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KRAS-G12C mutation is associated with poor outcome in surgically-resected lung adenocarcinoma

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In response

We appreciate the comments made by Dr. Egber Smit and collaborators to our article on *KRAS* codon variants as prognostic markers in resected lung adenocarcinoma.[1] In our manuscript, we performed a multivariate analysis comparing *KRAS-G12C* and *nonG12C* versus *KRAS* wild-type, as shown in the Supplementary Table S4, but we agree with Dr. Smit that we did not present the multivariate analysis comparing *KRAS-G12C* with the other *KRAS* codon variants. Here, we show the results from the multivariate Cox analysis for overall survival according to *KRAS* amino acid substitution using each subtype of *KRAS-nonG12C* as a reference: G12D vs. G12C, HR = 2.81 (1.07 – 7.36, $p = 0.035$); G12A vs. G12C, HR = 5.99 (1.39 – 25.7, $p = 0.016$); G12V vs. G12C, HR = 1.62 (0.70 – 3.76, $p = 0.259$). These data indicate that the patients harboring *KRAS-G12C* mutations have significantly worse overall survival as compared with *KRAS-G12D* and *KRAS-G12A*, but not with *KRAS-G12V* mutations. In keeping with this, Ihle et al. reported that patients whose tumors had *KRAS-G12C* or *KRAS-G12V* mutations also had significantly worse progression-free survival as compared with patients whose tumors had other *KRAS* codon variants or wild-type *KRAS*, albeit in metastatic NSCLC.[2]

We did not systematically assess the *EGFR* mutation status in early-stage lung adenocarcinoma patients, but these data were available in a subset of patients included in this study. Among the patients whose tumors had wild-type *KRAS* (n = 94), 9 patients (10%) harbored an *EGFR* mutation, 48 were *EGFR* wild-type and in 37 patients the *EGFR* status was unknown. When the 9 patients harboring an *EGFR* mutation were excluded from survival analysis, *KRAS* mutation and *KRAS-G12C* remained an independent predictor of poor outcome.

We indicated in the discussion of our manuscript that the prognostic value of *KRAS* mutation status in NSCLC remains controversial. Although effective therapies targeting *KRAS* represent an unmet crucial need, we consider that it is relevant to distinguish among the distinct *KRAS* codon variants that may in the future, have important biological and therapeutic implications for patients with surgically-resected lung adenocarcinoma.

Sincerely,

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