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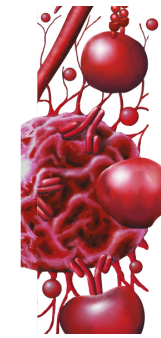

Pembrolizumab plus chemotherapy for advanced non-small-cell lung cancer without tumor PD-L1 expression in Asia

Ying Cheng*[,1], James Chih-Hsin Yang[2], Isamu Okamoto[3], Li Zhang[4], Jie Hu[5], Donglin Wang[6], Chengping Hu[7], Jianying Zhou[8], Lin Wu[9], Lejie Cao[10], Jiwei Liu[11], Helong Zhang[12], Hong Sun[13], Ziping Wang[14], Hongjun Gao[15], Yan Yan[16], Suijun Xiao[16], Jianxin Lin[17], M. Catherine Pietanza[17] & Takayasu Kurata[18]

[1]Jilin Cancer Hospital, Chaoyang Borough, Changchun, 130012, China
[2]National Taiwan University Hospital & National Taiwan University Cancer Center, 106, Taipei, China
[3]Kyushu University Hospital, Fukuoka, 812-8582, Japan
[4]Peking Union Medical College Hospital, Beijing, 100730, China
[5]Zhongshan Hospital Fudan University, Shanghai Geriatric Center, Shanghai, 200032, China
[6]Chongqing Cancer Hospital, Chongqing, 400030, China
[7]Xiangya Hospital Central South University, Changsha, 410008, China
[8]The First Affiliated Hospital of Zhejiang University, Hangzhou, 310003, China
[9]Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, 410013, China
[10]The First Affiliated Hospital of University of Science & Technology of China (Anhui Provincial Hospital), Hefei, 230001, China
[11]The First Affiliated Hospital of Dalian Medical University, Dalian, 116011, China
[12]Tang Du Hospital, The Fourth Military Medical University, Xi'an, 710038, China
[13]The First Affiliated Hospital of Xi'An Jiaotong University, Xi'an, 710061, China
[14]Key Laboratory of Carcinogenesis & Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, 100142, China
[15]Affiliated Hospital of Academy of Military Medical Sciences, Beijing, 100071, China
[16]MSD China, Shanghai, 200233, China
[17]Merck & Co., Inc., Rahway, NJ 07065, USA
[18]Kansai Medical University Hospital, Osaka, 573-1010, Japan
*Author for correspondence: Tel: +86 431 8059 6315; jl.cheng@163.com

Aim: We pooled patient-level data from three randomized controlled studies to evaluate the combination of pembrolizumab plus chemotherapy in patients with untreated advanced/metastatic non-small-cell lung cancer (NSCLC) and programmed cell death ligand 1 (PD-L1) tumor proportion score <1% in East Asia. **Methods:** The analysis included 107 patients from China, Japan, Korea, Thailand and Taiwan (pembrolizumab plus chemotherapy, n = 56; chemotherapy alone, n = 51). **Results:** For pembrolizumab plus chemotherapy versus chemotherapy alone, median overall survival was 21.3 versus 12.6 months (HR, 0.55 [95% CI: 0.35–0.87]) and median progression-free survival was 8.4 versus 6.0 months (HR, 0.64 [95% CI: 0.43–0.96]). **Conclusion:** The analysis supports the use of pembrolizumab in combination with platinum-based chemotherapy for East Asian patients with PD-L1-negative, advanced NSCLC.

Plain language summary: This analysis evaluated outcomes for East Asian patients with a type of advanced lung cancer which does not express a protein called programmed cell death ligand 1 (PD-L1). The patients received either an immunotherapy, called pembrolizumab, in combination with chemotherapy or chemotherapy alone. Overall survival (how long people live) and progression-free survival (how long people live without their disease getting worse) were longer for patients who received treatment with pembrolizumab plus chemotherapy versus those who received chemotherapy alone. Side effects among East Asian patients were similar to those previously described for a global patient population. These results support the use of pembrolizumab in combination with chemotherapy for East Asian patients with lung cancer that does not express PD-L1.

Clinical Trial Registration: NCT02039674; NCT02578680; NCT03950674; NCT02775435; NCT03875092 (ClinicalTrials.gov)

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Lung cancer is a leading cause of cancer-related death in East Asian countries [1–5] and, in 2020, accounted for 720,000 deaths in China alone [6]. The majority of lung cancers are diagnosed at a locally advanced or metastatic stage, contributing to poor prognosis and low 2- and 5-year survival rates [7–9]. The anti-programmed cell death protein 1 (PD-1) monoclonal antibody pembrolizumab has been shown to improve outcomes among patients with previously untreated advanced or metastatic non-small-cell lung cancer (NSCLC) both when administered as a monotherapy in patients with tumors that express programmed cell death ligand 1 (PD-L1) [10–13] and when combined with platinum-based chemotherapy, irrespective of tumor PD-L1 expression [14–16]. In particular, cohort G of the phase II KEYNOTE-021 study [14], the phase III KEYNOTE-189 study [15], an extension study of KEYNOTE-189 that enrolled patients in Japan [17], the phase III KEYNOTE-407 study [16], and an extension study of KEYNOTE-407 that enrolled patients in China [18] all demonstrated clinical benefit associated with adding pembrolizumab to platinum-based chemotherapy that was maintained with long-term follow-up [19–22].

Pembrolizumab plus platinum-based chemotherapy has become a standard-of-care treatment both for patients with PD-L1–positive NSCLC and for patients with PD-L1-negative NSCLC (i.e,, PD-L1 tumor proportion score [TPS] <1%); the latter group are not eligible for pembrolizumab monotherapy [23,24]. A third to one-half of patients in East Asia with advanced/metastatic NSCLC have tumors that do not express PD-L1 [17,18,25,26], which represents a large patient population with an unmet treatment need that may be addressed by combinations of pembrolizumab with platinum-based chemotherapy. Notably, in subgroup analyses in the KEYNOTE-189 [15] and KEYNOTE-407 studies [16], hazard ratios (HRs) for overall survival (OS) favored pembrolizumab plus chemotherapy over placebo plus chemotherapy both among patients with PD-L1 TPS ≥1% and those with PD-L1 TPS <1%.

A pooled analysis of patients with PD-L1-negative NSCLC was recently published, in which the combination of pembrolizumab plus chemotherapy was associated with improved OS and progression-free survival (PFS) compared with chemotherapy alone (HR, 0.63 [95% CI: 0.50–0.79] and 0.68 [95% CI: 0.56–0.83], respectively), as well as a higher ORR (50.0% [95% CI: 43.7–56.3%] vs 29.8% [95% CI: 23.4–36.9%]) [27]. The analysis included 65 patients from East Asia but did not report results according to region of enrollment.

Evidence suggests that disease characteristics and the efficacy and safety of some treatments may differ between Asian and non-Asian populations with lung cancer [7,28]. Such differences may be attributable to genetic, socio-cultural, behavioral, clinical and environmental factors that may differ between Asian patients and those of other ethnicities [7]. Among patients with NSCLC, differences in tumor mutational profile and PD-1 antibody clearance have been hypothesized to influence treatment response among Asian versus non-Asian patients receiving anti-PD-1 monoclonal antibodies [28–31].

Limited data are available describing outcomes with immune checkpoint inhibitors combined with platinum-based chemotherapy among Asian patients with PD-L1-negative NSCLC. We sought to obtain a better understanding of the safety and efficacy of pembrolizumab plus chemotherapy among Asian patients with PD-L1-negative NSCLC and to assess the ability of this treatment regimen to address the unmet need in this setting. Therefore, we pooled data from randomized studies that evaluated pembrolizumab plus chemotherapy versus placebo plus chemotherapy or chemotherapy alone. Compared with the prior global analysis [27], our analysis included patients from two study extensions conducted solely in Japan [17] and China [18], resulting in an overall population of more than 100 patients.

Methods

Study design & patients

Individual patient data were pooled from three international, multicenter, randomized controlled studies of patients with NSCLC who received pembrolizumab plus chemotherapy or chemotherapy with or without placebo (i.e., chemotherapy alone) and two study extensions that exclusively enrolled patients in Japan and China. The studies included cohort G from the phase II, open-label KEYNOTE-021 study (ClinicalTrials.gov ID, NCT02039674) [14]; the phase III, double-blind, placebo-controlled KEYNOTE-189 study (NCT02578680) [15] and KEYNOTE-189 Japan extension study (NCT03950674) [17]; and the phase III, double-

blind, placebo-controlled KEYNOTE-407 study (NCT02775435) [16] and KEYNOTE-407 China extension study (NCT03875092) [18].

KEYNOTE-021 cohort G included patients with previously untreated, stage IIIB/IV nonsquamous NSCLC; KEYNOTE-189 included patients with previously untreated, stage IV nonsquamous NSCLC; and KEYNOTE-407 included patients with previously untreated, stage IV squamous NSCLC. For all three studies, inclusion criteria included patient age ≥18 years, histologically or cytologically confirmed advanced NSCLC with ≥1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) performance status ≤1. Exclusion criteria were prior systemic treatment for advanced disease, symptomatic central nervous system metastases, active autoimmune disease that required systemic immunosuppressive therapy within 2 years before study treatment, active infection requiring therapy, a history of pneumonitis that required glucocorticoid treatment, and any other condition, therapy, or laboratory abnormality that might confound the study results. Patients with sensitizing *EGFR* or *ALK* aberrations were excluded from KEYNOTE-021 cohort G and KEYNOTE-189. Each study required that patients provide a tumor biopsy sample for the evaluation of PD-L1 status. Additional details of the eligibility criteria have been published elsewhere [14–16]. The KEYNOTE-189 Japan extension study [17] and KEYNOTE-407 China extension study [18] were identical to the primary studies, except that they enrolled only patients from Japan and China, respectively.

The studies were conducted in compliance with the ethical principles originating from the Declaration of Helsinki and with the International Council on Harmonisation Good Clinical Practice guidelines and all applicable local and national regulations. For each study, the protocol was approved by an appropriate Institutional Review Board. All patients provided written informed consent before participation.

Treatment

In KEYNOTE-021 cohort G, eligible patients were randomized 1:1 to either pembrolizumab 200 mg every 3 weeks (Q3W) for up to 35 cycles, plus pemetrexed 500 mg/m^2 and carboplatin area under the curve (AUC) 5 ml/min Q3W for four cycles, followed by pemetrexed maintenance therapy or pemetrexed-carboplatin alone. Randomization was stratified according to PD-L1 TPS (<1% vs ≥1%) [14].

In KEYNOTE-189, eligible patients were randomized 2:1 to receive four cycles of pembrolizumab 200 mg Q3W or placebo plus pemetrexed 500 mg/m^2 and the investigator's choice of carboplatin AUC 5 ml/min or cisplatin 75 mg/m^2, followed by pembrolizumab 200 mg Q3W or placebo for an additional 31 cycles (for a total of 35 cycles) and pemetrexed maintenance therapy until disease progression, unacceptable toxicity, investigator's decision or patient withdrawal. Randomization was stratified according to PD-L1 TPS (<1% vs ≥1%), choice of platinum (carboplatin vs cisplatin), and smoking history (current/former vs never) [15,17].

In KEYNOTE-407, patients were randomized 1:1 to receive pembrolizumab 200 mg Q3W or placebo for four cycles plus carboplatin AUC 6 ml/min on day 1 and the investigator's choice of paclitaxel 200 mg/m^2 on day 1 or nab-paclitaxel 100 mg/m^2 on days 1, 8 and 15, followed by pembrolizumab 200 mg Q3W or placebo for an additional 31 cycles (total of 35 cycles). Randomization was stratified according to PD-L1 TPS (<1% vs ≥1%), choice of taxane (paclitaxel vs nab-paclitaxel), and, in the global study, by geographic region (East Asia vs rest of the world) [16,18].

In all three studies, patients randomized to chemotherapy alone (KEYNOTE-021) or chemotherapy plus placebo (KEYNOTE-189 and KEYNOTE-407) could cross over to open-label pembrolizumab monotherapy if they had disease progression that was verified by blinded independent central radiologic review (BICR) and they continued to meet eligibility criteria. Pembrolizumab was continued for up to 35 cycles or until disease progression, unacceptable toxicity, physician decision to discontinue treatment, intercurrent illness that prevented treatment, pregnancy, protocol noncompliance, or administrative reasons [14–18].

Assessments

PD-L1 expression was assessed centrally in formalin-fixed tumor samples from newly biopsied tissue or archival specimens using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, CA, USA). Tumor samples provided after a diagnosis of metastatic disease were preferred in KEYNOTE-189 and KEYNOTE-407. Investigators were blinded to PD-L1 status.

Tumor imaging was performed at weeks 6 and 12 (all studies) and week 18 (KEYNOTE-021 cohort G and KEYNOTE-407); then every 9 weeks until week 52 (KEYNOTE-021 cohort G), week 48 (KEYNOTE-189), or week 45 (KEYNOTE-407); and every 12 weeks thereafter (all studies). Tumor response was assessed per RECIST

version 1.1 by BICR. In posttreatment follow-up, survival was assessed every 8 weeks (KEYNOTE-021) or every 12 weeks (KEYNOTE-189 and KEYNOTE-407). Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [14–18].

End points

ORR was the primary end point in cohort G of the KEYNOTE-021 study; PFS was the key secondary end point [14]. OS and PFS were dual primary end points in both KEYNOTE-189 and KEYNOTE-407; ORR and duration of response (DOR) were secondary end points [15–18]. Each study also assessed progression-free survival 2 (PFS2) as an exploratory end point. PFS2 was defined as the time from randomization to subsequent disease progression after initiation of new anticancer therapy (including crossover to pembrolizumab), or death from any cause, whichever occurred first. PFS2 events were defined as the time of investigator-assessed disease progression that led to discontinuation of second-line therapy; time of death for patients who did not receive or stopped receiving second-line therapy without progressive disease and who did not start third-line therapy; and time that third-line therapy started in patients who stopped second-line therapy without disease progression. Patients without a PFS2 event as of data cut-off were censored when they were last known to be alive and without disease progression after initiating new anticancer therapy.

Statistical analysis

This pooled analysis included patients enrolled in KEYNOTE-021 cohort G, KEYNOTE-189 or KEYNOTE-407 from China, Japan, Korea, Thailand or Taiwan, and from the KEYNOTE-189 Japan extension and KEYNOTE-407 China extension studies, who had PD-L1-negative tumors, defined as PD-L1 TPS <1%. Patients with nonevaluable PD-L1 results were excluded from this analysis. Efficacy was analyzed for the pooled intent-to-treat (ITT) population. Safety was analyzed for the pooled population of patients who received ≥1 dose of study treatment. Analyses were descriptive only and were not adjusted for multiplicity.

OS, PFS, DOR and PFS2 were estimated using the Kaplan-Meier method. HRs (with 95% CIs) for the end points of OS, PFS, and PFS2 were assessed using a Cox regression model with the Efron method of tie handling using treatment as a covariate. SAS version 9.4 (SAS Institute Inc., NC, USA) was used for all analyses. The database cut-off dates were 19 August 2019 (KEYNOTE-021 cohort G), 28 August 2020 (KEYNOTE-189 and KEYNOTE-189 Japan extension), and 30 September 2020 (KEYNOTE-407 and KEYNOTE-407 China extension).

Results

Patient population

Of 1438 patients enrolled in the three studies and two study extensions, 262 patients (18.2%) were enrolled in East Asia (irrespective of PD-L1 expression). Among the overall population of 1438 patients, 107 (7.4%) from East Asia had PD-L1-negative NSCLC and were included in the pooled analysis.

56 patients (squamous, n = 40; nonsquamous, n = 14; other, n = 2) were randomized to receive pembrolizumab plus chemotherapy, and 51 (squamous, n = 44; nonsquamous, n = 7) were randomized to receive chemotherapy with or without placebo (i.e., chemotherapy alone; Figure 1). The majority were male (87.9%) and had an ECOG performance status of 1 (66.4%; Table 1).

The median time from randomization to data cut-off for the pooled analysis was 33.4 (range: 25.3–49.2) months. Nine patients in the pembrolizumab plus chemotherapy group and one in the chemotherapy alone group had completed treatment, and one patient from each treatment group was ongoing on study treatment at data cut-off. The most common reasons for study discontinuation were death (pembrolizumab plus chemotherapy, 57%; chemotherapy alone, 73%) and AEs (5% and 4%, respectively). 18 patients from the chemotherapy alone group (35%) crossed over and received pembrolizumab monotherapy. At data cut-off, patients had a mean treatment duration of 9.8 (SD: 8.0) months with pembrolizumab plus chemotherapy and 5.8 (SD: 6.0) months with chemotherapy alone and had received a median of 12 (range: 1–35) and 7 (range: 1–48) treatment cycles, respectively.

Efficacy outcomes

76 of the 107 patients (71%) had died by the time of data cut-off. The median OS was 21.3 (95% CI: 15.8–28.0) months for pembrolizumab plus chemotherapy and 12.6 (95% CI: 8.6–15.3) months for chemotherapy alone

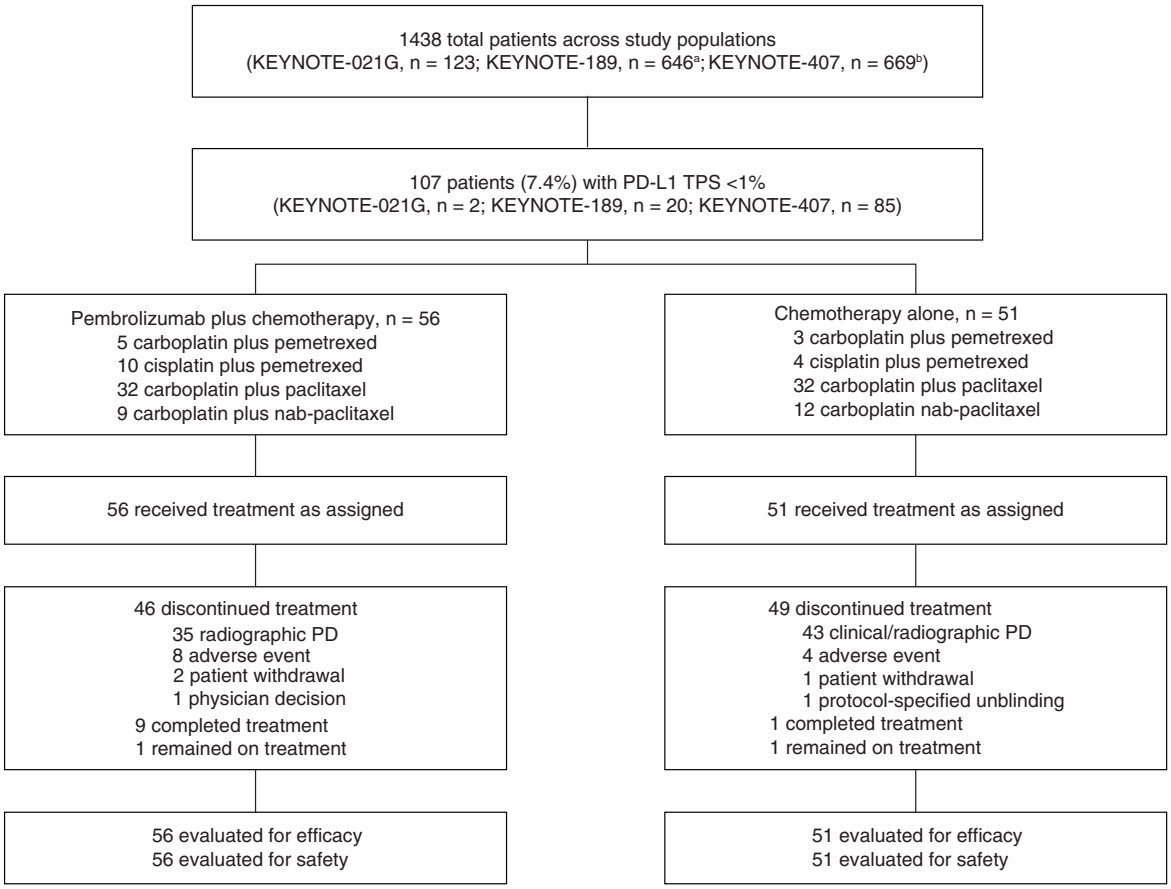

Figure 1. Patient disposition.
[a]Includes 30 patients enrolled in the KEYNOTE-189 Japan extension. [b]Includes 110 patients enrolled in the KEYNOTE-407 China extension.
PD: Progressive disease; PD-L1: Programmed cell death ligand 1; TPS: Tumor proportion score.

(HR, 0.55 [95% CI: 0.35–0.87]; Figure 2A). The estimated 12- and 24-month OS (95% CI) rates were 79% (65–87%) and 46% (33–59%), respectively, with pembrolizumab plus chemotherapy and 52% (38–65%) and 28% (17–41%), respectively, with chemotherapy alone. For the majority of subgroups analyzed, the HR point estimates for OS favored pembrolizumab plus chemotherapy over chemotherapy alone (Figure 2B). The HR for OS was greater than 1 for ECOG performance status of 0, never smokers, and for patients who received nab-paclitaxel; however, the limited number of patients/events and wide confidence intervals in these subgroups should be noted.

At data cut-off, disease progression or death had occurred for 94 of the 107 patients (88%). The median PFS was 8.4 (95% CI: 6.1–10.4) months for pembrolizumab plus chemotherapy and 6.0 (95% CI: 4.2–6.5) months for chemotherapy alone (HR, 0.64 [95% CI: 0.43–0.96]; Figure 3A). The estimated 12- and 24-month PFS (95% CI) rates were 33% (21–45%) and 17% (9–29%), respectively, with pembrolizumab plus chemotherapy and 16% (8–28%) and 10% (4–21%), respectively, with chemotherapy alone.

The ORR by BICR was 71% (95% CI: 58–83%) with pembrolizumab plus chemotherapy and 43% (95% CI: 29–58%) with chemotherapy alone (Table 2). This included 1 complete response (CR) and 39 partial responses (PRs) with pembrolizumab plus chemotherapy and 22 PRs with chemotherapy alone. Patients had a median DOR of 6.7 months (range: 2.1–34.5+ months; + indicates no progressive disease at the time of the last disease assessment) with pembrolizumab plus chemotherapy and 4.9 (range: 1.4+ to 36.6+) months with chemotherapy alone. The median PFS2 was 15.8 (95% CI: 13.2–20.1) months for pembrolizumab plus chemotherapy and 9.0 (95% CI: 6.7–10.5) months for chemotherapy alone (HR, 0.43 [95% CI: 0.28–0.66]; Figure 3B).

Table 1. Demographics and baseline disease characteristics.

	Pembrolizumab plus chemotherapy (n = 56)	Chemotherapy alone (n = 51)
Age		
Median (range), years	65.5 (31–87)	65.0 (43–82)
<65 years	25 (45)	23 (45)
Male sex	47 (84)	47 (92)
ECOG performance status		
0	21 (38)	15 (29)
1	35 (63)	36 (71)
Smoking history		
Current or former	51 (91)	48 (94)
Never	5 (9)	3 (6)
Histology		
Squamous	40 (71)	44 (86)
Nonsquamous	14 (25)	7 (14)
Other	2 (4)	0 (0)
Brain metastases		
Yes	6 (11)	10 (20)
No	50 (89)	41 (80)
Liver metastases		
Yes	1 (2)	5 (10)
No	35 (63)	24 (47)
Missing	20 (36)	22 (43)
Previous radiotherapy	6 (11)	4 (8)

Unless specified otherwise, all data are n (%).
ECOG: Eastern Cooperative Oncology Group; NSCLC: Non-small-cell lung cancer; PD-L1: Programmed cell death ligand 1; TPS: Tumor proportion score.

Outcomes among patients who crossed over to pembrolizumab

Among patients in the Asian subgroup, 18 in the chemotherapy alone group crossed over to pembrolizumab monotherapy on-study. Median OS from the time of pembrolizumab initiation of 11.7 (95% CI: 6.0–18.9) months and median PFS was 2.8 (95% CI: 1.5–3.0) months. The 6-month PFS rate was 17% (95% CI: 4–37%).

Outcomes among patients who completed 2 years (35 cycles) of treatment

Nine patients (16%) in the pembrolizumab plus chemotherapy group completed 2 years (35 cycles) of treatment. All patients were alive at the data cut-off. The 12- and 24-month PFS rates were both 89% (95% CI: 43–98%). All patients attained a PR. The median DOR was 31.1 (range: 9.1–34.5+) months.

Safety

AEs of any grade, regardless of attribution to study treatment by the investigator, occurred in all 107 patients. Treatment-related AEs were reported for 55 of 56 patients (98%) in the pembrolizumab plus chemotherapy group and all 51 patients (100%) in the chemotherapy alone group (Table 3). The most frequently reported treatment-related AEs in both groups were alopecia (54% with pembrolizumab plus chemotherapy vs 45% with chemotherapy alone), decreased white blood cell count (52 vs 51%), anemia (50 vs 63%), decreased neutrophil count (50 vs 49%), decreased appetite (43 vs 47%), and nausea (30 vs 25%). Treatment-related grade 3–5 AEs were reported for 71 and 76% of patients in the pembrolizumab plus chemotherapy and chemotherapy alone groups, respectively. The most common treatment-related grade 3–5 AEs in both groups were decreased neutrophil count (38% with pembrolizumab plus chemotherapy vs 39% with chemotherapy alone), decreased white blood cell count (21 vs 22%), neutropenia (13 vs 14%), and anemia (11 vs 16%). Two patients in the pembrolizumab plus chemotherapy group had fatal treatment-related adverse events (pneumonitis, n = 1; pneumonia, n = 1); no patients in the chemotherapy alone group died due to a treatment-related AE.

Immune-mediated AEs and infusion reactions (regardless of attribution to study treatment by the investigator) of any grade occurred in 22 of 56 patients (39%) in the pembrolizumab plus chemotherapy group and 4 of 51

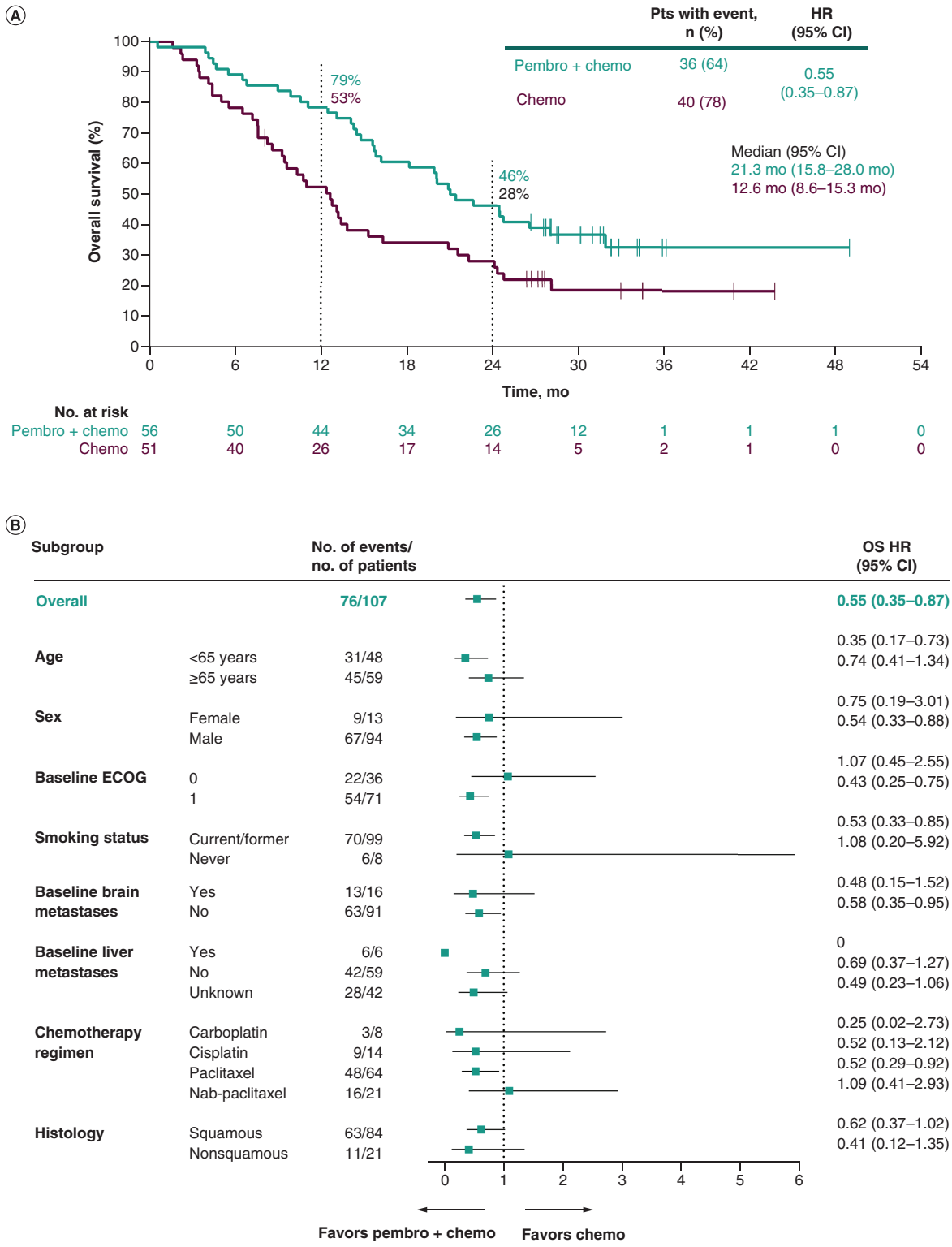

Figure 2. Kaplan-Meier estimates of overall survival. (A) Kaplan-Meier analysis of overall survival among patients who received pembrolizumab plus chemotherapy and those who received chemotherapy alone. **(B)** Overall survival in patient subgroups defined by demographics and baseline clinical characteristics.
ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; Pts: Patients.

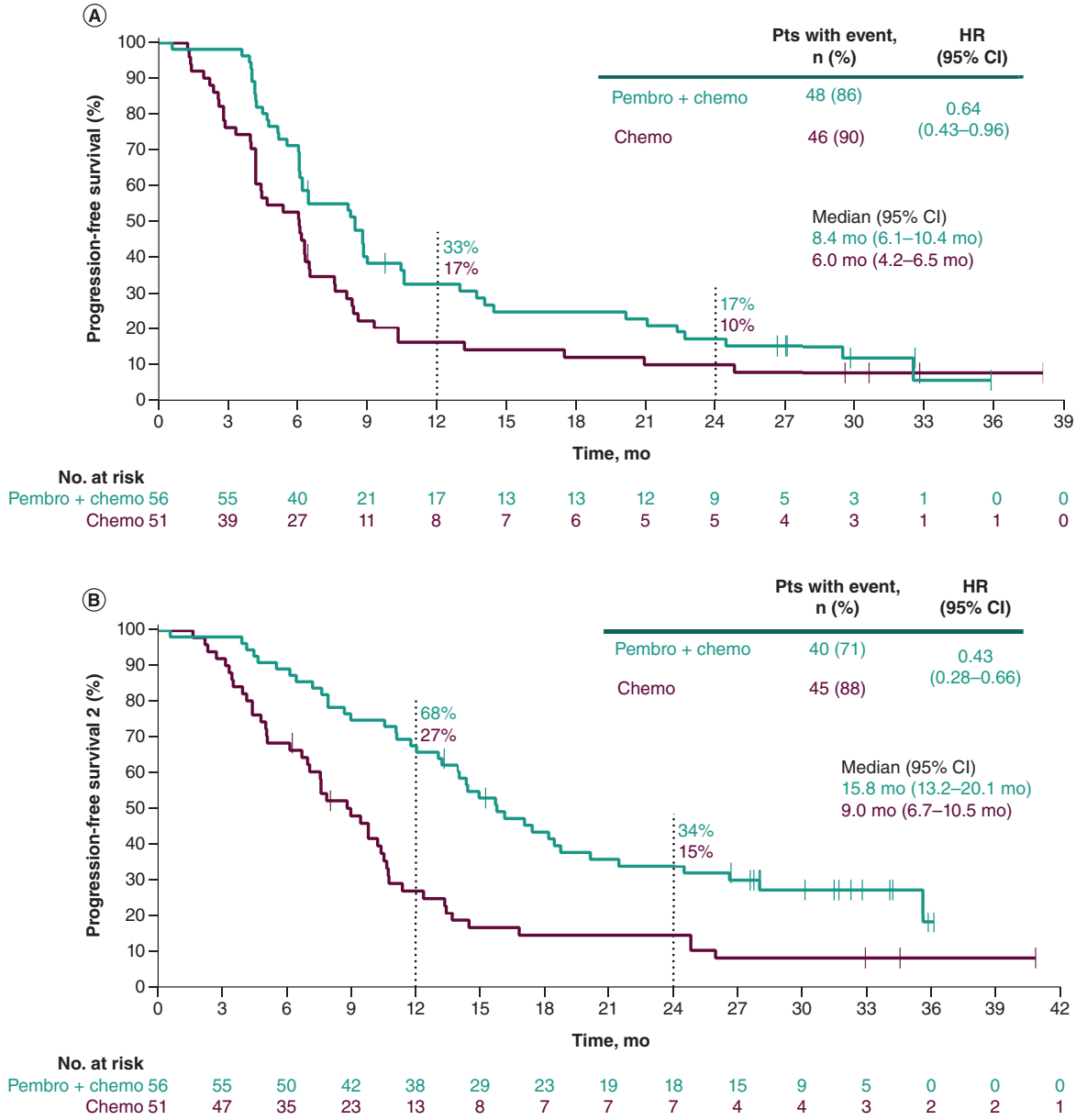

Figure 3. Kaplan-Meier estimates of progression-free survival. (A) Kaplan-Meier analysis of progression-free survival among patients who received pembrolizumab plus chemotherapy and those who received chemotherapy alone. **(B)** Progression-free survival after initiating new anticancer therapy (PFS2).
HR: Hazard ratio; Pt: Patient.

patients (8%) in the chemotherapy alone group. The most common immune-mediated AEs were hyperthyroidism (11% with pembrolizumab plus chemotherapy vs 0% with chemotherapy alone), hypothyroidism (9 vs 0%), and pneumonitis (7 vs 8%). Grade 3–5 immune-mediated AEs occurred in 6 patients (11%) in the pembrolizumab plus chemotherapy group and 2 patients (4%) in the chemotherapy alone group. Infusion reactions occurred in 7% of patients in the pembrolizumab plus chemotherapy group and 0% in the chemotherapy alone group. All infusion reactions were grade 1 or 2.

Discussion

To our knowledge, this analysis represents the largest patient-level pooled analysis and longest follow-up describing outcomes for pembrolizumab plus chemotherapy versus chemotherapy alone among East Asian patients with PD-

Table 2. Confirmed ORR assessed per RECIST version 1.1 by blinded independent central review.

	Pembrolizumab plus chemotherapy (n = 56)	Chemotherapy alone (n = 51)
ORR, % (95% CI)[†]		
Number of patients	40	22
% (95% CI)	71 (58–83)	43 (29–58)
Best overall response, n (%)		
Complete response	1 (2)	0
Partial response	39 (70)	22 (43)
Stable disease	13 (23)	18 (35)
Progressive disease	0	8 (16)
Not evaluable[‡]	3 (5)	2 (4)
No assessment[§]	0	1 (2)
Time to response, median (range), mo[†]	1.4 (1.2–3.0)	1.4 (0.8–4.9)
DOR, median (range), mo[¶]	6.7 (2.1 to 34.5+)	4.9 (1.4+ to 36.6+)
Response ≥12 mo, %[#]	30	26

[†]Includes confirmed complete responses plus partial responses.
[‡]Includes patients with ≥1 postbaseline tumor assessment, none of which were evaluable for response, and those with a postbaseline tumor assessment <6 wk from randomization showing a complete response, a partial response, or stable disease.
[§]No postbaseline assessment was available for a response evaluation.
[¶]+ indicates no progressive disease at the time of the last disease assessment.
[#]Percentage of patients with response ≥12 months was calculated using the product-limit (Kaplan-Meier) method for censored data.
DOR: Duration of response; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; PD-L1: Programmed cell death ligand 1; RECIST: Response Evaluation Criteria in Solid Tumor; TPS: Tumor proportion score.

L1-negative NSCLC. Our results demonstrate a long-term survival benefit for the combination of pembrolizumab plus chemotherapy, supporting this combination as a standard-of-care treatment option for this patient population.

In our analysis, the 2-year OS rate was 46% for pembrolizumab plus chemotherapy and 28% for chemotherapy alone, with an HR for OS that favored pembrolizumab plus chemotherapy (HR, 0.55 [95% CI: 0.35–0.87]). These rates were similar to the 41% and 25% rates observed in the global population [27]. The OS benefit was accompanied by improvements in ORR and DOR with pembrolizumab plus chemotherapy versus chemotherapy alone. Disease control (ie, complete or partial response or stable disease) was attained by 95% of patients who received pembrolizumab and 78% who received chemotherapy. The combination of pembrolizumab plus chemotherapy was also associated with improved PFS relative to chemotherapy alone. The Kaplan-Meier curves for PFS had separated by 3 months, suggesting that early disease control with pembrolizumab plus chemotherapy was an important contributor to the observed long-term benefit. Analyses of outcomes in patient subgroups showed that the OS and PFS benefits associated with addition of pembrolizumab to chemotherapy were observed regardless of whether patients had baseline liver or brain metastases.

The results of this analysis are consistent with those from the global pooled analysis, which included 65 patients from East Asia as well as patients from Europe, North America, and other regions. In the global analysis, pembrolizumab plus chemotherapy was associated with improved OS and PFS (median OS, 19.0 vs 11.4 months; HR, 0.63 [95% CI: 0.50–0.79]; median PFS, 6.9 vs 5.8 months; HR, 0.68 [95% CI: 0.56–0.83]) and a higher ORR compared with chemotherapy alone (50 vs 30%) [27]. Together, these results suggest that the magnitude of treatment benefit among Asian patients is consistent with that among the global study population. Interestingly, the magnitude of OS benefit among East Asian patients in this analysis appeared greater than that for patients in the global pooled analysis, particularly for patients with squamous disease (East Asia pooled analysis: HR for OS in the overall population, 0.55 [95% CI: 0.35–0.87]; HR for OS among patients with squamous histology, 0.62 [95% CI: 0.37–1.02]); global pooled analysis: HR for OS in the overall population, 0.63 [95% CI: 0.50–0.79]; HR for OS in patients with squamous histology, 0.81 [95% CI: 0.58–1.14]). However, when comparing these analyses it is important to note that the 95% confidence intervals were wide and overlapped. Although baseline disease characteristics were generally well balanced between the treatment groups, a higher proportion of patients had nonsquamous histology in the pembrolizumab plus chemotherapy group (likely owing to the 2:1 randomization ratio in KEYNOTE-189), and there was a higher proportion of patients with liver metastasis, a poor prognostic factor, in the chemotherapy alone group. Given these factors it is not clear that the numerical differences in OS benefit between the global and Asian populations are clinically meaningful. Moreover, to the extent that there may

Table 3. Summary of adverse events[†].

	Pembrolizumab plus chemotherapy (n = 56)		Chemotherapy alone (n = 51)	
	Any grade	Grade 3–5[‡]	Any grade	Grade 3–5[‡]
Patients with any AE	56 (100)	45 (80)	51 (100)	42 (82)
Treatment related	55 (98)	40 (71)	51 (100)	39 (76)
Led to discontinuation of any study drug	12 (21)	7 (13)	6 (12)	6 (12)
Led to death	3 (5)	3 (5)	2 (4)	2 (4)
Led to treatment-related death	2 (4)	2 (4)	0	0
Treatment-related AEs occurring in ≥10% of patients in either group				
Alopecia	30 (54)	0	23 (45)	0
Decreased white blood cell count	29 (52)	12 (21)	26 (51)	11 (22)
Anemia	28 (50)	6 (11)	32 (63)	8 (16)
Decreased neutrophil count	28 (50)	21 (38)	25 (49)	20 (39)
Decreased appetite	24 (43)	0	24 (47)	0
Nausea	17 (30)	0	13 (25)	0
Increased alanine aminotransferase	14 (25)	0	3 (6)	1 (2)
Hypoesthesia	13 (23)	0	8 (16)	0
Myalgia	13 (23)	0	7 (14)	2 (4)
Neutropenia	13 (23)	0	9 (18)	0
Decreased platelet count	13 (23)	4 (7)	8 (16)	1 (2)
Increased aspartate aminotransferase	12 (21)	0	4 (8)	1 (2)
Constipation	12 (21)	0	16 (31)	0
Diarrhea	12 (21)	3 (5)	7 (14)	1 (2)
Fatigue	10 (18)	1 (2)	5 (10)	0
Malaise	10 (18)	0	8 (16)	0
Rash	10 (18)	0	4 (8)	0
Arthralgia	9 (16)	0	7 (14)	0
Hyponatremia	8 (14)	5 (9)	1 (2)	1 (2)
Leukopenia	8 (14)	5 (9)	9 (18)	2 (4)
Hiccups	7 (13)	0	6 (12)	0
Stomatitis	7 (13)	0	3 (6)	0
Hyperthyroidism	6 (11)	0	0	0
Peripheral neuropathy	6 (11)	0	6 (12)	1 (2)
Vomiting	5 (9)	0	7 (14)	0
Pyrexia	5 (9)	0	6 (12)	0
Peripheral sensory neuropathy	4 (7)	0	6 (12)	0
Pain in extremity	2 (4)	0	6 (12)	0
Patients with any immune-mediated AE or infusion reaction	22 (39)	6 (11)	4 (8)	2 (4)
Hyperthyroidism	6 (11)	0	0	0
Hypothyroidism	5 (9)	0	0	0
Pneumonitis	4 (7)	2 (4)	4 (8)	2 (4)
Infusion reaction	4 (7)	0	0	0
Adrenal insufficiency	2 (4)	0	0	0
Severe skin reaction	2 (4)	1 (2)	0	0
Thyroiditis	2 (4)	0	0	0
Colitis	1 (2)	1 (2)	0	0
Hepatitis	1 (2)	1 (2)	0	0
Hypophysitis	1 (2)	0	0	0
Type 1 diabetes mellitus	1 (2)	1 (2)	0	0

[†]Nonserious AEs occurring ≤30 d after the last dose and serious AEs occurring ≤90 d after the last dose were included. For patients who crossed over from the control group to the pembrolizumab group, AEs that occurred after the first dose of the crossover phase were excluded.
[‡]AE grades were based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
All data are n (%).
AE: Adverse event.

be differences in treatment benefit between the global and Asian populations, it is uncertain what clinical and/or biologic factors might contribute to such differences.

Among patients who crossed over to receive pembrolizumab monotherapy on-study, the median OS from the time of starting pembrolizumab was 11.7 months and median PFS was 2.8 months. These outcomes are notable because patients with PD-L1-negative disease are not typically eligible for pembrolizumab monotherapy. Moreover, it should be noted that PFS2 (which accounts for second-line therapy) was longer with pembrolizumab plus chemotherapy than with chemotherapy alone, providing further support for a first-line pembrolizumab plus chemotherapy regimen.

To our knowledge, this is the only analysis showing a long-term survival benefit from combining immunotherapy with chemotherapy in patients in East Asia with PD-L1-negative NSCLC. Results from phase III studies of several other anti–PD-1 (tislelizumab [32,33], sintilimab [34], camrelizumab [35] and toripalimab [36]) or anti–PD-L1 monoclonal antibodies (sugemalimab [37]) have been evaluated in combination with platinum-based chemotherapy as first-line treatment for advanced/metastatic NSCLC in trials conducted in China. In each of these studies, addition of the anti–PD-1 or anti–PD-L1 antibody to chemotherapy was shown to improve PFS over chemotherapy alone in the ITT population, and HRs for PFS favored the treatment arm over the control arm among patients with tumors that did not express PD-L1. However, it is important to note that median follow-up in these studies was meaningfully shorter than in our analysis and that, at present, only toripalimab plus chemotherapy has been demonstrated to improve OS over chemotherapy alone [36]. Among patients with PD-L1-negative NSCLC, the HR for OS was 0.79 (95% CI: 0.49–1.31) for toripalimab plus chemotherapy versus placebo plus chemotherapy [36]. Notably, this HR for OS from the aforementioned study is less favorable than that in the current analysis of pembrolizumab plus chemotherapy in East Asian patients with PD-L1-negative NSCLC (0.55 [95% CI: 0.35–0.87]).

Until recently, the combination of bevacizumab plus chemotherapy was one of the only treatments demonstrated to improve OS over chemotherapy alone for patients with advanced/metastatic NSCLC. Combination treatment with bevacizumab plus chemotherapy versus chemotherapy alone was associated with HRs of 0.79 (95% CI: 0.67–0.92; p = 0.003) in the phase III E4599 study and 0.93 (95% CI: 0.78–1.11; p = 0.42) in the phase III AVAiL study [38,39]. Addition of the anti–PD-L1 monoclonal antibody to bevacizumab plus chemotherapy was evaluated in the IMpower150 study and shown to provide limited OS benefit over bevacizumab plus chemotherapy both in the ITT population without *EGFR*/*ALK* alterations (HR, 0.80 [95% CI: 0.67–0.95) and in patients with PD-L1-negative disease without *EGFR*/*ALK* alteration (HR, 0.90 [95% CI: 0.71–1.14]). Again, the HRs for OS in these studies are less favorable than that in the current analysis (0.55 [95% CI: 0.35–0.87]). In a network meta-analysis of outcomes that included patients irrespective of tumor PD-L1 expression level, HRs for OS were statistically significant for the combination of pembrolizumab plus chemotherapy versus chemotherapy alone (HR range, 0.42–0.61) and versus bevacizumab plus chemotherapy (HR range, 0.44–0.53) [40].

Dual immunotherapy approaches combining an anti-PD-1 or anti-PD-L1 antibody in combination with an anti–CTLA-4 antibody either with or without chemotherapy have been evaluated in patients with advanced/metastatic NSCLC. The combination of nivolumab plus ipilimumab was associated with improved OS (HR, 0.64 [95% CI: 0.51–0.81]) and PFS (0.74 [95% CI: 0.58–0.94]) versus chemotherapy alone in patients with PD-L1-negative NSCLC after 4 years of follow-up in the phase III CheckMate-227 study [41,42]. Results from the CheckMate-9LA study of nivolumab plus ipilimumab plus chemotherapy versus chemotherapy alone in patients with advanced/metastatic NSCLC were similar: among patients with PD-L1-negative disease, the HR for OS was 0.67 (95% CI: 0.51–0.88) and the HR for PFS was 0.69 (95% CI: 0.52–0.91) [43]. In the phase III POSEIDON study, the combination of durvalumab plus chemotherapy did not demonstrate an OS benefit relative to chemotherapy alone (HR, 0.86 [95% CI: 0.72–1.02]) and the addition of tremelimumab provided limited additional benefit (HR vs chemotherapy alone, 0.77 [95% CI: 0.65–0.92]) [44]. Of note, efficacy analyses among patients with tumors that did not express PD-L1 in these studies were not part of the statistical testing hierarchy and did not include an alpha allocation, which limits the interpretability of the results. Although direct comparisons are challenging given the different study populations, different assays to evaluate PD-L1 expression, timing of assessments, duration of follow-up, and statistical methods employed, comparison of results from studies evaluating pembrolizumab plus chemotherapy versus those from studies evaluating dual immunotherapy approaches (either with or without chemotherapy) suggest that dual immunotherapy treatment regimens may increase toxicity without providing meaningful improvements in efficacy outcomes among patients with PD-L1-negative disease.

All patients in our analysis experienced at least one AE and most experienced treatment-related AEs. Relative to the global analysis, a similar proportion of patients experienced grade 3–5 AEs in the current analysis, and a smaller proportion of patients in both the pembrolizumab plus chemotherapy group (37 and 21%, respectively) and in the chemotherapy alone group (17 and 12%, respectively) discontinued any treatment due to an AE [27]. Of note, the median time between randomization and data cut-off was longer in the current analysis (33 months) than in the global analysis (28 months).

Notably, the benefit in patients with PD-L1-negative NSCLC demonstrated in the current analysis is broadly consistent with those previously reported among patients with PD-L1–positive disease in KEYNOTE-021 cohort G, KEYNOTE-189, and KEYNOTE-407 studies, and support the clinically meaningful magnitude of benefit that we observed. In an updated analysis of the KEYNOTE-189 study, HRs for OS were 0.62 (95% CI: 0.42–0.92) for patients with PD-L1 TPS 1%–49% and 0.59 (95% CI: 0.39–0.88) for patients with PD-L1 TPS ≥50% [21]. Among patients with PD-L1 TPS ≥1% in an updated analysis of the KEYNOTE-407 study the HR for OS was 0.67 (95% CI: 0.49–0.91) [22].

Conclusion

Taken together, the findings from the current analysis suggest that the effects of pembrolizumab observed in the primary studies may translate into long-term survival benefits for patients in East Asia with PD-L1-negative, advanced NSCLC. The combination of pembrolizumab plus chemotherapy provided clinically meaningful benefit compared with chemotherapy alone: OS and PFS were prolonged, ORR was higher, and DOR was longer with pembrolizumab versus the control group. As expected, pembrolizumab demonstrated manageable safety in these patients. These results are consistent with the global phase III studies [15,16,27] and support the use of pembrolizumab plus chemotherapy as a standard of care, first-line therapy for East Asian patients with advanced NSCLC, regardless of PD-L1 expression.

Summary points

- Limited evidence is available for the combination of pembrolizumab plus platinum-based chemotherapy in East Asian patients with programmed cell death protein 1 (PD-L1)-negative non-small-cell lung cancer (NSCLC).
- Of 1438 patients enrolled in the three international, multicenter, randomized controlled studies and two study extensions, 107 patients (7.4%) from East Asia had PD-L1-negative NSCLC and were included in this pooled analysis.
- Pembrolizumab plus chemotherapy improved overall survival (hazard ratio: 0.55 [95% CI: 0.35–0.87]) and progression-free survival (0.64 [95% CI: 0.43–0.96]) versus chemotherapy alone.
- 2-year overall survival rates were 46% with pembrolizumab plus chemotherapy and 28% with chemotherapy alone.
- Median and progression-free survival after initiating new anticancer therapy, including crossover to pembrolizumab (PFS2) was longer in the pembrolizumab plus chemotherapy group versus chemotherapy alone (hazard ratio: 0.43 [95% CI: 0.28–0.66]).
- The safety profile of pembrolizumab plus chemotherapy was manageable and was consistent with that observed in the global study populations.
- These results demonstrate a long-term survival benefit for the combination of pembrolizumab plus chemotherapy and support this combination as a standard-of-care treatment option for East Asian patients with PD-L1-negative NSCLC.

Author contributions

Y Cheng had full access to all the data in the study and takes responsibility for the integrity and the accuracy of the data analysis. The work reported in the paper has been performed by the authors, unless clearly specified in the text. Conception, design, or planning of the study: Y Cheng, S Xiao, Y Yan, J Chih-Hsin Yang. Acquisition, analysis, or interpretation of the data: all authors. Provision of study materials/patients: Y Cheng, L Cao, T Kurata, J Hu, D Wang, J Chih-Hsin Yang. Review of the manuscript for important intellectual content: all authors. Decision to submit the manuscript for publication: all authors.

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Ethical conduct of research

The studies were conducted in compliance with the ethical principles originating from the Declaration of Helsinki and with the International Council on Harmonisation Good Clinical Practice guidelines and all applicable local and national regulations. For each study, the protocol was approved by an appropriate Institutional Review Board.

Informed consent

All patients provided written informed consent to participate.

Data availability statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (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.

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