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Role of immunotherapy and co-mutations on KRAS-mutant non-small cell lung cancer survival

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Background: *KRAS* mutations reported in non-small cell lung cancer (NSCLC) represent a significant percentage of patients diagnosed with NSCLC. However, there still remains no therapeutic option designed to target KRAS. In an era with immunotherapy as a dominant treatment option in metastatic NSCLC, the role of immunotherapy in *KRAS*-mutated patients is not clear.

Methods: Eligible patients diagnosed with NSCLC and found to have a *KRAS* mutation were identified in an institutional lung cancer database. Demographic, clinical, and molecular data was collected and analyzed.

Results: A total of 60 patients were identified for this retrospective analysis. Majority of patients were Caucasian (73%), diagnosed with stage IV (70%) adenocarcinoma (87%), and had a *KRAS* codon 12 mutation (78%). Twenty percent of patients were treated with immunotherapy. Median overall survival was 28 months in the cohort and patients who received immunotherapy were found to have better survival versus those who did not (33 *vs.* 22 months, P=0.31). Furthermore, there was an association between high survival and patients who received immunotherapy (P=0.007).

Conclusions: Patients with *KRAS* mutations have a unique co-mutation phenotype that requires further investigation. Immunotherapy seems to be an effective choice of treatment for KRAS positive patients in any treatment-line setting and yields better outcomes than conventional chemotherapy. The relationship between immunotherapy and *KRAS* mutations requires further studies to confirm survival advantage.

Keywords: Lung cancer; KRAS; immunotherapy; molecular testing; co-mutations

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Introduction

Lung cancer remains the leading cause of cancer death in the world with 1.69 million deaths in 2015 (1). It is estimated that there will be 228,150 new cases and 142,670 deaths in 2019 (2). Lung cancers are divided into two major subtypes, small cell and non-small cell. Majority of lung cancers are non-small cell lung cancer (NSCLC) accounting for around 85% of all cases with small-cell making up most of the remaining at 15% (3). NSCLC is composed of many histologic subtypes with 40% of lung cancers are adenocarcinoma, in addition squamous cell (25%) and large cell (15%) being the most common. A few other subtypes including adenosquamous and sarcomatoid carcinoma make up the remaining. Direct and indirect exposure to tobacco smoke is the predominant risk factor. Other risk factors include residential radon, indoor air pollution, asbestos, and paint dust (4). There is also increasing interest in genetic

susceptibility as one-fourth of all lung cancer patients are never smokers and the associated possibility of these patients harboring treatable oncogenic alterations (5).

The molecular era of oncology has changed the way lung cancer is treated, especially for NSCLC. NSCLC is a heterogeneous disease with variable molecular mutations. Vi-Ki-ras2 Kirsten rat sarcoma viral oncogene (*KRAS*) is one of the most common oncogenic drivers, especially in lung cancer, and is found in around 25–30% adenocarcinomas. The other molecular abnormalities related to RAS pathway are *EGFR* (10–23%), *BRAF* (2%), *MET* (2%), *HER2* (1%) and *NRAS* (0.2%). As there are no targeted therapies for KRAS patients, the majority of the patients are typically treated with cytotoxic chemotherapy in combination with immunotherapy or immunotherapy alone. However, a retrospective study of 282 patients with advanced NSCLC treated with ICI compared the efficacy of ICI in patients with *KRAS* mutations versus without *KRAS* mutations (6). Jeanson *et al.* showed no significant differences in treatment outcomes for patients with *KRAS* mutations compared to those without *KRAS* mutations with similar overall response rate (ORR: 18.7% *vs.* 14.4%, P=0.348), progression-free survival (PFS: 3.09 *vs.* 2.66 months; P=0.584) and overall survival (OS: 14.29 *vs.* 11.14 months; P=0.682) (6). However, there was a trend towards improved ORR and prolonged PFS in patients with *KRAS* mutations and programmed death-ligand 1 (PD-L1) ≥50%, which was not observed in the non-*KRAS* mutant cohort (6). This and other studies (7-9) warrant further investigation into the role of immunotherapy for KRAS patients and the correlation with PD-L1 expression.

KRAS gene and cancer

KRAS is one of the most common gene mutations in hematologic and solid tumors. The behavior of KRAS is varied across malignancies and this requires different strategies to manage. The *KRAS* gene (chromosome 12p12.1) is primarily involved in regulating cell division. It is a member of the RAS family of genes that encodes four proteins that are highly related mediators of the mitogen-activated protein kinase (MAPK) pathway: HRAS, KRAS 4a, KRAS 4b and NRAS (10). These proteins function as guanosine triphosphatases (GTPases), binary switches that turn on and turn off multiple pathways involved in survival, proliferation, angiogenesis and differentiation via effector proteins. Activation of KRAS is controlled by binding to guanine triphosphate (GTP) and deactivation by guanine diphosphate (GDP) and its function is thus dependent on GTP/GDP ratio. GTPase activity is regulated through an interchange between GTPase activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs) which control the ratio of active RAS-GTP and inactive RAS-GDP (11).

In the active GTP-bound state, the RAS family of proteins are involved in signaling of numerous downstream targets. The RAS/RAF/MEK/ERK is a pathway involved in regulation of the cell cycle and effecting other proliferation related proteins. The epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGF-R) among others are cell surface receptors that activate this pathway. RAS also promotes cell survival via PI3K/PDK1/AKT intracellular signaling. Tumor invasion and metastasis-inducing protein 1 (TIAM1), RALGDS and RALGDS-like proteins are involved in membrane trafficking. These downstream signaling pathways and others have been implicated in tumorigenesis.

Within *KRAS*, the most common mutations are G12C (40%), G12V (21%), G12D (17%), G12A (10%) and other (12%) G12 and G13 mutations (12). *KRAS* transversions (G-T, G-C) are typical for smokers and transitions (G-A) are typical for never smokers. *KRAS* mutations are associated with poorer outcomes in NSCLC (13). Renaud *et al.* showed that *KRAS* mutant patients had worse outcomes compared to wild type cases (13). Based off WHO classification system, there are five subtypes of adenocarcinoma (lepidic, acinar, papillary, micropapillary, solid). Lepidic invasive adenocarcinoma is divided into mucinous and non-mucinous types. Non-mucinous is associated with *EGFR* mutations whereas mucinous types are very commonly *KRAS*-mutated. These patients are often non-smokers. Mascaux *et al.* published a meta-analysis (14) showing a hazard ratio (HR) of 1.35 for patients that were *KRAS*-mutated with studies involving predominantly Asian populations confirmed these findings (15). In contrast, studies that included primarily western patients did not show that KRAS patients did worse as compared to KRAS wild type patients (15).

In these meta-analyses that had a poorer survival, it is postulated by Zer *et al.* that since *KRAS* mutants are generally mutually exclusive of *EGFR* mutants and Asian populations have higher percent of *EGFR* mutants (up to 40%) this selects for patients who are *KRAS* wild-type and possibly *EGFR* mutant, who have a better survival (16). *KRAS* mutations may have a weak association with worse

prognosis (HR 1.3–1.5) though western population data does not support this and therefore has limited clinical utility (14). It also remains unclear if *KRAS* mutations are predictive of benefit for certain NSCLC patients receiving chemotherapy. A prospective study of 482 patients evaluated cisplatin and vinorelbine in the adjuvant setting in patients with NSCLC (17). Patients stratified by *KRAS* status suggests that *KRAS* mutant patients did not receive as much benefit from adjuvant chemotherapy compared to *KRAS* wild type patients. However, further interaction tests comparing HR were not statistically significant. In evaluation of *KRAS* mutations stratified by codon, a meta-analysis was performed on 1,543 patients in four adjuvant chemotherapy studies (18). There appeared to be a non-significant trend of benefit for *KRAS* wild type patients who received adjuvant chemotherapy as opposed to *KRAS* codon 12 mutated NSCLC patients. In contrast, those who harbored a codon 13 *KRAS* mutation performed poorly in comparison to KRAS wild-type and other *KRAS* mutants (P<0.001) (18).

A retrospective study involving 1,971 NSCLC patients with *EGFR* and *KRAS* mutations performed by Renaud and colleagues have shown that *KRAS* mutations may be predictive of resistance to radiation therapy (19). Identifying ways to target these *KRAS* mutations may lead to benefit for patients in combination with other traditional means of treatment. Concurrent mutations have recently been found to possibly play a prognostic role and may indicate if patients may be more responsive to therapy (20). The most common co-existing mutations are *TP53* (39%), *STK11* (30%), *KEAP1* (24%), *RBM10* (15%) and *PTPRD* (15%) (21). *TP53* has been strongly associated with enhanced proliferation and *STK11* has been associated with suppression of immune surveillance (22).

Methods

Objectives

We performed a retrospective single center clinical study to determine survival of patients with a diagnosis of NSCLC and a *KRAS* mutation. We sought to determine possible associations between *KRAS* status and other co-occurring mutations, as well as the relationship between *KRAS* status and immunotherapy.

Study conduct

We screened a prospectively collected, single institute, NSCLC molecular database for patients with *KRAS* mutation. Patients with *KRAS* mutations with metastatic disease who were treated between January 1st, 2009 and January 1st, 2016 were selected for this study.

Electronic medical records of the identified patients were reviewed by the study investigators to capture patient characteristics, tumor molecular profile, and patient outcome. Demographics included age, sex, race, date of birth, treatment history, and metastatic sites. Molecular profiling data included *KRAS* status and other concurrent mutation status. All molecular assays were performed by Clinical Laboratory Improvement Amendments (CLIA) certified assays. Imaging studies were reviewed to assess metastatic sites. The City of Hope (COH) institutional review board approved this retrospective study.

Statistical analyses

Fisher exact test and independent *t*-test were used to examine associations between categorical and continuous variables, respectively. Survival was estimated using the Kaplan-Meier method and differences in survival were evaluated via the log-rank test. Cox proportional hazards were employed to assess effects of specific factors on survival. Statistical analysis was performed with SPSS v.18.

Results

Patient characteristics and treatment

From 2009 to 2016, 60 patients with *KRAS* mutations were identified in the COH registry. Of these patients identified, 42 (70%) were stage IV, 7 (12%) stage I, 7 (12%) stage II, and 4 (7%) stage III at diagnosis. Forty-seven (78%) patients were smokers (former plus current). Caucasian was the most common (n=44, 73%) racial group, followed by Asian (n=9, 15%), African-American (n=3, 5%) and Pacific Islander (n=1, 1.7%). The average age at diagnosis was 67 (median 69.50) years; 30 patients (50%) were over 70 years, 23 (38%) patients were 51–69 years, and 7 (12%) 50 years or below. The most common histology was adenocarcinoma (n=52, 87%), followed by adenosquamous (n=3, 5%), large cell (n=2, 3%) and small cell, squamous cell

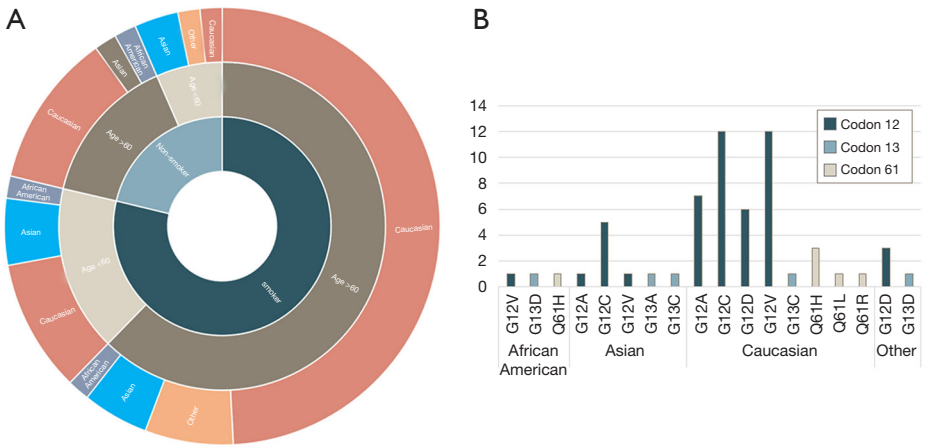

Figure 1 Patient characteristics. (A) Starburst plot of patient demographics according to their smoking history, age, and race; (B) distribution of *KRAS* mutant subtypes according to demographic groups by codons 12, 13, and 61.

Table 1 Patient characteristics

Characteristics	N [%] [n=60]
Race	
Caucasian	44 [73]
Asian	9 [15]
African-American	3 [5]
Other	3 [5]
Pacific Islander	1 [<2]
Histology	
Adenocarcinoma	52 [87]
Adenosquamous	3 [5]
Large cell	2 [3]
Small cell	1 [<2]
Squamous	1 [<2]
Carcinosarcoma	1 [<2]
Molecular alteration	
Codon 12	47 [78]
Codon 13	7 [12]
Codon 61	6 [10]
Smoker	47 [78]
Radiation	28 [47]
Surgery	22 [37]
Metastatic disease	
1 site	52 [87]
>2 sites	29 [48]
Brain	12 [20]
Age (years)	
≤50	7 [12]
51–69	23 [38]
≥70	30 [50]
Immunotherapy	
Nivolumab	6 [50]
Atezolizumab	4 [33]
Pembrolizumab	1 [8]
Ipilimumab	1 [8]

and carcinosarcoma (n=1 each, less than 2% each). Majority of the patients had metastatic disease (n=52, 87%) with 20% (n=12) having brain metastasis. The average number of metastatic sites was 1.6 and patients received on average 1.97 (range, 0–5) lines of therapy including chemotherapy, biologic agents or immunotherapy. Twelve (20%) patients received immunotherapy with additional treatment modalities including radiation in 28 (47%) and surgery in 22 (37%) patients with a median OS at 15 months. Patient characteristics are shown in *Figure 1A* and *Table 1*.

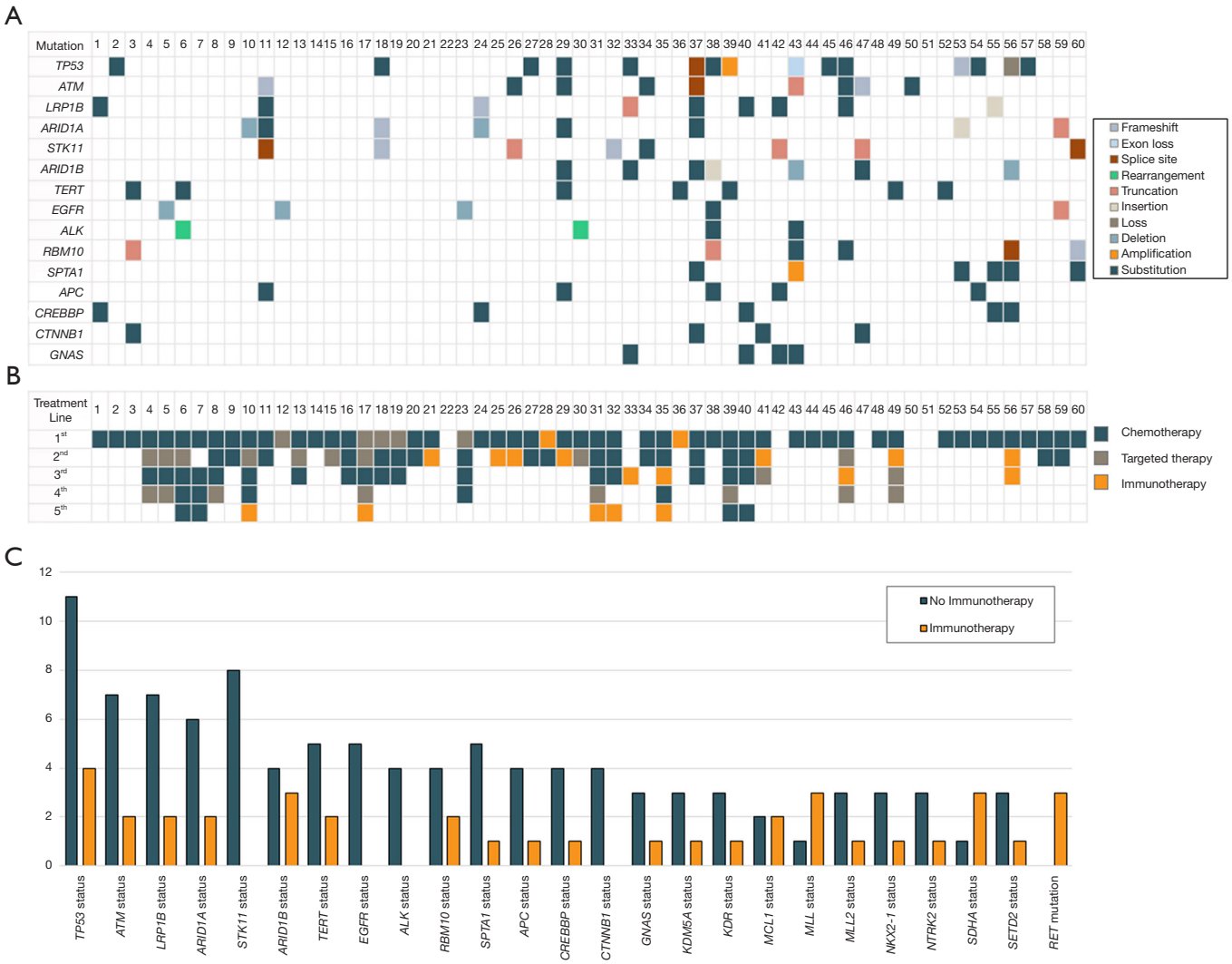

Figure 2 Frequency of mutations in the *KRAS* cohort. (A) A heatmap of co-occurring mutations according to their mutation type including frameshift, exon loss, splice site, rearrangement, truncation, insertion, loss, deletion, amplification and substitution; (B) a heatmap showing up to 5 lines of therapy that the patients received during the course of their care. (C) the presence of co-occurring mutations in patients who were treated with immunotherapy versus patients who received no immunotherapy treatment. *RET* mutated co-occurrence was the only unique instance in immunotherapy patients.

Molecular status

The most frequent molecular alteration was codon 12 mutation (n=47, 78%), followed by codon 13 (n=7, 12%) and codon 61 (n=6, 10%) mutations (*Table 1*). Patient *KRAS* mutations in each race is seen in *Figure 1B*. The most common co-occurring mutations in this cohort were *TP53* (n=15, 25%), *ATM* (n=9, 15%), *LRP1B* (n=9, 15%), *ARID1A* (n=8, 13%), *STK11* (n=8, 13%), *ARID1B* (n=7, 12%), *TERT* (n=7, 12%), *EGFR* (n=6, 10%), *RBM10* (n=6, 10%), *SPTA1* (n=6, 10%) (*Figure 2A*). Treatment characteristics are detailed in *Table 1*. In all 60 patients, systemic therapy given in up to 5 lines of treatment is shown in *Figure 2B*. The presence of co-occurring mutations in patients who were treated with immunotherapy versus patients who received no immunotherapy treatment is visualized in *Figure 2C*. *RET* mutated co-occurrence was the only unique instance in immunotherapy patients.

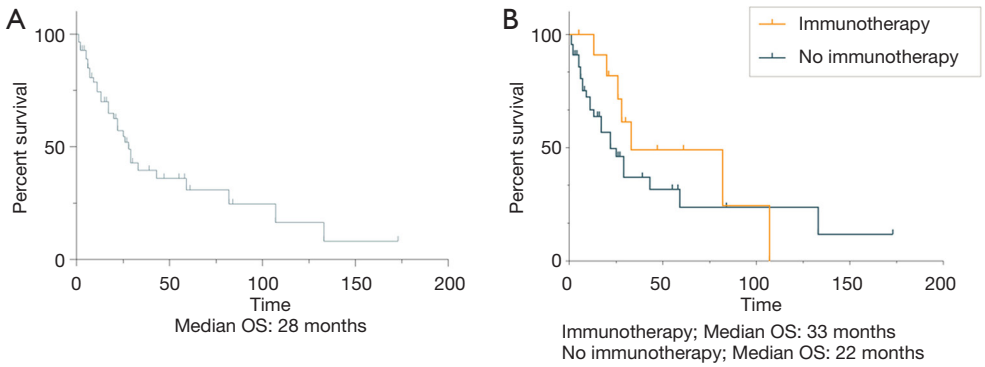

Figure 3 *KRAS* mutations and outcomes. (A) Kaplan-Meier survival curve showing the complete OS of all of the 60 *KRAS* mutated patients with a median OS of 28 months; (B) Kaplan-Meier survival curve showing improved median OS of 33 months in patients who received immunotherapy versus 22 months in patients who did not received immunotherapy. OS, overall survival.

Table 2 Multivariate analysis of survival with KRAS co-mutant NSCLC

Variable	HR (95% CI)	P value
TP53	0.53 (0.20–1.40)	0.19
ATM	1.10 (0.39–3.20)	0.85
LRP1B	1.00 (0.35–2.90)	0.98
ARID1A	1.20 (0.45–3.10)	0.74
STK11	1.80 (0.68–4.80)	0.23
ARID1B	0.94 (0.28–3.10)	0.92
TERT	1.20 (0.41–3.40)	0.76
EGFR	1.20 (0.40–3.30)	0.79
RBM10	1.30 (0.31–5.70)	0.69
SPTA1	1.90 (0.44–8.50)	0.38
Age	1.00 (0.99–1.10)	0.18
Gender	2.10 (1.00–4.10)	0.036
Smoking	2.80 (0.96–7.90)	0.059

NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval.

Survival

Median OS was 28 months in our patient cohort (*Figure 3A*). To evaluate the factors associated with likelihood of improved survival in this population, we focused on certain characteristics. There was an association with longer survival in patients who had an earlier stage, stages I, II, III, IV (58 *vs.* 26 *vs.* 3 *vs.* 11 months, respectively; P=0.002). In addition, there appeared to be a trend towards longer survival in those that received immunotherapy (33 months, n=12) in compared those who did not (22 months, n=48) (P=0.31) (*Figure 3B*). The most common co-occurring mutations in this cohort did not show a survival difference in comparison to patients who did not have those mutations: *TP53* (P=0.019), *ATM* (P=0.85), *LRP1B* (P=0.99), *ARID1A* (P=0.74), *STK11* (P=0.23), *ARID1B* (P=0.92), *TERT* (P=0.75), *EGFR* (P=0.79), *RBM10* (P=0.69) and *SPTA1* (P=0.38) (*Table 2*). Patients who harbored a codon 61 mutation had a median survival of 28 months compared to 11 months of codon 13 and 13 months of codon 12; this was not statistically significant (P=0.143). Based on the calculated median of survival (15 months; range, 1–173 months), we defined better survival as those patients who had a high survival (≥ median) and analyzed survival with those who received and did not receive immunotherapy. Our analysis revealed that there was an association between those patients who had high survival and who received immunotherapy (*Figure S1*, P=0.007).

Discussion

Lung cancer remains the number one cause of cancer death worldwide (1). *KRAS* mutations are among the most common molecular alterations identified in NSCLC. With decades of research, there are still no effective direct targets to the KRAS pathway. To better understand *KRAS* mutations, we evaluated co-mutations and identified factors associated with improved survival. The majority of *KRAS* mutations identified in our population were adenocarcinoma (87%), with small but similar distributions

of other histologies including adenosquamous, large cell and small cell, squamous cell and carcinosarcoma, which is consistent with other previously published work of *KRAS* mutant NSCLC (23). In contrast to the Lung Adjuvant Cisplatin Evaluation (LACE)-Bio group who conducted a pooled analysis of patients enrolled in four randomized trials of adjuvant chemotherapy, we did not identify a trend towards patients being earlier in stage or younger (24). Instead, our patient population average age was 67 and majority were stage IV at diagnosis (70%).

Twenty-two percent of the patients in our cohort were never smokers which is much higher than previously reported distributions (25,26). In a series of *KRAS*-mutated lung adenocarcinoma where 17% of patients were never smokers, transition mutations were more common in never smokers (15%) compared to transversion mutations that were common in patients with smoking history (22%) (26). Our population had a similar distribution of transition mutations in smokers and never smokers, 26% and 31% respectively (P=0.705), and thus likely transition mutations are not the explanation as to why there is an increase in never smokers in our *KRAS*-mutated NSCLC population. Smoking-associated lung cancer differs among populations and 45–71% of Asian patients with lung cancer are never smokers (27,28). Our cohort of patients has an overrepresented Asian population (15%) in relation to 2010 US Census data (5.6%) and likely plays a role in the increase of KRAS never smokers in our cohort.

There remains continued interest in using KRAS as a prognostic marker in NSCLC. In support of previously published work (29,30), the most frequent *KRAS* mutation in our study was located on codon 12. Previous work by Yu *et al.* demonstrated that patients with *KRAS* codon 12 mutations had superior survival compared to those with codon 13 tumors, with a median of 16- and 13-month survival respectively (P=0.009) (29). We found a trend towards improved survival in patients with codon 61 mutations compared to codons 12 and 13, but this was not statically significant. This indicates that there are likely other additional biological factors that need further evaluation. Most recently STK11/LKB1 and KEAP1/NFE2L2 were found to be associated with primary resistance and worse outcomes (20,31).

We observed a number of unique co-mutations that have not been previously reported in *KRAS* mutants (20,30), such as *RBM10* and *SPTA1*. RBM10 is a protein that binds RNA and functions by inhibiting proliferation of tumor cells and hence a tumor suppressor associated in regulation of Notch signaling (32). Defects in this gene are the cause of the X-linked recessive disorder, TARP syndrome that leads to several birth defects. RBM10 are frequently identified in adenocarcinomas of the lung and other cancer types including pancreatic, colorectal and thyroid. It is postulated that RBM10 is an RNA splicing regulator, once mutated leads to pathogenesis of adenocarcinoma due to deregulated splicing which can lead to proliferation (33). *SPTA1* is a gene that encodes an actin crosslinking and molecular scaffold protein that links the plasma membrane to the actin cytoskeleton. Its exact nature and function in oncogenesis are unknown but it has been postulated to function as an oncogene (34). Mutations in this gene is associated with a hereditary red blood cell disorders including spherocytic hemolytic anemia, elliptocytosis type 2 and pyropoikilocytosis. It is a gene that is highly mutated in lung cancer (35). A retrospective study performed on 38 patients with small-cell lung cancer (SCLC) showed *SPTA1* mutations expressed in all stages of SCLC and is thought to be associated with SCLC development (34).

Immunotherapy has recently become a vital therapeutic option in NSCLC as a first-line treatment alone or combined with chemotherapy (36,37). Twelve (20%) patients in our study received immunotherapy and we noted a correlation between patients who received immunotherapy and longer OS. However, a larger cohort analysis is necessary to evaluate the role of immunotherapy in *KRAS*-mutated patients. Ten of the 12 patients (83%) received immune checkpoint inhibitors as second-line or later lines of treatment. Despite this, there was a strong correlation between patients treated with immunotherapy and high survival. Previous studies have shown that *KRAS* mutations can induce PD-L1 overexpression through activation of the downstream pathways in NSCLC (7,38,39). Several co-occurring mutations, such as *TP53* and *LKB1*, have been described as predictive biomarkers of clinical benefit—with *TP53* co-mutations associated with clinical benefit while instances of *LKB1* and *KRAS* mutants showed ineffectiveness of immunotherapy (40,41). The identification of these *KRAS* mutant subgroups may be the key towards identifying a biomarker of immunotherapy efficacy, as several recent studies demonstrated that *KRAS* mutation alone was not sufficient to predict immunotherapy response (6,42,43).

Effective treatments targeting *KRAS* mutations have represented a challenge so far. Checkpoint blockade has presented an intriguing area of study considering there has been limited advancement in additional cytotoxic therapies

in the last few years. However, anti-PD-1 therapy has been an effective approach for *KRAS* mutated NSCLC patients without a validated biomarker (44). Most recent data show correlation of KRAS and high PD-L1 expression with improved outcomes (6,45). A large percentage of *KRAS* mutated NSCLC patients have positive smoking history (26). Tobacco-induced tumors present higher burden of mutation and neo-antigens. Higher neo-antigen burden was associated with improved PFS with anti-PD-1 therapy (44). Our findings are consistent with this in showing that there is a trend towards improved survival in *KRAS* mutant patients who received immunotherapy.

Ideally, prospective studies designed with interest in molecular alterations, prognosis, and ability for *KRAS*-mutated NSCLC to respond to various therapies would be helpful. Our study was limited to its retrospective design and limited selection of patients. Heterogeneity of treatment course in addition to next-generation sequencing (NGS) platforms used to analyze molecular alterations left our results not standardized. In conclusion, understanding the significance of co-mutations and their therapeutic implications, especially in response to immunotherapy and other agents represents an important step to develop better treatment options for *KRAS*-mutated lung cancers. Our findings warrant further investigation in a prospective setting with a larger data set.

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Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Ammar Chaudhry) for the series "Role of Precision Imaging in Thoracic Disease" published in *Journal of Thoracic Disease*. The article was sent for external peer review organized by the Guest Editor and the editorial office.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd.2020.04.18). The authors have no conflicts of interest to declare. The series "Role of Precision Imaging in Thoracic Disease" was commissioned by the editorial office without any funding or sponsorship.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the City of Hope Institutional Review Board (No. 18433). Individual consent for this retrospective analysis was waived.

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Supplementary

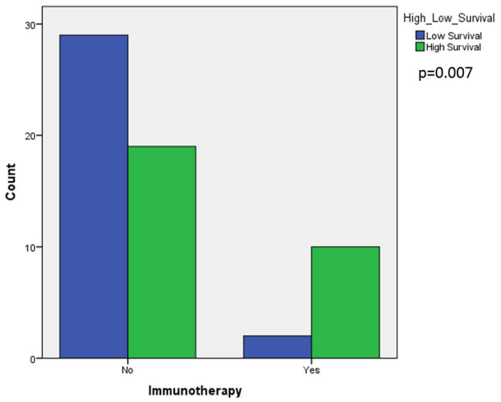

Figure S1 Immunotherapy and outcomes. In patients who received immunotherapy, there was observed a correlation with higher survival (P=0.007).