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ORIGINAL ARTICLE

First-line pembrolizumab vs chemotherapy in metastatic non-small-cell lung cancer: KEYNOTE-024 Japan subset*

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Abbreviations: AE, adverse event; BICR, blinded, independent, central radiologic review; CI, confidence interval; CR, complete response; HR, hazard ratio; NR, not reached; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; TPS, tumor proportion score.

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Abstract

This prespecified subanalysis of the global, randomized controlled phase III KEYNOTE-024 study of pembrolizumab vs chemotherapy in previously untreated metastatic non-small-cell lung cancer without *EGFR/ALK* alterations and a programmed death-ligand 1 (PD-L1) tumor proportion score of 50% or greater evaluated clinical outcomes among patients enrolled in Japan. Treatment consisted of pembrolizumab 200 mg every 3 weeks (35 cycles) or platinum-based chemotherapy (four to six cycles). The primary end-point was progression-free survival; secondary end-points included overall survival and safety. Of 305 patients randomized in KEYNOTE-024 overall, 40 patients were enrolled in Japan (all received treatment: pembrolizumab, n = 21; chemotherapy, n = 19). The hazard ratio (HR) for progression-free survival by independent central review (data cut-off date, 10 July 2017) was 0.25 (95% confidence interval [CI], 0.10-0.64; one-sided, nominal $P = .001$). The HR for overall survival (data cut-off date, 15 February 2019) was 0.39 (95% CI, 0.17-0.91; one-sided, nominal $P = .012$). Treatment-related adverse events occurred in 21/21 (100%) pembrolizumab-treated and 18/19 (95%) chemotherapy-treated patients; eight patients (38%) and nine patients (47%), respectively, had grade 3-5 events. Immune-mediated adverse events and infusion reactions occurred in 11 patients (52%) and four patients (21%), respectively; four patients (19%) and one patient (5%), respectively, had grade 3-5 events. Consistent with results from KEYNOTE-024 overall, first-line pembrolizumab improved progression-free survival and overall survival vs chemotherapy with manageable safety among Japanese patients with metastatic non-small-cell lung cancer without *EGFR/ALK* alterations and a PD-L1 tumor proportion score of 50% or greater. The trial is registered with ClinicalTrials.gov: NCT02142738.

KEYWORDS
Japan, non-small-cell lung carcinoma, PD-L1 protein, pembrolizumab, treatment outcome

1 | INTRODUCTION

A previous version of this article was published in *Cancer Science* (Satouchi et al *Cancer Sci* 2020;111:4480-4489)[1] and subsequently retracted by agreement between the authors and the journal because the required corrections were too numerous and extensive. This article is a revised version of the original article and reflects the different tumor response assessment data available at the time of this analysis. Progression-free survival and objective response data that were originally reported by BICR with a data cut-off date of 15 February 2019, have been corrected and updated in this article to be associated with a data cut-off date of 10 July 2017, because evaluation by BICR was discontinued after the second interim analysis (per protocol amendment 8). Additionally, PFS data are now reported per investigator review with a data cut-off date of 15 February 2019. These corrections and updates have been made in the text as well as in the figures: the PFS Kaplan-Meier curve has been replaced with two curves with data by BICR with a data cut-off date of 10 July 2017 (Figure 2A) and by investigator review with a data cut-off date of 15 February 2019 (Figure 2B). Figure 3 has been updated with data by investigator review with a data cut-off date of 15 February 2019.

Lung cancer is the leading cause of cancer-related deaths worldwide[2] and represents approximately 20% of all cancer-related deaths in Japan.[3] Platinum-based chemotherapy has historically been the standard first-line treatment for patients with advanced-stage NSCLC, particularly those without targetable *EGFR* or *ALK* alterations[4-6]; however, immunotherapy directed at the PD-1 checkpoint pathway has more recently provided patients with a therapeutic option that can improve clinical outcomes over standard chemotherapy regimens.[7] The most recent updates to lung cancer clinical practice guidelines in Japan now recommend the anti-PD-1 immunotherapy pembrolizumab as first-line treatment in patients with metastatic NSCLC without targetable gene alterations and a PD-L1 TPS of 50% or greater.[8]

Pembrolizumab is a humanized IgG4 mAb that blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2, thereby promoting cytotoxic T cell-mediated antitumor responses.[9] The phase I KEYNOTE-001 trial was the first study to show an association between PD-L1 expression and response to pembrolizumab, showing a higher response rate among patients with advanced NSCLC and a PD-L1 TPS of 50% or greater.[10] The global phase III KEYNOTE-024 study subsequently found that patients with previously untreated metastatic NSCLC without *EGFR* mutations or *ALK* translocations and a PD-L1 TPS of 50% or greater had significantly longer OS (HR, 0.60; 95% CI, 0.41-0.89; P =.005) and favorable safety outcomes with pembrolizumab vs platinum-based chemotherapy.[11] A recent updated analysis from KEYNOTE-024 showed that pembrolizumab continued to prolong OS compared with chemotherapy with longer follow-up (HR for OS, 0.63; 95% CI, 0.47-0.86; nominal P =.002), despite an increase in the number of patients who crossed over from chemotherapy to pembrolizumab (82 patients vs 66 patients who crossed over to pembrolizumab on study in the previous analysis).[12]

Previous analyses from registry data and clinical trials of anticancer therapies for NSCLC suggest that Asian patients might have better survival outcomes than non-Asian patients.[13,14] Here we report results from patients enrolled in the KEYNOTE-024 study in Japan.[11]

2 | MATERIALS AND METHODS

2.1 | Patients

Eligibility criteria for enrollment in the KEYNOTE-024 study have been previously published[11]; this subanalysis included patients enrolled in KEYNOTE-024 from 23 sites in Japan. In short, adult patients aged 18 years or older were eligible if they had previously untreated stage IV NSCLC without activating *EGFR* mutations or *ALK* translocations, a PD-L1 TPS of 50% or higher, measurable disease based on RECIST version 1.1, and an ECOG performance status of 0 or 1. For evaluation of PD-L1 status, patients must have provided a tumor tissue sample obtained at the time of or after diagnosis of metastatic disease and before any adjuvant or neoadjuvant therapy. Patients were ineligible if they had untreated brain metastases, active autoimmune disease that required systemic treatment, had received systemic steroid therapy within 3 days before the first dose of study medication or were receiving any other immunosuppressive medication, or had interstitial lung disease or a history of pneumonitis that required steroid treatment.

All patients provided written informed consent before enrollment. The trial protocol and all amendments were approved by an institutional review board or independent ethics committee at each study site, and the trial was carried out in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

2.2 | Study design

This was a prespecified subanalysis of the phase III, open-label, randomized KEYNOTE-024 study (ClinicalTrials.gov identifier, NCT02142738). As described previously,[11] patients were randomly assigned in a 1:1 ratio to receive either pembrolizumab 200 mg i.v. every 3 weeks for up to 35 cycles or the investigator's choice of one of the following five platinum-based chemotherapy regimens, selected before randomization, for four to six cycles: carboplatin or cisplatin plus pemetrexed, carboplatin or cisplatin plus gemcitabine, or carboplatin plus paclitaxel. Pemetrexed-containing regimens were permitted only for patients with nonsquamous tumors, and pemetrexed maintenance therapy could continue after the combination chemotherapy regimen was completed. Randomization was stratified by ECOG performance status (0 vs 1) and tumor histology (squamous vs nonsquamous). Treatment continued for the prespecified number of cycles or until radiologic disease progression per RECIST version 1.1 by investigator review, unacceptable toxicity, concurrent illness precluding further treatment, or a decision was made by the patient or the investigator to withdraw treatment. Crossover from chemotherapy to pembrolizumab was permitted for patients with documented disease progression (per RECIST version 1.1 by BICR) who met safety criteria. Patients in either treatment arm who were considered to be deriving clinical benefit and were clinically stable (ie, no signs or symptoms of clinically significant disease progression, no rapid disease progression or progressive tumor requiring urgent alternative treatment, and no decline in ECOG performance status) could continue to receive treatment after disease progression. Patients in the pembrolizumab arm who achieved a complete response could discontinue treatment if they had been treated for 6 months or more and had received at least two treatments beyond the initial date of complete response.[11] Patients who stopped pembrolizumab after a complete response or after completing 2 years (35 cycles) of pembrolizumab and subsequently had disease progression could receive a second course of pembrolizumab for up to 17 cycles if they had received no other anticancer therapy since the last pembrolizumab dose and continued to meet the required eligibility criteria.

2.3 | Endpoints

The end-points in this preplanned subgroup analysis of patients enrolled in KEYNOTE-024 in Japan were the same as for the overall study. The primary end-point in the KEYNOTE-024 study was PFS, defined as the time from randomization to the first of either documented disease progression (per RECIST version 1.1 by BICR) or death from any cause. Evaluation by BICR was discontinued after the second interim analysis (protocol amendment 8); therefore, PFS is reported by BICR with a data cut-off date of 10 July 2017, and additionally by investigator review with a data cut-off date of

15 February 2019. Secondary end-points were OS (defined as the time from randomization to death from any cause), ORR (defined as the proportion of patients with a confirmed complete or partial response), and safety. Objective response data are reported per RECIST version 1.1 by investigator review with a data cut-off date of 15 February 2019. Duration of response was an exploratory end-point, and was defined as the time from the first documentation of a complete or partial response to disease progression.[11]

2.4 | Assessments

A central laboratory assessed PD-L1 expression in formalin-fixed tumor samples obtained through core-needle or excisional biopsy or from tissue resected at the time of or after diagnosis of metastatic disease from a site not previously irradiated using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies).[15] Computed tomography (preferred) or MRI was carried out every 9 weeks, with tumor response assessed per RECIST version 1.1 by BICR and by investigator assessment. After the end of treatment, patients were monitored for disease status every 3 months until disease progression, initiation of new anticancer therapy, withdrawal of consent, loss to follow-up, or death; once imaging assessments were stopped (ie, for progressive disease or for starting a new anticancer therapy) survival follow-up was undertaken approximately every 2 months until death or withdrawal of consent. Safety was monitored throughout the study and for 30 days or more after treatment discontinuation (90 days for serious AEs and AEs of interest). All AEs were graded in severity per the NCI's Common Terminology Criteria for Adverse Events version 4.0.

2.5 | Statistical analysis

Statistical methods for this subanalysis of the KEYNOTE-024 study were the same as those of the primary analysis,[11] except that only those patients enrolled in Japan were included. Efficacy analyses included all randomized patients, according to the treatment assigned (intention-to-treat population); safety analyses included all patients who received at least one dose of treatment, according to the treatment received. Both PFS and OS were estimated using the Kaplan-Meier method. For the analysis of PFS, patients who were alive without disease progression and had not initiated new anticancer therapy or who were lost to follow-up were censored at the time of last tumor assessment. For the analysis of OS, patients without documented death were censored at the time of last follow-up. Between-group differences in PFS and OS were assessed using a stratified log-rank test. Hazard ratios and associated 95% CIs were assessed using a stratified Cox proportional hazards model with Efron's method of handling ties. The stratified Miettinen and Nurminen method was used to assess treatment differences in ORR; patients with missing data were considered nonresponders. Stratification factors used for randomization were also applied to the analyses. One-sided nominal *P* values are provided for this subanalysis. The data cut-off date for response data by BICR was 10 July 2017; for all other data for this analysis, the cut-off date was 15 February 2019.

3 | RESULTS

3.1 | Patients and treatment

Among 305 patients randomized in the overall KEYNOTE-024 study population (pembrolizumab, n = 154; chemotherapy, n = 151),[11] 40 patients were randomized at Japanese sites (pembrolizumab, n = 21; chemotherapy, n = 19; Figure 1) between November 2014 and October 2015, all of whom received treatment as assigned. In the chemotherapy arm, 10 patients crossed over to pembrolizumab on study (53%) and an additional three patients received anti-PD-1 treatment outside of crossover, for an effective crossover rate of 68% in the intention-to-treat population. Of patients initially allocated to pembrolizumab, eight patients (38%) received subsequent platinum-based chemotherapy.

Patient demographic and baseline clinical characteristics were generally well balanced between the treatment arms (Table 1). Most patients had nonsquamous tumors (86% in the pembrolizumab arm and 95% in the chemotherapy arm) and were former or current smokers (95% and 100%, respectively). Median treatment exposure as of the data cut-off date (15 February 2019) was 13.1 months (range, 0.03-47.6 months) in the pembrolizumab arm and 3.5 months (range, 0.03-11.8 months) in the chemotherapy arm, and the median time from randomization to data cut-off was 43.3 months (range, 40.7-50.5 months).

3.2 | Efficacy outcomes

As of 10 July 2017 and per BICR, a total of 24 PFS events occurred among the 40 patients enrolled in Japan, with only eight of them occurring in the pembrolizumab arm. The median PFS was not reached (95% CI, 4.2 months–NR) with pembrolizumab and was 4.1 (95% CI, 2.8-8.3) months with chemotherapy (HR, 0.25; 95% CI, 0.10-0.64; one-sided, nominal P =.001; Figure 2A). In addition, the estimated PFS rate at 1 year was higher in the pembrolizumab arm (64% [95% CI, 39%–81%]) vs the chemotherapy arm (24% [95% CI, 7%–46%]).

At the data cut-off date of 15 February 2019 and per investigator review, a total of 35 PFS events occurred among the 40 patients enrolled in Japan (pembrolizumab, 16; chemotherapy, 19). The median PFS was 14.6 (95% CI, 6.1-41.6) months with pembrolizumab and was 4.1 (95% CI, 2.2-6.3) months with chemotherapy (HR, 0.22; 95% CI, 0.10-0.49; one-sided, nominal P <.001; Figure 2B). In addition, the estimated PFS rate at 1 year was higher in the pembrolizumab arm (52% [95% CI, 30%–71%]) vs the chemotherapy arm (5% [95% CI, 0%–21%]).

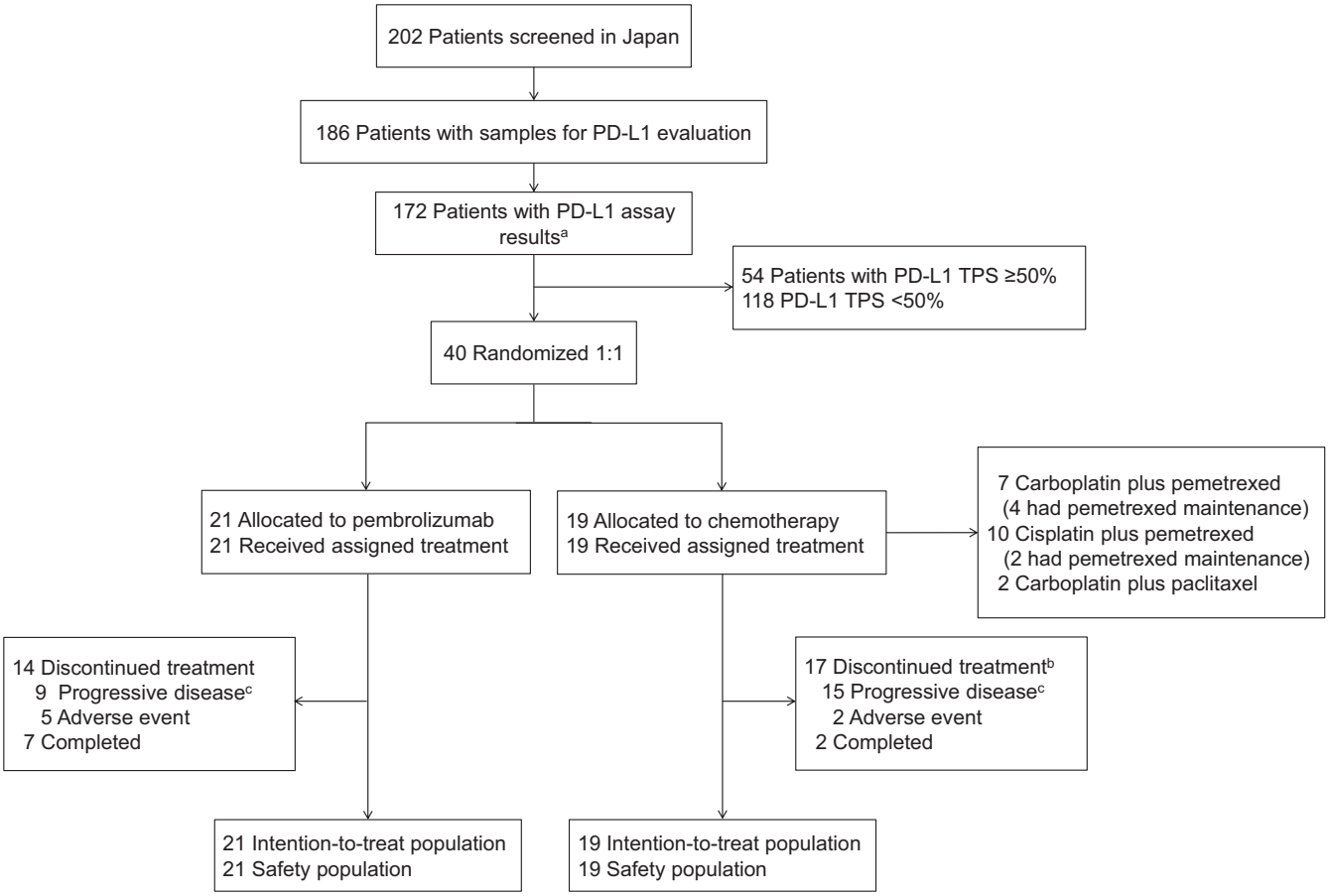

FIGURE 1 CONSORT flow diagram of recruitment of the Japan subset of patients with previously untreated metastatic non-small-cell lung cancer in the KEYNOTE-024 study of pembrolizumab vs chemotherapy. [a]The remaining patients did not meet study eligibility criteria (n = 14). [b]Includes 10 patients who crossed over to pembrolizumab treatment during the study. [c]Includes clinical progression. PD-L1, programmed death-ligand 1; TPS, tumor proportion score

TABLE 1 Demographic and baseline clinical characteristics of Japanese patients enrolled in the KEYNOTE-024 study subset

Characteristic	Pembrolizumab (n = 21) n (%)[a]	Chemotherapy (n = 19) n (%)[a]
Age (y)		
Median	66	67
Range	40-80	53-77
Male sex	16 (76)	18 (95)
ECOG performance status		
0	7 (33)	8 (42)
1	14 (67)	11 (58)
Smoking status		
Former/current	20 (95)	19 (100)
Never	1 (5)	0 (0)
Histology		
Squamous	3 (14)	1 (5)
Nonsquamous	18 (86)	18 (95)
Brain metastases	1 (5)	1 (5)
Prior neoadjuvant therapy	0 (0)	0 (0)
Prior adjuvant therapy	0 (0)	0 (0)

[a]Data are n (%), unless otherwise noted.

As of 15 February 2019, approximately half of the patients had died (pembrolizumab arm, n = 9; chemotherapy arm, n = 14). Overall survival was longer with pembrolizumab than with chemotherapy. Median OS was not reached in the pembrolizumab arm (22.9–NR) and was 21.5 months (95% CI, 5.2-35.0) in the chemotherapy arm (HR for OS, 0.39; 95% CI, 0.17-0.91; one-sided, nominal P =.012; Figure 2C). The estimated OS rates in the pembrolizumab arm vs the chemotherapy arm were 86% (95% CI, 62%-95%) vs 63% (95% CI, 38%-80%) at 1 year, 71% (95% CI, 47%-86%) vs 37% (95% CI, 17%-58%) at 2 years, and 67% (95% CI, 43%-83%) vs 26% (95% CI, 10%-47%) at 3 years.

The ORR by investigator review (data cut-off date, 15 February 2019) was 67% (95% CI, 43%-85%) in the pembrolizumab arm and 32% (95% CI, 13%-57%) in the chemotherapy arm (one-sided, nominal P =.014). The median duration of response was 29.1 (range, 4.2-39.5) months in the pembrolizumab arm and 6.4 (range, 3.1-10.4) months in the chemotherapy arm. Among patients in the pembrolizumab arm who had a response (n = 14; all partial responses), seven patients had completed 35 cycles (2 years) of treatment at the time of data cut-off (Figure 3). Of these seven patients, three received a second course of pembrolizumab (one completed 17 cycles and two discontinued due to PD; all three remained alive at the data cut-off of 15 February 2019).

3.3 | Safety

Treatment-related AEs of any grade occurred in all 21 patients treated with pembrolizumab and 18 of the 19 patients (95%) treated with chemotherapy in this Japanese cohort (Table 2). The most common treatment-related AEs in the pembrolizumab arm were pyrexia (n = 5), diarrhea (n = 4), and rash (n = 4), and the most common in the chemotherapy arm were decreased appetite (n = 12), nausea (n = 11), and anemia (n = 9). Treatment-related AEs of grade 3-5 occurred in eight patients (38%) in the pembrolizumab arm and nine patients

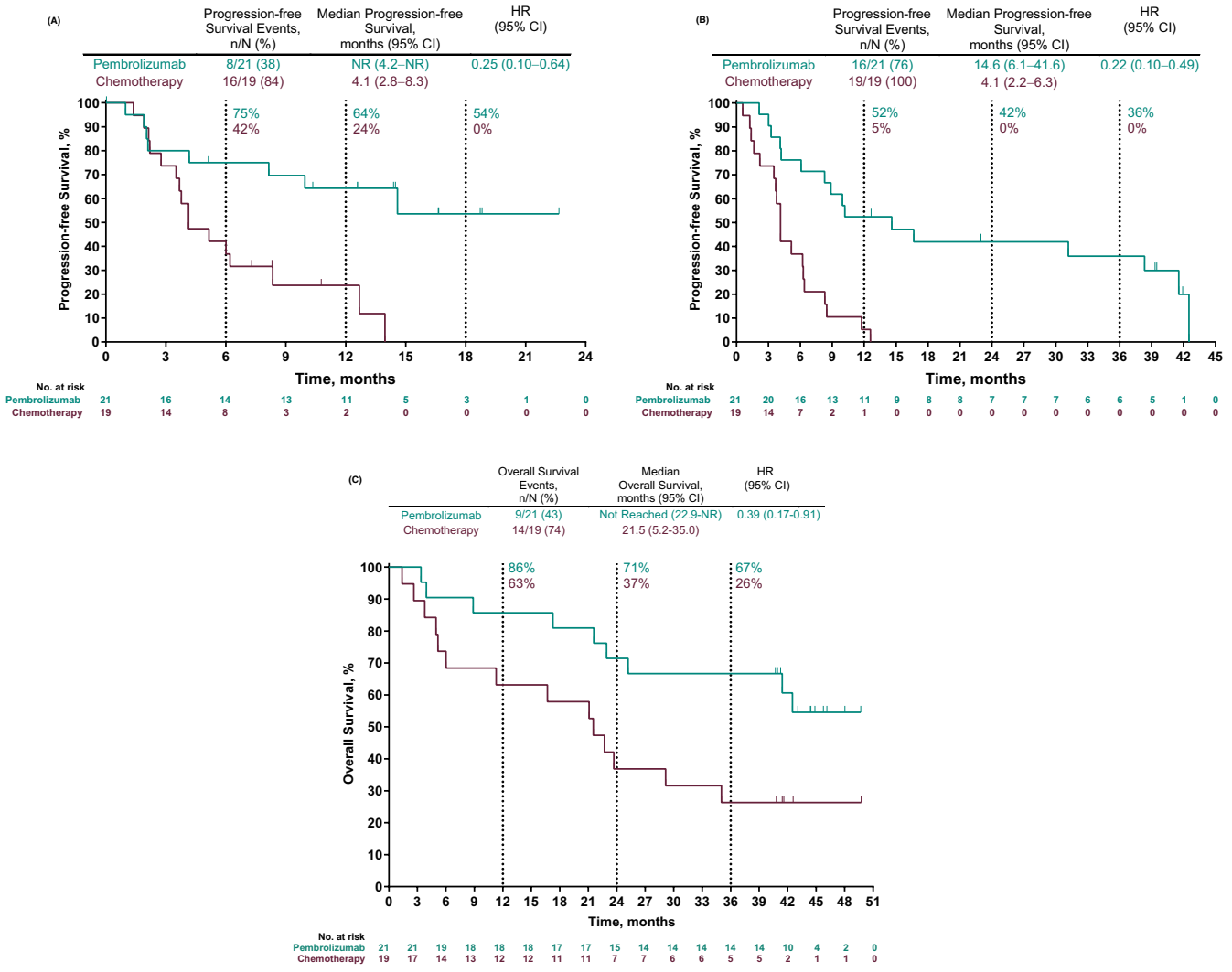

FIGURE 2 Kaplan-Meier estimates of (A) progression-free survival (PFS) per RECIST version 1.1 per independent central review (data cut-off date, 10 July 2017), (B) PFS per RECIST version 1.1 per investigator review (data cut-off date, 15 February 2019), and (C) overall survival (OS) in the subset of patients with previously untreated metastatic non-small-cell lung cancer in the KEYNOTE-024 study of pembrolizumab vs chemotherapy. CI, confidence interval; HR, hazard ratio; NR, not reached.

(47%) in the chemotherapy arm. Four patients (19%) in the pembrolizumab arm and one patient (5%) in the chemotherapy arm discontinued treatment because of treatment-related AEs. No patient in the pembrolizumab arm and one patient (5%) in the chemotherapy arm died due to a treatment-related AE. Immune-mediated AEs and infusion reactions of any grade, and regardless of relationship to treatment as assessed by the investigator, occurred in 11 patients (52%) in the pembrolizumab arm and in four patients (21%) in the chemotherapy arm (Table 2). The most common events in the pembrolizumab arm (occurring in at least 10% of patients) were infusion reactions (n = 4; 19%), and pneumonitis and hypothyroidism (each n = 3; 14%). Grade 3-5 immune-mediated AEs occurred in four patients (19%) in the pembrolizumab arm (grade 3 hepatitis, severe skin reaction, and uveitis, and grade 4 pneumonitis, all in one patient each) and one patient (5%) in the chemotherapy arm (grade 3 pneumonitis).

4 | DISCUSSION

This prespecified subanalysis of KEYNOTE-024 showed that pembrolizumab prolonged PFS over platinum-based chemotherapy (HR for disease progression or death: by BICR, 0.25 [one-sided, nominal P =.001]; by investigator review, 0.22 [one-sided, nominal P <.001]) among patients enrolled in Japan with previously untreated metastatic NSCLC without targetable *EGFR/ALK* alterations and a PD-L1 TPS of 50% or greater. In addition, pembrolizumab prolonged OS over chemotherapy (HR for death, 0.39; one-sided, nominal P =.012). With few OS events occurring in the pembrolizumab arm, median OS was not reached. Treatment with pembrolizumab was associated with a higher ORR compared with chemotherapy (67% vs 32%). In addition, pembrolizumab had a manageable safety profile, and no new safety signals were identified in this subset of Japanese patients relative to previous studies evaluating pembrolizumab monotherapy in patients with advanced NSCLC.[10,11,16]

The favorable efficacy observed with pembrolizumab in this subanalysis among patients in KEYNOTE-024 enrolled in Japan is consistent with the significantly longer PFS (HR, 0.50; P <.001) and OS (HR, 0.60; P =.005) observed with pembrolizumab vs chemotherapy in the overall study population,[10,11,16] with somewhat lower HRs for PFS (0.25 by BICR; 0.22 by investigator review) and OS (0.39) in the current analysis. Although the reason for these lower HRs is uncertain, several factors may have contributed, including potential

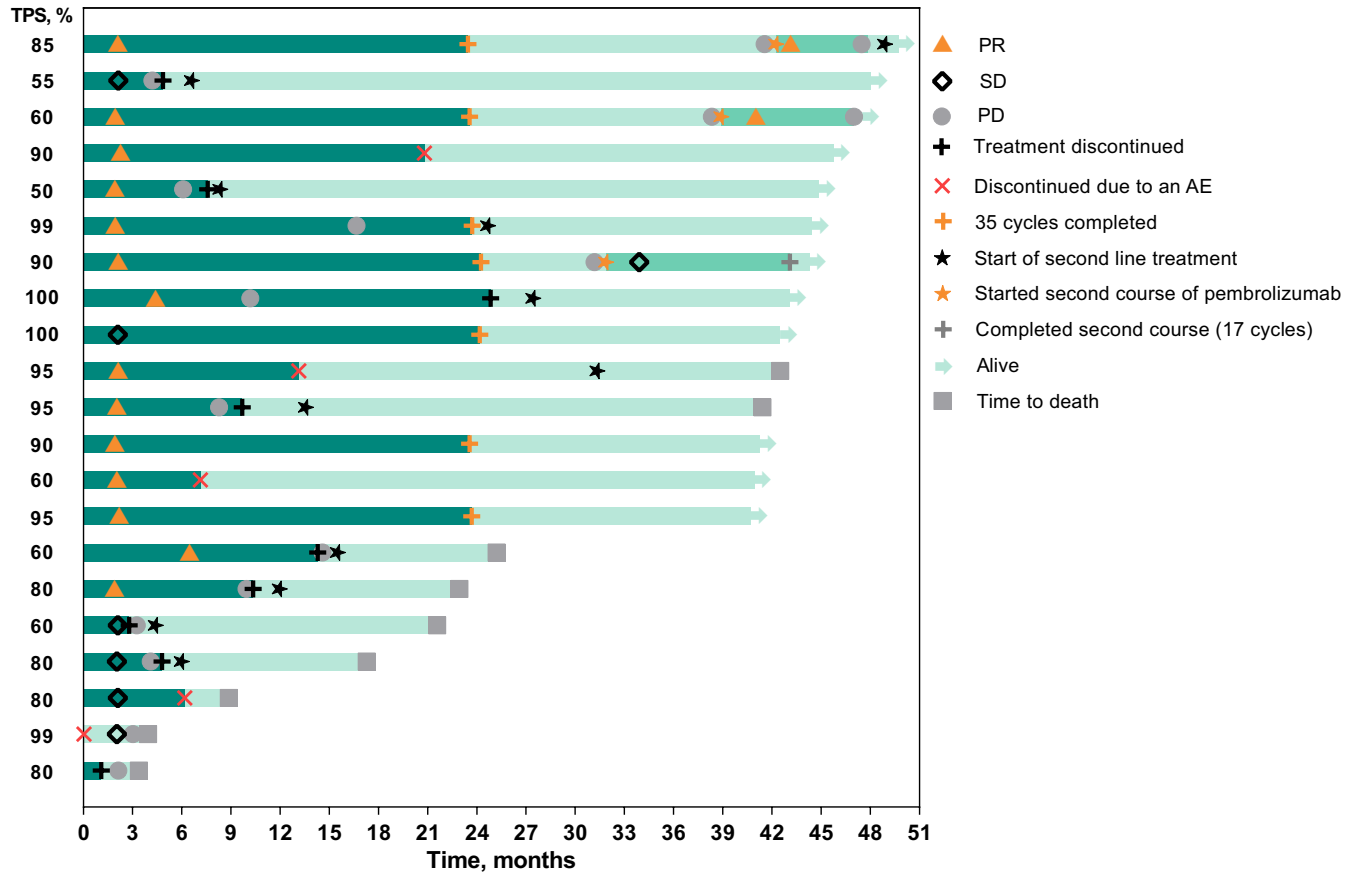

FIGURE 3 Duration of treatment and time to response among patients in the pembrolizumab arm of the KEYNOTE-024 study with an objective response (ie, complete response or partial response [PR]) per RECIST version 1.1 by investigator review (data cut-off, date 15 February 2019). Bar lengths indicate duration of treatment (first course, dark green; second course, medium green) and months of follow-up (light green). Tumor response (ie, PR, stable disease [SD], and progressive disease [PD]) is expressed per RECIST version 1.1 by investigator review only. AE, adverse event; PD–L1, programmed death-ligand 1; TPS, tumor proportion score

TABLE 2 Summary of adverse events (AEs) among patients from Japan in the as-treated population of the KEYNOTE-024 study[a]

	Pembrolizumab (n = 21)		Chemotherapy (n = 19)	
Treatment-related AEs[b]	**n (%)**		**n (%)**	
Any grade	21 (100)		18 (95)	
Grade 3-5	8 (38)		9 (47)	
Led to discontinuation[c]	4 (19)		1 (5)	
Led to death	0 (0)		1 (5)	
Treatment-related AEs[b] occurring in ≥15% of patients in either arm	**Any grade** **n (%)**	**Grade 3-5** **n (%)**	**Any grade** **n (%)**	**Grade 3-5** **n (%)**
Pyrexia	5 (24)	0 (0)	2 (11)	0 (0)
Diarrhea	4 (19)	1 (5)	3 (16)	0 (0)
Rash	4 (19)	0 (0)	0 (0)	0 (0)
Decreased appetite	3 (14)	0 (0)	12 (63)	2 (11)
Anemia	2 (10)	1 (5)	9 (47)	5 (26)
Malaise	2 (10)	0 (0)	8 (42)	0 (0)
Hypoalbuminemia	2 (10)	2 (10)	4 (21)	2 (11)
Hiccups	1 (5)	0 (0)	6 (32)	0 (0)
Constipation	1 (5)	0 (0)	5 (26)	0 (0)
Peripheral sensory neuropathy	1 (5)	0 (0)	3 (16)	0 (0)
Nausea	0 (0)	0 (0)	11 (58)	0 (0)
Platelet count decreased	0 (0)	0 (0)	8 (42)	3 (16)
White blood cell count decreased	0 (0)	0 (0)	8 (42)	1 (5)
Neutrophil count decreased	0 (0)	0 (0)	4 (21)	1 (5)
Immune-mediated AEs and infusion reactions[d]	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any	11 (52)	4 (19)	4 (21)	1 (5)
Infusion reactions	4 (19)	0 (0)	1 (5)	0 (0)
Pneumonitis	3 (14)	1 (5)	1 (5)	1 (5)
Hypothyroidism	3 (14)	0 (0)	2 (11)	0 (0)
Colitis	1 (5)	0 (0)	0 (0)	0 (0)
Hepatitis	1 (5)	1 (5)	0 (0)	0 (0)
Hyperthyroidism	1 (5)	0 (0)	0 (0)	0 (0)
Severe skin reactions	1 (5)	1 (5)	0 (0)	0 (0)
Thyroiditis	1 (5)	0 (0)	0 (0)	0 (0)
Uveitis	1 (5)	1 (5)	0 (0)	0 (0)
Adrenal insufficiency	0 (0)	0 (0)	1 (5)	0 (0)

[a]The as-treated population comprised all randomized patients who received at least one dose of study treatment, according to the treatment received.

[b]AEs that were attributed to treatment by the investigator are listed.

[c]Treatment-related AEs that led to discontinuation were: pneumonitis (n = 2), fatigue (n = 1), and uveitis (n = 1) among four patients in the pembrolizumab group; and hypoxia (n = 1) and pulmonary alveolar hemorrhage (resulting in death) in one patient in the chemotherapy group.

[d]Immune-mediated AEs and infusion reactions are listed irrespective of attribution to study treatment by the investigator.

differences in baseline characteristics, patient care practices in Japan, or in treatment responses between Japanese and non-Asian populations.[14,17] The smaller number of patients in this subgroup analysis and few PFS (by BICR) and OS events in either treatment arm could have also contributed. Notably, the positive results from the current analysis are consistent with the positive findings in the large, multicenter, randomized controlled phase III KEYNOTE-042 study as well.[18] Similar to results from the overall KEYNOTE-024 study noted above, KEYNOTE-042 showed an OS benefit with pembrolizumab vs platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic NSCLC without *EGFR* or *ALK* alterations and a PD-L1 TPS of 50% or greater (HR,

0.69; P =.0003); and additionally showed OS benefit in the overall population with PD-L1 TPS of 1% or greater (HR, 0.81; P =.0018).[18] Together, these findings provide support for the use of pembrolizumab monotherapy as first-line treatment for PD-L1-positive (TPS ≥1%) advanced NSCLC, which has received regulatory approval in Japan.[19] Significant OS benefit has also been shown with pembrolizumab plus platinum-based chemotherapy vs chemotherapy alone in patients with previously untreated metastatic NSCLC without *EGFR* or *ALK* alterations, irrespective of PD-L1 expression, in the phase III placebo-controlled studies KEYNOTE-189 (nonsquamous; HR, 0.49; P <.001) and KEYNOTE-407 (squamous; HR, 0.64; P <.001).[20,21]

Importantly, the OS benefits with pembrolizumab monotherapy over chemotherapy among patients in this subanalysis and in the global KEYNOTE-024 study were observed despite relatively high crossover rates (53% in the current analysis and 44% in the primary analysis of the global study).[11] Moreover, the effective crossover rate of 68% in the current analysis (after accounting for patients in the chemotherapy arm who received anti-PD-1/PD-L1 therapy outside of on-study crossover) was similar to the effective crossover rate in the most recent updated analysis from the KEYNOTE-024 global study (65%), which continued to show an OS benefit with pembrolizumab (HR, 0.63; P =.002), further supporting the efficacy gains with pembrolizumab.[12]

With a median treatment exposure of 13.1 (range, 0.03-47.6) months in this subanalysis compared with 7 (range, 0.03-18.7) months) in the primary analysis of the KEYNOTE-024 study,[11] there were no additional safety concerns identified, supporting the tolerability of pembrolizumab in Japanese patients with metastatic NSCLC. In addition, the immune-mediated AEs and infusion reactions that occurred with pembrolizumab among the patients included in this subanalysis were consistent with those observed in previous clinical trials evaluating pembrolizumab monotherapy in advanced NSCLC,[10,11,16] with few events of grade 3 or greater—a finding that is of particular clinical relevance, as monitoring for these events is necessary in practice.

Key limitations of this subanalysis are that no alpha was allocated, and because the data represent a subset of patients from the global KEYNOTE-024 study, the sample size was smaller (40 patients of 305 who were randomized in the global study). Accordingly, with fewer patients, fewer events of PFS (by BICR) and OS occurred, as noted above. However, despite the limited power of this analysis, the HRs for these end-points suggested substantial PFS and OS benefits with pembrolizumab over chemotherapy. Importantly, these results provide support for the efficacy and safety of pembrolizumab in Japanese patients with advanced NSCLC.

In conclusion, this subanalysis among patients enrolled in KEYNOTE-024 in Japan demonstrated the efficacy and safety benefits of pembrolizumab vs platinum-based chemotherapy, as also observed in the primary analysis. These findings provide further support for the use of pembrolizumab monotherapy as first-line treatment in patients from Japan with metastatic NSCLC without activating *EGFR* mutations or *ALK* translocations and a PD-L1 TPS of 50% or greater.

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DATA AVAILABILITY STATEMENT

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the United States and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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