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Associations of Tissue Tumor Mutational Burden and Mutational Status With Clinical Outcomes With Pembrolizumab Plus Chemotherapy Versus Chemotherapy For Metastatic NSCLC

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TMB and Pembrolizumab + Chemotherapy Clinical Outcomes

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1. Tables/figures: 5 figures (limit, 6 tables and/or figures)

2. Abbreviations:

   - AUC, area under the concentration–time curve; AUROC, area under the receiver operating characteristic; CTLA-4, cytotoxic T lymphocyte antigen 4; GEP, gene expression profile; HR, hazard ratio; ICI, immune checkpoint inhibitors; NSCLC, non–small-cell lung cancer; OS, overall survival; ORR, objective response rate; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; TPS, tumor proportion score; tTMB, tissue tumor mutational burden; WES, whole-exome sequencing.
tTMB and Pembrolizumab + Chemotherapy Clinical Outcomes

ABSTRACT (250/250 limit)

Introduction: We evaluated tissue tumor mutational burden (tTMB) and mutations in STK11, KEAP1, and KRAS as biomarkers for outcomes with pembrolizumab-combination for NSCLC among patients in the phase 3 KEYNOTE-189 (ClinicalTrials.gov, NCT02578680; nonsquamous) and KEYNOTE-407 (ClinicalTrials.gov, NCT02775435; squamous) trials.

Methods: This retrospective exploratory analysis evaluated prevalence of high tTMB and STK11, KEAP1, and KRAS mutations in patients enrolled in KEYNOTE-189 and KEYNOTE-407, and the relationship between these potential biomarkers and clinical outcomes. tTMB, and STK11, KEAP1, and KRAS mutation status was assessed using whole-exome sequencing (WES) in patients with available tumor and matched normal DNA. Clinical utility of tTMB was assessed using a prespecified cutpoint of 175 mutations/exome.

Results: Among patients with evaluable data from WES for evaluation of tTMB (KEYNOTE-189, n=293; KEYNOTE-407, n=312) and matched normal DNA, no association was found between continuous tTMB score and overall survival (OS) or progression-free survival (PFS) for pembrolizumab-combination (Wald test, one-sided \( P>0.05 \)) or placebo-combination (Wald test, two-sided \( P>0.05 \)) in patients with squamous or nonsquamous histology. Pembrolizumab-combination improved outcomes for patients with tTMB \( \geq 175 \) compared with tTMB <175 mutations/exome in KEYNOTE-189 (OS, HR: 0.64 [95% CI, 0.38–1.07] and 0.64 [95% CI, 0.42–0.97], respectively) and KEYNOTE-407 (OS, HR: 0.74 [95% CI, 0.50–1.08 and 0.86 [95% CI, 0.57–1.28], respectively) versus placebo-combination. Treatment outcomes were similar regardless of KEAP1, STK11, or KRAS mutation status.
Conclusions: These findings support pembrolizumab-combination as first-line treatment in patients with metastatic NSCLC and do not suggest utility for tTMB, STK11, KEAP1, or KRAS mutation status as a biomarker for this regimen.

Keywords: tissue tumor mutational burden, single-gene genetic alterations, pembrolizumab, metastatic non–small-cell lung cancer, biomarker
INTRODUCTION

Pembrolizumab plus platinum-based chemotherapy (pembrolizumab-combination) is a standard-of-care first-line treatment for patients with metastatic NSCLC irrespective of tumor PD-L1 expression.\textsuperscript{1,2} The role of pembrolizumab-combination in treatment is supported by two placebo-controlled randomized phase 3 studies that demonstrated improved OS and progression-free survival (PFS) among patients with previously untreated metastatic nonsquamous NSCLC without sensitizing EGFR mutation or ALK alteration (KEYNOTE-189; NCT02578680) or metastatic squamous NSCLC (KEYNOTE-407; NCT02775435) irrespective of PD-L1 expression levels.\textsuperscript{3,4}

Tumor mutational burden (TMB), defined as the number of somatic mutations in the tumor genome, is of interest as a biomarker for immune checkpoint inhibitors (ICI).\textsuperscript{5-7} There is discordant evidence for TMB as a biomarker for treatment outcomes with first-line immunotherapy versus immunotherapy plus chemotherapy in advanced NSCLC.\textsuperscript{8} Using whole-exome sequencing (WES) of patients with NSCLC who received pembrolizumab monotherapy, tTMB was found to be associated with OS and PFS benefit.\textsuperscript{9} Findings from other studies of immunotherapy with anti–PD-(L)1 agents alone or in combination with anti–cytotoxic T lymphocyte antigen 4 (CTLA-4) therapy suggest that tTMB may have clinical utility as a biomarker for treatment outcomes.\textsuperscript{5,10-14}

Mutations in driver genes, including in STK11 (also known as LKB1), KEAP1, and KRAS occur in a meaningful proportion of patients with advanced/metastatic NSCLC and are of interest as potential biomarkers for outcomes with anti–PD-(L)1 therapy.\textsuperscript{15-17} Mutations in STK11 and KRAS are more common in patients with nonsquamous histology (including adenocarcinoma) than those with squamous histology.\textsuperscript{18} KRAS G12C is the most frequently occurring KRAS
mutation in NSCLC, comprising approximately 35% of identified KRAS mutations.\textsuperscript{18,19} Mutations in KRAS are a common oncogenic driver in nonsquamous NSCLC\textsuperscript{18} and some studies have suggested that KRAS mutations may be associated with improved outcomes with anti–PD-(L)1 therapy plus chemotherapy.\textsuperscript{17} STK11 and KEAP1 mutations have been associated with poor outcomes in nonsquamous NSCLC, may occur concurrently with KRAS mutations, and have been associated with potential lack of benefit with anti–PD-(L)1 therapy plus chemotherapy.\textsuperscript{15-17,20,21}

To investigate the prevalence and potential clinical utility of tTMB and STK11, KEAP1, and KRAS mutations as biomarkers of outcomes, we conducted separate exploratory analyses of the KEYNOTE-189 and KEYNOTE-407 trials in patients with metastatic NSCLC who received pembrolizumab or placebo plus platinum-based chemotherapy.
MATERIALS AND METHODS

Study Design and Patients

The KEYNOTE-189 (ClinicalTrials.gov, NCT02578680) and KEYNOTE-407 (ClinicalTrials.gov, NCT02775435) trials were randomized, double-blind, placebo-controlled phase 3 trials enrolling patients with previously untreated metastatic NSCLC regardless of tumor PD-L1 expression. Patients had nonsquamous NSCLC without sensitizing EGFR/ALK alterations in KEYNOTE-189 and squamous NSCLC in KEYNOTE-407. The study protocols and all amendments were approved by the appropriate ethics committee at each study site. Patients provided written informed consent before participation.

Treatment

In KEYNOTE-189, patients were randomized 2:1 to receive four 3-week cycles of intravenous pembrolizumab 200 mg or placebo, plus pemetrexed 500 mg/m² and either cisplatin (75 mg/m²) or carboplatin (AUC, 5 mg/mL/min) followed by pembrolizumab or placebo once every 3 weeks for an additional 31 cycles (35 cycles in total) and indefinite pemetrexed maintenance therapy.

In KEYNOTE-407, patients were randomized 1:1 to four 3-week cycles of intravenous pembrolizumab 200 mg or placebo plus carboplatin (AUC, 6 mg/mL/min) and either paclitaxel (200 mg/m²) or nab-paclitaxel (100 mg/m²) followed by pembrolizumab or placebo once every 3 weeks for an additional 31 cycles (35 cycles in total).

Assessments

tTMB and select single-gene mutations (STK11, KEAP1, and KRAS) were assessed centrally by WES of tumor tissue and matched normal DNA as previously described. tTMB was assessed using a prespecified cutpoint of 175 mut/exome to define subgroups with high tTMB (≥175
tTMB and Pembrolizumab + Chemotherapy Clinical Outcomes

1 mut/exome; tTMB-high) versus low tTMB (<175 mut/exome; tTMB-low). This cutpoint was
derived using GEP and WES TMB data from a training set of patients with multiple tumor types
across the pembrolizumab clinical program in which 175 mut/exome yielded the most
statistically significant difference in the distribution of a gene expression profile comprising 18
genes. This cutpoint most closely approximates the 10 mut/Mb used by the updated pipeline
FoundationOne F1Dx_v3.2 assay (Foundation Medicine, Cambridge, MA). Full
methodology for WES analysis is included in Supplemental Methods.

Endpoints

The clinical objectives of KEYNOTE-189 and KEYNOTE-407 have been reported previously. The
objectives of these analyses were to evaluate the prevalence of high tTMB and STK11,
KEAP1, and KRAS mutations in patients enrolled in KEYNOTE-189 and KEYNOTE-407 and to
evaluate the relationship between these potential biomarkers and clinical outcomes (OS, PFS,
and objective response rate [ORR]) in patients treated with pembrolizumab-combination and
placebo-combination. Additional objectives were to investigate the relationship between tTMB
and tumor PD-L1 expression, the association between tTMB and treatment efficacy, and the
clinical utility of tTMB as a predictor of efficacy. Exploratory biomarker analyses were
prespecified in the study protocol for each study. The statistical analysis plan was prespecified
before merging clinical and biomarker data.

Statistical Analysis

Efficacy was assessed in the biomarker-evaluable populations, which comprised randomized
patients who had evaluable samples for WES and received ≥1 dose of study treatment. The
association between tTMB, assessed as a continuous log_{10} transformed variable, and treatment
efficacy were evaluated separately for each trial, with significance level set at 0.05 and no
multiplicity adjustment. Wald tests on the tTMB regression coefficients were used to calculate one-sided $P$ values for pembrolizumab, under the hypothesis that higher tTMB positively associates with improved outcomes. Two-sided $P$ values were calculated for chemotherapy because there was no a priori hypothesis regarding the direction of the association. Descriptive analyses were performed to assess the association between $STK11$, $KEAP1$, and $KRAS$ status and clinical outcomes (OS, PFS, and ORR). The prespecified statistical analysis plan is described in Supplemental Methods.
RESULTS

Patients

In KEYNOTE-189, 293/616 (47.6%) randomized patients had evaluable WES data and were included in the tTMB-evaluable population (pembrolizumab, n=207; control, n=86) and 289 (46.9%) had matched normal DNA and were included in the single-gene mutation-evaluable population (STK11, KEAP1, and KRAS). The data cutoff for all analyses from KEYNOTE-189 was September 21, 2018 (Supplemental Figure-1A). In KEYNOTE-407, 312/559 (55.8%) randomized patients with evaluable WES data were included in the tTMB-evaluable population (pembrolizumab, n=143; control, n=169) and 285 (46.9%) were included in the single-gene mutation-evaluable population (KEAP1; STK11 and KRAS were not evaluated in squamous patients due to low prevalence of these mutations in squamous NSCLC). The data cutoff date for all analyses from KEYNOTE-407 was May 9, 2019 (Supplemental Figure-1B). Baseline demographics and clinical characteristics are described in Table 1.

Clinical Outcomes in the tTMB-Evaluable Population and Association of tTMB With Efficacy

In each study, clinical outcomes (ie, OS, PFS, and ORR) in the tTMB-evaluable groups for pembrolizumab-combination versus placebo-combination were similar to that in the intent-to-treat [ITT] population (Supplemental Table-1). tTMB and PD-L1 TPS were not strongly associated with one another in either treatment arm in either study (Supplemental Figure 2A, B). For assessment of association of tTMB with efficacy, based on the area under the receiver operating characteristic (AUROC) curve for ORR, higher tTMB assessed as a continuous variable was not associated with ORR, in either treatment arm (Figure 1A, C). No association was found between tTMB (assessed as a continuous variable) and ORR (in logistic regression
analyses) or OS and PFS (in Cox proportional hazard regression analyses) in either treatment arm in either study (Wald test one-sided, $P>0.05$ for the pembrolizumab-combination arm and two-sided $P>0.05$ for the placebo-combination arm in each study; Figure 1B, D).

**Clinical Outcomes in Patients With tTMB ≥175 Mutations/Exome and tTMB <175 Mutations/Exome**

In KEYNOTE-189, 134 patients had tTMB ≥175 mut/exome (pembrolizumab-combination, $n=100$; placebo-combination, $n=34$) and 159 with tTMB <175 mut/exome (pembrolizumab-combination, $n=107$; placebo-combination, $n=52$). HRs (95% CI) for OS favored the pembrolizumab-combination group in patients with tTMB ≥175 mut/exome (0.64, 0.38–1.07) and in patients with tTMB <175 mut/exome (0.64, 0.42–0.97; Figure 2A). HRs (95% CI) for PFS favored the pembrolizumab-combination group in patients with tTMB ≥175 mut/exome (0.32, 0.21–0.51) and in patients with tTMB <175 mut/exome (0.51, 0.35–0.74; Figure 2B). In the tTMB ≥175 mut/exome group, ORR (95% CI) was 50.0% (39.8%–60.2%) with pembrolizumab-combination versus 11.8% (3.3%–27.5%) with placebo-combination. For patients with tTMB <175 mut/exome, ORR (95% CI) was 40.2% (30.8%–50.1%) versus 19.2% (9.6%–32.5%), respectively (Supplemental Figure 3A).

In KEYNOTE-407, 162 patients had tTMB ≥175 mut/exome (pembrolizumab-combination, $n=73$; placebo-combination, $n=89$) and 150 patients had tTMB <175 mut/exome (pembrolizumab-combination, $n=70$; placebo-combination, $n=80$). HRs (95% CI) for OS favored pembrolizumab-combination in the tTMB ≥175 mut/exome group (0.74, 0.50–1.08) and <175 mut/exome group (0.86, 0.57–1.28; Figure 2C). PFS was improved with pembrolizumab-combination among patients with tTMB ≥175 mut/exome (HR, 0.57; 95% CI, 0.41–0.81) and <175 mut/exome (HR, 0.68; 95% CI, 0.48–0.96; Figure 2D). In the tTMB ≥175 mut/exome
group, ORR (95% CI) was 58.9% (46.8%–70.3%) with pembrolizumab-combination versus 44.9% (34.4%–55.9%) with placebo-combination. For patients with tTMB <175 mut/exome, ORR (95% CI) was 64.3% (51.9%–75.4%) versus 38.8% (28.1%–50.3%), respectively (Supplemental Figure 3B).

**Clinical Outcomes in Patients With Versus Without Single-Gene Mutations**

**STK11**

Of 289 evaluable patients in KEYNOTE-189, 54 (18.7%) had STK11 mutations. In KEYNOTE-407, 8/285 (2.8%) evaluable patients had STK11 mutations. Because STK11 mutations occurred infrequently in KEYNOTE-407, associations between STK11 status and PD-L1/tTMB or outcomes were not evaluated.

In KEYNOTE-189, median (interquartile range [IQR]) PD-L1 TPS tended to be numerically lower (0% [0–16] vs 15% [0–75]) and median (IQR) TMB scores (209 [132–265] vs 146 [89–264] mut/exome) tended to be numerically higher among patients with versus without an STK11 mutation; Supplemental Figure 4A). Prevalence of STK11 mutations by PD-L1 (TPS) and tTMB score (mut/exome) in the STK11-evaluable population is shown in Supplemental Figure 4B.

In KEYNOTE-189, HRs (95% CI) for OS among patients with an STK11 mutation was 0.75 (0.37–1.50), and 0.59 (0.41–0.85) with wild-type STK11 (Figure 3A). HRs (95% CI) for PFS was 0.81 (0.44–1.47) in patients with an STK11 mutation and 0.38 (0.27–0.52) with wild-type STK11 (Figure 3B). ORRs (95% CI) for pembrolizumab-combination versus placebo-combination were 30.6% (16.4%–48.1%) versus 16.7% (3.6%–41.4%), respectively, in the
1 STK11 mutation group and 48.8% (41.0%–56.6%) versus 16.4% (8.5%–27.5%), respectively, in
the STK11 wild-type group (Supplemental Figure 5).

2 KEAP1

3 Of 289 patients in KEYNOTE-189 with evaluable WES data from matched tumor and normal
DNA, 68 (23.5%) had KEAP1 mutation. In KEYNOTE-407, 285 patients had evaluable WES
data from matched tumor and normal DNA, 36 (12.6%) had KEAP1 mutations.

4 Among patients in KEYNOTE-189 with KEAP1 mutations, median ([IQR]) PD-L1 TPS was
numerically lower (1% [0–13] vs 20% [0–75]) and median (IQR) tTMB score was numerically
higher versus wild-type KEAP1 (173 [124–267] vs 147 [89–263] mut/exome; Supplemental
Figure 6A). Prevalence of KEAP1 mutations by PD-L1 (TPS) and tTMB score (mut/exome) in
the KEAP1-evaluable population is shown in Supplemental Figure 6B. Among patients in
KEYNOTE-407 with KEAP1 mutations, median (IQR) PD-L1 TPS (11% [1–57]) and median
(IQR) tTMB scores (205 [140–296]) were numerically higher versus patients with wild-type
KEAP1 (Supplemental Figure 6C). No association between PD-L1 (TPS) and tTMB score
(mut/exome) in the KEAP1-evaluable population was observed (Supplemental Figure 6D).

5 In KEYNOTE-189, pembrolizumab-combination was associated with improved OS and PFS
compared with placebo-combination, regardless of KEAP1 mutation status (KEAP1 mutation HR
[95% CI] for OS, 0.81 [0.44–1.49]; KEAP1 wild-type HR [95% CI] for OS, 0.57 [0.39–0.84];
Figure 4A). HRs (95% CI) for PFS was 0.65 (0.38–1.12) in patients with KEAP1 mutation and
0.38 (0.28–0.53) with KEAP1 wild-type (Figure 4C). ORR (95% CI) for pembrolizumab-
combination versus placebo-combination was 35.6% (21.9%–51.2%) versus 17.4% (5.0%–
38.8%), respectively, in patients with KEAP1 mutations and 48.4% (40.4%–56.5%) versus
1 16.1% (8.0%–27.7%), respectively, in patients with wild-type KEAP1 (Supplemental Figure 7A).
2
3 In KEYNOTE-407, HRs (95% CI) for OS were 1.08 (0.48–2.41) in patients with KEAP1 mutation, and 0.75 (0.55–1.02) for wild-type KEAP1 (Figure 4B). HRs (95% CI) for PFS was 0.40 (0.19–0.86) in patients with KEAP1 mutations and 0.63 (0.48–0.83) for wild-type KEAP1 (Figure 4D). ORRs (95% CI) for pembrolizumab-combination versus placebo-combination was 66.7% (34.9%–90.1%) versus 54.2% (32.8%–74.5%), respectively, in patients with KEAP1 mutations and 61.7% (52.4%–70.4%) versus 41.9% (33.2%–50.9%), respectively, for wild-type KEAP1 (Supplemental Figure 7B).

KRAS

5 Of 289 evaluable patients in KEYNOTE-189, 89 (32.2%) had KRAS mutations, of which 37 (12.8%) were KRAS G12C mutations. In KEYNOTE-407, 14/285 (4.9%) patients had KRAS mutations; none were KRAS G12C. Because KRAS occurred infrequently in KEYNOTE-407 (squamous NSCLC), associations between KRAS status and PD-L1/tTMB or outcomes were not evaluated.

6 In KEYNOTE-189, median (IQR) PD-L1 TPS (30% [1%–71%] versus 5% [0%–60%]) and median (IQR) TMB scores (204 [137–276] versus 141 [85–252] mut/exome) tended to be higher in patients with versus without KRAS mutation (Supplemental Figure 8A). Joint association between PD-L1 (TPS) and tTMB score (mut/exome) for KRAS mutant and KRAS wild-type patients is shown in Supplemental Figure 8B.

7 HRs (95% CI) for OS were 0.79 (0.45–1.38) for any KRAS mutation and 0.55 (0.37–0.81) for KRAS wild-type (Figure 5A). For PFS, HRs (95% CI) were 0.47 (0.29–0.77) for any KRAS
mutation, and 0.40 (0.29–0.57) for KRAS wild-type (Figure 5B). ORR (95% CI) for pembrolizumab-combination versus placebo-combination was 40.7% (28.1%–54.3%) versus 26.7% (12.3%–45.9%) for any KRAS mutation and 47.6% (39.2%–56.0%) versus 10.9% (4.1%–22.3%) for wild-type KRAS (Supplemental Figure 9).

For the subgroup of patients with KRAS G12C mutation (pembrolizumab-combination, n=26; placebo-combination, n=11), HRs for patients who received pembrolizumab-combination or placebo-combination were 1.14 (0.45–2.92) and 0.48 (0.22–1.06) for OS and PFS, respectively (Figure 5A, B). Corresponding ORRs were 50.0% (29.9%–70.1%) and 18.2% (2.3%–51.8%), respectively (Supplemental Figure 9).
DISCUSSION

Among patients with advanced NSCLC in the KEYNOTE-189 (nonsquamous) and KEYNOTE-407 (squamous) studies, first-line treatment with platinum-based chemotherapy with or without pembrolizumab showed no association between tTMB, KEAP1 mutation (nonsquamous or squamous) or STK11, or KRAS mutation (nonsquamous) and treatment outcomes. There was no significant association between tTMB for either treatment arm and NSCLC histology. Furthermore, there was no strong correlation between tTMB and PD-L1 TPS in either treatment arm in either study. Pembrolizumab-combination demonstrated improved clinical benefit versus placebo-combination irrespective of mutations in STK11, KEAP1, and KRAS. These findings do not support clinical utility of tTMB as a biomarker for pembrolizumab plus platinum-based chemotherapy for metastatic squamous or nonsquamous NSCLC.

Prevalence of tTMB, STK11, KEAP1 and KRAS mutations were generally consistent with that previously reported. The predictive value of tTMB as a biomarker for outcomes with anti–PD-(L)1 therapies may vary when administered as monotherapy or in combination with chemotherapy. In an exploratory analysis of biomarker-evaluable data from the phase 3 KEYNOTE-042 trial of pembrolizumab monotherapy in patients with PD-L1 TPS ≥1% advanced NSCLC that employed a similar analytical approach, higher tTMB levels were associated with improved outcomes with pembrolizumab but not with chemotherapy. Moreover, patients with tTMB ≥175 mut/exome had improved OS and PFS compared with chemotherapy, whereas those with tTMB <175 mut/exome did not. In other studies of anti–PD-(L)1 therapies in NSCLC, a relationship between tissue or plasma TMB and clinical outcomes has been reported for studies of both monotherapies, including pembrolizumab, nivolumab, and atezolizumab, and immunotherapy combination therapies, such as nivolumab plus...
tTMB and Pembrolizumab + Chemotherapy Clinical Outcomes

ipilimumab\textsuperscript{11,13,31} and durvalumab plus tremelimumab.\textsuperscript{32} A review of multiple studies of anti–PD-(L)1 therapies given as single agents across various solid tumor types, including nonsquamous and squamous NSCLC, demonstrated a significant correlation between increasing TMB and increasing ORR ($P<0.001$).\textsuperscript{33} This finding of an association between tTMB and outcomes with pembrolizumab monotherapy but not with pembrolizumab-combination represents a parallel to the use of PD-L1 as a biomarker in first-line NSCLC: PD-L1 provides a biomarker for response with pembrolizumab monotherapy,\textsuperscript{34-36} but its predictive value is diminished among patients receiving pembrolizumab-combination.\textsuperscript{3,4} For patients with PD-L1–negative disease (who are not eligible for pembrolizumab monotherapy), pembrolizumab plus chemotherapy remains an appropriate treatment option irrespective of tTMB.

We also investigated relationships between mutations in \textit{STK11}, \textit{KEAP1}, and \textit{KRAS}, and clinical outcomes in KEYNOTE-189 and KEYNOTE-407, each of which has been suggested to be potentially associated with outcomes among patients receiving anti–PD-(L)1 therapy.\textsuperscript{17} Our results indicate OS benefit persisted among patients who received pembrolizumab-combination regardless of \textit{STK11} or \textit{KEAP1} mutation status. There was no difference in PFS, however given the relatively small number of patients there is low precision for estimating HRs for OS and PFS, as reflected in the very wide confidence intervals. Pembrolizumab-combination was generally associated with improved clinical outcomes compared with placebo-combination, regardless of \textit{STK11}, \textit{KEAP1}, or \textit{KRAS} mutation status; nonetheless, the magnitude of benefit in some groups remains uncertain. In KEYNOTE-407, HR for OS was 0.96 versus 0.76 among patients with \textit{KEAP1} mutations versus wild-type \textit{KEAP1}. However, given the small number of patients with a mutation there is insufficient evidence to support the hypothesis of no benefit for pembrolizumab-combination in patients with squamous NSCLC with \textit{KEAP1} mutations or vice
versa. KEYNOTE-189 did not provide evidence of an association between $KRAS$ mutation status and outcomes with pembrolizumab-combination. Among patients with $KRAS$ G12C mutation, HR (95% CI) for OS was 1.14 (0.45–2.92), although sample size was too small to make definitive conclusions. The improvement in OS, PFS and ORR with pembrolizumab-combination versus placebo-combination was observed irrespective of $KRAS$ mutation status.

These findings are consistent with other studies of the associations between these mutations and response and resistance to anti–PD-(L)1 therapies, with $KRAS$ mutations generally associated with improved outcomes and $STK11$ and $KEAP1$ mutations being associated with poorer outcomes compared with the corresponding wild-types.\(^9,17,37-40\) In contrast to studies that have suggested $STK11$ and $KEAP1$ mutations confer resistance to anti–PD-(L)1 therapies, patients with these mutations were shown to have improved outcomes with pembrolizumab monotherapy versus chemotherapy in patients with advanced NSCLC in the KEYNOTE-042 study.\(^41\)

These analyses were exploratory with few patients in some groups. Biomarker analyses were prespecified in the study protocol for both KEYNOTE-407 (squamous) and KEYNOTE-189 (nonsquamous) and the analysis plan was prespecified before the clinical and biomarker data were merged. Furthermore, our analysis only included patients with WES-evaluable samples, resulting in small sizes for certain groups. Notably, improvements in clinical outcomes observed with pembrolizumab-combination versus placebo-combination in the biomarker-evaluable populations were similar to the total populations of each study. As discussed, there is discordant evidence for TMB as a biomarker for treatment outcomes with first-line immunotherapy versus chemotherapy compared to immunotherapy plus chemotherapy versus chemotherapy in advanced NSCLC.\(^8\) While WES is considered the gold-standard measurement of TMB, this technique is time-consuming, costly, and laborious.\(^5\) Additionally, while there can be variations
across cancer types\textsuperscript{,42} TMB 175 mut/exome assessed by WES has been shown to be well aligned with the FoundationOne CDx TMB cutpoint of 10 mut/Mb that is known to enrich for response across multiple solid tumor types, including NSCLC\textsuperscript{.28}

In conclusion, the results of this exploratory analysis suggest that tTMB as well as \textit{STK11}, \textit{KEAP1}, and \textit{KRAS} mutation status have limited clinical utility as biomarkers for patients treated with first-line pembrolizumab plus platinum-based chemotherapy in metastatic nonsquamous and squamous NSCLC. Our findings support the use of pembrolizumab plus platinum-based chemotherapy as a standard first-line combination therapy for patients with metastatic nonsquamous NSCLC, regardless of tTMB or \textit{STK11}, \textit{KEAP1}, and \textit{KRAS} mutation status.
FUNDING

Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

ACKNOWLEDGMENTS

We thank the patients and their families and caregivers for participating in these trials; all the investigators and site personnel; Eli Lilly and company (Indianapolis, IN, USA) for providing pemetrexed; and the Merck & Co., Inc., Rahway, NJ, USA employees who supported the studies and the tTMB analysis. Medical writing and editorial assistance was provided by Christabel Wilson, MSc, of ICON plc (North Wales, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

DATA SHARING STATEMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (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 assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made
available for request after product approval in the 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.
REFERENCES


https://doi.org/10.1126/science.aaa1348.


https://doi.org/10.1200/jco.18.01042.


https://doi.org/10.1056/NEJMoa1613493.


Table 1. Baseline Demographics and Clinical Characteristics in the tTMB-Evaluable Populations in Each Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>KEYNOTE-189</th>
<th>KEYNOTE-407</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tTMB-Evaluable Population (n = 293)</td>
<td>tTMB-Evaluable Population (n = 312)</td>
</tr>
<tr>
<td></td>
<td>Total Population (n = 616)</td>
<td>Total Population (n = 559)</td>
</tr>
<tr>
<td>Median age, y (IQR)</td>
<td>64 (56–69)</td>
<td>66 (60–71)</td>
</tr>
<tr>
<td></td>
<td>63 (56–69)</td>
<td>66 (60–71)</td>
</tr>
<tr>
<td>Male</td>
<td>166 (56.7)</td>
<td>252 (80.8)</td>
</tr>
<tr>
<td></td>
<td>162 (56.1)</td>
<td>230 (80.7)</td>
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<td>ECOG performance status 1</td>
<td>164 (55.9)</td>
<td>194 (68.1)</td>
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<tr>
<td></td>
<td>162 (56.1)</td>
<td>396 (70.8)</td>
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<tr>
<td>Former/current smoker</td>
<td>260 (88.7)</td>
<td>265 (93.0)</td>
</tr>
<tr>
<td></td>
<td>256 (88.6)</td>
<td>518 (92.7)</td>
</tr>
<tr>
<td>PD-L1 TPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>99 (33.8)</td>
<td>111 (35.6)</td>
</tr>
<tr>
<td></td>
<td>98 (33.9)</td>
<td>100 (35.1)</td>
</tr>
<tr>
<td>1%–49%</td>
<td>910 (31.1)</td>
<td>117 (37.5)</td>
</tr>
<tr>
<td></td>
<td>90 (31.1)</td>
<td>111 (38.9)</td>
</tr>
<tr>
<td>≥50%</td>
<td>98 (33.4)</td>
<td>83 (26.6)</td>
</tr>
<tr>
<td></td>
<td>96 (33.2)</td>
<td>74 (26.0)</td>
</tr>
<tr>
<td></td>
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<td>146 (26.1)</td>
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### tTMB and Pembrolizumab + Chemotherapy Clinical Outcomes

<table>
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<tr>
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<th>5 (1.7)</th>
<th>38 (6.2)</th>
<th>0</th>
<th>0 (0.0)</th>
<th>12 (2.1)</th>
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<tr>
<td>Could not be</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>evaluated(^b)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD-L1 TPS, programmed death ligand 1 tumor proportion score; tTMB, tissue tumor mutational burden.

Data are presented as \( n \) (%), unless otherwise noted.

\(^a\)KRAS and STK11 mutation data were excluded for KEYNOTE-407 because these mutations are rare in squamous NSCLC, and the number of patients with these mutations who also had evaluable WES data from both tumor and normal DNA was small.

\(^b\)Specimens had an inadequate number of tumor cells or no tumor cells.
FIGURE LEGENDS

Figure 1. Association of tTMB with efficacy outcomes in (A) and (B) KEYNOTE-189 and (C) and (D) KEYNOTE-407. In panels A and C, graph shows area under the ROC curve for ORR. Panels B and D provide P values for OS, PFS, and ORR in each respective study from logistic regression analysis. aP values were calculated using the Wald test and are one-sided for pembrolizumab-combination (a priori hypothesis that tTMB was positively associated with improved outcomes for pembrolizumab-combination) and two-sided for placebo-combination (no a priori hypothesis regarding direction of the association between tTMB and outcomes) with significance level set at 0.05 and no multiplicity adjustment. tTMB was graphed on a log_{10} scale for the ROC curve. AUC, area under the curve; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; r, correlation coefficient; ROC, receiver operating characteristics; tTMB, tissue tumor mutational burden; TPS, tumor proportion score.

Figure 2. Clinical utility of tTMB for OS and PFS in each study at cutpoints of ≥175 mut/exome and <175 mut/exome. Kaplan-Meier estimates of OS (A) and PFS (B) in KEYNOTE-189. Kaplan-Meier estimates of OS (C) and PFS (D) in KEYNOTE-407. Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; mut, mutation; NR, not reached; OS, overall survival; PFS, progression-free survival; tTMB, tissue tumor mutational burden.

Figure 3. Kaplan-Meier estimates of OS and PFS by STK11 status in the single-gene mutation-evaluable population in KEYNOTE-189. (A) OS and (B) PFS. Chemo,
chemotherapy; CI, confidence interval; HR, hazard ratio; mut, mutation; NR, not reached; OS, overall survival; Pembro, pembrolizumab; PFS, progression-free survival; wt, wild-type.

Figure 4. Kaplan-Meier estimates of OS and PFS by KEAP1 status in the single-gene mutation-evaluable populations. OS in (A) KEYNOTE-189 and (B) KEYNOTE-407. PFS in (C) KEYNOTE-189 and (D) KEYNOTE-407. Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; mut, mutation; NR, not reached; OS, overall survival; Pembro, pembrolizumab; PFS, progression-free survival; wt, wild-type.

Figure 5. Kaplan-Meier estimates of OS and PFS by KRAS status in the single-gene mutation-evaluable population in KEYNOTE-189. (A) OS and (B) PFS. Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; mut, mutation; NR, not reached; OS, overall survival; Pembro, pembrolizumab; PFS, progression-free survival; wt, wild-type.
A.

**AUROC (95% CI)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>0.55 (0.47–0.63)</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>0.41 (0.25–0.57)</td>
</tr>
</tbody>
</table>

**KEYNOTE-189**

A.

B.

Journal Pre-proof
### B. KEYNOTE-189

<table>
<thead>
<tr>
<th>Nominal $P$ value $^a$</th>
<th>Pembro + Chemo (n = 207)</th>
<th>Placebo + Chemo (n = 86)</th>
</tr>
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<tbody>
<tr>
<td>OS</td>
<td>0.174</td>
<td>0.856</td>
</tr>
<tr>
<td>PFS</td>
<td>0.075</td>
<td>0.055</td>
</tr>
<tr>
<td>ORR</td>
<td>0.072</td>
<td>0.434</td>
</tr>
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</table>

$^a$ Significant results are highlighted.
C.

<table>
<thead>
<tr>
<th></th>
<th>AUROC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>0.51 (0.41–0.61)</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>0.56 (0.47–0.65)</td>
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</table>

**KEYNOTE-407**

Journal Pre-proof
### D. KEYNOTE-407

<table>
<thead>
<tr>
<th>Nominal $P$ value$^a$</th>
<th>Pembro + Chemo (n = 143)</th>
<th>Placebo + Chemo (n = 169)</th>
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<tbody>
<tr>
<td>OS</td>
<td>0.160</td>
<td>0.818</td>
</tr>
<tr>
<td>PFS</td>
<td>0.052</td>
<td>0.560</td>
</tr>
<tr>
<td>ORR</td>
<td>0.393</td>
<td>0.086</td>
</tr>
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</table>

$^a$Nominal $P$ values

AUROC (95% CI)
- Pembro + chemo: 0.51 (0.41–0.61)
- Placebo + chemo: 0.56 (0.47–0.65)
A. STK11\textsuperscript{mut}

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>17.4 (4.7–NR)</td>
<td>0.75</td>
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<tr>
<td>Placebo + chemo</td>
<td>8.4 (6.5–NR)</td>
<td>(0.37–1.50)</td>
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STK11\textsuperscript{wt}

<table>
<thead>
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<th>Median (95% CI), mo</th>
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<tr>
<td>Pembro + chemo</td>
<td>22.5 (20.1–NR)</td>
<td>0.59</td>
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<tr>
<td>Placebo + chemo</td>
<td>12.4 (7.6–25.0)</td>
<td>(0.41–0.85)</td>
</tr>
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</table>

B. STK11\textsuperscript{mut}

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>6.1 (3.6–9.2)</td>
<td>0.81</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>4.8 (4.5–8.6)</td>
<td>(0.44–1.47)</td>
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STK11\textsuperscript{wt}

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>10.4 (8.2–14.0)</td>
<td>0.38</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>4.7 (4.6–5.3)</td>
<td>(0.27–0.52)</td>
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</table>
A. KEYNOTE-189

**KEAP1^{mut}**

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Pembro + chemo</strong></td>
<td>13.3 (7.5–NR)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Placebo + chemo</strong></td>
<td>8.7 (6.6–NR)</td>
<td>(0.44–1.49)</td>
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**KEAP1^{wt}**

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pembro + chemo</strong></td>
<td>23.5 (20.4–NR)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Placebo + chemo</strong></td>
<td>12.2 (7.6–25.0)</td>
<td>(0.39–0.84)</td>
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---

**Journal Pre-proof**
### KEAP1\textsuperscript{mut}

<table>
<thead>
<tr>
<th>Time, months</th>
<th>OS, %</th>
<th>No. at Risk</th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Pembro + chemo</td>
<td>12.9 (6.7–NR)</td>
<td>24–19–13–9–8–6–3–1–0</td>
<td>1.08</td>
<td>(0.48–2.41)</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>8.6 (7.3–NR)</td>
<td>12–11–8–6–4–3–1–0–0</td>
<td></td>
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</tr>
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### KEAP1\textsuperscript{wt}

<table>
<thead>
<tr>
<th>Time, months</th>
<th>OS, %</th>
<th>No. at Risk</th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>16.9 (14.0–23.1)</td>
<td>129–109–83–62–49–37–19–5–0</td>
<td>0.75</td>
<td>(0.55–1.02)</td>
</tr>
</tbody>
</table>

**B. KEYNOTE-407**

**KEAP1\textsuperscript{mut}**

- Median OS: 12.9 months (95% CI: 6.7–NR)
- Adjusted HR: 1.08 (95% CI: 0.48–2.41)

**KEAP1\textsuperscript{wt}**

- Median OS: 16.9 months (95% CI: 14.0–23.1)
- Adjusted HR: 0.75 (95% CI: 0.55–1.02)
C. **KEYNOTE-189**

### KEAP1\textsuperscript{mut}

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>5.1 (3.7–11.1)</td>
<td>0.65</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>4.8 (4.6–8.8)</td>
<td>(0.38–1.12)</td>
</tr>
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</table>

### KEAP1\textsuperscript{wt}

<table>
<thead>
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<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>10.4 (8.2–14.0)</td>
<td>0.38</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>4.7 (4.5–5.3)</td>
<td>(0.28–0.53)</td>
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### D. KEYNOTE-407

**KEAP1^{mut}**

<table>
<thead>
<tr>
<th>Time, months</th>
<th>No. at Risk</th>
<th>Median (95% CI), mo</th>
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<tbody>
<tr>
<td>Pembro + chemo</td>
<td>24 15 2 0 0 0 0 0 0</td>
<td>6.3 (5.7–NR)</td>
<td>0.40 (0.19–0.86)</td>
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<tr>
<td>Placebo + chemo</td>
<td>12 11 5 2 0 0 0 0 0</td>
<td>4.2 (4.0–5.3)</td>
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**KEAP1^{wt}**

<table>
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<tr>
<th>Time, months</th>
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<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Pembro + chemo</td>
<td>129 85 38 25 16 10 5 0 0</td>
<td>7.8 (6.2–10.4)</td>
<td>0.63 (0.48–0.83)</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>120 92 59 42 27 17 9 2 0</td>
<td>5.3 (4.2–6.2)</td>
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</table>
**KRAS**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS (95% CI), mo</th>
<th>HR (95% CI)</th>
<th>KRAS Mutant (KRASmut)</th>
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</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>21.1 (16.0–NR)</td>
<td>0.79</td>
<td>21.1 (16.0–NR)</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>14.1 (8.1–NR)</td>
<td>0.79</td>
<td>14.1 (8.1–NR)</td>
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<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS (95% CI), mo</th>
<th>HR (95% CI)</th>
<th>KRAS Wild Type (KRASwt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>22.2 (19.3–NR)</td>
<td>0.55</td>
<td>22.2 (19.3–NR)</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>9.2 (7.3–17.1)</td>
<td>0.55</td>
<td>9.2 (7.3–17.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS (95% CI), mo</th>
<th>HR (95% CI)</th>
<th>KRAS G12C (KRASG12C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>18.1 (10.9–NR)</td>
<td>1.14</td>
<td>18.1 (10.9–NR)</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>25.0 (8.1–NR)</td>
<td>1.14</td>
<td>25.0 (8.1–NR)</td>
</tr>
</tbody>
</table>
B. 

**KRAS**\textsuperscript{mut}

<table>
<thead>
<tr>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo: 9.3 (6.9–14.0)</td>
<td>0.47 (0.29–0.77)</td>
</tr>
<tr>
<td>Placebo + chemo: 4.8 (4.2–4.9)</td>
<td></td>
</tr>
</tbody>
</table>

**KRAS**\textsuperscript{wt}

<table>
<thead>
<tr>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo: 9.1 (7.0–13.8)</td>
<td>0.48 (0.22–1.06)</td>
</tr>
<tr>
<td>Placebo + chemo: 4.7 (4.6–NR)</td>
<td></td>
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</tbody>
</table>

**KRAS**\textsuperscript{G12C}

<table>
<thead>
<tr>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo: 11.3 (6.5–18.0)</td>
<td>0.46 (0.22–1.06)</td>
</tr>
<tr>
<td>Placebo + chemo: 4.7 (4.6–NR)</td>
<td></td>
</tr>
</tbody>
</table>

Data Curation – J. Kobie


Formal analysis – J. Kobie