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Characteristics and outcomes of patients with metastatic *KRAS* mutant lung adenocarcinomas: The Lung Cancer Mutation Consortium experience.

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Abstract

Background: Mutations in the KRAS gene are the most common driver oncogenes present in lung adenocarcinomas. We analyzed the largest multi-institutional database available containing patients with metastatic KRAS mutant lung adenocarcinomas.

Methods: The Lung Cancer Mutation Consortium (LCMC) is a multi-institutional collaboration to study the genomic characteristics of lung adenocarcinomas, treat them with genomically directed therapeutic approaches, and assess their outcomes. Since its inception in 2009, the LCMC has enrolled over 1900 patients and has performed pretreatment, multiplexed, molecular characterization along with collecting clinical data. We evaluated the characteristics of patients with KRAS mutation in the LCMC and the association with overall survival (OS).

Results: Data from 1655 patients with metastatic lung adenocarcinomas were analyzed. 450 (27%) patients had a KRAS mutation, 58% female, 93% smokers, and median age of 65 years. Main KRAS subtypes were: G12C 39%; G12D and G12V at 18% each. Among patients with KRAS mutation, G12D had a higher proportion of never smokers (22%, P<0.001). Patients with KRAS mutant tumors had a trend toward shorter median survival compared to all others in the series (1.96 vs. 2.22; P=0.08) and lower 2-year survival rate (49% (95% CI: 44-54%) and 55% (95% CI: 52-58%), respectively.

Conclusions: In the LCMC study, 27% of lung adenocarcinomas patients harbored a KRAS mutation and up to third of them had another oncogenic driver. Patients with both KRAS and STK11 mutations had a significantly inferior clinical outcome.

1. Introduction

Non-small cell lung cancers (NSCLC) have two major subtypes, adenocarcinoma and squamous cell carcinomas each with unique and shared clinico-pathological characteristics[1]. They account for nearly 85% of all lung cancers and include a number of distinct molecular subsets based on their genomic characteristics. Many of these genomic aberrations can be effectively targeted including *EGFR*[2] sensitizing mutations, *ALK*[3] and *ROS1*[4] rearrangements, and *BRAF V600E*[5] mutations. Treatment with specific targeted therapies improves survival for patients in these molecular cohorts. *KRAS* was one of the first oncogenes found to be mutated in human cancers including in lung, colorectal and pancreatic cancers[6]. This somatic mutation is the most frequently found in non-Asian patients with lung adenocarcinoma than Asian patients[7] with an incidence rate of 25-35%.

In a 500 patients' cohort with lung adenocarcinomas[8], *KRAS* mutations were present in 22%. While tranversion mutations (G→T or G→C) were more common in ever-smokers, transition mutations (G→A) were more common in never-smokers.

KRAS mutations have been linked with a poor prongosis[9-12], though this observation has not been consistent across studies[13-15]. The majority of *KRAS* mutations occur at codon 12 and 13; all three common G12 mutations (G12C, G12V, and G12R) have been associated with poor outcomes[10]. In particular, point mutations in G12C and G12V are associated with worst survival compared to other *KRAS* mutant subtypes[16]. It is thought that all *KRAS* mutations lead to tumor development and growth by activating a complex set of downstream signaling pathways including mitogen-activated protein kinase. Targeting *KRAS* mutations has proven extremely challenging and current drug development is focused on inhibition of downstream activated pathways[17-20]. In addition, cells harboring these mutations create an immunosuppressive tumor microenvironment, thus allowing them to evade the immune system[20].

To better understand the clinical significance of *KRAS* mutations in lung adenocarcinomas, we analyzed the findings of patients with *KRAS* mutant lung adenocarcinomas from the Lung Cancer Mutation Consortium (LCMC). The goals of the LCMC were: to conduct molecular tests (LCMC1) on consecutive patients with advanced lung adenocarcinomas across 11 academic medical centers; and to enroll patients with driver mutations on targeted therapy clinical trials to improve patient outcomes (2009-2012)[21, 22]. Oncogenic driver events were detected in 64% of lung adenocarcinomas; approximately half of those drivers (30%) were felt to be actionable for therapy[21]. In the second phase (LCMC2), the consortium adopted an expanded testing panel to cover 16 molecular alterations and included 16 academic centers (2012-2015)[23]. Patients with an oncogenic driver alteration who received a matched targeted therapy experienced the most favorable overall survival[23]. These findings supported the use of next generation sequencing (NGS) panels for lung adenocarcinomas to make treatment decisions[24].

Here, we describe the characteristics of patients with *KRAS* mutant lung adenocarcinomas in the entire LCMC cohort and the association of this mutation with their survival.

2. Materials and methods

We analyzed data and interpreted results of patients who consented to LCMC between 2009-2015 and had known *KRAS* mutation status, complete dates of birth, distant metastasis and last follow up. LCMC1 and LCMC2 data were combined for analysis. We obtained patient's baseline characteristics (age, gender, race, smoking history, performance status, and treatment history), *KRAS* mutation status, subtype and codon, and other associated mutations (co-mutations). We evaluated patients' characteristics and the association of their *KRAS* status with overall survival (OS). In addition, we evaluated for the presence of co-mutations, and their impact on OS. *AKT1, BRAF V600E, BRAF non-V600E, ERBB2, MAP2K1, NRAS, PIK3CA*, sensitizing *EGFR*, non-sensitizing *EGFR*, and *ALK*, were checked in LCMC1 and LCMC2. During enrollment in LCMC2, most institutions switched from focused testing to NGS which enabled simultaneous analysis of non-targetable mutations in several other genes in lung cancer (specifically tumor suppressor genes, *TP53* and *STK11*). In addition, amplification of MET (*ampMET), ROS1* and *RET* rearrangements, and *PTEN* loss of expression, were also tested in the LCMC2. The molecular testing methods used for detection of mutations have been described previously[21-23].

Data were presented as frequency (percentage,%) for categorical variables and median (interquartile range, IQR) for continuous variables. Associations between variables were examined with either Wilcoxon rank-sum test, Kruskal-Wallis test, chi-square test or Fisher's exact test as appropriate. Survival functions were estimated by the Kaplan- Meier method and compared using a log-rank test[25]. Univariate and multivariable survival analyses were carried out using a Cox proportional hazards model[26]. The proportional hazards assumption was assessed with scaled Schoenfeld residuals[27]. Variable selections were carried out by a stepwise procedure based on Akaike Information Criterion[28] and the possibility of multicollinearity was assessed by tolerance and the variance inflation factor. Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina) with two-sided tests and a significance level of 0.05.

3. Results

3.1 Clinical characteristics of patients with KRAS mutant lung adenocarcinomas

Data from all patients (N=1918) with lung adenocarcinomas who consented to the LCMC between 2009 and 2015 were available. Out of these, 263(13.71%) patients were excluded from this analysis: 190(9.9%) patients had an incomplete date of birth, date of consent, or date of distant metastasis; 73(3.8%) patients had unknown *KRAS* status. *KRAS* mutation was present in 450(27%) of 1655 patients; 260(58%) were female; 401(94%) were white, and 416(93%) were smokers. The median age was 65 years and 59% of the patients had performance status of 1 as assessed by the ECOG (Eastern Cooperative Oncology Group) scale (Tables 1A, 1B, and 1C). There were significant differences between *KRAS* mutant (no associated co-mutation) and *KRAS* wildtype (no associated co-mutation) patients in median age, race, and smoking history (Table 3). Patients with *KRAS* mutations (no associated co-mutation) (33;8.31%) were more likely to have received targeted therapy than patient with *KRAS* wildtype (no associated co-mutation) lung adenocarcinomas (21;3.87%) (P=0.004). This is likely due to the fact that *EGFR* inhibitors were available for routine clinical use for an unselected patient population during the LCMC study.

3.2 KRAS mutation subtypes

The most common nucleotide change in tumor specimens was guanine to thymidine (34_G>T or G12C) seen in 176(39.11%) patients; 35_G>A (or G12D) was present in 83(18.44%) patients. The 35_G>T (or G12V) was present in 80(17.78%) patients. The most common codons of *KRAS* mutations were: codon 12 (389 patients;86.44%), codon 13 (32 patients;7.11%), and codon 61 (29 patients;6.44%) (Table 1C).

Representation of never-smokers was more common in the G12D subtype than the G12V or G12C subtypes (22%vs.5%vs.1.7%, respectively;P<0.001); there was no significant difference between different mutation subtypes in term of median age, gender, race, ECOG score, incidence of co-mutations, and treatment history (Table 4). There was no association between these covariates and the main three codons of *KRAS* mutation (Table 5).

3.3 Other mutations associated with KRAS mutation

Of 450 patients with *KRAS* mutant lung adenocarcinomas, co-mutation of *TP53* (48(52%) of 93patients studied) was the most frequent, followed by *STK11* (17(18%) of 92patients). As mentioned earlier, the adoption of NGS occurred during the course of the study period and hence only a subset of patients were tested for *TP53* and *STK11*. 14(3.11%) patients had a driver co-mutation or a molecular aberration (*AKT1, BRAF V600E, BRAF non-V600E, ERBB2, MAP2K1, NRAS, PIK3CA*, sensitizing *EGFR* (*sEGFR*), non-sensitizing *EGFR* (*oEGFR*), or *ALK*) (Table 1). The incidence of specific mutations associated with *KRAS* mutations (referred to *KRAS* co-mutation) among the 16 molecular aberrations checked is summarized in Table 2. 93(40%) of 232 *KRAS* mutant patients were tested for *TP53* and 92(39.66%) of 232 were tested for *STK11*. The incidence of targetable co-mutations were less frequent; concurrent s*EGFR* mutation was found in 3(1.3%) of 232 patients. No concurrent *ALK* or *ROS1* rearrangements were found. There was no significant difference between patients with *KRAS* mutant lung adenocarcinomas with and without any associated co-mutation in terms of median age, gender, race, smoking history, and ECOG score. However, patients with *KRAS* mutant lung adenocarcinomas with co-mutation were more likely to receive targeted therapy (30.77%vs.8.31%;$P<0.001$;data not shown).

3.4 KRAS mutation and overall survival

The median follow-up for all study patients was 2.15 years (95%CI:2.01-2.27) with median OS of 2.15 years (95%CI:2.02-2.30) and 2-year OS rate of 53.38%(95%CI:50.50-56.18). 888(53.7%) of patients were alive at the time of the analyses. Patients with *KRAS* mutations (with or without co-mutation; N=450) had a shorter overall survival compared to *KRAS* wildtype patients (with or without co-mutation; N=1205) (HR:1.22;95%CI:1.05-1.43;$P=0.011$) with estimated 2-year OS rates of 49.1%(95%CI:43.6-54.3%) and 55% (95%CI:51.6-58.3%), respectively. In multivariable analysis stratified by chemotherapy history for lung cancer, there was a trend towards inferior survival for these patients with *KRAS* mutation compared to *KRAS* wildtype (HR:1.24;95%CI:0.97-1.58;$P=0.081$) after adjusting for gender, smoking history, performance status, number of co-mutations, and surgical intervention. In multivariable analysis stratified by chemotherapy for lung cancer, *KRAS* mutant patients (with no associated co-mutation) had worse survival than *KRAS* wildtype patients (with no associated co-mutation) after adjusting for gender, performance status, and surgical intervention (HR: 1.32; 95% CI: 1.03-1.70; $P=0.028$).

There was no statistically significant difference in OS between the main three subtypes (G12C vs. G12D vs. G12V) ($P=0.81$;Figure 2) and codons (12 vs. 13 vs. 61) ($P=0.36$;Figure 3) of *KRAS* mutations; codon 13 had a lower estimated 2-year OS rate of 38.6% (95%CI:21.0-55.9) and codon 61 had relatively higher 2-year OS rate of 65.0%(95%CI:42.5-80.5). The presence or absence of co-mutation did not affect OS in patients with *KRAS* mutant in univariate analysis (HR:0.68;95% CI:0.28-1.65;$P=0.39$;Table 7) with estimated 2-year OS rates of 52.75%(95%CI: 16.59-79.63) vs. 48.83%(95%CI:43.32-54.10), respectively (Figure 1). However, in multivariable analysis, the presence of any associated co-mutation had an improved OS after adjusting for gender, performance status, history of surgical resection for lung cancer treatment, and

chemotherapy for lung cancer (HR:0.35;95%CI:0.13-0.97;*P*=0.044;Table 7). Patients with *EGFR* mutation or *ALK* rearrangement had a better OS than *KRAS* mutant (no co-mutations) patients (*P*<0.01;Figure 4) with estimated 2-year OS rates of 64.7%(95%CI:53.7-73.7) for non-sensitizing *EGFR* mutation (*oEGFR*), 70.7%(95%CI:61.5-78.0) for sensitizing *EGFR* mutation (*sEGFR*), 64.8%(95%CI:52.3-74.8) for *ALK* vs. 48.8%(95%CI:43.3-54.1) for *KRAS* mutation. Patients with *sEGFR* or *ALK* rearrangement were more likely to be younger, never smoker, with better performance status and receive targeted therapy compared to patients with *KRAS* mutation (no co-mutation) (Table 6).

3.5 Univariate association and multivariable analysis (Tables 3 and 7)

When compared to patients with *KRAS* wild type (no co-mutation) lung adenocarcinomas, patients with *KRAS* mutation (no co-mutation) lung adenocarcinomas were more likely to be older, white, smoker, and received targeted therapy (*P*<0.001). *KRAS* co-mutation vs. no co-mutation, *KRAS* main subtypes (G12C vs. G12D vs. G12V), and codons (12 vs. 13 vs. 61) were not associated with OS.

3.6 Co-mutation STK11

KRAS and associated *STK11* mutations were reported in 17(18%) of 92 (Table 2). These patients had were younger than the remaining 75 *KRAS* mutant patients without associated *STK11* mutation (median,IQR): 61(58-71) vs. 67(58-71) years;*P*=0.08); no difference in other characteristics were observed (gender,race,smoking history,performance status,prior therapy) (Table 8). Co-mutation with *STK11* was associated with poor OS in univariate analyses (HR:2.66;95%CI:1.07-6.60;*P*=0.035). In addition, *STK11* mutation worsened OS of patients with either *KRAS* mutation (0.9year vs. not reached) or *KRAS* wildtype (1.46vs.2.03years) and who did not have any other associated co-mutation (Table 9 and Figure 5).

4. Discussion

KRAS mutation is a common event in lung adenocarcinomas; there is increasing knowledge that *KRAS* mutations include a heterogeneous group of patients defined by mutation subtype and presence of co-mutations. Despite being a common molecular event in lung adenocarcinomas, few studies have thoroughly analyzed the biological impact of various *KRAS* mutation subtypes and their impact of disease behavior and clinical outcomes. In a large series of 677 KRAS mutated patients from a single-institution study[10], certain differences were noted between the mutation sub-type and patient survival; however outcomes with conventional therapies appears to be similar.

Our analysis allowed for studying *KRAS* mutations in a multi-institutional setting and with robust associated clinical findings. Among the three main *KRAS* mutation subtypes, *KRAS* transition mutation (35 G→A; known as *KRAS* G12D) was more commonly seen in never smoker patients (21.69%; *P*<0.001) compared to G12C and G12V subtypes. Despite our findings of *KRAS* mutation's association to smoking history, our study suggest that these mutations can occur in never-smokers (7%) and these patients may have a distinct mutation

subtype. Our analyses showed that never smoker lung cancer patients with KRAS mutation and no associated co-mutation (N=31) had a shorter OS compared to never smoker lung cancer patients (N=168) with KRAS wildtype and no associated co-mutation with and estimated 2-year OS rates of 43.3%(21.4%,63.5%) vs. 61.42%(51.5%,69.9%) (P=0.005), respectively.

We noted that *KRAS* mutation with only *STK11* tumor suppressor loss had a tendency to occur in younger patients (median age, 61years). These patients had the worst overall survival (0.9year) compared to patients with *KRAS* mutation without *STK11* or other co-mutation. In addition, we were able to define the impact of baseline patient characteristics with various *KRAS* mutation sub-types and the overall outcome. These findings add to the growing knowledge about the differences between various KRAS mutation sub-types and the presence of co-mutations.

We observed that *KRAS* mutation and s*EGFR* were not entirely mutually exclusive: 3(4.11%) of 73 patients had both mutations. In a prior study by Yu *et al*[10], none of the 677 patients with *KRAS* mutant lung cancers had a concurrent *EGFR* mutation. *KRAS* mutations have been linked to resistance to anti-*EGFR* therapy; therefore, our observation could represent either an acquired resistance through *KRAS* or a de novo phenomenon. Our study showed that *KRAS* mutation and *ALK* rearrangements in lung adenocarcinomas were mutually exclusive.

There are limitations to our analysis. First, the molecular analysis was limited to testing for 10 mutations in LCMC1 and 16 mutations in LCMC2. In addition, some of the patients did not have all these mutations tested probably because of lack of tissue. Second, molecular testing was not uniform among different sites. In LCMC1, FISH technique was used. In LCMC2, most sites used NGS but with different technologies which can lead to different target and different results, particularly for non-hotspot mutations (as are more common in tumor suppressor genes like *TP53* and *STK11*). Third, LCMC1 and LCMC2 findings were not homogeneous: *EGFR* and *ALK* were seen less in LCMC2 than LCMC1 probably because patients were treated in the community with erlotinib or crizotinib instead of being referred to the study. We were limited to make conclusions regarding rare subsets of *KRAS* mutation and duration of therapy.

LCMC did not test for mutations in *KEAP1/NFE2L2*. Arbour *et al*[29] found that *KRAS* and *KEAP1/NFE2L2* co-mutations were associated with shorter overall survival and duration of response. This further emphasizes the notion that *KRAS* mutant NSCLC represents a heterogeneous group of patients with co-mutations playing a key role in the biological behavior of the cancer.

Presently, targeted therapy options for patients with *KRAS* mutation are being explored in first-in-human clinical trials[30-32]. Systemic chemotherapy remains as the main treatment modality. The combination of docetaxel and *MEK* inhibitor was associated with promising outcomes for these patients. Notably, the objective response rate was higher for patients with *KRAS* G12C and G12V mutation in this trial[19]. Though this regimen was not developed further due to failure to confirm this observation in phase 3 trial, the implications of varying

sensitivity to *MEK* inhibition based on mutation sub-type provide an important lesson for future trial design to not group *KRAS* mutations as one entity.

In recent years, immunotherapy has emerged as an effective treatment approach for NSCLC. Smokers and patients with high tumor mutation burden are more likely to respond to immune checkpoint inhibitors (ICI); it is notable that these characteristics enrich for *KRAS* mutations. Conversely, never-smokers and patients with *EGFR* and *ALK* gene abnormalities are less likely to respond to ICI. Presently, there is no firm evidence to indicate varying clinical outcomes with ICI based on the presence or absence of *KRAS* mutation. However, patients with *KRAS* and *STK11* co-mutation do not derive durable clinical benefit with ICI[33]. This has been attributed to a 'cold' immune microenvironment in patients harboring the co-mutation. The LCMC is moving forward with ICI as neoadjuvant and adjuvant treatment with surgical resection[34]. Defining the role of *KRAS* mutation and subtypes, drug response phenotypes and effect on immune system are important for designing future trials in this heterogeneous population.

We are expecting adoption of NGS and a shift away from targeted testing for treatable molecular abnormalities with the recent FDA approval of NGS use for molecular testing. Consequently, the impact of *KRAS* mutation sub-types on disease biology and outcomes with various standard treatment approaches will become increasingly evident. ICI and systemic chemotherapy use will remain the mainstay of treatment of patients with *KRAS* mutations while research for effective novel and combined targeted approaches continues[35-37].

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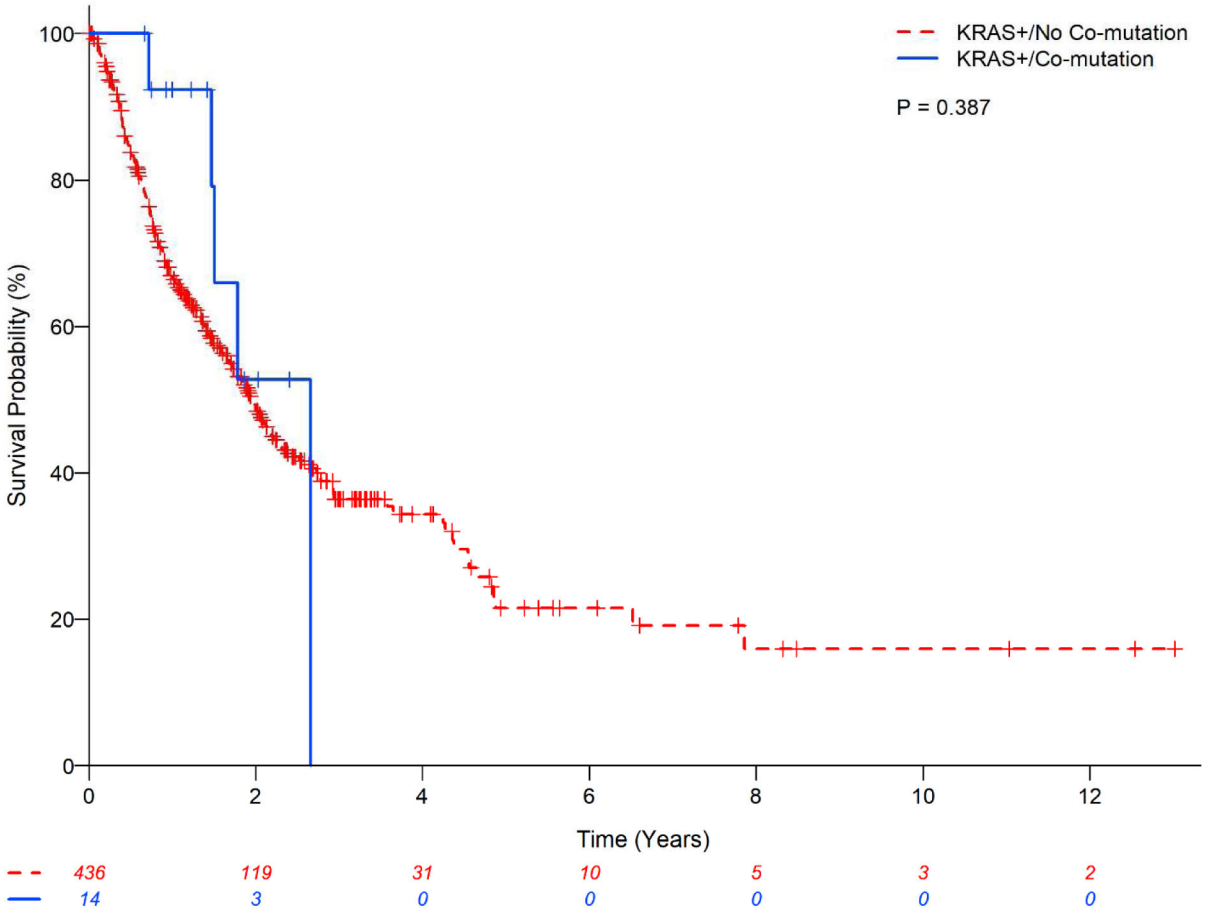

Figure 1.
Kaplan-Meier estimates for KRAS mutant patients with lung adenocarcinomas with and without co-mutation.

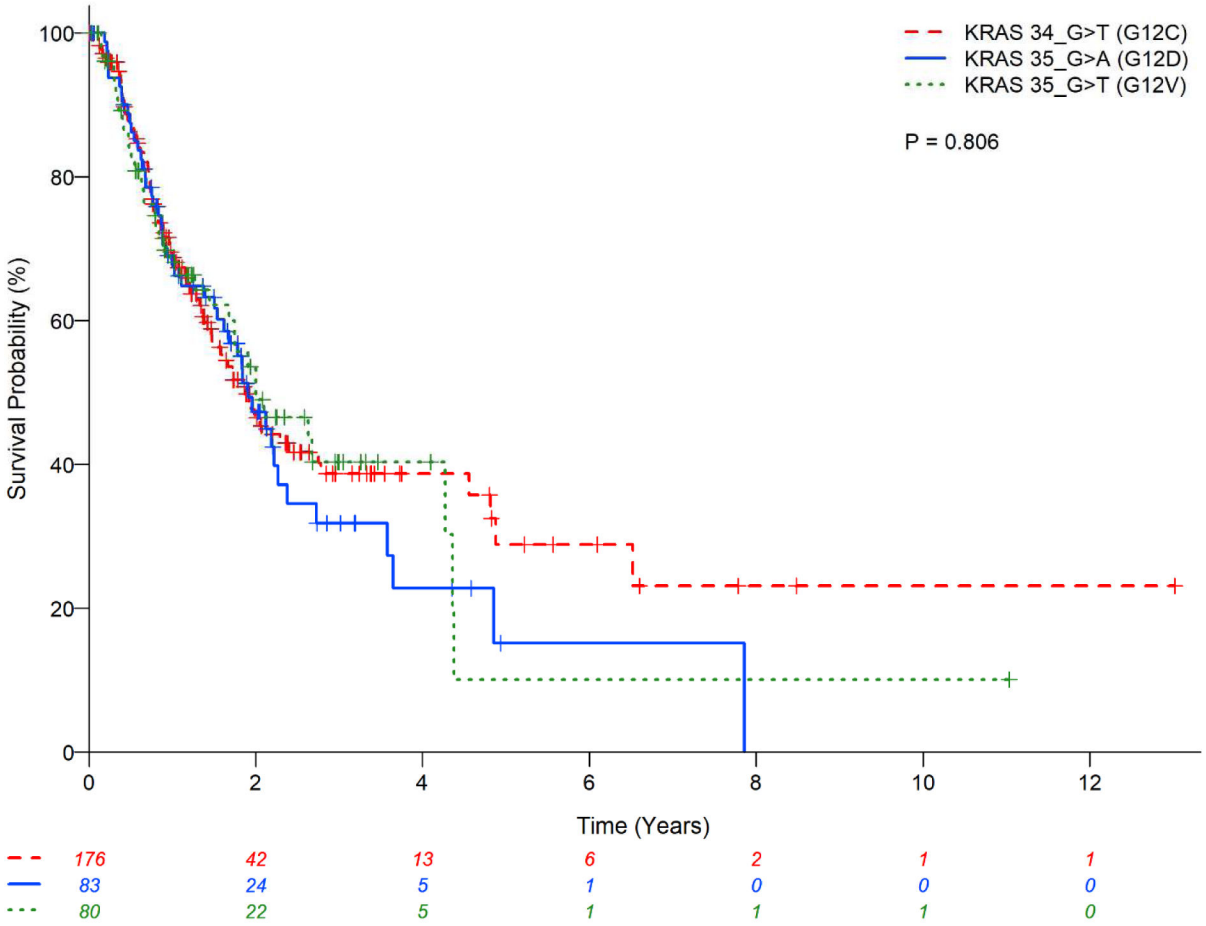

Figure 2.

Kaplan-Meier estimates for KRAS mutant patients with lung adenocarcinomas stratified by main 3 subtypes of KRAS mutation.

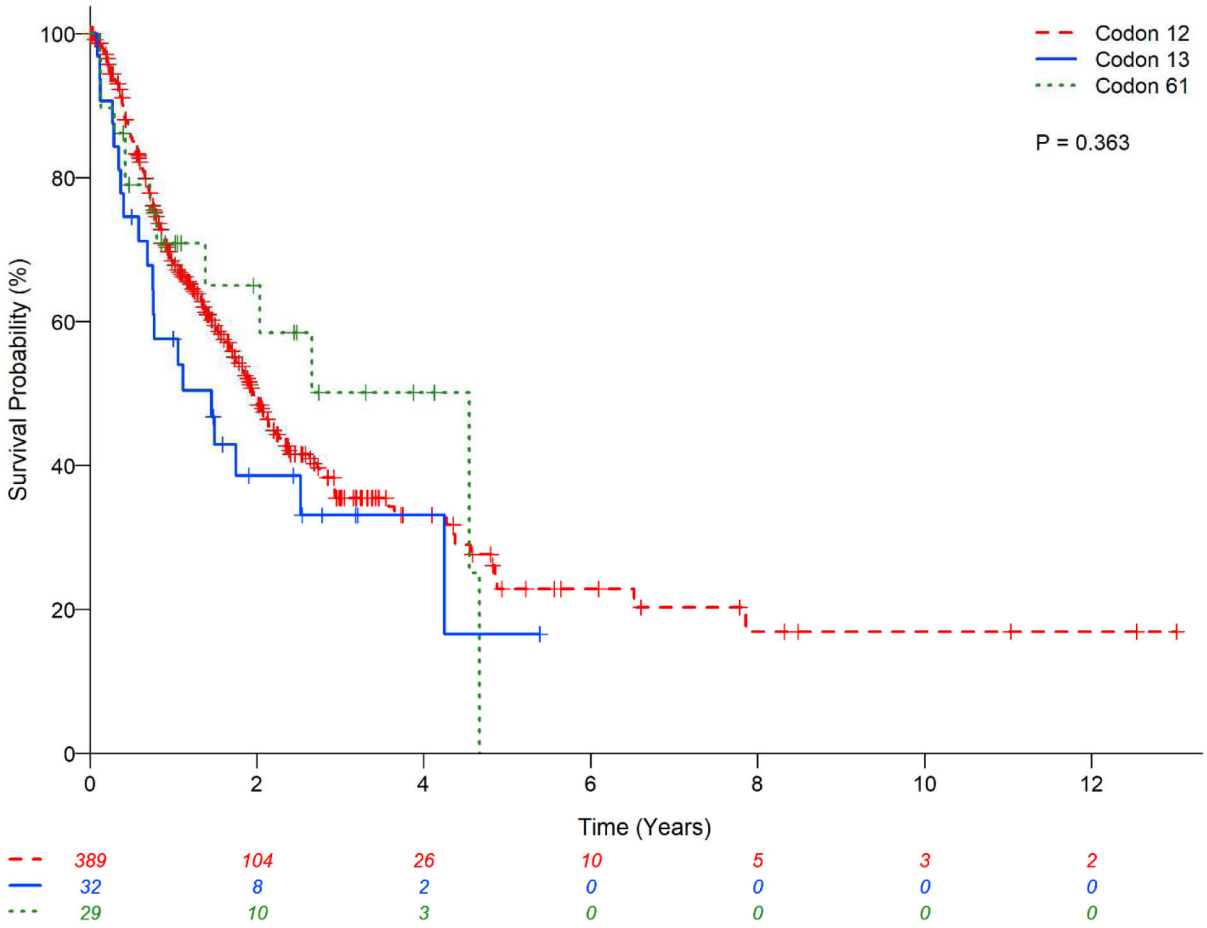

Figure 3.

Kaplan-Meier estimates for KRAS mutant patients with lung adenocarcinomas stratified by codon of KRAS mutation.

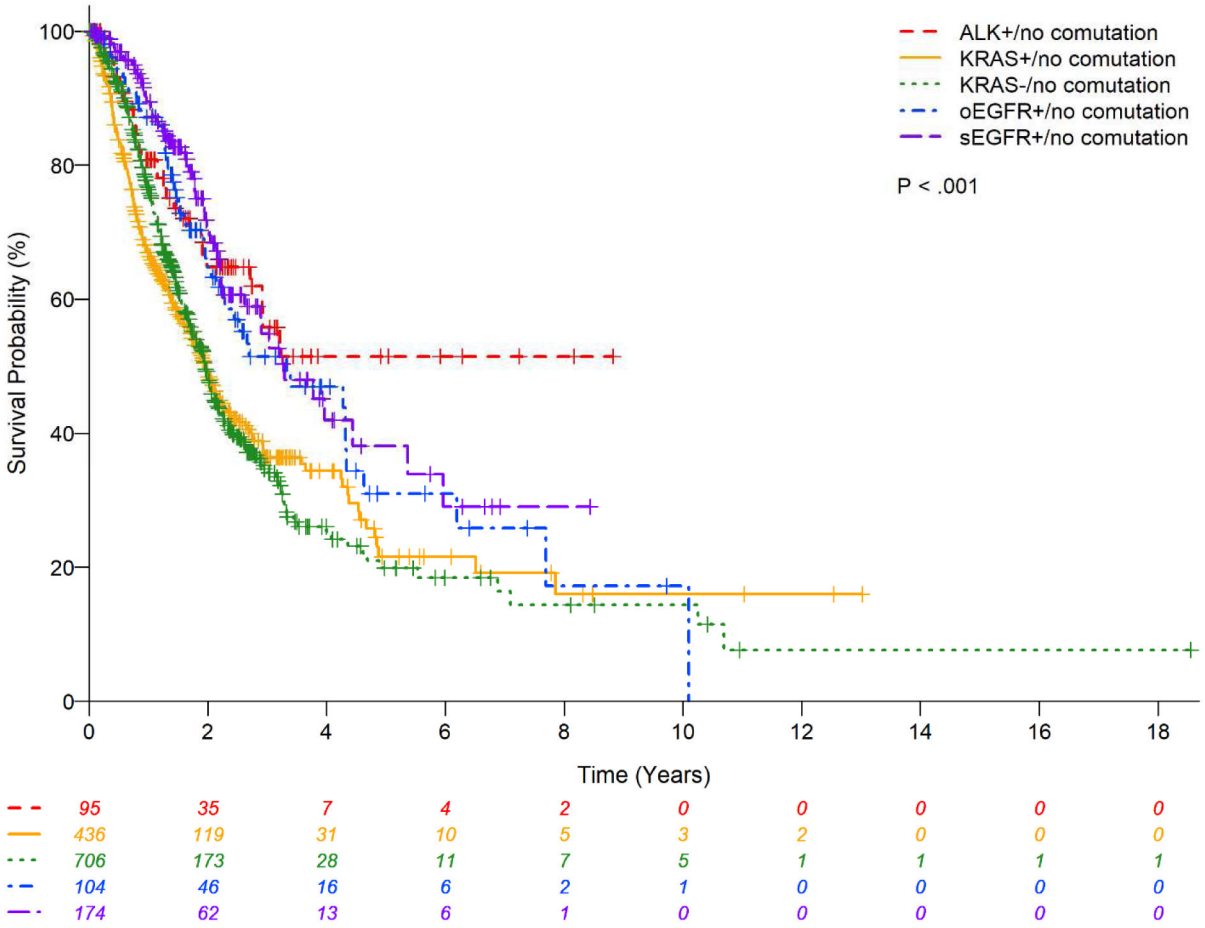

Figure 4.

Kaplan-Meier estimates for patients with lung adenocarcinomas stratified by molecular status.

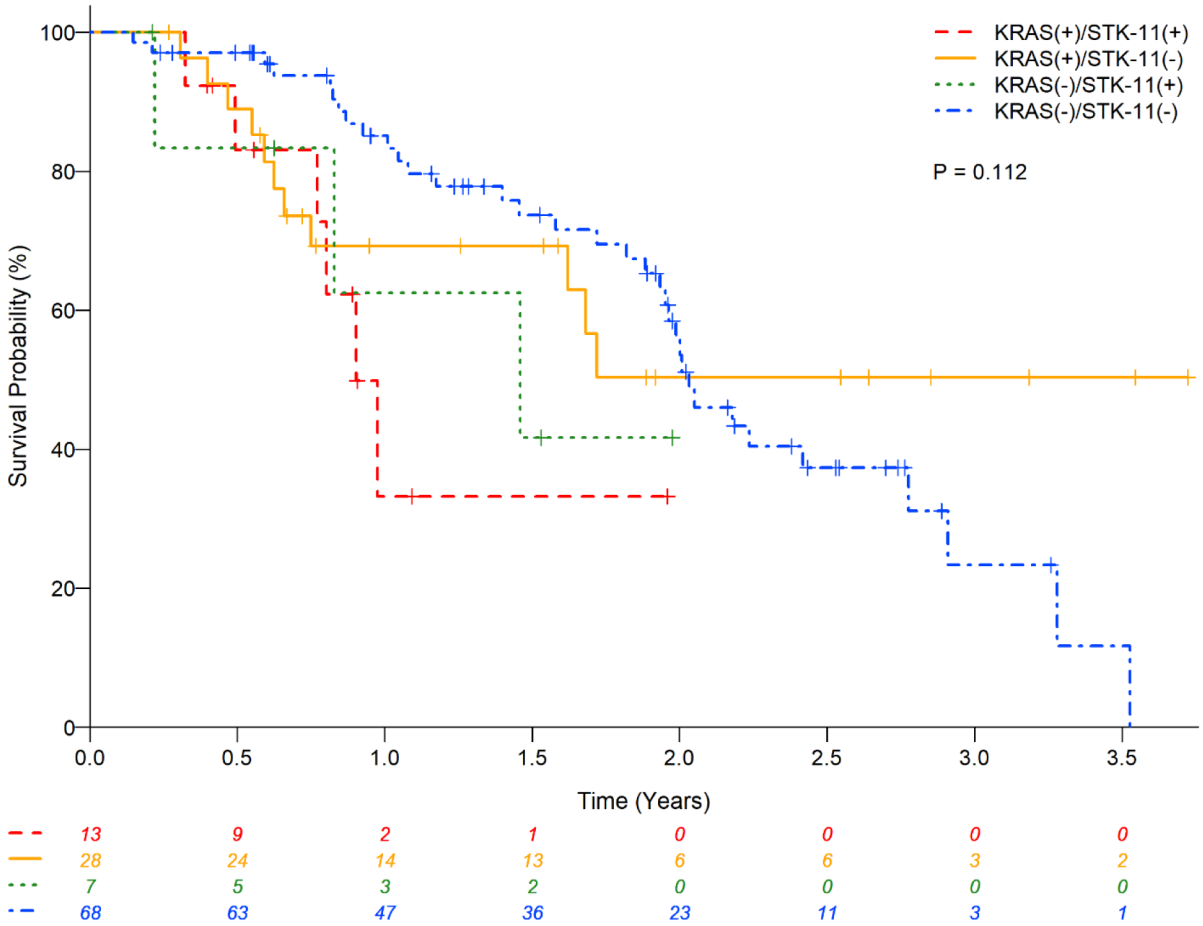

Figure 5.

Kaplan-Meier estimates for patients with lung adenocarcinomas stratified by KRAS and STK11 molecular status.

Table 1A.

Characteristics of patients with *KRAS* mutant and wild type lung adenocarcinomas.

Variable	*N*= 1655
KRAS mutation	
Mutation	450 (27.19)
Wildtype	1205 (72.81)
KRAS associated co-mutation	
Yes	509 (30.83)
No	1142 (69.17)
Missing	4
KRAS with/without associated Co-mutation	
KRAS mutation/Co-mutation	14 (0.85)
KRAS mutation/No co-mutation	436 (26.41)
KRAS wildtype/Co-mutation	495 (29.98)
KRAS wildtype/No co-mutation	706 (42.76)
Missing	4
Age (Years)	
Median (IQR)	63 (56 - 70)
Missing	6
Gender	
Male	713 (43.08)
Female	942 (56.92)
Race	
African American	100 (6.46)
Asian/Other	74 (4.78)
White	1374 (88.76)
Missing	107
Smoking history	
Current Smoker	165 (10.05)
Former smoker	1014 (61.75)
Never smoker	463 (28.2)
Missing	13
ECOG	
Asymptomatic	529 (32.2)
Symptomatic, fully ambulatory	969 (58.98)
Symptomatic, in bed less than 50% of day	145 (8.83)
Missing	12
Surgery history for lung cancer treatment	
Yes	779 (49.3)
No	801 (50.7)
Missing	75
Radiation treatment history for lung cancer	

Variable	*N*= 1655
Yes	592 (36.39)
No	1035 (63.61)
Missing	28
Chemotherapy history for lung cancer	
Yes	454 (54.18)
No	384 (45.82)
Missing	817
Targeted therapy given	
Yes	384 (26.85)
No	1046 (73.15)
Missing	225

Data are presented as number of patients (%) or median (IQR, interquartile range).

Table 1B.

Number of patients tested for a given marker in all patients (*N*= 1655)

Variable	*N*= 1655
AKT1 tested	
No	164 (19.32)
Yes	685 (80.68)
Missing	806
BRAF V600E tested	
No	93 (10.95)
Yes	756 (89.05)
Missing	806
oBRAF tested	
No	93 (10.95)
Yes	756 (89.05)
Missing	806
ERBB2 tested	
No	304 (35.81)
Yes	545 (64.19)
Missing	806
KRAS tested	
Yes	849 (100)
Missing	806
MAP2K1 tested	
No	133 (15.67)
Yes	716 (84.33)
Missing	806
NRAS tested	
No	93 (10.95)
Yes	756 (89.05)
Missing	806
PIK3CA tested	
No	93 (10.95)
Yes	756 (89.05)
Missing	806
sEGFR tested	
No	91 (10.72)
Yes	758 (89.28)
Missing	806
oEGFR tested	
No	91 (10.72)
Yes	758 (89.28)
Missing	806

Variable	***N*= 1655**
ALK tested	
No	49 (5.77)
Yes	800 (94.23)
Missing	806
ampMET tested	
No	190 (22.38)
Yes	659 (77.62)
Missing	806
ROS1 tested	
No	54 (6.36)
Yes	795 (93.64)
Missing	806
RET tested	
No	69 (8.13)
Yes	780 (91.87)
Missing	806
mutPTEN tested	
No	502 (59.13)
Yes	347 (40.87)
Missing	806
TP53 tested	
No	469 (55.24)
Yes	380 (44.76)
Missing	806
STK11 tested	
No	470 (55.36)
Yes	379 (44.64)
Missing	806

Data are presented as number of patients (%).

oBRAF: BRAF other than *V600E; sEGFR*: sensitizing *EGFR; oEGFR*: non-sensitizing *EGFR*.

Table 1C.

Characteristics of patients with *KRAS* mutant lung adenocarcinomas.

Variable	*N*= 450
KRAS mutation	
With associated co-mutation	14 (3.11%)
Without associated co-mutation	436 (96.89%)
Age (years)	
Median (IQR)	65 (58 – 71)
Missing	1
Gender	
Male	190 (42.22%)
Female	260 (57.78%)
Race	
White	401 (93.91%)
Non-White	26 (6.09%)
Missing	23
Smoking history	
Ever Smoker	416 (92.86%)
Never Smoker	32 (7.14%)
Missing	2
ECOG	
0	134 (29.84%)
1	267 (59.47%)
2	48 (10.69%)
Missing	1
KRAS subtype	
*KRAS*_c.34G.T (G12C)	176 (39.11%)
*KRAS*_c.35G.A (G12D)	83 (18.44%)
*KRAS*_c.35G.T (G12V)	80 (17.78%)
KRAS codon	
Codon 12	389 (86.44%)
Codon 13	32 (7.11%)
Codon 61	29 (6.44%)
Surgery history for lung cancer treatment	
Yes	227 (52.42%)
No	206 (47.58%)
Missing	17
Radiation treatment history for lung cancer	
Yes	156 (35.14%)
No	288 (64.86%)
Missing	6
Chemotherapy history for lung cancer	

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Variable	*N*= 450
Yes	117 (50.87%)
No	113 (49.13%)
Missing	220
Targeted therapy given	
Yes	37 (9.02%)
No	373 (90.98%)
Missing	40

Data are presented as number of patients (%, percentage) or median (IQR, interquartile range).

Table 2.

Incidence of associated co-mutations in *KRAS* mutant patients with lung adenocarcinomas.

Associated Co-mutation	Number of patients tested for a specific co-mutation	Number of patients with a specific co-mutation (%)
TP53	93	48 (52%)
STK11	92	17 (18%)
ampMET	174	7 (4%)
PIK3CA	231	9 (3.9%)
sEGFR	232	3 (1.3%)
BRAF V600E	231	1 (0.4%)
NRAS	231	1 (0.4%)
AKT1	207	0 (0%)
oBRAF	231	0 (0%)
ERBB2	151	0 (0%)
MAP2K1	221	0 (0%)
oEGFR	232	0 (0%)
ALK	218	0 (0%)
ROS1	213	0 (0%)
RET	207	0 (0%)
mutPTEN	91	0 (0%)

Table 3.

Univariate association of *KRAS* mutation vs. wildtype with covariates in patients with lung adenocarcinomas.

Variable	*KRAS* mutation/No associated co-mutation (*N*= 436)	*KRAS* wildtype/No associated co-mutation (*N*= 706)	*P*
Age (years), median (IQR)	65 (56 - 70)	64 (56 - 70)	0.031
Male	185 (42.43)	339 (48.02)	0.066
White	390 (94.2)	595 (88.94)	0.003
Ever smoker	403 (92.86)	528 (75.86)	<.001
ECOG			0.470
0	132 (30.34)	207 (29.49)	
1	256 (58.85)	433 (61.68)	
2	47 (10.8)	62 (8.83)	
Surgery history for lung cancer treatment	221 (52.74)	354 (52.29)	0.883
Radiation treatment history for lung cancer	154 (35.81)	271 (39.11)	0.269
Chemotherapy history for lung cancer	111 (51.15)	245 (61.56)	0.013

Data are presented as number of patients (%) or median (IQR, interquartile range).

P-value is calculated by Wilcoxon rank-sum test for age, and chi-square test or Fisher's exact test for categorical variables, where appropriate.

Table 4.

Univariate association of *KRAS* mutations subtypes with covariates in patients with KRAS mutant lung adenocarcinomas.

Variable	*KRAS*_c.34G.T (G12C) (*N*= 176)	*KRAS*_c.35G.A (G12D) (*N*= 83)	*KRAS*_c.35G.T (G12V) (*N*= 80)	*P*
Age (years), median (IQR)	64 (58 – 71)	65 (58 – 71)	66 (58 – 71)	0.925
Male	74 (42.05)	37 (44.58)	35 (43.75)	0.920
White	157 (95.73)	77 (96.25)	67 (90.54)	0.230
Ever smoker	173 (98.3)	65 (78.31)	75 (94.94)	<0.001
ECOG				0.984
0	52 (29.71)	24 (28.92)	22 (27.5)	
1	106 (60.57)	50 (60.24)	51 (63.75)	
2	17 (9.71)	9 (10.84)	7 (8.75)	
Co-mutations	4 (2.27)	4 (4.82)	1 (1.25)	0.397
Surgery history for lung cancer treatment	89 (52.66)	42 (52.5)	37 (48.05)	0.783
Radiation treatment history for lung cancer	63 (36.42)	24 (29.27)	28 (35.44)	0.520
Chemotherapy history for lung cancer	43 (48.31)	23 (67.65)	21 (44.68)	0.092
Targeted therapy given	9 (5.63)	9 (12.16)	8 (10.96)	0.169

Data are presented as number of patients (%) or median (IQR, interquartile range).

P-value is calculated by Kruskal-Wallis test for age, and chi-square test or Fisher's exact test for categorical variables, where appropriate.

Table 5.

Univariate association of *KRAS* mutation subtypes with covariates in *KRAS* mutant patients with lung adenocarcinomas.

Variable	Codon 12 (*N*= 389)	Codon 13 (*N*= 32)	Codon 61 (*N*= 29)	*P*
Age (years), median (IQR)	65 (58 – 71)	61.5 (58 – 71)	65 (58 – 71)	0.285
Male	164 (42.16)	16 (50)	10 (34.48)	0.471
White	346 (94.28)	27 (87.1)	28 (96.55)	0.236
Ever smoker	360 (92.78)	30 (96.77)	26 (89.66)	0.544
ECOG				0.105
0	109 (28.09)	13 (40.63)	12 (41.38)	
1	240 (61.86)	14 (43.75)	13 (44.83)	
2	39 (10.05)	5 (15.63)	4 (13.79)	
Co-mutations	11 (2.83)	1 (3.13)	2 (6.9)	0.284
Surgery history for lung cancer treatment	195 (51.86)	14 (50)	18 (62.07)	0.550
Radiation treatment history for lung cancer	131 (34.11)	15 (48.39)	10 (34.48)	0.277
Chemotherapy history for lung cancer	102 (51.52)	7 (43.75)	8 (50)	0.834
Targeted therapy given	31 (8.78)	3 (9.68)	3 (11.54)	0.805

Data are presented as number of patients (%) or median (IQR, interquartile range).

P-value is calculated by Kruskal-Wallis test for age, and chi-square test or Fisher's exact test for categorical variables, where appropriate.

Table 6.

Comparison of covariates in patients with lung adenocarcinomas with different molecular status.

Variable	*KRAS* mutation/ no associated co-mutation (*N*= 436)	*sEGFR* mutation/ no associated co-mutation (*N*= 174)	*oEGFR* mutation/ no associated co-mutation (*N*= 104)	*ALK* rearrangemen/ no associated co-mutation (*N*= 95)	*KRAS* wildtype/ no associated co-mutation (*N*= 706)	*P*
Age (years), median (IQR)	65 (56 - 70)	61 (56 - 70)	63 (56 - 70)	54.5 (46 - 63)	64 (56 - 70)	<0.001
White	390 (94.2)	124 (79.49)	78 (81.25)	79 (92.94)	595 (88.94)	<0.001
Ever smoker	403 (92.86)	75 (43.1)	42 (40.38)	41 (43.16)	528 (75.86)	<0.001
ECOG						
0	132 (30.34)	68 (39.53)	41 (40.59)	38 (40.43)	207 (29.49)	0.023
1	256 (58.85)	96 (55.81)	51 (50.5)	49 (52.13)	433 (61.68)	
2	47 (10.8)	8 (4.65)	9 (8.91)	7 (7.45)	62 (8.83)	
Surgery history for lung cancer treatment	221 (52.74)	52 (31.9)	49 (51.58)	45 (48.39)	354 (52.29)	<0.001
Radiation treatment history for lung cancer	154 (35.81)	49 (28.82)	44 (43.14)	39 (41.49)	271 (39.11)	0.067
Chemotherapy history for lung cancer	111 (51.15)	39 (41.49)	9 (52.94)	12 (35.29)	245 (61.56)	<0.001
Targeted therapy given	33 (8.31)	151 (88.82)	70 (70.71)	65 (69.15)	21 (3.87)	<0.001

Data are presented as number of patients (%) or median (IQR, interquartile range).

P-value is calculated by Kruskal-Wallis test for age, and chi-square test or Fisher's exact test for categorical variables, where appropriate.

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Table 7.

Univariate and multivariable analyses with *KRAS* mutation with and without co-mutation, *KRAS* subtypes, *KRAS* codon on overall survival in Patients with *KRAS* mutation.

Variable		Univariate		Multivariable analysis with					
				KRAS co-mutation		*KRAS* subtypes		*KRAS* codon	
	N	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
KRAS mutation/co-mutation									
KRAS mutation/co-mutation	14	0.68 (0.28-1.65)	0.390	0.35 (0.13-0.97)	**0.044**	Not included		Not included	
KRAS mutation/No co-mutation	436	1 (Reference)		1 (Reference)					
KRAS main subtypes			0.806 *				0.112 *		
*KRAS*_c.34G.T (G12C)	176	0.96 (0.65-1.41)	0.836	Not included		0.95 (0.54-1.68)	0.866	Not included	
*KRAS*_c.35G.A (G12D)	83	1.08 (0.70-1.67)	0.720			1.68 (0.88-3.23)	0.116		
*KRAS*_c.35G.T (G12V)	80	1 (Reference)				1 (Reference)			
KRAS codon			0.367 *	Not included		Not included			0.574 *
Codon 12	389	1.12 (0.64-1.97)	0.689					1.09 (0.48-2.52)	0.833
Codon 13	32	1.53 (0.76-3.08)	0.232					1.61 (0.55-4.74)	0.389
Codon 61	29	1 (Reference)						1 (Reference)	
Age (Years)	449	1.00 (0.98-1.01)	0.531	†		†		†	
Gender									
Male	190	1.29 (0.99-1.67)	0.057	1.37 (0.93-2.01)	0.109	1.54 (0.98-2.43)	0.061	1.43 (0.97-2.11)	0.068
Female	260	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Race									
Non-White	26	0.78 (0.42-1.42)	0.412	†		†		†	
White	401	1 (Reference)							
Smoking history									
Ever Smoker	416	0.76 (0.45-1.29)	0.313	†		†		†	
Never smoker	32	1 (Reference)							
ECOG			**<0.001** *		**<0.001** *		**<0.001** *		**<0.001** *
1	267	1.96 (1.42-2.72)	**<0.001**	2.46 (1.44-4.20)	**<0.001**	2.37 (1.23-4.57)	**0.010**	2.42 (1.41-4.14)	**0.001**
2	48	3.77 (2.45-5.80)	**<0.001**	4.76 (2.33-9.71)	**<0.001**	5.82 (2.58-13.14)	**<0.001**	4.77 (2.31-9.83)	**<0.001**

Variable		Univariate		Multivariable analysis with					
				KRAS co-mutation		*KRAS* subtypes		*KRAS* codon	
	N	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
0	134	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Surgery history for lung cancer treatment									
Yes	227	0.44 (0.33-0.58)	**<0.001**	0.62 (0.42-0.92)	**0.017**	†		0.65 (0.44-0.97)	**0.035**
No	206	1 (Reference)		1 (Reference)				1 (Reference)	
Radiation treatment history for lung cancer									
Yes	156	0.67 (0.51-0.89)	**0.006**	†		†		†	
No	288	1 (Reference)							
Chemotherapy history for lung cancer									
Yes	117	0.58 (0.39-0.85)	**0.005**	0.60 (0.40-0.90)	**0.013**	0.64 (0.39-1.04)	0.070	0.63 (0.42-0.94)	**0.024**
No	113	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Targeted therapy given									
Yes	37	0.71 (0.44-1.14)	0.157	†		†		†	
No	373	1 (Reference)							

230 observations were used in the multivariable models with KRAS co-mutation and with KRAS codon.

170 observations were used in the multivariable mode with KRAS main subtypes.

*Overall *P*-value for variables with more than 2 categories.

†Dropped out of the final multivariable model.

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Table 8.

Univariate Association of *STK11* co-mutation vs. No co-mutation with Covariates in Patients with *KRAS* mutation from LCMC 2 (N=232).

Variable	*STK11* mutation (*N*= 17)	*STK11* No mutation (*N*= 75)	*P*
Age (Years)			
Median (IQR)	61 (58 - 71)	67 (58 - 71)	0.081
Gender			
Male	9 (52.94)	30 (40)	0.330
Female	8 (47.06)	45 (60)	
Race			
Non-White	1 (5.88)	3 (4)	0.322
Unknown	0 (0)	10 (13.33)	
White	16 (94.12)	62 (82.67)	
Smoking history			
Current Smoker	2 (11.76)	11 (14.86)	1.000
Former smoker	14 (82.35)	58 (78.38)	
Never smoker	1 (5.88)	5 (6.76)	
ECOG			
0	5 (29.41)	12 (16)	0.442
1	10 (58.82)	51 (68)	
2	2 (11.76)	12 (16)	
Surgery history for lung cancer			
Yes	7 (41.18)	30 (40)	0.929
No	10 (58.82)	45 (60)	
Radiation treatment history for lung cancer			
Yes	3 (17.65)	26 (34.67)	0.173
No	14 (82.35)	49 (65.33)	
Chemotherapy history for lung cancer			
Yes	8 (47.06)	40 (54.05)	0.602
No	9 (52.94)	34 (45.95)	
Targeted therapy given			
Yes	1 (6.67)	3 (4.55)	0.567
No	14 (93.33)	63 (95.45)	

Data are presented as number of patients (column %) or median (IQR, interquartile range). *P*-value is calculated by Wilcoxon rank-sum test for age; and chi-square or Fisher's exact test for categorical variables, where appropriate.

Table 9.

Univariate and multivariable analyses with presence or absence of mutation *STK11* on overall survival in patients with lung adenocarcinomas.

Variable	Univariate				Multivariable	
	N	**Median OS years (95% CI)**	**Hazard Ratio (95% CI)**	***P***	**Hazard Ratio (95% CI)**	**P**
KRAS/STK11/No other comutations				0.135 *		0.158 *
KRAS (+) / *STK11* (+)	13	0.9 (0.49 – n/a)	2.66 (1.07-6.60)	0.035	2.22 (0.88-5.61)	0.093
KRAS (+) / *STK11* (−)	28	NA (0.75 – n/a)	0.90 (0.45-1.80)	0.762	0.84 (0.42-1.68)	0.625
KRAS (−) / *STK11* (+)	7	1.46 (0.22 – n/a)	1.85 (0.56-6.13)	0.312	2.38 (0.70-8.05)	0.164
KRAS (−) / *STK11* (−)	68	2.03 (1.93 - 2.78)	1 (Reference)		1 (Reference)	

* Overall *P*-value.

116 observations were used in the multivariable model. Multivariable model was adjusted for chemotherapy history.