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ORIGINAL ARTICLE

Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189

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Background: In the phase III KEYNOTE-189 study (NCT02578680), pembrolizumab plus pemetrexed and platinum-based chemotherapy (pemetrexed—platinum) significantly improved overall survival (OS) and progression-free survival (PFS) in patients with previously untreated metastatic nonsquamous non-small-cell lung cancer (NSCLC) versus placebo plus pemetrexed—platinum. We report updated efficacy outcomes from the protocol-specified final analysis, including outcomes in patients who crossed over to pembrolizumab from pemetrexed—platinum and in patients who completed 35 cycles (~2 years) of pembrolizumab.

Patients and methods: Eligible patients were randomized 2 : 1 to receive pembrolizumab 200 mg ($n = 410$) or placebo ($n = 206$) every 3 weeks (for up to 35 cycles, ~2 years) plus four cycles of pemetrexed (500 mg/m^2) and investigators' choice of cisplatin (75 mg/m^2) or carboplatin (area under the curve 5 mg·min/ml) every 3 weeks, followed by pemetrexed until progression. Patients assigned to placebo plus pemetrexed—platinum could cross over to pembrolizumab upon progression if eligibility criteria were met. The primary endpoints were OS and PFS.

Results: After a median follow-up of 31.0 months, pembrolizumab plus pemetrexed—platinum continued to improve OS [hazard ratio (HR), 0.56; 95% confidence interval (CI), 0.46-0.69] and PFS (HR, 0.49; 95% CI, 0.41-0.59) over placebo plus pemetrexed—platinum regardless of programmed death-ligand 1 expression. Objective response rate (ORR) (48.3% versus 19.9%) and time to second/subsequent tumor progression on next-line treatment (PFS2; HR, 0.50; 95% CI, 0.41-0.61) were improved in patients who received pembrolizumab plus pemetrexed—platinum. Eighty-four patients (40.8%) from the placebo plus pemetrexed—platinum group crossed over to pembrolizumab on-study. Grade 3-5 adverse events occurred in 72.1% of patients receiving pembrolizumab plus pemetrexed—platinum and 66.8% of patients receiving placebo plus pemetrexed—platinum. Fifty-six patients completed 35 cycles (~2 years) of pembrolizumab; ORR was 85.7% and 53 (94.6%) were alive at data cut-off.

Conclusions: Pembrolizumab plus pemetrexed—platinum continued to show improved efficacy outcomes compared with placebo plus pemetrexed—platinum, with manageable toxicity. These findings support first-line pembrolizumab plus pemetrexed—platinum in patients with previously untreated metastatic nonsquamous NSCLC.

Key words: pembrolizumab, chemotherapy, nonsquamous non-small-cell lung cancer

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INTRODUCTION

Pembrolizumab, an anti-programmed death 1 (PD-1) monoclonal antibody, has been approved as a first-line therapy for metastatic non-small-cell lung cancer (NSCLC), both as monotherapy [in patients with NSCLC expressing programmed death-ligand 1 (PD-L1) and without sensitizing *EGFR*/*ALK* genomic aberrations] and combined with platinum-based chemotherapy (pemetrexed—platinum in patients with metastatic nonsquamous NSCLC without sensitizing *EGFR*/*ALK* genomic aberrations; carboplatin and paclitaxel or nab-paclitaxel protein-bound in patients with metastatic squamous NSCLC).[1-4]

Approval for pembrolizumab in combination with pemetrexed—platinum chemotherapy in patients with metastatic nonsquamous NSCLC without sensitizing *EGFR*/*ALK* alterations was based on results from the KEYNOTE-021 study[5] and, predominantly, from the protocol-specified analysis from the phase III KEYNOTE-189 study.[6] In the randomized, double-blind, placebo-controlled KEYNOTE-189 study with a median time from randomization to date of death/data cut-off of 10.5 months, pembrolizumab plus pemetrexed and carboplatin/cisplatin (pembrolizumab plus pemetrexed—platinum) significantly improved overall survival (OS) [hazard ratio (HR), 0.49; 95% confidence interval (CI), 0.38-0.64; $P < 0.001$], progression-free survival (PFS) (HR, 0.52; 95% CI, 0.43-0.64; $P < 0.001$), and objective response rate (ORR) (47.6% versus 18.9%; $P < 0.001$) versus placebo plus pemetrexed—platinum in patients with previously untreated metastatic nonsquamous NSCLC without sensitizing *EGFR*/*ALK* alterations.[6,7] These findings were confirmed in a subsequent analysis with ∼10 additional calendar months of follow-up, demonstrating continued improvement in OS (HR, 0.56; 95% CI, 0.45-0.70) and PFS (HR, 0.48; 95% CI, 0.40-0.58).[7] The safety profile of pembrolizumab plus pemetrexed—platinum was manageable in the interim and updated analyses.[6,7]

We report efficacy and safety outcomes from the protocol-specified final analysis of KEYNOTE-189, with an additional 18 calendar months of follow-up compared to the first interim analysis. For the first time, we also describe outcomes among patients who crossed over from placebo plus pemetrexed—platinum to pembrolizumab and in patients who completed 35 cycles (∼2 years) of pembrolizumab treatment.

PATIENTS AND METHODS

Patients and study design

The KEYNOTE-189 study design (ClinicalTrials.gov, NCT02578680) has been previously described.[6,7] Briefly, eligible patients were ≥18 years of age, with previously untreated histologically/cytologically confirmed stage IV nonsquamous NSCLC, without *EGFR*/*ALK* aberrations, Eastern Cooperative Oncology Group (ECOG) performance status of 0/1, measurable disease as per RECIST v1.1, and provided a tumor sample for PD-L1 evaluation. Patients with clinically stable previously treated brain metastases and with asymptomatic untreated brain metastases ≤1.5 cm were eligible. Patients were excluded if they had known active brain metastases and/or carcinomatous meningitis, had active autoimmune disease that required systemic treatment in the last 2 years, had a history of noninfectious pneumonitis that required steroids or current pneumonitis, had received radiation therapy >30 Gy to the lung within 6 months of the first dose of trial treatment, or were receiving systemic immunosuppressive treatment. Study procedures were approved by an institutional review board/ethics committee at each institution. Patients provided written informed consent.

Patients were randomized 2 : 1 to receive pembrolizumab 200 mg or saline placebo, both administered intravenously every 3 weeks, for up to 35 cycles; all patients received pemetrexed 500 mg/m^2 and investigator's choice of either cisplatin 75 mg/m^2 or carboplatin area under the curve 5 mg·min/ml for the first four cycles, followed by pemetrexed maintenance therapy until progression or unacceptable toxicity. Randomization was stratified by PD-L1 tumor proportion score (TPS; ≥1% versus <1%), choice of platinum chemotherapy (cisplatin versus carboplatin), and smoking status (never versus former/current). Treatment continued until documented disease progression, unacceptable adverse events (AEs), intercurrent illness preventing further treatment administration, investigator decision, or withdrawal of patient consent. Patients in the placebo plus pemetrexed—platinum group who experienced disease progression confirmed by blinded independent central review using RECIST v1.1 could cross over to receive pembrolizumab monotherapy for up to 35 cycles if safety criteria were met and the patient had no new/progressing brain metastases, had not received any systemic anticancer therapies other than the allocated chemotherapies, and had completed palliative radiotherapy (≤30 Gy) ≥7 days before the first dose of crossover treatment. Patients in the pembrolizumab group who stopped treatment after attaining an investigator-determined confirmed complete response (CR) as per RECIST v1.1 or those who completed 35 cycles of pembrolizumab with best overall response of stable disease (SD), partial response (PR), or CR, and experienced subsequent disease progression (by blinded independent central review) and had not received new anticancer treatment after the last dose of trial treatment, could receive a second course of pembrolizumab monotherapy for up to 17 cycles if all eligibility criteria related to safety were met.

Assessments

Tumor PD-L1 expression was assessed as previously described.[6,7] Tumor imaging occurred at weeks 6 and 12, every 9 weeks for the first 48 weeks, and every 12 weeks thereafter. Patients were contacted every 12 weeks to assess survival. AEs were assessed throughout the trial and 30 days after the last dose of study treatment (90 days for serious AEs) and were graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

Endpoints

The primary endpoints were OS and PFS assessed as per RECIST v1.1 by blinded independent central review. Secondary endpoints included ORR, duration of response (DOR), and safety. Exploratory endpoints included PFS2, defined as time from randomization to second/subsequent tumor progression on next-line treatment (including subsequent anti-PD-1/PD-L1 therapy) or death from any cause, and PFS (investigator assessment as per RECIST v1.1) and OS in patients who crossed over from placebo plus pemetrexed—platinum to pembrolizumab monotherapy.[7,8] Events for PFS2 were characterized as previously described.[7]

Statistical analyses

Efficacy was assessed in the intention-to-treat (ITT) population and included all randomized patients. Safety analyses were carried out in the as-treated population, which included all randomized subjects who received ≥1 dose of study drug. OS, PFS and PFS2 were estimated using the Kaplan—Meier method. The magnitude of treatment difference (HRs and associated 95% CIs) was calculated using the stratified Cox proportional hazards model with Efron's method of tie-handling. Stratification factors used for randomization were applied. This final analysis was carried out without multiplicity adjustment; no alpha was assigned.

RESULTS

Patients and treatments

Six hundred and sixteen eligible patients from 118 sites were randomized to receive pembrolizumab plus pemetrexed—platinum ($n = 410$) or placebo plus pemetrexed—platinum ($n = 206$). Baseline characteristics were well balanced between treatment groups (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.04.008).

At the time of data cut-off (20 May 2019), median time from randomization to data cut-off was 31.0 (range, 26.5-38.8) months, and median time from randomization to death/data cut-off was 18.8 (range, 0.2-38.8) months. Seventeen patients in the pembrolizumab plus pemetrexed—platinum group and one patient in the placebo plus pemetrexed—platinum group were continuing to receive pemetrexed. Median duration of treatment was 7.2 months (range, 1 day-35.4 months) in the pembrolizumab plus pemetrexed—platinum group and 4.2 months (range, 1 day-27.2 months) in the placebo plus pemetrexed—platinum group. At data cut-off, 75 patients (18.3%) in the pembrolizumab plus pemetrexed—platinum group and 11 patients (5.3%) in the placebo plus pemetrexed—platinum group were alive and had discontinued or completed study treatment without subsequent treatment. Fifty-six patients (13.7%) allocated to pembrolizumab plus pemetrexed—platinum had completed 35 cycles of pembrolizumab treatment. Two hundred and three patients (49.5%) in the pembrolizumab plus pemetrexed—platinum group and 127 patients (61.7%; including patients in the on-study crossover) in the placebo plus pemetrexed—platinum group received ≥1 subsequent therapy. Among patients assigned to placebo plus pemetrexed—platinum, 84 patients (40.8%) crossed over to pembrolizumab monotherapy on-study, and an additional 31 patients (15.0%) received anti-PD-1/anti-PD-L1 immunotherapy as a subsequent therapy off-study (2 of whom were randomized to, but did not receive, placebo plus pemetrexed—platinum on-study; Supplementary Figure S1 and Table S2, available at https://doi.org/10.1016/j.annonc.2021.04.008). Thus, of 206 patients in the placebo plus pemetrexed—platinum group, 115 received subsequent anti-PD-1/anti-PD-L1 therapy for an effective crossover rate of 55.8%.

Efficacy outcomes in the intention-to-treat population

At data cut-off, 258 patients (62.9%) in the pembrolizumab plus pemetrexed—platinum group and 163 (79.1%) in the placebo plus pemetrexed—platinum group had died, representing an additional 64 deaths since the previous analysis.[7] Median (95% CI) OS was 22.0 (19.5-24.5) months in the pembrolizumab plus pemetrexed—platinum group and 10.6 (8.7-13.6) months in the placebo plus pemetrexed—platinum group (HR, 0.56; 95% CI, 0.46-0.69; Figure 1A). Estimated OS rates at 24 months were 45.7% and 27.3%, respectively. OS benefit was greater in patients in the pembrolizumab plus pemetrexed—platinum group versus placebo plus pemetrexed—platinum group, regardless of PD-L1 TPS (Figure 1B-D; Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2021.04.008) and across all key patient subgroups assessed including brain metastases status, liver metastases status, M1a/M1b stage at baseline, age, ECOG performance status, sex, smoking status, and allocated platinum chemotherapy (Figure 1E).

At data cut-off, events of disease progression/death had occurred in 337 patients (82.2%) in the pembrolizumab plus pemetrexed—platinum group and 197 patients (95.6%) in the placebo plus pemetrexed—platinum group. Median (95% CI) PFS was 9.0 (8.1-10.4) months in the pembrolizumab plus pemetrexed—platinum group and 4.9 (4.7-5.5) months in the placebo plus pemetrexed—platinum group (HR, 0.49; 95% CI, 0.41-0.59; Figure 2A). Estimated PFS rates at 24 months were 22.0% and 3.4%, respectively. PFS was prolonged in patients treated with pembrolizumab plus pemetrexed—platinum versus placebo plus pemetrexed—platinum irrespective of PD-L1 TPS (Figure 2B-D; Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2021.04.008) and across subgroups (Figure 2E).

The ORR was 48.3% (CR, $n = 5$; PR, $n = 193$) in the pembrolizumab plus pemetrexed—platinum group and 19.9% (CR, $n = 1$; PR, $n = 40$) in the placebo plus pemetrexed—platinum group (Table 1). ORRs in the pembrolizumab plus pemetrexed—platinum group were improved versus the placebo plus pemetrexed—platinum

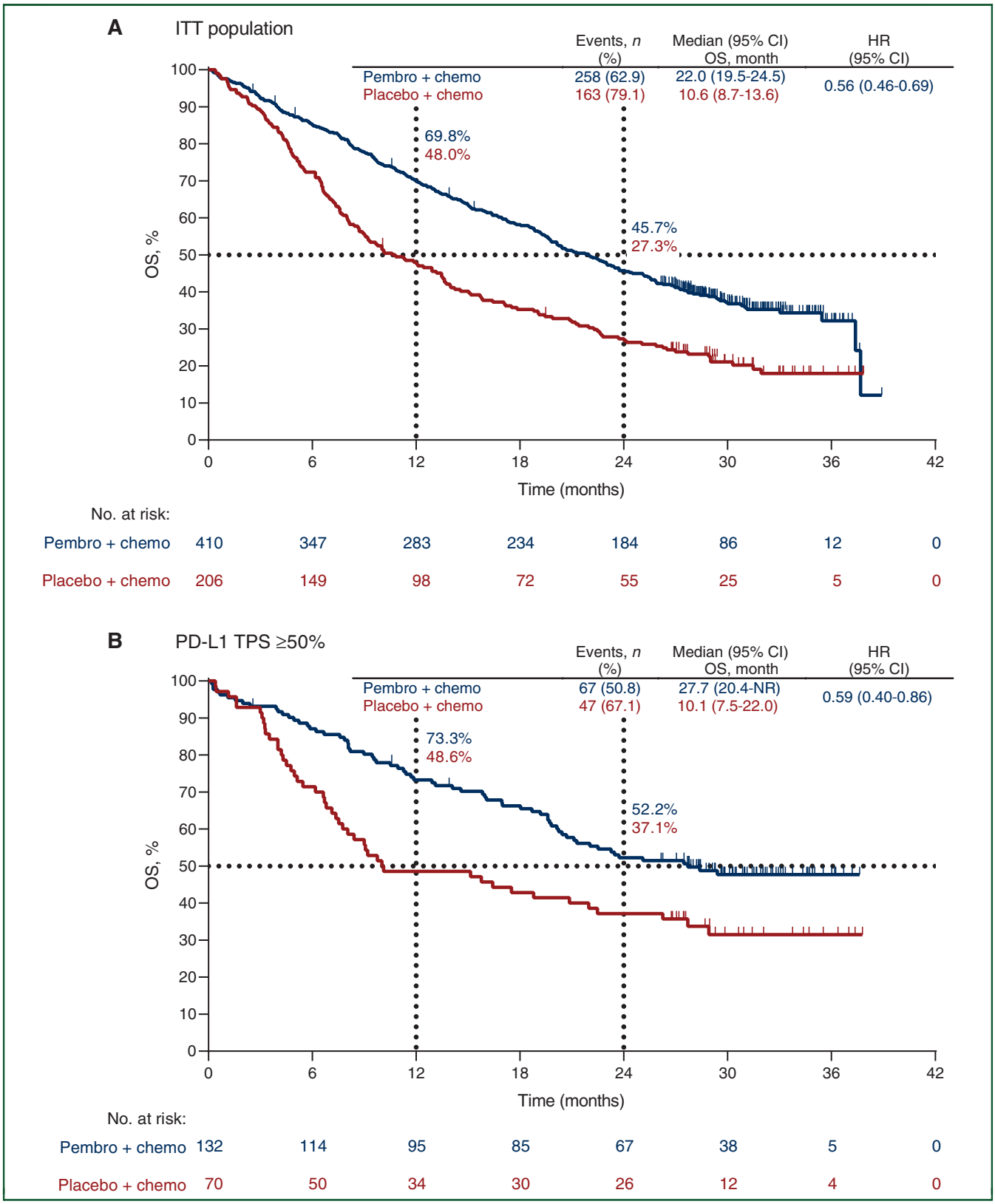

Figure 1. Overall survival.
Analysis of OS in the (A) ITT population, in patients with (B) PD-L1 TPS ≥50%, (C) PD-L1 TPS 1%-49%, (D) PD-L1 TPS <1%, and in (E) key subgroups of patients. Chemo, pemetrexed—platinum; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; NR, not reached; OS, overall survival; PD-L1 TPS, programmed death-ligand 1 tumor proportion score; Pembro, pembrolizumab.

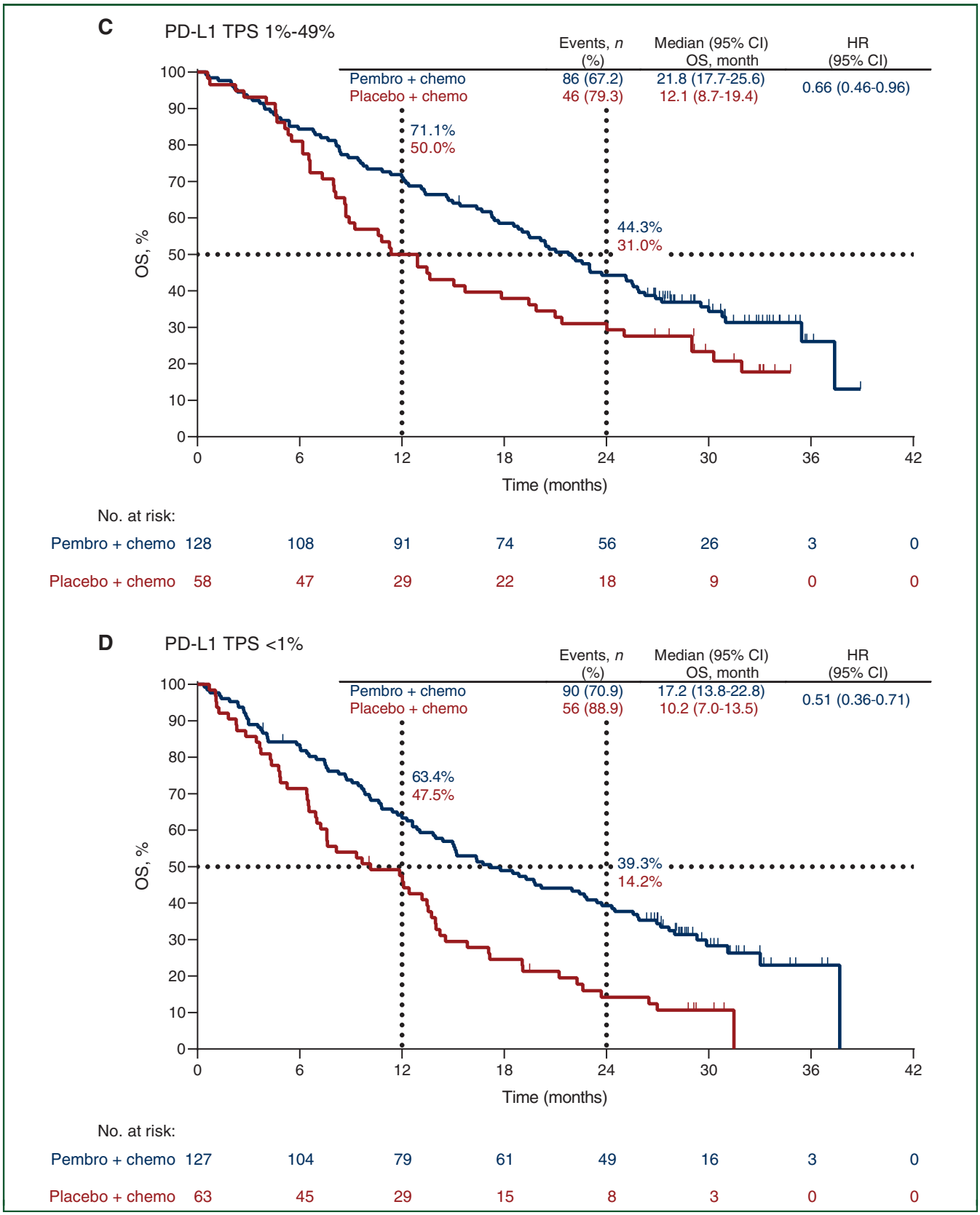

Figure 1. **(Continued)**

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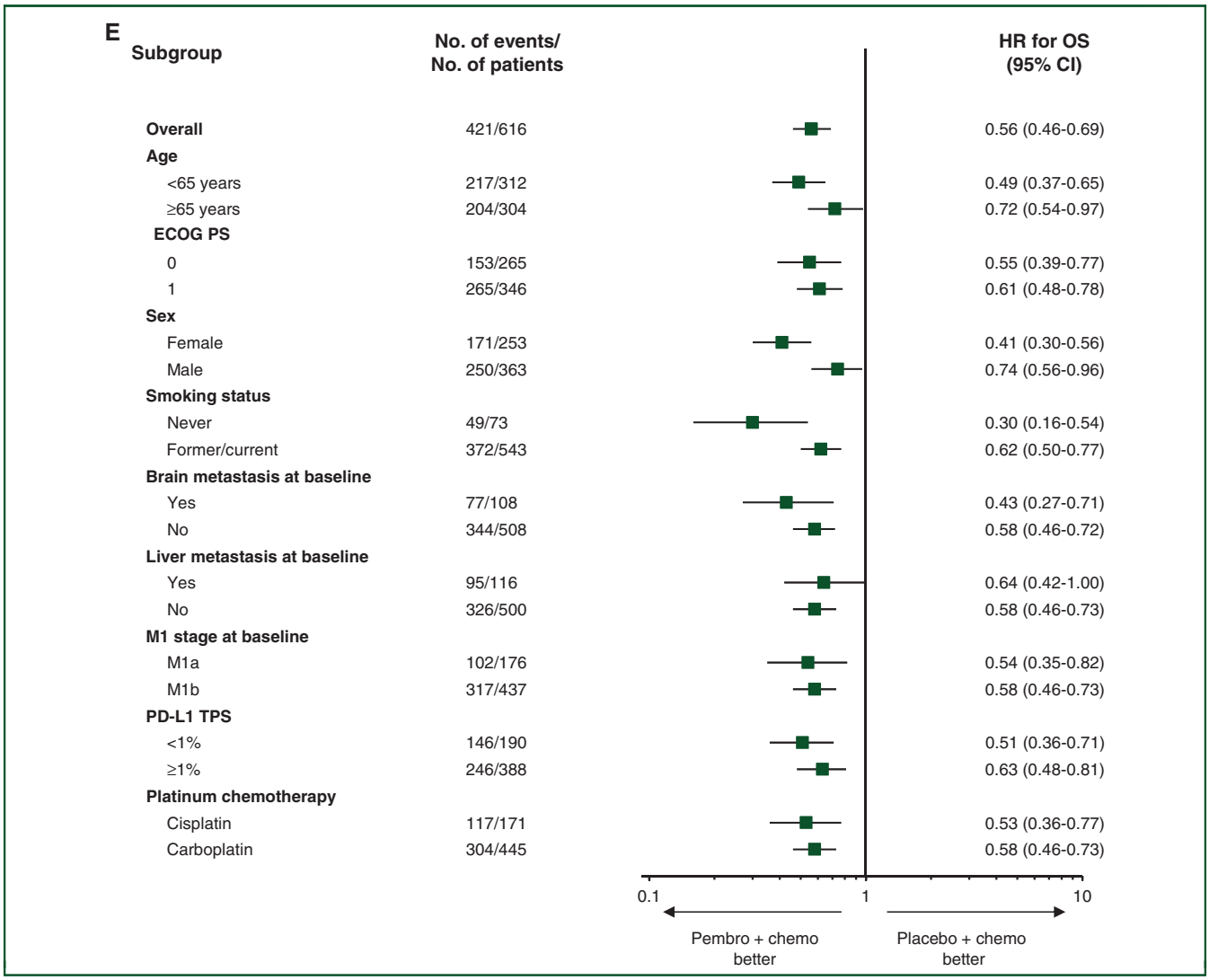

Figure 1. (Continued)

group regardless of PD-L1 TPS (Table 1; Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2021.04.008). Median (range) DOR was 12.5 (1.1+ to 34.9+) months in the pembrolizumab plus pemetrexed—platinum group and 7.1 (2.4 to 27.8+) months in the placebo plus pemetrexed—platinum group (Table 1) and the proportion of patients with an ongoing response at 24 months was 28.4% with pembrolizumab plus pemetrexed—platinum versus 9.9% with placebo plus pemetrexed—platinum.

Median (95% CI) PFS2 was 17.0 (15.1-19.1) months in the pembrolizumab plus pemetrexed—platinum group and 9.0 (7.4-10.4) months in the placebo plus pemetrexed—platinum group (HR, 0.50; 95% CI, 0.41-0.61); PFS2 rates at 24 months were 38.2% and 16.2%, respectively (Figure 3).

Efficacy of pembrolizumab in patients in the on-study crossover

Among the 84 patients in the placebo plus pemetrexed—platinum group who crossed over to on-study pembrolizumab monotherapy, 28.6% had PD-L1 TPS <1%. Median (95% CI) OS from the time of starting pembrolizumab crossover was 6.9 (4.8-10.5) months and the OS rate at 24 months was 20.7%. Median (95% CI) PFS was 2.8 (2.5-2.9) months based on investigator assessment as per RECIST v1.1; PFS rate at 24 months was 12.1%. Fifteen patients (17.9%) had a confirmed objective response (PD-L1 TPS ≥50%, $n = 8$; PD-L1 TPS 1%-49%, $n = 5$; PD-L1 <1%, $n = 1$; and PD-L1 not evaluable, $n = 1$). Median (range) DOR was 21.9 (3.9 to 25.9+) months; the proportion of patients with an ongoing response at 12 months was 60.0%.

Safety in the intention-to-treat population

AEs (irrespective of relationship to treatment) occurred in 404 patients (99.8%) in the pembrolizumab plus pemetrexed—platinum group and 200 patients (99.0%) in the placebo plus pemetrexed—platinum group; treatment-related AEs occurred in 376 patients (92.8%) and 183 patients (90.6%), respectively (Table 2; Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.04.008). In both treatment groups, the most frequently occurring AEs were nausea, anemia, and fatigue

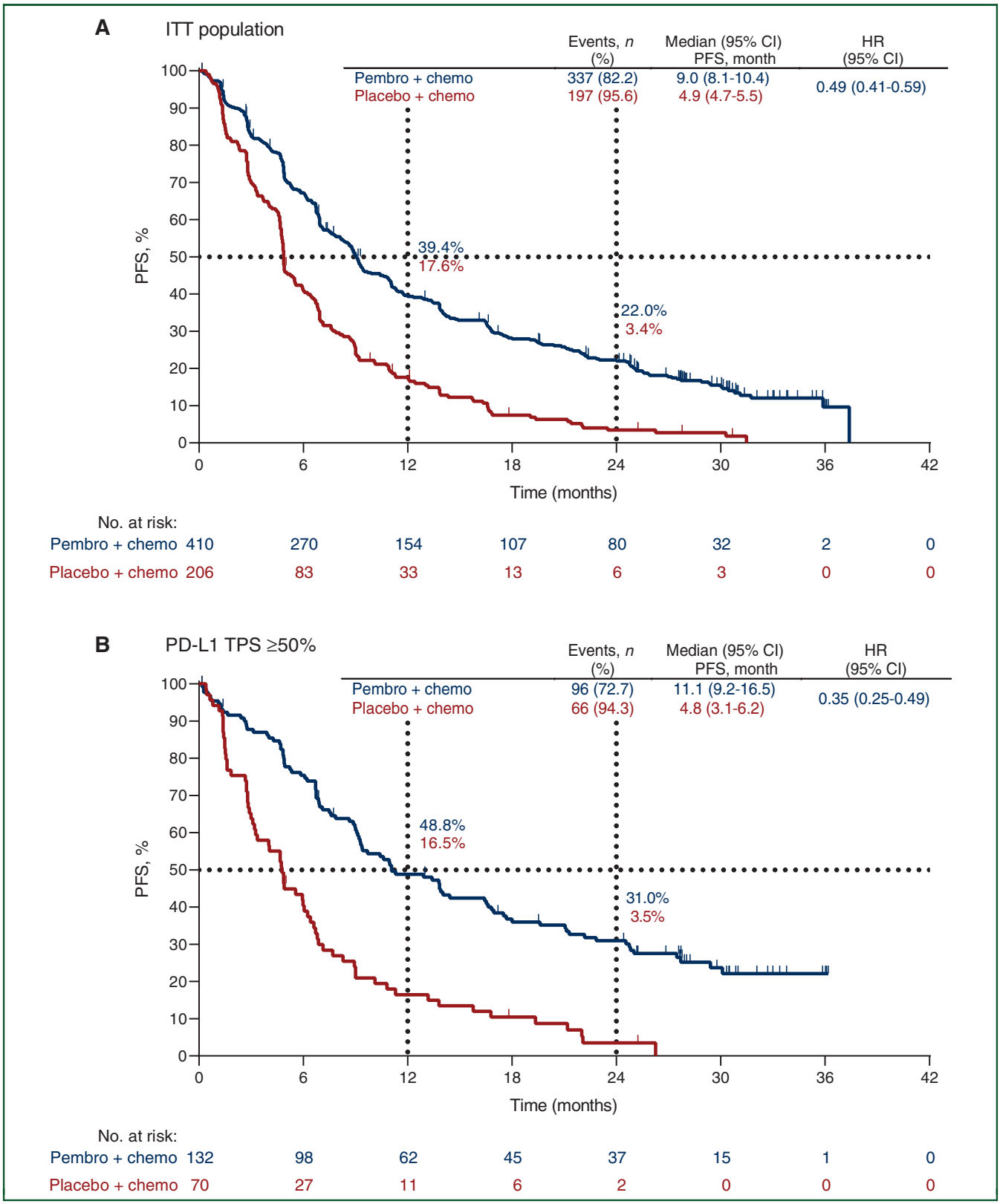

Figure 2. Progression-free survival.
Analysis of PFS in the (A) ITT population, in patients with (B) PD-L1 TPS ≥50%, (C) PD-L1 TPS 1%-49%, (D) PD-L1 TPS <1%, and in (E) key subgroups of patients. Chemo, pemetrexed—platinum; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; PD-L1 TPS, programmed death-ligand 1 tumor proportion score; Pembro, pembrolizumab; PFS, progression-free survival.

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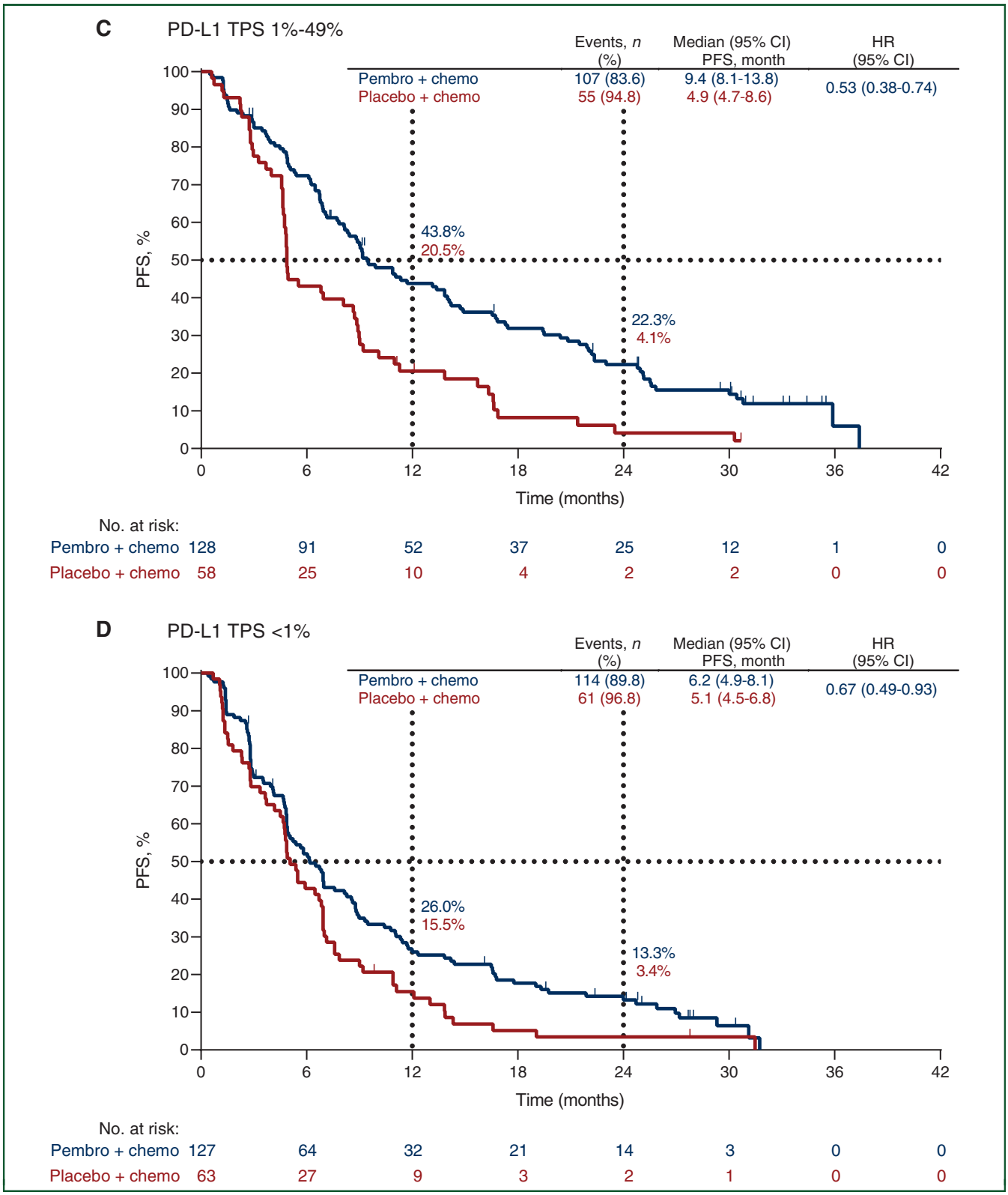

Figure 2. (Continued)

(Table 2). Grade 3-5 AEs (all cause) occurred in 292 patients (72.1%) in the pembrolizumab plus pemetrexed—platinum group and 135 patients (66.8%) in the placebo plus pemetrexed—platinum group. Overall, 29 patients (7.2%) in the pembrolizumab plus pemetrexed—platinum group and 14 patients (6.9%) in the placebo plus pemetrexed—platinum group had a fatal AE (Table 2).

There were no new safety signals identified with long-term follow-up. There were no new AEs of acute kidney injury since the prior analysis.[7] No additional fatal AEs

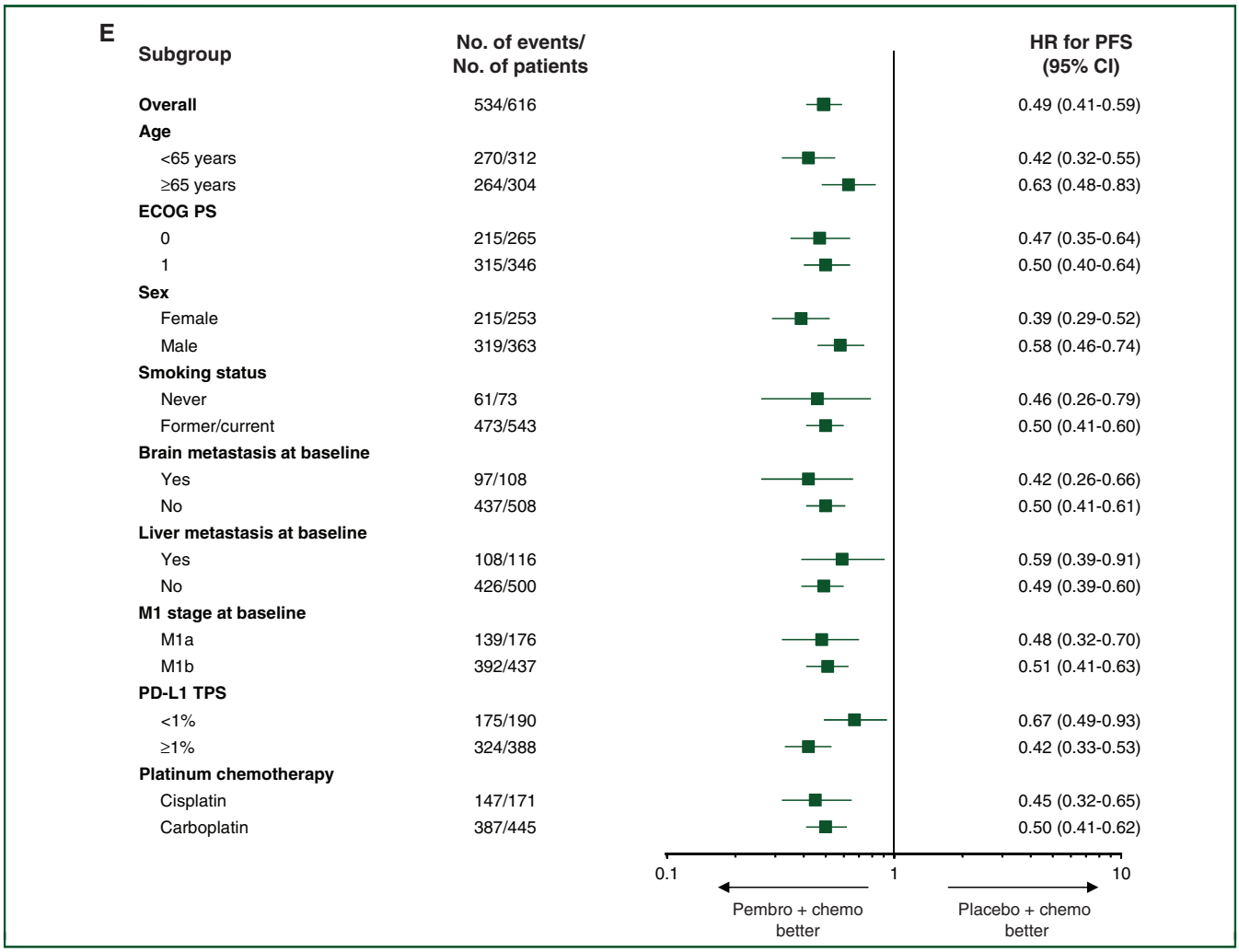

Figure 2. (Continued)

occurred since the prior analysis.[7] Treatment-related AEs leading to death were acute kidney injury ($n = 2$), pneumonitis ($n = 2$), death (unknown cause), encephalopathy, neutropenic sepsis, and pneumonia ($n = 1$ each) in the pembrolizumab plus pemetrexed—platinum group and pneumonia and septic shock ($n = 1$ each) in the placebo plus pemetrexed—platinum group. Additionally, there was no evidence of an increase in exposure-adjusted AE rates in the overall study population in either treatment group (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.04.008).

Immune-mediated AEs and infusion reactions of any grade and irrespective of relationship to treatment occurred in 110 patients (27.2%) in the pembrolizumab plus pemetrexed—platinum group and 26 patients (12.9%) in the placebo plus pemetrexed—platinum group. The most common immune-mediated AEs in the pembrolizumab plus pemetrexed—platinum group were hypothyroidism (7.9%), hyperthyroidism (4.9%), and pneumonitis (4.9%). Grade 3-5 immune-mediated AEs and infusion reactions occurred in 49 patients (12.1%) in the pembrolizumab plus pemetrexed—platinum group and 9 patients (4.5%) in the placebo plus pemetrexed—platinum group. Two patients in the pembrolizumab plus pemetrexed—platinum group had grade 5 pneumonitis; there were no other grade 5 immune-mediated AEs and infusion reactions. Infusion reactions occurred in 11 patients (2.7%) and 3 patients (1.5%), respectively (Table 2).

Outcomes in patients who completed 35 cycles (~2 years) of treatment with pembrolizumab

In the pembrolizumab plus pemetrexed—platinum group, 56 patients had completed 35 cycles (~2 years) of pembrolizumab treatment at the time of data cut-off (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.04.008). The median time from randomization to data cut-off was 31.5 (range, 26.6-38.8) months. Baseline characteristics were generally similar between these patients and the ITT population; the majority of patients had PD-L1 TPS ≥1% (83.9%; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.04.008). Median duration of treatment was 25.6 (range, 23.5-35.4) months. ORR (RECIST v1.1 by blinded independent central review) was 85.7%, 4 patients had CR, 44 patients had PR, and 8 patients had SD as their best

Table 1. Confirmed objective response based on blinded independent central review as per RECIST v1.1

	All Patients $N = 616$		TPS ≥50% $n = 202$[a]		TPS 1%-49% $n = 186$[a]		TPS <1% $n = 190$[a]	
	Pembrolizumab combination $n = 410$	Placebo combination $n = 206$	Pembrolizumab combination $n = 132$	Placebo combination $n = 70$	Pembrolizumab combination $n = 128$	Placebo combination $n = 58$	Pembrolizumab combination $n = 127$	Placebo combination $n = 63$
Best overall response, *n* (%)								
CR	5 (1.2)	1 (0.5)	1 (0.8)	0	3 (2.3)	1 (1.7)	0	0
PR	193 (47.1)	40 (19.4)	81 (61.4)	18 (25.7)	61 (47.7)	11 (19.0)	42 (33.1)	9 (14.3)
SD[b]	149 (36.3)	104 (50.5)	33 (25.0)	28 (40.0)	46 (35.9)	33 (56.9)	58 (45.7)	36 (57.1)
PD	37 (9.0)	36 (17.5)	6 (4.5)	16 (22.9)	15 (11.7)	7 (12.1)	15 (11.8)	9 (14.3)
Not evaluable	12 (2.9)	8 (3.9)	5 (3.8)	1 (1.4)	0	2 (3.4)	7 (5.5)	4 (6.3)
No assessment	14 (3.4)	17 (8.3)	6 (4.5)	7 (10.0)	3 (2.3)	4 (6.9)	5 (3.9)	5 (7.9)
ORR, % (95% CI)	48.3 (43.4-53.2)	19.9 (14.7-26.0)	62.1 (53.3-70.4)	25.7 (16.0-37.6)	50.0 (41.0-59.0)	20.7 (11.2-33.4)	33.1 (25.0-42.0)	14.3 (6.7-25.4)
Median DOR,[c] months (range)	12.5 (1.1+ to 34.9+)	7.1 (2.4 to 27.8+)	15.1 (1.2+ to 34.9+)	7.1 (3.4 to 19.4)	13.6 (2.1+ to 34.5)	7.6 (2.4 to 27.8+)	10.8 (1.1+ to 26.9)	7.8 (4.1 to 26.4+)

+, no progressive disease by the time of last disease assessment; CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TPS, tumor proportion score.

[a] Excludes 38 patients for whom programmed death-ligand 1 (PD-L1) expression could not be evaluated.

[b] SD includes both SD and non-CR/non-PD.

[c] Kaplan–Meier estimate.

response. Median DOR was 34.5 (range, 7.6 to 34.9+) months and 33 patients were without disease progression or subsequent therapy at data cut-off (Figure 4). Median OS was not reached. Fourteen of 56 patients had disease progression before completing 35 cycles of pembrolizumab and were allowed to continue treatment beyond progression, as specified by protocol. At data cut-off, 7 of 42 patients who had not experienced disease progression before completing 35 cycles of pembrolizumab had a PFS event (12-month PFS rate following completion of 35 cycles, 78.5%). Among these seven patients, one received docetaxel, three were without therapy, and one had received a second course of pembrolizumab; two patients had death as their progression event. At data cut-off, 53 patients (94.6%) were alive (PD-L1 TPS ≥50%, $n = 30$; PD-L1 TPS 1%-49%, $n = 15$; PD-L1 <1%, $n = 6$; and PD-L1 not evaluable, $n = 2$) and 3 patients (5.4%) had died.

All patients who completed 35 cycles of pembrolizumab experienced an AE (all cause). Grade 3-4 AEs occurred in 34 patients (60.7%); the most common were neutropenia (17.9%), anemia (12.5%), and asthenia (7.1%). Immune-mediated AEs occurred in 21 patients (37.5%); 6 patients (10.7%) had grade 3-4 immune-mediated AEs (severe skin reactions, $n = 2$; colitis, hypothyroidism, myocarditis, type 1 diabetes mellitus, $n = 1$ each). There were no fatal AEs among patients who completed 35 cycles of pembrolizumab.

DISCUSSION

In this protocol-specified final analysis of the KEYNOTE-189 study, pembrolizumab plus pemetrexed–platinum continued to show clinically meaningful improvements in OS and PFS compared with placebo plus pemetrexed–platinum in patients with previously untreated metastatic nonsquamous NSCLC without sensitizing *EGFR*/*ALK* alterations. With a median time from randomization to data cut-off of 31.0 months, median OS and PFS were approximately two-fold longer with pembrolizumab plus pemetrexed–platinum compared with placebo plus pemetrexed–platinum. This analysis continued to demonstrate improved ORR and PFS2 benefits with pembrolizumab plus pemetrexed–platinum versus placebo plus pemetrexed–platinum. Importantly, the OS benefit with pembrolizumab plus pemetrexed–platinum was observed both in patients with tumors expressing PD-L1 and in patients with tumors that did not express PD-L1. Responses were durable and clinically meaningful in patients who completed 35 cycles (~2 years) of pembrolizumab. AEs were manageable with no new safety signals identified.

Long-term efficacy outcomes in this analysis confirm and extend findings from prior analyses.[6,7] We continued to observe OS benefit with pembrolizumab plus pemetrexed–platinum versus placebo plus pemetrexed–platinum (HR, 0.56), with estimated 24-month survival rates of 45.7% in the pembrolizumab plus pemetrexed–platinum group and 27.3% in the placebo plus pemetrexed–platinum group. The magnitude of treatment effect favoring pembrolizumab plus

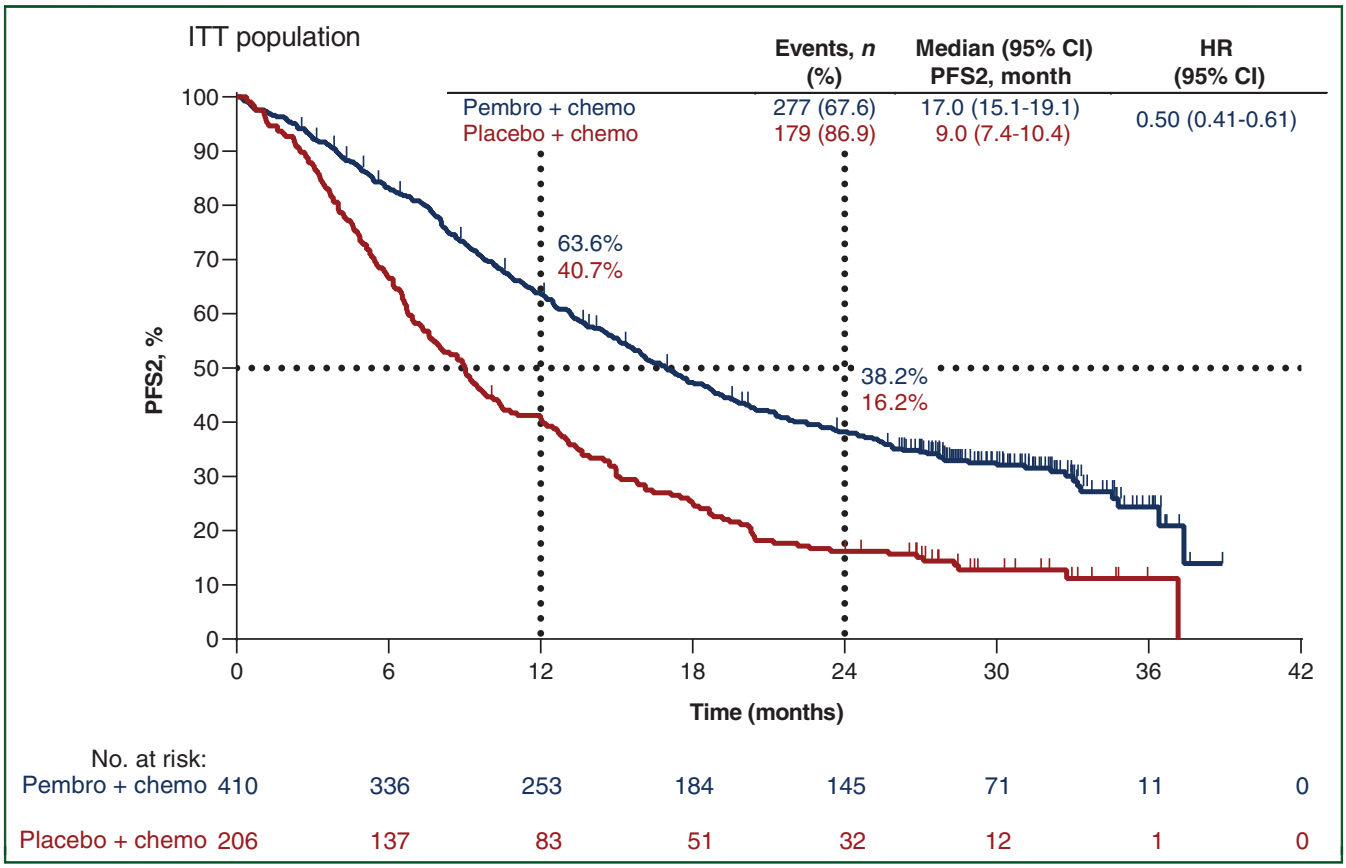

Figure 3. Analysis of PFS2 in the ITT population. PFS2 was defined as the time from randomization to objective tumor progression on next-line treatment [including subsequent anti-PD-(L)1 therapy] or death from any cause, whichever occurred first. Events for PFS2 were characterized as the time from randomization to investigator-assessed disease progression that led to cessation of second-line therapy, the start of third-line therapy for patients who stopped second-line therapy without disease progression, and the time from randomization to death for patients who either stopped second-line therapy without disease progression and did not initiate third-line therapy or did not receive second-line therapy. Patients were censored for PFS2 at the time of last known survival if they were alive and either had not received second-line therapy or had stopped second-line therapy without disease progression and had not initiated third-line therapy.
Chemo, pemetrexed—platinum; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PD-(L)1, programmed death 1/programmed death-ligand 1; Pembro, pembrolizumab; PFS2, progression-free survival 2.

pemetrexed—platinum was consistent with that reported in an analysis from cohort G of the phase II KEYNOTE-021 study with ~4 years of follow-up, which reported a median OS of 34.5 months with pembrolizumab plus pemetrexed—carboplatin versus 21.1 months with pemetrexed—carboplatin (HR, 0.71).[9] Notably, median OS was longer in both arms of KEYNOTE-021 cohort G than in the corresponding treatment arms in KEYNOTE-189. This difference in outcomes may be explained, in part, by the inclusion of patients in KEYNOTE-021 with better prognosis (e.g. a higher proportion of women and patients who had never smoked).

Improvements in OS with pembrolizumab plus pemetrexed—platinum versus placebo plus pemetrexed—platinum were observed despite a high effective crossover rate (55.8%) from the placebo plus pemetrexed—platinum group to subsequent anti-PD-(L)1 therapy. This high crossover rate may potentially explain the plateau in the Kaplan—Meier curve for OS among patients in the placebo plus pemetrexed—platinum group. To further evaluate the effect of pembrolizumab plus pemetrexed—platinum on outcomes during subsequent therapy, we assessed PFS2. Importantly, median PFS2 was substantially improved in patients in the pembrolizumab plus pemetrexed—platinum group versus the placebo plus pemetrexed—platinum group (HR, 0.50), demonstrating that the treatment effects observed in the first line were maintained after initial progression.

Among the 84 patients who received pembrolizumab in the on-study crossover, there was evidence of meaningful antitumor activity, with an ORR of 17.9% and a median OS of 6.9 months. Notably, 28.6% of patients in the crossover population had PD-L1 TPS <1%. Pembrolizumab has been shown to improve outcomes versus docetaxel as second-line or later therapy in metastatic NSCLC in the phase II/III KEYNOTE-010 study in which median OS was 11.8 versus 8.4 months in patients with TPS ≥1% in a long-term follow-up analysis.[10] In KEYNOTE-189, patients with PD-L1 TPS <1% were permitted to cross over to pembrolizumab monotherapy. Among this group, 1 of 24 patients (4.2%) had an objective response. Patients with PD-L1 TPS <1% are not typically eligible for pembrolizumab monotherapy and this may have attenuated the antitumor activity of pembrolizumab in the crossover group.

Table 2. Summary of all-cause adverse events

Event	Pembrolizumab plus chemotherapy $n = 405$		Placebo plus chemotherapy $n = 202$	
Any AE, *n* (%)	404 (99.8)		200 (99.0)	
Grade 3-5	292 (72.1)		135 (66.8)	
Led to death[a]	29 (7.2)		14 (6.9)	
Led to treatment discontinuation				
Any treatment	146 (36.0)		35 (17.3)	
	Any grade	**Grade 3-5**	**Any grade**	**Grade 3-5**
AEs occurring in ≥15% of patients in either treatment group, *n* (%)				
Nausea	232 (57.3)	14 (3.5)	108 (53.5)	8 (4.0)
Anemia	193 (47.7)	75 (18.5)	98 (48.5)	35 (17.3)
Fatigue	175 (43.2)	31 (7.7)	78 (38.6)	7 (3.5)
Constipation	144 (35.6)	4 (1.0)	67 (33.2)	1 (0.5)
Diarrhea	131 (32.3)	21 (5.2)	44 (21.8)	6 (3.0)
Decreased appetite	121 (29.9)	5 (1.2)	64 (31.7)	2 (1.0)
Neutropenia	114 (28.1)	66 (16.3)	50 (24.8)	24 (11.9)
Vomiting	106 (26.2)	16 (4.0)	48 (23.8)	6 (3.0)
Cough	104 (25.7)	0	61 (30.2)	0
Dyspnea	102 (25.2)	16 (4.0)	53 (26.2)	8 (4.0)
Peripheral edema	101 (24.9)	2 (0.5)	34 (16.8)	0
Asthenia	88 (21.7)	27 (6.7)	49 (24.3)	7 (3.5)
Pyrexia	88 (21.7)	1 (0.2)	34 (16.8)	1 (0.5)
Rash	88 (21.7)	8 (2.0)	26 (12.9)	3 (1.5)
Thrombocytopenia	76 (18.8)	34 (8.4)	30 (14.9)	15 (7.4)
Lacrimation increased	74 (18.3)	0	22 (10.9)	0
Back pain	68 (16.8)	6 (1.5)	27 (13.4)	4 (2.0)
Immune-mediated AEs and infusion reactions, *n* (%)	110 (27.2)	49 (12.1)	26 (12.9)	9 (4.5)
Hypothyroidism	32 (7.9)	2 (0.5)	5 (2.5)	0
Hyperthyroidism	20 (4.9)	0	6 (3.0)	0
Pneumonitis	20 (4.9)	12 (3.0)	6 (3.0)	4 (2.0)
Colitis	13 (3.2)	7 (1.7)	0	0
Infusion reactions	11 (2.7)	1 (0.2)	3 (1.5)	0
Severe skin reactions	10 (2.5)	10 (2.5)	5 (2.5)	4 (2.0)
Nephritis	8 (2.0)	6 (1.5)	0	0
Hepatitis	7 (1.7)	6 (1.5)	0	0
Hypophysitis	3 (0.7)	0	0	0
Myositis	3 (0.7)	0	0	0
Pancreatitis	3 (0.7)	2 (0.5)	0	0
Encephalitis	2 (0.5)	2 (0.5)	0	0
Type 1 diabetes mellitus	2 (0.5)	2 (0.5)	0	0
Adrenal insufficiency	2 (0.5)	1 (0.2)	1 (0.5)	1 (0.5)
Myocarditis	1 (0.2)	1 (0.2)	0	0
Thyroiditis	1 (0.2)	0	0	0
Guillain–Barre syndrome	1 (0.2)	1 (0.2)	0	0

Reported in all patients who received ≥1 dose of study treatment.
AE, adverse event.
[a] Eight patients (2.0%) in the pembrolizumab combination group and two patients (1%) in the placebo combination group died from AEs attributed to study treatment by the investigator.

This is the largest study to report on outcomes in patients who received pembrolizumab plus pemetrexed–platinum and who completed 35 cycles (~2 years) of pembrolizumab therapy. The majority of patients who completed 35 cycles of pembrolizumab had PD-L1 TPS ≥1%. Responses were durable, with 55% of patients having an ongoing response at a median follow-up of 31.5 months and with 94.6% of patients alive at data cut-off. Similarly, findings from cohort G of KEYNOTE-021 demonstrated durable responses in patients who completed 35 cycles or 2 years of pembrolizumab therapy, albeit with a smaller patient population.[9] Together, these data support the 2-year treatment duration for pembrolizumab plus pemetrexed–platinum used in KEYNOTE-189 and demonstrate the potential for long-term benefit with this combination regimen.

Other phase III studies have investigated the role of immunotherapies in combination with platinum-based chemotherapy or immunotherapy in patients with nonsquamous NSCLC but are yet to report long-term survival data. In the IMpower132 study in patients with stage IV nonsquamous NSCLC, first-line atezolizumab plus carboplatin/cisplatin plus pemetrexed showed a non-significant improvement in OS (HR, 0.81; 95% CI, 0.64-1.03).[11] In part 1 of the CheckMate-227 study, early crossing of survival curves with delayed treatment benefit was observed with nivolumab plus ipilimumab versus chemotherapy (OS rate at 2 years of 40.1% versus 29.7%, respectively), and the nonsquamous NSCLC subgroup demonstrated an OS HR of 0.85 (95% CI, 0.69-1.04).[12] Furthermore, in part 2 of the CheckMate-227 study, the combination of nivolumab plus

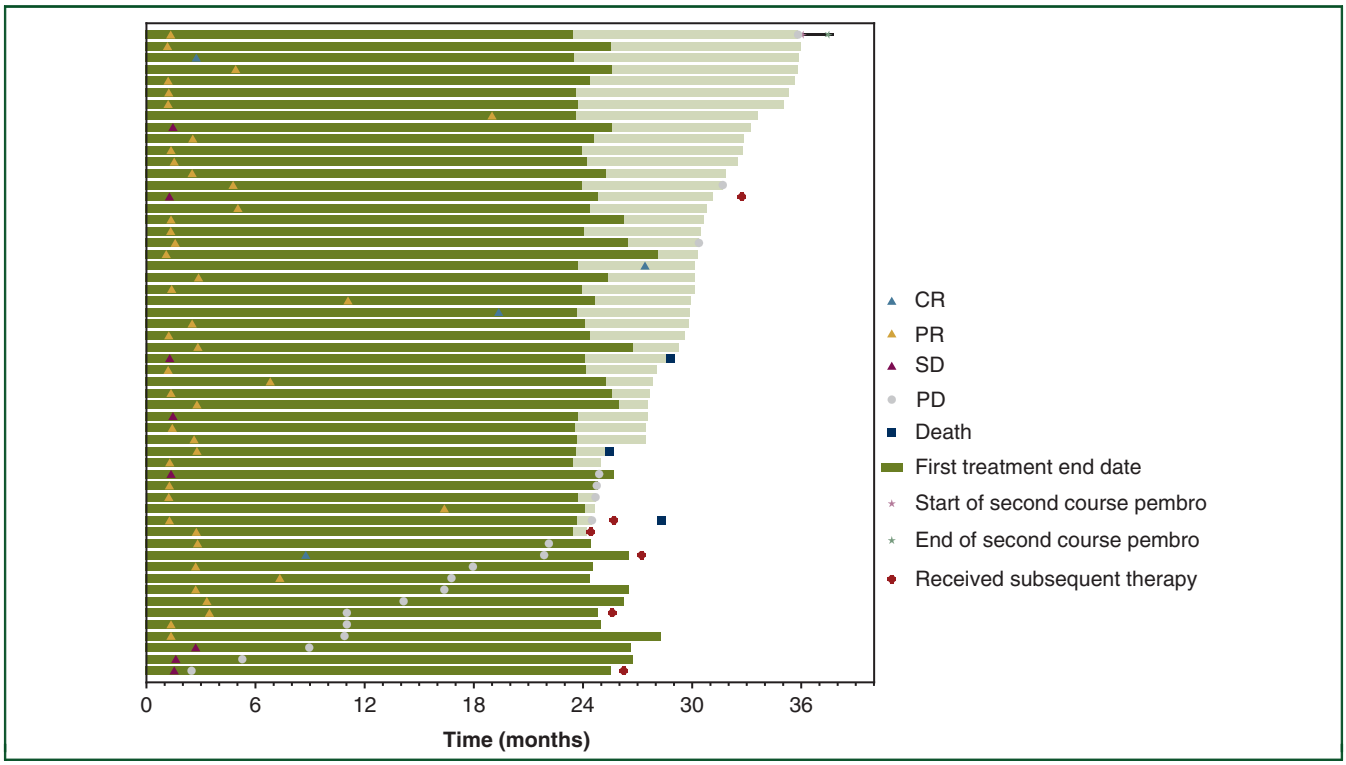

Figure 4. Time to response and response duration in patients who completed 35 cycles of pembrolizumab. Bar length (light green) represents the follow-up duration following first course treatment.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

chemotherapy did not improve OS compared with chemotherapy in patients with stage IV nonsquamous NSCLC (HR, 0.86; 95% CI, 0.69-1.08).[13] In an analysis of the CheckMate-9LA trial (median follow-up of 13.2 months), nivolumab plus ipilimumab plus platinum-doublet chemotherapy improved OS versus chemotherapy alone (HR, 0.66; 95% CI, 0.55-0.80; median OS, 15.6 versus 10.9 months).[14] At final efficacy analysis of the IMpower150 study, atezolizumab plus bevacizumab and carboplatin plus paclitaxel improved OS versus bevacizumab and carboplatin plus paclitaxel (HR, 0.80; 95% CI, 0.67-0.95) in the ITT-wild-type (WT) population (i.e. patients with no *EGFR*/*ALK* alterations). Additionally, OS was not improved with atezolizumab plus carboplatin plus paclitaxel versus bevacizumab and carboplatin plus paclitaxel (ITT-WT; HR, 0.84; 95% CI, 0.71-1.00).[15]

The improvements in OS, PFS, and ORR with pembrolizumab plus pemetrexed—platinum continued to be observed in patients with PD-L1 TPS <1% (who are not eligible for treatment with pembrolizumab monotherapy) with longer follow-up.[16] Efficacy of pembrolizumab in combination with chemotherapy in patients with PD-L1 TPS <1% has been further described in a pooled analysis.[17] Although cross-trial comparisons are challenging, KEYNOTE-189 demonstrates a more favorable HR for OS among patients with tumors that did not express PD-L1 (HR, 0.51; 95% CI, 0.36-0.71; median OS, 17.2 versus 10.2 months) than was observed in IMpower150 (HR, 0.90; 95% CI, 0.71-1.14; median OS, 16.9 versus 14.1 months),[15] CheckMate-227 (HR, 0.62; 95% CI, 0.48-0.78; median OS, 17.2 versus 12.2 months),[18] and in an analysis of the CheckMate-9LA trial (HR, 0.62; 95% CI, 0.45-0.85; median OS, 16.8 versus 9.8 months).[14]

OS and PFS were improved in all key patient subgroups, including patients with baseline M1a and M1b disease (HR, 0.54 and 0.58, respectively). Although some evidence has suggested prognostic value for the baseline metastasis stage (M descriptors) for treatment with immune checkpoint inhibitors in NSCLC,[19] our findings support a role for pembrolizumab plus pemetrexed—platinum as a treatment option in these patient subgroups.

The nature and severity of AEs were consistent with prior experience with this regimen, and with the toxicity profile commonly associated with pemetrexed—platinum therapy and pembrolizumab monotherapy.[20,21] There were no new safety signals and no evidence of cumulative toxicity with long-term exposure. Grade 3-5 AEs occurred more frequently in the pembrolizumab plus pemetrexed—platinum group versus the placebo plus pemetrexed—platinum group. However, exposure-adjusted event rates of AEs were similar between the treatment groups. The greater exposure in the pembrolizumab plus pemetrexed—platinum group resulted in an increased possibility for an AE to develop and be recorded. The addition of pembrolizumab continues to show manageable toxicity with longer treatment duration. Compared with prior analysis,[7] there were no additional deaths due to AEs.

In conclusion, in this protocol-specified final analysis of KEYNOTE-189, the combination of pembrolizumab plus pemetrexed—platinum continued to show a long-term, clinically meaningful survival benefit compared with

placebo plus pemetrexed—platinum with a manageable safety profile. Pembrolizumab plus pemetrexed—platinum provided durable responses, with 94.6% of patients who completed 35 cycles (~2 years) of pembrolizumab alive at data cut-off. Our results support use of pembrolizumab plus pemetrexed—platinum as a standard-of-care therapy for patients with newly diagnosed metastatic nonsquamous NSCLC, irrespective of PD-L1 TPS.

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DISCLOSURE

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DATA SHARING

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, 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.

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