364 KRAS MUTATIONS IN PATIENTS WITH NONSQUAMOUS NON–SMALL-CELL LUNG CANCER: PREVALENCE AND RELATIONSHIP WITH PD-L1 EXPRESSION, TUMOR MUTATION BURDEN AND SMOKING STATUS

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Background Pembrolizumab is a standard-of-care first-line treatment for advanced/metastatic NSCLC, either as monotherapy (for patients with PD-L1 tumor proportion score [TPS] ≥1%) or combined with platinum chemotherapy. An improved OS benefit has been demonstrated for both pembrolizumab monotherapy and pembrolizumab plus chemotherapy in patients with higher tumor PD-L1 expression, and for pembrolizumab monotherapy in patients with higher tissue tumor mutation burden (tMB). Mutations in *KRAS* occur relatively frequently in patients with nonsquamous NSCLC but infrequently in those with squamous NSCLC; most mutations are in codon 12. Notably, the pembrolizumab OS treatment effect was not diminished in patients with *KRAS* G12C mutations in phase 3 studies evaluating pembrolizumab monotherapy and pembrolizumab in combination with chemotherapy.[1 2] Herein we describe prevalence of *KRAS* mutations among patients with advanced nonsquamous NSCLC from two phase 3 clinical studies evaluating first-line pembrolizumab (KEYNOTE-042 and KEYNOTE-189) and the relationship of such mutations with select patient characteristics.

Methods KEYNOTE-042 (NCT02220894) evaluated pembrolizumab versus platinum-based chemotherapy for advanced PD-L1–positive NSCLC (any histology) without *EGFR/ALK* alterations. KEYNOTE-189 (NCT02578680) evaluated pembrolizumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone for metastatic nonsquamous NSCLC without *EGFR/ALK* alterations irrespective of tumor PD-L1 expression. Whole-exome sequencing of tumor tissue and matched normal DNA (blood) was performed for patients with nonsquamous histology. PD-L1 TPS was evaluated using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA). Prevalence of *KRAS* mutations and their relationships with TMB, PD-L1 TPS, and smoking status were analyzed descriptively.

Results 590 patients with nonsquamous NSCLC were included in these analyses (KEYNOTE-042, n=301; KEYNOTE-189, n=289). Overall, 42.9% of patients had tTMB ≥175 mut/exome, 81.4% were current/former smokers and, 40.3%, 42.7%, and 16.9% had PD-L1 TPS ≥50%, 1–49% and <1% respectively. *KRAS* G12C, G12D, and G12V mutations occurred in 11.0%, 4.1%, and 5.4% of patients, respectively. Prevalence of *KRAS* mutations by patient characteristics is summarized in the table (table 1). *KRAS* G12C mutations occurred almost exclusively in current/former smokers. *KRAS* G12C was enriched in tumors with tTMB ≥175 mut/exome and tumors with PD-L1 TPS ≥50%. Prevalence was highest in tumors with both tTMB ≥175 mut/exome and PD-L1 TPS ≥50%.

Abstract 364 Table 1 *KRAS* Mutation Prevalence

KRAS Mutation Prevalence, n (%)	N	*KRAS* G12C	*KRAS* G12D	*KRAS* G12V
Smoking status				
Current/former	480	64 (13.3)	22 (4.6)	29 (6.0)
Never	110	1 (0.9)	2 (1.8)	3 (2.7)
tTMB				
≥175 mutations/exome	253	44 (17.4)	7 (2.8)	16 (6.3)
<175 mut/exome	337	21 (6.2)	17 (5.0)	16 (4.7)
PD-L1 expression[a]				
TPS ≥50%	236	39 (16.5)	11 (4.7)	12 (5.1)
TPS 1%-49%	250	21 (8.4)	9 (3.6)	12 (4.8)
TPS <1%	99	5 (5.1)	4 (4.0)	8 (8.1)
tTMB and PD-L1 expression				
≥175 mut/exome and PD-L1 TPS ≥50%	109	31 (28.4)	3 (2.8)	7 (6.4)
≥175 mut/exome and PD-L1 TPS 1%-49%	94	11 (11.7)	4 (4.3)	5 (5.3)
≥175 mut/exome and PD-L1 TPS<1%	50	2 (4.0)	0	4 (8.0)
<175 mut/exome and PD-L1 TPS ≥50%	127	8 (6.3)	8 (6.3)	5 (3.9)
<175 mut/exome and TPS 1%-49%	156	10 (6.4)	5 (3.2)	7 (4.5)
<175 mut/exome and TPS <1%	49	3 (6.1)	4 (8.2)	4 (8.2)

[a]5 patients were unevaluable for PD-L1 TPS.

Conclusions *KRAS* G12C mutations occurred with moderate frequency in patients with nonsquamous NSCLC, with most occurring in current/former smokers. *KRAS* G12C mutations occurred at higher frequency in patient subgroups defined by higher tTMB and PD-L1 TPS.

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Trial Registration KEYNOTE-042, ClinicalTrials.gov, NCT02220894; KEYNOTE-189, ClinicalTrials.gov, NCT02578680

REFERENCES

1. . Gadgeel S, Rodriguez-Abreu D, Felip E, *et al*. KRAS mutational status and efficacy in KEYNOTE-189: pembrolizumab (pembro) plus chemotherapy (chemo) vs placebo plus chemo as first-line therapy for metastatic non-squamous NSCLC. *Ann Oncol* 2019;**30**(suppl 11):xi64-xi5.
2.. Herbst RS, Lopes G, Kowalski DM, *et al*. Association of KRAS mutational status with response to pembrolizumab monotherapy given as first-line therapy for PD-L1-positive advanced non-squamous NSCLC in KEYNOTE-042. *Ann Oncol* 2019;**30**(suppl 11):xi63-xi4.

Ethics Approval For both trials, the protocol and all amendments were approved by the appropriate ethics committee at each center, the study was conducted in accordance with the standards of Good Clinical Practice. Patients provided written informed consent before enrollment.

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