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Pembrolizumab Plus Ipilimumab or Placebo for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%: Randomized, Double-Blind Phase III KEYNOTE-598 Study

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abstract

PURPOSE Pembrolizumab monotherapy is standard first-line therapy for metastatic non–small-cell lung cancer (NSCLC) with programmed death ligand 1 (PD-L1) tumor proportion score (TPS) ≥ 50% without actionable driver mutations. It is not known whether adding ipilimumab to pembrolizumab improves efficacy over pembrolizumab alone in this population.

METHODS In the randomized, double-blind, phase III KEYNOTE-598 trial (ClinicalTrials.gov identifier: NCT03302234), eligible patients with previously untreated metastatic NSCLC with PD-L1 TPS ≥ 50% and no sensitizing *EGFR* or *ALK* aberrations were randomly allocated 1:1 to ipilimumab 1 mg/kg or placebo every 6 weeks for up to 18 doses; all participants received pembrolizumab 200 mg every 3 weeks for up to 35 doses. Primary end points were overall survival and progression-free survival.

RESULTS Of the 568 participants, 284 were randomly allocated to each group. Median overall survival was 21.4 months for pembrolizumab-ipilimumab versus 21.9 months for pembrolizumab-placebo (hazard ratio, 1.08; 95% CI, 0.85 to 1.37; $P = .74$). Median progression-free survival was 8.2 months for pembrolizumab-ipilimumab versus 8.4 months for pembrolizumab-placebo (hazard ratio, 1.06; 95% CI, 0.86 to 1.30; $P = .72$). Grade 3-5 adverse events occurred in 62.4% of pembrolizumab-ipilimumab recipients versus 50.2% of pembrolizumab-placebo recipients and led to death in 13.1% versus 7.5%. The external data and safety monitoring committee recommended that the study be stopped for futility and that participants discontinue ipilimumab and placebo.

CONCLUSION Adding ipilimumab to pembrolizumab does not improve efficacy and is associated with greater toxicity than pembrolizumab monotherapy as first-line treatment for metastatic NSCLC with PD-L1 TPS ≥ 50% and no targetable *EGFR* or *ALK* aberrations. These data do not support use of pembrolizumab-ipilimumab in place of pembrolizumab monotherapy in this population.

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ASSOCIATED CONTENT

Appendix

Protocol

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

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A complete list of investigators who participated in the KEYNOTE-598 study is provided in the Appendix.

INTRODUCTION

Immune checkpoint inhibitors targeting programmed death 1 (PD-1) or its ligand programmed death ligand 1 (PD-L1) are important components of first-line treatment of metastatic non–small-cell lung cancer (NSCLC) without actionable driver mutations. PD-L1 expression on tumor and/or immune cells helps identify patients with NSCLC who experience better outcomes with this treatment class. For patients with the highest PD-L1 expression levels, defined as a tumor proportion score (TPS) ≥ 50%, pembrolizumab monotherapy is a widely approved and accepted standard of care based on results of KEYNOTE-024, in which pembrolizumab significantly improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) versus platinum-doublet chemotherapy.[1,2] Despite the effectiveness of pembrolizumab monotherapy in this population, which was confirmed in KEYNOTE-042,[3] almost 50% of patients die within 2 years[1] and more effective therapies are needed.

Ipilimumab is an inhibitory antibody directed against cytotoxic T-lymphocyte antigen 4 (CTLA-4) and thus has a distinct mechanism of action from pembrolizumab. The combination of ipilimumab and the anti–PD-1 antibody nivolumab was shown to improve

CONTEXT

Key Objective

We wanted to determine whether adding ipilimumab to pembrolizumab improves outcomes compared with pembrolizumab alone in patients with previously untreated metastatic non–small-cell lung cancer (NSCLC) with a programmed death ligand 1 tumor proportion score ≥ 50% and no actionable driver mutations.

Knowledge Generated

We found no apparent differences in overall survival, progression-free survival, objective response rate, or duration of response between pembrolizumab plus ipilimumab and pembrolizumab plus placebo. Conversely, pembrolizumab plus ipilimumab was accompanied by higher incidences of serious, grade ≥ 3, and grade 5 adverse events, as well as adverse events leading to treatment discontinuation.

Relevance

Immune checkpoint inhibition is an important component of first-line treatment for metastatic NSCLC in patients without actionable driver mutations. Our findings do not support the use of dual checkpoint inhibition with pembrolizumab and ipilimumab in place of pembrolizumab monotherapy in patients with metastatic NSCLC with programmed death ligand 1 tumor proportion score ≥ 50% and no actionable driver mutations.

outcomes compared with ipilimumab alone in advanced melanoma and sunitinib in renal cell carcinoma, although with an increased rate of immune-mediated adverse events (AEs).[4-7] In NSCLC, nivolumab-ipilimumab improves OS compared with platinum-doublet chemotherapy in patients with a PD-L1 expression level ≥ 1%,[8] and nivolumab-ipilimumab plus platinum-doublet chemotherapy for two cycles followed by nivolumab-ipilimumab improves OS compared with chemotherapy alone in a PD-L1–unselected population.[9] It is unclear whether dual immunotherapy is superior to anti–PD-1 monotherapy in patients whose tumors have high PD-L1 expression.

In KEYNOTE-598, we compared the combination of pembrolizumab and ipilimumab with pembrolizumab monotherapy in patients with untreated metastatic NSCLC with PD-L1 TPS ≥ 50% and no targetable *EGFR* or *ALK* aberrations (ClinicalTrials.gov identifier: NCT03302234).

METHODS

Study Design and Participants

This randomized, double-blind, placebo-controlled phase III study was conducted at 171 sites in 24 countries (Appendix, online only) in accordance with Good Clinical Practice guidelines and the study protocol and all amendments, which were approved by the appropriate ethics body at each participating center. All participants provided written informed consent. An external data and safety monitoring committee (eDSMC) oversaw the trial, periodically assessed safety, and assessed efficacy at the prespecified interim analysis.

Eligible patients were ≥ 18 years of age and had histologically or cytologically confirmed stage IV NSCLC, PD-L1 TPS ≥ 50%, no previous systemic therapy for metastatic NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1,[10] and ≥ 1 lesion measurable per RECIST v1.1.[11] Patients with nonsquamous tumors could not be allocated unless it was documented that no sensitizing *EGFR* mutation or *ALK* translocation was present; patients with *ROS1* rearrangement were excluded if *ROS1* testing and treatment were locally approved and accessible. Other key exclusion criteria included known untreated CNS metastases, active autoimmune disease that required systemic treatment in the prior 2 years, history of noninfectious pneumonitis that required systemic glucocorticoids, radiotherapy administered within 2 weeks of study treatment, and > 30 Gy radiotherapy administered to the lungs within 6 months of study treatment. Full eligibility criteria are available in the Protocol (online only).

Treatment

Participants were randomly allocated in a 1:1 ratio to receive ipilimumab 1 mg/kg or saline placebo administered intravenously every 6 weeks for up to 18 doses (approximately 2 years). All participants received pembrolizumab 200 mg intravenously every 3 weeks for up to 35 doses (approximately 2 years). Pembrolizumab was infused first, followed by ipilimumab or placebo. Each treatment cycle was 3 weeks in duration. Treatment was continued until progression, unacceptable toxicity, use of prohibited medication, investigator decision, or withdrawal of consent. Participants with confirmed complete response (CR) could discontinue treatment if they received ≥ 8 cycles of combination therapy, including ≥ 2 cycles beyond CR. Participants who experienced unacceptable toxicity attributed to combination therapy and not pembrolizumab monotherapy in the opinion of the investigator could discontinue ipilimumab or placebo and continue pembrolizumab; ipilimumab or placebo could not be continued if pembrolizumab was discontinued. Full details regarding treatment decisions and AE management are found in the

Protocol. Random allocation was performed via an integrated interactive voice-response and Web-response system and was stratified by ECOG performance-status score (0 *v* 1), geographic region (East Asia *v* not East Asia), and predominant tumor histology (squamous *v* nonsquamous).

Assessments

PD-L1 expression was assessed during screening at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA) in formalin-fixed tumor samples collected from nonirradiated lesions. Newly obtained core or excisional biopsy samples were preferred over archival tumor samples. Expression was categorized according to the TPS (ie, percentage of tumor cells with membranous PD-L1 staining). Tumor imaging was scheduled for week 9, then every 9 weeks through week 54 and every 12 weeks thereafter. Response was assessed according to RECIST v1.1,[11] by blinded independent central review for determination of study end points and according to iRECIST[12] by the investigator to make treatment decisions after disease progression. AEs and laboratory abnormalities were collected throughout treatment and for 30 days thereafter (up to 90 days for serious events) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Participants were contacted every 12 weeks to assess survival during follow-up.

End Points

The dual primary end points were OS (ie, time from random allocation to death) and PFS (ie, time from random allocation to disease progression or death, whichever occurred first). Secondary end points included ORR (ie, proportion of participants with complete or partial response), duration of response (ie, time from first evidence of complete or partial response to disease progression or death, whichever occurred first), and safety. PFS, ORR, and duration of response were assessed per RECIST v1.1, by blinded, independent central review.

Statistical Analysis

Efficacy was assessed in the intention-to-treat population (ie, all randomly allocated participants). Safety was assessed in the as-treated population (ie, all randomly allocated participants who received ≥ 1 dose of study treatment). OS, PFS, and duration of response were estimated using the Kaplan-Meier method and the censoring rules outlined in Appendix Table A1 (online only). Between-group differences in OS and PFS were assessed using the stratified logrank test; all *P* values are one-sided. The magnitude of the treatment difference was assessed using the stratified Cox proportional hazards model and Efron's method of tie handling. The random assignment stratification factors were applied to all stratified analyses.

The full statistical analysis plan is available in the Protocol. The graphical method of Maurer and Bretz[13] was used to control the family-wise type I error rate at a one-sided α = .025 across all hypotheses and interim analyses. With 568 participants and for the comparison of pembrolizumab-ipilimumab versus pembrolizumab-placebo, the study had at least 87% power to detect a hazard ratio (HR) for disease progression or death of 0.69 at a one-sided α = .006, assuming 389 events of disease progression or death and one interim analysis, and at least 90% power to detect an HR for death of 0.70 at a one-sided α = .019, assuming 361 deaths and two interim analyses. The first interim analysis was to be performed when approximately 255 deaths occurred and approximately 12 months after the last participant was allocated; it was estimated that approximately 357 events of disease progression or death would be observed at this time. Although the protocol did not specify a futility analysis at the first interim analysis, the eDSMC requested futility criteria after an initial review of the unblinded efficacy and safety data from the first interim analysis. The nonbinding futility boundaries at the first interim analysis were based on between-group differences in the restricted mean survival time[14] of ≤ 0.2 at the maximum observation time (ie, minimum of the latest event or censoring time in each group) and ≤ 0.1 at 24 months of follow-up. All reported data are based on the first interim analysis.

RESULTS

Participants

Between January 12, 2018, and August 22, 2019, 568 participants from 137 sites in 24 countries were randomly allocated to receive pembrolizumab-ipilimumab (n = 284) or pembrolizumab-placebo (n = 284) (Fig 1). Baseline demographics and disease characteristics were generally well balanced between treatment groups (Table 1). With respect to stratification factors, most participants had ECOG performance-status score 1 (63.9%), were enrolled outside of East Asia (88.9%), and had nonsquamous tumors (72.2%).

A total of 282 participants in the pembrolizumab-ipilimumab group and 281 in the pembrolizumab-placebo group received ≥ 1 dose of study treatment (Fig 1). As of the September 1, 2020, data cutoff for the first interim analysis, median study follow-up was 20.6 months (range, 12.4-31.7 months). In the pembrolizumab-ipilimumab group, 212 (75.2%) participants discontinued all treatment, 10 (3.5%) completed all 35 cycles, and 60 (21.3%) remained on treatment; in the pembrolizumab-placebo group, 195 (69.4%) discontinued, 19 (6.8%) completed, and 67 (23.8%) remained on treatment (Fig 1). The most common reason for treatment discontinuation in both groups was disease progression. The median (range) number of treatment cycles was 10 (1-35) in the pembrolizumab-ipilimumab group and 15 (1-35) in the pembrolizumab-placebo group (Appendix Table A2, online only). Median treatment duration in the pembrolizumab-ipilimumab versus

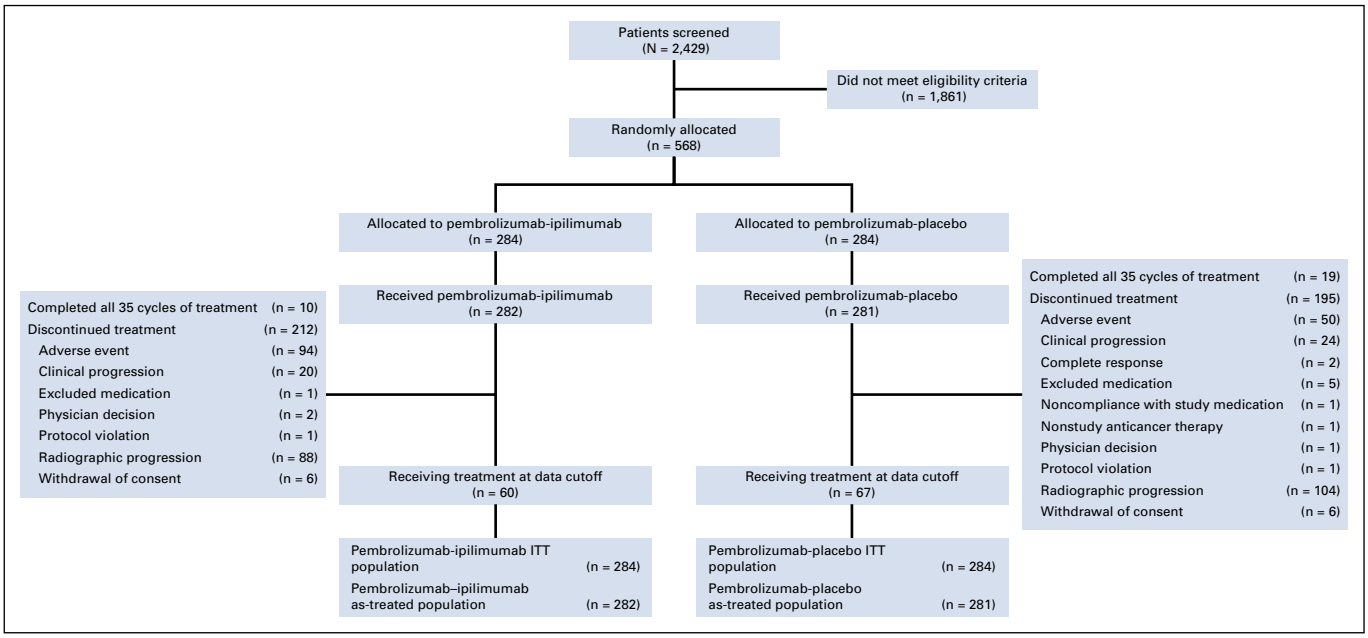

FIG 1. CONSORT diagram. ITT, intention-to-treat.

TABLE 1. Baseline Demographic and Disease Characteristics

Characteristic	Pembrolizumab-Ipilimumab (N = 284)	Pembrolizumab-Placebo (N = 284)
Age		
Median (range)—years	64 (35-85)	65 (35-85)
< 65 years—no. (%)	147 (51.8)	134 (47.2)
Male sex—no. (%)	202 (71.1)	191 (67.3)
Region of enrollment—no. (%)		
East Asia	32 (11.3)	31 (10.9)
Not East Asia	252 (88.7)	253 (89.1)
ECOG performance-status score—no. (%)		
0	101 (35.6)	104 (36.6)
1	183 (64.4)	180 (63.4)
Smoking status—no. (%)		
Current	58 (20.4)	76 (26.8)
Former	197 (69.4)	183 (64.4)
Never	29 (10.2)	25 (8.8)
Histologic features—no. (%)		
Squamous	77 (27.1)	81 (28.5)
Nonsquamous	207 (72.9)	203 (71.5)
Brain metastases—no. (%)	31 (10.9)	29 (10.2)
Previous therapy for nonmetastatic disease—no. (%)		
Adjuvant or neoadjuvant	8 (2.8)	16 (5.6)
Radiation	60 (21.1)	57 (20.1)
Thoracic radiation	15 (5.3)	10 (3.5)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

pembrolizumab-placebo group was 6.3 versus 9.7 months for pembrolizumab and 5.6 versus 8.8 months for ipilimumab or placebo (Appendix Table A2).

Efficacy

With 272 deaths, median OS was 21.4 months (95% CI, 16.6 to not reached) in the pembrolizumab-ipilimumab group and 21.9 months (95% CI, 18.0 to not reached) in the pembrolizumab-placebo group; 12-month survival estimates were 63.6% and 67.9%, respectively (Fig 2A). The HR was 1.08 (95% CI, 0.85 to 1.37; P = .74), with similar results across subgroups (Fig 2B). Restricted mean survival time in the pembrolizumab-ipilimumab group versus the pembrolizumab-placebo group was 16.09 versus 16.61 months at 24 months (difference, –0.52) and 18.76 versus 19.32 months at the maximum observation time (difference, –0.56).

With 372 events of disease progression or death, median PFS was 8.2 months (95% CI, 6.0 to 10.5) in the pembrolizumab-ipilimumab group and 8.4 months (95% CI, 6.3 to 10.5) in the pembrolizumab-placebo group; 12-month PFS estimates were 41.3% and 42.1%, respectively (Fig 2C). The HR was 1.06 (95% CI, 0.86 to 1.30; P = .72). Results were generally similar across all subgroups examined (Fig 2D).

ORR was 45.4% (95% CI, 39.5 to 51.4) in each treatment group, with CRs observed in 4.6% of participants in the pembrolizumab-ipilimumab group and 2.8% in the pembrolizumab-placebo group (Table 2). Median time to response was 2.1 months in each group. Median duration of response was 16.1 months (range, 1.1+ to 26.0 months) in the pembrolizumab-ipilimumab group and 17.3 months (range, 2.0+ to 29.4+ months) in the pembrolizumab-placebo group (Appendix Fig A1, online only; plus signs in the ranges indicate the response was ongoing at cutoff).

Safety

AEs occurred in 96.5% of 282 treated participants in the pembrolizumab-ipilimumab group and 93.6% of 281 treated participants in the pembrolizumab-placebo group. AEs were serious in 51.4% and 38.4% of participants, respectively, and were of grade ≥ 3 in 62.4% and 50.2%, respectively. In the pembrolizumab-ipilimumab group, AEs led to discontinuation of pembrolizumab and ipilimumab in 30.9% and ipilimumab only in 6.4%. In the pembrolizumab-placebo group, AEs led to discontinuation of pembrolizumab and placebo in 17.1% and placebo only in 3.2%. AEs led to interruption of both drugs in 40.1% and 26.3% of participants in the pembrolizumab-ipilimumab and pembrolizumab-placebo groups, respectively. Grade 5 AEs occurred in 13.1% of participants in the pembrolizumab-ipilimumab group and 7.5% in the pembrolizumab-placebo group; these AEs were considered treatment-related for seven participants (2.5%) in the pembrolizumab-ipilimumab group (n = 2 from myocarditis and n = 1 each from adrenal insufficiency, cholestatic jaundice, disease progression, lymphocytic hypophysitis, and pneumonitis) and no participants in the pembrolizumab-placebo group. AEs with incidence ≥ 20% were diarrhea, pruritus, and decreased appetite in the pembrolizumab-ipilimumab group and cough in the pembrolizumab-placebo group (Table 3). Among AEs with incidence ≥ 10%, there was a greater risk of diarrhea, increased AST, decreased appetite, and pneumonitis in the pembrolizumab-ipilimumab group (Appendix Fig A2A, online only). Among grade ≥ 3 AEs with incidence ≥ 2%, the risk of diarrhea, rash, and colitis was greater in the pembrolizumab-ipilimumab group (Appendix Fig A2B, online only). The most common treatment-related AEs in both groups were pruritus, rash, and hypothyroidism (Appendix Fig A3, online only).

Immune-mediated AEs and infusion reactions, which were defined on the basis of a list of terms specified by the sponsor and considered regardless of attribution to treatment by the investigator, occurred in 44.7% of treated participants in the pembrolizumab-ipilimumab group and 32.4% of treated participants in the pembrolizumab-placebo group, including 20.2% and 7.8%, respectively, who had grade ≥ 3 events. Six participants (2.1%) in the pembrolizumab-ipilimumab group died from immune-mediated AEs compared with no participants in the pembrolizumab-placebo group. Immune-mediated AEs led to discontinuation of all treatment in 12.1% of participants in the pembrolizumab-ipilimumab group versus 4.3% in the pembrolizumab-placebo group and discontinuation of ipilimumab or placebo only in 1.8% versus 1.1%. The most common immune-mediated AEs in both groups were hypothyroidism, pneumonitis, hyperthyroidism, and colitis; the risk of pneumonitis (any grade) and colitis (any grade and grade ≥ 3) was greater in the pembrolizumab-ipilimumab group compared with the pembrolizumab-placebo group (Fig 3).

DISCUSSION

In the protocol-specified first interim analysis of this placebo-controlled phase III study, we found that adding ipilimumab to pembrolizumab did not improve efficacy compared with pembrolizumab monotherapy as first-line therapy for participants with metastatic NSCLC with PD-L1 TPS ≥ 50% and no actionable *EGFR* or *ALK* mutations. Median OS was 21.4 months in the pembrolizumab-ipilimumab group versus 21.9 months in the pembrolizumab-placebo group, and the nonbinding futility criteria were met. Similarly, there were no apparent differences in PFS (median, 8.2 *v* 8.4 months), ORR (45.4% *v* 45.4%), or duration of response (median, 16.1 *v* 17.3 months). There was no subgroup for which pembrolizumab-ipilimumab improved efficacy versus pembrolizumab-placebo as the 95% CIs for all subgroups, including age, sex, and tumor histologic features, overlapped the 95% CI of the overall population. In addition to a lack of improved efficacy, adding ipilimumab to pembrolizumab increased toxicity, including

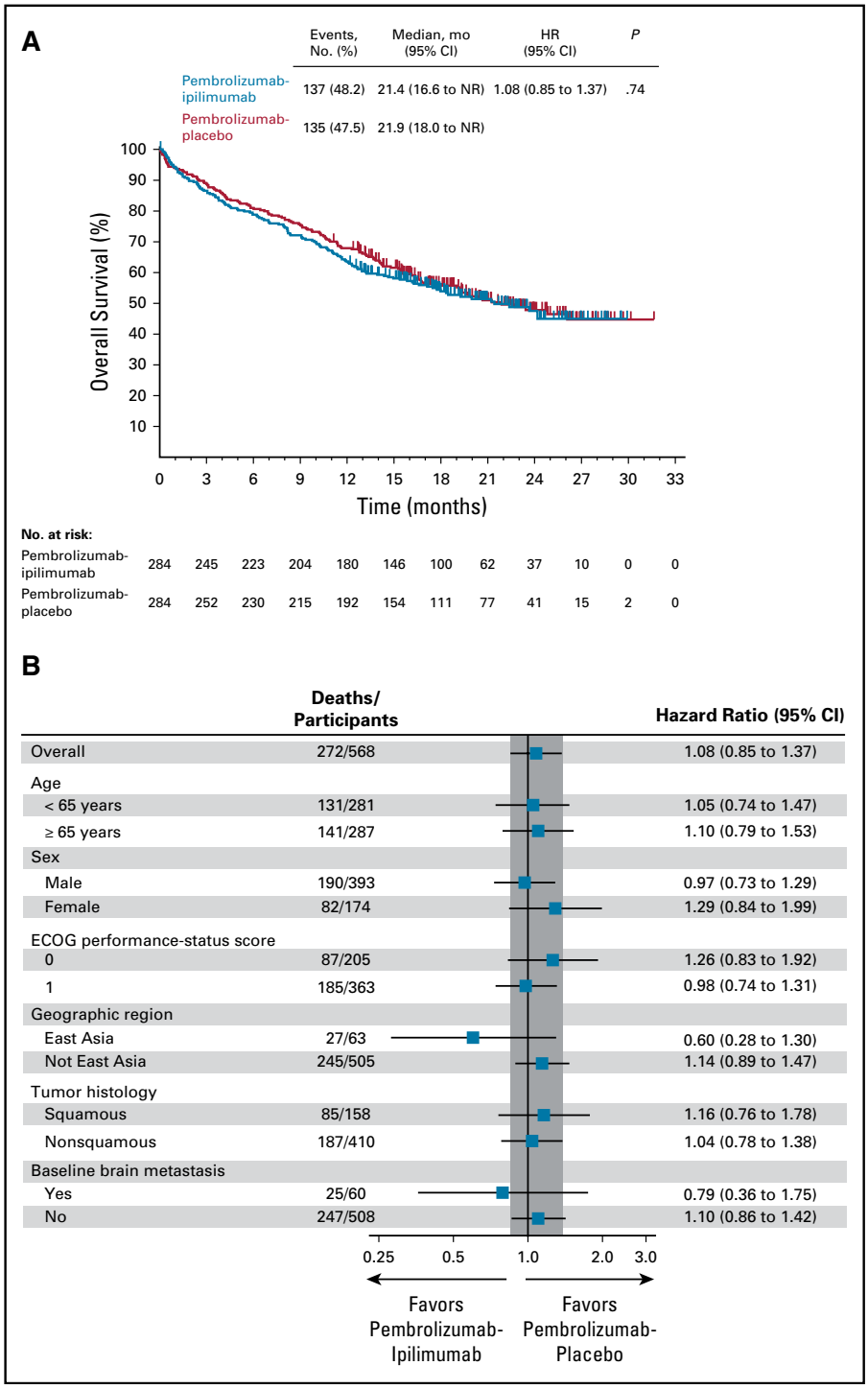

FIG 2. OS and PFS. (A) Kaplan-Meier estimates of OS. (B) Analysis of OS in key subgroups. (C) Kaplan-Meier estimates of PFS. (D) Analysis of progression-free survival in key subgroups. PFS was assessed according to RECIST v1.1, by means of blinded, independent central review of radiology imaging. Tick marks in (A) represent data censored at the last time the patient was known to be alive. Tick marks in (C) represent data censored at the last time the patient was known to be alive and free from disease progression. In (B) and (D), the analysis for the overall population was based on Cox regression with treatment as a covariate stratified by the random assignment stratification factors, whereas the analyses for subgroups were based on unstratified Cox regression with treatment as a covariate. Only those subgroups for which both levels of the subgroup accounted for ≥ 10% of the overall population were included in (B) and (D); because never smokers accounted for only 9.5% of the overall population, outcomes by smoking status are not shown. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

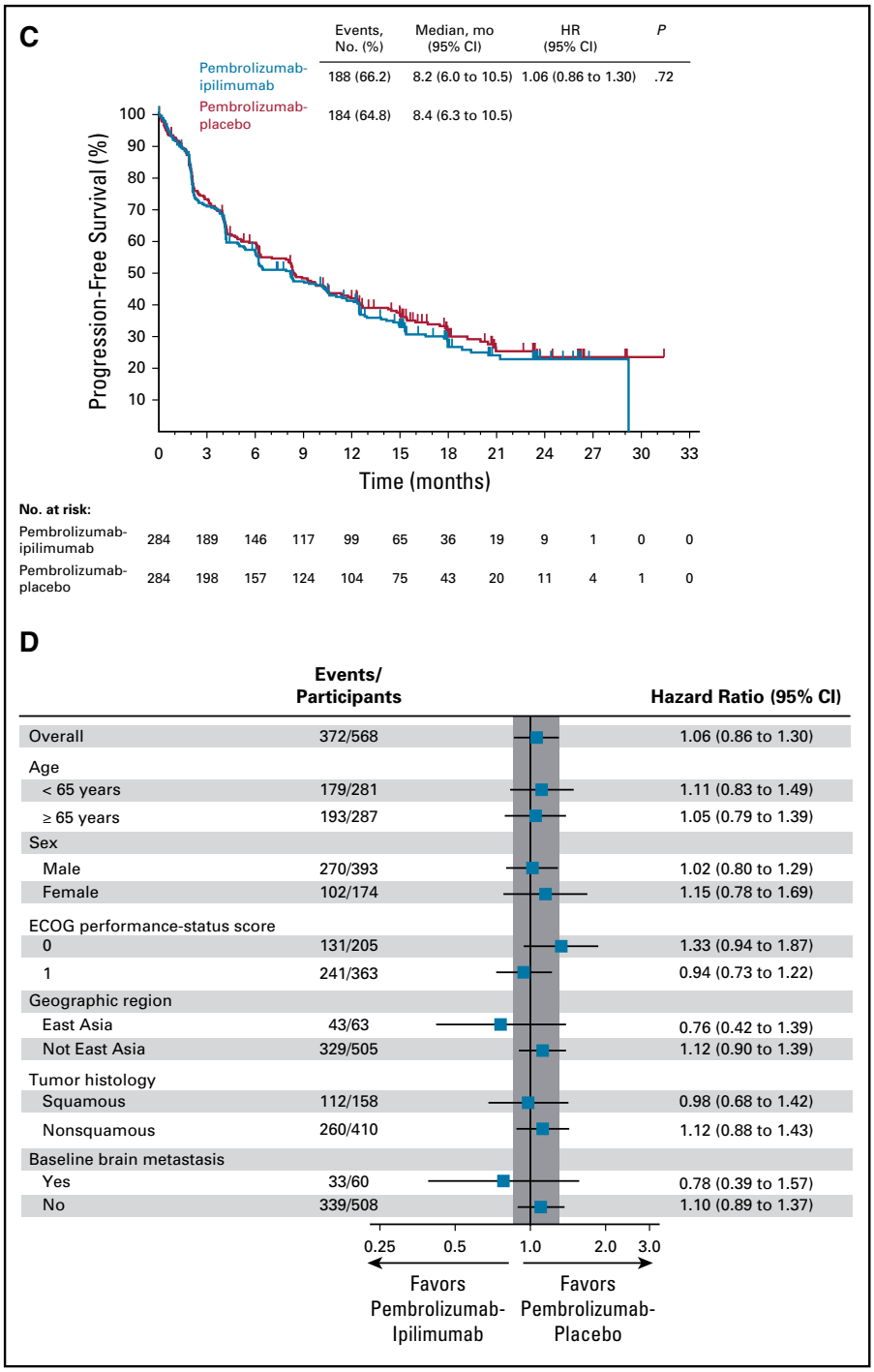

FIG 2. (Continued).

increases in the incidence of serious AEs (51.4% *v* 38.4%) and grade ≥ 3 AEs (62.4% *v* 50.2%). We stopped the study for futility, and participants discontinued ipilimumab and placebo at the recommendation of the eDSMC.

KEYNOTE-598 was specifically designed and adequately powered to prospectively assess whether combined PD-1 and CTLA-4 inhibition significantly improves efficacy versus PD-1 inhibition alone in patients with PD-L1 TPS ≥ 50%. The efficacy observed for the pembrolizumab-placebo group of KEYNOTE-598 was consistent with that previously observed for pembrolizumab monotherapy in participants with TPS ≥ 50% in KEYNOTE-024[1,2] and KEYNOTE-042.[3] Similar results have been shown for the PD-1 inhibitor cemiplimab[15] and the PD-L1 inhibitor atezolizumab[16] in patients with TPS ≥ 50%. Furthermore, the OS observed in the pembrolizumab-ipilimumab group of KEYNOTE-598 was

TABLE 2. Summary of Confirmed Objective Response Assessed per RECIST v1.1 by Blinded, Independent Central Review

Variable	Pembrolizumab-Ipilimumab (N = 284)	Pembrolizumab-Placebo (N = 284)
Objective response rate—% (95% CI)	45.4 (39.5 to 51.4)	45.4 (39.5 to 51.4)
Best overall response—no. (%)		
Complete response	13 (4.6)	8 (2.8)
Partial response	116 (40.8)	121 (42.6)
Stable disease	70 (24.6)	73 (25.7)
Progressive disease	51 (18.0)	44 (15.5)
Not evaluable[a]	6 (2.1)	6 (2.1)
Not assessed[b]	28 (9.9)	32 (11.3)
Median time to response (range)—mo[c]	2.1 (1.6-12.5)	2.1 (1.3-18.1)
Median duration of response (range)—mo[c]	16.1 (1.1+ to 26.0)	17.3 (2.0+ to 29.4+)

[a]Participants who were not evaluable included those who had at least 1 postbaseline imaging assessment, none of which could be evaluated for response according to RECIST v1.1.

[b]Participants who were not assessed included those who did not have any postbaseline imaging assessments.

[c]Time to response and median duration of response were calculated in participants with a best response of complete or partial response using the Kaplan-Meier method (n = 129 in each treatment group). Plus signs in the ranges indicate responses that were ongoing at the time of data cutoff.

TABLE 3. Adverse Events of Any Attribution With Incidence ≥ 10% in Either Treatment Group of the As-Treated Population

	Pembrolizumab-Ipilimumab (N = 282)		Pembrolizumab-Placebo (N = 281)	
Event	Any Grade	Grade 3-5	Any Grade	Grade 3-5
No. of Participants (%)				
Diarrhea	70 (24.8)	10 (3.5)	45 (16.0)	1 (0.4)
Pruritus	69 (24.5)	1 (0.4)	55 (19.6)	2 (0.7)
Decreased appetite	59 (20.9)	3 (1.1)	38 (13.5)	0
Rash	56 (19.9)	8 (2.8)	42 (14.9)	0
Asthenia	51 (18.1)	1 (0.4)	44 (15.7)	4 (1.4)
Nausea	49 (17.4)	2 (0.7)	38 (13.5)	0
Cough	48 (17.0)	0	57 (20.3)	1 (0.4)
Fatigue	48 (17.0)	6 (2.1)	49 (17.4)	4 (1.4)
Dyspnea	45 (16.0)	7 (2.5)	44 (15.7)	8 (2.8)
Hypothyroidism	43 (15.2)	1 (0.4)	33 (11.7)	1 (0.4)
Anemia	40 (14.2)	8 (2.8)	40 (14.2)	7 (2.5)
Constipation	40 (14.2)	2 (0.7)	50 (17.8)	2 (0.7)
AST increased	36 (12.8)	5 (1.8)	14 (5.0)	2 (0.7)
Pyrexia	36 (12.8)	3 (1.1)	27 (9.6)	0
Pneumonia	34 (12.1)	24 (8.5)	30 (10.7)	18 (6.4)
ALT increased	32 (11.3)	9 (3.2)	19 (6.8)	4 (1.4)
Pneumonitis	32 (11.3)	14 (5.0)	13 (4.6)	6 (2.1)
Vomiting	32 (11.3)	4 (1.4)	27 (9.6)	1 (0.4)
Back pain	29 (10.3)	1 (0.4)	29 (10.3)	2 (0.7)
Arthralgia	28 (9.9)	4 (1.4)	33 (11.7)	2 (0.7)

NOTE. AEs are listed in descending order of frequency in the pembrolizumab-ipilimumab group and classified according to the *Medical Dictionary for Regulatory Activities*, version 23.0.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

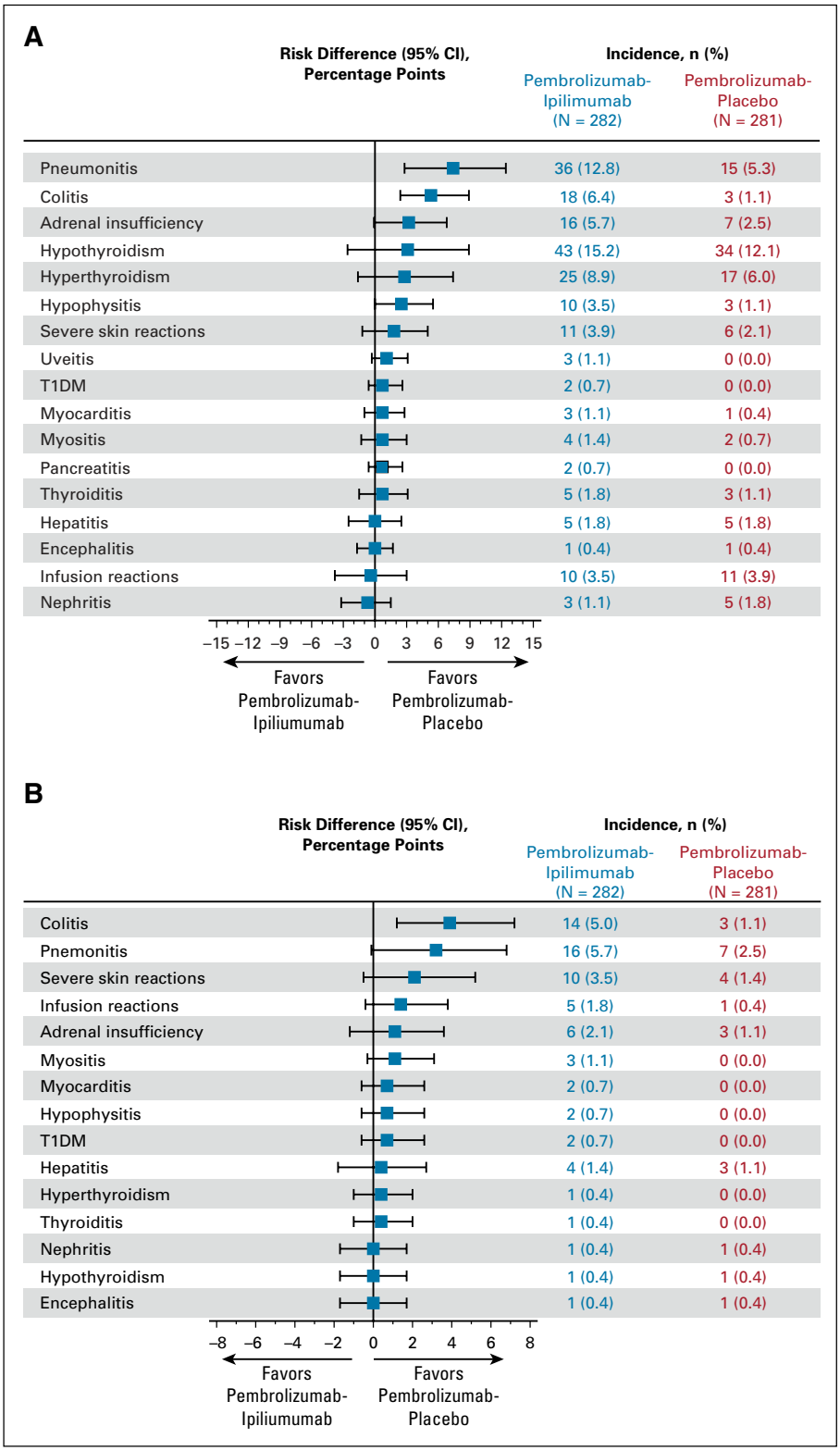

FIG 3. Risk difference between treatment groups for immune-mediated AEs and infusion reactions. (A) Events of any grade. (B) Events of grade ≥ 3. Immune-mediated AEs and infusion reactions were based on a list specified by the sponsor and were considered regardless of attribution to study treatment by the investigator. In addition to the specific preferred terms listed, related terms were also included. There were no cases of grade ≥ 3 pancreatitis or uveitis. AE, adverse event; T1DM, type 1 diabetes mellitus.

almost identical to that observed for nivolumab-ipilimumab in the exploratory PD-L1 expression ≥ 50% subgroup of the CheckMate 227 study.[8] Although cross-trial comparisons should be undertaken with caution, these findings suggest that the lack of benefit for pembrolizumab-ipilimumab cannot be explained by overperformance of the pembrolizumab-placebo group or underperformance of the pembrolizumab-ipilimumab group. It is plausible that despite having different targets and mechanisms of action, combined CTLA-4 and PD-1 inhibition may not provide benefit beyond PD-1 inhibition alone in this NSCLC population most likely to benefit from immunotherapy.

The double-blind, placebo-controlled design of our study ensured unbiased assessment of AEs. The AE profile observed for the pembrolizumab-placebo group was consistent with that previously observed for pembrolizumab monotherapy in metastatic NSCLC.[1-3] The overall safety profile and incidences of treatment-related AEs of any grade, of grade ≥ 3, that were serious or that led to discontinuation observed for pembrolizumab-ipilimumab were similar to those of nivolumab-ipilimumab in CheckMate 227, which used the same dose and schedule of ipilimumab.[8] Compared with pembrolizumab-placebo, and as anticipated based on previous studies of combined PD-1 and CTLA-4 inhibition,[4-8,17] pembrolizumab-ipilimumab was associated with increased incidence of grade ≥ 3, serious, and immune-mediated AEs. The incidence of treatment discontinuation and interruption was also greater in the pembrolizumab-ipilimumab group, as was the risk of diarrhea, increased AST, decreased appetite, pneumonitis, and colitis.

There are limitations to this study. KEYNOTE-598 was designed in 2017, when the only randomized, phase III data available for pembrolizumab as first-line therapy for metastatic NSCLC were from the KEYNOTE-024 study that demonstrated superiority of pembrolizumab monotherapy versus chemotherapy for metastatic NSCLC with PD-L1 TPS ≥ 50% and no *EGFR* or *ALK* alterations.[1] Thus, KEYNOTE-598 did not assess the role of combined PD-1 and CTLA-4 inhibition in patients with low or negative PD-L1 expression. Although KEYNOTE-042 subsequently showed that pembrolizumab monotherapy significantly improved efficacy versus chemotherapy in patients with TPS ≥ 1%, the benefit was modest in the TPS 1%-49% subgroup.[3] Similarly, although CheckMate 227 demonstrated superiority for nivolumab-ipilimumab in patients with metastatic NSCLC and PD-L1 expression ≥ 1%, much of the benefit appeared to be driven by the PD-L1 ≥ 50% subgroup.[8] Additional phase III studies published since KEYNOTE-598 was designed have shown that the combination of pembrolizumab and chemotherapy is superior to chemotherapy alone as first-line therapy for squamous and nonsquamous metastatic NSCLC, including those with PD-L1 TPS ≥ 50%.[18,19] The ongoing EA5163/S1709 INSIGNA study (ClinicalTrials.gov identifier: NCT03793179) is assessing whether first-line pembrolizumab monotherapy followed by pemetrexed and carboplatin with or without pembrolizumab after disease progression is superior to first-line pembrolizumab, pemetrexed, and carboplatin followed by pembrolizumab and pemetrexed maintenance in patients with metastatic nonsquamous NSCLC with PD-L1 TPS ≥ 1%.

In conclusion, this randomized phase III study of patients with previously untreated metastatic NSCLC with PD-L1 TPS ≥ 50% without sensitizing *EGFR* or *ALK* mutations showed that the combination of pembrolizumab and ipilimumab did not improve either OS or PFS compared with pembrolizumab alone and was associated with greater toxicity. These data do not support the use of pembrolizumab-ipilimumab in place of pembrolizumab monotherapy in this population.

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DATA SHARING STATEMENT

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pembrolizumab Plus Ipilimumab or Placebo for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%: Randomized, Double-Blind Phase III KEYNOTE-598 Study

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	Hospital Fundacion Jimenez Diaz—Clin. Concepcion	Domine Gomez, Manuel
	Hospital Universitari Vall d Hebron	Felip, Enriqueta
	Hospital Duran i Reynals	Nadal, Ernest
	Hospital Universitario Insular de Gran Canaria	Rodriguez Abreu, Delvys
Taiwan	China Medical University Hospital	Hsia, Te-Chun
	Changhua Christian Hospital	Lin, Sheng-Hao
	Mackay Memorial Hospital	Su, Jian

(continued on following page)

List of Investigators[a] (continued)

Country/Region	Site Name	Principal Investigator
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	Chang Gung Medical Foundation—Kaohsiung	Tseng, Chia-Cheng (current) Wang, Chin-Chou (former)
	Chang Gung Medical Foundation-Linkou Branch	Yang, Cheng-Ta
	National Taiwan University Hospital	Yang, Chih-Hsin
Thailand	Ramathibodi Hospital	Ativitavas, Touch (current) Reungwetwattana, Thanyanan (former)
	Pramongkutklao Hospital	Seetalarom, Kasan
	Khon Kaen University	Sookprasert, Aumkhae
	Siriraj Hospital	Soparattanapaisarn, Nopadol (current) Srimuninnimit, Vichien (former)
	Chulalongkorn Hospital	Sriuranpong, Virote
	Bangkok Hospital Chiangmai	Thongprasert, Sumitra
Turkey	Medical Park Izmir Hospital	Arslan, Cagatay
	Kocaeli Universitesi Tip Fakultesi	Cabuk, Devrim
	Trakya Uni. Tip Fakultesi	Cicin, Irfan
	Marmara Universitesi Pendik Egitim ve Arastirma Hastanesi	Ercelep, Ozlem (current) Yumuk, Perran Fulden (former)
	Hacettepe Universitesi Tip Fakultesi Hastanesi	Erman, Mustafa
	Ege Universitesi Tip Fakultesi Hastanesi	Goksel, Tuncay
	Inonu Universitesi Medical Fakultesi	Harputluoglu, Hakan
	Uludag Universitesi Tip Fakultesi	Kanat, Ozkan
	Karadeniz Teknik Universitesi	Kavgaci, Halil
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Ukraine	MI Kryviy Rih Center of Dnipropetrovsk Regional Council	Adamchuk, Hryhoriy
	City Clinical Hosp.4 of DCC	Bondarenko, Igor
	National Cancer Institute of the MoH of Ukraine	Kolesnik, Olena
	MI Prykarpatskyi Clinical Oncology Centrum	Kryzhanivska, Anna
	Cherkasy Regional Oncology Dispensary	Paramonov, Viktor
	Regional Clinical Onco Dispensary, State Medical University	Semehen, Yuriy (current) Hontsa, Anatoliy (former)
	Lviv State Oncology Regional Treatment and Diagnostic Center	Shparyk, Yaroslav
	MI Odessa Regional Oncological Centre	Trukhin, Dmytro
	PP PPC Acinus Medical and Diagnostic Centre	Ursol, Grygorii
	Kyiv City Clinical Oncological Center	Voitko, Nataliia
United Kingdom	Royal Wolverhampton Hospitals NHS Trust	Belitei, Petru
	St Georges University Hospital NHS Foundation Trust	Benepal, Tim
	Royal Free NHS Foundation Trust	Boleti, Ekaterini (current) Ariyaratne, Hemal (former)
	The Christie NHS Foundation Trust	Califano, Raffaele
	The Royal Marsden NHS Foundation Trust	O'Brien, Mary
	Mount Vernon Cancer Centre	Polychronis, Andreas
	Royal Cornwall Hospital	Talbot, Toby

(continued on following page)

List of Investigators[a] (continued)

Country/Region	Site Name	Principal Investigator
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	Boston Medical Center	Everett, Peter (current) Charlot, Marjory (former)
	University of Tennessee Erlanger Oncology and Hematology	Kingsley, C. Daniel
	University of Wisconsin Carbone Cancer Center	Leal, Ticiana
	Tennessee Cancer Specialists	Lee, Richard (current)
		DeVore, Russell (former)
	The Ohio State University Wexner Medical Center	Otterson, Gregory (current) Olugbile, Sope (former)
	Mayo Clinic Cancer Center	Savvides, Panayiotis (current) Ross, Helen (former)
	Texas Oncology, P.A. Texas Oncology-Tyler	Socoteanu, Matei P.
	Pacific Cancer Care	Stampleman, Laura
	Medical College of Wisconsin Clinical Cancer Center	Thompson, Jonathan
	Northwest Cancer Specialists, P.C.	Van Ho, Anthony (current) Smith, David (former)

[a]Includes the 137 sites at which ≥ 1 participant was randomly allocated to study treatment and the 34 sites that actively screened patients but did not have any patients randomly allocated to study treatment.

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TABLE A1. Censoring Rules for Kaplan-Meier Analyses

Situation	Censoring Rule
Progression-free survival	
PD or death documented after ≤ 1 missed disease assessment and before new anticancer therapy, if any	Progressed at date of documented PD or death
PD or death immediately after ≥ 2 consecutive missed disease assessments or after new anticancer therapy	Censored at the last disease assessment before the earlier date of ≥ 2 consecutive missed disease assessments or new anticancer therapy, if any
No PD, no death, no new anticancer therapy	Censored at last disease assessment
No PD, no death, new anticancer therapy	Censored at last disease assessment before new anticancer therapy
Overall survival	
No death	Censored at the date of last known contact
Duration of response[a]	
No PD, no death, no new anticancer therapy	Censored at last adequate disease assessment
No PD, no death, new anticancer therapy	Censored at last adequate disease assessment before new anticancer therapy initiated
PD or death documented after ≥ 2 missed disease assessments or after new anticancer therapy, if any	Censored at the last disease assessment before the earlier date of ≥ 2 consecutive missed disease assessments or new anticancer therapy, if any
PD or death documented after ≤ 1 missed adequate disease assessment and before any new anticancer therapy, if any	End of response at date of documented PD or death

Abbreviation: PD, progressive disease.

[a]For duration of response, a missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluating response.

TABLE A2. Summary of Exposure to Study Treatment in the As-Treated Population

Treatment	Pembrolizumab-Ipilimumab (n = 282)	Pembrolizumab-Placebo (n = 281)
No. of cycles[a]		
Median (range)	10 (1-35)	15 (1-35)
Mean (SD)	12.9 (10.4)	15.5 (11.1)
Months on pembrolizumab		
Median (range)	6.3 (0.03-25.1)	9.7 (0.03-25.8)
Mean (SD)	8.8 (7.6)	10.4 (7.9)
Months on ipilimumab or placebo		
Median (range)	5.6 (0.03-25.1)	8.8 (0.03-25.8)
Mean (SD)	8.0 (7.5)	9.9 (7.9)

[a]Each cycle was 3 weeks in duration.

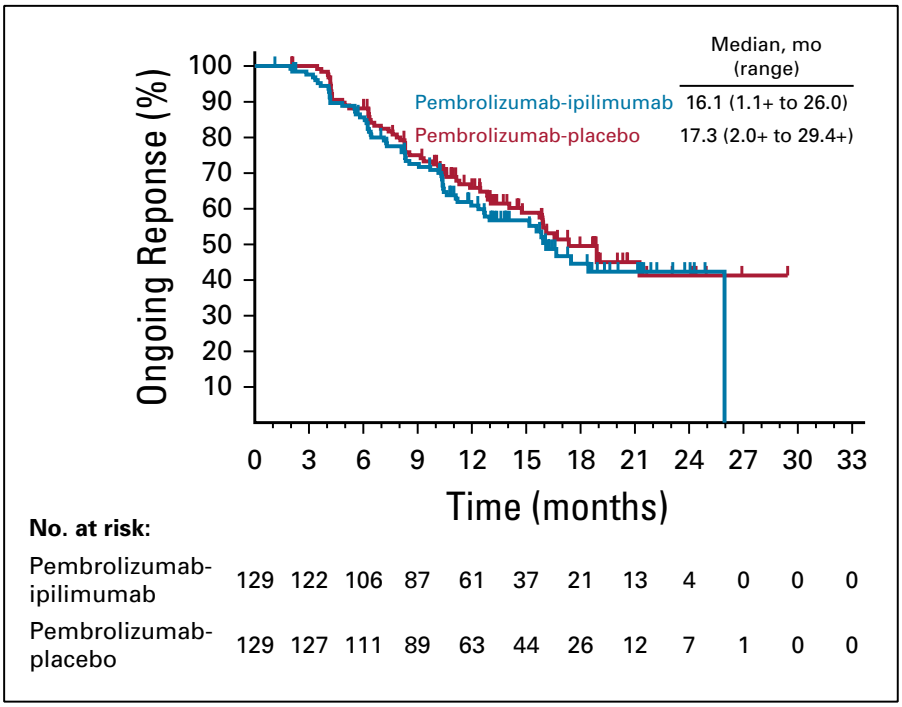

FIG A1. Kaplan-Meier estimates of duration of response in participants with a best response of complete or partial response. Response was assessed according to RECIST v1.1, by means of blinded, independent central review of radiology imaging.

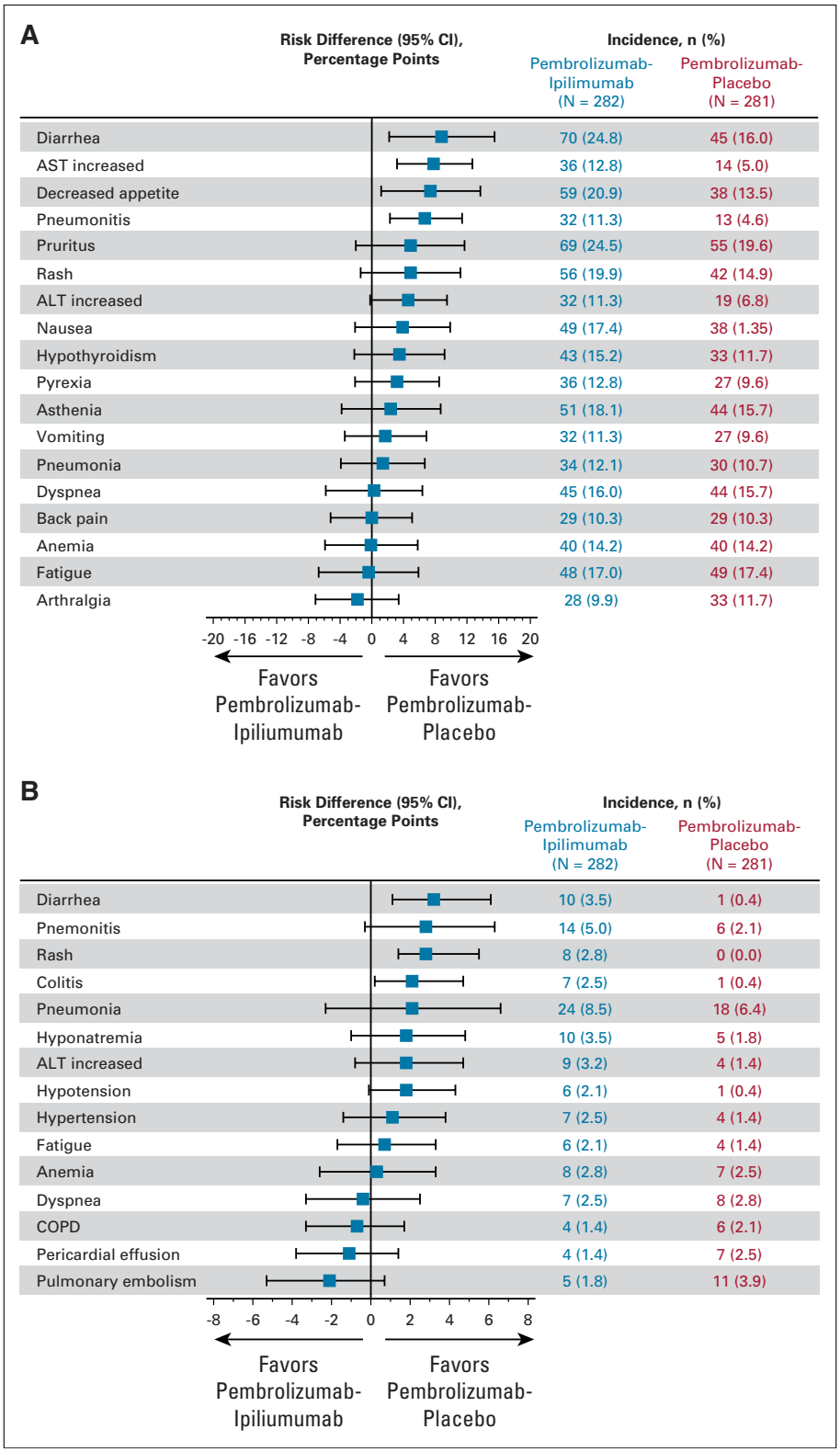

FIG A2. Risk difference between treatment groups for adverse events of any attribution. (A) Adverse events of any grade with incidence ≥ 10% in either treatment group; the overall incidence of any-grade adverse events was 96.5% in the pembrolizumab-ipilimumab group and 93.6% in the pembrolizumab-placebo group. (B) Adverse events of grade ≥ 3 with incidence ≥ 2% in either treatment group; the overall incidence of grade ≥ 3 adverse events was 62.4% in the pembrolizumab-ipilimumab group and 50.2% in the pembrolizumab-placebo group. ALT, alanine aminotransferase; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disorder.

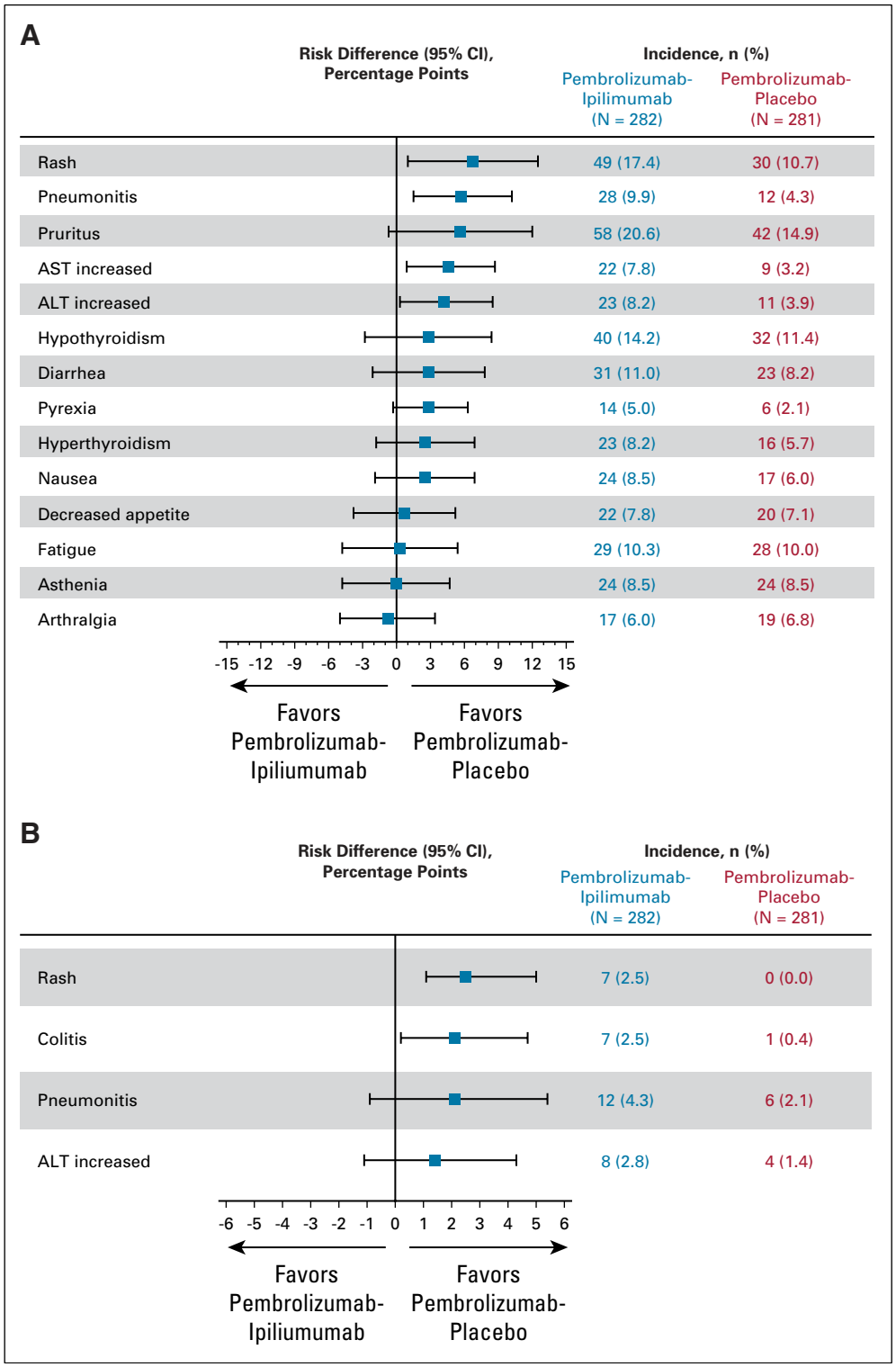

FIG A3. Risk difference between treatment groups for treatment-related adverse events. (A) Treatment-related adverse events of any grade with incidence ≥ 5% in either treatment group; the overall incidence of any-grade treatment-related adverse events was 76.2% in the pembrolizumab-ipilimumab group and 68.3% in the pembrolizumab-placebo group. (B) Treatment-related adverse events of grade ≥ 3 with incidence ≥ 2% in either treatment group; the overall incidence of treatment-related grade ≥ 3 adverse events was 35.1% in the pembrolizumab-ipilimumab group and 19.6% in the pembrolizumab-placebo group. ALT, alanine aminotransferase; AST, aspartate aminotransferase.