3,15,16] Additionally, chemotherapy enhances antitumor immunity through direct or indirect activation of the immune system, providing a rationale for combination strategies with immunotherapy.[17] In the phase II NADIM trial, neoadjuvant nivolumab plus chemotherapy (paclitaxel and carboplatin) demonstrated promising pCR and survival, while maintaining a manageable safety profile, in patients with previously untreated resectable stage IIIA NSCLC.[18]

CheckMate 816 was a global, randomized, phase III study, which demonstrated that neoadjuvant nivolumab plus chemotherapy versus chemotherapy alone provided statistically significant and clinically meaningful improvements in EFS (median 31.6 vs. 20.8 months; HR 0.63; 97.38% CI, 0.43–0.91; $p = 0.005$) and pCR rate (24.0% vs. 2.2%; OR 13.94; 99% CI, 3.49–55.75; $p < 0.001$) in patients with resectable NSCLC.[19] Additionally, improvements were observed in the rate of MPR and surgical outcomes, including numerically shorter median duration of surgery and greater use of minimally invasive approaches, among patients treated with neoadjuvant nivolumab plus chemotherapy versus chemotherapy alone. The addition of nivolumab to chemotherapy did not result in a higher incidence or greater severity of AEs, and the feasibility of surgery was not impeded. Based on data from this trial, nivolumab plus platinum-doublet chemotherapy was approved in the United States, Japan, and other countries as a neoadjuvant therapy for adult patients with resectable NSCLC (tumors ≥4 cm or node-positive).[20–24]

Similar to data from the global population,[4] the 5-year survival rates in Japanese patients with resectable NSCLC range from 73%–77% for stage IB to 32%–48% for stage IIIA (AJCC Cancer Staging Manual 7th edition, pathological stages).[25,26] However, studies have reported variations, including genetic characteristics, differences in health-care systems, and epidemiological and demographic differences, between Asian and non-Asian populations that could influence course of disease and response to treatments for NSCLC.[27–30] Given the potential for differences in treatment outcomes and safety in Asian patients, it is important to evaluate the efficacy of therapies in Japanese patients to guide treatment decisions. Here we present the results of neoadjuvant nivolumab plus chemotherapy versus chemotherapy alone for patients with resectable NSCLC in the Japanese subpopulation of CheckMate 816.

2 | MATERIALS AND METHODS

2.1 | Patients

The study design and eligibility criteria for CheckMate 816 (NCT02998528) have been described previously.[19] Briefly, eligible patients were 18 years of age or older with treatment-naïve, resectable stage IB (≥4 cm) to IIIA NSCLC (staging criteria per the AJCC Cancer Staging Manual, 7th edition) and an ECOG PS of 0 or 1. Patients with known sensitizing *EGFR* mutations or *ALK* translocations were excluded. This subgroup analysis included patients enrolled at 16 treatment centers in Japan.

2.2 | Study design and treatment

In this open-label, phase III trial, patients were randomly assigned in a 1:1 ratio to receive nivolumab 360 mg plus platinum-doublet chemotherapy or platinum-doublet chemotherapy alone every 3 weeks for three cycles before undergoing definitive surgery within 6 weeks of completing neoadjuvant therapy. Neoadjuvant chemotherapy regimens in both treatment arms included paclitaxel plus carboplatin for patients with any histology, gemcitabine plus cisplatin for patients with squamous NSCLC, and pemetrexed plus cisplatin for patients with nonsquamous NSCLC. In addition to these regimens, patients in the chemotherapy-only arm as well as patients receiving adjuvant chemotherapy after surgery could also receive vinorelbine plus cisplatin or docetaxel plus cisplatin. Patients were stratified by disease stage (IB–II or IIIA), tumor PD-L1 expression (<1%/not evaluable/indeterminate or ≥1%), and sex (male or female). The enrollment of patients with nonevaluable or indeterminate PD-L1 status to the tumor PD-L1 <1% subgroup was limited to 10% of patients within this group. After surgery, all patients could receive up to four cycles of adjuvant chemotherapy or radiotherapy, or both.

2.3 | End-points and assessments

The primary and secondary end-points of the CheckMate 816 trial have been reported previously.[19] The trial had two primary end-points: (i) EFS assessed by BICR, defined as the time from randomization to any disease progression precluding surgery, disease progression, or recurrence after surgery (based on BICR assessment per RECIST version 1.1), disease progression in the absence of surgery, or death due to any cause, with data on patients who received subsequent therapy censored at last assessment on or before the start of subsequent therapy during which tumor evaluation could be performed; and (ii) pCR by BIPR, defined as 0% residual viable tumor cells in the primary tumor and sampled lymph nodes. The following assessments were included in this exploratory analysis in Japanese patients: EFS as defined previously and additionally analyzed using a previously described secondary definition (i.e., the time from randomization to any one of the following events: any disease progression precluding surgery, disease progression or recurrence after surgery [based on BICR assessment per RECIST version 1.1], or death due to any cause; excluded censoring for subsequent therapies)[19]; pCR per BIPR; MPR per BIPR, defined as ≤10% residual viable tumor cells in the primary lung tumor and sampled lymph nodes; depth of pathological response, measured by percent of residual viable tumor in the primary tumor; ORR, defined as a complete or partial response from baseline to the presurgery scan per RECIST version 1.1, per BICR; EFS2, defined as the time from randomization to the first of the following events: objectively documented progression, per investigator assessment, after the next line of therapy or death from any cause (patients without documented progression on the next line who started a second next line of subsequent therapy were considered to have had an event at the start of second next line of therapy); and TTDM, defined as the time from randomization to the first occurrence of distant metastases or death, whichever occurs first.

Safety and tolerability were assessed in all patients who received one or more doses of study drug and included any-cause AEs, TRAEs (both reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose), IMAEs (defined as AEs considered potentially immune-mediated by the investigator, regardless of causality, that occurred within 100 days of the last dose, with no clear alternative etiology per investigator assessment or with an immune-mediated component, and were treated with immune-modulating medication; endocrine events were considered immune-mediated regardless of immune-modulating medication use, as they are often managed without immune-modulating medication), and surgery-related AEs reported within 90 days after definitive surgery. AEs were graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 and Medical Dictionary for Regulatory Activities version 24.0. Tumor PD-L1 expression, tumor mutation burden, and pathological response were determined as previously described.[31–33]

2.4 | Statistical analysis

Efficacy and safety data analyses of nivolumab plus chemotherapy versus chemotherapy alone in Japanese patients were exploratory and summarized using descriptive statistics. All randomized Japanese patients were included in the efficacy analyses. Time-to-event analyses were undertaken using the Kaplan–Meier method; HRs and corresponding CIs were calculated using an unstratified Cox proportional hazards model. The pCR and MPR rates between treatment arms were compared using an unstratified analysis; exact 95% CIs for pCR and MPR rates were calculated using the Clopper–Pearson method. Objective response rates were reported with 95% CIs calculated by the Clopper–Pearson method.

3 | RESULTS

3.1 | Patients and treatment

The EFS and pCR results reported in this subgroup analysis (database lock date: October 20, 2021) were based on the prespecified interim analysis of EFS and the final analysis of pCR. Among Japanese patients, 33 patients were randomized to nivolumab plus chemotherapy and 35 to chemotherapy alone; 32 patients received nivolumab plus chemotherapy (1 patient did not receive treatment due to an AE unrelated to study drug) and 35 received chemotherapy (Figure 1). Baseline characteristics were generally balanced between treatment arms (Table 1). However, the proportions of patients who were ≥65 years old (66.7% vs. 57.1%), never

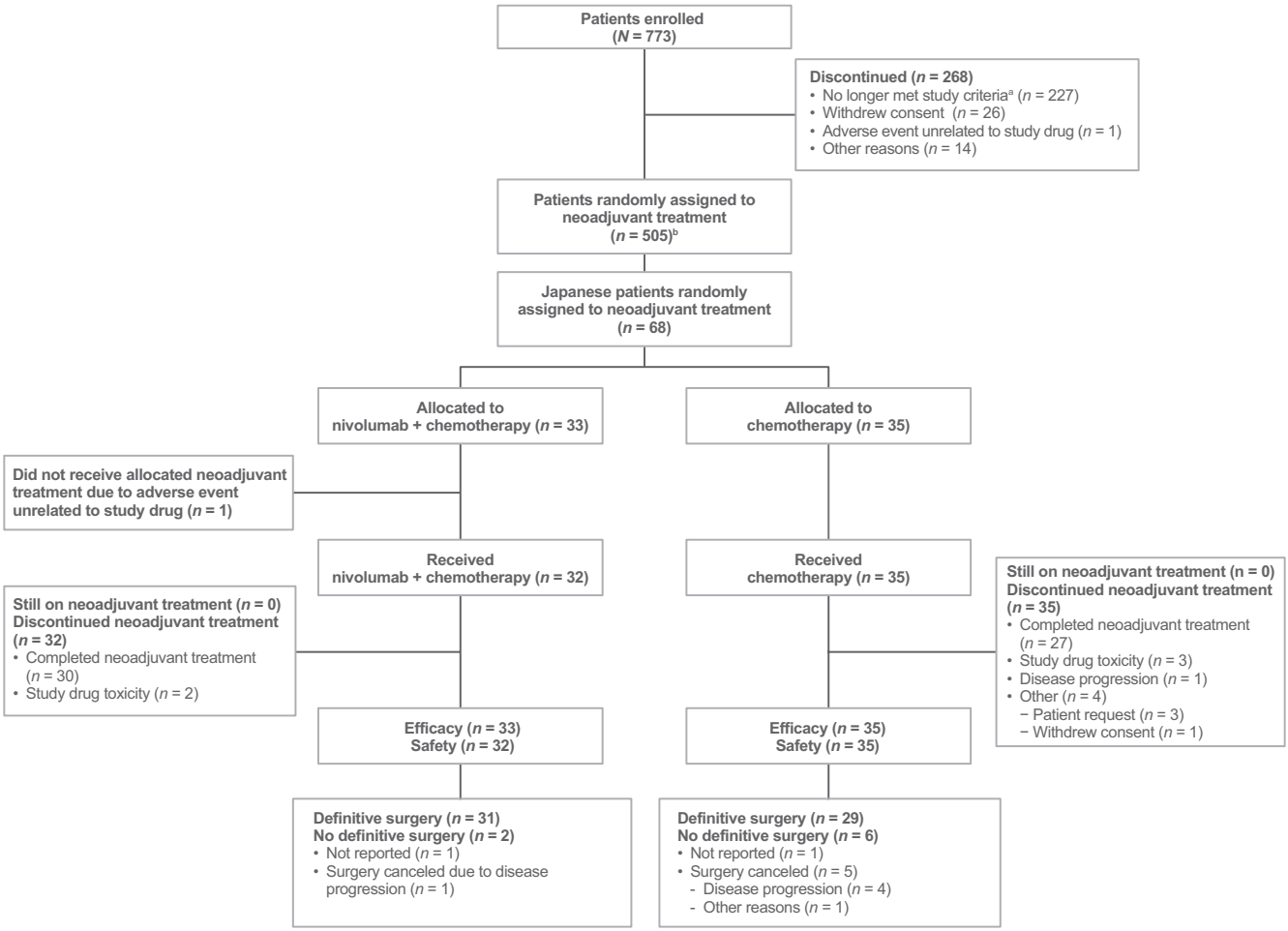

FIGURE 1 Treatment disposition in Japanese patients with resectable non-small-cell lung cancer treated with neoadjuvant nivolumab plus chemotherapy or chemotherapy alone. Database lock: October 20, 2021; minimum follow-up, 21.5 months; median follow-up, 29.7 months. [a]Screen failure. [b]Includes the following patients: (i) 113 patients who were randomized to an exploratory treatment arm (neoadjuvant nivolumab plus ipilimumab); enrollment for this arm was closed early and the arm discontinued. (ii) 34 patients who were randomized to chemotherapy in the initial protocol (i.e., before the addition of the nivolumab plus chemotherapy arm) who were not included in the primary analysis population.

smoked (18.2% vs. 8.6%), and had tumor PD-L1 expression ≥50% (36.4% vs. 22.9%) were higher in the nivolumab plus chemotherapy arm versus chemotherapy alone arm.

At the time of analysis, all Japanese patients were off treatment. Of the 32 patients who received nivolumab plus chemotherapy and the 35 patients who received chemotherapy alone, 30 (93.8%) and 27 (77.1%) patients, respectively, completed all three cycles of neoadjuvant treatment (Figure 1). Reasons for not completing neoadjuvant treatment included study drug toxicity (nivolumab plus chemotherapy, $n=2$ [6.2%]; chemotherapy, $n=3$ [8.6%]), disease progression (chemotherapy, $n=1$ [2.9%]), and other reasons (chemotherapy, $n=4$ [11.4%]; 3 patient requests to discontinue treatment and 1 withdrawal of consent). Following surgery, 6 (18.8%) patients in the nivolumab plus chemotherapy arm versus 8 (22.9%) patients in the chemotherapy arm received adjuvant chemotherapy; no patients received radiotherapy. Among all randomized Japanese patients, subsequent cancer therapy was received by 6 (18.2%) patients in the nivolumab plus chemotherapy arm versus 16 (45.7%) patients in the chemotherapy arm; subsequent systemic therapy was received by 4 (12.1%) versus 13 (37.1%) patients, respectively (Table 2).

3.2 | Surgical outcomes

Thirty-one patients (93.9%) in the nivolumab plus chemotherapy arm versus 29 patients (82.9%) in the chemotherapy arm underwent definitive surgery (Table 3). Surgery was canceled for 1 (3.0%) versus 5 patients (14.3%), respectively; reasons for cancellation included disease progression (1 [3.0%] vs. 4 [11.4%] patients, respectively) and other (0 vs. 1 [2.9%] patient). The percentage of delayed surgeries was lower in the nivolumab plus chemotherapy versus chemotherapy arms (2 [6.5%] vs. 4 [13.8%] patients, respectively); reasons for delay included AEs (1 [3.2%] vs. 4 [13.8%] patients, respectively) and other (1 [3.2%] vs. 0 patients). The median duration of surgery was 207.0 (IQR,170.0–262.0) min in the nivolumab plus chemotherapy arm and 261.0 (IQR, 230.0–309.0) min in the chemotherapy arm.

TABLE 1 Baseline characteristics of Japanese patients with resectable non-small-cell lung cancer treated with neoadjuvant nivolumab plus chemotherapy or chemotherapy alone.

	Nivolumab plus chemotherapy (*n* = 33)	Chemotherapy (*n* = 35)
Age, years; median (range)	70 (47–82)	67 (44–77)
Age category		
<65 years	11 (33.3)	15 (42.9)
≥65 years	22 (66.7)	20 (57.1)
Male sex	27 (81.8)	29 (82.9)
ECOG PS		
0	31 (93.9)	31 (88.6)
1	2 (6.1)	4 (11.4)
Stage[a]		
IB	2 (6.1)	0 (0.0)
IIA	7 (21.2)	11 (31.4)
IIB	6 (18.2)	4 (11.4)
IIIA	18 (54.5)	20 (57.1)
Histology		
Squamous	14 (42.4)	16 (45.7)
Nonsquamous	19 (57.6)	19 (54.3)
Smoking status		
Current/former smoker	27 (81.8)	32 (91.4)
Never smoked	6 (18.2)	3 (8.6)
Tumor PD-L1 expression[b]		
<1%	14 (42.4)	15 (42.9)
≥1%	17 (51.5)	20 (57.1)
1%–49%	5 (15.2)	12 (34.3)
≥50%	12 (36.4)	8 (22.9)
Not evaluable	2 (6.1)	0 (0.0)
Tumor mutational burden[c]		
<12.3 mut/Mb	15 (45.5)	14 (40.0)
≥12.3 mut/Mb	10 (30.3)	17 (48.6)
Not evaluable/not reported	8 (24.2)	4 (11.4)

Note: Data are shown as *n* (%) unless otherwise indicated.

Abbreviations: mut/Mb, mutations per megabase; PD-L1, programmed death ligand 1; PS, performance status.

[a]Disease stage per case report form.

[b]Tumor PD-L1 expression was determined using PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako); patients with tumor tissue that could not be assessed for PD-L1 expression (≤10% of all patients who underwent randomization) were stratified to the subgroup with a PD-L1 expression level <1% at randomization.

[c]Evaluated using the Illumina Omni TruSight 500 (TSO500) assay; the 12.3 mut/Mb cut-off per the TSO500 assay (Illumina) corresponds with 10 mut/Mb per FoundationOne®CDx (FoundationOne Medicine).[32]

The use of minimally invasive approaches was more common with nivolumab plus chemotherapy versus chemotherapy (9 [29.0%] vs. 4 [13.8%] patients), and fewer pneumonectomies were performed (2 [6.5%] vs. 4 [13.8%] patients, respectively). R0 resection (no residual tumor) was performed in 27 (87.1%) patients in the nivolumab plus chemotherapy arm versus 24 (82.8%) patients in the chemotherapy arm. Surgical outcomes by baseline stage of disease are shown in Table S1.

3.3 | Efficacy

At a minimum follow-up of 21.5 months, the median EFS with nivolumab plus chemotherapy was 30.6 months (95% CI, 16.8–NR) versus 19.6 months (95% CI, 8.5–NR) with chemotherapy (HR 0.60; 95% CI, 0.30–1.24) (Figure 2). The 1-year EFS rate was 87.3% (95% CI, 69.6–95.0) with nivolumab plus chemotherapy versus 64.5% (95% CI, 45.9–78.0) with chemotherapy; 2-year EFS rates

TABLE 2 Subsequent cancer therapy[a] in Japanese patients with resectable non-small-cell lung cancer (NSCLC) treated with neoadjuvant nivolumab plus chemotherapy or chemotherapy alone.

Subsequent cancer therapies, *n* (%)	Nivolumab plus chemotherapy (*n* = 33)	Chemotherapy (*n* = 35)
Any	6 (18.2)	16 (45.7)
Radiotherapy	4 (12.1)	10 (28.6)
Surgery[b]	2 (6.1)	1 (2.9)
Systemic therapy	4 (12.1)	13 (37.1)
Chemotherapy	4 (12.1)	11 (31.4)
Targeted therapy	3 (9.1)	3 (8.6)
Immunotherapy	3 (9.1)	12 (34.3)
Pembrolizumab	0 (0.0)	6 (17.1)
Nivolumab	0 (0.0)	2 (5.7)
Atezolizumab	2 (6.1)	4 (11.4)
Durvalumab	1 (3.0)	3 (8.6)

[a]Defined as therapy starting on or after first dosing date (or randomization date if patient never treated), outside of the protocol-specified adjuvant therapy. Patients may have received more than one type of subsequent therapy.
[b]Any subsequent anticancer surgery for NSCLC.

were 64.3% (95% CI, 44.9–78.5) versus 43.7% (95% CI, 25.9–60.3), respectively. Numerical EFS benefit with nivolumab plus chemotherapy versus chemotherapy was observed regardless of baseline disease stage (Table S2), tumor PD-L1 expression (Table S3), or tumor histology (Table S4). Among patients with a pCR, median EFS was NR (95% CI, 27.7–NR) months in the nivolumab plus chemotherapy arm versus not computed for the chemotherapy arm due to small sample size (Figure S1). In patients without a pCR, median EFS was NR (95% CI, 11.0–NR) months with nivolumab plus chemotherapy versus 19.6 (5.8–NR) months with chemotherapy (HR 0.89; 95% CI, 0.38–2.09). The EFS benefit with nivolumab plus chemotherapy was also noted when EFS was assessed using the secondary definition (Figure S2).

The pCR rate was 30.3% (95% CI, 15.6–48.7) with nivolumab plus chemotherapy versus 5.7% (95% CI, 0.7–19.2) with chemotherapy (OR 7.17; 95% CI, 1.44–35.85) (Figure 3A). The MPR rate was also higher with nivolumab plus chemotherapy versus chemotherapy (39.4% [95% CI, 22.9–57.9] vs. 11.4% [95% CI, 3.2–26.7]; OR 5.04; 95% CI, 1.44–17.65) (Figure 3B). The depth of pathological response in the primary tumor was greater with nivolumab plus chemotherapy versus chemotherapy alone (Figure 4). The ORR was higher with nivolumab plus chemotherapy (60.6%) versus chemotherapy (34.3%) (Table S5). The proportion of patients with radiographic downstaging following neoadjuvant therapy was greater with nivolumab plus chemotherapy (42.4%) versus chemotherapy (22.9%) (Table S6). Treatment with nivolumab plus chemotherapy versus chemotherapy improved EFS2 (HR 0.43; 95% CI, 0.15–1.25) (Figure 5) and TTDM (HR 0.63; 95% CI, 0.27–1.45) (Figure 6).

3.4 | Safety

A summary of AEs is reported in Japanese and non-Japanese patients (Table 4). Among Japanese patients, a numerically higher incidence of grade 3/4 any-cause AEs and TRAEs was noted with nivolumab plus chemotherapy versus chemotherapy alone (62.5% vs. 45.7%, and 59.4% vs. 42.9%, respectively). The most common (≥5%) grade 3/4 TRAEs were decreased neutrophil count (31.2% with nivolumab plus chemotherapy vs. 20.0% with chemotherapy), neutropenia (9.4% vs. 8.6%), decreased white blood cell count (9.4% vs. 5.7%), decreased appetite (6.2% vs. 8.6%), decreased platelet count (6.2% vs. 0%), and constipation (0% vs. 5.7%) (Table 5). The incidence of any-grade TRAEs leading to discontinuation was 12.5% with nivolumab plus chemotherapy and 11.4% with chemotherapy. No treatment-related deaths were reported in either treatment arm (Table 4).

Any-grade IMAEs in the nivolumab plus chemotherapy arm were rash (12.5%), adrenal insufficiency (6.2%), diabetes mellitus (6.2%), hypothyroidism/thyroiditis (6.2%), hyperthyroidism (3.1%), and hypophysitis (3.1%) (Table 6). The only grade 3/4 IMAE occurring in ≥5% of patients was adrenal insufficiency (6.2%).

Surgery-related AEs of any grade were reported in 64.5% of patients receiving nivolumab plus chemotherapy versus 55.2% of patients receiving chemotherapy (Table S7). Grade 3/4 surgery-related AEs were reported in 19.4% versus 20.7% of patients, respectively. No grade 5 surgery-related AEs were reported in either treatment arm.

4 | DISCUSSION

In the Japanese subpopulation of CheckMate 816, neoadjuvant treatment with nivolumab plus chemotherapy demonstrated clinically meaningful improvement in EFS versus chemotherapy alone (HR 0.60; 95% CI, 0.30–1.24) and was associated with a higher proportion of patients achieving pCR (30.3% vs. 5.7%). Other efficacy outcomes, including MPR, TTDM, EFS2, ORR, and proportion of patients with radiographic downstaging, also favored nivolumab plus

TABLE 3 Surgical outcomes in Japanese patients with resectable non-small-cell lung cancer treated with neoadjuvant nivolumab plus chemotherapy or chemotherapy alone.

	Nivolumab plus chemotherapy ($n=33$)	Chemotherapy ($n=35$)
Patients with definitive surgery[a]	31 (93.9)	29 (82.9)
Patients with canceled definitive surgery	1 (3.0)	5 (14.3)
Disease progression	1 (3.0)	4 (11.4)
Other	0 (0.0)	1 (2.9)[b]
Patients with delayed definitive surgery[c,d]	2 (6.5)[e]	4 (13.8)[f]
Adverse event	1 (3.2)	4 (13.8)
Other	1 (3.2)	0 (0.0)
Duration of surgery, min	207.0 (170.0–262.0)	261.0 (230.0–309.0)
Length of hospital stay, days	11.0 (9.0–18.0)	13.0 (10.5–17.5)
Surgical approach[c]		
Thoracotomy	13 (41.9)	21 (72.4)
Minimally invasive[g]	9 (29.0)	4 (13.8)
Minimally invasive to thoracotomy	9 (29.0)	4 (13.8)
Extent of resection[c,h]		
Lobectomy	29 (93.5)	19 (65.5)
Pneumonectomy	2 (6.5)	4 (13.8)
Sleeve lobectomy	0 (0.0)	5 (17.2)
Bilobectomy	0 (0.0)	2 (6.9)
Other	4 (12.9)	2 (6.9)
Completeness of resection[c]		
R0 (no residual tumor)	27 (87.1)	24 (82.8)
R1 (microscopic residual tumor)	3 (9.7)	3 (10.3)
R2 (macroscopic residual tumor)	1 (3.2)	2 (6.9)

Note: Data are shown as *n* (%) or median (interquartile range).

[a]Definitive surgery was not reported in 1 patient in each treatment arm.

[b]Due to unresectability and poor lung function.

[c]Proportion based on number of patients with definitive surgery.

[d]Surgery was considered as delayed if time from last neoadjuvant dose to surgery was >6 weeks.

[e]Surgery was delayed by 1 week in each of the 2 patients.

[f]Surgery was delayed by 1, 2, 9, and 20 weeks in the 4 patients.

[g]Thoracoscopic or robotic.

[h]Patients may have had more than one type of surgery.

chemotherapy over chemotherapy alone. Results from the Japanese subpopulation were consistent with those of all randomized patients in this global study.[19] No new safety signals were observed among Japanese patients. Compared with non-Japanese patients, a numerically higher incidence of grade 3/4 TRAEs was observed in both treatment arms among Japanese patients.

Overall, the baseline characteristics of Japanese patients were generally similar to those of the global population.[19] However, the proportion of patients who were ≥65 years old, male, had an ECOG PS of 0, and stage IB–II disease at baseline in both treatment arms, and the proportion of patients with tumor PD-L1 expression ≥50% in the nivolumab plus chemotherapy arm were higher in the Japanese subpopulation versus the global population. Potentially, the favorable efficacy outcomes reported in this subpopulation could be attributed to the higher proportions of Japanese patients with ECOG PS 0 and stage IB–II disease.

A greater EFS benefit with nivolumab plus chemotherapy versus chemotherapy was observed in Japanese patients with stage IIIA disease at baseline, a subpopulation associated with poorer prognosis, with a 5-year survival rate of approximately 32%–48%,[25,26] compared with those with stage IB–II disease. Similar differences in treatment efficacy between early- and late-stage NSCLC have been observed in the global population and reported in several other clinical trials.[19,34–36] A longer follow-up may be needed to demonstrate the clinical benefits of neoadjuvant nivolumab plus chemotherapy in patients with earlier stages of disease who have a more favorable prognosis. Additionally, in Japanese patients, numerically greater EFS benefit was observed regardless of tumor PD-L1 expression, but these data should be interpreted with caution due to the smaller sample size.

Pathological response to neoadjuvant therapy has been suggested as a potential surrogate marker for survival in NSCLC.[37–39]

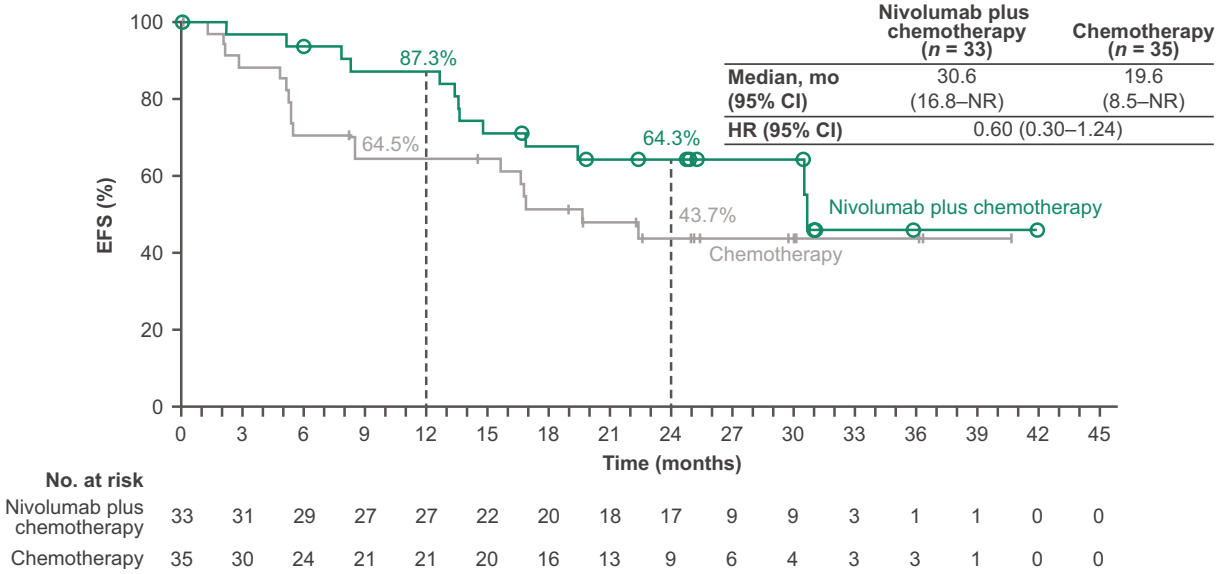

FIGURE 2 Event-free survival (EFS)[a] per blinded independent central review (BICR) in Japanese patients with resectable non-small-cell lung cancer treated with neoadjuvant nivolumab plus chemotherapy or chemotherapy alone. [a]Defined as the time from randomization to any of the following events: any disease progression precluding surgery, disease progression or recurrence after surgery (based on BICR assessment per RECIST version 1.1), disease progression in the absence of surgery, or death due to any cause; data on patients who received subsequent therapy were censored at the last assessment on or before the start of subsequent therapy during which tumor evaluation could be performed. CI, confidence interval; HR, hazard ratio; mo, months; NR, not reached.

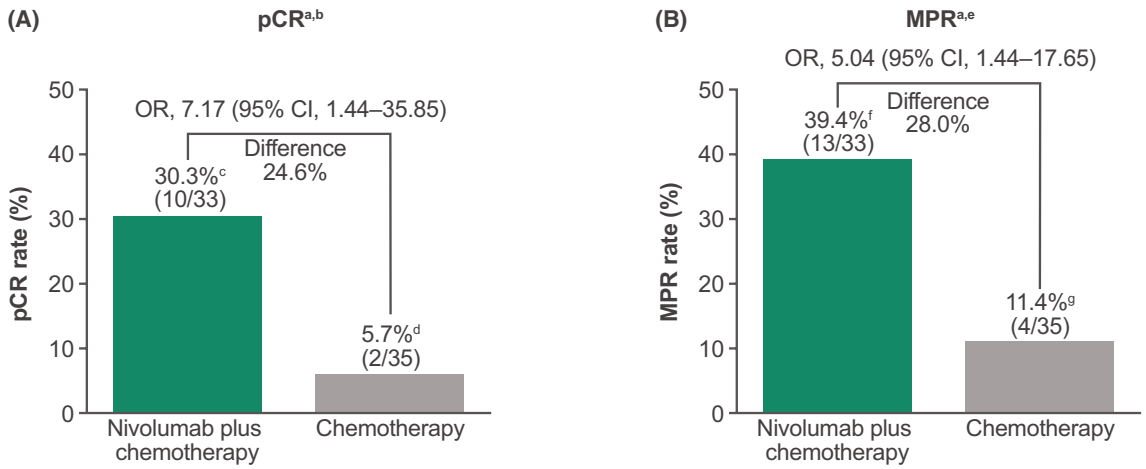

FIGURE 3 (A) Pathological complete response (pCR) and (B) major pathological response (MPR) per blinded independent pathological review in Japanese patients with resectable non-small-cell lung cancer treated with neoadjuvant nivolumab plus chemotherapy or chemotherapy alone. [a]Patients who did not undergo surgery were classified as nonresponders. [b]Defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes. 95% confidence interval (CI) for pCR: [c]15.6–48.7; [d]0.7–19.2. [e]Defined as ≤10% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes. 95% CI for MPR: [f]22.9–57.9; [g]3.2–26.7. OR, odds ratio.

The robust association between pCR and EFS in the global population of this trial[19] supports pCR as an early indicator of therapeutic efficacy for neoadjuvant immunotherapy. Although greater pCR benefit was observed with nivolumab plus chemotherapy versus chemotherapy alone in Japanese patients, the association between pCR and EFS in the nivolumab plus chemotherapy arm was inconclusive for this subpopulation, possibly due to small sample sizes. Further research evaluating the association between pCR and survival outcomes is required.

Among Japanese patients, neoadjuvant nivolumab plus chemotherapy did not negatively impact the patients' ability to undergo surgery compared with chemotherapy alone. Notably, fewer pneumonectomies, a procedure associated with worse outcomes,[40] were carried out in the nivolumab plus chemotherapy arm. A greater proportion of patients in the nivolumab plus chemotherapy arm had R0 resection (no residual tumor) and underwent minimally invasive surgery, an approach associated with improved physical recovery and reduction in AEs,[41] versus the chemotherapy arm. The addition

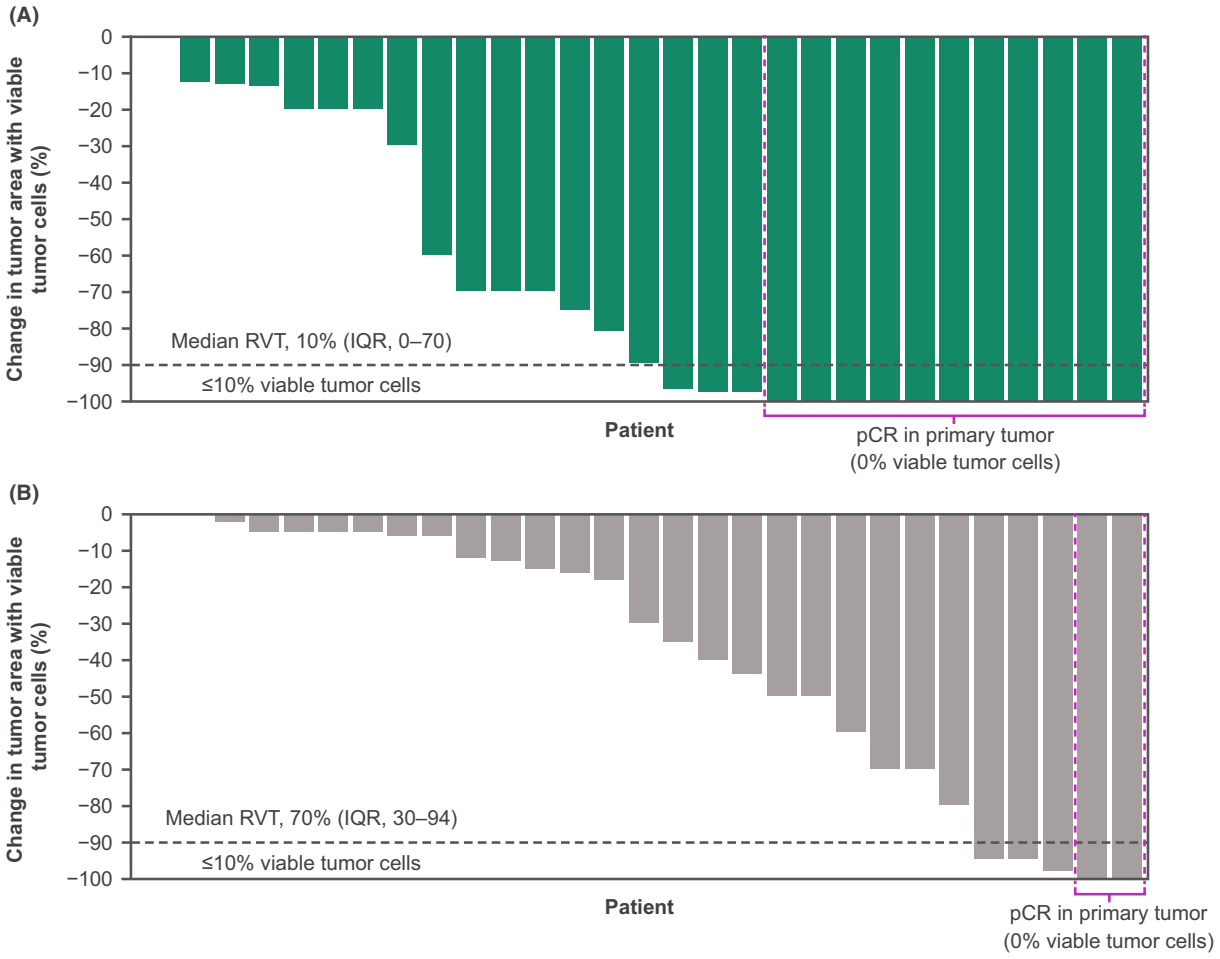

FIGURE 4 Depth of pathological response in the primary tumor in Japanese patients[a] with resectable non-small-cell lung cancer: (A) nivolumab plus chemotherapy arm, $n = 29$ and (B) chemotherapy arm, $n = 29$. [a]Only patients who underwent definitive surgery and had an evaluable pathology sample for blinded independent pathological review were included. IQR, interquartile range; pCR, pathological complete response; RVT, residual viable tumor.

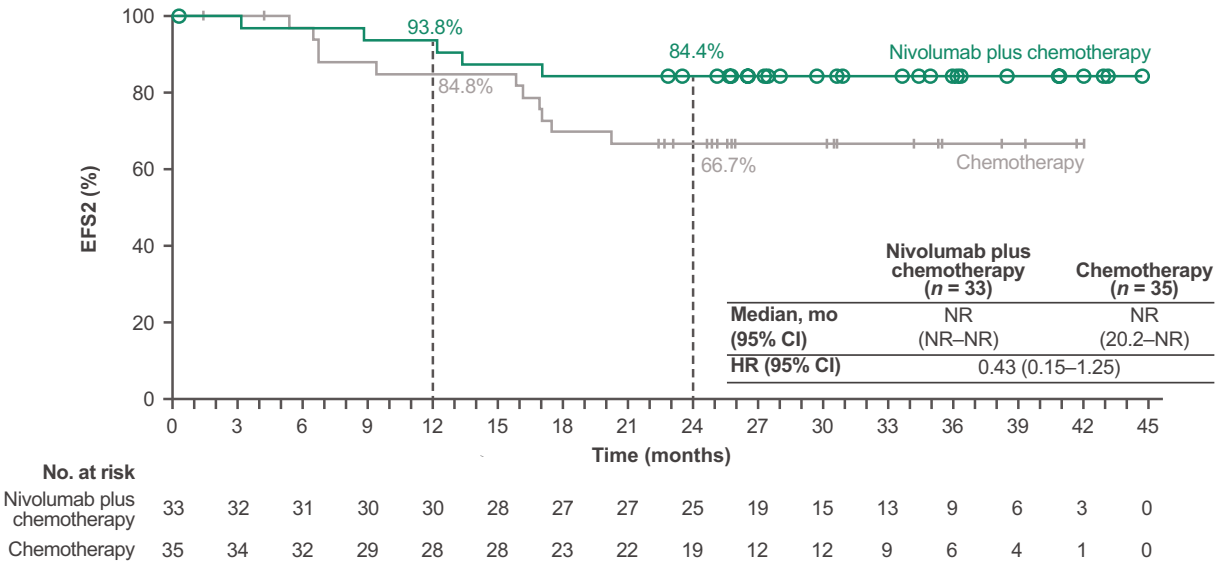

FIGURE 5 Event-free survival (EFS2)[a] in Japanese patients with resectable non-small-cell lung cancer treated with neoadjuvant nivolumab plus chemotherapy or chemotherapy alone. [a]Defined as the time from randomization to the first of the following events: objectively documented progression per investigator assessment, after the next line of therapy or death from any cause; patients without documented progression on the next line who started a second next line of subsequent therapy were considered to have had an event at the start of second next line of therapy. CI, confidence interval; HR, hazard ratio; mo, months; NR, not reached.

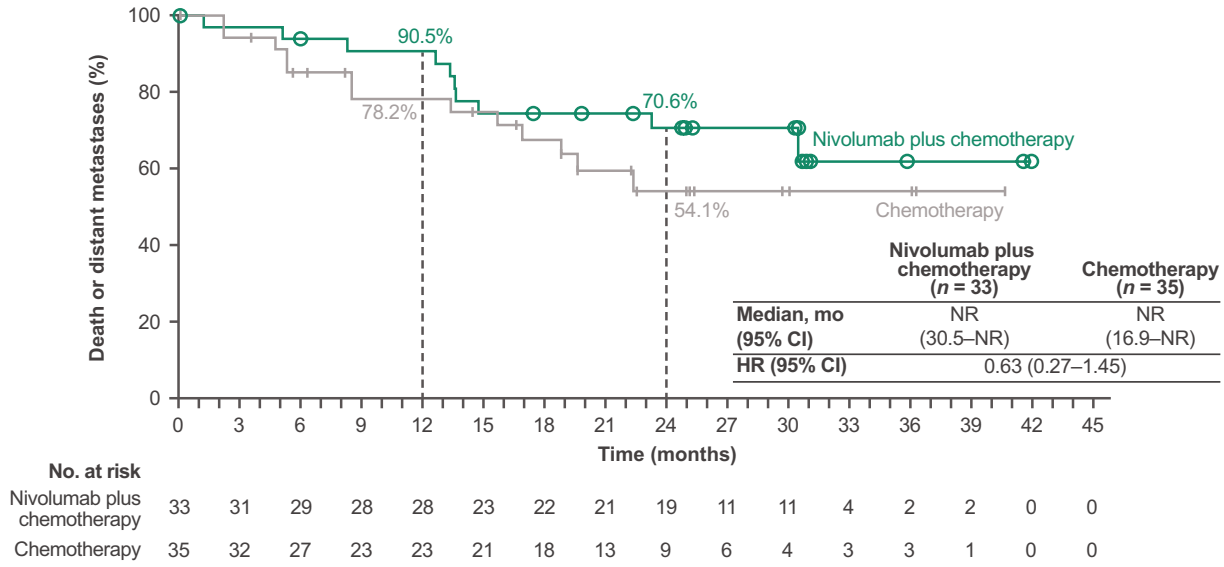

FIGURE 6 Time to death or distant metastases[a] in Japanese patients with resectable non-small-cell lung cancer treated with neoadjuvant nivolumab plus chemotherapy or chemotherapy alone. [a]Defined as the time from randomization to the first occurrence of distant metastases or death, whichever occurs first. CI, confidence interval; HR, hazard ratio; mo, months; NR, not reached.

TABLE 4 Adverse events (AEs)[a] in Japanese and non-Japanese patients with resectable non-small-cell lung cancer treated with neoadjuvant nivolumab plus chemotherapy or chemotherapy alone.

	Japanese patients				Non-Japanese patients			
	Nivolumab plus chemotherapy (*n* = 32)		Chemotherapy (*n* = 35)		Nivolumab plus chemotherapy (*n* = 144)		Chemotherapy (*n* = 141)	
AE, *n* (%)	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any-cause AEs[b]	31 (96.9)	20 (62.5)	35 (100)	16 (45.7)	132 (91.7)	52 (36.1)	136 (96.5)	61 (43.3)
Any-cause AEs leading to discontinuation[b]	4 (12.5)	3 (9.4)	4 (11.4)	1 (2.9)	14 (9.7)	7 (4.9)	16 (11.3)	6 (4.3)
Any-cause SAEs[b]	3 (9.4)	3 (9.4)	4 (11.4)	3 (8.6)	27 (18.8)	16 (11.1)	20 (14.2)	14 (9.9)
TRAEs[b,c]	31 (96.9)	19 (59.4)	35 (100.0)	15 (42.9)	114 (79.2)	40 (27.8)	121 (85.8)	50 (35.5)
TRAEs leading to discontinuation[b,c]	4 (12.5)	3 (9.4)	4 (11.4)	1 (2.9)	14 (9.7)	7 (4.9)	13 (9.2)	5 (3.5)
Treatment-related SAEs[b,c]	3 (9.4)	3 (9.4)	4 (11.4)	3 (8.6)	18 (12.5)	12 (8.3)	14 (9.9)	11 (7.8)
Surgery-related AEs[d,e,f]	20 (64.5)	6 (19.4)	16 (55.2)	6 (20.7)	42 (35.6)	11 (9.3)	47 (44.3)	14 (13.2)
Treatment-related deaths[g]	0		0		0		3	

Abbreviations: SAE, serious adverse event; TRAE, treatment-related adverse event.

[a]AEs per Common Terminology Criteria for Adverse Events version 4.0 and Medical Dictionary for Regulatory Activities version 24.0.

[b]Includes events reported between the first dose and 30 days after the last dose of neoadjuvant study treatment.

[c]No grade 5 events were reported.

[d]Proportions based on number of patients who underwent definitive surgery (Japanese patients: 31 [nivolumab plus chemotherapy], 29 [chemotherapy]; non-Japanese patients: 118 [nivolumab plus chemotherapy], 106 [chemotherapy]).

[e]Includes events reported within 90 days after definitive surgery.

[f]Grade 5 surgery-related AEs (defined as events that led to death ≤24 h after the onset of an AE) were reported in 2 patients in the nivolumab plus chemotherapy arm in non-Japanese patients and were deemed by the investigator to be unrelated to the trial drugs (one each due to pulmonary embolism and aortic rupture); no grade 5 surgery-related AEs were reported in Japanese patients.

[g]Included events that occurred any time between the first dose and 100 days after the last dose of neoadjuvant study treatment.

of nivolumab to chemotherapy did not increase the incidence of grade 3/4 surgery-related AEs. Although the incidence of any-grade surgery-related AEs in the nivolumab plus chemotherapy arm in the Japanese subpopulation was numerically higher compared to that in the non-Japanese population (64.5% vs. 35.6%), the AEs were mostly grade 1 or 2 and manageable. The greater depth of pathological response as well as the increased incidences of response and radiographic downstaging noted with nivolumab plus chemotherapy

TABLE 5 Most frequent treatment-related adverse events (TRAEs)[a,b] (≥15% of patients in either treatment arm) in Japanese patients with resectable non-small-cell lung cancer treated with neoadjuvant nivolumab plus chemotherapy or chemotherapy alone.

	Nivolumab plus chemotherapy (*n* = 32)		Chemotherapy (*n* = 35)	
TRAE, *n* (%)	Any grade	Grade 3/4	Any grade	Grade 3/4
All	31 (96.9)	19 (59.4)	35 (100.0)	15 (42.9)
Nausea	21 (65.6)	0 (0.0)	18 (51.4)	0 (0.0)
Constipation	18 (56.2)	0 (0.0)	22 (62.9)	2 (5.7)
Malaise	15 (46.9)	0 (0.0)	13 (37.1)	1 (2.9)
Decreased appetite	14 (43.8)	2 (6.2)	19 (54.3)	3 (8.6)
Decreased neutrophil count	13 (40.6)	10 (31.2)	16 (45.7)	7 (20.0)
Anemia	11 (34.4)	0 (0.0)	5 (14.3)	0 (0.0)
Decreased white blood cell count	10 (31.2)	3 (9.4)	5 (14.3)	2 (5.7)
Decreased platelet count	8 (25.0)	2 (6.2)	0 (0.0)	0 (0.0)
Hiccups	8 (25.0)	0 (0.0)	15 (42.9)	0 (0.0)
Neutropenia	6 (18.8)	3 (9.4)	5 (14.3)	3 (8.6)
Alopecia	5 (15.6)	0 (0.0)	4 (11.4)	0 (0.0)

[a]TRAEs per Common Terminology Criteria for Adverse Events version 4.0 and Medical Dictionary for Regulatory Activities version 24.0.

[b]Included events reported between the first dose and 30 days after the last dose of neoadjuvant treatment.

TABLE 6 Immune-mediated adverse events (IMAEs)[a,b] in Japanese patients with resectable non-small-cell lung cancer treated with neoadjuvant nivolumab plus chemotherapy or chemotherapy alone.

	Nivolumab plus chemotherapy (*n* = 32)		Chemotherapy (*n* = 35)	
IMAE, *n* (%)	Any grade	Grade 3/4	Any grade	Grade 3/4
Nonendocrine				
Rash	4 (12.5)	1 (3.1)	1 (2.9)	0 (0.0)
Pneumonitis	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.9)
Endocrine				
Adrenal insufficiency	2 (6.2)	2 (6.2)	0 (0.0)	0 (0.0)
Diabetes mellitus	2 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism/thyroiditis	2 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hypophysitis	1 (3.1)	1 (3.1)	0 (0.0)	0 (0.0)
Hyperthyroidism	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)

[a]IMAEs per Common Terminology Criteria for Adverse Events version 4.0 and Medical Dictionary for Regulatory Activities version 24.0.

[b]Defined as events considered potentially immune-mediated by the investigator, regardless of causality, that occurred within 100 days of the last dose, with no clear alternative etiology based on investigator assessment or with an immune-mediated component, and were treated with immune-modulating medication. Endocrine events were considered immune-mediated regardless of immune-modulating medication use, as they are often managed without immune-modulating medication.

versus chemotherapy alone in Japanese patients were consistent with findings in the global population and could have potentially contributed to the benefits in surgical outcomes.

In recent clinical trials evaluating treatments in the adjuvant setting in NSCLC, findings in Japanese patients were consistent with those in the respective global populations. In the phase III ADAURA trial, adjuvant osimertinib showed favorable DFS benefit versus placebo (HR 0.25; 95% CI, 0.14–0.44) in a subgroup of Japanese patients with completely resected *EGFR*-mutated stage II–IIIA NSCLC, consistent with the global population.[9,42] Additionally, an analysis of Japanese patients enrolled in the phase III IMpower010 study, which evaluated adjuvant atezolizumab versus best supportive care following platinum-based chemotherapy in patients with resected stage II–IIIA NSCLC, demonstrated a trend towards DFS improvement in patients with tumor PD-L1 expression ≥1%, consistent with the global population.[11,43] Long-term follow-up of ongoing phase III trials,[12,44–50] which includes enrollment of Japanese patients, assessing perioperative immunotherapy-based regimens will provide further insights into

new treatment algorithms for resectable NSCLC. Of note, preliminary data from the phase III AEGEAN study, which included Japanese patients, demonstrated a significant improvement in pCR with neoadjuvant durvalumab plus chemotherapy versus chemotherapy in patients with resectable NSCLC.[51]

This exploratory analysis of Japanese patients in CheckMate 816 was not powered to carry out statistical testing for differences between treatment arms. Additionally, interpretation and generalization of data were limited by a small sample size. At the data cut-off, overall survival data in the global population was immature, and long-term overall survival data are needed to fully establish the survival benefit of nivolumab plus chemotherapy in the Japanese subpopulation.

In conclusion, neoadjuvant nivolumab plus chemotherapy demonstrated longer EFS and a higher proportion of patients with pCR versus chemotherapy in the Japanese subpopulation of patients with resectable NSCLC in the CheckMate 816 study. The addition of nivolumab to chemotherapy did not impede feasibility of surgery and no new safety signals were observed with this combination. Consistent with findings in the global population, these data support the use of neoadjuvant nivolumab plus chemotherapy as an effective treatment option for Japanese patients with resectable NSCLC.

AUTHOR CONTRIBUTIONS

Tetsuya Mitsudomi: Data curation; investigation; writing – review and editing. **Hiroyuki Ito:** Data curation; investigation; writing – review and editing. **Morihito Okada:** Data curation; investigation; writing – review and editing. **Shunichi Sugawara:** Data curation; investigation; writing – review and editing. **Yutaka Shio:** Data curation; investigation; writing – review and editing. **Keisuke Tomii:** Data curation; investigation; writing – review and editing. **Jiro Okami:** Data curation; investigation; writing – review and editing. **Noriaki Sakakura:** Data curation; investigation; writing – review and editing. **Kaoru Kubota:** Data curation; investigation; writing – review and editing. **Kazuya Takamochi:** Data curation; investigation; writing – review and editing. **Shinji Atagi:** Data curation; investigation; writing – review and editing. **Masahiro Tsuboi:** Data curation; investigation; writing – review and editing. **Satoshi Oizumi:** Data curation; investigation; writing – review and editing. **Norihiko Ikeda:** Data curation; investigation; writing – review and editing. **Yasuhisa Ohde:** Data curation; investigation; writing – review and editing. **Ives Ntambwe:** Formal analysis; investigation; writing – review and editing. **Javed Mahmood:** Conceptualization; investigation; methodology; writing – review and editing. **Junliang Cai:** Conceptualization; investigation; methodology; writing – review and editing. **Fumihiro Tanaka:** Conceptualization; data curation; formal analysis; investigation; methodology; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

T. Mitsudomi is an Associate Editor of *Cancer Science*, received honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, MSD, and Ono Pharmaceutical, and received grants/research support from AstraZeneca, Boehringer Ingelheim, Bridge Bio, Chugai, and Ono Pharmaceutical. H. Ito received honoraria from Johnson & Johnson. M. Okada received honoraria from Bristol Myers Squibb and Ono Pharmaceutical, and received scholarship grants from Ono Pharmaceutical. S. Sugawara received honoraria from AstraZeneca, Bristol Myers Squibb, Chugai Pharma, MSD KK, and Ono Pharmaceutical, and received grants/research support from AbbVie, AnHeart, AstraZeneca, Bristol Myers Squibb, Chugai Pharma, Daiichi Sankyo, MSD KK, and Ono Pharmaceutical. K. Kubota received honoraria from Chugai Pharmaceuticals and Taiho Pharmaceutical. S. Atagi received grants/research support from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Eli Lilly, F. Hoffman-La Roche, MSD, Ono Pharmaceutical, Pfizer, and Taiho Pharmaceutical. M. Tsuboi acted in a consultancy or advisory role for AstraZeneca, Chugai Pharmaceutical, MSD, and Novartis, received honoraria from AstraZeneca, Bristol Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Johnson & Johnson Japan, Medtronic Japan, MSD, Novartis, Ono Pharmaceutical, Taiho Pharmaceutical, and Teijin Pharma, and received grants/research support from AstraZeneca, Bristol Myers Squibb, Eli Lilly Japan, MiRXES Japan, MSD, Novartis, and Ono Pharmaceutical. S. Oizumi received

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FUNDING INFORMATION

This study was funded by Bristol Myers Squibb.

ETHICS STATEMENT

Approval of the research protocol by an institutional reviewer board: The CheckMate 816 trial was conducted according to the principles of the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines. Independent ethics committees or institutional review boards at each participating center approved the protocol.

Informed consent: All patients provided written informed consent.

Registry and the registration no. of the study/trial: CheckMate 816 was registered at ClinicalTrials.gov, number NCT02998528.

Animal studies: N/A.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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