The Prevalence and Concurrent Pathogenic Mutations of KRAS<sup>G12C</sup> in Northeast Chinese Non-small-cell Lung Cancer Patients

**Objective:** KRAS mutation is one of important driver genes in non-small-cell lung cancer (NSCLC) and the patients with KRAS<sup>G12C</sup> mutations benefit from the inhibitor AMG510. However, the frequency, concurrent pathogenic mutations, and clinical characteristic of KRAS<sup>G12C</sup> is unknown in the NSCLC population of Northeast China.

**Methods:** The retrospective analysis was derived from 431 NSCLC patients in Jilin Cancer Hospital between January 2018 and June 2019. The mutation frequency and concurrent mutations of KRAS<sup>G12C</sup> in tumor or peripheral blood was detected by next-generation sequencing (NGS).

**Results:** The RAS mutant rate was observed in 10.7% (46/431) of this cohort. All RAS-driver cancers are caused by mutations in the KRAS isoform, while the NRAS and HRA isoforms were not detected. Among KRAS-mutant patients, 42 (91.3%) showed exon 2 mutation in 12 codon and 13 codon. KRAS<sup>G12C</sup> showed a 4.6% (20/431) mutation rate in this cohort and the highest frequency (43.5%, 20/46) in KRAS-mutant-positive patients. There was no difference between tumor tissue and plasma in terms of either KRAS or KRAS<sup>G12C</sup> mutation. The most frequent co-occurrence mutations with KRAS<sup>G12C</sup> were TP53, followed by PTEN. Furthermore, KRAS<sup>G12C</sup> was exclusive with STK11 mutation. KRAS<sup>G12C</sup> mutation was associated with age, disease stage, and smoking status ($P=0.024$; $P=0.02$; $P=0.006$), smoking remained an independent factor for KRAS<sup>G12C</sup> mutation ($P=0.037$), and higher mutation frequency in patients older than 60, stage I–III, or smoking in NSCLC ($P=0.0151$, $P=0.0343$, $P=0.0046$, respectively).

**Conclusion:** KRAS mutation was the only isoforms of RAS family, of these 43.5% harbored the KRAS<sup>G12C</sup> subtype in northeastern Chinese NSCLC patients. KRAS<sup>G12C</sup> is associated with age, pathological stage and smoking status, more commonly harbored TP53/PTEN mutations, and providing more genome profile for targeted therapy in local clinical practice.

**Keywords:** next-generation sequencing, non-small-cell lung cancer, KRAS<sup>G12C</sup>, tissue, plasma, mutations

**Introduction**

Non-small-cell lung cancer (NSCLC) is the most common histological type of lung cancer, accounting for 80–85% of lung cancers and has become the most fatal cancer in the world. Recently, targeted therapy based on various driver oncogene variants (EGFR, ALK and ROS1, KRAS, MET, PIK3CA, RET, BRAF) has shown great antitumor activity; unfortunately, KRAS mutations had a more complicated mechanism in comparison with other driver genes such as EGFR, with poor prognosis and high risk of tumor recurrence. Although prevalent, no specific treatment has been successfully developed for these NSCLCs.

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KRAS mutations are some of the most prevalent alterations, approximately 10% of Asian NSCLC patients and 7.5% of Chinese NSCLC patients harbor the KRAS mutation, with codon 12 and 13 mutations being the most frequent and the most common subtypes are G12C, G12V and G12D. KRAS<sup>G12C</sup> is a mutant type of KRAS guanosine triphosphatase (GTPase), and an inhibitor targeting KRAS<sup>G12C</sup> is a promising novel tumor-specific therapy for tumors driven by mutant proteins. Current studies on KRAS<sup>G12C</sup> inhibitors and the mechanism of drug resistance have confirmed that patients with KRAS<sup>G12C</sup> mutations benefit from the inhibitor AMG510, which has also been approved by the FDA as an orphan drug for NSCLC and colon cancer with KRAS<sup>G12C</sup> mutation. KRAS<sup>G12C</sup> can induce allosteric switch II pocket (s-ii) and take cys-12 as the specific covalent target of alleles, which were considered as potential drug targets. Now, KRAS<sup>G12C</sup> mutation was verified by the NGS, various clinical parameters and genetic mutation have been proposed to predict the relevance with KRAS<sup>G12C</sup> (such as sex, age, smoking, co-mutation gene). In the current study we aim to discover a more precise delineation of candidate target populations and distinctive KRAS<sup>G12C</sup> co-mutation subtypes in the northeast Chinese population. We retrospectively investigated and evaluated the KRAS<sup>G12C</sup> mutation in northeast Chinese NSCLC, and the association between clinical factors and KRAS<sup>G12C</sup> mutation status.

**Materials and Methods**

### Patients and Samples

Four hundred and thirty-one samples were collected from Jilin Cancer Hospital between January 2018 and June 2019, 268 cases were tested through eight gene panel, 81 cases by 168 gene panel and 82 matched cases using 520 gene panel, respectively (Figure 1). Clinic pathological data were collected from the electronic medical records in Jilin Cancer Hospital, and the factors included age, sex, and clinical stage, smoking history, brain metastasis, PS score and histology. All participants signed the informed consent agreement before participating in the study, the data was anonymized, the study was approved by the Clinical Research Ethics Committee of Jilin Cancer Hospital and was conducted in accordance with the Declaration of Helsinki.

### DNA Extraction

DNA was extracted by DNA FFPE tissue kit (AmoyDx, China) and ctDNA extraction kit (QIAGEN, Germany) according to the manufacturer’s instructions. DNA concentration was quantified by Nanodrop 3000C and Qubit 4.0 (Thermo Fisher Scientific, Waltham, MA, USA).

### Next-generation Sequencing Analysis

Library preparation was performed following manufacturer’s protocol (Burning Rock Biotech, Guangzhou, China). DNA Fragments (range: 200–400 bp) were purified by AMPure beads (Beckman Coulter, CA, USA), and captured with probe baits, hybrid selection with magnetic beads by RT-PCR amplification. Subsequently, DNA quality and size were assessed by high-sensitivity DNA assay. Indexed samples were sequenced on a MiSeq system (Beckman Coulter) with paired-end reads. The input of extracted DNA should be in the range of (30–200 ng). Sequencing platform was used by Illumina NextSeq 500 Sequencing Platform with tissue DNA (1000X) and cfDNA (20000X). All samples were analyzed by NGS targeted panel (Burning Rock Dx, China), which eight-gene panel covers well-known lung adenocarcinoma driver genes, 168 genes covers known lung cancer-related genes and 520 genes covers solid tumor-related genes. (Supplemental Table 1).

### Statistical Analysis

All data was performed by SPSS Statistics 19.0 software (IBM Corporation, Armonk, NY, USA). Fisher’s exact test was used to evaluate mutation differences and clinical factor between KRAS<sup>G12C</sup> and KRAS<sup>wt</sup>. Logistic regression analysis was used.
to identify as independent factors for \( \text{KRAS}^{G12C} \) mutations. A \( P \)-value of <0.05 was considered statistically significant.

## Results

### Patient Population

Among 431 samples were those from tumor tissue 332 (77.04%), 99 (22.96%) plasma; 198 women (54.07%) and 233 men (45.93%), with a median age of 63 years (range: 34–86 years), respectively. Of the 431 patients, 263 (61.02%) were smokers, and 168 were nonsmokers. The histological characterization of tumors revealed that 370 samples were adenocarcinoma (85.85%), 61 were squamous cell carcinoma (14.15%). Of the 431 patients, characterization of the pathological stage showed 115 samples in stage I–III (26.68%), and 316 samples in stage IV (73.32%) (Table 1).

**KRAS\(^{G12C}\) is the Most Common Mutation Type of KRAS in NSCLC**

The \( \text{RAS} \) mutation rate was 10.7% (46/431), and \( \text{KRAS} \) was the only mutation subtype of \( \text{RAS} \) (\( \text{NRAS} \), \( \text{KRAS} \), \( \text{HRAS} \)). 42 (91.3%) indicated \( \text{KRAS} \) gene exon 2 mutation, 12 and 13 codon of \( \text{KRAS} \) gene mutations were detected, and \( \text{KRAS}^{G12C} \) showed the highest frequency, the total mutation rate of \( \text{KRAS}^{G12C} \) in NSCLC was 4.6% (20/431) and 43.5% (20/46) of \( \text{KRAS} \) mutant subtypes, followed by 17.4% (8/46) of \( \text{KRAS}^{G12D} \), 8.7% (4/46) of \( \text{KRAS}^{G12V} \), and 8.7% (4/46) of \( \text{KRAS}^{G12A} \). The mutation frequency of other \( \text{KRAS} \) types was lower (Figure 2).

**Figure 2** Mutation frequencies of \( \text{KRAS} \) subtypes.

### KRAS\(^{G12C}\) Mutation Between Tumor Tissue and Plasma

We compared the \( \text{KRAS} \) mutation spectrums between tumor tissue and ctDNA derived from peripheral blood in this study. Collectively, 37 (11.14%) and 16 (4.81%) patients had \( \text{KRAS} \) and \( \text{KRAS}^{G12C} \) mutation spectrum in tumor tissue, nine (9.09%) and four (4.04%) patients in ctDNA, but no significant difference was found in the two sample types (\( P = 0.711 \), \( P = 1.000 \), Table 2), respectively.

### Co-occurring Genomic Alterations Between \( \text{KRAS}^{G12C} \) and Lung Cancer Pathogenic Gene

Lung cancer driver genes (include \( \text{EGFR} \), \( \text{RAS} \), \( \text{ALK} \), \( \text{ROS1} \), \( \text{MET} \), \( \text{RET BRAF} \), and \( \text{HER-2} \)) mutation samples were observed in 332 (77.3%) of 431 patients. Eight (40%) of 20 patients harbored only \( \text{KRAS}^{G12C} \)

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**Table 1** Patient Characteristics

| Characteristics | n (%)     |
|-----------------|-----------|
| Age (years)     | 63 (34–86)|
| Sex             |           |
| Male            | 198 (45.93) |
| Female          | 233 (54.07) |
| Stage I–III     | 115 (26.68) |
| IV              | 316 (73.32) |
| Smoking history |           |
| Yes             | 168 (38.98) |
| No              | 263 (61.02) |
| Brain metastasis|           |
| Yes             | 106 (24.59) |
| No              | 325 (75.41) |
| PS score 0–1    | 365 (84.68) |
| 2–3             | 66 (15.32)  |
| Histology       |           |
| Adenocarcinoma  | 370 (85.85) |
| Squamous cell carcinoma | 61 (14.15) |

**Table 2** Mutation Frequencies of KRAS Subtypes Between Tumor Tissue and Plasma

| Sample Type | \( \text{KRAS} \) | \( \text{KRAS}^{G12C} \) |
|-------------|------------------|----------------------|
|             | mut  | wt  | mut  | wt  | mut  | wt  | P     |
| Tumor tissue| 37   | 295 | 0.711| 16   | 316  | 0.001|
| Plasma      | 9    | 90  | 4    | 95   |      |      | 0.35  |
| Total       | 46   | 385 | 20   | 411  |      |      | 0.01  |
mutations, and 12 (60%) had multiple KRAS\textsuperscript{G12C} mutations, including eight (40%) KRAS\textsuperscript{G12C} patients had co-occurring driver oncogenes, was higher trend than KRAS\textsuperscript{other} with driver oncogenes mutations (6/26, 23%), but no statistical significance ($P=0.33$), the most commonly co-occurring genomic alterations with KRAS\textsuperscript{G12C} were EGFR (10%, 2/20), ROSI (10%, 2/20), MET (10%), HER2 (5%, 1/20), ALK (5%, 1/20), BRAF (5%, 1/20), and RET (0%), respectively (Figure 3, Supplemental Table 2). One hundred and sixty-three patients from 168 gene panel or 520 gene panel found that the KRAS\textsuperscript{G12C} gene is often accompanied by TP53 and PTEN mutation, the mutation rates were 50% (3/6) and 16.7% (1/6), respectively, but STK11 (0.0%, 0/6).

![Figure 3 Driver genetic mutations spectrums identified by next-generation sequencing of 332 patients with NSCLC tumor tissue and plasma. Side bar represents the percentage of patients with driver gene mutation. Top bar represents the number of mutations per patient. Different types of mutations are denoted in different colors.](https://www.dovepress.com/figure-3-driver-genetic-mutations-spectrums-identified-by-next-generation-sequencing-of-332-patients-cl1308782g2.png)
Age, Smoking History and Pathological Stage Associated with KRAS<sup>G12C</sup> Mutation

The mutation rate of KRAS<sup>G12C</sup> gene in smokers was higher than that in nonsmokers, 8.33% (14/168) vs 2.28% (6/263), P=0.0046. KRAS<sup>G12C</sup> has a higher mutation rate in age (≥60 years) 15.2% (18/274) vs 1.27% (2/157); P=0.0151. KRAS<sup>G12C</sup> mutation was associated with the pathological staging of the patients, 8.69% (10/115) vs 3.16% (10/316), P=0.0343, but was not associated with gender, brain metastasis, PS score, and histology (P=0.2515, P=0.4282, P=0.5266 and P=0.7526) (Table 3), to further identify the values of clinical factor on KRAS<sup>G12C</sup> mutations, logistic regression analysis was included. In the univariate logistic analysis, age, smoker, clinical stage were identified as independent factors for KRAS<sup>G12C</sup> mutations (OR=0.551, P=0.02; OR=0.343, P=0.006). In the multivariate logistic model, smoker (OR=0.306, P=0.037) remained independent factors for KRAS<sup>G12C</sup> (Table 4).

Furthermore, we found that KRAS<sup>G12C</sup> was dominant in male smokers (100%, 4/4).

**Discussion**

Previously reported RAS was detected in about 25–30% of tumors, several studies consistently reported that Westerners have a higher mutation rate than Asians (26% vs 11%). Another report similarly indicated 30% of RAS mutations in Western patients and 5–15% in the Asian population, which accounts for about 86% KRAS, 11% NRAS and 3% HRAS mutation of RAS-induced NSCLC, KRAS accounts for 90% of RAS gene mutations in lung adenocarcinoma and is the most common oncogene in NSCLC. Our data are consistent with recent studies, our results might indicate the current view that KRAS was the only RAS-mutant isoform, the mutation rate was 10.7% in 431 NSCLC patients, similar to the rates reported by Jia’s group and Liu’s group. Further studies showed that the KRAS<sup>G12C</sup> mutation rate is 4.6% in lung cancer, and 43.5% in KRAS mutation for our study. It was similar to several studies in that the KRAS<sup>G12C</sup> mutation frequency range is from 35% to 45% followed by EGFR<sup>-</sup>-TKI resistance. Unfortunately, neither were the four cases derived from two separate tumor tissue. The incidence rate of EGFR-KRAS in the Chinese cohort might be likely ethnic-unique, based on the knowledge that the prevalence of EGFR mutation is higher in the Asian population. The co-occurrence of EGFR and KRAS was 0.92% (4/431) in our study, which was supported by Scheffler et al (1.2%). The four concomitant mutations were KRAS<sup>G12C</sup> (n=2) co-occurring with either EGFR V1097I (n=1) or EGFR amplification (n=1) and KRAS<sup>S61H</sup> (n=2) co-occurring with EGFR 19del (n=2). Although previous studies had reported that KRAS are mutually exclusive with mutations in EGFR and ALK in NSCLC, but coexisting EGFR and KRAS mutations have also been reported. (Zhu et al reported that three

| Table 3 | Correlation Analysis Between KRAS<sup>G12C</sup> and Clinic Pathological Factors in Patients |
|---------|---------------------------------------------|
|         | KRAS<sup>G12C</sup>, mut n=20 | KRAS<sup>G12C</sup>, wt n=411 | P-value |
| Sex     |                                |                                |         |
| Male    | 12                             | 186                            | 0.2515  |
| Female  | 8                              | 225                            |         |
| Age     |                                |                                |         |
| <60 year| 2                              | 155                            | 0.0151* |
| ≥60 year| 18                             | 256                            |         |
| Stage   |                                |                                |         |
| I–III   | 10                             | 105                            | 0.0343* |
| IV      | 10                             | 306                            |         |
| Smoking history |                    |                                |         |
| Yes     | 14                             | 154                            | 0.0046**|
| No      | 6                              | 257                            |         |
| Brain metastasis |                   |                                |         |
| Yes     | 3                              | 103                            | 0.4282  |
| No      | 17                             | 308                            |         |
| PS score |                               |                                |         |
| 0–1     | 16                             | 349                            | 0.5266  |
| 2–3     | 4                              | 62                             |         |
| Histology |                             |                                |         |
| Adenocarcinoma |                |                                |         |
| Squamous cell carcinoma | |                                |         |

Notes: *P-value <0.05; **P-value <0.01.
Abbreviations: mut, mutation; wt, wild type.
patients with coexisting EGFR and KRAS mutations were found in 206 patients (1.4%). We infer that genetic mutation status could be related with different races, sample numbers, as well as test methodology. Nevertheless, current data about KRAS co-occurring mutations in lung cancer is insufficient. Co-occurrence with TP53 or STK11 mutations is common in KRAS mutations. KRAS and TP53 co-mutations indicated that tumors harboring those mutations could be more responsive to immune checkpoint inhibition in lung cancer. Conversely, tumors harboring concurrent KRAS and STK11 mutations could be associated with an immunosuppressive microenvironment. Furthermore, the absence of PTEN promotes resistance to T cell-mediated immunotherapy. So we evaluated the mutation status of TP53, STK11 or PTEN in KRASG12C mutant patients, and it indicated that in the landscape of concurrent genetic alterations in patients with KRASG12C, the co-mutation rates were 50% and 16.7%, but KRASG12C was exclusive with STK11 mutation.

KRASG12C (c.34G>T) alteration is a transversion and KRAS transversion mutations (G→T or G→C) were more common in smokers, in contrast, transition mutations (G→A) were more common in never-smokers in lung adenocarcinomas (n=500). Our data showed that smokers more commonly harbored KRASG12C mutations than KRAS<sup>wt</sup> (70% vs 37.5%), which is consistent with reports by Liu et al and Dogan et al. Data showed that KRAS mutant NSCLC is genetically complex, with a higher frequency of co-occurring mutations with TP53, STK11, MET and ERBB2 amplifications, however, no conclusions implied that the co-occurrence mutations were related to the transversion. In comparison to KRAS<sup>other</sup>, KRASG12C showed higher mutation frequency in patients older than 60 years, and stage I–III. Our findings were supported by other studies.

In summary, our study indicated that KRASG12C mutations were the most frequent mutant subtype of KRAS in northeast Chinese NSCLC patients and might be involved in the smoking, age, and clinical stage, especially we demonstrated a high frequency of KRASG12C concomitant TP53/PTEN/EGFR. In addition, no difference was observed between tissue and plasma in the KRASG12C.

### Table 4 Univariate and Multivariate Analysis of KRASG12C and Clinical Factor

|                     | Univariate Analysis | Multivariate Analysis |
|---------------------|---------------------|-----------------------|
|                     | OR 95%CI P-value    | OR 95%CI P-value      |
| Sex                 |                     |                       |
| Male                | 1 0.551 0.221–1.377 | 0.202 1 0.363–3.001 0.936 |
| Female              | 0.551 0.221–1.377   |                       |
| Age                 | 1 5.449 1.247–23.805 | 0.024 1 0.868–17.823 0.076 |
| <60                 | 1 5.449 1.247–23.805 | 0.024 1 0.868–17.823 0.076 |
| ≥60                 | 1 3.932 0.868–17.823 |                       |
| Stage               | 1 0.343 0.139–0.847 | 0.02 1 0.154–1.118 0.082 |
| I–III               | 1 0.343 0.139–0.847 |                       |
| IV                  | 1 3.932 0.868–17.823 |                       |
| Smoking history     | 1 0.257 0.097–0.682 | 0.006 1 0.101–0.929 0.037 |
| Yes                 | 1 0.257 0.097–0.682 |                       |
| No                  | 1 0.306 0.101–0.929 |                       |
| Brain metastasis    | 1 1.895 0.544–6.598 | 0.315 1 0.226–3.516 0.871 |
| Yes                 | 1 1.895 0.544–6.598 |                       |
| No                  | 1 0.892 0.226–3.516 |                       |
| PS score            | 1 1.407 0.455–4.350 | 0.553 1 0.388–4.066 0.704 |
| 0–1                 | 1 1.407 0.455–4.350 |                       |
| 2–3                 | 1 1.256 0.388–4.066 |                       |
| Histology           | 1 0.663 0.15–2.932 | 0.588 1 0.147–3.116 0.617 |
| Adenocarcinoma      | 1 0.663 0.15–2.932 |                       |
| Squamous cell cancer| 1 0.677 0.147–3.116 |                       |
subgroup of the northeast Chinese NSCLC patients. Our findings might contribute to distinct therapeutic guidance in NSCLC. More data should be collected and explored to address predictive and prognostic value of KRAS<sup>G12C</sup> in future studies.

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**Disclosure**

Qiang Zhang is an employee of Burning Rock Biotech. The authors report no other potential conflicts of interests.

**References**

1. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115–132. doi:10.3322/caac.21338
2. Janes MR, Zhang J, Li LS, et al. Targeting KRAS Mutant Cancers with a Covalent G12C-Specific Inhibitor. *Cell*. 2018;172:578–589. e17. doi:10.1016/j.cell.2018.01.006
3. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014;511(7511):543–550. doi:10.1038/nature13385
4. Zhuang X, Zhao C, Li J, et al. Clinical features and therapeutic options in non-small cell lung cancer patients with concomitant mutations of EGFR, ALK, ROS1, KRAS or BRAF. *Cancer Med*. 2019;8(6):2585–2586. doi:10.1002/cam4.2183
5. Lou K, Steri V, Ge AY, et al. KRAS G12C inhibition produces a driver-limited state revealing collateral dependencies. *Sci Signal*. 2019;12(583):eaaw9450. doi:10.1126/scisignal.aaw9450
6. Lannman BA, Allen JR, Allen JG, et al. Discovery of a Covalent Inhibitor of KRASG12C (AMG 510) for the Treatment of Solid Tumors. *J Med Chem*. 2020;63:52–65. doi:10.1021/acs.jmedchem.9b01180
7. Ricciuti B, Leonardi GC, Metro G, et al. Targeting the KRAS variant for treatment of non-small cell lung cancer: potential therapeutic applications. *Expert Rev Respir Med*. 2016;10(1):53–68. doi:10.1586/17476388.2016.1115349
8. Palyayeva-Gupta Y, Grabbecka E, Bar-Sagi D. RAS oncogenes: weaving a tumorigenic web. *Nat Rev Cancer*. 2011;11:761–774.
9. Ni D, Li X, He X, Zhang H, Zhang J, Lu S. Drugging K-RasG12C through covalent inhibitors: mission possible? *Pharmacol Ther*. 2019;202:1–17. doi:10.1016/j.pharmthera.2019.06.007
10. Jia Y, Jiang T, Li X, et al. Characterization of distinct types of KRAS mutation and its impact on first-line platinum-based chemotherapy in Chinese patients with advanced non-small cell lung cancer. *Oncol Lett*. 2017;14:6525–6532. doi:10.3892/ol.2017.7016
11. Liu SY, Sun H, Zhou JY, et al. Clinical characteristics and prognostic value of the KRAS G12C mutation in Chinese non-small cell lung cancer patients. *Biomark Res*. 2020;8:22. doi:10.1186/s40364-020-00199-z
12. Aredo JV, Padda SK, Kunder CA, et al. Impact of KRAS mutation subtype and concurrent pathogenic mutations on non-small cell lung cancer outcomes. *Lung Cancer*. 2019;133:144–150. doi:10.1016/j.lungcan.2019.05.015
13. Scheffler M, Ihle MA, Hein R, et al. K-ras mutation subtypes in NSCLC and associated co-occurring mutations in other oncogenic pathways. *J Thorac Oncol*. 2019;14(4):606–616. doi:10.1016/j.jtho.2018.12.013
14. Izar B, Zhou H, Heist RS, et al. The prognostic impact of KRAS, its codon and amino acid specific mutations, on survival in resected stage I lung adenocarcinoma. *J Thorac Oncol*. 2014;9(9):1363–1369. doi:10.1097/JTO.0000000000000266
15. Nadal E, Chen G, Prensner JR, et al. KRASG12C mutation is associated with poor outcome in surgically resected lung adenocarcinoma. *J Thorac Oncol*. 2014;9(10):1513–1522. doi:10.1097/JTO.0000000000000305
16. Ortiz-Cuaron S, Scheffler M, Plenker D, et al. Heterogeneous mechanisms of primary and acquired resistance to third-generation EGFR inhibitors. *Clin Cancer Res*. 2016;22(19):4837–4847. doi:10.1158/1078-0432.CCR-15-1915
17. Han SW, Kim TY, Hwang PG, et al. Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol*. 2005;23(11):2493–2501. doi:10.1200/JCO.2005.01.388
18. Gainor JF, Varghese AM, Ou SH, et al. ALK rearrangements are mutually exclusive with mutations in EGFR and KRAS in non-small cell lung cancer. *Clin Cancer Res*. 2015;21(15):4273–4281. doi:10.1158/1078-0432.CCR-14-3918
19. Unni AM, Lockwood WW, Zejnullahu K, et al. That synthetic lethality underlies the mutual exclusivity of oncogenic KRAS and EGFR mutations in lung adenocarcinoma. *Elife*. 2015;4(4):e06907. doi:10.7554/elife.06907
20. Gumerlock PH, Holland WS, Chen H, et al. Mutational analysis of K-RAS and EGFR implicates K-RAS as a resistance marker in the Southwest Oncology Group (SWOG) trial S0126 of bronchioalveolar carcinoma (BAC) patients (pts) treated with gefitinib. *J Clin Oncol*. 2005;23:623s. doi:10.1200/jco.2005.23.16_suppl.7008
21. Han SW, Kim TY, Jeon YK, et al. Optimization of patient selection for gefitinib in non-small cell lung cancer by combined analysis of epidermal growth factor receptor mutation, K-ras mutation, and Akt phosphorylation. *Clin Cancer Res*. 2006;12:2538–2544. doi:10.1158/1078-0432.CCR-05-2845
22. Zhu CQ, Sants GC, Ding K, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer institute of Canada Clinical Trial Group study BR.21. *J Clin Oncol*. 2008;26(26):4268–4275. doi:10.1200/JCO.2007.14.8924
23. Pao W, Girard N. New driver mutations in non-small-cell lung cancer: potential therapeutic applications. *J Natl Cancer Inst*. 2014;106(1):53–68. doi:10.1093/jnci/djt170
24. Ding L, Getz G, Wheeler DA, et al. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature*. 2008;455(7216):1069e1075. doi:10.1038/nature07423
25. Dong ZY, Zhong WZ, Zhang XC, et al. Potential predictive value of TP53 and KRAS mutation status for response to PD-1 Blockade Immunotherapy in Lung Adenocarcinoma. *Clin Cancer Res*. 2017;23(12):3012–3024. doi:10.1158/1078-0432.CCR-16-2554
26. Skoulidis F, Goldberg ME, Greenawalt DM, et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. *Cancer Discov*. 2018;8:822–835. doi:10.1158/2159-8290.CD-18-0099
27. Schabath MB, Welsh EA, Fulpi WJ, et al. Differential association of STK11 and TP53 with KRAS mutation-associated gene expression, proliferation and immune surveillance in lung adenocarcinoma. *Oncogene*. 2016;35(24):3209–3216. doi:10.1038/onc.2015.375
28. Peng W, Chen JQ, Liu C, et al. Loss of PTEN Promotes Resistance to T Cell-Mediated Immunotherapy. *Cancer Discov*. 2016;6:202–216. doi:10.1158/2159-8290.CD-15-0283
29. El Osta B, Behera M, Kim S, et al. Characteristics and outcomes of patients with metastatic KRAS-mutant lung adenocarcinomas: the lung cancer mutation consortium experience. *J Thorac Oncol*. 2019;14(5):876–889. doi:10.1016/j.jtho.2019.01.020

30. Dogan S, Shen R, Ang DC, et al. Molecular epidemiology of EGFR and KRAS mutations in 3026 lung adenocarcinomas: higher susceptibility of women to smoking-related KRAS-mutant cancers. *Clin Cancer Res*. 2012;18:6169–6177. doi:10.1158/1078-0432.CCR-11-3265

31. Arbour KC, Jordan E, Kim HR, et al. Effects of co-occurring genomic alterations on outcomes in patients with KRAS-mutant non-small cell lung cancer. *Clin Cancer Res*. 2018;24:334–340. doi:10.1158/1078-0432.CCR-17-1841