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Response to comment on "Impact of *KRAS* mutation subtype and concurrent pathogenic mutations on non-small cell lung cancer outcomes"

We appreciate the interest and comments for our manuscript titled "Impact of *KRAS* mutation subtype and concurrent pathogenic mutations on non-small cell lung cancer outcomes" [1].

We agree that there are multiple approaches for variable selection in building a multivariable Cox regression model. Given that our study cohort consisted of a relatively heterogeneous group of patients with *KRAS*-mutant non-small cell lung cancer (NSCLC)—with more than half female, a wide age range, various stages of disease at diagnosis, and several who were non-smoking—it was necessary to control for the factors that could potentially influence outcomes. Thus, we preselected age, sex, and smoking status as key demographic factors and stage and prior therapies as key disease-related factors for adjustment. Of note, these demographic factors are common in studies pertaining to *KRAS*-mutant NSCLC [2,3] and have been previously retained in multivariable Cox regression analyses despite having statistical insignificance in univariable analyses [4,5]. We presented both the univariable and multivariable Cox regression data in Table 4 of the manuscript to show the effect of these adjustments on overall survival (OS) and to confirm that the statistically significant changes are unidirectional and sensible.

The method of choosing variables according to statistical significance is one that is utilized in some research studies, as Wen et al. have stated. However, we caution against relying solely on the achievement of statistical significance on univariable analysis when selecting variables for a multivariable regression model. This approach, known as "bivariable analysis," has been shown to overestimate the coefficients of the selected variables and distort their statistical significance [6–8]. Furthermore, bivariable analysis may omit variables that have meaningful relationships with the outcome—relationships obscured by a confounder—and include inappropriate noise variables [6]. Thus, in observational studies, there remains an important role for clinical judgment in the decisions regarding variable selection. In addition, had we utilized the bivariable analysis approach, this would have excluded virtually all *KRAS* mutation subtypes and concurrent pathogenic mutations under consideration from our model except *STK11* co-mutations and limited our ability to assess the prognostic impact of these molecular markers.

Wen et al. also suggested loosening the *P* value cutoff on univariable analysis to $P < 0.5$ when selecting variables for our multivariable Cox

Table 1
Univariable and Multivariable Analyses for Overall Survival.

	Univariable Analysis				†Multivariable Analysis			
		95% CI				95% CI		
Variable	Crude HR	Lower	Upper	*P*	Adjusted HR	Lower	Upper	*P*
Age	1.03	1.00	1.06	0.091	1.04	1.01	1.07	0.024*
Female	0.93	0.57	1.50	0.764	–	–	–	–
Ever Smoking	1.27	0.58	2.78	0.554	–	–	–	–
Stage								
Local		Reference				Reference		
Regional	1.62	0.78	3.34	0.196	1.99	0.88	4.49	0.096
Distant	5.05	2.68	9.53	< 0.001***	5.33	1.93	14.73	0.001**
KRAS Mutation								
G12C	0.73	0.44	1.23	0.239	1.10	0.62	1.97	0.741
G12D	1.63	0.90	2.95	0.107	2.16	1.04	4.48	0.039*
Co-mutation								
TP53	0.82	0.49	1.35	0.430	0.76	0.44	1.34	0.346
STK11	2.18	1.14	4.19	0.019*	2.60	1.14	5.93	0.023*
KEAP1	1.59	0.69	3.70	0.279	0.54	0.19	1.51	0.241
PIK3CA	1.56	0.57	4.31	0.387	0.59	0.18	1.89	0.372
Therapies								
Localized	0.26	0.16	0.42	< 0.001***	0.55	0.26	1.15	0.113
Systemic	1.58	0.95	2.62	0.077	0.70	0.35	1.42	0.326

† Variables included in the multivariable regression model are selected based on $P < 0.5$ on univariable analysis. Abbreviations: *HR* hazard ratio; *CI* confidence interval. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

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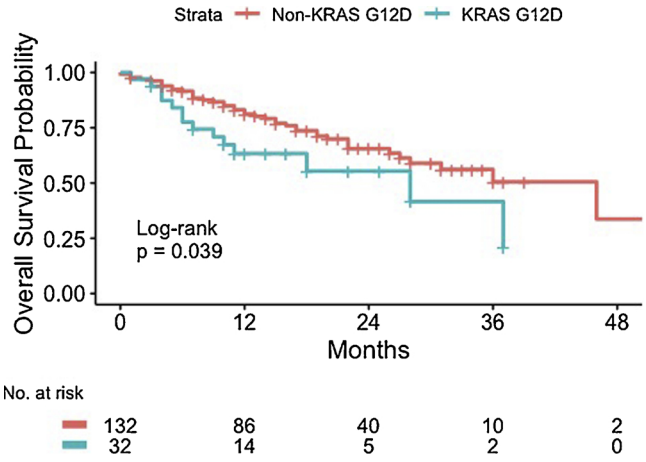

Fig. 1. Kaplan-Meier survival analysis of patients with tumors lacking *STK11* co-mutations stratified by *KRAS* G12D mutation status. Abbreviation: *No.* number.

regression model. We conducted this analysis which removed sex and smoking status from the model (Table 1). We found that *KRAS* G12D mutations remained significantly associated with poor OS (hazard ratio [HR] 2.16, 95% confidence interval [CI] 1.04–4.48; $P = 0.039$) as well as every one-year increase in age (HR 1.04, 95% CI 1.01–1.07; $P = 0.024$), distant disease stage (HR 5.33, 95% CI 1.93–14.73; $P = 0.001$), and the presence of *STK11* co-mutations (HR 2.60, 95% CI 1.14–5.93; $P = 0.023$).

Lastly, we discuss in our manuscript that the role of *KRAS* mutation subtype as a prognostic factor for NSCLC remains unclear until today. As Wen et al. have noted, *KRAS* G12D mutations did not have a statistically significant association with poor OS on univariable Cox regression and Kaplan-Meier analyses, though they had a notable trend towards statistical significance on both analyses. On multivariable analysis, after adjusting for other prognostic factors such as age, stage, and *STK11* co-mutations, we found that the effect size of the relationship between *KRAS* G12D mutations and poor OS increased and became statistically significant. We inferred that there may be confounders at play that bias the relationship observed on univariable analysis which we adjusted for. For example, in our dataset, the 32 patients with *KRAS* G12D mutations were less likely to have a positive smoking history compared to the 154 patients without *KRAS* G12D mutations (68.8% versus 89.0%; $P = 0.007$). Perhaps more importantly, none of the patients who had *KRAS* G12D mutations had concurrent *STK11* co-mutations, which were identified only among non-*KRAS* G12D patients (0.0% versus 14.3%; $P = 0.048$). When we stratify our cohort based on *STK11* co-mutations, we find on Kaplan-Meier analysis that among the 164 patients who lack *STK11* co-mutations, those with *KRAS* G12D mutations have a significantly shorter OS compared to non-*KRAS* G12D patients (median OS: 28 months versus 46 months; log-rank $P = 0.039$; Fig. 1). This is in line with our finding on multivariable Cox regression analysis, and together these data implicate *KRAS* G12D mutations as a poor prognostic factor in *KRAS*-mutant NSCLC and *STK11* co-mutations as a potential confounder for the relationship between *KRAS* G12D mutations and OS.

Disclosures

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Jacqueline V. Aredo, Sukhmani K. Padda
Stanford Cancer Institute, Stanford University School of Medicine, 875 Blake Wilbur Drive, Stanford, CA, 94305, USA

Christian A. Kunder
Department of Pathology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA, 94305, USA

Summer S. Han, Joel W. Neal, Joseph B. Shrager, Heather A. Wakelee*
Stanford Cancer Institute, Stanford University School of Medicine, 875 Blake Wilbur Drive, Stanford, CA, 94305, USA
E-mail address: hwakelee@stanford.edu (H.A. Wakelee).

* Corresponding author.