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

Kathryn C. Arbour1, Emmett Jordan1, Hyunjae Ryan Kim2, Jordan Dienstag1, Helena A. Yu1,2, Francisco Sanchez-Vega4, Piro Lito1,4, Michael Berger4,5, David B. Solit1,4,5, Matthew Hellmann1,3, Mark G. Kris1,3, Charles M. Rudin1,3, Ai Ni6, Maria Arcila2, Marc Ladanyi4,5, and Gregory J. Riely1,3

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 = 0.001], STK11 (HR, 1.3; P = 0.22) and TP53 (HR 1.11, P = 0.58) co-mutation status 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.

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 ROSI (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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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.

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 either gene were grouped (18). An additional 3% of patients

Genotype analysis

Tumor and germline DNA were processed to generate bar-coded 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

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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).

Concluding remarks

This study demonstrated that the addition of NGS testing at diagnosis and follow-up identifies a molecularly diverse population of KRAS-mutant NSCLC patients with unique clinical characteristics compared to those with wild-type KRAS. This highlights the importance of including broad NGS testing in clinical practice to better understand the molecular landscape of NSCLC, which may allow for more tailored treatment strategies.
(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

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**Table 1.** Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 330 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (stage IV)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>61 (45–80)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>195 (59)</td>
</tr>
<tr>
<td>Men</td>
<td>135 (41)</td>
</tr>
<tr>
<td>KPS (%)</td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>241 (73)</td>
</tr>
<tr>
<td>&lt;80</td>
<td>72 (22)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Smoking history category</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>37 (11)</td>
</tr>
<tr>
<td>Former</td>
<td>271 (82)</td>
</tr>
<tr>
<td>Never</td>
<td>22 (7)</td>
</tr>
<tr>
<td>Smoking history, pack-years</td>
<td></td>
</tr>
<tr>
<td>Median pack-year</td>
<td>30</td>
</tr>
<tr>
<td>Range</td>
<td>0–135</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>204 (61)</td>
</tr>
<tr>
<td>Squamous</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>21 (6)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>42% (138)</td>
</tr>
<tr>
<td>STK11</td>
<td>29% (95)</td>
</tr>
<tr>
<td>KEAP1/NFE2L2</td>
<td>27% (93)</td>
</tr>
<tr>
<td>RBM10</td>
<td>16% (52)</td>
</tr>
<tr>
<td>PTPRD</td>
<td>15% (50)</td>
</tr>
<tr>
<td>SMARCA4</td>
<td>14% (46)</td>
</tr>
<tr>
<td>ATM</td>
<td>13% (42)</td>
</tr>
<tr>
<td>FAT1</td>
<td>10% (32)</td>
</tr>
<tr>
<td>ARID1A</td>
<td>9% (31)</td>
</tr>
<tr>
<td>PTPRT</td>
<td>9% (31)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53 (+ vs. –)</td>
<td>1.10 (0.77-1.58)</td>
<td>0.581</td>
</tr>
<tr>
<td>STK11 (+ vs. –)</td>
<td>1.30 (0.86-1.97)</td>
<td>0.216</td>
</tr>
<tr>
<td>KEAP1/NFE2L2 (+/–)</td>
<td>1.96 (1.35-2.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>1.20 (0.86-1.68)</td>
<td>0.284</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.02 (1.01-1.05)</td>
<td>0.003</td>
</tr>
<tr>
<td>Smoking (former/current vs. never)</td>
<td>1.43 (0.86-1.68)</td>
<td>0.402</td>
</tr>
<tr>
<td>KPS at diagnosis (KPS 80–100 vs. &lt;80)</td>
<td>0.88 (0.60-1.29)</td>
<td>0.514</td>
</tr>
</tbody>
</table>

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 mutations in NEF2L2 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.
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. Skoulidis 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

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).
response 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. Skoulodros 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.

Authors’ Contributions


Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.C. Arbour, E. Jordan, J. Dienstag, H.A. Yu, D.B. Solit, M. Hellmann, M.G. Kris, C.M. Rudin, M. Arcila, M. Ladanyi, G.J. Riely


Writing, review, and/or revision of the manuscript: K.C. Arbour, H.A. Yu, P. Lito, D.B. Solit, M. Hellmann, M.G. Kris, C.M. Rudin, A. Ni, M. Arcila, M. Ladanyi, G.J. Riely

Study supervision: G.J. Riely

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