original reports

Long-Term Outcomes and Retreatment Among Patients With Previously Treated, Programmed Death-Ligand 1–Positive, Advanced Non–Small-Cell Lung Cancer in the KEYNOTE-010 Study

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abstract

PURPOSE In the KEYNOTE-010 study, pembrolizumab improved overall survival (OS) versus docetaxel in previously treated, programmed death-ligand 1 (PD-L1)–expressing advanced non–small-cell lung cancer (NSCLC) in patients with a tumor proportion score (TPS) ≥ 50% and ≥ 1%. We report KEYNOTE-010 long-term outcomes, including after 35 cycles/2 years or second-course pembrolizumab.

METHODS Of 1,033 patients randomly assigned (intention to treat), 690 received up to 35 cycles/2 years of pembrolizumab 2 mg/kg (n = 344) or 10 mg/kg (n = 346) every 3 weeks, and 343 received docetaxel 75 mg/m^2 every 3 weeks. Eligible patients with disease progression after 35 cycles/2 years of pembrolizumab could receive second-course treatment (up to 17 cycles). Pembrolizumab doses were pooled because no between-dose difference was observed at primary analysis.

RESULTS Pembrolizumab continued to improve OS over docetaxel in the PD-L1 TPS ≥ 50% and ≥ 1% groups (hazard ratio [HR], 0.53; 95% CI, 0.42 to 0.66; $P < .00001$; and HR, 0.69; 95% CI, 0.60 to 0.80; $P < .00001$, respectively) after a 42.6-month (range, 35.2-53.2 months) median follow-up. Estimated 36-month OS rates were 34.5% versus 12.7% and 22.9% versus 11.0%, respectively. Grade 3-5 treatment-related adverse events occurred in 16% versus 37% of patients, respectively. Seventy-nine of 690 patients completed 35 cycles/2 years of pembrolizumab; 12-month OS and progression-free survival rates after completing treatment were 98.7% (95% CI, 91.1% to 99.8%) and 72.5% (95% CI, 59.9% to 81.8%), respectively. Seventy-five patients (95%) had objective response (RECIST v1.1, blinded independent central review) and 48 (64%) had ongoing response. Grade 3-5 treatment-related adverse events occurred in 17.7% of patients. Fourteen patients received second-course pembrolizumab: 5 completed 17 cycles, 6 (43%) had partial response, and 5 (36%) had stable disease.

CONCLUSION Pembrolizumab provided long-term OS benefit over docetaxel, with manageable safety, durable responses among patients receiving 2 years of treatment, and disease control with second-course treatment, further supporting pembrolizumab for previously treated, PD-L1–expressing advanced NSCLC.

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ASSOCIATED CONTENT

Data Supplement
Protocol

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

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INTRODUCTION

Pembrolizumab is a monoclonal antibody that blocks the interaction between programmed death-1 (PD-1) and its ligands programmed death-ligand 1 (PD-L1) and -ligand 2, thus promoting T-cell–mediated antitumor activity via the PD-1 pathway.[1] Randomized controlled studies have shown improved overall survival (OS) with pembrolizumab monotherapy versus standard chemotherapy in patients with PD-L1–expressing advanced non–small-cell lung cancer (NSCLC) in both the first- and second-line or later settings[2-4] and with pembrolizumab plus platinum-based chemotherapy compared with chemotherapy alone in patients with metastatic NSCLC irrespective of PD-L1 expression in the first-line setting.[5-7]

In the phase II/III KEYNOTE-010 study, pembrolizumab monotherapy at doses of 2 mg/kg or 10 mg/kg every 3 weeks improved OS versus docetaxel in coprimary analyses of patients with previously treated advanced NSCLC with PD-L1 tumor proportion score (TPS) ≥ 50%

and TPS ≥ 1%.[2] There were no differences in OS between the 2 pembrolizumab doses. Thus, data for the 2-mg/kg and 10-mg/kg pembrolizumab dose groups were pooled in an updated analysis at a median follow-up of 31 months, which continued to show OS benefit with pembrolizumab over docetaxel (PD-L1 TPS ≥ 50%: hazard ratio [HR], 0.50; 95% CI, 0.39 to 0.64; and PD-L1 TPS ≥ 1%: HR, 0.66; 95% CI, 0.57 to 0.77).[8]

We present efficacy and safety results for the PD-L1 TPS ≥ 50% and TPS ≥ 1% groups in KEYNOTE-010 at a median follow-up of 42.6 months (range, 35.2-53.2 months), an additional year of follow-up from the prior analysis.[8] In addition, because the clinical outcomes of patients who stopped pembrolizumab after 2 years of treatment are unknown, we explored long-term outcomes with pembrolizumab in patients who completed 35 cycles or 2 years of treatment and those who received second-course pembrolizumab after disease progression.

METHODS

Patients

This multicenter, international trial enrolled patients from 202 academic medical centers in 24 countries (protocol number: MK-3475-010). Eligible patients were ≥ 18 years of age and had histologically/cytologically confirmed NSCLC with ≥ 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, by investigator review.[9] Patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status of 0/1 and PD-L1–expressing, stage IIIB/IV disease with investigator-determined disease progression after ≥ 2 cycles of platinum-based chemotherapy. Additional enrollment criteria have been previously described.[2]

All patients provided written informed consent before participation. The protocol was approved by an investigational review board/ethics committee at each study site, and all trial procedures were conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki.

Study Design and Endpoints

Patients were randomly assigned 1:1:1 to open-label pembrolizumab 2 mg/kg every 3 weeks, pembrolizumab 10 mg/kg every 3 weeks, or docetaxel 75 mg/m^2 every 3 weeks. Randomization was managed centrally using an interactive voice/Web response system and was stratified according to ECOG performance status (0/1), geographic region (east Asia/non–east Asia), and PD-L1 TPS (≥ 50%/1%-49%). Pembrolizumab treatment continued for 35 treatment cycles/2 years, and docetaxel treatment continued for the maximum duration allowed by local regulations, until disease progression, unacceptable toxicity, investigator decision, withdrawal of patient consent, intercurrent illness preventing continued treatment, noncompliance with study treatment/procedures, or the patient was lost to follow-up. Patients allocated to pembrolizumab could stop treatment if they had a confirmed complete response per immune-related response criteria (irRC) as determined by the investigator after receiving ≥ 6 months of pembrolizumab, with ≥ 2 cycles of pembrolizumab beyond the initial date of response. Patients who stopped pembrolizumab after a complete response or after completing 35 cycles/2 years of pembrolizumab and subsequently had disease progression per irRC as determined by the investigator could receive up to 17 cycles/1 year of second-course pembrolizumab treatment if they had received no other anticancer therapy since the last pembrolizumab dose.

The primary endpoints 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 v1.1 by blinded independent central review [BICR] or death from any cause, whichever occurred first). Safety was assessed as a secondary endpoint.

Assessments

Radiographic imaging was performed by computed tomography every 9 weeks or more frequently if clinically indicated, with treatment response evaluated according to RECIST v1.1 by BICR. Treatment decisions were based on irRC per the investigator. After the end of treatment (for reasons other than disease progression), disease status, including disease progression or start of a new anticancer therapy, was monitored until death, withdrawal of consent, or loss to follow-up. Disease status assessments occurred every 9 weeks through week 54 and then every 12 weeks thereafter, including during second-course treatment. Adverse events (AEs) were monitored through 30 days after the end of treatment (90 days for serious AEs) using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 to grade severity.

Eligibility on the basis of tumor PD-L1 expression was centrally assessed in formalin-fixed tissue samples obtained from a nonirradiated tumor lesion (44% of samples were archival, 56% were newly collected)[8] using a clinical trial version of the approved 22C3 antibody-based immunohistochemistry pharmDx assay (Agilent Technologies, Carpinteria, CA). Tumor samples with membranous staining on ≥ 1% of tumor cells were considered PD-L1 positive.[10]

Statistical Considerations

Statistical analysis methods for this trial have been previously reported.[2] Briefly, the stratified log-rank test was used to evaluate treatment differences between arms, with HRs and 95% CIs calculated using a stratified Cox proportional hazard model with Efron's tie handling method; randomization stratification factors were applied to the analyses. The primary endpoints were OS and PFS in the PD-L1 TPS ≥ 50% group and the TPS ≥ 1% group (overall population) and were estimated using the Kaplan-Meier method. Efficacy analyses were performed according to the treatment assigned (ie, intention to treat). Because no

difference between pembrolizumab doses was observed in the primary analysis,[2] pembrolizumab dose groups were pooled for this analysis. AEs were summarized by treatment received. Exploratory analyses evaluated OS and PFS among patients who completed 35 cycles/2 years of pembrolizumab and objective response among patients who received second-course pembrolizumab. The PFS analysis excluded patients who experienced disease progression or were censored for other reasons before completing treatment. No alpha was allocated for these updated analyses; *P* values were nominal.

RESULTS

Patients

Of 1,034 patients enrolled in KEYNOTE-010 between August 28, 2013, and February 27, 2015, 691 patients were randomly assigned to pembrolizumab (pembrolizumab 2 mg/kg, n = 345; pembrolizumab 10 mg/kg, n = 346) and 343 patients were assigned to docetaxel, as previously reported (Fig 1).[2] One patient in the pembrolizumab 2-mg/kg dose group was excluded from efficacy analyses because tumor response could not be adequately assessed. This patient continued treatment and was included in safety analyses. Baseline demographics/disease characteristics were similar between treatment groups in the intention-to-treat population (Table 1).

Among the 1,033 patients in the intention-to-treat population, median duration of follow-up from randomization to data cutoff (March 16, 2018) for this updated analysis was 42.6 months (range, 35.2-53.2 months), with a median treatment duration of 3.5 months (range, 1 day-31.7 months) in the pembrolizumab group and 2.0 months (1 day-26.4 months) in the docetaxel group.

Long-Term Results in the Intention-to-Treat Population

The risk of death was reduced with pembrolizumab versus docetaxel in both the PD-L1 TPS ≥ 50% group (HR, 0.53; 95% CI, 0.42 to 0.66; $P < .00001$; Fig 2A) and the TPS ≥ 1% group (HR, 0.69; 95% CI, 0.60 to 0.80; $P < .00001$; Fig 2B). Median OS was 16.9 months (95% CI, 12.3 to 21.4 months) versus 8.2 months (95% CI, 6.4 to 9.8 months) in the TPS ≥ 50% group and 11.8 months (95% CI, 10.4 to 13.1 months) versus 8.4 months (95% CI, 7.6 to 9.5 months) in the TPS ≥ 1% group. Kaplan-Meier estimates of OS at 36 months were higher with pembrolizumab versus docetaxel in both TPS groups, with OS rates of 34.5% versus 12.7% in the TPS ≥ 50% group and 22.9% versus 11.0% in the TPS ≥ 1% group. Outcomes in select subgroups are summarized in Figure 2C.

The risk of disease progression or death (per RECIST v1.1 by BICR rather than per investigator) was reduced with pembrolizumab versus docetaxel in the PD-L1 TPS ≥ 50% (HR, 0.57; 95% CI, 0.45 to 0.71; $P < .00001$; Fig 3A) and TPS ≥ 1% groups (HR, 0.83; 95% CI, 0.72 to 0.96; $P = .005$; Fig 3B). Kaplan-Meier estimates of PFS at 36 months were higher with pembrolizumab versus docetaxel in both TPS groups, with PFS rates of 21.9% versus 1.2% in the TPS ≥ 50% group and 12.7% versus 1.0% in the TPS ≥ 1% group.

Among 682 pembrolizumab-treated patients and 309 docetaxel-treated patients, treatment-related AEs, grade 3-5 treatment-related AEs, and treatment-related AEs that led to discontinuation occurred less frequently with pembrolizumab than with docetaxel (Table 2). Incidence of specific treatment-related AEs was consistent with those reported at the primary analysis; fatigue was the most

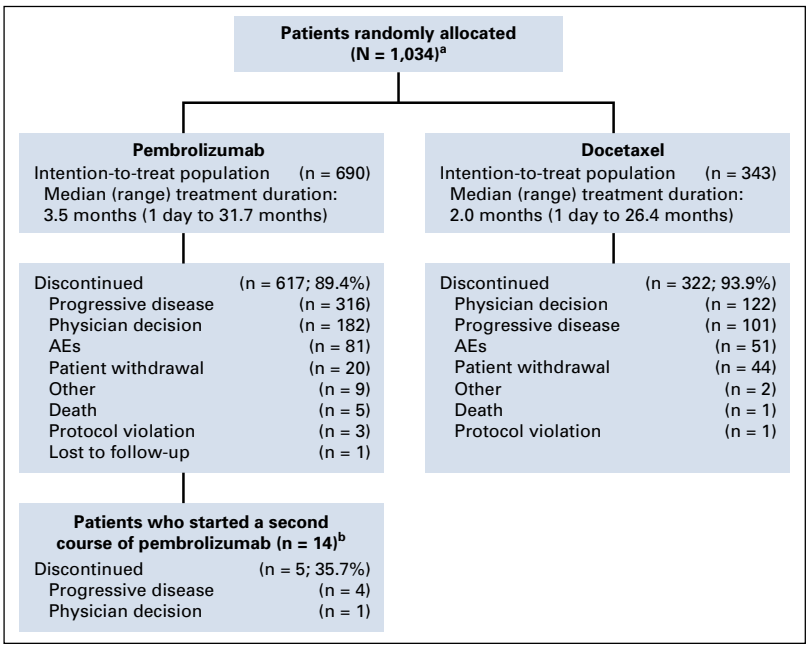

FIG 1. Patient disposition during the study. ([a]) One patient was excluded from efficacy analyses because it was not possible to adequately assess tumor response, but the patient was permitted to remain on treatment and was included in safety analyses. ([b]) One patient did not meet criteria for completing 35 cycles or 2 years of treatment as of the March 16, 2018, data cutoff date. AEs, adverse events.

TABLE 1. Baseline Demographic and Disease Characteristics

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

NOTE. Data are No. (%).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

[a]Excludes adjuvant and/or neoadjuvant therapies.

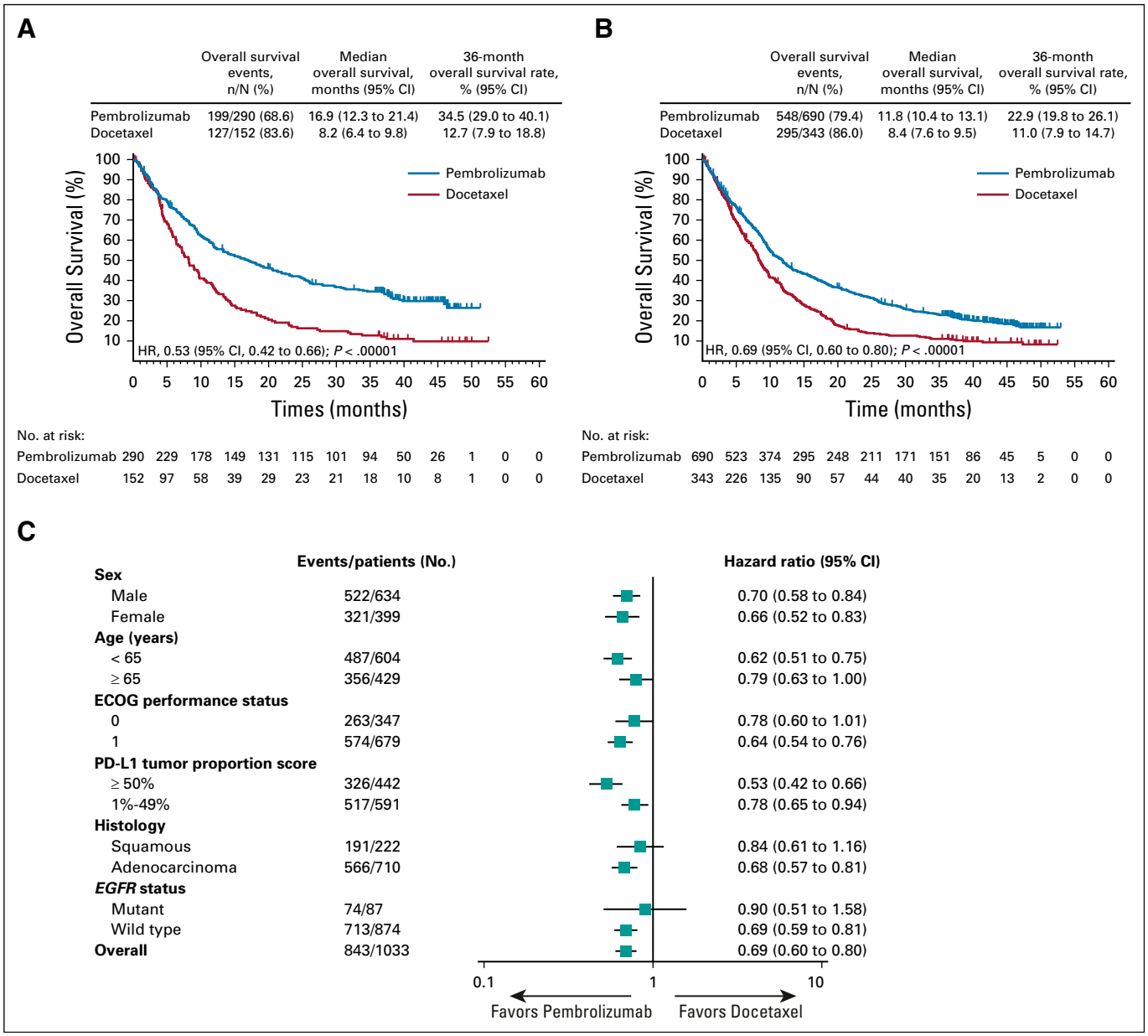

FIG 2. Kaplan-Meier analysis of overall survival by blinded independent central review in patients with (A) programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) ≥ 50% and (B) PD-L1 TPS ≥ 1%; and (C) treatment differences in overall survival across patient subgroups among patients with PD-L1 TPS ≥ 1%. ECOG, Eastern Cooperative Oncology Group.

common treatment-related AE among pembrolizumab-treated patients (15.8%), whereas the most common treatment-related AEs in the docetaxel group were alopecia (34.0%) and fatigue (24.9%). Five patients in each treatment group had treatment-related AEs that led to death: myocardial infarction (n = 1), pneumonia (n = 1), and pneumonitis (n = 3) in the pembrolizumab group and febrile neutropenia, acute cardiac failure, respiratory tract infection, dehydration, and interstitial lung disease (n = 1 each) in the docetaxel group. One additional patient in the pembrolizumab group had grade 5 pneumonia that was considered treatment related at the primary analysis, but later deemed not treatment related by the investigator.

Immune-mediated AEs and infusion reactions, irrespective of attribution to study treatment or immune relatedness as determined by the investigator, occurred in 23.0% of patients in the pembrolizumab group and 10.0% in the docetaxel group. The most frequently occurring immune-mediated AEs are described in Table 2. Grade 3 immune-mediated AEs and infusion reactions occurred in 5.1% of patients in the pembrolizumab group, and grade 4 events of pneumonitis and type 1 diabetes mellitus occurred in

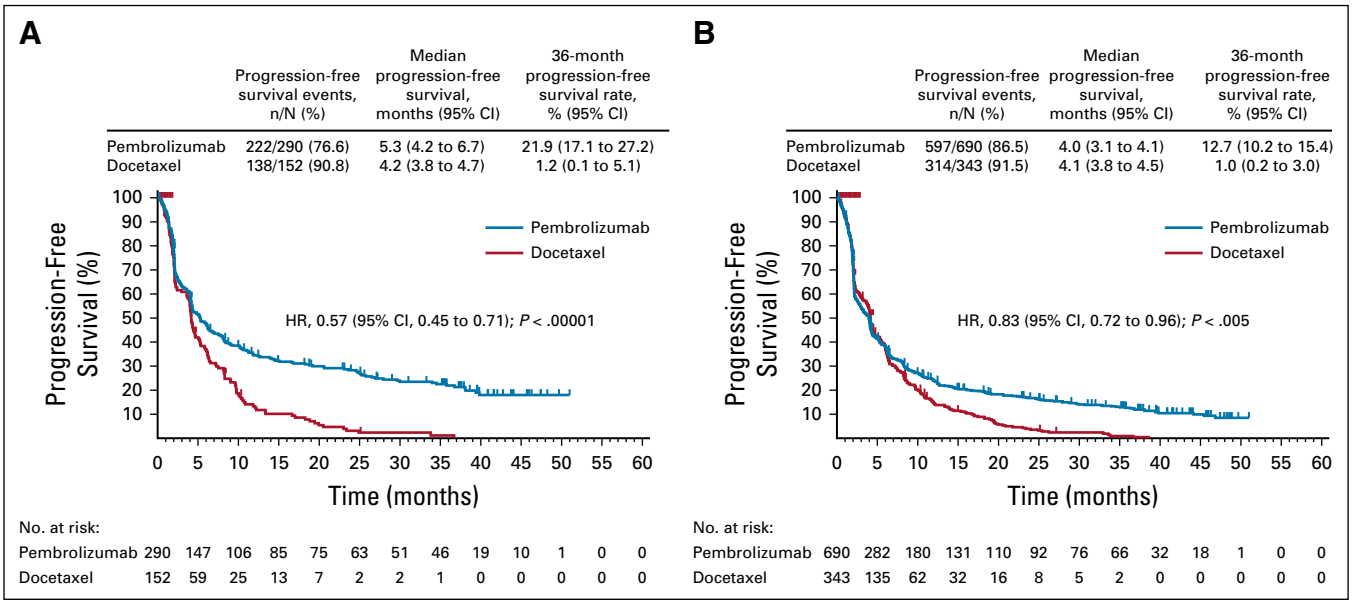

FIG 3. Kaplan-Meier analysis of progression-free survival per RECIST v1.1. by blinded independent central review in patients with (A) programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) ≥ 50% and (B) PD-L1 TPS ≥ 1%.

4 patients and 1 patient, respectively. Three pembrolizumab-treated patients had grade 5 pneumonitis, as noted in the paragraph immediately above.

Patients Who Completed 35 Cycles/2 Years of Pembrolizumab

As of the March 16, 2018, data cutoff date, a total of 79 patients had completed 35 cycles/2 years of pembrolizumab, with a median follow-up of 43.4 (range, 35.7-49.8) months (Data Supplement). Baseline disease characteristics were generally similar between these patients and the intention-to-treat population, except that there were lower percentages of patients aged ≥ 65 years (30.4% *v* 42.8%, respectively) and patients who received ≥ 2 prior treatment lines (19.0% *v* 28.7%), and higher percentages of patients with current/former smoking history (91.1% *v* 81.9%) and squamous tumor histology (26.6% *v* 22.6%; Table 1). Percentages of patients with brain metastasis were similar (15.2% *v* 15.1%). Of the 79 patients who completed 2 years of treatment, 73.4% had PD-L1 TPS ≥ 50% and 26.6% had TPS 1%-49%.

Objective response rate (RECIST v1.1, independent central review) among patients who completed 35 cycles was 94.9%, with ongoing response in 48 patients (64.0%); 72/79 patients (91.0%) remained alive at the data cutoff date (Fig 4). OS rates at 12 and 24 months after completing 35 cycles were 98.7% (95% CI, 91.1% to 99.8%) and 86.3% (95% CI, 72.7% to 93.4%), respectively; median OS was not reached. Eight of the 79 patients experienced disease progression (n = 3) or were censored because of starting new anticancer therapy (n = 3), discontinuing study treatment (n = 1), or nonevaluable response at follow-up (n = 1) before completing 35 cycles. Among the remaining 71 patients, 23 had PFS events postcompletion (22 patients experienced disease progression per irRC as determined by the investigator; 1 patient died; Data Supplement). PFS rates at 12 and 24 months postcompletion were 72.5% (95% CI, 59.9% to 81.8%) and 57.7% (95% CI, 41.2% to 71.0%), respectively; median PFS was not reached (95% CI, 14.3 months to not reached). Baseline characteristics for the 22 patients (27.8%) with confirmed disease progression postcompletion are summarized in the Data Supplement.

Among all 25 patients who completed treatment and had confirmed progression (including the 3 patients who experienced disease progression before completing treatment; Data Supplement), 12 received second-course pembrolizumab (all had confirmed progression after completing treatment), 9 of whom were alive at the data cutoff date (Fig 4). The remaining patients either received no additional treatment (n = 6; all remained alive) or received chemotherapy (n = 5; 2 remained alive) or tyrosine kinase inhibitors (n = 2; both remained alive; 1 had *EGFR* mutation).

Treatment-related AEs occurred in 66/79 patients (83.5%) who completed 35 cycles/2 years of pembrolizumab; the most common events were pruritus (27.8%), rash (26.6%), and hypothyroidism (22.8%). Grade 3-5 treatment-related AEs occurred in 17.7% of patients. One of the 79 patients had a treatment-related AE that the investigator considered to be the primary reason for treatment discontinuation. There were no treatment-related AEs that led to death.

Thirty-one patients (39.2%) had ≥ 1 immune-mediated AE, regardless of treatment or immune relatedness as

TABLE 2. Incidence of Adverse Events Among Treated Patients

Adverse Event	Pembrolizumab (n = 682)		Docetaxel (n = 309)		Completed 2 Years of Pembrolizumab (n = 79)	
Treatment-related adverse events						
Any	462 (67.7)		255 (82.5)		66 (83.5)	
Grade 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	
Treatment-related adverse events occurring in ≥ 10% of patients	Any Grade	Grade 3-5	Any Grade	Grade 3-5	Any Grade	Grade 3-5
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	70 (10.3)	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 adverse events and infusion reactions[a]						
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. Data are No. (%).

[a]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.

determined by the investigator: hypothyroidism (n = 20); hyperthyroidism (n = 7); pneumonitis (n = 7); adrenal insufficiency, hypophysitis, severe skin reaction, and thyroiditis (n = 2 each); and colitis and pancreatitis (n = 1 each).

Patients Who Received Second-Course Pembrolizumab

Fourteen patients started a second course of pembrolizumab (Data Supplement; Fig 5). These 14 patients included 1 patient among the 79 patients described previously who had unconfirmed disease progression during the first course

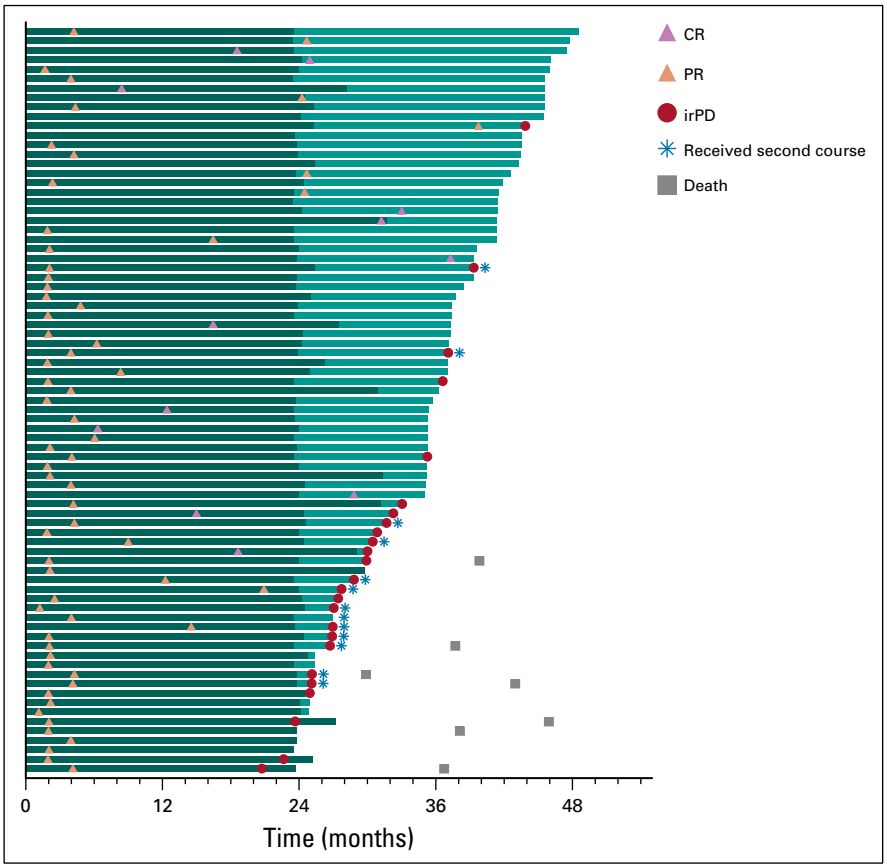

FIG 4. Treatment duration and time to response among patients who completed 35 cycles/2 years of pembrolizumab. Bar lengths indicate duration of treatment (dark green) and months of follow-up (light green). Follow-up was defined as date of progression or date of last investigator assessment when the patient was alive. Responses are per RECIST v1.1 by blinded independent central review. CR, complete response; irPD, disease progression per immune-related response criteria; PR, partial response.

(Fig 4) and 1 additional patient who did not meet the criteria for completing 35 cycles/2 years of treatment as of the data cutoff and was not included among the 79 patients described earlier.

Six patients (42.9%) had a partial response, and 5 patients (35.7%) had stable disease as best overall response in second-course treatment, per RECIST v1.1 by BICR (Fig 5). As of the data cutoff, 5 patients (35.7%) had completed treatment (17 cycles of pembrolizumab; Fig 1) and 11 patients (78.6%) remained alive.

DISCUSSION

At a median follow-up of 42.6 months, pembrolizumab continued to prolong OS versus docetaxel in patients with previously treated, PD-L1–positive, advanced NSCLC, with OS HRs of 0.53 in patients with PD-L1 TPS ≥ 50% and 0.69 in those with TPS ≥ 1%. This finding confirms and extends results from the KEYNOTE-010 primary analysis in which HRs for OS were 0.54 with pembrolizumab 2 mg/kg and 0.50 with pembrolizumab 10 mg/kg in the PD-L1 TPS ≥ 50% group and 0.71 and 0.61, respectively, in the TPS ≥ 1% group.[2] Additionally, pembrolizumab improved PFS versus docetaxel with HRs of 0.57 and 0.83 in patients with PD-L1 TPS ≥ 50% and ≥ 1%, respectively. Long-term safety with pembrolizumab was manageable, with no new safety signals identified.

Efficacy outcomes in this long-term analysis, with a significant proportion of the study population surviving multiple years, confirm the role of pembrolizumab as a standard second-line treatment option in patients with PD-L1–expressing advanced NSCLC. Importantly, Kaplan-Meier estimates of OS suggest that after 36 months, a plateau in the risk of death was reached among pembrolizumab-treated patients in the overall KEYNOTE-010 population. In addition, the OS rate at 36 months (22.9%) remained high relative to the previously reported 12-month OS rates with pembrolizumab 2 mg/kg (43.2%) and 10 mg/kg (52.3%).[2] Among patients with PD-L1 TPS ≥ 50%, the OS rate at 36 months was 34.5%. A recent report described 5-year OS outcomes among patients with advanced NSCLC who received pembrolizumab in the phase I KEYNOTE-001 study.[11] Five-year OS was 25.0% among previously treated patients with PD-L1 TPS ≥ 50% and 12.6% among those with PD-L1 TPS of 1%-49%. Notably, the 3-year OS in the KEYNOTE-001 study (20.9% among all previously treated patients) was broadly consistent with the OS rate at the same timepoint in this study.

Long-term OS rates among patients with previously treated advanced NSCLC, irrespective of PD-L1 expression, have also been reported for nivolumab (4-year OS rate of 14% in a pooled analysis from CheckMate 017, 057, 063, and 003)[12] and atezolizumab (2-year OS rate of 30.9% in an updated analysis from the OAK study).[13]

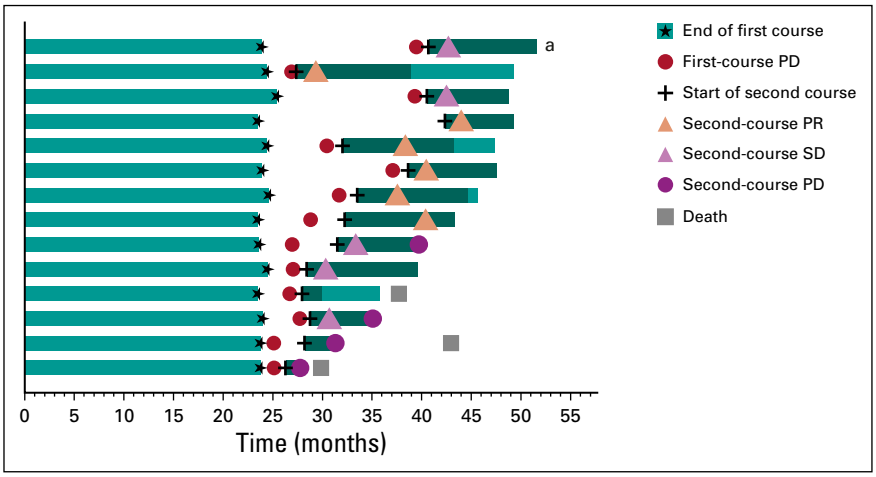

FIG 5. Treatment duration and time to response among patients who completed a second course of pembrolizumab treatment. Bar lengths indicate duration of second-course treatment (dark green) and months of second-course follow-up (light green bar after dark green bar). Follow-up was defined as the date of progression or last investigator assessment when the patient was alive. Partial response (PR) is per RECIST v1.1 by independent central review; disease progression (PD) is per immune-related response criteria (irRC) by investigator review, because this was the basis of treatment decisions. ([a])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; one additional patient had unconfirmed disease progression in the first course. SD, stable disease.

Although results from this analysis demonstrate long-term OS benefit with pembrolizumab over docetaxel in the second-line setting, pembrolizumab may provide greater benefit when used as first-line treatment, when possible and appropriate. Notably, pembrolizumab monotherapy has demonstrated an OS benefit over platinum-based chemotherapy in patients with previously untreated metastatic NSCLC without sensitizing *EGFR* or *ALK* alterations with PD-L1 TPS ≥ 50%[3] and with PD-L1 TPS ≥ 1%.[4] In addition, pembrolizumab plus platinum-based chemotherapy improved OS compared with placebo plus platinum-based chemotherapy, irrespective of PD-L1 expression, in patients with previously untreated metastatic nonsquamous NSCLC without sensitizing *EGFR* or *ALK* alterations[6] and in patients with previously untreated metastatic squamous NSCLC.[7] It is also important to note that only a minority of patients with NSCLC ever receive second-line therapy[14,15]; as such, delaying treatment to the second line would deny them the benefit associated with first-line pembrolizumab.

Pembrolizumab also showed remarkable long-term outcomes among the subset of patients (79 of 690 in the pembrolizumab group) who completed 35 cycles/2 years of pembrolizumab and those who received second-course pembrolizumab. Responses were durable among patients who completed 35 cycles/2 years of pembrolizumab: 64% of patients had ongoing response at a median follow-up of 43.4 months from the start of therapy. In addition, a majority of the patients who had disease progression per irRC by investigator review after stopping pembrolizumab were able to receive second-course pembrolizumab. Of those who received second-course treatment, 79% had a partial response or stable disease and remained alive at the data cutoff date for this analysis. These are the first data to demonstrate that a 2-year treatment duration with pembrolizumab may be an appropriate approach. The majority of patients who completed 2 years of treatment remain in remission, and those who had recurrence could be rechallenged with pembrolizumab at the time of progression and achieve disease control.

Although differences in several baseline characteristics were observed between the intention-to-treat population and those who completed 35 cycles/2 years of pembrolizumab (age, number of prior lines of therapy, smoking history, and squamous histology), any conclusions regarding associations between these baseline characteristics and pembrolizumab efficacy would be speculative considering the relatively small number of patients who completed 35 cycles/2 years of pembrolizumab. Notably, patients with *EGFR/ALK* alteration (sensitizing/nonsensitizing) were under-represented among both the intention-to-treat population and those who completed 35 cycles/2 years of pembrolizumab. Although retrospective data have suggested PFS may be short among patients with sensitizing *EGFR/ALK* alterations who receive immunotherapy,[16] subgroup analyses from KEYNOTE-010 have previously demonstrated OS benefit with pembrolizumab in patients with *EGFR* mutation (HR *v* docetaxel, 0.88; 95% CI, 0.45 to 1.70).[2]

Of note, pembrolizumab was given at doses of 2 mg/kg and 10 mg/kg in KEYNOTE-010. These doses were pooled for

this analysis because no evidence of an OS difference between doses was observed in the primary analysis. Pembrolizumab has been approved in the United States at a 200-mg fixed dose,[17] which was shown in a pharmacokinetic analysis to provide similar pembrolizumab exposure to that associated with optimal clinical response and tolerability in NSCLC clinical trials that used weight-based dosing.[18]

In conclusion, these results demonstrate the long-term durable benefit of pembrolizumab in previously treated, PD-L1–expressing NSCLC. Importantly, these data show that a 2-year treatment duration with pembrolizumab is reasonable and suggest that patients who experience disease progression after stopping treatment can be successfully retreated and achieve disease control. Additional molecular studies are needed to better understand the characteristics of responding patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Long-Term Outcomes and Retreatment Among Patients With Previously Treated, Programmed Death-Ligand 1–Positive, Advanced Non–Small-Cell Lung Cancer in the KEYNOTE-010 Study

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