

1 *Brief Report*2 **24-Month Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and**
3 **Carboplatin With or Without Pembrolizumab As First-Line Therapy for Advanced**
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Pembrolizumab plus PC as first-line therapy for advanced nonsquamous NSCLC

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44 **Abstract**

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

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

56 **Results:** As of December 1, 2017, median follow-up was 23.9 mo. ORR was 56.7% with
57 pembrolizumab plus PC versus 30.2% with PC alone (estimated difference, 26.4%; 95% CI,
58 8.9%–42.4%; $P = 0.0016$). PFS was significantly improved with pembrolizumab plus PC versus
59 PC alone (HR, 0.53; 95% CI, 0.33–0.86; $P = 0.0049$). 41 patients in the PC alone group received
60 subsequent anti-PD-1/anti-PD-L1 therapy. The HR for OS was 0.56 (95% CI, 0.32–0.95;
61 $P = 0.0151$). 41% of patients in the pembrolizumab plus PC group and 27% in the PC alone group
62 had grade 3–5 treatment-related adverse events.

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

Pembrolizumab plus PC as first-line therapy for advanced nonsquamous NSCLC

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70 Introduction

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

81 We previously published results from the primary analysis of cohort G of the multicohort phase
82 1/2 KEYNOTE-021 study (ClinicalTrials.gov, NCT02039674), an open-label, randomized phase
83 2 trial that evaluated pembrolizumab plus pemetrexed-carboplatin (PC) versus PC alone in
84 patients with previously untreated advanced nonsquamous NSCLC.⁵ With a minimum 6-month
85 follow-up (median 10.6 months), patients in the pembrolizumab plus PC group had significant
86 improvements in both the objective response rate (ORR, 55% versus 29%; $P=0.0016$) and PFS
87 (hazard ratio [HR], 0.53; 95% CI, 0.31–0.91; $P=0.010$), with a manageable safety profile. The
88 HR for OS was 0.90 (95% CI, 0.42–1.91; nominal $P=0.39$), although only 27 of 123 patients
89 (22%) had died at the time of the initial analysis. Based on these results, pembrolizumab plus PC
90 has received accelerated approval from the US Food and Drug Administration (FDA) for first-
91 line treatment of metastatic nonsquamous NSCLC.⁶ Herein, we report updated efficacy and
92 safety with a median follow up of approximately 24 months.

93 **Methods**

94 Full eligibility criteria and other aspects of the study design and protocol (MK-3475-021-03)
95 have been described previously.⁵ In brief, to be eligible for cohort G of KEYNOTE-021, patients
96 were required to have previously untreated stage IIIB/IV nonsquamous NSCLC without
97 activating *EGFR* mutations or *ALK* translocations, Eastern Cooperative Oncology Group
98 performance status 0 or 1, no untreated brain metastases, and no interstitial lung disease or
99 pneumonitis requiring systemic steroids. All patients were required to provide a tumor sample
100 for assessment of tumor PD-L1 expression. Patients were stratified by PD-L1 TPS (<1% or ≥1%)
101 and randomized to receive PC (pemetrexed 500 mg/m² plus carboplatin area under the
102 concentration time curve [AUC] 5 mg/mL/min every 3 weeks [Q3W] for 4 cycles), alone or with
103 pembrolizumab 200 mg Q3W for 2 years. Pemetrexed 500 mg/m² Q3W was permitted as
104 maintenance therapy and continued in the absence of disease progression or unacceptable
105 toxicity. Patients in the PC alone group could cross over to receive pembrolizumab monotherapy
106 at the time of disease progression if they met eligibility criteria.

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

113 Results

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

135 Compared with the prespecified primary analysis,⁵ 2 additional confirmed responses were
136 identified in the pembrolizumab plus PC group (n=1) or PC alone group (n=1). The ORR was
137 56.7% with pembrolizumab plus PC and 30.2% with PC alone, with a between-group difference
138 in ORR of 26.4% (95% CI, 8.9%–42.4%; nominal $P=0.0016$). Among the responses observed, 1
139 patient in each group experienced a complete response that had evolved from a partial response
140 at the previous analysis. Median response duration had not been reached (NR) in patients treated
141 with pembrolizumab plus PC (range, 1.4 [ongoing] to 29.3 months [ongoing]) or PC alone
142 (range, 2.8 [ongoing] to 30.1 months [ongoing]). At the time of data cutoff, 47% of responders in
143 the pembrolizumab plus PC group and 32% in the PC alone group had ongoing responses.

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

149 At the time of analysis, 22 of 60 patients (37%) in the pembrolizumab plus PC group and 35 of
150 63 patients (56%) in the PC alone group had died. Of the 35 deceased patients in the PC alone
151 group, 26 (74%) had received second-line immunotherapy. This represents an additional 30
152 deaths since the initial report (9 in the pembrolizumab plus PC group; 21 in the PC alone
153 group).⁵ The HR for OS was 0.56 (95% CI, 0.32–0.95; nominal $P=0.0151$). Median OS was NR
154 in the pembrolizumab plus PC group (95% CI, 24.5 to NR months) and 21.1 months (95% CI,
155 14.9 to NR months) in the PC alone group (**Figure 1B**).

156 There were no new safety trends observed since the initial report. As of the current analysis, 55
157 of 59 patients (93.2%) in the pembrolizumab plus PC group and 57 of 62 patients (91.9%) in the
158 PC alone group experienced treatment-related adverse events (AEs; **Table**). Ten patients
159 (16.9%) in the pembrolizumab plus PC group and 8 (12.9%) in the PC alone group experienced
160 treatment-related AEs that led to discontinuation of any component of study medication. Grade
161 3–5 treatment-related AEs occurred in 24 patients (40.7%) and 17 patients (27.4%), respectively.
162 Treatment-related fatal AEs occurred in 1 patient in the pembrolizumab plus PC group (1.7%;
163 sepsis) and 2 patients in the PC group (3.2%; pancytopenia and sepsis), with no additional deaths
164 occurring since the initial analysis. AEs with a presumed immunological mechanism of action
165 (regardless of attribution to study treatment or immune relatedness by the investigator) occurred
166 in 17 patients (28.8%) in the pembrolizumab plus PC group and 7 patients (11.3%) in the PC
167 alone group.

168 **Discussion**

169 In this updated analysis, the HR for OS for pembrolizumab plus PC versus PC alone after a
170 median 23.9-month follow-up was 0.56 (95% CI, 0.32–0.95; nominal $P=0.0151$), compared with
171 an HR of 0.90 in the primary analysis (median 10.6-month follow-up).⁵ The HR for OS favoring
172 the pembrolizumab plus PC group occurred despite a high effective crossover rate to anti-PD-
173 1/PD-L1 therapy in the PC alone group and despite the OS in the PC alone group exceeding that
174 for historical controls.⁷ Statistically significant and clinically meaningful improvements in ORR
175 and PFS observed in prior analyses of KEYNOTE-021G were maintained in this updated
176 analysis. At the time of the current data cutoff, median PFS in the pembrolizumab plus PC group
177 was 24.0 months. As with OS, median PFS in the PC alone arm (9.3 months) was also longer
178 than previously reported with pemetrexed-platinum in patients with NSCLC.^{2,7} The relatively

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

181 The findings from this phase 2 study have subsequently been confirmed by results from the
182 phase 3 KEYNOTE-189 study, where pembrolizumab plus pemetrexed-platinum reduced the
183 risk of death by more than half compared with placebo plus pemetrexed-platinum (OS HR, 0.49
184 [95% CI, 0.38–0.64]; $P < 0.001$) in previously untreated metastatic nonsquamous NSCLC without
185 sensitizing *EGFR* mutations or *ALK* translocations.⁸ Notably, the OS benefit observed with the
186 combination of pembrolizumab plus pemetrexed and platinum in KEYNOTE-189 occurred
187 regardless of tumor PD-L1 expression, with similar HRs across all PD-L1 TPS subgroups (TPS
188 $\geq 50\%$, 0.42 [95% CI, 0.26–0.68]; TPS 1–49%, 0.55 [95% CI, 0.34–0.90]; TPS $< 1\%$, 0.59 [95%
189 CI, 0.38–0.92]). Likewise, KEYNOTE-189 confirmed superior PFS with pembrolizumab plus
190 pemetrexed-platinum over placebo plus pemetrexed-platinum with a similar HR for PFS (0.52
191 [95% CI, 0.43–0.64]; $P < 0.001$) to that shown in this long-term analysis from KEYNOTE-021
192 cohort G.⁸

193 In addition to the noteworthy efficacy findings with long-term follow up in KEYNOTE-021
194 cohort G, the combination of pembrolizumab plus PC continued to show a manageable safety
195 profile. In comparison with pembrolizumab monotherapy in KEYNOTE-024, a greater
196 percentage of patients treated with pembrolizumab plus PC in this long-term analysis of
197 KEYNOTE-021 cohort G experienced treatment-related AEs leading to discontinuation (7% vs
198 17%, respectively) and grade 3-5 treatment-related AEs (27% vs 41%, respectively).² However,
199 additional toxicity with a combination treatment regimen containing platinum chemotherapy is
200 not unexpected. Importantly, in the larger, double-blind, placebo-controlled, phase 3 study,

201 KEYNOTE-189, there was no evidence that AEs commonly associated with pemetrexed-
202 platinum were exacerbated with the addition of pembrolizumab; the exception may be renal
203 toxicity, which was overall manageable.⁸ Moreover, the increased toxicity with pembrolizumab
204 plus PC compared with pembrolizumab alone may be offset by improved efficacy outcomes.
205 Although cross-trial comparisons should be made with caution, it is notable that the OS HR of
206 0.42 for patients with PD-L1 TPS $\geq 50\%$ in KEYNOTE-189⁸ compares favorably with the OS
207 HR of 0.58 (95% CI, 0.41–0.83) for the nonsquamous subgroup of KEYNOTE-024.⁹ Notably,
208 outcomes for patients with TPS $\geq 50\%$ and any histology treated with pembrolizumab versus
209 platinum-based chemotherapy in the phase 3 KEYNOTE-042 study were similar (OS HR, 0.69
210 [95% CI, 0.56–0.85]).¹⁰ Pembrolizumab plus PC, which has been granted accelerated FDA
211 approval, represents an effective and tolerable treatment option for use as initial therapy for
212 eligible patients with advanced nonsquamous NSCLC.

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- 282

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 ^aAny component of study medication.

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286 ^bAdverse events with a possible immune etiology regardless of attribution to study treatment or
287 immune-relatedness by the investigator.

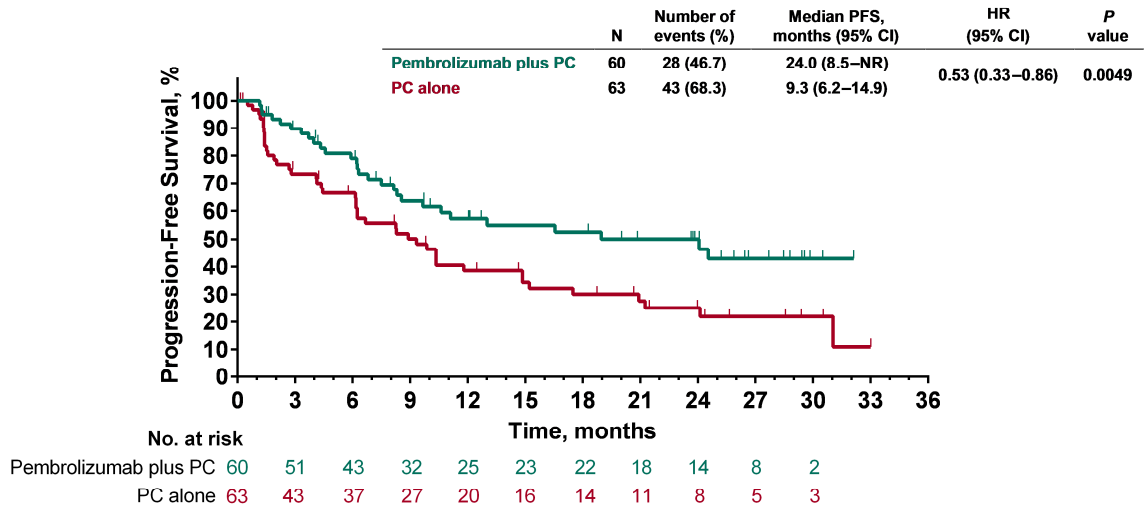
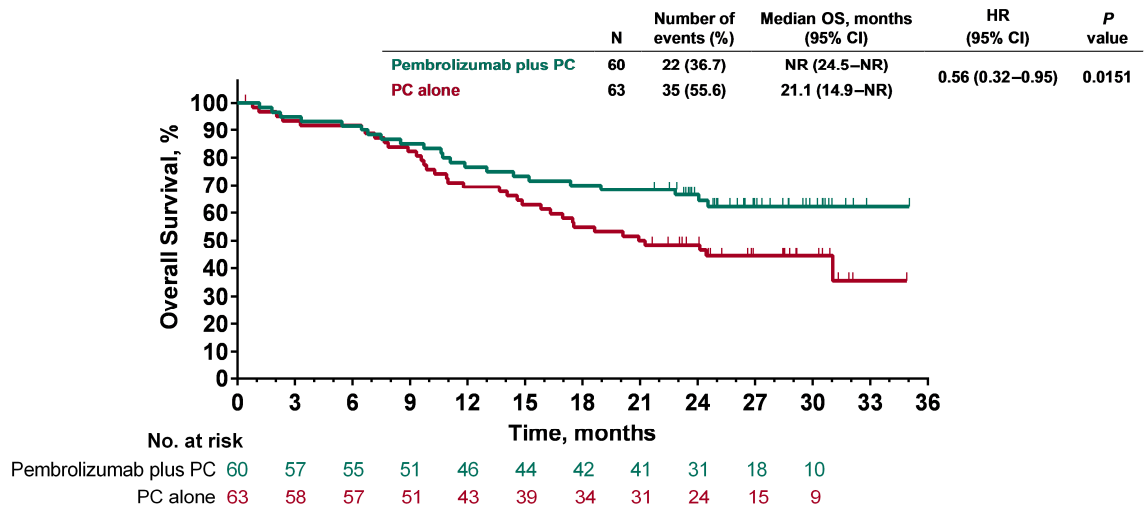
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288 **Figure Legend**

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

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293 **Figure 1.****A****B**

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AC

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

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Corey J. Langer report advisory/consultancy fees from Merck, Astrazeneca, Genentech and Bristol Myers Squibb, outside the submitted work.

Shirish Gadgeel has nothing to disclose.

Vassiliki A. Papadimitrakopoulou reports personal fees from Merck, outside the submitted work.

Amita Patnaik reports other from Merck, during the conduct of the study.

Steven F. Powell reports grants and other from Merck, other from Bristol Myers Squibb, other from Incyte, other from Pfizer, other from Vyriad, other from Genentech, outside the submitted work.

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Shadia I. Jalal has nothing to disclose.

Amit Panwalkar has nothing to disclose.

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Lecia V. Sequist discloses advisory board payments from BMS, AZ, Pfizer, and Genentech and unpaid consulting for BI, Merrimack, Novartis and Clovis Oncology.

Mark M. Awad reports personal fees from Merck, outside the submitted work.

Joseph Fiore reports personal fees from Merck & Co., Inc., during the conduct of the study; personal fees from Merck & Co., Inc., outside the submitted work.

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

Steven Keller is an employee of Merck.

Leena Gandhi reports other from BMS IION Foundation, other from Genentech/Roche, other from Merck, outside the submitted work.