rapid communications

Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study

Charles M. Rudin, MD, PhD[1]; Mark M. Awad, MD, PhD[2]; Alejandro Navarro, MD[3]; Maya Gottfried, MD[4]; Solange Peters, MD, PhD[5]; Tibor Csőszi, MD[6]; Parneet K. Cheema, MD[7]; Delvys Rodriguez-Abreu, MD[8]; Mirjana Wollner, MD[9]; James Chih-Hsin Yang, MD, PhD[10]; Julien Mazieres, MD, PhD[11]; Francisco J. Orlandi, MD[12]; Alexander Luft, PhD, MD[13]; Mahmut Gümüş, MD[14]; Terufumi Kato, MD[15]; Gregory P. Kalemkerian, MD[16]; Yiwen Luo, PhD[17]; Victoria Ebiana, MD[17]; M. Catherine Pietanza, MD[17]; and Hye Ryun Kim, MD[18] on behalf of the KEYNOTE-604 Investigators

abstract

PURPOSE Pembrolizumab monotherapy has shown antitumor activity in patients with small-cell lung cancer (SCLC). The randomized, double-blind, phase III KEYNOTE-604 study compared pembrolizumab plus etoposide and platinum (EP) with placebo plus EP for patients with previously untreated extensive-stage (ES) SCLC.

METHODS Eligible patients were randomly assigned 1:1 to pembrolizumab 200 mg once every 3 weeks or saline placebo for up to 35 cycles plus 4 cycles of EP. Primary end points were progression-free survival (PFS; RECIST version 1.1, blinded central review) and overall survival (OS) in the intention-to-treat population. Objective response rate (ORR) and duration of response were secondary end points. Prespecified efficacy boundaries were one-sided $P = .0048$ for PFS and .0128 for OS.

RESULTS Of the 453 participants, 228 were randomly assigned to pembrolizumab plus EP and 225 to placebo plus EP. Pembrolizumab plus EP significantly improved PFS (hazard ratio [HR], 0.75; 95% CI, 0.61 to 0.91; $P = .0023$). Twelve-month PFS estimates were 13.6% with pembrolizumab plus EP and 3.1% with placebo plus EP. Although pembrolizumab plus EP prolonged OS, the significance threshold was not met (HR, 0.80; 95% CI, 0.64 to 0.98; $P = .0164$). Twenty-four-month OS estimates were 22.5% and 11.2%, respectively. ORR was 70.6% in the pembrolizumab plus EP group and 61.8% in the placebo plus EP group; the estimated proportion of responders remaining in response at 12 months was 19.3% and 3.3%, respectively. In the pembrolizumab plus EP and placebo plus EP groups, respectively, any-cause adverse events were grade 3-4 in 76.7% and 74.9%, grade 5 in 6.3% and 5.4%, and led to discontinuation of any drug in 14.8% and 6.3%.

CONCLUSION Pembrolizumab plus EP significantly improved PFS compared with placebo plus EP as first-line therapy for patients with ES-SCLC. No unexpected toxicities were seen with pembrolizumab plus EP. These data support the benefit of pembrolizumab in ES-SCLC.

J Clin Oncol 38. © 2020 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 30, 2020 and published at ascopubs.org/journal/jco on May 29, 2020: DOI https://doi.org/10.1200/JCO.20.00793

Written on behalf of the KEYNOTE-604 Investigators.

INTRODUCTION

Small-cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy strongly associated with tobacco use that accounts for approximately 15% of all lung cancers.[1] SCLC is characterized by a rapid doubling time and high growth fraction, and approximately two thirds of patients present with metastases at diagnosis.[2] The 5-year survival rate for patients with SCLC is only approximately 6%-7%.[3,4] Despite extensive study of different combinations, standard-of-care first-line therapy for extensive-stage (ES) SCLC has remained chemotherapy with etoposide and platinum (EP) for the past 30 years. Although EP is associated with high response rates, responses are not durable, and median overall survival (OS) is approximately 10 months.[5,6]

Monoclonal antibodies against programmed death 1 (PD-1) and its ligand PD-L1 have shown efficacy in patients with ES-SCLC in the monotherapy[7,8] and combination therapy[9,10] settings. In a pooled analysis of the 83 participants who received ≥ 2 prior therapies for recurrent or metastatic SCLC before enrolling in the

CONTEXT

Key Objective

Small-cell lung cancer (SCLC) is an aggressive cancer associated with a 5-year survival rate of < 10%. Availability of more efficacious first-line therapy would improve this prognosis. The phase III KEYNOTE-604 study of 453 patients with previously untreated extensive-stage (ES) SCLC assessed whether the addition of pembrolizumab to standard-of-care etoposide and platinum (EP) improved progression-free and overall survival.

Knowledge Generated

Although the addition of pembrolizumab to EP did not significantly prolong overall survival, it did significantly prolong the time that patients lived without disease progression. The adverse event profile of pembrolizumab plus EP was as expected and generally manageable.

Relevance

Pembrolizumab has clinical activity in ES-SCLC as well as an adverse event profile that allows it to be combined with other therapies. There is value in exploring pembrolizumab in combination with other therapies in patients with SCLC to identify a regimen that significantly prolongs overall survival.

KEYNOTE-028 and KEYNOTE-158 studies, monotherapy with pembrolizumab (anti–PD-1) was associated with a confirmed objective response rate (ORR) of 19.3% and a grade 3-5 treatment-related adverse event (AE) rate of 9.6%.[7] Responses were durable, with an estimated 67.7% of responses lasting ≥ 12 months. On the basis of these data, pembrolizumab was approved as third-line or later therapy for patients with metastatic SCLC in several countries, including the United States. In KEYNOTE-604, we assessed the efficacy and safety of adding pembrolizumab to EP as first-line therapy for ES-SCLC.

METHODS

Study Design and Participants

This randomized, double-blind, placebo-controlled phase III trial was conducted at 140 sites in 18 countries (Data Supplement, online only) in accordance with Good Clinical Practice and the protocol and its amendments, which were approved by the ethics body at each study site. All participants provided written informed consent. An independent data and safety monitoring committee periodically assessed safety and assessed efficacy at prespecified interim analyses.

Key eligibility criteria were age ≥ 18 years; histologically or cytologically confirmed SCLC not previously treated with systemic therapy; stage IV disease per American Joint Committee on Cancer, seventh edition, criteria[11]; measurable disease per RECIST version 1.1[12]; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; provision of a tumor sample for biomarker assessment; life expectancy ≥ 3 months; and adequate organ function. Patients with brain metastases were eligible if they completed treatment (eg, whole-brain radiation, stereotactic radiosurgery) ≥ 14 days before starting study treatment, had no evidence of new or enlarging brain metastases, and were neurologically stable without corticosteroids for ≥ 7 days before starting study treatment. Full eligibility criteria are summarized in the protocol (Data Supplement).

Treatment

Participants were randomly allocated in a 1:1 ratio to receive pembrolizumab 200 mg or matching saline placebo once every 3 weeks for 35 cycles or until disease progression, intolerable toxicity, or physician or participant decision. For the first 4 cycles, participants also received etoposide 100 mg/m^2 on days 1, 2, and 3 and the investigator's choice of carboplatin area under the plasma drug concentration-time curve 5 or cisplatin 75 mg/m^2 on day 1 of each 3-week cycle. All treatment was administered intravenously. Participants who achieved complete response (CR) or partial response (PR) after cycle 4 could receive up to 25 Gy of prophylactic cranial irradiation (PCI) in 10 fractions at the discretion of the investigator. Random allocation was performed using an interactive voice response/integrated web-response system and stratified by choice of platinum (carboplatin or cisplatin), baseline ECOG performance status (0 or 1), and baseline lactate dehydrogenase (LDH) concentration (≤ or > upper limit of normal [ULN]).

Assessments

Tumor imaging was performed at baseline, every 6 weeks for the first 48 weeks, and every 9 weeks thereafter. AEs were collected throughout treatment and for 30 days thereafter (90 days for serious AEs) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Survival was assessed every 8 weeks during follow-up. PD-L1 expression was assessed retrospectively using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA) and measured using the combined positive score (CPS), defined as the number of PD-L1–staining cells (tumor cells,

lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.[13]

End Points

The dual primary end points were progression-free survival (PFS; ie, the time from random assignment to disease progression or death, whichever occurred first) and OS (ie, the time from random assignment to death). Secondary end points were ORR (ie, the proportion of participants with CR or PR), duration of response (DOR; ie, the time from first evidence of CR or PR to disease progression or death, whichever occurred first), and safety. PFS, ORR, and DOR were assessed per RECIST version 1.1 by blinded, independent central review (BICR).

Statistical Analysis

Efficacy was assessed in the intention-to-treat (ITT) population, defined as all participants randomly allocated to treatment. Safety was assessed in the as-treated population, defined as all participants who received ≥ 1 dose of study treatment. A post hoc analysis of OS in the as-treated population was also performed. PFS, OS, and DOR were assessed using the Kaplan-Meier method; censoring rules are summarized in the Data Supplement. Between-group differences in PFS and OS were assessed using the stratified log-rank test; all resultant *P* values are one-sided. A stratified Cox proportional hazards model with Efron's method of tie handling was used to estimate the hazard ratios (HRs) and 95% CIs for PFS and OS. To account for possible nonproportional hazards of PFS and OS, exploratory analyses using the restricted mean survival time (RMST) method[14] were performed. Stratified Miettinen and Nurminen's method was used to assess the treatment difference in ORR. All stratified analyses were performed using the randomization stratification factors.

The protocol specified two interim analyses and a final analysis. The second interim analysis (IA2) was the prespecified final PFS analysis. The graphical method of Maurer and Bretz[15] was used to control the familywise type I error rate at one-sided $\alpha = .025$ across all hypotheses and interim analyses (Appendix Fig A1, online only). With the assumption of 453 participants enrolled over 14.5 months, median PFS of 4.3 months and median OS of 10 months in the placebo plus EP group, and an exponential dropout rate of 1% per month, the study had 96% power to demonstrate a PFS HR of 0.65 at $\alpha = .006$ with 387 PFS events at the final PFS analysis and 94% power to demonstrate an OS HR of 0.65 at $\alpha = .019$ with 294 deaths at the final OS analysis. The study was positive if pembrolizumab plus EP significantly prolonged at least one of the primary end points.

The first interim analysis was planned to occur approximately 18 months after study start when the estimated number of PFS events and deaths was 332 and 175, respectively. The analysis was based on a data cutoff of November 6, 2018, at which time 345 PFS events and 182 deaths accrued. IA2 was planned to occur approximately 22 months after study start when the estimated number of PFS events and deaths was 387 and 224, respectively. IA2 was based on a data cutoff of March 29, 2019, at which time 396 PFS events and 274 deaths accrued; the superiority boundary for PFS was one-sided $P = .0048$. The final analysis was planned to occur when 294 deaths accrued or approximately 31 months from study start, whichever occurred later. The final analysis was based on a data cutoff of December 2, 2019, at which time 357 deaths accrued; the superiority boundary for OS was one-sided $P = .0128$. All superiority boundaries were calculated using the Lan-DeMets O'Brien-Fleming spending function.

RESULTS

Participants

Between May 15, 2017, and July 30, 2018, 453 participants from 133 sites in 18 countries met eligibility criteria and were randomly allocated to receive pembrolizumab plus EP (n = 228) or placebo plus EP (n = 225; Fig 1). Baseline demographics and disease characteristics were generally balanced between groups (Table 1). Median age was 65 years, 74.4% of participants had an ECOG performance status of 1, 56.5% had an LDH concentration > ULN, and 40.8% had PD-L1 CPS ≥ 1; more participants in the pembrolizumab plus EP group had baseline brain metastases (14.5% *v* 9.8%).

At least 1 dose of study treatment was received by 224 participants in the pembrolizumab plus EP group and 222 participants in the placebo plus EP group. One participant in the pembrolizumab plus EP group was cross-treated with placebo plus EP for the duration of treatment; the as-treated population, therefore, included 223 participants for each group. Among the 446 treated participants, 317 (71.1%) received carboplatin, and 129 (28.9%) received cisplatin. At final analysis, median time from random assignment to data cutoff was 21.6 months (range, 16.1-30.6 months), 20 participants in the pembrolizumab plus EP group (8.9%) and 3 (1.4%) in the placebo plus EP group remained on treatment, and 2 (0.9%) and 1 (0.5%), respectively, completed 35 cycles. The remainder of participants discontinued treatment, most commonly for disease progression (Fig 1). PCI was received by 27 participants in the pembrolizumab plus EP group (11.8%) and by 32 (14.2%) participants in the placebo plus EP group. In the as-treated population, ≥ 1 subsequent anticancer therapy was received by 118 participants in the pembrolizumab plus EP group (52.9%) and 146 (65.5%) in the placebo plus EP group, including 9 (4.0%) and 31 (13.9%), respectively, who received immunotherapy (Data Supplement).

Efficacy

At IA2, 188 participants in the pembrolizumab plus EP group (82.5%) and 208 (92.4%) in the placebo plus EP group experienced disease progression or death. Median PFS was 4.5 months (95% CI, 4.3 to 5.4 months) in the

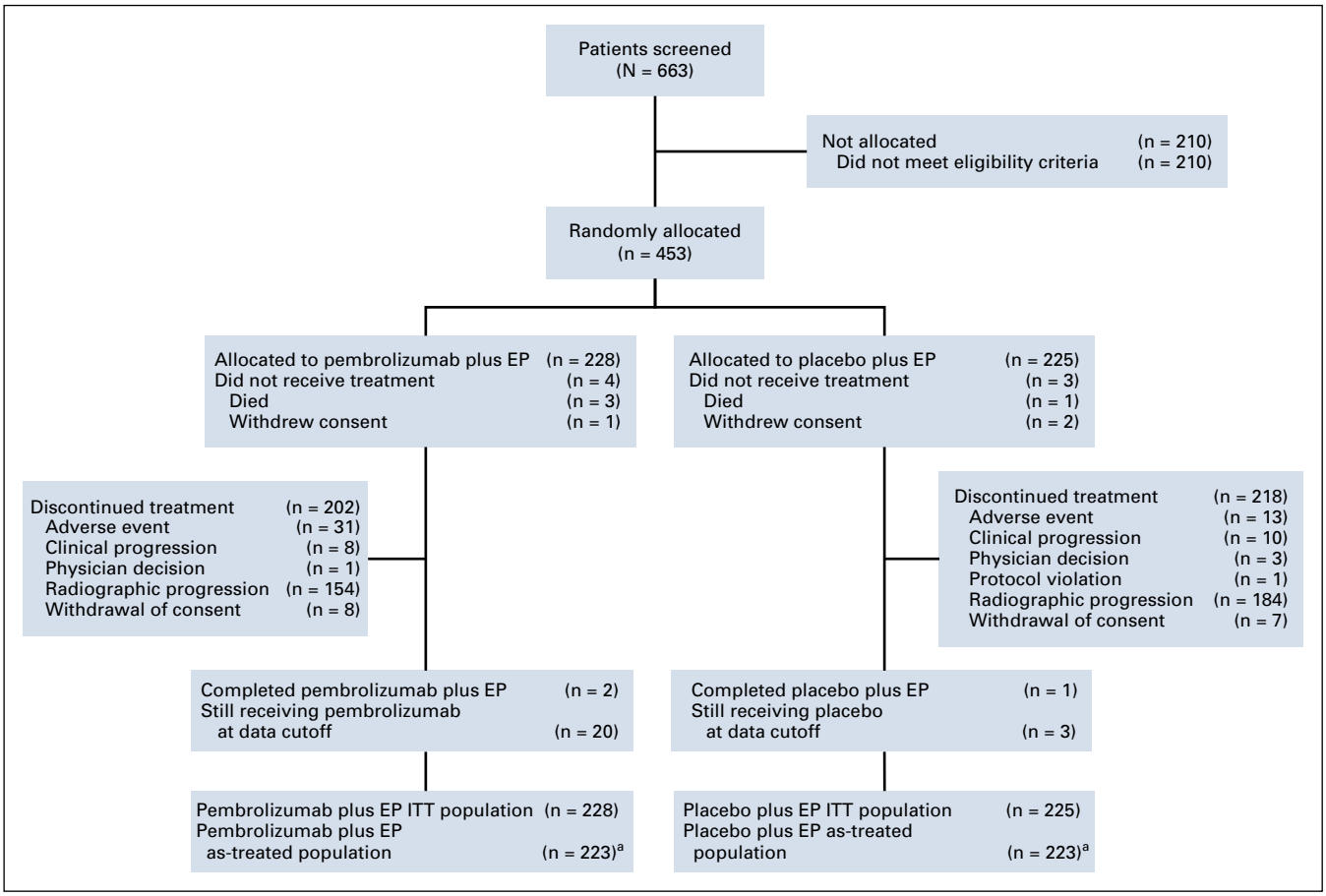

FIG 1. CONSORT diagram. ([a]) The participant allocated to the pembrolizumab plus etoposide and platinum (EP) group who received placebo plus EP in error was included in the placebo plus EP as-treated population. ITT, intention to treat.

pembrolizumab plus EP group and 4.3 months (95% CI, 4.2 to 4.4 months) in the placebo plus EP group, and 12-month PFS estimates were 13.6% and 3.1%, respectively (Fig 2A). Pembrolizumab plus EP significantly prolonged PFS at IA2 (HR, 0.75; 95% CI, 0.61 to 0.91; $P = .0023$). RMST for PFS at 12 months also favored pembrolizumab plus EP (5.86 *v* 5.14 months; difference, 0.72 months; 95% CI, 0.14 to 1.29). The PFS benefit was observed in most subgroups (Fig 2B) and was maintained at final analysis (HR, 0.73; 95% CI, 0.60 to 0.88; Appendix Fig A2, online only). Although the point estimate for participants with brain metastases was > 1, the CI was wide and overlapped that of the total population and the population without brain metastases.

At final analysis, 169 participants in the pembrolizumab plus EP group (74.1%) and 188 (83.6%) in the placebo plus EP group had died. Median OS was 10.8 months (95% CI, 9.2 to 12.9 months) in the pembrolizumab plus EP group and 9.7 months (95% CI, 8.6 to 10.7 months) in the placebo plus EP group, and estimated OS rates were 45.1% and 39.6%, respectively, at 12 months and 22.5% and 11.2%, respectively, at 24 months (Fig 3A). The significance boundary was not reached in the ITT population (HR, 0.80; 95% CI, 0.64 to 0.98; $P = .0164$). In a post hoc analysis of OS in the as-treated population, nominal $P = .0124$ (HR, 0.78; 95% CI, 0.63 to 0.97; Appendix Fig A3, online only). RMST for OS at 24 months was 12.77 months for pembrolizumab plus EP and 11.56 months for placebo plus EP (difference, 1.21 months; 95% CI, 0.18 to 2.60). In subgroup analysis, all HRs favored pembrolizumab plus EP except for the subgroups of participants with brain metastases and those with < 3 metastases (Fig 3B); in both subgroups, the CIs were wide and crossed those of the total population.

At final analysis, ORR was 70.6% (95% CI, 64.2% to 76.4%) in the pembrolizumab plus EP group and 61.8% (95% CI, 55.1% to 68.2%) in the placebo plus EP group (Table 2). Among responders, median DOR was 4.2 months (range, 1.0+ to 26.0+ months) in the pembrolizumab plus EP group and 3.7 months (range, 1.4+ to 25.8+ months) in the placebo plus EP group (Fig 4; + indicates no PD at last assessment); at 1 year, the estimated proportion of ongoing responses was 19.3% and 3.3%, respectively.

TABLE 1. Participant Demographics and Disease Characteristics at Baseline

Characteristic	Pembrolizumab Plus EP (n = 228)	Placebo Plus EP (n = 225)
Median age, years (range)	64 (24-81)	65 (37-83)
Age ≥ 65 years	113 (49.6)	124 (55.1)
Male sex	152 (66.7)	142 (63.1)
Region of enrollment		
East Asia	52 (22.8)	32 (14.2)
Not East Asia	176 (77.2)	193 (85.8)
ECOG performance status		
0	60 (26.3)	56 (24.9)
1	168 (73.7)	169 (75.1)
Smoking status		
Current	148 (64.9)	133 (59.1)
Former	72 (31.6)	84 (37.3)
Never	8 (3.5)	8 (3.6)
LDH concentration		
≤ ULN	100 (43.9)	95 (42.2)
> ULN	127 (55.7)	129 (57.3)
Unknown	1 (0.4)	1 (0.4)
Median sum of largest diameters of target lesions, mm (range)	134.8 (24.4-431.7)	126.6 (20.8-408.8)
No. of metastatic sites		
< 3	88 (38.6)	73 (32.4)
≥ 3	140 (61.4)	152 (67.6)
Brain metastases	33 (14.5)	22 (9.8)
Liver metastases	95 (41.7)	92 (40.9)
PD-L1 CPS		
< 1	97 (42.5)	78 (34.7)
≥ 1	88 (38.6)	97 (43.1)
Unknown	43 (18.9)	50 (22.2)

Abbreviations: CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; EP, etoposide and platinum; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

Safety

Median number of cycles was 7 (range, 1-35 cycles) in the pembrolizumab plus EP group and 6 (range, 1-35 cycles) in the placebo plus EP group. AEs of any cause occurred in all 223 participants in the pembrolizumab plus EP group (100%) and 222 (99.6%) participants in the placebo plus EP group, including 171 (76.7%) and 167 (74.9%), respectively, who experienced grade 3-4 AEs. Discontinuation of any study treatment because of AEs occurred in 33 of participants in the pembrolizumab plus EP group (14.8%) and 14 (6.3%) in the placebo plus EP group; discontinuation of all treatment occurred in 9 (4.0%) and 8 (3.6%), respectively. AEs were generally similar in participants treated with carboplatin (Data Supplement) and with cisplatin (Data Supplement). AEs led to death in 14 participants in the pembrolizumab plus EP group (6.3%) and 12 (5.4%) in the placebo plus EP group (Data Supplement).

In both groups, neutropenia, anemia, nausea, and alopecia were the most common any-grade AEs, and neutropenia, anemia, thrombocytopenia, and leukopenia were the most common grade 3-4 AEs (Table 3). Among AEs with incidence ≥ 10%, pyrexia, hypothyroidism, dizziness, and rash were more frequent in the pembrolizumab plus EP group (Appendix Fig A4A, online only). There were no grade 3-5 AEs that occurred more frequently in the pembrolizumab plus EP group (Appendix Fig A4B). A summary of treatment-related AEs is available in the Data Supplement. Immune-mediated AEs, which were defined on the basis of a list of terms specified by the sponsor, occurred in 55 participants in the pembrolizumab plus EP group (24.7%) and 23 (10.3%) in the placebo plus EP group (Data Supplement). The most common immune-mediated AEs were hypothyroidism (10.3% in the pembrolizumab plus EP group and 2.2% in the placebo plus EP

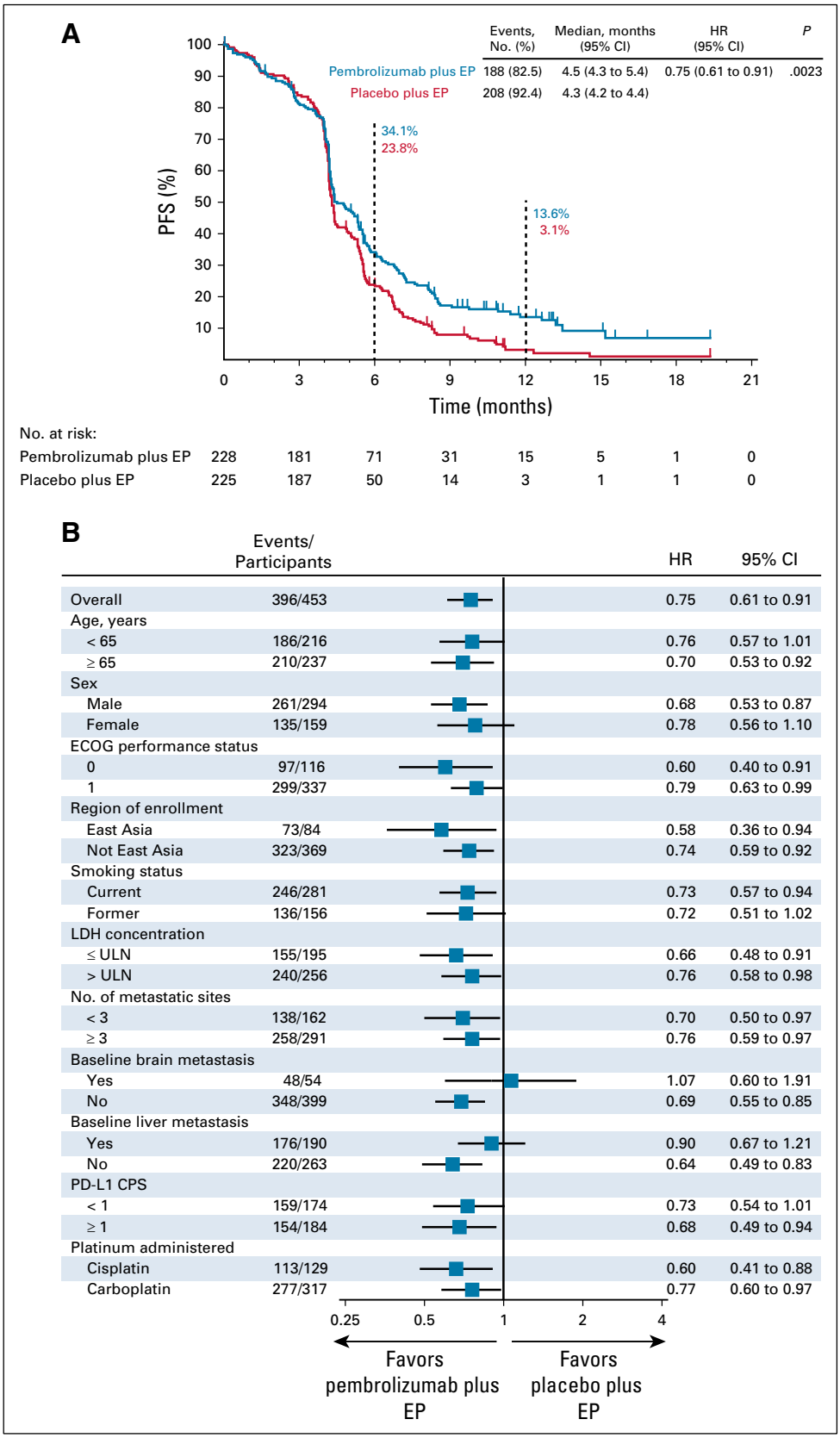

FIG 2. Progression-free survival (PFS) assessed per RECIST version 1.1 by blinded, independent central review in the intention-to-treat population at the second interim analysis. (A) Kaplan-Meier estimates of PFS. (B) Forest plot of PFS in subgroups. The protocol-specified final analysis of PFS occurred at the second interim analysis. In (B), analysis for the overall population is based on a Cox regression model with treatment as a covariate stratified by platinum chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status, and lactate dehydrogenase (LDH) concentration; for subgroups, analyses are based on an unstratified Cox regression model with treatment as a covariate. +, no PD at the last disease assessment; CPS, combined positive score; EP, etoposide and platinum; HR, hazard ratio; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

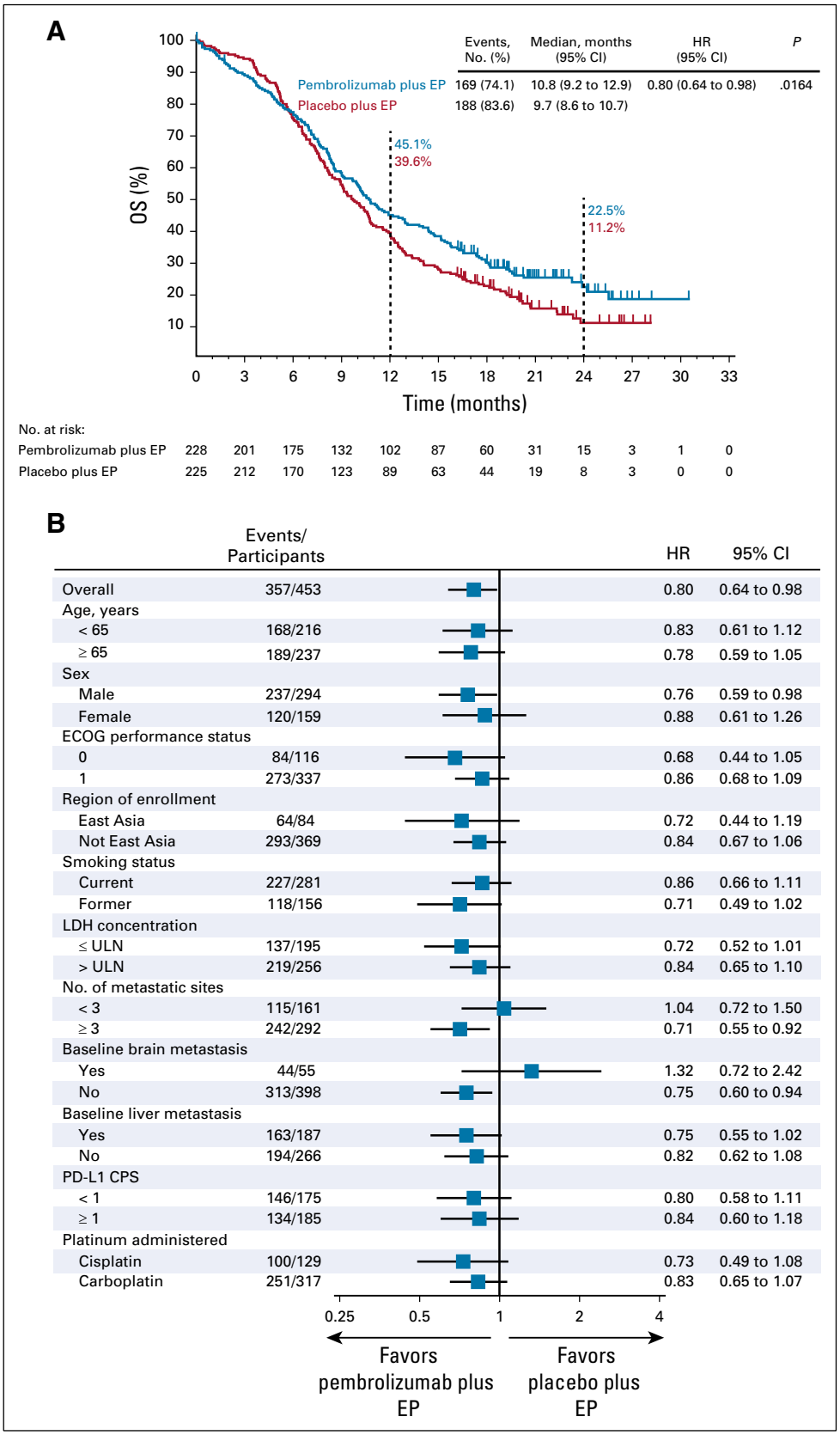

FIG 3. Overall survival (OS) in the intention-to-treat population at final analysis. (A) Kaplan-Meier estimates of OS. (B) Forest plot of OS in subgroups. In (B), analysis for the overall population is based on a Cox regression model with treatment as a covariate stratified by platinum chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status, and lactate dehydrogenase (LDH) concentration; for subgroups, analyses are based on an unstratified Cox regression model with treatment as a covariate. CPS, combined positive score; EP, etoposide and platinum; HR, hazard ratio; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

TABLE 2. Summary of Confirmed Response Assessed Per RECIST Version 1.1 by Blinded, Independent Central Review at Final Analysis

Confirmed Response	Pembrolizumab Plus EP (n = 228), No. (%)	Placebo Plus EP (n = 225), No (%)
ORR, % (95% CI)	70.6 (64.2 to 76.4)	61.8 (55.1 to 68.2)
Treatment difference,[a] percentage points (95% CI)	8.9 (0.2 to 17.4)	
Best response		
Complete response	4 (1.8)	2 (0.9)
Partial response	157 (68.9)	137 (60.9)
Stable disease	40 (17.5)	56 (24.9)
Progressive disease	8 (3.5)	12 (5.3)
Not evaluable[b]	6 (2.6)	5 (2.2)
Not assessed[c]	13 (5.7)	13 (5.8)

Abbreviations: EP, etoposide and platinum; ORR, objective response rate.
[a]Calculated using stratified Miettinen and Nurminen's method, with strata weighting by sample size.
[b]Participants who had ≥ 1 postbaseline imaging assessment, none of which were evaluable for response.
[c]Participants who did not have ≥ 1 postbaseline imaging assessment.

group), hyperthyroidism (6.7% and 2.7%, respectively), and pneumonitis (4.0% and 2.2%, respectively). Grade 3 immune-mediated AEs occurred in 16 participants (7.2%) and 2 participants (0.9%), respectively. There were no grade 4 or 5 immune-mediated AEs in the pembrolizumab plus EP group. Infusion-related reactions occurred in 8 participants in the pembrolizumab plus EP group (3.6%) and in 4 (1.8%) in the placebo plus EP group.

DISCUSSION

In this randomized, double-blind, phase III study of patients with previously untreated ES-SCLC, the addition of pembrolizumab to EP significantly improved PFS assessed per RECIST version 1.1 by BICR (HR, 0.75; $P = .0023$). Although the OS HR favored pembrolizumab plus EP, the prespecified significance threshold was narrowly missed (HR, 0.80; $P = .0164$). ORR was numerically higher in the pembrolizumab plus EP group. The proportion of participants who experienced grade 3-4 AEs and who died as a result of AEs was similar in the treatment groups; more participants in the pembrolizumab plus EP group discontinued treatment because of AEs.

A generally consistent treatment effect for pembrolizumab plus EP was observed across key subgroups. The only subgroup that did not seem to benefit from pembrolizumab plus EP was participants with baseline brain metastases. Given the small population size for this subgroup and wide CIs, it is difficult to make conclusions. The PFS and OS HRs were similar in participants with PD-L1–positive and PD-L1–negative tumors and regardless of the choice of platinum. These findings are consistent with those of pembrolizumab plus chemotherapy in NSCLC.[16,17]

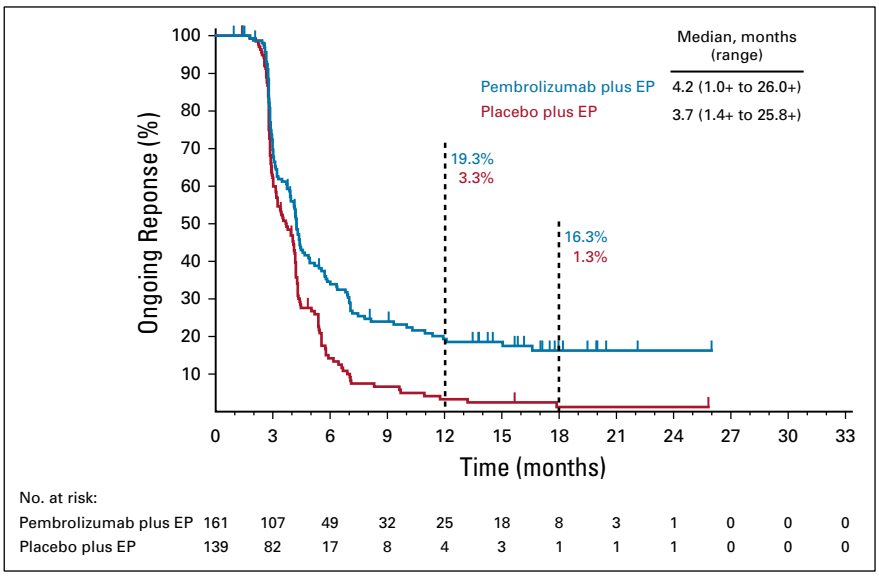

FIG 4. Kaplan-Meier estimates of duration of response assessed per RECIST version 1.1 by blinded, independent central review at final analysis in participants who experienced complete or partial response. EP, etoposide and platinum.

TABLE 3. All-Cause Adverse Events With Incidence ≥ 10% in Either Group in the As-Treated Population at Final Analysis

	Pembrolizumab Plus EP (n = 223), No. (%)		Placebo plus EP (n = 223), No. (%)	
Adverse Event	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Neutropenia	127 (57.0)	97 (43.5)	119 (53.4)	91 (40.8)
Anemia	108 (48.4)	35 (15.7)	104 (46.6)	34 (15.2)
Nausea	86 (38.6)	2 (0.9)	96 (43.0)	3 (1.3)
Alopecia	75 (33.6)	0 (0.0)	84 (37.7)	1 (0.4)
Decreased appetite	69 (30.9)	1 (0.4)	55 (24.7)	4 (1.8)
Constipation	66 (29.6)	1 (0.4)	59 (26.5)	2 (0.9)
Fatigue	61 (27.4)	6 (2.7)	61 (27.4)	4 (1.8)
Thrombocytopenia	59 (26.5)	31 (13.9)	49 (22.0)	25 (11.2)
Leukopenia	50 (22.4)	26 (11.7)	46 (20.6)	21 (9.4)
Diarrhea	47 (21.1)	6 (2.7)	42 (18.8)	6 (2.7)
Cough	44 (19.7)	1 (0.4)	45 (20.2)	2 (0.9)
Asthenia	41 (18.4)	8 (3.6)	43 (19.3)	11 (4.9)
Dyspnea	40 (17.9)	3 (1.3)	38 (17.0)	4 (1.8)
Vomiting	36 (16.1)	2 (0.9)	40 (17.9)	4 (1.8)
Pyrexia	34 (15.2)	1 (0.4)	15 (6.7)	1 (0.4)
Dizziness	32 (14.3)	0 (0.0)	15 (6.7)	0 (0.0)
Headache	30 (13.5)	0 (0.0)	34 (15.2)	1 (0.4)
Rash	30 (13.5)	3 (1.3)	13 (5.8)	0 (0.0)
Back pain	26 (11.7)	1 (0.4)	26 (11.7)	0 (0.0)
Pneumonia	26 (11.7)	15 (6.7)	25 (11.2)	10 (4.5)
Hyponatremia	25 (11.2)	0 (0.0)	20 (9.0)	0 (0.0)
Insomnia	25 (11.2)	0 (0.0)	28 (12.6)	0 (0.0)
Pruritus	25 (11.2)	0 (0.0)	18 (8.1)	0 (0.0)
Hypothyroidism	23 (10.3)	0 (0.0)	5 (2.2)	0 (0.0)
Peripheral edema	17 (7.6)	0 (0.0)	27 (12.1)	0 (0.0)

Data are presented in order of descending incidence in the pembrolizumab plus etoposide and platinum (EP) group.

With results of the phase III IMpower133 and CASPIAN studies, immune checkpoint inhibitors became the first class of agents to improve first-line outcomes in ES-SCLC in approximately 3 decades. The lack of a statistically significant survival benefit in KEYNOTE-604 was unexpected on the basis of the findings of these studies. In IMpower133, adding atezolizumab (anti–PD-L1) to 4 cycles of etoposide and carboplatin significantly improved the dual primary end points of investigator-assessed PFS (HR, 0.77; 95% CI, 0.62 to 0.96) and OS (HR, 0.70; 95% CI, 0.54 to 0.91) compared with placebo plus 4 cycles of etoposide and carboplatin.[9] In CASPIAN, the addition of durvalumab (anti–PD-L1) to 4 cycles of EP significantly improved the primary end point of OS compared with 6 cycles of EP (HR, 0.73; 95% CI, 0.59 to 0.91).[10] Although cross-study comparisons should be made with caution, OS in KEYNOTE-604 was shorter than in IMpower133 and CASPIAN, which suggests that KEYNOTE-604 may have enrolled sicker patients. KEYNOTE-604 enrolled more participants with brain metastases and a performance status of 1 than IMpower133 and CASPIAN, as well as high proportions of participants with large tumor dimensions, elevated LDH concentration, and ≥ 3 metastases at baseline; these factors are associated with poor prognosis in SCLC.[18] The findings of KEYNOTE-604 are generally consistent with those of IMpower133 and CASPIAN and together with data from studies of monotherapy in later lines of therapy,[7,8] support the value of checkpoint inhibitors in treating ES-SCLC.

There is increasing recognition that medians do not fully capture the PFS and OS benefits of immunotherapy and that there is a need for therapies that raise the survival curve.[19] The KEYNOTE-604 Kaplan-Meier curves support a long-term benefit of pembrolizumab plus EP for a subset

of participants with ES-SCLC. The PFS curves overlap for the first 4-5 months, which likely reflects the effect of EP, then separate after the medians are reached (approximately the time of the third postbaseline imaging assessment) with an evident plateau for pembrolizumab plus EP. The OS curves diverged in favor of pembrolizumab plus EP starting at approximately 5 months. Separation was maintained over time, as evidenced by 12-month OS rates of 45.1% in the pembrolizumab plus EP group and 39.6% in the placebo plus EP group and 24-month OS rates of 22.5% and 11.2%, respectively. RMST analysis of PFS and OS supports divergence of outcomes in favor of pembrolizumab plus EP over long-term follow-up. Similar to the PFS curves, the DOR curves diverged around the time the medians were reached and remained separated in favor of pembrolizumab plus EP over long-term follow-up. These findings are consistent with those observed in IMpower133[9] and CASPIAN,[10] which likely underscores the inherent heterogeneity of this disease. Additional correlative analyses, including exploration of molecular biomarkers such as tumor mutational burden and gene expression signatures[20,21] and the recently described SCLC molecular subtypes,[22] may help to identify patients who derive long-term benefit from checkpoint inhibitors.

No unexpected toxicities were observed in KEYNOTE-604. The most frequently observed AEs in both treatment groups were hematologic events, rates of which did not seem to be increased by pembrolizumab. AE profiles were similar in carboplatin- and cisplatin-treated participants. The incidence and types of immune-mediated AEs observed in the pembrolizumab plus EP group were consistent with those observed for pembrolizumab monotherapy in SCLC.[7] Although more participants treated with pembrolizumab plus EP discontinued any study therapy, the proportion of participants who discontinued all study therapy and who died as a result of AEs was similar in the treatment groups, which suggests that AEs associated with pembrolizumab plus EP can be successfully managed.

In conclusion, results of KEYNOTE-604 show that adding pembrolizumab to standard first-line EP significantly improves PFS in patients with ES-SCLC and is associated with durable responses in a subset of patients. The statistical threshold for declaring significant prolongation of OS was narrowly missed. Pembrolizumab monotherapy remains approved as third-line or later therapy for metastatic SCLC in several countries. Overall, these data support the benefit of pembrolizumab in SCLC and add to the growing body of evidence that supports the value of immune checkpoint inhibitors in this historically difficult-to-treat cancer.

AFFILIATIONS

[1]Memorial Sloan Kettering Cancer Center, New York, NY
[2]Dana-Farber Cancer Institute, Boston, MA
[3]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain
[4]Meir Medical Center, Kfar-Saba, Israel
[5]Lausanne University Hospital, Lausanne, Switzerland
[6]Hetényi Géza Kórház Onkológiai Központ, Szolnok, Hungary
[7]William Osler Health System, University of Toronto, Brampton, Ontario, Canada
[8]Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain
[9]Rambam Medical Center, Haifa, Israel
[10]National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan
[11]Centre Hospitalier Universitaire de Toulouse, Université Paul Sabatier, Toulouse, France
[12]Oncología-Health and Care, Santiago, Chile
[13]Leningrad Regional Clinical Hospital, St Petersburg, Russia
[14]Istanbul Medeniyet University Hospital, Istanbul, Turkey
[15]Kanagawa Cancer Center, Yokohama, Japan
[16]University of Michigan, Ann Arbor, MI
[17]Merck & Co, Kenilworth, NJ
[18]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

CORRESPONDING AUTHOR

Charles M. Rudin, MD, PhD, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065; e-mail: rudinc@mskcc.org.

PRIOR PRESENTATION

Presented at the ASCO20 Virtual Scientific Program, Chicago, IL, May 29-31, 2020.

SUPPORT

Supported by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co.

CLINICAL TRIAL INFORMATION

NCT03066778

DATA AVAILABILITY

Data will be available according to Merck Sharp & Dohme's data sharing policy, which, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or by e-mail to dataacess@merck.com.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.00793.

AUTHOR CONTRIBUTIONS

Conception and design: Charles M. Rudin, Solange Peters, Yiwen Luo, M. Catherine Pietanza

Provision of study material or patients: Charles M. Rudin, Mark M. Awad, Alejandro Navarro, Maya Gottfried, Solange Peters, Tibor Csőszi, Parneet K. Cheema, Delvys Rodriguez-Abreu, Mirjana Wollner, James Chih-Hsin

Yang, Julien Mazieres, Francisco J. Orlandi, Alexander Luft, Terufumi Kato, Gregory P. Kalemkerian, Hye Ryun Kim
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank the patients and their families and caregivers for participating in this trial; all investigators and site personnel; and all employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Kenilworth, NJ (MSD), who made contributions to this study, particularly Ananya Roy for previous service as the lead study statistician, Xiaodong Li and Yue Shentu for statistical support, Diana Francisco for support of data collection, and Gregory Lubiniecki for contributions to study design and oversight of the research. Medical writing and editorial assistance were provided by Melanie Leiby, an employee of MSD.

REFERENCES

1. Govindan R, Page N, Morgensztern D, et al: Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 24:4539-4544, 2006
2. Waqar SN, Morgensztern D: Treatment advances in small cell lung cancer (SCLC). Pharmacol Ther 180:16-23, 2017
3. Gaspar LE, McNamara EJ, Gay EG, et al: Small-cell lung cancer: Prognostic factors and changing treatment over 15 years. Clin Lung Cancer 13:115-122, 2012
4. Wang S, Tang J, Sun T, et al: Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. Sci Rep 7:1339, 2017
5. Farago AF, Keane FK: Current standards for clinical management of small cell lung cancer. Transl Lung Cancer Res 7:69-79, 2018
6. Jones GS, Elimian K, Baldwin DR, et al: A systematic review of survival following anti-cancer treatment for small cell lung cancer. Lung Cancer 141:44-55, 2020
7. Chung HC, Piha-Paul SA, Lopez-Martin J, et al: Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: Results from the KEYNOTE-028 and KEYNOTE-158 studies. J Thorac Oncol 15:618-627, 2020
8. Ready N, Farago AF, de Braud F, et al: Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. J Thorac Oncol 14:237-244, 2019
9. Horn L, Mansfield AS, Szczęsna A, et al: First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 379:2220-2229, 2018
10. Paz-Ares L, Dvorkin M, Chen Y, et al: Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): A randomised, controlled, open-label, phase 3 trial. Lancet 394:1929-1939, 2019
11. American Joint Committee on Cancer: AJCC Cancer Staging Manual (ed 7). New York, NY, Springer, 2010
12. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009
13. Kulangara K, Zhang N, Corigliano E, et al: Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. Arch Pathol Lab Med 143:330-337, 2019
14. Uno H, Claggett B, Tian L, et al: Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. J Clin Oncol 32:2380-2385, 2014
15. Maurer W, Bretz F: Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 5:311-320, 2013
16. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al: Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 378:2078-2092, 2018
17. Paz-Ares L, Luft A, Vicente D, et al: Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 379:2040-2051, 2018
18. Pietanza MC, Krug LM, Wu AJ, et al: Small cell and neuroendocrine tumors of the lung, in DeVita VT, Lawrence TS, Rosenberg SA (eds): DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology (ed 10). Alphen aan den Rijn, the Netherlands, Wolters Kluwer Adis, 2015
19. Hellmann MD, Kris MG, Rudin CM: Medians and milestones in describing the path to cancer cures: Telling "tails". JAMA Oncol 2:167-168, 2016
20. Ott PA, Bang YJ, Piha-Paul SA, et al: T-cell-inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. J Clin Oncol 37:318-327, 2019
21. Marabelle A, Fakih M, Lopez J, et al: Association of tumor mutational burden with outcomes in patients with select advanced solid tumors treated with pembrolizumab in KEYNOTE-158. Ann Oncol 30:v477, 2019
22. Rudin CM, Poirier JT, Byers LA, et al: Molecular subtypes of small cell lung cancer: A synthesis of human and mouse model data. Nat Rev Cancer 19:289-297, 2019 [Erratum: Nat Rev Cancer 19:415, 2019]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Charles M. Rudin
Consulting or Advisory Role: AbbVie, Harpoon Therapeutics, Genentech, Roche, AstraZeneca, Ascentage Pharma, Bicycle Therapeutics, Celgene, Daiichi Sankyo, Ipsen, Loxo Oncology, PharmaMar, Bridge Medicines, Amgen
Research Funding: AbbVie (Inst), Stemcentrx (Inst), Viralytics (Inst), Daiichi Sankyo (Inst), Merck Sharp & Dohme Corp (Inst)

Mark M. Awad
Consulting or Advisory Role: Genentech, Merck & Co, Pfizer, Boehringer Ingelheim, AbbVie, AstraZeneca, MedImmune, Clovis Oncology, Nektar, Bristol-Myers Squibb, ARIAD Pharmaceuticals, Foundation Medicine, Syndax, Novartis, Blueprint Medicines, Maverick Therapeutics, Achilles Therapeutics, Neon Therapeutics, Hengrui Therapeutics, Gritstone Oncology
Research Funding: Genentech (Inst), Roche (Inst), Eli Lilly (Inst), AstraZeneca (Inst), Bristol-Myers Squibb (Inst), Merck Sharp & Dohme Corp (Inst)

Alejandro Navarro
Honoraria: Pfizer, Roche, AstraZeneca
Consulting or Advisory Role: Boehringer Ingelheim
Expert Testimony: Oryzon Genomics
Research Funding: Merck Sharp & Dohme Corp (Inst)
Travel, Accommodations, Expenses: Boehringer Ingelheim, Pfizer

Maya Gottfried
Consulting or Advisory Role: Pfizer, Boehringer Ingelheim, Roche
Research Funding: Merck Sharp & Dohme Corp (Inst)
Travel, Accommodations, Expenses: Pfizer, Roche, Boehringer Ingelheim

Solange Peters
Honoraria: Roche (Inst), Bristol-Myers Squibb (Inst), Novartis (Inst), Pfizer (Inst), MSD (Inst), AstraZeneca (Inst), Takeda Pharmaceuticals (Inst), Illumina (Inst)
Consulting or Advisory Role: Roche (Inst), Genentech (Inst), Novartis (Inst), Bristol-Myers Squibb (Inst), Pfizer (Inst), MSD (Inst), Amgen (Inst), AstraZeneca (Inst), Janssen Pharmaceuticals (Inst), Regeneron Pharmaceuticals (Inst), Merck Serono (Inst), Boehringer Ingelheim (Inst), Takeda Pharmaceuticals (Inst), Eli Lilly (Inst), AbbVie (Inst), Bayer AG (Inst), Biocartis (Inst), Debiopharm Group (Inst), Illumina (Inst), PharmaMar (Inst), Sanofi (Inst), Seattle Genetics (Inst), Blueprint Medicines, Daiichi Sankyo, Incyte, Bioinvent (Inst), Clovis Oncology (Inst), Vaccibody (Inst)
Research Funding: Roche (Inst), Bristol-Myers Squibb (Inst), Merck Sharp & Dohme Corp (Inst), Amgen (Inst), Eli Lilly (Inst), AstraZeneca (Inst), Pfizer (Inst), Illumina (Inst), Merck Serono (Inst), Novartis (Inst), Biodesix (Inst), Boehringer Ingelheim (Inst), Iovance (Inst)
Travel, Accommodations, Expenses: Roche, Bristol-Myers Squibb, MSD, Sanofi, Incyte
Uncompensated Relationships: *Journal of Thoracic Oncology* Deputy Editor, European Society for Medical Oncology President 2020/2021, European Thoracic Oncology Platform Scientific Coordinator

Tibor Csőszi
Consulting or Advisory Role: Novartis
Speakers' Bureau: Ipsen, Janssen-Cilag
Research Funding: Merck Sharp & Dohme Corp (Inst)
Travel, Accommodations, Expenses: Sanofi, Pfizer

Parneet K. Cheema
Honoraria: Merck, F. Hoffmann-La Roche, AstraZeneca, Pfizer, Takeda Pharmaceuticals, Novartis
Consulting or Advisory Role: AstraZeneca, Bristol Myers Squibb, Pfizer, Amgen, F. Hoffmann-La Roche, EMD Serono, Novartis, Genomic Health, Takeda Pharmaceuticals, Merck & Co
Research Funding: Merck Sharp & Dohme Corp (Inst)

Delvys Rodriguez-Abreu
Consulting or Advisory Role: Roche, Bristol-Myers Squibb, MSD
Speakers' Bureau: Roche, Bristol-Myers Squibb, MSD
Research Funding: Merck Sharp & Dohme Corp (Inst)
Travel, Accommodations, Expenses: Roche, Bristol-Myers Squibb, MSD

Mirjana Wollner
Honoraria: MSD, AstraZeneca
Consulting or Advisory Role: Roche Israel (Inst), Takeda Pharmaceuticals, Bristol-Myers Squibb, AstraZeneca, MSD, Pfizer
Speakers' Bureau: Roche Israel, Boehringer Ingelheim, Novartis, Bristol-Myers Squibb
Research Funding: Merck Sharp & Dohme Corp (Inst)
Travel, Accommodations, Expenses: Pfizer, Bristol-Myers Squibb

James Chih-Hsin Yang
Honoraria: Boehringer Ingelheim, Roche, MSD, AstraZeneca, Novartis, Bristol-Myers Squibb, Ono Pharmaceutical, Takeda Pharmaceuticals, Eli Lilly, Pfizer
Consulting or Advisory Role: Boehringer Ingelheim, Novartis, AstraZeneca, Roche, Genentech, Clovis Oncology, Eli Lilly, MSD, Merck Serono, Celgene, Astellas Pharma, Bayer AG, Pfizer, Ono Pharmaceutical, Bristol-Myers Squibb, Boehringer Ingelheim (Inst), AstraZeneca (Inst), Yuhan, Hansoh, Blueprint Medicines, Daiichi Sankyo, G1 Therapeutics, AbbVie, Amgen, Takeda Oncology, Incyte
Research Funding: Merck Sharp & Dohme Corp (Inst)
Travel, Accommodations, Expenses: Pfizer

Julien Mazieres
Consulting or Advisory Role: Novartis, Roche, Genentech, Pfizer, Bristol-Myers Squibb, Eli Lilly, ImClone, MSD, AstraZeneca, Pierre Fabre
Research Funding: Roche (Inst), Bristol-Myers Squibb (Inst), AstraZeneca (Inst), Merck Sharp & Dohme Corp (Inst)
Travel, Accommodations, Expenses: Pfizer, Roche, Bristol-Myers Squibb

Francisco J. Orlandi
Honoraria: Roche, Genentech
Consulting or Advisory Role: AstraZeneca, Roche, Genentech, Bristol-Myers Squibb, MSD, Eli Lilly, Pfizer, Novartis, Sanofi
Speakers' Bureau: AstraZeneca, MedImmune, Roche
Research Funding: AstraZeneca, MedImmune, Amgen, Genentech, Roche, Boehringer Ingelheim, Astellas Pharma, Medivation, Merck Sharp & Dohme Corp (Inst), Bristol-Myers Squibb, Celltrion, Pfizer, mAbxience, Nektar, Sanofi
Travel, Accommodations, Expenses: Pfizer, MSD, AstraZeneca, MedImmune, Roche, Bristol-Myers Squibb, Genentech, Roche,

Mahmut Gümüş
Consulting or Advisory Role: Roche, Eli Lilly (Inst), Amgen (Inst)
Speakers' Bureau: Roche (Inst), MSD (Inst)
Research Funding: Merck Sharp & Dohme Corp (Inst)
Travel, Accommodations, Expenses: Pfizer

Terufumi Kato
Employment: Eli Lilly (I)
Honoraria: Chugai Pharma, Roche, Boehringer Ingelheim, Ono Pharmaceutical, Eli Lilly, AstraZeneca, Taiho Pharmaceutical, Pfizer, Bristol-Myers Squibb Japan, MSD, Novartis, Sumitomo Dainippon, Takeda Pharmaceuticals, AbbVie, Merck KGaA, Nitto Denko, Daiichi Sankyo, Shionogi, Nippon Kayaku
Consulting or Advisory Role: AstraZeneca, MSD, Eli Lilly, Chugai Pharma, Nitto Denko, AbbVie, Merck Serono, Pfizer
Research Funding: Chugai Pharma (Inst), Merck Sharp & Dohme Corp (Inst), Kyowa Hakko Kirin (Inst), Pfizer (Inst), Taiho Pharmaceutical (Inst), AstraZeneca (Inst), Eli Lilly (Inst), AbbVie (Inst), Ono Pharmaceutical (Inst), Merck Serono (Inst), Kyorin, Regeneron Pharmaceuticals, Bristol-Myers Squibb, Novartis, Kyowa Hakko Kirin

Gregory P. Kalemkerian
Consulting or Advisory Role: BioMed Valley Discoveries (I), Takeda (I), Unum Therapeutics (I), Molecular Templates (I), Boston Biomedical (I), Skyline Biosciences (I), Synlogic (I)
Research Funding: Takeda Pharmaceuticals (Inst), AbbVie (Inst), Merck Sharp & Dohme Corp (Inst)

Yiwen Luo
Employment: Merck & Co
Stock and Other Ownership Interests: Merck & Co

Victoria Ebiana
Employment: Merck & Co
Stock and Other Ownership Interests: Merck & Co

M. Catherine Pietanza
Employment: Merck & Co
Stock and Other Ownership Interests: Merck & Co

Hye Ryun Kim
Honoraria: AstraZeneca, Bristol-Myers Squibb, Ono Pharmaceutical, Roche
Consulting or Advisory Role: AstraZeneca, Bristol-Myers Squibb
Research Funding: Merck Sharp & Dohme Corp (Inst)

No other potential conflicts of interest were reported.

APPENDIX

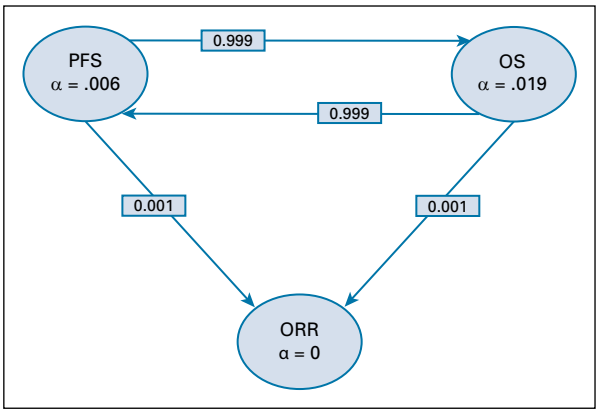

FIG A1. Multiplicity diagram for type I error control. The initial α allocated to each hypothesis is represented in the ovals; the weights for reallocation from each hypothesis to the others are represented in the boxes on the lines that connect the hypotheses. If the progression-free survival (PFS) test is significant, the overall survival (OS) hypothesis may be tested at α = .025. If the OS test is significant, the PFS hypothesis may be tested at α = .025. If both PFS and OS are significant, objective response rate (ORR) may be tested at α = .025. The actual boundaries were updated on the basis of the number of events observed and the α spent at previous analyses using the Lan-DeMets O'Brien-Fleming spending function.

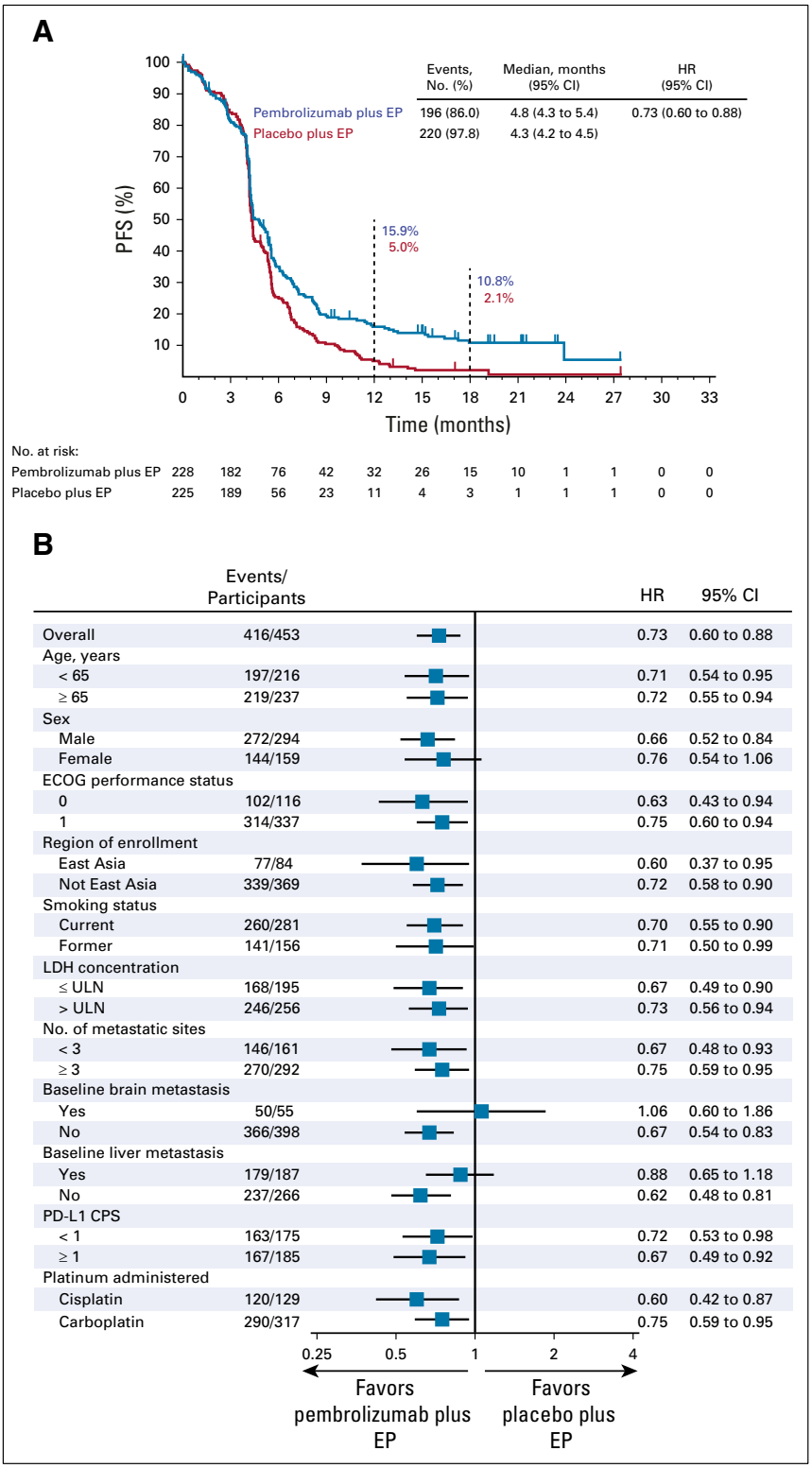

FIG A2. Progression-free survival (PFS) assessed per RECIST version 1.1 by blinded, independent central review in the intention-to-treat population at the final analysis. (A) Kaplan-Meier estimates of PFS. (B) Forest plot of PFS in subgroups. In (B), analysis for the overall population is based on a Cox regression model with treatment as a covariate stratified by platinum chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status, and lactate dehydrogenase (LDH) concentration; for subgroups, analyses are based on an unstratified Cox regression model with treatment as a covariate. CPS, combined positive score; EP, etoposide and platinum; HR, hazard ratio; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

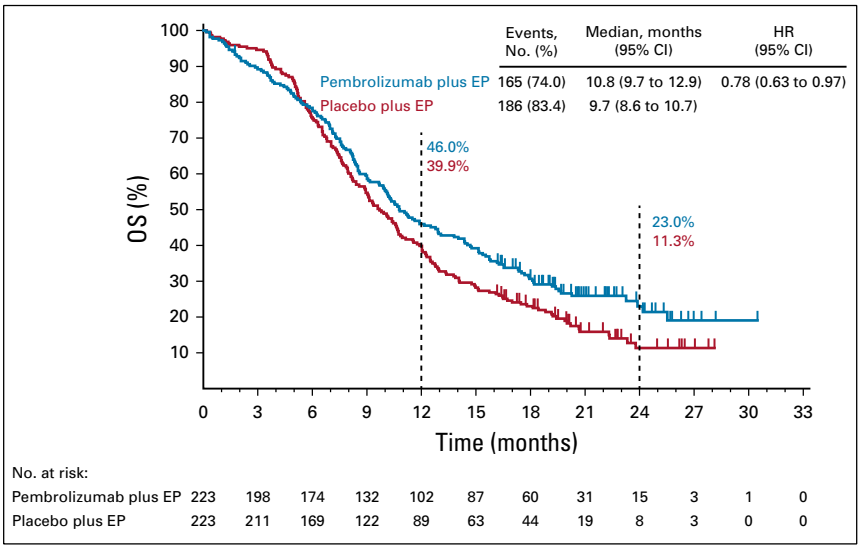

FIG A3. Kaplan-Meier estimates of overall survival (OS) in a post hoc analysis of the as-treated population at final analysis. EP, etoposide and platinum; HR, hazard ratio.

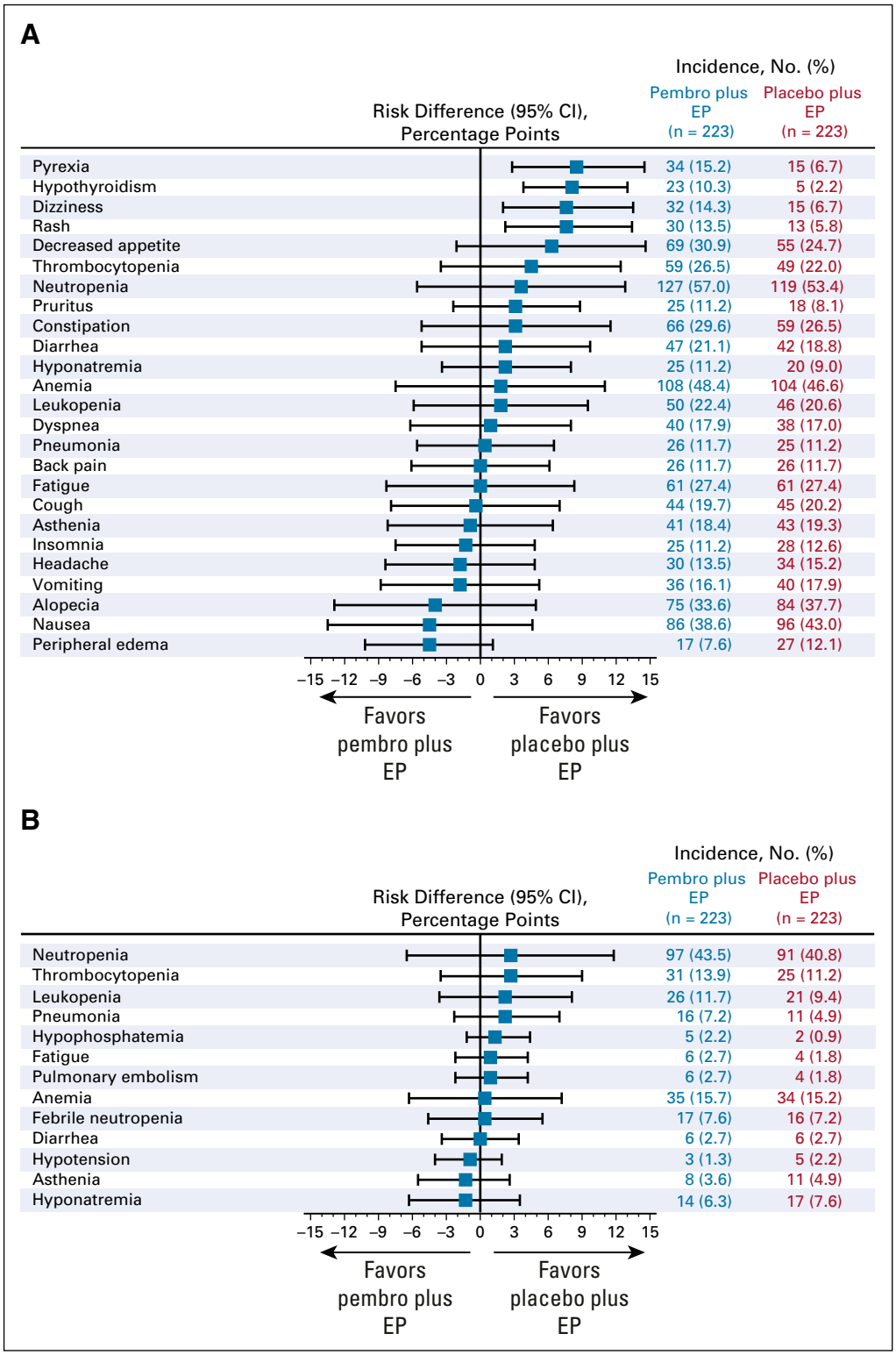

FIG A4. Risk difference between treatment groups for adverse events of any cause in the as-treated population. (A) Adverse events of any grade with incidence ≥ 10%. (B) Adverse events of grade 3-5 with incidence ≥ 2%. EP, etoposide and platinum; pembro, pembrolizumab.