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 (tTMB). Mutations in KRAS occur relatively frequently in patients with nonsquamous NSCLC but infrequently in those with squamous NSCLC; most mutations are in exon 2, 3, 4. The prevalence of KRAS mutations was not diminished in patients with KRAS G12C mutations in tumors with both tTMB and PD-L1 TPS.

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 rTMB ≥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 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 rTMB ≥175 mut/exome and tumors with PD-L1 TPS ≥50%. Prevalence was highest in tumors with both rTMB ≥175 mut/exome and PD-L1 TPS ≥50%.

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 rTMB and PD-L1 TPS.

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

REFERENCES

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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