Received: 29 March 2022 | Revised: 13 February 2023 | Accepted: 15 February 2023

DOI: 10.1002/ijc.34532

CANCER THERAPY AND PREVENTION

IJC INTERNATIONAL JOURNAL of CANCER

KEYNOTE-033: Randomized phase 3 study of pembrolizumab vs docetaxel in previously treated, PD-L1-positive, advanced NSCLC

Shengxiang Ren[1] | Jifeng Feng[2] | Shenglin Ma[3] | HuaJun Chen[4] | Zhiyong Ma[5] | Cheng Huang[6] | Li Zhang[7] | Jianxing He[8] | Changli Wang[9] | Jianying Zhou[10] | Pongwut Danchaivijitr[11] | Chin-Chou Wang[12] | Ihor Vynnychenko[13] | Kai Wang[14] | Francisco Orlandi[15] | Virote Sriuranpong[16] | Ben Li[17] | Jun Ge[18] | Thao Dang[19] | Caicun Zhou[1]

[1]Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

[2]Oncology Department, Jiangsu Cancer Hospital, Nanjing, China

[3]Department of Thoracic Oncology, Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Zhejiang University Cancer Center, Zhejiang, People's Republic of China

[4]Guangdong Provincial People's Hospital, Guangdong Lung Cancer Institute, Guangzhou, China

[5]Medical Oncology, The Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital, Zhengzhou, China

[6]Department of Pneumology, Fujian Provincial Cancer Hospital, Fuzhou, China

[7]Cancer Center, Sun Yat-Sen University, Guangzhou, China

[8]Department of Thoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

[9]Department of Biotherapy 17F, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China

[10]Department of Respiratory Medicine, The First Affiliated Hospital of Zhejiang University College of Medicine, Hangzhou, China

[11]Division of Medical Oncology, Siriraj Hospital, Bangkok, Thailand

[12]Chang Gung Medical Foundation, Kaohsiung, Taiwan

[13]RMI Sumy Regional Clinical Oncology Dispensary, Sumy State University, Sumy, Ukraine

[14]Department of Respiration Medicine, The Second Affiliated Hospital of Zhejiang University College of Medicine, Hangzhou, China

[15]Region Metropolitana de Santiago, Orlandi Oncologia, Providencia, Chile

[16]Medical Oncology Unit, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

[17]MSD China, Beijing, China

[18]MSD China, Shanghai, China

[19]Merck & Co., Inc., Rahway, NJ, USA

Abbreviations: AE, adverse event; BICR, blinded-independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mo, month; 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; PD-L2, programmed death-ligand 2; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TPS, tumor proportion score.

Shengxiang Ren, Jifeng Feng and Shenglin Ma contributed equally to our study.

Prior presentation: Results from our study were presented in part at the ESMO Virtual Congress 2020 (19-21 September 2020; abstract 1262P).

Correspondence
Caicun Zhou, Shanghai Pulmonary Hospital, Tongji University School of Medicine, No. 507 Zhengmin Road, Shanghai 200 443, China.
Email: caicunzhoudr@tongji.edu.cn

Funding information
Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ

Abstract

KEYNOTE-033 (NCT02864394) was a multicountry, open-label, phase 3 study that compared pembrolizumab vs docetaxel in previously treated, programmed death-ligand 1 (PD-L1)-positive, advanced non-small cell lung cancer (NSCLC), with most patients enrolled in mainland China. Eligible patients were randomized (1:1) to pembrolizumab 2 mg/kg or docetaxel 75 mg/m^2 every 3 weeks. Primary endpoints were overall survival (OS) and progression-free survival and were evaluated sequentially using stratified log-rank tests, first in patients with PD-L1 tumor proportion score (TPS) ≥50% and then in patients with PD-L1 TPS ≥1% (significance threshold: $P < .025$, one-sided). A total of 425 patients were randomized to pembrolizumab (N = 213) or docetaxel (N = 212) between 8 September 2016 and 17 October 2018. In patients with a PD-L1 TPS ≥50% (n = 227), median OS was 12.3 months with pembrolizumab and 10.9 months with docetaxel; the hazard ratio (HR) was 0.83 (95% confidence interval [CI]: 0.61-1.14; $P = .1276$). Because the significance threshold was not met, sequential testing of OS and PFS was ceased. In patients with a PD-L1 TPS ≥1%, the HR for OS for pembrolizumab vs docetaxel was 0.75 (95% CI: 0.60-0.95). In patients from mainland China (n = 311) with a PD-L1 TPS ≥1%, HR for OS was 0.68 (95% CI: 0.51-0.89). Incidence of grade 3 to 5 treatment-related AEs was 11.3% with pembrolizumab vs 47.5% with docetaxel. In summary, pembrolizumab improved OS vs docetaxel in previously treated, PD-L1-positive NSCLC without unexpected safety signals; although the statistical significance threshold was not reached, the numerical improvement is consistent with that previously observed for pembrolizumab in previously treated, advanced NSCLC.

KEYWORDS
immunotherapy, NSCLC, pembrolizumab, programmed death 1, programmed death-ligand 1

What's new?

In the phase 2/3 KEYNOTE-010 study, pembrolizumab significantly improved overall survival compared to docetaxel in patients with previously treated advanced non-small cell lung cancer with PD-L1 tumor proportion scores ≥50% and ≥1%. Here, the authors report outcomes from the randomized phase 3 KEYNOTE-033 study that compared pembrolizumab vs docetaxel with most patients enrolled in mainland China. Although there was a numerical improvement in overall survival with pembrolizumab compared with docetaxel, the statistical signficance threshold was not met. The numerical improvement was consistent with previous observations in patients with previously treated, PD-L1-positive non-small cell lung cancer. There were no unexpected safety signals.

1 | INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide.[1] The estimated global incidence of lung cancer in 2018 was 2.1 million, with an associated 1.8 million deaths.[2] The highest incidence rates of lung cancer are observed in Micronesia/Polynesia, Eastern Europe and Eastern Asia, including China.[2] NSCLC represents ~80% to 85% of all lung cancers.[3] At the time of diagnosis, most patients with lung cancer have locally advanced or metastatic disease that is not amenable to surgical resection. Among patients with metastatic lung cancer, the 5-year relative survival rate is only 6%.[4]

Immunotherapy represents a new treatment paradigm for NSCLC, and targeting the PD-1 pathway has demonstrated promising clinical benefits.[5-10] Pembrolizumab, a humanized monoclonal antibody against PD-1 that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2,[11,12] has shown significant OS benefit in both treatment-naive and previously treated NSCLC.[7,8,13] In 2019, pembrolizumab was approved as the first anti-PD-1 monotherapy in the first-line setting for NSCLC in China based on the OS findings from the

phase 3 KEYNOTE-042 trial, including data from an extension of the global study in Chinese patients.[14,15]

In the phase 2/3 KEYNOTE-010 study, pembrolizumab improved OS vs docetaxel as second-line therapy or beyond for advanced NSCLC with PD-L1 TPS ≥1% and ≥50%.[8] However, KEYNOTE-010 did not enroll patients from mainland China. The phase 1 KEYNOTE-032 study demonstrated encouraging antitumor activity and manageable toxicity for pembrolizumab in Chinese patients with advanced NSCLC.[16] We conducted the KEYNOTE-033 study (NCT02864394) to compare pembrolizumab 2 mg/kg every 3 weeks with docetaxel 75 mg/m^2 every 3 weeks in patients with PD-L1-positive NSCLC that had progressed after platinum-containing systemic therapy predominantly enrolled in mainland China.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

KEYNOTE-033 is a randomized, open-label, phase 3 trial conducted in 62 centers predominately in mainland China and seven other countries/regions (Taiwan, Argentina, Chile, Philippines, Thailand, Mexico and Ukraine).[17,18] Eligible patients were at least 18 years old, had histologically or cytologically confirmed stage IIIb/IV or recurrent NSCLC with at least one measurable lesion as per Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1),[19] investigator-assessed progression after two or more cycles of platinum-doublet chemotherapy per RECIST 1.1, as well as an appropriate tyrosine kinase inhibitor for those with an *ALK* gene rearrangement; an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; provision of a tumor sample (archival or new tumor sample); and PD-L1 TPS ≥1%. Chinese patients needed to be born, raised and reside in mainland China.

Key exclusion criteria included previous treatment with PD-(L)1 checkpoint inhibitors or docetaxel, known active brain metastases or carcinomatous meningitis, an active autoimmune disease that required systemic treatment and history of pneumonitis that required steroids or current pneumonitis. Each site had to provide documentation of a patient's tumor *EGFR* mutation and *ALK* translocation status using standard techniques. If the site was unable to provide this documentation, then the Sponsor offered molecular testing of the tumor. In March 2017, the protocol was amended to exclude patients with an *EGFR* sensitizing mutation. The supplementary material (Data S1) includes the study protocol that shows all the inclusion and exclusion criteria.

2.2 | Randomization, treatment and masking

Patients were randomly assigned (1:1) with a central interactive voice-response/integrated web response system to receive pembrolizumab 2 mg/kg intravenously over 30 minutes every 3 weeks or docetaxel 75 mg/m^2 intravenously over 1 hour every 3 weeks. Patients were stratified by the extent of tumoral PD-L1 expression (TPS 1%-49% vs TPS ≥50%).

Patients, investigators and the sponsor were not masked to treatment assignment. The study sites, investigators and their staff and clinical research coordinators involved in on-site monitoring were blinded to the details of PD-L1 TPS. Imaging data for the primary analysis were assessed by blinded independent central review (BICR).

2.3 | Procedures

PD-L1 expression was assessed during screening at a central laboratory using the PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent). Corticosteroid predocetaxel and/or postdocetaxel treatment was permitted in the docetaxel arm. Patients in the docetaxel arm received the treatment until disease progression, toxicity, investigator's decision to discontinue or consent withdrawal. Patients in the pembrolizumab arm received the treatment for up to 35 cycles (~2 years); the protocol was amended to allow patients who completed 2 years of therapy or stopped therapy due to having a complete response to enter a second-course phase for up to 17 additional treatments (~12 months) with pembrolizumab. Treatment was continued for the specified number of cycles or until confirmed disease progression, intolerable toxicity, patient withdrawal or physician decision. Patients who showed first radiologic evidence of progression could remain on treatment until a confirmatory scan was conducted 4 weeks later. Patients in the docetaxel arm were not allowed to cross over to receive pembrolizumab.

Radiographic imaging was performed every 9 weeks. Response was assessed as per RECIST 1.1 by BICR (for efficacy) and as per immune-related response criteria by investigator (to inform treatment decisions). During the survival follow-up, survival status was assessed every 2 months. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

2.4 | Study endpoints

Primary endpoints were OS (the time from randomization to death due to any cause) and PFS (the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first) both in patients with PD-L1 TPS ≥1% and in patients with TPS ≥50%. Secondary endpoints included objective response rate (ORR, the proportion of patients who achieved a complete response or partial response), duration of response (DOR, the time from first documented evidence of complete response or partial response until disease progression per RECIST 1.1 or death due to any cause, whichever occurred first) and safety/tolerability.

2.5 | Statistical analysis considerations

Assuming that OS follows an exponential distribution with a median of 10 months in the docetaxel arm, an enrollment period of

~24 months, a yearly drop-out rate of 2% and a hazard ratio (HR) of 0.6 (between pembrolizumab and docetaxel), we calculated that we would need to randomize ~216 subjects with TPS ≥50% in a 1:1 ratio into pembrolizumab arm and docetaxel arm, with a projected overall sample size of ~400.

The final analysis was planned to be performed about 36 months after trial started (~150 OS events were expected to be observed in TPS ≥50% stratum). With 150 deaths, the trial has ~87% power to demonstrate that, among patients with PD-L1 TPS ≥50%, pembrolizumab is superior to docetaxel at a one-sided 2.5% alpha-level, if the underlying HR for OS is 0.6. The power was increased to ~90% if the underlying HR for OS was 0.58. One prespecified interim analysis was conducted, and the independent data monitoring committee recommended continuing the study.

Efficacy analyses were conducted in the intention-to-treat population (ie, all patients who were randomized), including TPS ≥50% and ≥1% populations. Safety was assessed in the treated population (ie, all randomized patients who received at least one dose of study treatment).

We conducted prespecified subgroup analyses of age (≤65 vs >65 years), sex, ECOG PS (0 vs 1), disease status (locally advanced vs metastatic) and the extent of PD-L1 expression (TPS 1%-49% vs TPS ≥50%) to assess the consistency of treatment effect across various subgroups. An exploratory analysis of outcomes in the Chinese population was also performed.

Differences in OS and PFS were evaluated sequentially at the type I error rate of 2.5% (one-sided) using the stratified log-rank test in the following order: (a) OS in patients with TPS ≥50%, (b) OS in patients with TPS ≥1%, (c) PFS in patients with TPS ≥50% and (d) PFS in patients with TPS ≥1%. A Cox proportional hazards model with Efron's method for tie handling was used to assess the magnitude of the treatment difference and the associated 95% confidence interval [95% CI]. The stratification factor used for randomization (PD-L1 expression TPS ≥50% vs TPS 1%-49%) was applied to both the stratified log-rank test and the stratified Cox model for analysis of the TPS ≥1% population. An unstratified log-rank test and unstratified Cox model were used for the analysis of the TPS ≥50% population. Differences in ORR were evaluated by using the stratified Miettinen and Nurminen's method. Event rates (ie, OS, PFS and DOR) over time were estimated within each treatment arm using the Kaplan-Meier method. For OS, patients without documented death at the time of the final analysis were censored at the date of the last follow-up. For PFS, patients without documented progression or death were censored at the last disease assessment date. For DOR, patients without progression, death and new anticancer treatment were censored at the last adequate disease assessment, those without progression and death but with new anticancer therapy initiated were censored at last adequate disease assessment before new anticancer therapy initiated, those with death or progression immediately after more than two consecutive missed disease assessments or after new anticancer therapy (if any) were censored at the earlier date of last adequate disease assessment prior to missed adequate disease assessments and new anticancer therapy.

The study is ongoing for follow-up but is no longer enrolling patients.

3 | RESULTS

3.1 | Patients

Between 8 September 2016 and 17 October 2018, 1234 patients were screened and 425 patients met the eligibility criteria and were randomized in the study: 213 were allocated to pembrolizumab and 212 were allocated to docetaxel. A total of 411 patients received at least one dose of the assigned study drug: 213 in the pembrolizumab arm and 198 in the docetaxel arm (Figure S1). At the data cutoff date of 9 September 2019, the median time from randomization to cutoff date was 22.3 (range, 10.8-34.4) months.

Baseline characteristics were representative of the population with advanced or metastatic NSCLC and were generally well balanced between the arms. There were 311 patients (73.2%) enrolled from mainland China. Most patients were male, <65 years old, current or former smokers, had tumors of nonsquamous histology and had a baseline ECOG PS of 1 and stage IV disease. Similar baseline characteristics were observed in the 227 patients who had a PD-L1 TPS ≥50% (Table 1).

At the time of data cutoff, patients who completed the assigned study treatment were 12 (5.6%) in the pembrolizumab and 15 (7.6%) in the docetaxel arm. There were 25 (11.7%) patients in the pembrolizumab and 2 (1.0%) in the docetaxel arm who were still receiving study treatment. Discontinuation occurred in 176 (82.6%) with pembrolizumab and 181 (91.4%) with docetaxel (Figure S1). After discontinuation of study treatment, 89 (41.8%) patients in the pembrolizumab arm and 112 (52.8%) patients in the docetaxel arm received subsequent anticancer therapy, including 5 (2.3%) and 43 (20.3%) patients, respectively, who received immunotherapies (Table S1).

3.2 | Efficacy in total population

In patients with a PD-L1 TPS ≥50%, the HR for OS for pembrolizumab vs docetaxel was 0.83 (95% CI: 0.61-1.14; $P = .1276$). Per the statistical analysis plan, sequential testing of OS and PFS was ceased because the significance threshold was not met in the TPS ≥50% population. Median OS was 12.3 months (95% CI: 10.0-16.3) in the pembrolizumab arm and 10.9 months (8.3-13.1) in the docetaxel arm. One-year OS rate was 51.7% vs 47.3%, and 2-year OS rate was 25.1% vs 22.4% in pembrolizumab and docetaxel arms, respectively (Figure 1A).

In patients with PD-L1 TPS ≥1%, the HR for OS for pembrolizumab vs docetaxel was 0.75 (95% CI: 0.60-0.95). Median OS was 12.9 months (95% CI: 10.3-16.5) in the pembrolizumab arm and 10.6 months (8.7-12.5) in the docetaxel arm. There were 285 deaths, including 135 (63.4%) with pembrolizumab and 150 (70.8%) with

TABLE 1 Baseline demographics and disease characteristics.

	PD-L1 TPS ≥ 1%		PD-L1 TPS ≥ 50%	
Characteristic, n (%)	**Pembrolizumab, N = 213**	**Docetaxel, N = 212**	**Pembrolizumab, N = 114**	**Docetaxel, N = 113**
Median age (range), years	61 (28-83)	61 (34-81)	61 (28-83)	63 (35-79)
Male	157 (73.7)	164 (77.4)	91 (79.8)	91 (80.5)
Geographic region of enrolling site				
East Asia	181 (85.0)	177 (83.5)	98 (86.0)	100 (88.5)
Mainland China	162 (76.1)	149 (70.3)	87 (76.3)	82 (72.6)
Non-East Asia	32 (15.0)	35 (16.5)	16 (14.0)	13 (11.5)
ECOG PS				
0	25 (11.7)	19 (9.0)	13 (11.4)	12 (10.6)
1	188 (88.3)	193 (91.0)	101 (88.6)	101 (89.4)
Cancer stage				
IIIB	15 (7.0)	21 (9.9)	8 (7.0)	11 (9.7)
IV	198 (93.0)	191 (90.1)	106 (93.0)	102 (90.3)
Smoking status				
Current/former	143 (67.1)	147 (69.3)	79 (69.3)	85 (75.2)
Never	70 (32.9)	65 (30.7)	35 (30.7)	28 (24.8)
PD-L1 TPS				
≥50%	114 (53.5)	112 (52.8)	114 (100.0)	112 (99.1)
1%-49%	98 (46.0)	98 (46.2)	0	1 (0.9)
<1%[a]	0	2 (0.9)	–	–
Not available[a]	1 (0.5)	0	–	–
Histology				
Squamous	81 (38.0)	89 (42.0)	38 (33.3)	47 (41.6)
Nonsquamous	121 (56.8)	113 (53.3)	66 (57.9)	60 (53.1)
Adenosquamous	11 (5.2)	7 (3.3)	10 (8.8)	5 (4.4)
Other/not specified	0	3 (1.4)	0	1 (0.9)
Metastasis status				
Brain	11 (5.2)	15 (7.1)	7 (6.1)	11 (9.7)
Liver	47 (22.1)	38 (17.9)	27 (23.7)	18 (15.9)
Genetic alterations detected[b]				
EGFR mutation	10 (4.7)	4 (1.9)	3 (2.6)	1 (0.9)
ALK translocation	1 (0.5)	2 (0.9)	1 (0.9)	0
No. of lines of prior therapy				
Adjuvant	14 (6.6)	19 (9.0)	6 (5.3)	10 (8.8)
1[c]	185 (86.9)	168 (79.2)	100 (87.7)	91 (80.5)
≥2[c]	14 (6.6)	25 (11.8)	8 (7.0)	12 (10.6)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, Non-small cell lung cancer; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

[a]Protocol deviation.

[b]For patients who were enrolled and had a known tumor histology status of pure squamous NSCLC, molecular testing for *EGFR* mutation and *ALK* translocation were not required. In March 2017, the protocol was amended to exclude patients with an *EGFR* sensitizing mutation.

[c]Systemic therapy.

docetaxel. One-year OS rate was 52.0% vs 46.9%, and 2-year OS rate was 29.4% vs 19.0% in pembrolizumab and docetaxel arms, respectively (Figure 1B). Results were similar across subgroups (eg, age, disease status and baseline tumor size; Figure S2).

In patients with a PD-L1 TPS ≥50%, 139 patients had a PFS event, including 71 (62.3%) of 114 patients with pembrolizumab and 68 (60.2%) of 113 patients with docetaxel. Median PFS was 4.0 months (95% CI: 2.1-8.0) in the pembrolizumab arm and

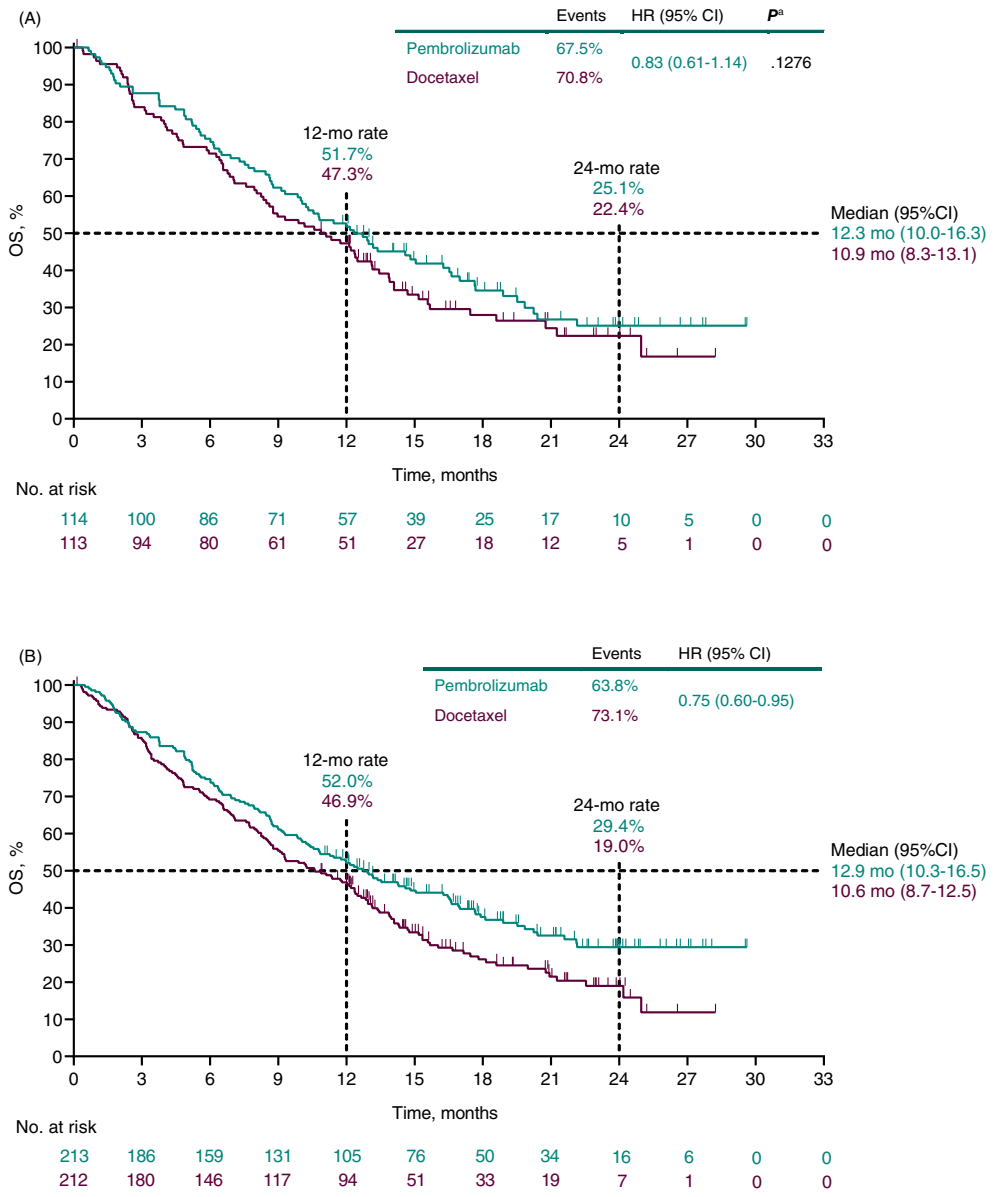

FIGURE 1 Kaplan-Meier Estimates of OS. (A) For patients with a PD-L1 TPS ≥50%. (B) For patients with a PD-L1 TPS ≥1%. [a]One-sided *P* value based on the log-rank test. CI, confidence interval; HR, hazard ratio; mo, month; OS, overall survival; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

2.5 months (2.1-4.2) in the docetaxel arm, with an HR of 0.76 (95% CI: 0.54-1.07; Figure 2A).

In patients with PD-L1 TPS ≥1%, 261 patients had died or had disease progression, including 138 (64.8%) of 213 patients with pembrolizumab and 123 (58.0%) of 212 patients with docetaxel. Median PFS was 3.3 months (95% CI: 2.1-4.1) in the pembrolizumab arm and 3.0 months (2.3-4.0) in the docetaxel arm, with an HR of 0.84 (95% CI: 0.66-1.08; Figure 2B).

Among patients with a PD-L1 TPS ≥50%, ORR occurred in 32 (28.1%) of 114 patients with pembrolizumab and 8 (7.1%) of 113 with docetaxel. Complete responses were observed in two patients with pembrolizumab and none with docetaxel. Response duration was longer in the pembrolizumab arm than in the docetaxel arm (median DOR, 16.6 vs 6.4 months; Table 2). In patients with PD-L1 TPS ≥1%, 44 (20.7%) of 213 patients with pembrolizumab vs 12 (5.7%) of 212 patients with docetaxel had an objective response. Complete responses were seen in two patients with pembrolizumab and one patient with docetaxel. Median time to response was 2.1 months with pembrolizumab and 2.0 months with docetaxel. Longer response duration was observed in the pembrolizumab arm than in the docetaxel arm (median DOR, 16.6 months vs 6.3 months; Table 2).

PFS and OS outcomes by smoking status are shown in Table S2.

3.3 | Efficacy in mainland China population

In patients with PD-L1 TPS ≥50% from mainland China (n = 169), HR for OS was 0.79 (95% CI: 0.55-1.13). Median OS was 13.2 months (95% CI: 10.2-17.0) with pembrolizumab and 10.6 months (7.1-13.1) with docetaxel. There were 116 deaths, including 58 (66.7%) patients in the pembrolizumab arm and 58 (70.7%) patients in the docetaxel

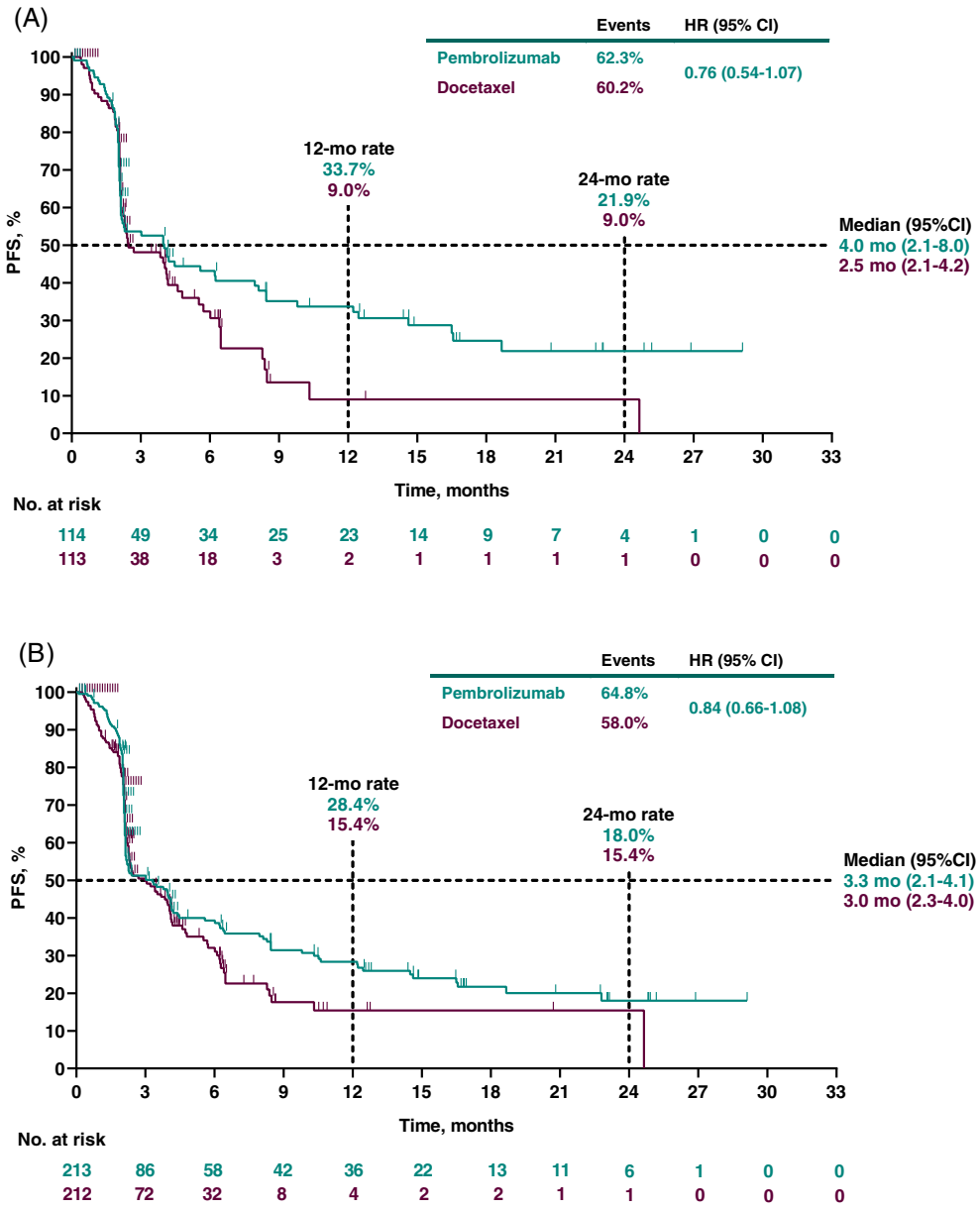

FIGURE 2 Kaplan-Meier Estimates of PFS per RECIST v1.1 by BICR. (A) For patients with a PD-L1 TPS ≥50%. (B) For patients with a PD-L1 TPS ≥1%. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, month; PFS, progression-free survival; PD-L1, programmed death-ligand 1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TPS, tumor proportion score.

arm. Events of progression or deaths occurred in 101 patients, including 53 (60.9%) patients with pembrolizumab and 48 (58.5%) patients with docetaxel. Median PFS was 4.2 months (95% CI: 2.1-8.4) in the pembrolizumab arm and 2.3 months (2.1-4.0) in the docetaxel arm, with an HR of 0.74 (95% CI: 0.49-1.10). Responses occurred in 27 (31.0%) patients in the pembrolizumab arm and 7 (8.5%) patients in the docetaxel arm (Table 3).

In patients with PD-L1 TPS ≥1% enrolled in mainland China (n = 311), there were 203 deaths, including 97 (59.9%) of 162 patients in the pembrolizumab arm and 106 (71.1%) of 149 patients in the docetaxel arm. HR for OS was 0.68 (95% CI: 0.51-0.89). Median OS was 15.0 months (95% CI: 12.2-17.9) for the pembrolizumab arm and 9.6 months (8.0-12.5) for the docetaxel arm (Figure S3). Events of progression or deaths occurred in 183 patients, including 98 (60.5%) patients in the pembrolizumab arm and 85 (57.0%) in the docetaxel arm. Median PFS was 4.0 months (95% CI: 2.2-8.0) in the pembrolizumab arm and 2.3 months (2.1-3.4) in the docetaxel arm, with an HR of 0.74 (95% CI: 0.55-0.99). Responses occurred in 38 (23.5%) patients with pembrolizumab and 9 (6.0%) patients with docetaxel (Table 3).

3.4 | Five-year outcomes in the ITT population

In addition to the prespecified analysis, we conducted a long-term follow-up analysis with a data cutoff of 14 October 2022. The median time from randomization to cutoff date was 59.4 (range, 47.9-71.5) months in the pembrolizumab group and 59.5 (range, 48.3-71.0) months in the placebo group.

In the PD-L1 TPS ≥50% population, median OS was 12.5 months (95% CI: 10.0-16.5 months) in the pembrolizumab arm and 11.0 months (8.3-13.1 months) in the docetaxel arm (HR, 0.79 [95%

TABLE 2 Confirmed ORR and DOR per RECIST v1.1 by BICR.

PD-L1 TPS ≥ 50%	Pembrolizumab, N = 114	Docetaxel, N = 113
ORR (95% CI), %	28.1 (20.1-37.3)	7.1 (3.1-13.5)
CR, n (%)	2 (1.8)	0
PR, n (%)	30 (26.3)	8 (7.1)
SD, n (%)	29 (25.4)	45 (39.8)
PD, n (%)	38 (33.3)	40 (35.4)
Not evaluable/no assessment, n (%)	15 (13.2)	20 (17.7)
Ongoing responses,[a] n (%)	16 (50.0)	1 (12.5)
Median duration of response (range),[b] mo	16.6 (1.1+ to 24.9+)	6.4 (1.4+ to 22.3)
PD-L1 TPS ≥ 1%	**Pembrolizumab, N = 213**	**Docetaxel, N = 212**
ORR (95% CI), %	20.7 (15.4-26.7)	5.7 (3.0-9.7)
CR, n (%)	2 (0.9)	1 (0.5)
PR, n (%)	42 (19.7)	11 (5.2)
SD, n (%)	66 (31.0)	89 (42.0)
PD, n (%)	77 (36.2)	73 (34.4)
Not evaluable/no assessment, n (%)	26 (12.2)	38 (17.9)
Ongoing responses,[a] n (%)	21 (47.7)	1 (8.3)
Median duration of response (range),[b] mo	16.6 (1.1+ to 24.9+)	6.3 (1.4+ to 22.3)

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; mo, month; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TPS, tumor proportion score.

[a]Includes patients who were alive, had not progressed, had not initiated new anticancer treatment, were not lost to follow-up and whose last disease assessment was <5 months prior to the data cutoff date.

[b]Includes patients with confirmed complete response or partial response. From the product-limit (Kaplan-Meier) method for censored data.

TABLE 3 OS, PFS and ORR in patients from mainland China.

PD-L1 TPS ≥ 50%	Pembrolizumab, n = 87	Docetaxel, n = 82
OS		
Median (95% CI), mo	13.2 (10.2-17.0)	10.6 (7.1-13.1)
HR (95% CI)	0.79 (0.55-1.13)	
PFS		
Median (95% CI), mo	4.2 (2.1-8.4)	2.3 (2.1-4.0)
HR (95% CI)	0.74 (0.49-1.10)	
ORR		
% (95% CI)	31.0 (21.5-41.9)	8.5 (3.5-16.8)
PD-L1 TPS ≥ 1%	**Pembrolizumab, n = 162**	**Docetaxel, n = 149**
OS		
Median (95% CI), mo	15.0 (12.2-17.9)	9.6 (8.0-12.5)
HR (95% CI)	0.68 (0.51-0.89)	
PFS		
Median (95% CI), mo	4.0 (2.2-8.0)	2.3 (2.1-3.4)
HR (95% CI)	0.74 (0.55-0.99)	
ORR		
% (95% CI)	23.5 (17.2-30.7)	6.0 (2.8-11.2)

Abbreviations: CI, confidence interval; mo, month; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

CI: 0.59-1.04]). The Kaplan-Meier estimate for the 5-year OS rate was 12.5% in the pembrolizumab arm and was not reached (ie, no evaluable patient at 60 months) in the docetaxel arm (Figure S4). In the PD-L1 TPS ≥1% population, median OS was 12.9 months (95% CI: 10.3-16.5 months) and 10.6 months (8.7-12.6 months), respectively (HR, 0.75 [95% CI: 0.61-0.92]). The Kaplan-Meier estimate for the 5-year OS rate was 11.8% in the pembrolizumab arm and was not reached in the docetaxel arm (Figure S5).

In the PD-L1 TPS ≥50% population, the HR for PFS for pembrolizumab vs docetaxel was 0.70 (95% CI: 0.51-0.95; Figure S6). In the PD-L1 TPS ≥1% population, the HR for PFS was 0.79 (95% CI: 0.63-0.99; Figure S7).

In the PD-L1 TPS ≥50% population, ORR was 28.1% (95% CI: 20.1%-37.3%) in the pembrolizumab arm and 7.1% (95% CI: 3.1%-13.5%) in the docetaxel arm. Three patients (2.6%) in the pembrolizumab arm and no patient in the docetaxel arm achieved a complete response. Median DOR was 25.8 months (range 1.1+ to 62.1+ months; "+" indicates there was no progressive disease at the time of last disease assessment) in the pembrolizumab arm and 6.4 months (range, 1.4+ to 22.3 months) in the docetaxel arm.

In the PD-L1 TPS ≥1% population, ORR was 20.7% (95% CI: 15.4%-26.7%) in the pembrolizumab arm and 5.7% (95% CI: 3.0%-9.7%) in the docetaxel arm. Three patients (1.4%) in the pembrolizumab arm and 1 patient (0.5%) in the docetaxel arm achieved a complete response. Median DOR was 18.7 months (range, 1.1+ to 62.1+ months) in the pembrolizumab arm and 6.3 months (range, 1.4+ to 22.3 months) in the docetaxel arm.

3.5 | Five-year outcomes in patients who completed 35 cycles of pembrolizumab in the ITT population

At the October 14, 2022 data cutoff, 26 of 213 (12.2%) patients initially assigned to pembrolizumab in the PD-L1 TPS ≥1% population had completed 35 cycles (ie, ~2 years), of treatment. Median time from randomization to data cutoff date was 60.8 (range, 50.2-66.8) months. Seventeen patients (65.4%) had disease that had a PD-L1

TABLE 4 AEs in all treated patients.

n (%)	Pembrolizumab, N = 213		Docetaxel, N = 198	
Related to treatment				
Any grade	149 (70.0)		174 (87.9)	
Grade 3-5	24 (11.3)		94 (47.5)	
Led to discontinuation	21 (9.9)		15 (7.6)	
Led to death	4 (1.9)		4 (2.0)	
	Any grade	**Grade 3-5**	**Any grade**	**Grade 3-5**
Common treatment-related AEs (incidence ≥10% in any arm)				
Aspartate aminotransferase increased	32 (15.0)	0	12 (6.1)	0
Rash	32 (15.0)	2 (0.9)	9 (4.5)	0
Anemia	29 (13.6)	2 (0.9)	74 (37.4)	10 (5.1)
Hypothyroidism	25 (11.7)	0	2 (1.0)	0
Fatigue	13 (6.1)	1 (0.5)	32 (16.2)	4 (2.0)
Decreased appetite	12 (5.6)	0	37 (18.7)	2 (1.0)
Diarrhea	5 (2.3)	0	26 (13.1)	2 (1.0)
White blood cell count decreased	5 (2.3)	0	53 (26.8)	28 (14.1)
Neutrophil count decreased	4 (1.9)	0	28 (14.1)	21 (10.6)
Leukopenia	2 (0.9)	0	35 (17.7)	21 (10.6)
Nausea	2 (0.9)	0	28 (14.1)	1 (0.5)
Alopecia	1 (0.5)	0	88 (44.4)	0
Neutropenia	0	0	48 (24.2)	38 (19.2)
Immune-mediated AEs and infusion reactions				
Hypothyroidism	28 (13.1)	1 (0.5)	2 (1.0)	0
Pneumonitis	21 (9.9)	5 (2.3)	4 (2.0)	1 (0.5)
Hyperthyroidism	20 (9.4)	0	0	0
Infusion reactions	5 (2.3)	1 (0.5)	7 (3.5)	0
Hepatitis	4 (1.9)	4 (1.9)	1 (0.5)	0
Nephritis	3 (1.4)	0	0	0
Severe skin reactions	3 (1.4)	3 (1.4)	0	0
Myositis	1 (0.5)	1 (0.5)	0	0

Note: AEs were followed 30 days after the last dose of study treatment.
Abbreviation: AE, adverse event.

TPS ≥50% and 9 (34.6%) had a PD-L1 TPS 1% to 49%. Baseline characteristics for these patients were generally similar to the total study population (Table S3). Among these patients, ORR was 92.3% (95% CI: 74.9%-99.1%). Best response was complete response in 2 patients (7.7%), partial response in 22 (84.6%) and stable disease in 2 patients (7.7%). Median DOR was 39.2 months (range, 8.4 to 62.1+ months). At data cutoff, 20 patients were alive. The OS rate at 3 years after completion of 35 cycles of pembrolizumab (ie, ~5 years from randomization) was 72.9% (95% CI: 48.2%-87.2%).

3.6 | Safety in the total treated population

In the safety population, median treatment duration was 4.2 months (range, 1 day to 25.8 months) for pembrolizumab and 1.5 months (range, 1 day to 21.4 months) for docetaxel. Incidence of treatment-related AEs was lower with pembrolizumab vs docetaxel (any grade, 70.0% vs 87.9%; grade 3-5, 11.3% vs 47.5%). There were 21 (9.9%) patients in the pembrolizumab arm and 15 (7.6%) patients in the docetaxel arm who discontinued study drug because of treatment-related AEs. Eight deaths were attributed to study treatment, including four patients in each treatment arm (pembrolizumab, one case each of pneumonia and respiratory distress and two cases of pneumonitis; docetaxel, one case each of febrile neutropenia, lung infection, pulmonary sepsis and interstitial lung disease). Common treatment-related AEs were as expected for pembrolizumab and docetaxel (Table 4). Immune-mediated AEs and infusion reactions occurred in 28.6% with pembrolizumab and 6.1% with docetaxel but were mostly of grade 1 to 2 severity. Grade 3 to 5 immune-mediated AEs that occurred in more than one patient treated with pembrolizumab were pneumonitis (n = 5), hepatitis (n = 4) and severe skin reactions (n = 3; Table 4). The only immune-mediated AEs that led to death were the two cases of grade 5 treatment-related pneumonitis mentioned above.

4 | DISCUSSION

In this phase 3 study of patients with previously treated advanced NSCLC enrolled predominantly in mainland China, pembrolizumab did not lead to statistically significant improvement in OS in the PD-L1 TPS ≥50% population; thus, all sequential statistical testing ceased. Although HRs for OS and PFS favored pembrolizumab in both PD-L1 TPS populations, there was no evidence of a greater OS or PFS benefit for pembrolizumab over docetaxel in the PD-L1 TPS ≥50% population than among the PD-L1 TPS ≥1% population. As the rate of crossover in the docetaxel arm to subsequent immunotherapy following disease progression in both the PD-L1 TPS ≥1% and the PD-L1 TPS ≥50% groups were similar (20.3% and 18.6%, respectively) it does not appear likely that the difference in crossover rate between these groups contributed to the difference in HR for OS between the PD-L1 TPS ≥1% and PD-L1 TPS ≥50% groups. Notably, a higher ORR and durable responses (as demonstrated by longer DOR) were observed in the pembrolizumab group in both PD-L1 TPS populations. Similar results were observed in the patient population from mainland China. Although the primary endpoint was not met in our study, these results provide evidence for activity of pembrolizumab in this setting.

The lack of significant OS benefit of pembrolizumab observed in our study is in contrast to the phase 2/3 KEYNOTE-010 study, in which pembrolizumab significantly improved OS in both PD-L1 TPS ≥50% and PD-L1 TPS ≥1% populations and PFS in patients with PD-L1 TPS ≥50% as second-line therapy or beyond for advanced NSCLC.[8] One factor that may have contributed to this difference might be the "crossover effect" resultant from the increased availability of immunotherapies, which was also observed in other trials.[20] An additional factor

that may have contributed to the difference in the magnitude of treatment effect is differences in baseline demographics and disease characteristics between patients in the KEYNOTE-010[8] and KEYNOTE-033 trials. For example; overall, KEYNOTE-033 included a higher proportion of men, a higher proportion of patients with an ECOG performance status of 1, a higher proportion of patients with squamous histology and a lower proportion of patients with an *EGFR* mutation than in the KEYNOTE-010 study. Since our study was initiated, several immunotherapies have been approved for previously treated advanced NSCLC,[21-23] including nivolumab's approval in 2018 in China[24] based on the findings from the CheckMate 078 trial.[25] In PD-L1 TPS ≥50% population of our study, 3.5% of patients in the pembrolizumab arm received subsequent immunotherapy vs 18.6% of 212 patients in the docetaxel arm. This "crossover" of patients in the docetaxel arm who received subsequent immunotherapy may have confounded the OS outcome and reduced the study power. Another factor that may have contributed to the lack of statistically significant OS benefit with pembrolizumab in patients with PD-L1 TPS ≥50% could be the small sample size in this population (n = 227), which could affect the ability of statistical hypothesis testing. Cross-trial comparisons should be interpreted with caution because there are differences in trial designs, patient characteristics and dates of recruitment. However, median OS with pembrolizumab in patients with PD-L1 TPS ≥1% in our trial was similar as seen in other trials evaluating immunotherapies (eg, pembrolizumab, atezolizumab and nivolumab) for previously treated NSCLC.[8,25,26] Early investigation of anti-PD-1 therapies in advanced NSCLC demonstrated that patients with tumors that express PD-L1 were more likely to respond to anti-PD-1 therapy than those who did not.[6,7] These early findings provided the rationale for enrolling PD-L1-positive patients in the KEYNOTE-010 study and the current investigation.

The safety profile of pembrolizumab was consistent with that previously observed for pembrolizumab, and there were no unexpected toxicities. Despite longer treatment exposure with pembrolizumab, rates of any-grade and grade 3 to 5 treatment-related AEs, especially hematological AEs, were lower with pembrolizumab vs docetaxel. Immune-mediated AEs were mostly mild to moderate in severity (grade 1 or 2) and generally manageable with the use of steroids and appropriate hormone replacement therapy, although there were two fatal cases of treatment-related pneumonitis.

There was evidence of long-term benefit with pembrolizumab. In an updated analysis with ~5 years of follow-up, HRs for OS and PFS continued to favor the pembrolizumab arm over the docetaxel arm in both PD-L1 TPS ≥50% and PD-L1 TPS ≥1% populations. Among patients who completed 35 cycles of pembrolizumab, ORR was 92.3% and the OS rate at 3 years after completion of pembrolizumab (ie, ~5 years from randomization) was 72.9%.

Although the phase 3 KEYNOTE-033 did not meet its primary endpoint, the efficacy and safety profiles observed for pembrolizumab were generally consistent with those previously observed for pembrolizumab in previously treated, advanced NSCLC. Thus, our findings could support the use of pembrolizumab for patients with previously treated, PD-L1 positive, advanced NSCLC in China and the further investigation of pembrolizumab-based regimens for NSCLC.

AUTHOR CONTRIBUTIONS

Shengxiang Ren: Collected data. **Jifeng Feng:** Collected data. **Shenglin Ma:** Collected data. **HuaJun Chen:** Collected data. **Zhiyong Ma:** Collected data. **Cheng Huang:** Collected data. **Li Zhang:** Collected data. **Jianxing He:** Collected data. **Changli Wang:** Collected data. **Jianying Zhou:** Collected data. **Pongwut Danchaivijitr:** Collected data. **Chin-Chou Wang:** Collected data. **Ihor Vynnychenko:** Collected data. **Kai Wang:** Collected data. **Francisco Orlandi:** Collected data. **Virote Sriuranpong:** Collected data. **Ben Li:** Analyzed data; verified the data. **Jun Ge:** Verified the data. **Thao Dang:** Verified the data. **Caicun Zhou:** Collected data.

ACKNOWLEDGEMENTS

The authors thank the patients and their families and all investigators and site personnel. Medical writing assistance was provided by Yue Liu of Merck & Co., Inc., Rahway, NJ.

FUNDING INFORMATION

Funding for our study was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ. The funder had a role in study design, collection, analysis and interpretation of data and medical writing support. The funder maintained the study database.

CONFLICT OF INTEREST STATEMENT

Shengxiang Ren, Jifeng Feng, Shenglin Ma, HuaJun Chen, Zhiyong Ma, Cheng Huang, Li Zhang, Jianxing He, Changli Wang, Jianying Zhou, Chin-Chou Wang, Ihor Vynnychenko and Kai Wang received research grant from Merck Sharp & Dohme. Francisco Orlandi: research grants from Merck Sharp & Dohme, AstraZeneca/MedImmune, Amgen, Genentech/Roche, Boehringer Ingelheim, Astellas Medivation, Bristol Myers Squibb, Celltrion, Pfizer, mAbxience, Nektar, Sanofi; speaker bureau: AstraZeneca/MedImmune, Roche; travel accommodations: Merck Sharp & Dohme, Genentech Roche; nonfinancial support: AstraZeneca, Roche/Genentech, BMS, MSD, Pfizer, Novartis, Sanofi. Pongwut Danchaivijitr: research grant from Merck Sharp & Dohme (Institution), research grant from Roche (Institution), research grant from AstraZeneca (Institution). Virote Sriuranpong for speaker fee: AstraZeneca, Novartis, Eisai, Boehringer, Taiho, MSD, BMS, Amgen, Roche, Astellas, Janssen; advisory board meeting: MSD, Roche, Eisai, Amgen, Astellas, Janssen; clinical research through institution: AstraZeneca, Novartis, Pfizer, MSD, Amgen. Ben Li and Jun Ge: employee of MSD, China. At the time of the study, TD was an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, as well as owned stocks in the company. Caicun Zhou: consulting fees from Innovent Biologics, QiLu, Hengrui, TopAlliance Biosciences Inc; honoraria for lectures: Eli Lily, Sanofi, BI, Roche, MSD, Qilu, Hengrui, Innovent Biologics, Alice, C-Stone, TopAlliance Biosciences Inc., Amoy Diagnostics, AnHeart.

DATA AVAILABILITY STATEMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ (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 US 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. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The study protocol and amendments were approved by the appropriate institutional review boards and ethics review committees at each institution. The study was conducted in accordance with the protocol, Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent for participating in the study. The study is registered with ClinicalTrials.gov (NCT02864394).

ORCID

Shenglin Ma https://orcid.org/0000-0003-2851-8875
Caicun Zhou https://orcid.org/0000-0002-6958-0766

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249. doi:10.3322/caac.21660
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424. doi:10.3322/caac.21492
3. American Cancer Society. Non-small cell lung cancer. https://www.cancer.org/cancer/lung-cancer/about/what-is.html. Accessed March 9, 2021
4. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346:92-98. doi:10.1056/NEJMoa011954
5. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123-135. doi:10.1056/NEJMoa1504627
6. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627-1639. doi:10.1056/NEJMoa1507643
7. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372:2018-2028. doi:10.1056/NEJMoa1501824
8. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540-1550. doi:10.1016/S0140-6736(15)01281-7
9. Peters S, Kerr KM, Stahel R. PD-1 blockade in advanced NSCLC: a focus on pembrolizumab. *Cancer Treat Rev*. 2018;62:39-49. doi:10.1016/j.ctrv.2017.10.002
10. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389:255-265. doi:10.1016/S0140-6736(16)32517-X
11. Na Z, Yeo SP, Bharath SR, et al. Structural basis for blocking PD-1-mediated immune suppression by therapeutic antibody pembrolizumab. *Cell Res*. 2017;27:147-150. doi:10.1038/cr.2016.77
12. Scapin G, Yang X, Prosise WW, et al. Structure of full-length human anti-PD1 therapeutic IgG4 antibody pembrolizumab. *Nat Struct Mol Biol*. 2015;22:953-958. doi:10.1038/nsmb.3129
13. Chatterjee M, Turner DC, Felip E, et al. Systematic evaluation of pembrolizumab dosing in patients with advanced non-small-cell lung cancer. *Ann Oncol*. 2016;27:1291-1298. doi:10.1093/annonc/mdw174
14. Merck & Co., Inc., Kenilworth, NJ, USA., KEYTRUDA is First Anti-PD-1 Therapy Approved as Monotherapy and in Combination with Chemotherapy in First-Line Setting for NSCLC in China. https://www.merck.com/news/mercks-keytruda-pembrolizumab-now-approved-as-monotherapy-in-china-for-first-line-treatment-of-certain-patients-with-advanced-non-small-cell-lung-cancer-nsclc-whose-tumors-express-p/. Accessed March 9, 2021
15. Wu YL, Zhang L, Fan Y, et al. Randomized clinical trial of pembrolizumab versus chemotherapy for previously untreated Chinese patients with PD-L1-positive locally advanced or metastatic non-small-cell lung cancer: KEYNOTE-042 China study. *Int J Cancer*. 2021;148(9):2313-2320. doi:10.1002/ijc.33399
16. Ma Y, Fang W, Zhang Y, et al. KEYNOTE-032: a randomized phase I study of pembrolizumab in Chinese patients with advanced non-small-cell lung cancer. *Oncologist*. 2020;25:650. doi:10.1634/theoncologist.2020-0067
17. Zhou C, Caglevic C, Zhou J, et al. KEYNOTE-033: phase 3 study of pembrolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (NSCLC). *Ann Oncol*. 2017;28:x143. doi:10.1093/annonc/mdx671.055
18. Zhou C, Feng J, Ma S, et al. Randomized, open-label phase III study of pembrolizumab (pembro) vs docetaxel (doce) in patients (pts) with previously treated NSCLC with PD-L1 tumour proportion score (TPS) ≥1%: KEYNOTE-033. *Ann Oncol*. 2020;31:S816. doi:10.1016/j.annonc.2020.08.1576
19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247. doi:10.1016/j.ejca.2008.10.026
20. Barlesi F, Vansteenkiste J, Spigel D, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN lung 200): an open-label, randomised, phase 3 study. *Lancet Oncol*. 2018;19:1468-1479. doi:10.1016/S1470-2045(18)30673-9
21. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371:2167-2177. doi:10.1056/NEJMoa1408440

22. Roach C, Zhang N, Corigliano E, et al. Development of a companion diagnostic PD-L1 immunohistochemistry assay for pembrolizumab therapy in non-small-cell lung cancer. *Appl Immunohistochem Mol Morphol*. 2016;24:392-397. doi:10.1097/PAI.0000000000000408
23. Apetoh L, Ladoire S, Coukos G, Ghiringhelli F. Combining immunotherapy and anticancer agents: the right path to achieve cancer cure? *Ann Oncol*. 2015;26:1813-1823. doi:10.1093/annonc/mdv209
24. Sorensen SF, Zhou W, Dolled-Filhart M, et al. PD-L1 expression and survival among patients with advanced non-small cell lung cancer treated with chemotherapy. *Transl Oncol*. 2016;9:64-69. doi:10.1016/j.tranon.2016.01.003
25. Wu YL, Lu S, Cheng Y, et al. Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced NSCLC: CheckMate 078 randomized phase III clinical trial. *J Thorac Oncol*. 2019;14:867-875. doi:10.1016/j.jtho.2019.01.006
26. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016;387:1837-1846. doi:10.1016/S0140-6736(16)00587-0

SUPPORTING INFORMATION

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

How to cite this article: Ren S, Feng J, Ma S, et al. KEYNOTE-033: Randomized phase 3 study of pembrolizumab vs docetaxel in previously treated, PD-L1-positive, advanced NSCLC. *Int J Cancer*. 2023;153(3):623-634. doi:10.1002/ijc.34532