Brief Report

24-Month Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab As First-Line Therapy for Advanced Nonsquamous Non–Small-Cell Lung Cancer

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Abstract

Introduction: Cohort G of KEYNOTE-021 (NCT02039674) evaluated the efficacy and safety of pembrolizumab plus pemetrexed-carboplatin (PC) versus PC alone as first-line therapy for advanced nonsquamous NSCLC. At the primary analysis (median follow-up, 10.6 months), pembrolizumab significantly improved objective response rate (ORR) and progression-free survival (PFS); hazard ratio (HR) for overall survival (OS) was 0.90 (95% CI, 0.42–1.91). Herein, we present an updated analysis.

Methods: 123 patients with previously untreated stage IIIB/IV nonsquamous NSCLC without *EGFR/ALK* aberrations were randomized 1:1 to 4 cycles of PC with/without pembrolizumab 200 mg Q3W. Pembrolizumab treatment continued for 2 years; maintenance pemetrexed was permitted in both groups. Eligible patients in the PC alone group with radiologic progression could cross over to pembrolizumab monotherapy. *P* values are nominal (one-sided $P<0.025$).

Results: As of December 1, 2017, median follow-up was 23.9 mo. ORR was 56.7% with pembrolizumab plus PC versus 30.2% with PC alone (estimated difference, 26.4%; 95% CI, 8.9%–42.4%; $P=0.0016$). PFS was significantly improved with pembrolizumab plus PC versus PC alone (HR, 0.53; 95% CI, 0.33–0.86; $P=0.0049$). 41 patients in the PC alone group received subsequent anti-PD-1/anti-PD-L1 therapy. The HR for OS was 0.56 (95% CI, 0.32–0.95; $P=0.0151$). 41% of patients in the pembrolizumab plus PC group and 27% in the PC alone group had grade 3–5 treatment-related adverse events.

Conclusions: Significant improvements in PFS and ORR with pembrolizumab plus PC versus PC alone observed in the primary analysis were maintained and the HR for OS with 24-month median follow-up was 0.56, favoring pembrolizumab plus PC.

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69

Introduction

Platinum-doublet chemotherapy has been the standard of care for first-line treatment of patients with advanced non–small-cell lung cancer (NSCLC) without targetable genetic aberrations.[1] Monotherapy with pembrolizumab, an anti–programmed death (PD)-1 monoclonal antibody, has demonstrated a benefit in both progression-free survival (PFS) and overall survival (OS) compared with platinum-based chemotherapy as first-line therapy for patients with advanced NSCLC with a programmed death ligand 1 (PD-L1) tumor proportion score (TPS) ≥50%.[2] An OS benefit was also demonstrated with pembrolizumab compared with docetaxel in previously treated patients with advanced NSCLC with a PD-L1 TPS ≥1%.[3] Because chemotherapy mediates immunologic effects,[4] combining chemotherapy with anti–PD-1 immunotherapy may have a synergistic antitumor effect.

We previously published results from the primary analysis of cohort G of the multicohort phase 1/2 KEYNOTE-021 study (ClinicalTrials.gov, NCT02039674), an open-label, randomized phase 2 trial that evaluated pembrolizumab plus pemetrexed-carboplatin (PC) versus PC alone in patients with previously untreated advanced nonsquamous NSCLC.[5] With a minimum 6-month follow-up (median 10.6 months), patients in the pembrolizumab plus PC group had significant improvements in both the objective response rate (ORR, 55% versus 29%; *P*=0.0016) and PFS (hazard ratio [HR], 0.53; 95% CI, 0.31–0.91; *P*=0.010), with a manageable safety profile. The HR for OS was 0.90 (95% CI, 0.42–1.91; nominal *P*=0.39), although only 27 of 123 patients (22%) had died at the time of the initial analysis. Based on these results, pembrolizumab plus PC has received accelerated approval from the US Food and Drug Administration (FDA) for first-line treatment of metastatic nonsquamous NSCLC.[6] Herein, we report updated efficacy and safety with a median follow up of approximately 24 months.

Methods

Full eligibility criteria and other aspects of the study design and protocol (MK-3475-021-03) have been described previously.[5] In brief, to be eligible for cohort G of KEYNOTE-021, patients were required to have previously untreated stage IIIB/IV nonsquamous NSCLC without activating *EGFR* mutations or *ALK* translocations, Eastern Cooperative Oncology Group performance status 0 or 1, no untreated brain metastases, and no interstitial lung disease or pneumonitis requiring systemic steroids. All patients were required to provide a tumor sample for assessment of tumor PD-L1 expression. Patients were stratified by PD-L1 TPS (<1% or ≥1%) and randomized to receive PC (pemetrexed 500 mg/m^2 plus carboplatin area under the concentration time curve [AUC] 5 mg/mL/min every 3 weeks [Q3W] for 4 cycles), alone or with pembrolizumab 200 mg Q3W for 2 years. Pemetrexed 500 mg/m^2 Q3W was permitted as maintenance therapy and continued in the absence of disease progression or unacceptable toxicity. Patients in the PC alone group could cross over to receive pembrolizumab monotherapy at the time of disease progression if they met eligibility criteria.

The primary endpoint was ORR and PFS was the key secondary endpoint; both were evaluated by blinded independent central review. OS was an additional secondary endpoint. Planned enrollment (in the primary analysis) was 108 patients. The primary analysis (one-sided alpha=0.025) was controlled by a fixed-sequence, closed-testing procedure stepping down from ORR to PFS. Because no alpha was assigned for this analysis, all reported *P* values are descriptive (one-sided $P<0.025$).

Results

Overall, 123 patients were randomized (pembrolizumab plus PC, n=60; PC alone, n=63). Baseline demographic and clinical characteristics have been previously reported.[5] One patient in each treatment group did not initiate treatment. At the current data cutoff (December 1, 2017), median follow up across both treatment groups was 23.9 months (range, 0.8–35.1 months). Median duration of randomized treatment was 10.1 months (range, 0–29.0 months) in patients treated with pembrolizumab plus PC and 4.9 months (range, 0–31.0 months) for patients treated with PC alone. Of the 59 patients treated with pembrolizumab plus PC, 5 (8.5%) were continuing treatment as of the data cut-off, and 11 (18.6%) had completed treatment; 43 (72.9%) discontinued treatment (n=26 for progression). Of the 62 patients treated with PC, 6 patients (9.7%) were continuing treatment, and 2 (3.2%) had completed treatment; 54 (87.1%) had discontinued treatment (38 due to disease progression). Among the 56 patients in the PC alone group who had discontinued or completed treatment, 26 patients (46.4%) crossed over to pembrolizumab on study and 15 additional patients (26.8%) received anti–PD-1/PD-L1 therapy outside of crossover. Patients in the pembrolizumab plus PC group received a median of 14 (range, 1 to 41) cycles of pembrolizumab. Fifty-two patients (88.1%) in the pembrolizumab plus PC group and 44 (71.0%) in the PC alone group received 4 cycles of carboplatin. All patients in both treatment groups received ≥1 cycle of pemetrexed; 50 patients (84.8%) in the pembrolizumab plus PC group and 42 (67.7%) in the PC alone group received more than the initial 4 planned cycles of pemetrexed induction (ie, received maintenance pemetrexed). The median number of cycles of pemetrexed was 14 in the pembrolizumab plus PC group and 42 in the PC alone group.

Compared with the prespecified primary analysis,[5] 2 additional confirmed responses were identified in the pembrolizumab plus PC group (n=1) or PC alone group (n=1). The ORR was 56.7% with pembrolizumab plus PC and 30.2% with PC alone, with a between-group difference in ORR of 26.4% (95% CI, 8.9%–42.4%; nominal P=0.0016). Among the responses observed, 1 patient in each group experienced a complete response that had evolved from a partial response at the previous analysis. Median response duration had not been reached (NR) in patients treated with pembrolizumab plus PC (range, 1.4 [ongoing] to 29.3 months [ongoing]) or PC alone (range, 2.8 [ongoing] to 30.1 months [ongoing]). At the time of data cutoff, 47% of responders in the pembrolizumab plus PC group and 32% in the PC alone group had ongoing responses.

As of this updated analysis, disease progression or death had occurred in 28 of 60 patients (47%) in the pembrolizumab plus PC group and 43 of 63 patients (68%) in the PC alone group. The HR for PFS was 0.53 (95% CI, 0.33–0.86; nominal *P*=0.0049), with a median PFS of 24.0 months in patients in the pembrolizumab plus PC group and 9.3 months for patients in the PC alone group (**Figure 1A**).

At the time of analysis, 22 of 60 patients (37%) in the pembrolizumab plus PC group and 35 of 63 patients (56%) in the PC alone group had died. Of the 35 deceased patients in the PC alone group, 26 (74%) had received second-line immunotherapy. This represents an additional 30 deaths since the initial report (9 in the pembrolizumab plus PC group; 21 in the PC alone group).[5] The HR for OS was 0.56 (95% CI, 0.32–0.95; nominal *P*=0.0151). Median OS was NR in the pembrolizumab plus PC group (95% CI, 24.5 to NR months) and 21.1 months (95% CI, 14.9 to NR months) in the PC alone group (**Figure 1B**).

There were no new safety trends observed since the initial report. As of the current analysis, 55 of 59 patients (93.2%) in the pembrolizumab plus PC group and 57 of 62 patients (91.9%) in the PC alone group experienced treatment-related adverse events (AEs; **Table**). Ten patients (16.9%) in the pembrolizumab plus PC group and 8 (12.9%) in the PC alone group experienced treatment-related AEs that led to discontinuation of any component of study medication. Grade 3–5 treatment-related AEs occurred in 24 patients (40.7%) and 17 patients (27.4%), respectively. Treatment-related fatal AEs occurred in 1 patient in the pembrolizumab plus PC group (1.7%; sepsis) and 2 patients in the PC group (3.2%; pancytopenia and sepsis), with no additional deaths occurring since the initial analysis. AEs with a presumed immunological mechanism of action (regardless of attribution to study treatment or immune relatedness by the investigator) occurred in 17 patients (28.8%) in the pembrolizumab plus PC group and 7 patients (11.3%) in the PC alone group.

Discussion

In this updated analysis, the HR for OS for pembrolizumab plus PC versus PC alone after a median 23.9-month follow-up was 0.56 (95% CI, 0.32–0.95; nominal *P*=0.0151), compared with an HR of 0.90 in the primary analysis (median 10.6-month follow-up).[5] The HR for OS favoring the pembrolizumab plus PC group occurred despite a high effective crossover rate to anti–PD-1/PD-L1 therapy in the PC alone group and despite the OS in the PC alone group exceeding that for historical controls.[7] Statistically significant and clinically meaningful improvements in ORR and PFS observed in prior analyses of KEYNOTE-021G were maintained in this updated analysis. At the time of the current data cutoff, median PFS in the pembrolizumab plus PC group was 24.0 months. As with OS, median PFS in the PC alone arm (9.3 months) was also longer than previously reported with pemetrexed-platinum in patients with NSCLC.[2,7] The relatively

long OS and PFS in the PC alone arm may have been due, at least in part, to the eligibility criteria excluding patients with poor prognosis (eg, untreated brain metastases).

The findings from this phase 2 study have subsequently been confirmed by results from the phase 3 KEYNOTE-189 study, where pembrolizumab plus pemetrexed-platinum reduced the risk of death by more than half compared with placebo plus pemetrexed-platinum (OS HR, 0.49 [95% CI, 0.38–0.64]; *P*<0.001) in previously untreated metastatic nonsquamous NSCLC without sensitizing *EGFR* mutations or *ALK* translocations.[8] Notably, the OS benefit observed with the combination of pembrolizumab plus pemetrexed and platinum in KEYNOTE-189 occurred regardless of tumor PD-L1 expression, with similar HRs across all PD-L1 TPS subgroups (TPS ≥50%, 0.42 [95% CI, 0.26–0.68]; TPS 1–49%, 0.55 [95% CI, 0.34–0.90]; TPS <1%, 0.59 [95% CI, 0.38-0.92]). Likewise, KEYNOTE-189 confirmed superior PFS with pembrolizumab plus pemetrexed-platinum over placebo plus pemetrexed-platinum with a similar HR for PFS (0.52 [95% CI, 0.43–0.64]; *P*<0.001) to that shown in this long-term analysis from KEYNOTE-021 cohort G.[8]

In addition to the noteworthy efficacy findings with long-term follow up in KEYNOTE-021 cohort G, the combination of pembrolizumab plus PC continued to show a manageable safety profile. In comparison with pembrolizumab monotherapy in KEYNOTE-024, a greater percentage of patients treated with pembrolizumab plus PC in this long-term analysis of KEYNOTE-021 cohort G experienced treatment-related AEs leading to discontinuation (7% vs 17%, respectively) and grade 3-5 treatment-related AEs (27% vs 41%, respectively).[2] However, additional toxicity with a combination treatment regimen containing platinum chemotherapy is not unexpected. Importantly, in the larger, double-blind, placebo-controlled, phase 3 study,

KEYNOTE-189, there was no evidence that AEs commonly associated with pemetrexed-platinum were exacerbated with the addition of pembrolizumab; the exception may be renal toxicity, which was overall manageable.[8] Moreover, the increased toxicity with pembrolizumab plus PC compared with pembrolizumab alone may be offset by improved efficacy outcomes. Although cross-trial comparisons should be made with caution, it is notable that the OS HR of 0.42 for patients with PD-L1 TPS ≥50% in KEYNOTE-189[8] compares favorably with the OS HR of 0.58 (95% CI, 0.41–0.83) for the nonsquamous subgroup of KEYNOTE-024.[9] Notably, outcomes for patients with TPS ≥50% and any histology treated with pembrolizumab versus platinum-based chemotherapy in the phase 3 KEYNOTE-042 study were similar (OS HR, 0.69 [95% CI, 0.56–0.85]).[10] Pembrolizumab plus PC, which has been granted accelerated FDA approval, represents an effective and tolerable treatment option for use as initial therapy for eligible patients with advanced nonsquamous NSCLC.

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283 **Table. Incidence of Adverse Events**

	Pembrolizumab plus PC N=59		PC Alone N=62	
Treatment-related AEs, n (%)				
Any grade	55 (93)		57 (92)	
Grades 3–5	24 (41)		17 (27)	
Leading to discontinuation[a]	10 (17)		8 (13)	
Leading to death	1 (2)		2 (3)	
Treatment-related AEs occurring in ≥15% of patients, n (%)	Any Grade	Grades 3/4	Any Grade	Grades 3/4
Fatigue	40 (68)	2 (3)	27 (44)	0 (0)
Nausea	35 (59)	1 (2)	30 (48)	0 (0)
Anemia	20 (34)	7 (12)	33 (53)	8 (13)
Vomiting	18 (31)	1 (2)	11 (18)	0 (0)
Rash	17 (29)	1 (2)	9 (15)	0 (0)
Diarrhea	14 (24)	0 (0)	9 (15)	1 (2)
Decreased appetite	13 (22)	0 (0)	12 (19)	0 (0)
Aspartate aminotransferase increased	11 (19)	1 (2)	8 (13)	1 (2)
Constipation	11 (19)	0 (0)	6 (10)	0 (0)
Dysgeusia	11 (19)	0 (0)	7 (11)	0 (0)
Alanine aminotransferase increased	10 (17)	1 (2)	8 (13)	1 (2)
Blood creatinine increased	10 (17)	0 (0)	4 (7)	0 (0)
Neutrophil count decreased	10 (17)	4 (7)	8 (13)	2 (3)
Lacrimation increased	9 (15)	0 (0)	8 (13)	0 (0)
Pruritus	9 (15)		3 (5)	
Immune-mediated AEs,[b] n (%)	Any Grade	Grades 3/4	Any Grade	Grades 3/4
Hypothyroidism	9 (15)	0 (0)	2 (3)	0 (0)
Hyperthyroidism	6 (10)	0 (0)	1 (2)	0 (0)
Pneumonitis	4 (7)	1 (2)	0 (0)	0 (0)
Infusion reactions	1 (2)	1 (2)	3 (5)	0 (0)
Severe skin toxicity	1 (2)	1 (2)	1 (2)	1 (2)
Colitis	1 (2)	0 (0)	0 (0)	0 (0)

284 AE, adverse event; PC, pemetrexed-carboplatin.

285 [a]Any component of study medication.

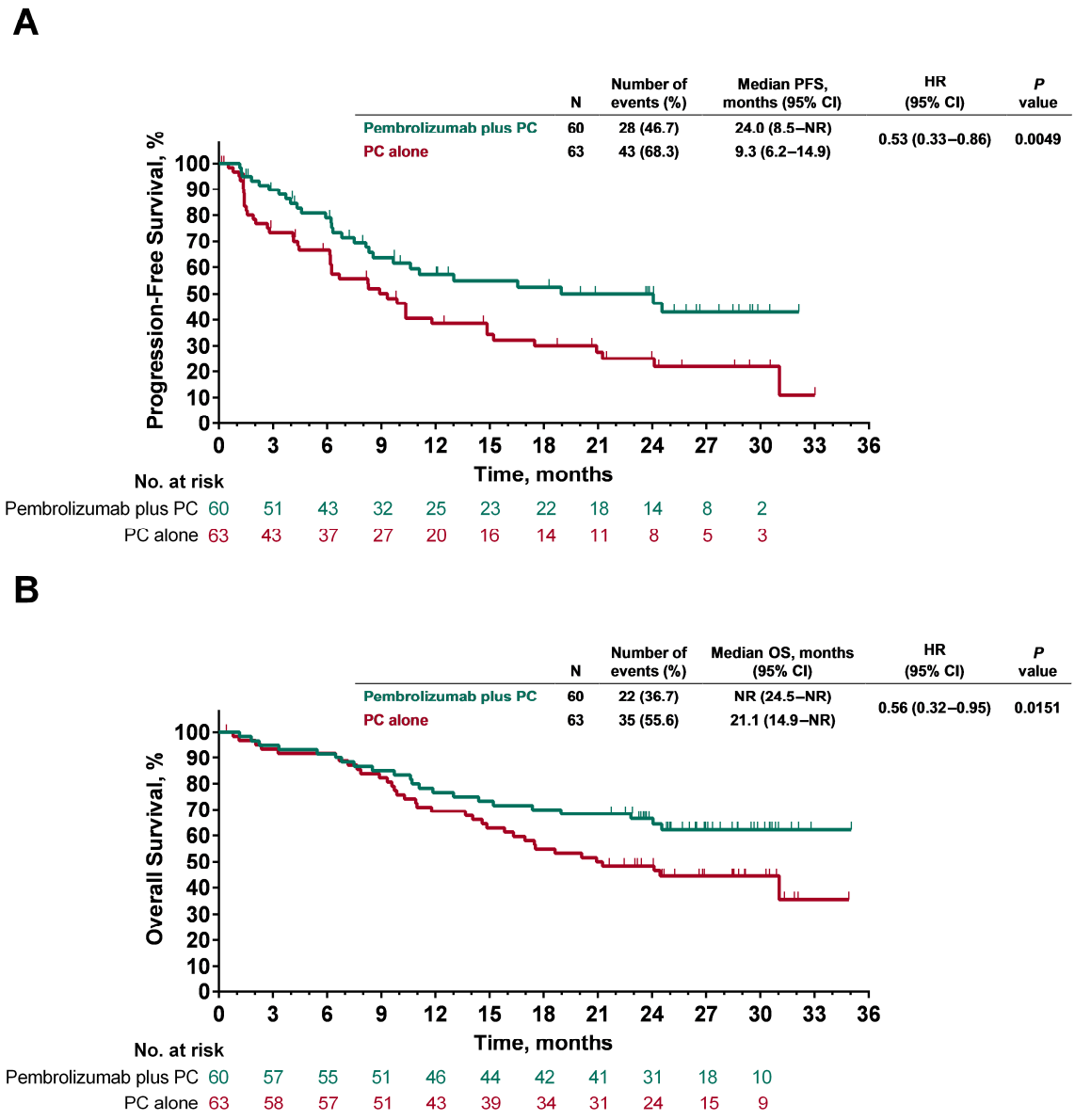
286 [b]Adverse events with a possible immune etiology regardless of attribution to study treatment or
287 immune-relatedness by the investigator.

288 **Figure Legend**

289 **Figure 1.** Kaplan-Meier analysis of A) progression-free survival (RECIST v1.1 by blinded,
290 independent central review) and B) overall survival. [a]P value is descriptive (one-
291 sided $P<0.025$). RECIST=Response Evaluation Criteria in Solid Tumors.

292

293 **Figure 1.**



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24-Month Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab As First-Line Therapy for Advanced Nonsquamous Non–Small-Cell Lung Cancer

DISCLOSURES

Hossein Borghaei reports other from Merck, during the conduct of the study; grants and personal fees from Merck, grants and personal fees from BMS, grants and personal fees from Lilly, grants and personal fees from Celgene, personal fees from Astra Zeneca, personal fees from Genmab, personal fees from Genentech, personal fees from Novartis, personal fees from Boehringer-Ingelheim, outside the submitted work.

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Sanatan Saraf reports other from Merck & Co., during the conduct of the study.

Steven Keller is an employee of Merck.

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