Clinical Cancer Research

Effects of Co-occurring Genomic Alterations on Outcomes in Patients with *KRAS*-Mutant Non–Small Cell Lung Cancer

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Abstract

Purpose: *KRAS* mutations occur in approximately 25% of patients with non–small cell lung cancer (NSCLC). Despite the uniform presence of *KRAS* mutations, patients with *KRAS*-mutant NSCLC can have a heterogeneous clinical course. As the pattern of co-occurring mutations may describe different biological subsets of patients with *KRAS*-mutant lung adenocarcinoma, we explored the effects of co-occurring mutations on patient outcomes and response to therapy.

Experimental Design: We identified patients with advanced *KRAS*-mutant NSCLC and evaluated the most common co-occurring genomic alterations. Multivariate analyses were performed incorporating the most frequent co-mutations and clinical characteristics to evaluate association with overall survival as well as response to platinum–pemetrexed chemotherapy and immune checkpoint inhibitors.

Results: Among 330 patients with advanced *KRAS*-mutant lung cancers, the most frequent co-mutations were found in *TP53* (42%), *STK11* (29%), and *KEAP1/NFE2L2* (27%). In a multivariate analysis, there was a significantly shorter survival in patients with co-mutations in *KEAP1/NFE2L2* [HR, 1.96; 95% confidence interval (CI), 1.33–2.92; $P \leq 0.001$]. *STK11* (HR, 1.3; $P = 0.22$) and *TP53* (HR 1.11, $P = 0.58$) co-mutation statuses were not associated with survival. Co-mutation in *KEAP1/NFE2L2* was also associated with shorter duration of initial chemotherapy (HR, 1.64; 95% CI, 1.04–2.59; $P = 0.03$) and shorter overall survival from initiation of immune therapy (HR, 3.54; 95% CI, 1.55–8.11; $P = 0.003$).

Conclusions: Among people with *KRAS*-mutant advanced NSCLC, *TP53*, *STK11*, and *KEAP1/NFE2L2* are the most commonly co-occurring somatic genomic alterations. Co-mutation of *KRAS* and *KEAP1/ NFE2L2* is an independent prognostic factor, predicting shorter survival, duration of response to initial platinum-based chemotherapy, and survival from the start of immune therapy. *Clin Cancer Res; 24(2); 334–40. ©2017 AACR.*

Introduction

Somatic *KRAS* mutations are identified in 25% of patients with non–small cell lung cancers (NSCLCs). Patients with these mutations have shorter survival compared with patients with *EGFR*-mutant NSCLC or *KRAS* wild-type tumors (1). As there is significant clinical heterogeneity in patients with *KRAS*-mutant NSCLC, defining clinically relevant subsets of KRAS-mutant NSCLC is important. In small cohorts, investigators have found specific *KRAS* point mutations (such as G12V and C12R) were associated with poorer outcomes (2). However, in a large retrospective analysis of nearly 700 patients with metastatic disease, no apparent differences in outcome based on *KRAS* mutation subtype were identified (3).

In patients with lung cancer, the predictive utility of *KRAS* mutations as a marker of response to both targeted therapy and standard cytotoxic chemotherapy has been of particular interest. The presence of a *KRAS* mutation suggests lack of response to *EGFR* tyrosine kinase inhibitors (4, 5), likely because *EGFR* and *KRAS* mutations only rarely occur together. Patients with *KRAS* codon 13 mutations appear to have poorer outcomes with adjuvant cisplatin-based chemotherapy following resection of early-stage disease (6), but in the metastatic setting, *KRAS* mutations do not appear to independently predict response or resistance to chemotherapy treatments (7, 8).

Although the identification of subsets of NSCLC with oncogenic drivers has transformed the treatment of this disease, these advances have thus far largely been limited to patients with mutations in *EGFR* (9) or oncogenic fusions involving *ALK* (10), *RET* (11), or *ROS1* (12) kinases. There has been progress in the development of compounds that selectively target KRAS G12C, but efforts to specifically target mutant KRAS in the clinic

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Although *KRAS* mutations identify the largest group of patients with oncogene-driven non–small cell lung cancer (NSCLC), patients with *KRAS*-mutant NSCLC have a heterogenous clinical course. We used the results of next-generation sequencing of tumors from patients with *KRAS*-mutant NSCLC to describe the pattern of co-occurring mutations and explore clinical outcomes. In a multivariable analysis, we identified a molecular subtype of *KRAS*-mutant NSCLC, with co-mutations in *KEAP1/NFE2L2* in which patients had a significantly shorter overall survival than other patients with *KRAS*-mutant NSCLC. Patients with concurrent mutations in *KRAS* and *KEAP1/NFE2L2* had a shorter duration of therapy with platinum-based chemotherapy than other patients with *KRAS*-mutant lung cancer. These clinical findings align with prior preclinical work showing that mutations in *KEAP1* or *NFE2L2* result in activation of the Nrf2 pathway inducing constitutive expression of cytoprotective enzymes, thus conferring resistance to platinum agents. Mutations in *KEAP1/NFE2L2* were also associated with decreased overall survival from the start of immune checkpoint inhibitors, independent of tumor mutational burden. As our results indicate that patients with *KEAP1* or *NFE2L2* mutations occurring in the context of *KRAS* mutations have a worse clinical course than other patients with *KRAS*-mutant NSCLC, we recommend that this information be captured as part of clinical trials evaluating therapy for these patients.

have thus far been largely unsuccessful. Clinical testing of agents targeting downstream pathways, such as MEK and PI3K-AKT, in patients with *KRAS*-mutant tumors has yielded relatively low response rates (13, 14). This may be due to the fact that there is a significant molecular diversity in *KRAS*-mutant tumors compared with other known driver events, and it is these underlying mechanisms that drive divergent biologic and clinical behavior (15). However, even KRAS G12C-mutant cell lines exhibit a range of responses to pharmacologic inhibition of KRAS G12C, a finding that further highlights the molecular diversity of *KRAS*-mutant lung cancers (16).

We hypothesized that broad next-generation sequencing (NGS) may allow an in-depth description of clinically heterogenous group of patients and offer prognostic and predictive markers based on the presence of co-occurring mutations in patients with *KRAS*-mutant NSCLC. To evaluate this hypothesis, we investigated the effect of commonly co-occurring genomic alterations, clinical characteristics on survival, and treatment response in patients with advanced *KRAS*-mutant NSCLC.

Materials and Methods

Patients

Consecutive patients with metastatic or recurrent lung cancers found to have a *KRAS* mutation by NGS were included in the analysis. A medical record search was used to identify individuals seen at Memorial Sloan Kettering with a primary tumor diagnosis of lung cancer by ICD-O code who had also undergone hybridization capture-based NGS testing from January of 2014 to October 2016. The list was then manually reviewed to exclude patients who did not have metastatic or recurrent disease, or a tumor diagnosis of primary lung cancer. Data collection was approved by the MSKCC Institutional Review Board/Privacy Board. Clinical characteristics and treatment course were collected for all patients. Overall survival (OS) was defined as the time from date of diagnosis of advanced disease (stage IV or recurrent cancer) until date of death or last follow-up.

Genotype analysis

Tumor and germline DNA were processed to generate barcoded libraries and subjected to exon capture using custom-designed probes. Matched normal DNA was analyzed simultaneously to identify and filter out germline SNPs. Genomic analysis was performed using the MSK-IMPACT assay (17), a clinical test approved by the New York State Department of Health designed to detect mutations, copy-number alterations, and select fusions involving 341 (version 1), 410 (version 2), or 468 (version 3) cancer-associated genes. Genomic analysis was performed using assay version 1 (341 genes) for 66 samples, version 2 (410 genes) for 250 samples, and version 3 (468 genes) for 14 samples. Normalized mutation burden was calculated as the absolute mutation burden (number of nonsynonymous mutations/sample) divided by the genomic coverage for that sample (0.98 Mb for version 1, 1.06 Mb for version 2, and 1.22 Mb for version 3).

Statistical analysis

Survival following diagnosis of stage IV lung cancer and treatment duration was estimated using Kaplan–Meier methodology. Patients were followed until death; patients alive at the end of the study were censored at the time of last available follow-up. Univariate group comparisons were performed using log-rank tests. A multivariable Cox proportional hazards model was used to assess the independent effect of co-occurring mutations (*STK11*, *KEAP1/NFE2L2*, and *TP53*), adjusting for age, gender, performance status, and smoking history. Tumor mutational burden normalized by the size of the coding region (MB) captured by sequencing was evaluated as a continuous variable.

Results

Clinical characteristics

We identified 550 patients with lung cancer and *KRAS* mutations on NGS testing between January of 2014 and October 2016. Of that cohort of patients, 330 had metastatic or recurrent lung cancer. Seventy-two percent of patients had metastatic disease at the time of initial diagnosis ($n = 240$) while 28% ($n = 90$) had recurrent disease. The predominant histology was adenocarcinoma ($n = 298$, 90%). Patient demographics and histology are noted in Table 1. The most common *KRAS* mutation observed was G12C (44%; Fig. 1A).

Co-occurring mutations

Along with *KRAS*, 377 different genes were mutated in this group of patients. The median number of co-occurring mutations per tumor was eight (range, 0–58). The most frequent mutations were found in *TP53* (41%), *STK11* (28%), *KEAP1* (24%), *RBM10* (16%), and *PTPRD* (15%; Table 2). Given that genomic alteration in *NFE2L2* elicits similar effects as alterations in *KEAP1* in their effects on the Nrf2 pathway, patients with genomic alterations in either gene were grouped (18). An additional 3% of patients

Table 1. Baseline patient characteristics

Characteristics	*N* = 330 (%)
Age at diagnosis (stage IV)	
Median (range)	61 (45–80)
Sex	
Women	195 (59)
Men	135 (41)
KPS (%)	
≥80	241 (73)
<80	72 (22)
Not recorded	17 (5)
Smoking history category	
Current	37 (11)
Former	271 (82)
Never	22 (7)
Smoking history, pack-years	
Median pack-year	30
Range	0–135
Unknown	2
Pathology	
Adenocarcinoma	294 (89)
Squamous	11 (3)
Adenosquamous	4 (1)
Other	21 (6)

Table 2. Most frequent co-occurring mutations among patients with *KRAS*-mutant NSCLC

Mutation	Frequency (*n*)
TP53	42% (138)
STK11	29% (95)
KEAP1/NFE2L2	27% (93)
RBM10	16% (52)
PTPRD	15% (50)
SMARCA4	14% (46)
ATM	13% (42)
FAT1	10% (32)
ARID1A	9% (31)
PTPRT	9% (31)

($n = 9$) were found to have mutations in *NFE2L2*, and therefore, 27% of patients were grouped as having either *KEAP1* or *NFE2L2* mutations concurrent with *KRAS*. The three most frequently co-occurring genomic alterations (*TP53*, *STK11*, and *KEAP1*) were selected for further statistical analysis. The distributions of the three most frequent co-occurring mutations (*TP53*, *STK11*, and *KEAP1/NFE2L2*) are depicted in a proportional Venn diagram in Fig. 1B.

Co-occurring mutations and survival

The median follow-up among the 177 patients alive at the data cutoff of January 2017 was 12 months (range, 1–114). The median OS (mOS) for all patients with *KRAS*-mutant advanced lung cancers in this cohort was 17 months [95% confidence interval (CI), 14–25]. Patients with and without concurrent mutation in *TP53* had a similar OS (HR, 0.9; 95% CI, 0.6–1.2; $P = 0.5$). Patients with a concurrent mutation in *STK11* (*KRAS/STK11*) were found to have a shorter OS (HR, 1.7; 95% CI, 1.1–2.4; $P = 0.002$; Fig. 2A). In addition, patients with concurrent mutation in *KEAP1* or *NFE2L2* (*KRAS/KEAP1/NFE2L2*) were also found to have a shorter OS (HR, 2.1; 95% CI, 1.4–3.1; $P < 0.0001$; Fig. 2B). A multivariable Cox proportional hazards model was used to assess the independent effect of the most frequently identified co-occurring mutations (*TP53*, *STK11*, *KEAP1/NFE2L2*), adjusting for age, gender, performance status, and smoking history. After adjustment for these clinical variables, only *KEAP1/NFE2L2* was independently associated with shorter OS (HR, 1.96; 95% CI, 1.33–2.92; $P < 0.001$; Table 3).

Initial chemotherapy and co-mutational status

To evaluate the effects of co-mutations on outcomes after chemotherapy, we obtained treatment history of patients who received initial chemotherapy treatment with a platinum agent, pemetrexed, ± bevacizumab following diagnosis of recurrent or metastatic NSCLC. In a univariate analysis, the presence of a co-occurring mutation in *KEAP1/NFE2L2* was associated with a shorter duration of therapy (HR, 1.6; 95% CI, 1.1–2.4; $P = 0.008$; Supplementary Fig. S1). The presence of either a *STK11* or *TP53* mutation was not associated with a difference in duration of platinum-based therapy. A multivariable Cox proportional

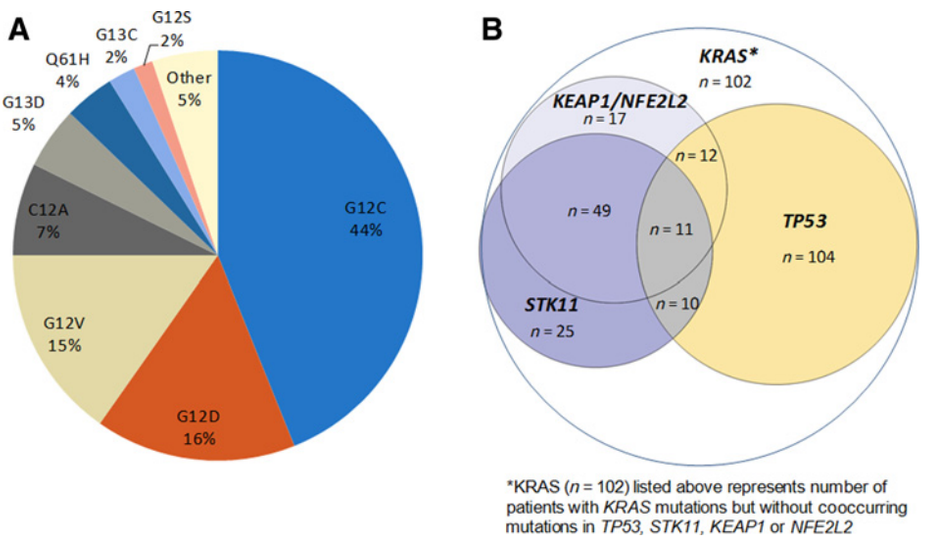

Figure 1.
KRAS genotype analysis. **A,** Type of *KRAS* codons: *KRAS* point mutations in dataset. Mutations occurring in less than 1% of patients grouped into "other" category. **B,** Distribution of three most frequently co-occurring mutations as depicted in a proportional Venn diagram.

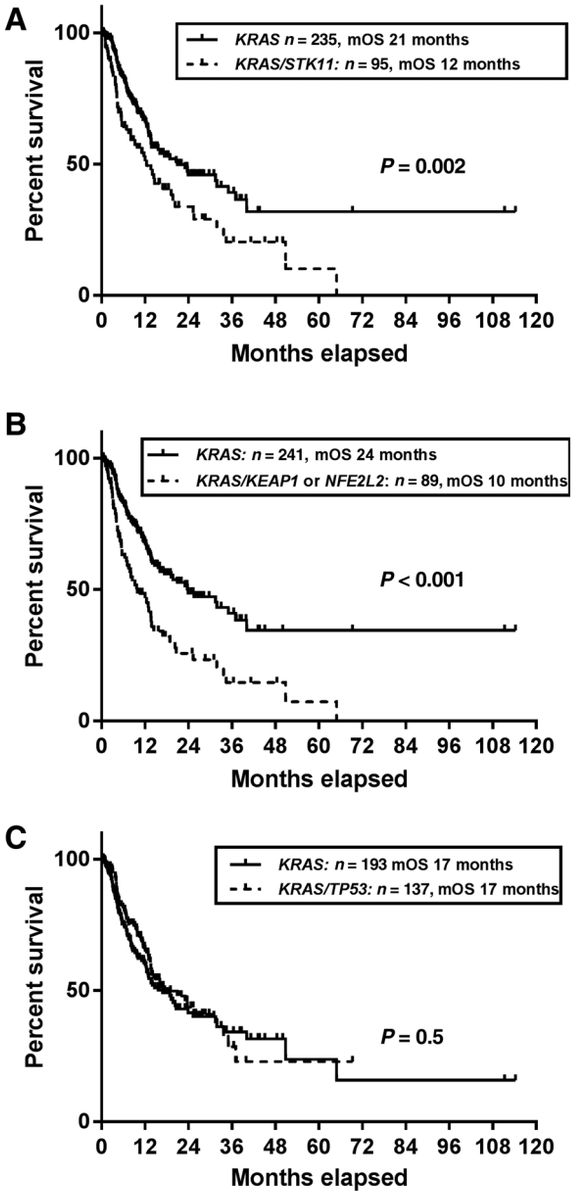

Figure 2.
Associations of co-occurring genomic alterations and *KRAS* with OS from time stage IV diagnosis **A,** *STK11*. **B,** *KEAP1* or *NFE2L2*. **C,** TP53.

hazards model (adjusting for *STK11*, *TP53*, *KEAP1*/*NFE2L2* as well as clinical characteristics of age, gender, performance status, and smoking history, and bevacizumab use), found *KEAP1*/*NFE2L2* was associated with shorter treatment duration (HR, 1.64; 95% CI, 1.04–2.59; $P = 0.03$; Supplementary Table S1).

Immunotherapy and co-mutation

To evaluate the effects of co-mutations on outcomes after immunotherapy, we obtained treatment history of 86 patients that underwent therapy with an immune checkpoint inhibitor as monotherapy (nivolumab or pembrolizumab). In a univariate analysis, neither the presence of *TP53*, *SKT11*, nor *KEAP1*/*NFE2L2* was associated with a difference in duration of immune therapy (Supplementary Fig. S2). These results were confirmed in a multivariate analysis adjusting for these three co-mutations as well as, age, gender, performance status, and line of therapy. Patients with a co-occurring mutation in *KEAP1* or *NFE2L2* were found to have a shorter OS from the start of immune checkpoint inhibitor in both a univariate (Fig. 3) and multivariate analysis (HR, 3.54; 95% CI, 1.55–8.11; $P = 0.003$; Supplementary Table S3) adjusting for co-mutations as well as tumor mutation burden, age, gender, performance status, and line of therapy. The presence of a co-occurring mutation in neither *STK11* nor *TP53* was associated with a significant difference in mOS from the start of therapy. Tumor mutation burden was associated with difference in OS from the time of initiation of immunotherapy as patients with higher mutation burdens were found to have longer survival from the start of treatment (HR, 0.9; 95% CI, 0.83–0.99; $P = 0.025$; Supplementary Table S3).

Table 3. Multivariate analysis of OS in patients with *KRAS*-mutant NSCLC

Variable	HR (95% CI)	*P*
TP53 (+ vs. −)	1.11 (0.77–1.58)	0.581
STK11 (+ vs. −)	1.30 (0.86–1.97)	0.216
KEAP1/*NFE2L2* (+/−)	1.96 (1.33–2.92)	<0.001
Gender (male vs. female)	1.20 (0.86–1.68)	0.284
Age at diagnosis	1.03 (1.01–1.05)	0.003
Smoking (former/current vs. never)	1.43 (0.86–1.68)	0.402
KPS at diagnosis (KPS 80–100 vs. <80)	0.88 (0.60–1.29)	0.514

Discussion

We report the landscape of co-occurring genomic alterations in a series of 330 patients with advanced *KRAS*-mutant lung cancer, highlighting the most common events and identifying mutations in the *KEAP1*/*NFE2L2* pathway as a significant, independent negative prognostic factor for patients with *KRAS*-mutant NSCLC. We go on to demonstrate that this association with poor OS is also associated with shorter duration of therapy with platinum-doublet chemotherapy and OS after immunotherapy. These data suggest that the observed clinical heterogeneity in patients with KRAS-mutant NSCLC is likely due in part to differences in co-occurring molecular events.

Concurrent mutations are common in patients with *KRAS*-mutant NSCLC, with the most common events in *STK11* and *TP53*. Although *TP53* mutations are common, our analysis concurs with that of others, reporting that concurrent *TP53* mutation in *KRAS*-mutant NSCLC is not prognostic (19). Multiple prior analyses have reported *STK11* mutations are more frequent in *KRAS*-mutant NSCLC as opposed to *KRAS* wild-type tumors (20). Preclinical data have suggested that loss of *STK11* leads to a more aggressive tumor phenotype (21). However, there has been conflicting evidence whether *STK11* mutations have prognostic or predictive implications (15, 22). Our initial univariate analysis also demonstrated that concurrent *STK11* mutations were associated with shorter OS in patients with advanced *KRAS*-mutant NSCLC. However, when a multivariable analysis was conducted adjusting for concurrent mutations in *KEAP1*/*NFE2L2*, *TP53*, and other clinical variables, concurrent mutation in *STK11* was no longer associated with difference in OS.

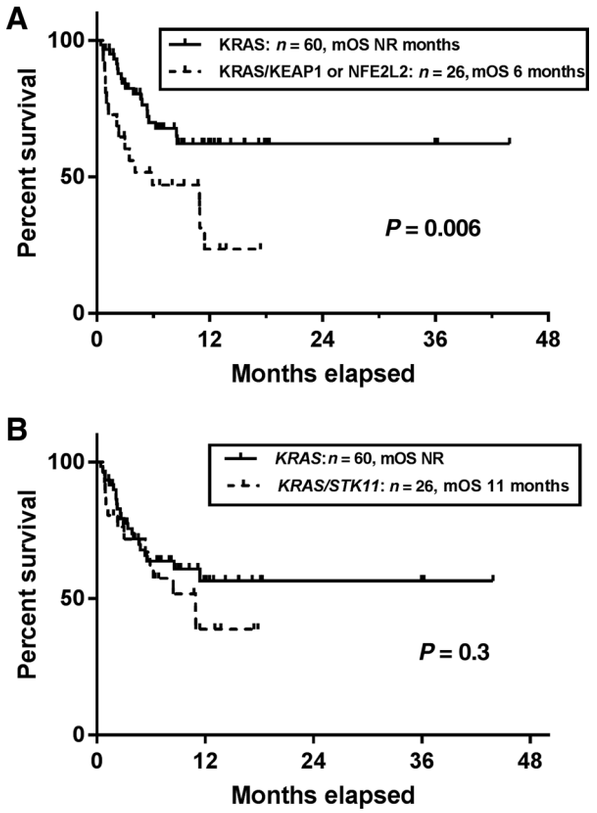

Figure 3.
OS (from time of start of immune checkpoint inhibitor therapy) for treatment of stage IV disease based on presence of *KEAP1*/*NFE2L2* co-mutation (**A**) and *STK11* co-mutation (**B**).

The differences seen in the univariate analysis compared with multivariable analysis is likely due to significant overlap between patients with *STK11* and *KEAP1* concurrent mutations (also observed by others; ref. 15). Our analysis suggests, however, that it is not the concurrent *STK11* mutation that is associated with adverse outcomes in these patients, but rather the presence of concurrent *KEAP1* or *NFE2L2* mutation. This observation is limited as we evaluated only somatic mutations and not protein expression, and therefore, it is possible that we did not capture tumors that have suppressed *STK11* mRNA expression through a mechanism other than *STK11* mutation, which were observed in the subsets described by Skoulidis and colleagues (15). These results highlight the importance of multivariable analyses, incorporating not just clinical features but also genomic features, to more accurately describe prognostic features in the genomically complicated landscape of *KRAS*-mutant NSCLC.

Mutations in the *KEAP1*/*NFE2L2* pathway identify 27% of patients with KRAS-mutant lung cancer as having an independent negative prognostic factor. *KEAP1* and *NFE2L2* mutations have been best described in squamous cell lung cancer. Activation of the NRF2 pathway (through activation of *NFE2L2* or inactivation of KEAP1) was found to be altered in 34% of squamous cell cancers of the lung when evaluated by TCGA investigators (23). Solis and colleagues also showed increased nuclear expression of Nrf2 and decreased or absent expression of KEAP1 in 38% and 46% of patients with squamous cell carcinoma, respectively, and less commonly in adenocarcinoma (18%; ref. 24). Although low cytoplasmic KEAP1 expression was associated with worse OS in squamous cell carcinomas, no association was found between KEAP1 expression and outcomes in patients with adenocarcinoma. That analysis, similar to the TCGA analysis, is heavily weighted toward patients with early-stage resected disease as opposed to advanced stage disease, which is the focus of our report.

The poor prognosis of patients with concurrent *KEAP1* or *NFE2L2* mutations may be due in part to the observation that activation of the Nrf2 pathway may be associated with resistance to chemotherapy. Mutations in KEAP1 affect the repressive activity of KEAP1, stimulating nuclear accumulation of Nrf2, and induce constitutive expression of cytoprotective enzymes (25). Cell lines expressing lower levels of KEAP1 or *KEAP1*-mutant cells demonstrated greater resistance to cisplatin than cell lines with normal *KEAP1* (26). Concordant with this, we observed that patients with a concurrent *KEAP1* or *NFE2L2* mutation who were treated with a platinum/pemetrexed combination had more rapid disease progression (as suggested by shorter duration of therapy) compared with *KEAP1* or *NFE2L2* wild-type patients. Our analysis was limited to patients with *KRAS*-mutant NSCLC, suggesting a cooperativity between these mutations in *KEAP1* or *NFE2L2* and *KRAS*. Moreover, the frequency of KEAP1/NFE2L2 in KRAS-mutant NSCLC is much higher than that seen in other lung cancer with other oncogenic drivers.

Treatment with immune checkpoint inhibitors has been a significant advance in the treatment of NSCLC (27, 28), particularly for patients without targetable oncogenic drivers. Despite these advances, single-agent response rates in unselected populations remain relatively low (10%–30% in reported clinical trials). Various biomarkers have been reported that may potentially predict response to immune checkpoint inhibitors in solid tumors including PD-L1 expression (29) and tumor mutation burden or neoantigen load (30, 31). We attempted to explore the impact of concurrent genomic alterations in patients who received single-agent immune checkpoint inhibitors during the treatment of their disease. Our analysis of clinical benefit with immunotherapy was limited in size, as only a subset of the patients in our larger analysis received this therapy. Keeping these limitations in mind, our analysis suggests that patients with *KRAS*-mutant advanced NSCLC and a concurrent mutation in *KEAP1* or *NFE2L2* have significantly shorter OS from initiation of immune checkpoint therapy. No statistically significant differences in OS from the start of therapy were observed on the basis of concurrent *STK11* or *TP53* mutations. Formal response assessment was available on a subset of these patients (data not shown), and no significant difference in response was observed on the basis of concurrent mutation in either *KEAP1*/*NFE2L2*, *STK11*, or *TP53*.

It is possible that mutations in *KEAP1*/*NFE2L2* are associated with other features that have been associated with outcomes after immunotherapy, such as PD-L1 expression status, which was not available in this series of patients. PD-L1 expression has been reported in *KRAS*-mutant NSCLC and was more frequently observed in smokers (32); however, relationship to concurrent mutation is thus far unknown. Skouldolis and colleagues described that the cluster of *KRAS*-mutant NSCLC with low *STK11* expression demonstrated a lack of immune system engagement; however, concurrent mutations in *KEAP1* were also common in this cluster (15). In a follow-up analysis, they reported that patients with concurrent mutations in *STK11* had lower objective

response rates to immunotherapy agents (33), a finding we did not observe in our larger series of patients.

Higher nonsynonymous mutation burden in tumors has been associated with improved objective response, durable clinical benefit, and progression-free survival in patients treated with the PD-1 antibody pembrolizumab (30). More recently, normalized mutation count calculated from results of routine NGS was reported to be predictive of response to nivolumab in NSCLC (34, 35). Our multivariable analysis did incorporate normalized tumor mutation count and demonstrated that tumor mutation burden was associated with longer OS from initiation of immune checkpoint inhibitor. However, the presence of concurrent mutation in *KEAP1* or *NFE2L2* was associated with significantly shorter mOS independent of tumor mutation burden.

Although the findings we have described are consistent with other reports analyzing the molecular characteristics of patients with *KRAS*-mutant lung cancer, there are some limitations to our analysis. All patients were identified on the basis of molecular testing at a single institution. Although molecular analysis is offered routinely for all patients, some patients may have had inadequate biopsy specimens, precluding NGS analysis. Patients received diverse treatments, and therefore, the analyses of initial platinum/pemetrexed chemotherapy and immunotherapy involve a much smaller subset of patients. Duration of therapy was used as a surrogate marker for progression-free survival when describing treatment history, which has potential pitfalls as patients may discontinue therapy for other reasons (e.g., toxicity) as opposed to progression.

Although it has been evident that there is significant clinical heterogeneity in patients with *KRAS*-mutant NSCLC, it is now becoming clear that this clinical heterogeneity is likely due to biologic heterogeneity. Skouldolis and colleagues have previously reported molecular stratification of *KRAS*-mutant lung adenocarcinomas using RNA sequencing expression data from a subset of lung adenocarcinomas in the TCGA. These results were further validated in other small cohorts; however, this dataset focused on primarily early-stage disease with only a subset of patients analyzed having stage IV disease (and all of these from the BATTLE-2 clinical trial and therefore platinum refractory; ref. 15).

Our analysis shows that routine NGS can not only provide information regarding potential actionable mutations, but also suggest prognostic and predictive features of a patient's cancer by exploring the presence of various co-occurring mutations. Considering any given mutation in the context of other mutations and using multivariate analyses is crucial in evaluating the significance of somatic genetic events. Prospective identification of patients with concurrent *KEAP1* or *NFE2L2* mutations in patients with *KRAS*-mutant NSCLC should be considered as a prognostic factor in clinical trials evaluating therapies for these patients. Our results indicate that patients with concurrent *KRAS* and *KEAP1*/*NFE2L2* have a clinically distinct behavior and may require stratification in trials.

Disclosure of Potential Conflicts of Interest

H. Yu is a consultant/advisory board member for AstraZeneca and Lilly. M.G. Kris is a consultant/advisory board member for AstraZeneca. C.M. Rudin is a consultant/advisory board member for AstraZeneca, Bristol-Myers Squibb, Celgene, G1 Therapeutics, Harpoon, and Seattle Genetics. No potential conflicts of interest were disclosed by the other authors.

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