Five year survival update from KEYNOTE-010: pembrolizumab versus docetaxel for previously treated, programmed death-ligand 1-positive advanced NSCLC

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ORIGINAL ARTICLE

Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1–Positive Advanced NSCLC

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ABSTRACT

Introduction: In the KEYNOTE-010 study, pembrolizumab improved overall survival (OS) versus docetaxel in patients with previously treated, advanced NSCLC with programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) ≥50% and ≥1%. We report 5-year efficacy and safety follow-up for the KEYNOTE-010 study.

Methods: Patients were randomized to pembrolizumab 2 mg/kg or 10 mg/kg once every 3 weeks or docetaxel 75 mg/m^2 once every 3 weeks for up to 35 cycles (2 y). Patients who completed pembrolizumab treatment and subsequently had recurrence could receive second-course pembrolizumab for up to 17 cycles (1 y). Pembrolizumab doses were pooled in this analysis.

Results: A total of 1034 patients were randomized (pembrolizumab, n = 691; docetaxel, n = 343). Median study follow-up was 67.4 months (range: 60.0–77.9). The hazard ratio (95% confidence interval) for OS was 0.55 (0.44–0.69) for patients with PD-L1 TPS ≥50% and 0.70 (0.61–0.80) with PD-L1 TPS ≥1%. The 5-year OS rates for pembrolizumab versus docetaxel were 25.0% versus 8.2% in patients with PD-L1 TPS ≥50% and 15.6% versus 6.5% with PD-L1 TPS ≥1%. Among 79 patients who completed 35 cycles/2 years of pembrolizumab, the OS rate 3 years after completion (~5 y from randomization) was 83.0%. A total of 21 patients received second-course pembrolizumab; 11 (52.4%) had an objective response after starting the second course and 15 (71.4%) were alive at data cutoff. Exploratory biomarker analysis revealed that higher tissue tumor mutational burden (≥175 mutations per exome) was associated with improved outcomes with pembrolizumab.

Conclusions: Pembrolizumab continued to provide long-term benefit than docetaxel in patients with previously treated advanced NSCLC with PD-L1 TPS ≥50% and ≥1%. Our findings confirm pembrolizumab as a standard-of-care treatment in the second-line or later setting.

Keywords: Pembrolizumab; Non–small-cell lung cancer; Chemotherapy; PD-L1

Introduction

Pembrolizumab, a humanized monoclonal antibody against programmed death 1 (PD-1), promotes T cell-mediated antitumor activity by inhibiting the interaction between PD-1 and its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2).[1] Pembrolizumab has been found to improve overall survival (OS) compared with standard chemotherapy in the first- and second-line or later settings among patients with advanced or metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥1% and to improve OS when combined with platinum-based chemotherapy in patients with metastatic NSCLC regardless of PD-L1 TPS in the first-line setting.[2-7]

The primary analysis of the phase 2/3 KEYNOTE-010 study (data cutoff, September 30, 2015; median follow-up, 13.1 mo) showed significantly improved OS with pembrolizumab monotherapy (2 mg/kg or 10 mg/kg once every 3 weeks) versus docetaxel once every 3 weeks in patients with previously treated advanced NSCLC with PD-L1 TPS ≥50% and PD-L1 TPS ≥1%.[2] The hazard ratios (HRs) for OS were 0.54 (95% confidence interval [CI]: 0.38–0.77) with pembrolizumab 2 mg/kg and 0.50 (95% CI: 0.36–0.70) with pembrolizumab 10 mg/kg in patients with PD-L1 TPS ≥50% and 0.71 (95% CI: 0.58–0.88) and 0.61 (95% CI: 0.49–0.75), respectively, in patients with PD-L1 TPS ≥1%.[2] Because OS was

comparable for the two pembrolizumab doses, data were pooled for later analyses. In previously reported updated analyses with median follow-up of 31.0 and 42.6 months, pembrolizumab continued to show improvement in OS over docetaxel in patients with PD-L1 TPS ≥50% and TPS ≥1%.[8,9]

We report an updated analysis of efficacy and safety outcomes for the intent-to-treat population in KEYNOTE-010 with approximately 5 years of follow-up from randomization to data cutoff, an additional 2 years of follow-up since previous analysis.[9] In addition, outcomes are reported for the 79 patients who completed 35 cycles/2 years of pembrolizumab treatment (as specified in the study protocol and consistent with the pembrolizumab prescribing information[10]) and for the 21 patients who received second-course pembrolizumab. For the first time, we report the findings from an exploratory biomarker analysis of the prevalence and association with outcomes of tissue tumor mutational burden (tTMB) among patients in KEYNOTE-010.

Materials and Methods

Study Design and Patients

KEYNOTE-010 was a multicenter, international trial that enrolled patients from 202 academic medical centers in 24 countries (ClinicalTrials.gov, NCT01905657). Eligible patients were aged more 18 years or older with histologically or cytologically confirmed stage IIIB/IV NSCLC with 1 or more measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (RECIST v1.1) by investigator review and PD-L1 TPS ≥1%, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and investigator-determined disease progression after 2 or more cycles of platinum-based chemotherapy, and an appropriate tyrosine kinase inhibitor for those with an *EGFR* or *ALK* alteration. Full inclusion and exclusion criteria have been published previously.[2]

The study protocol and amendments were approved by an investigational review board or ethics committee at each study site. Patients provided written informed consent before participation.

Treatment Allocation

Patients were randomly assigned (1:1:1) to open-label pembrolizumab 2 mg/kg once every 3 weeks, pembrolizumab 10 mg/kg once every 3 weeks, or docetaxel 75 mg/m^2 once every 3 weeks. Randomization was stratified according to ECOG performance status (0 versus 1), geographic region (east Asia versus non-east Asia), and PD-L1 TPS (≥50% versus 1%–49%) and was managed centrally using an interactive voice/web response system. Patients allocated to pembrolizumab received up to 35 cycles/2 years of treatment; patients allocated to docetaxel continued treatment for the maximum duration allowed by local regulations or until disease progression, unacceptable toxicity, investigator decision, withdrawal of patient consent, intercurrent illness preventing continued treatment, noncompliance with study treatment or procedures, or loss to follow-up. Patients who achieved investigator-confirmed complete response per immune-related response criteria (irRC) after treatment with pembrolizumab for 6 months or longer, and with an additional 2 or more cycles of pembrolizumab beyond the initial date of response, could discontinue treatment. Patients who discontinued pembrolizumab after achieving complete response, or after 35 cycles/2 years of pembrolizumab, but who experienced disease progression per irRC (determined by investigator) were eligible for up to 17 cycles (1 y) of pembrolizumab retreatment (i.e., second course) if they had received no other anticancer therapy since the last dose of pembrolizumab. After the KEYNOTE-010 study met its primary objective, a protocol amendment allowed patients in the docetaxel group who had disease progression on the study or who had started subsequent anticancer therapy after study participation and then experienced disease progression could crossover to pembrolizumab 200 mg every 3 weeks for up to 35 cycles/2 years or until discontinuation criteria were met.

Assessments

Patients were evaluated by computed tomography every 9 weeks until week 54 and at 12-week intervals thereafter, or more frequently if clinically indicated. Response to treatment was evaluated according to RECIST v.1.1 by independent central review and treatment decisions made on the basis of irRC per investigator. After completion of study treatment or discontinuation for reasons other than disease progression, disease status was assessed until disease progression, start of an alternative cancer therapy, death, withdrawal of consent, or loss to follow-up. Disease status assessments continued with the same schedule during second-course treatment. Patients were contacted every 2 months to assess survival status.

Adverse events (AEs) were monitored to 30 days after the end of treatment (90 d for serious AEs) using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 to grade severity.

PD-L1 expression was evaluated in formalin-fixed tissue samples from a nonirradiated tumor lesion (44% of samples were archival, 56% were newly collected)[8] at a central laboratory with an immunohistochemistry assay (Agilent Technologies, Carpinteria, CA) with the murine 22C3 antihuman PD-L1 antibody.

Table 1. Baseline Demographic and Disease Characteristics

Characteristic, n (%)	ITT Population		Completed 35 Cycles of Pembrolizumab, n = 79	Patients Who Received Second-Course Pembrolizumab, n = 21
	Pembrolizumab, n = 690	Docetaxel, n = 343		
Age group				
<65 y	395 (57.2)	209 (60.9)	55 (69.6)	15 (71.4)
≥65 y	295 (42.8)	134 (39.1)	24 (30.4)	6 (28.6)
Men	425 (61.6)	209 (60.9)	53 (67.1)	16 (76.2)
Race				
White	496 (71.9)	251 (73.2)	56 (70.9)	14 (66.7)
Asian	145 (21.0)	72 (21.0)	17 (21.5)	6 (28.6)
Black or African American	21 (3.0)	7 (2.0)	5 (6.3)	1 (4.8)
Other	10 (1.4)	2 (0.6)	0	0
Missing	18 (2.6)	11 (3.2)	1 (1.3)	0
Geographic region				
East Asian	128 (18.6)	62 (18.1)	17 (21.5)	6 (28.6)
Non-east Asian	562 (81.4)	281 (81.9)	62 (78.5)	15 (71.4)
ECOG performance status				
0	231 (33.5)	116 (33.8)	25 (31.6)	5 (23.8)
1	455 (65.9)	224 (65.3)	54 (68.4)	16 (76.2)
≥2	4 (0.6)	2 (0.6)	0	0
Missing	0	1 (0.3)	0	0
Smoking history				
Current or former	565 (81.9)	269 (78.4)	72 (91.1)	16 (76.2)
Never	123 (17.8)	67 (19.5)	7 (8.9)	5 (23.8)
Missing	2 (0.3)	7 (2.0)	0	0
Histologic type				
Squamous	156 (22.6)	66 (19.2)	21 (26.6)	6 (28.6)
Nonsquamous	486 (70.4)	240 (70.0)	53 (67.1)	14 (66.7)
Mixed histology	6 (0.9)	4 (1.2)	0	0
Other	9 (1.3)	6 (1.7)	1 (1.3)	0
Unknown	33 (4.8)	27 (7.9)	4 (5.1)	1 (4.8)
Brain metastasis	104 (15.1)	48 (14.0)	12 (15.2)	3 (14.3)
PD-L1 TPS				
≥50%	290 (42.0)	152 (44.3)	58 (73.4)	12 (57.1)
1%–49%	400 (58.0)	191 (55.7)	21 (26.6)	9 (42.9)
EGFR mutation status				
Mutant	61 (8.8)	26 (7.6)	1 (1.3)	0
Wild type	581 (84.2)	293 (85.4)	68 (86.1)	21 (100.0)
Undetermined/missing	48 (7.0)	24 (7.0)	10 (12.7)	0
ALK translocation present				
Yes	6 (0.9)	2 (0.6)	0	0
No	612 (88.7)	309 (90.1)	70 (88.6)	21 (100.0)
Undetermined/missing	72 (10.4)	32 (9.3)	9 (11.4)	0
Prior lines of systemic therapy[a]				
1	477 (69.1)	236 (68.8)	63 (79.7)	18 (85.7)
≥2	198 (28.7)	104 (30.3)	15 (19.0)	3 (14.3)

[a]Excludes adjuvant and neoadjuvant therapies.
ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

Tumor samples with TPS ≥1% were considered PD-L1 positive.

Tumor TMB status was assessed using whole-exome sequencing (WES) of tumor tissue and matched normal DNA as previously described.[11] A prespecified cutpoint of 175 mutations per exome (mut/exome) was used to define subgroups with high tTMB (≥175 mut/exome) versus low tTMB (<175 mut/exome). The TMB cutpoint was previously identified as the biologically optimal threshold across multiple tumor types in pembrolizumab studies using WES.[11,12]

Study Outcomes

Primary end points were OS (time from randomization to death from any cause) and progression-free survival (PFS; time from randomization to first documented disease progression per RECIST v.1.1 by

independent central review or death from any cause, whichever occurred first). Safety and overall response rate (ORR) were assessed as secondary end points. Evaluation of tTMB and its association with outcomes was an exploratory analysis.

Statistical Analysis

Statistical analysis methods for this trial have been previously reported.[2,9] Efficacy analyses were performed according to the treatment assigned (i.e., intent-to-treat); safety analyses were conducted among patients who received treatment analyzed according to treatment received (i.e., all patients as-treated). The primary end points of OS and PFS in the intent-to-treat population were estimated using the Kaplan-Meier method. HRs and 95% CIs were calculated using a stratified Cox proportional hazards model with Efron's tie handling method; randomization stratification factors were applied to the analyses. Consistent with previous analyses, pembrolizumab dose groups were pooled for this analysis. No alpha was assigned to these analyses.

The tTMB-evaluable population comprised all patients with PD-L1 TPS $\geq$1% who received either pembrolizumab or docetaxel (all patients as-treated population) and had evaluable samples for tTMB using WES. A statistical analysis plan for tTMB analysis was prespecified before merging the clinical and biomarker data sets. Relationships between tTMB and ORR were assessed using logistic regression analysis adjusted for ECOG performance status and a receiver-operating characteristic curve analysis. Relationships between tTMB and OS and PFS were evaluated using Cox proportional hazards models (adjusted for ECOG performance status). For the association of tTMB with outcomes, tTMB was assessed as a continuous $\log_{10}$-transformed variable. The Wald test was used to calculate one-sided p values for pembrolizumab because the a priori hypothesis was that higher tTMB was positively associated with improved outcomes with pembrolizumab. For chemotherapy, two-sided p values were calculated because there was no a priori hypothesis regarding the direction of the association between tTMB and outcomes with chemotherapy. Statistical significance was determined at the 0.05 level; there was no adjustment for multiplicity, and no alpha was assigned.

Results

Patients

A total of 1034 patients were randomized in KEYNOTE-010 between August 28, 2013, and February 27, 2015, of whom 691 were randomized to pembrolizumab (pembrolizumab 2 mg/kg, n = 345; pembrolizumab 10 mg/kg, n = 346) and 343 to docetaxel (Supplementary Fig. 1).[2] As previously reported, one patient in the pembrolizumab 2 mg/kg group was excluded from the efficacy analysis population because it was not possible to adequately assess tumor response; however, this patient was included in the safety analysis population. Baseline demographics and disease characteristics were similar between treatment groups in the intent-to-treat population (Table 1).

Median (range) time from randomization to the data cutoff date of April 8, 2020, was 67.4 (60.0–77.9) months for the intent-to-treat population (N = 1033). All patients had discontinued their initially assigned treatment as of the data cutoff date. Median (range) duration of treatment for first course was 3.5 months (1 d to 31.7 mo) for the two pembrolizumab treatment groups (pooled) and 2.0 months (1 d to 26.4 mo) for docetaxel. Among patients randomized to the docetaxel group, eight patients (2.3%) crossed over to pembrolizumab on-study, and an additional 68 patients (19.8%) crossed over to anti–PD-(L)1 immunotherapy off-study, for an effective crossover rate of 22.2%.

Long-Term Outcomes in the Intent-to-Treat Population

At the time of analysis, 893 of 1033 patients (86.4%) in the intent-to-treat population had died. The HR (95% CI) for OS was 0.55 (0.44–0.69) for patients with PD-L1 TPS $\geq$50% (Fig. 1*A*) and 0.70 (0.61–0.80) for patients with PD-L1 TPS $\geq$1% (Fig. 1*B*). Median OS (95% CI) was 16.9 (12.3–21.4) months versus 8.2 (6.4–9.8) months in the PD-L1 TPS $\geq$50% group and 11.8 (10.4–13.1) months versus 8.4 (7.6–9.5) months in the PD-L1 TPS $\geq$1% group. Kaplan-Meier estimates of the 5-year OS rate for pembrolizumab versus docetaxel were 25.0% versus 8.2% in the PD-L1 TPS $\geq$50% group and 15.6% versus 6.5% in the PD-L1 TPS $\geq$1% group. Among patients with PD-L1 TPS 1%–49%, the HR (95% CI) for OS was 0.79 (0.65–0.94). Figure 1*C* shows HRs for survival in key patient subgroups.

The HR (95% CI) for PFS (per RECIST v.1.1 by independent central review) was 0.57 (0.46–0.71) for patients with PD-L1 TPS $\geq$50% and 0.84 (0.73–0.96) for patients with PD-L1 TPS $\geq$1%. Median (95% CI) PFS was 5.3 (4.2–6.5) months versus 4.2 (3.8–5.1) months in the PD-L1 TPS $\geq$50% group and 4.0 (3.1–4.1) months versus 4.1 (3.8–4.5) months in the PD-L1 TPS $\geq$1% group. In the PD-L1 TPS $\geq$50% group, the PFS rate at 5 years was 18.2% with pembrolizumab; all in the docetaxel group had disease progression or were censored before 5 years. The PFS rates at 5 years were 9.4% versus 0.7% for the PD-L1 TPS $\geq$1% group, respectively (Fig. 2*A* and *B*).

The ORR (95% CI, per RECIST v.1.1 by independent central review) was 33.1% (27.7–38.8) with pembrolizumab versus 9.2% (5.1–15.0) with docetaxel for

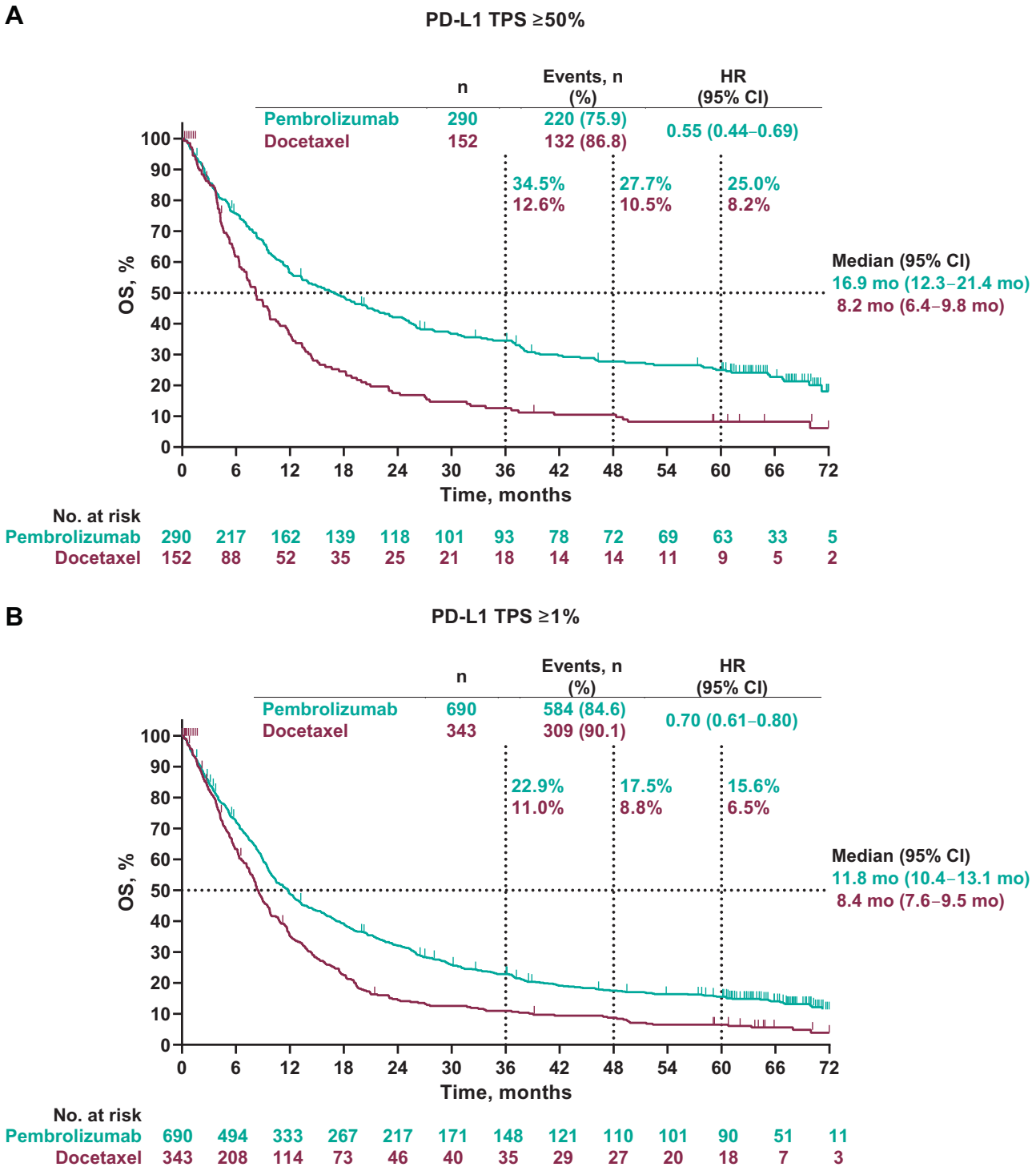

Figure 1. Kaplan-Meier analysis of OS in patients with (*A*) PD-L1 TPS ≥50% and (*B*) PD-L1 TPS ≥1% and treatment differences in OS across patient subgroups among patients with (*C*) PD-L1 TPS ≥1%. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

patients in the PD-L1 TPS ≥50% group and 21.2% (18.2–24.4) versus 9.6% (6.7–13.2) for patients in the PD-L1 TPS ≥1% group. Median (range) duration of response (DOR) was 68.4 (2.0+ to 71.7+) months with pembrolizumab versus 8.5 (2.6–16.8) months with docetaxel in the PD-L1 TPS ≥50% group and 68.4 (2.0+ to 71.7+) versus 7.5 (1.4+ to 16.8) months in the PD-L1 TPS ≥1% group ("+" indicates that there was no progressive disease by the time of last disease assessment). At data cutoff, 41 patients (43.0%) who received

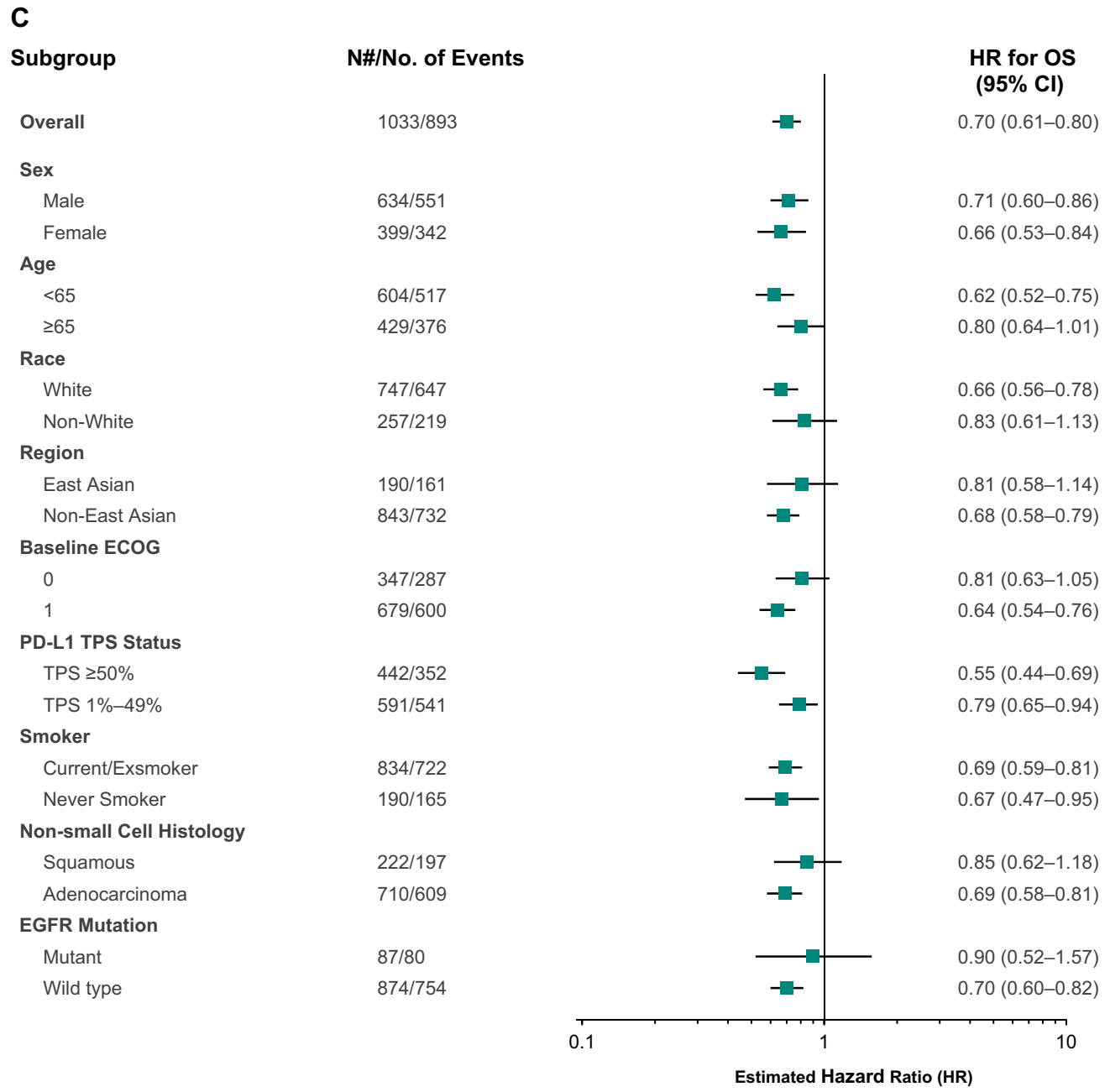

Figure 1. (*continued*).

pembrolizumab in the PD-L1 TPS ≥50% group and 51 (35.0%) in the PD-L1 TPS ≥1% group (of whom 10 had PD-L1 TPS 1%–49%) had an ongoing response; no patient who received docetaxel in either PD-L1 TPS group had an ongoing response.

Incidence of treatment-related AEs (any grade), grade 3 to 5 AEs, and treatment-related AEs leading to discontinuation or death was lower in patients treated with pembrolizumab than in patients treated with docetaxel (Table 2). The most frequently occurring treatment-related AEs in the pembrolizumab group were fatigue (15.8%), decreased appetite (12.8%), and rash (12.2%), whereas the most frequently occurring treatment-related AEs in the docetaxel group were alopecia (34.0%), fatigue (24.9%), and diarrhea (19.1%). Treatment-related AEs leading to death occurred in 0.7% of patients in the pembrolizumab group and 1.6% in the docetaxel group: there were no new treatment-related deaths since the previous analysis.[9] Serious treatment-related AEs were reported by similar proportions of patients in the two treatment groups (pembrolizumab, 11.3%; docetaxel, 14.2%).

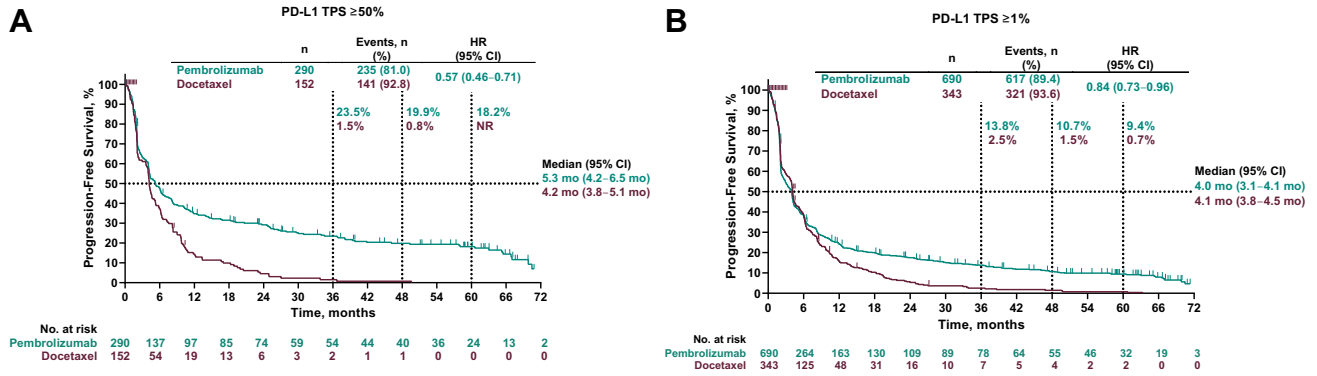

Figure 2. Kaplan-Meier analysis of progression-free survival per RECIST version 1.1 by independent central review in patients with (*A*) PD-L1 TPS ≥50% and (*B*) PD-L1 TPS ≥1%. CI, confidence interval; HR, hazard ratio; NR, not reached; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tumor proportion score.

Immune-mediated AEs and infusion reactions (irrespective of attribution to treatment by the investigator) occurred in 23.0% of patients in the pembrolizumab group and 10.0% of patients in the docetaxel group. No additional patients experienced immune-mediated AEs and infusion reactions since the previous analysis.[9] Grade 3 to 5 immune-mediated AEs and infusion reactions occurred in 6.3% of patients in the pembrolizumab group and 1.6% of patients in the docetaxel group. The most frequently occurring immune-mediated AEs in the pembrolizumab group were hypothyroidism (8.8%), pneumonitis (5.9%), and hyperthyroidism (4.8%).

Long-Term Outcomes in Patients Who Completed 35 Cycles/2 Years of Pembrolizumab

At data cutoff, 79 patients had completed 35 cycles/2 years of pembrolizumab. Median (range) time from randomization to data cutoff was 68.1 (60.5–74.5) months for these patients. Baseline characteristics were generally similar between these patients and patients allocated to pembrolizumab in the intent-to-treat population, although a higher percentage of patients were less than 65 years of age (69.6% versus 57.2%) and had PD-L1 TPS ≥50% (73.4% versus 42.0%) in the patients who completed 35 cycles/2 years of pembrolizumab, whereas fewer had received two or more prior lines of systemic therapy (19.0% versus 28.7%) or had mutant *EGFR* status (1.3% versus 8.8%); presence of brain metastases at baseline was similar (15.2% versus 15.1%; Table 1).

ORR (per independent central review per RECIST v.1.1) for patients who completed 35 cycles/2 years of pembrolizumab was 98.7%: 15 of 79 patients (19.0%) achieved complete response, 63 (79.7%) achieved partial response; and one (1.3%) further patient had stable disease. Treatment duration, time to response, and DOR for patients who completed 35 cycles/2 years of pembrolizumab are shown in Figure 3*A*. At data cutoff, 18 of 79 patients (22.8%) who completed 35 cycles/2 years of treatment had died. The OS rate 3 years after completion of pembrolizumab treatment (~5 years from randomization) was 83.0%. A total of 38 of 79 patients (48.1%) were alive without disease progression.

Treatment-related AEs occurred in 66 of 79 patients (83.5%), including 14 (17.7%) with grade 3 to 4 treatment-related AEs (Table 2). One patient received pembrolizumab for more than 2 years (but did not complete 35 cycles of pembrolizumab). Immune-mediated AEs occurred in 31 of 79 patients (39.2%), most often hypothyroidism (25.3%), hyperthyroidism (8.9%), and pneumonitis (8.9%). Five patients (6.3%) had grade 3/4 immune-mediated AEs (pneumonitis, n = 2; hypophysitis, n = 2; adrenal insufficiency, n = 1; pancreatitis, n = 1). There were no fatal immune-mediated AEs.

Patients Who Received Second-Course Pembrolizumab

At data cutoff, 21 patients had received second-course pembrolizumab. Demographic and clinical characteristics for these patients are summarized in Table 1. Of 21 patients, 11 (52.3%) experienced an objective response per RECIST by independent central review (complete response, n = 1; partial response, n = 10) after starting second-course pembrolizumab. A further six patients had stable disease, for an overall disease control rate of 81.0%. In addition, three patients had progressive disease per RECIST by independent central review and one patient was unevaluable. Eight patients experienced subsequent disease progression per irRC by investigator assessment, including three patients who had achieved a partial response and five who had stable disease. At data cutoff, six patients (28.6%) who received second-course pembrolizumab had died. Treatment duration, time to response, and DOR for patients who received second-course pembrolizumab are found in Figure 3*B*.

A total of 10 patients (47.6%) experienced treatment-related AEs after initiation of second-course

Table 2. Incidence of Treatment-Related AEs Among Treated Patients

Adverse Events	Pembrolizumab, n = 682		Docetaxel, n = 309		Completed 35 Cycles/ 2y of Pembrolizumab, n = 79	
Treatment-related AEs, n (%)						
Any	462 (67.7)		255 (82.5)		66 (83.5)	
Grades 3–5	110 (16.1)		113 (36.6)		14 (17.7)	
Led to treatment discontinuation	40 (5.9)		37 (12.0)		1 (1.3)	
Led to death	5 (0.7)		5 (1.6)		0	
	Any Grade	Grades 3–5	Any Grade	Grades 3–5	Any Grade	Grades 3–5
Treatment-related AEs occurring in ≥10% of patients,[a] n (%)						
Fatigue	108 (15.8)	10 (1.5)	77 (24.9)	11 (3.6)	15 (19.0)	1 (1.3)
Decreased appetite	87 (12.8)	5 (0.7)	52 (16.8)	3 (1.0)	9 (11.4)	1 (1.3)
Rash	83 (12.2)	2 (0.3)	14 (4.5)	0	21 (26.6)	0
Nausea	81 (11.9)	3 (0.4)	52 (16.8)	1 (0.3)	9 (11.4)	0
Pruritus	72 (10.6)	2 (0.3)	5 (1.6)	1 (0.3)	22 (27.8)	0
Diarrhea	58 (8.5)	2 (0.3)	59 (19.1)	7 (2.3)	15 (19.0)	0
Asthenia	48 (7.0)	4 (0.6)	38 (12.3)	6 (1.9)	9 (11.4)	0
Anemia	27 (4.0)	5 (0.7)	43 (13.9)	5 (1.6)	4 (5.1)	1 (1.3)
Stomatitis	22 (3.2)	1 (0.1)	44 (14.2)	3 (1.0)	4 (5.1)	0
Alopecia	7 (1.0)	0	105 (34.0)	2 (0.6)	3 (3.8)	0
Neutropenia	2 (0.3)	0	44 (14.2)	38 (12.3)	0	0
Hypothyroidism	53 (7.8)	0	1 (0.3)	0	18 (22.8)	0
Pyrexia	40 (5.9)	2 (0.3)	17 (5.5)	1 (0.3)	8 (10.1)	0
Arthralgia	38 (5.6)	2 (0.3)	18 (5.8)	0	8 (10.1)	0
Immune-mediated AEs and infusion reactions,[b] n (%)						
Hypothyroidism	60 (8.8)	0	1 (0.3)	0	20 (25.3)	0
Pneumonitis	40 (5.9)	18 (2.6)	6 (1.9)	2 (0.6)	7 (8.9)	2 (2.5)
Hyperthyroidism	33 (4.8)	1 (0.1)	3 (1.0)	0	7 (8.9)	0
Infusion reactions	15 (2.2)	3 (0.4)	20 (6.5)	2 (0.6)	0	0
Severe skin reactions	11 (1.6)	7 (1.0)	1 (0.3)	1 (0.3)	2 (2.5)	0
Adrenal insufficiency	6 (0.9)	1 (0.1)	0	0	2 (2.5)	1 (1.3)
Colitis	6 (0.9)	4 (0.6)	0	0	1 (1.3)	0
Thyroiditis	6 (0.9)	0	0	0	2 (2.5)	0
Pancreatitis	5 (0.7)	3 (0.4)	0	0	1 (1.3)	1 (1.3)
Hypophysitis	4 (0.6)	3 (0.4)	0	0	2 (2.5)	2 (2.5)
Myositis	4 (0.6)	0	1 (0.3)	0	0	0
Hepatitis	3 (0.4)	1 (0.1)	0	0	0	0
Type 1 diabetes mellitus	3 (0.4)	3 (0.4)	0	0	0	0
Nephritis	1 (0.1)	1 (0.1)	0	0	0	0

Note: AEs were monitored through 30 days after the end of treatment (90 d for serious AEs). The National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 were used to grade severity.

[a]Includes events that occurred in ≥10% of patients in either treatment group or among patients who completed 35 cycles of pembrolizumab.

[b]Events were based on a list of terms specified at the time of analysis and were included regardless of attribution to study treatment or immune relatedness by the investigator. Related terms were included.

AE, adverse events.

pembrolizumab. Two had grade 3 treatment-related AEs: one patient with pneumonitis and one patient with increased alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase. No grade 4 or 5 treatment-related AEs occurred during the second course. All 10 of these patients had treatment-related AEs during the first course.

Clinical Outcomes in the tTMB-Evaluable Population

Of the 1034 randomized patients, 254 (24.6%) had samples evaluable for analysis of tTMB by WES. One patient in the tTMB-evaluable population was excluded from the efficacy analyses because (as noted previously) it was not possible to adequately assess this patient's tumor response (Supplementary Fig. 2). Baseline characteristics were similar in the tTMB-evaluable population compared with the overall population (Supplementary Table 1). OS, PFS, and ORR outcomes for pembrolizumab versus docetaxel were similar in the tTMB-evaluable population and in the overall efficacy population (Supplementary Table 2).

When assessed as a continuous variable, higher tTMB was significantly associated with improved OS, PFS, and

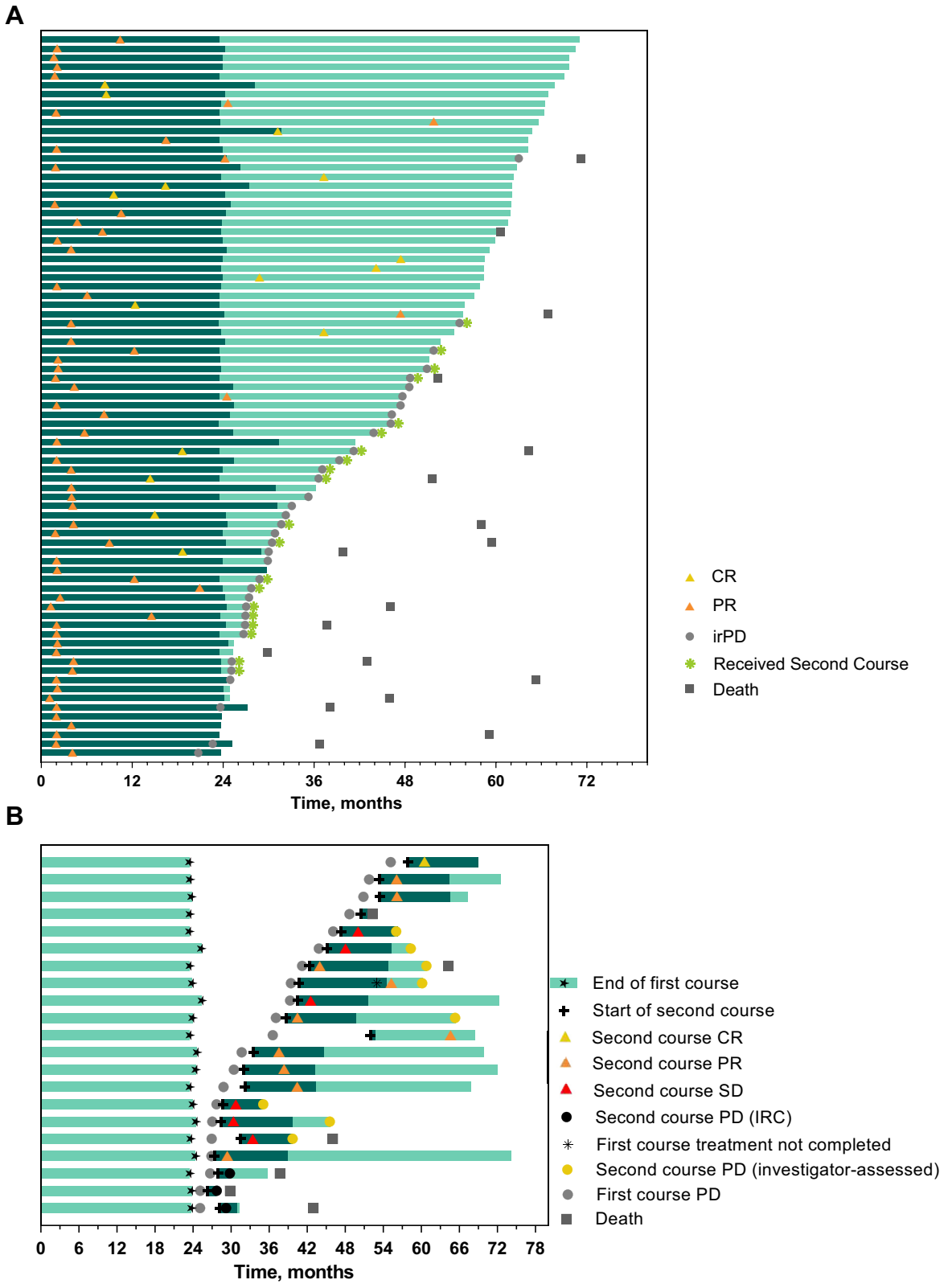

Figure 3. (*A*) Outcomes in patients who completed 35 cycles of pembrolizumab. Bar lengths indicate duration of treatment (dark green) and months of follow-up (light green). Follow-up was defined as date of the last known nonprogression scan or date of last investigator assessment the patient was alive. Response evaluation is per RECIST version 1.1 by independent central assessment. (*B*) Outcomes in patients who started second-course pembrolizumab. Bar lengths indicate duration of second-course treatment (dark green) and months of second-course follow-up (light green bar after dark green bar). Follow-up was defined as the last known nonprogression scan or date of last investigator assessment the patient was alive. Response

ORR for patients receiving pembrolizumab (Wald test, one-sided $p \leq 0.005$ for all) but not in patients who received docetaxel (Wald test, two-sided $p > 0.05$ for all) (Supplementary Table 3). There was no correlation between tTMB and PD-L1 TPS in either the pembrolizumab group (r = 0.16) or the docetaxel group (r = 0.18) (Supplementary Fig. 3).

The clinical utility of tTMB as a biomarker for pembrolizumab was assessed in 253 patients with evaluable tTMB and with available PFS and OS data. Among these patients, 132 (52.2%) had tTMB ≥175 mut/exome (the prespecified tTMB cutpoint; pembrolizumab, n = 81; docetaxel, n = 51) and 121 patients (47.8%) had tTMB <175 mut/exome (pembrolizumab, n = 83; docetaxel, n = 38). The HR (95% CI) for OS was 0.54 (0.37–0.79) among patients with tTMB ≥175 mut/exome and 0.87 (0.58–1.31) in patients with tTMB <175 mut/exome. Similarly, the HR (95% CI) for PFS was 0.61 (0.42–0.89) and 1.05 (0.70–1.56) in the tTMB ≥175 and tTMB <175 mut/exome groups, respectively (Fig. 4*A* and *B*). ORR was higher among patients with tTMB ≥175 mut/exome who received pembrolizumab versus docetaxel (24.7% versus 9.8%), whereas in patients with tTMB <175 mut/exome, the ORR favored patients who received docetaxel (16.9% versus 21.1%; Fig. 4*C*).

Discussion

In this 5-year long-term follow-up analysis of the KEYNOTE-010 study of pembrolizumab versus docetaxel in patients with previously treated, PD-L1–positive advanced NSCLC, pembrolizumab continued to improve OS than docetaxel in patients with PD-L1 TPS ≥50% and TPS ≥1%. Outcomes among patients in the pembrolizumab group represented a clinically meaningful improvement over docetaxel with 5-year OS rates of 25.0% versus 8.2% in patients with PD-L1 TPS ≥50% and 15.6% versus 6.5% in patients with PD-L1 TPS ≥1%, despite 22.2% of patients in the docetaxel group crossing over to either pembrolizumab on-study or other anti–PD-(L)1 immunotherapies. Median OS among patients in the pembrolizumab group was 16.9 versus 8.2 months for patients in the docetaxel group (HR = 0.55) among those with PD-L1 TPS ≥50% and 11.8 versus 8.4 months (HR = 0.70), respectively, among those with PD-L1 TPS greater than or equal to 1%. These data extend and confirm findings from previous analyses of KEYNOTE-010, in which pembrolizumab was found to improve OS versus docetaxel.[2,9] Consistent with OS, HRs for PFS favored the pembrolizumab group. Notably, our findings are consistent with 5-year OS outcomes from the single-arm phase 1b KEYNOTE-001 study of pembrolizumab (2 or 10 mg/kg) in patients with advanced NSCLC, in which the 5-year OS rate was 25.0% among previously treated patients with PD-L1 TPS ≥50% and 15.5% in previously treated patients with PD-L1 TPS ≥1%.[13] A pooled analysis of the phase 3 CheckMate 017 and CheckMate 057 studies revealed a 5-year OS rate of 13.4% with nivolumab versus 2.6% with docetaxel.[14] Finally, in an updated analysis of the OAK study, atezolizumab revealed a 4-year OS rate of 15.5%.[15] In all studies, 5-year OS was higher with anti–PD-(L)1 therapy than the historical 5-year relative survival rate of 6.9% for patients with distant metastases in the United States from 2010 to 2016.[16]

Pembrolizumab monotherapy revealed long-term responses in a subset of patients who completed 35 cycles or 2 years of treatment. Responses were durable among these patients, with some patients having a response duration exceeding 5 years. Most of these patients (77.2%) were alive at data cutoff. These results are consistent with outcomes in patients from KEYNOTE-001, who received 2 or more years of pembrolizumab treatment with an ORR of 91% among patients in the previously treated group and a 5-year OS rate of 75.8%.[13]

Notably, most patients who received second-course pembrolizumab had disease control (i.e., an objective response or stable disease) during treatment, illustrating the effectiveness of retreatment in initial responders at the time of progression after completing 2 years of pembrolizumab treatment. Findings from the KEYNOTE-024 study were consistent with these findings: in that study, 4 of 12 patients (33.3%) who received second-course pembrolizumab after disease progression, with an additional six patients having stable disease.[17] Potentially, a meta-analysis of outcomes among patients who have received second-course pembrolizumab treatment in clinical studies may be warranted to provide more definitive results. An exploratory analysis from the CheckMate 153 study evaluated outcomes among patients with previously treated NSCLC who ceased treatment with the anti–PD-1 monoclonal antibody nivolumab at 1 year (with an option of subsequent retreatment) compared with those who received continuous treatment after 1 year and found that median PFS was longer for patients in the continuous group (24.7 mo versus 9.4 mo).[18]

assessment is per RECIST version 1.1 by independent central review; PD is per irRC by investigator review, as this was the basis of treatment decisions. *One patient received a second course of pembrolizumab but did not meet eligibility criteria for having completed 35 cycles/2 years of first-course pembrolizumab. CR, complete response; irPD, progressive disease per immune-related response criteria; irRC, immune-related response criteria; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

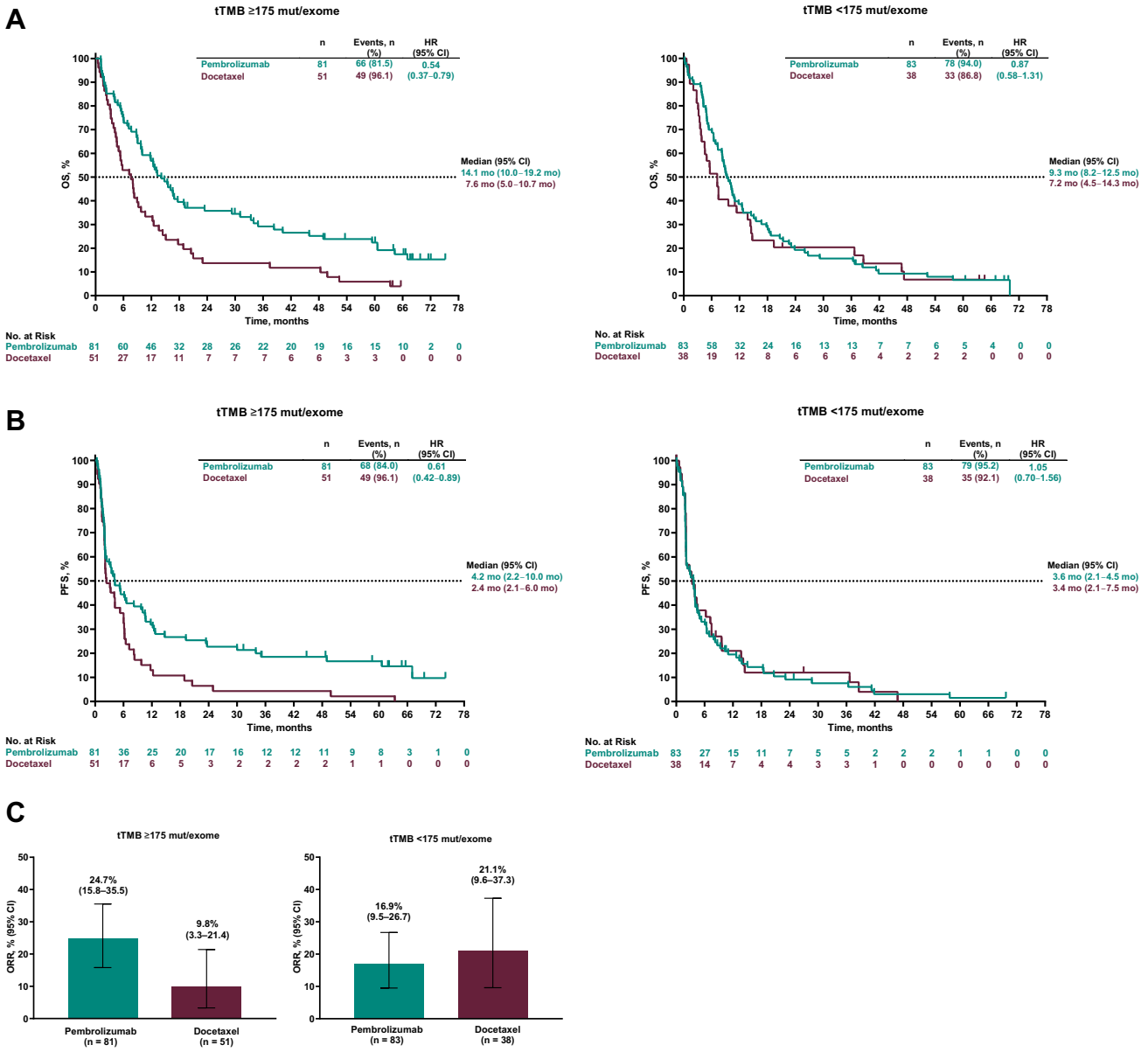

Figure 4. Outcomes in patients with tTMB ≥175 and ≥175 mut/exome. (*A*) OS, (*B*) PFS, and (*C*) ORR. CI, confidence interval; HR, hazard ratio; mut/exome, mutation per exome; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; tTMB, tissue tumor mutational burden.

Several studies have found that higher levels of tTMB are associated with response among patients receiving pembrolizumab.[19,20] However, there have been limited data supporting this hypothesis derived from controlled studies. In the current exploratory analysis, tTMB ≥175 mut/exome was associated with improved clinical outcomes (OS, PFS, and ORR) for pembrolizumab versus docetaxel. Our findings are consistent with those from an analysis of outcomes by tTMB in the KEYNOTE-042 study, which showed an association between tTMB ≥175 mut/exome and improved outcomes (OS, PFS, and ORR) for pembrolizumab in patients with previously untreated advanced NSCLC with a PD-L1 TPS ≥1%.[21] The finding of an association with OS contrasts with other studies evaluating tTMB as a biomarker for anti–PD-(L)1 therapies in patients with advanced NSCLC, which have identified associations only with PFS and ORR.[22-24] Because there was no strong association between tumor PD-L1 expression and tTMB, this finding is likely not due to increased tumor PD-L1 expression among patients with higher tTMB. These findings suggest that tTMB may provide additional information regarding the clinical benefit of pembrolizumab monotherapy in patients with PD-L1–positive advanced

NSCLC in the first-line and previously treated settings. The exploratory analysis of tTMB had several limitations. tTMB ascertainment was low; therefore, only a small subset of the intent-to-treat population was included. In addition, because KEYNOTE-010 only included patients with PD-L1 TPS $\geq$1%, the study cannot provide information on the potential predictive value of tTMB in patients whose tumors do not express PD-L1.

The present analysis confirms the efficacy of pembrolizumab as second-line or later treatment for advanced NSCLC. Notably, in the first-line setting, pembrolizumab has been reported to improve OS in patients with NSCLC as monotherapy (in patients with PD-L1–expressing tumors)[3,7] and when combined with platinum-based chemotherapy (irrespective of tumor PD-L1 expression),[4-6] suggesting first-line pembrolizumab options may provide greater benefit. In the real-world setting, approximately 50% of patients with advanced NSCLC do not receive second-line therapy because of rapid clinical deterioration.[25] Consequently, delaying pembrolizumab to second line may deprive patients of potential treatment benefit from pembrolizumab in the first-line setting. In the phase 3 KEYNOTE-024 study, the 5-year OS rate among patients with metastatic NSCLC with PD-L1 TPS $\geq$50% and without *EGFR* or *ALK* alterations was 31.9% for those in the pembrolizumab group versus 16.3% for those in the platinum-based chemotherapy group.[17] Findings from the current study, more than any other, have revealed the predictive value of the PD-L1 IHC 22C3 pharmDx assay.

In this updated analysis, no new safety signals were identified for pembrolizumab with long-term follow-up. AEs were manageable among patients who received second-course pembrolizumab after disease progression, with no grade 4 or 5 treatment-related AEs reported during the second course. The updated safety data are consistent with the long-term (5-y) safety profile observed in the phase 1 KEYNOTE-001 study.[13] Notably, the rate of any treatment-related AEs, grade 3 to 5 AEs, and treatment-related AEs leading to discontinuation or death was lower in patients who received pembrolizumab versus those who received docetaxel. These results support the long-term tolerability of pembrolizumab monotherapy.

In conclusion, pembrolizumab continued to provide long-term OS and PFS benefit than docetaxel in patients with previously treated, PD-L1–expressing advanced NSCLC. Treatment benefit was observed in patients who received 35 cycles/2 years of pembrolizumab and in those who received second-course pembrolizumab. Exploratory analyses suggested an association between tTMB $\geq$175 mut/exome and pembrolizumab treatment effect.

CRediT Authorship Contribution Statement

Bilal Piperdi, **Edward B. Garon, Byoung Chul Cho, Roy S. Herbst:** Conception, design or planning of the study.

Dong-Wan Kim, Edward B. Garon, Isabelle Monnet, Radj Gervais, Jose L. Perez-Gracia, Byoung Chul Cho, Ji-Youn Han, Roy S. Herbst, Ayman Samkari, Margarita Majem, Matthew A. Gubens, Paul Baas: Acquisition of the data.

Bilal Piperdi, Byoung Chul Cho, Erin H. Jensen, Ji-Youn Han, Roy S. Herbst, Wu-Chou Su, Julie Kobie, Ayman Samkari: Analysis of the data.

Bilal Piperdi, Dong-Wan Kim, Edward B. Garon, Jose L. Perez-Gracia, Byoung Chul Cho, Erin H. Jensen, Ji-Youn Han, Martin D. Forster, Michael Boyer, Roy S. Herbst, Julie Kobie, Ayman Samkari, Margarita Majem, Paul Baas, Silvia Novello: Interpretation of the results.

Bilal Piperdi, Byoung Chul Cho, Ji-Youn Han, Ayman Samkari: Drafting of the manuscript.

Roy S. Herbst, Edward B. Garon, Dong-Wan Kim, Byoung Chul Cho, Radj Gervais, Jose L. Perez-Gracia, Ji-Youn Han, Margarita Majem, Martin D. Forster, Isabelle Monnet, Silvia Novello, Matthew A. Gubens, Michael Boyer, Wu-Chou Su, Ayman Samkari, Erin H. Jensen, Julie Kobie, Bilal Piperdi, Paul Baas: Review of the manuscript for important intellectual content, Decision to submit the manuscript for publication, Access to study data and related analyses.

Dong-Wan Kim, Edward B. Garon, Perez-Gracia, Ji-Youn Han, Michael Boyer, Matthew A. Gubens, Silvia Novello: Provision of study materials/patients.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.05.001.

Data Sharing Statement

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

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