KRAS G12C—An Emerging Biomarker and Novel Investigational Target in NSCLC
<table>
<thead>
<tr>
<th>1</th>
<th>Review the evolving NSCLC landscape, including actionable and emerging biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Raise awareness that <em>KRAS G12C</em> is the most prevalent emerging molecular target in NSCLC and define patient and tumor characteristics</td>
</tr>
<tr>
<td>3</td>
<td>Discuss clinical guideline recommendations for molecular testing at diagnosis of NSCLC</td>
</tr>
</tbody>
</table>
Lung Cancer Is the Leading Cause of Cancer Death

<table>
<thead>
<tr>
<th>Global Statistics</th>
<th>Histological Subtypes</th>
<th>Late Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Cases</td>
<td>2.1 million</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>1.8 million</td>
<td></td>
</tr>
</tbody>
</table>

2.1 million new cases and 1.8 million deaths due to lung cancer were estimated in 2018, representing 18.4% of cancer-related mortality.

Histological Subtypes

- **NSCLC**
  - Adenocarcinoma: 40%
  - Squamous cell carcinoma: 15%
  - Larger cell cancer: 10%
  - Other: 30%

NSCLC accounts for 80%–85% of all lung cancer cases with adenocarcinoma being the most common subtype.

Late Diagnosis

Most NSCLC patients (66%) are diagnosed with advanced or metastatic disease.

---

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.


Do not copy or distribute. © 2020 Amgen Inc. All rights reserved.
Despite Recent Treatment Advancements, Opportunities Remain to Improve Outcomes for Patients With NSCLC\textsuperscript{1-5}

Survival rates for patients with NSCLC are improving; however, 5-year survival is only 6% for patients with metastatic disease\textsuperscript{1,5}

NSCLC, non-small cell lung cancer; OS, overall survival.

NSCLC Is a Heterogeneous Disease With an Increasing Number of Actionable and Emerging Biomarkers\textsuperscript{1,2}

**Actionable Biomarkers in NSCLC\textsuperscript{3-7}**

- Sensitizing \textit{EGFR} Mutations
- \textit{ALK} Rearrangements
- \textit{ROS1} Rearrangements
- \textit{BRAF} V600E Point Mutation
- \textit{RET} Rearrangements
- \textit{NTRK} Gene Fusions
- \textit{MET} Exon 14 Skipping Mutations

**Emerging Biomarkers Currently Under Investigation in NSCLC\textsuperscript{4,8}**

- \textit{KRAS} Mutations
- \textit{MET} Amplifications
- \textit{ERBB2 (HER2)} Alterations

**Targeted Therapy Under Investigation**

**FDA-Approved Targeted Therapy**

**FDA-Approved Immunotherapy**

Greater understanding of NSCLC heterogeneity has driven personalized approaches to patient management\textsuperscript{2}

ALK, anaplastic lymphoma kinase; \textit{BRAF}, proto-oncogene B-Raf; \textit{EGFR}, epidermal growth factor receptor; \textit{ERBB2}, erb-B2 receptor tyrosine kinase 2; \textit{HER2}, human epidermal growth factor receptor 2; \textit{KRAS}, Kirsten rat sarcoma; \textit{MET}, mesenchymal-to-epithelial transition; NSCLC, non-small cell lung cancer; \textit{NTRK}, neurotrophic tyrosine receptor kinase; \textit{PD-L1}, programmed cell death ligand 1; \textit{RET}, rearranged during transfection; \textit{ROS1}, c-ros oncogene 1; TMB, tumor mutational burden.


Do not copy or distribute. © 2020 Amgen Inc. All rights reserved.
**KRAS G12C** is the Most Prevalent Emerging Molecular Target in NSCLC\(^1,2\)

Identifying driver mutations in NSCLC allows for the potential for personalized medicine\(^1\)

\(13\%\) (1 in 8) of patients with NSCLC have the **KRAS G12C** mutation, which is comparable to the prevalence of **EGFR** mutations (15\%)\(^1,2\)

**KRAS** is one of the most prevalent driver mutations in lung adenocarcinomas\(^1\)

**KRAS G12C in NSCLC**

---

The *KRAS G12C* Mutation Rarely Overlaps With Actionable Driver Mutations

*A retrospective study of 743 adult patients with advanced NSCLC treated in the Flatiron Health network between 2011 and 2019 with a *KRAS G12C* mutation detected via FoundationOne® tumor sequencing.*¹

ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer; ROS1, c-ros oncogene 1.  
1. Aggarwal S. et al. Presented at: The European Society for Medical Oncology; September 2020; Virtual Congress.  

Since *KRAS* mutations do not usually overlap with actionable driver mutations, patients with a *KRAS G12C* mutation are unlikely to be eligible for therapies targeting these other specific mutations¹,²

---

Since *KRAS* mutations do not usually overlap with actionable driver mutations, patients with a *KRAS G12C* mutation are unlikely to be eligible for therapies targeting these other specific mutations¹,²

---

*Amgen Inc. All rights reserved.*
KRAS G12C-Mutated NSCLC Tumors Are Heterogeneous

The KRAS G12C Mutation Can Occur Regardless of Patient Characteristics

While KRAS G12C mutations are more common in patients with nonsquamous histology, ever-smokers, and Caucasian patients, they can be found in any patient with NSCLC.

Comutations Contribute to the Heterogeneity of KRAS G12C Tumors

Patterns of Co-occurring Mutations in KRAS G12C-mutated NSCLC

- KEAP1: 23%
- STK11: 28%
- TP53: 43%

TP53, STK11, and KEAP1 mutations occur frequently in KRAS G12C-mutated NSCLC.

KRAS G12C Tumors Demonstrate Varying Levels of PD-L1 Expression

PD-L1 Expression in Patients With KRAS G12C

- 0%: 48%
- 1%–49%: 25%
- ≥ 50%: 27%

Patients with KRAS G12C mutations have a range of PD-L1 expression; however, more than 60% of patients have no or low PD-L1 expression (< 49%).

TP53, STK11, and KEAP1 mutations contribute to the heterogeneity of KRAS G12C tumors.

KEAP1, kelch-like ECH-associated protein 1; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; STK11, serine/threonine kinase 11; TP53, tumor protein p53.

Patients With **KRAS G12C** Advanced NSCLC Have Limited Treatment Options Following Frontline Treatment$^1,2$

---

**2L+ Treatment for Patients Ineligible for Targeted Therapy$^4$**

- **IO**
- **Chemotherapy**
- **BSC**

---

1. in 5 advanced NSCLC patients with **KRAS G12C** mutations do not receive systemic therapy$^1$

- Patients may only receive best supportive care, potentially due to more advanced disease, comorbidities, and poor performance status$^5,6$

---

There are no currently approved therapies specifically targeting the **KRAS G12C** mutation$^3$

Platinum-based chemotherapies and immunotherapy are the most common treatments$^2$

---

2L, second line; BSC, best supportive care; IO, immunotherapy; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer.

1. Aggarwal S, et al. Presented at: The European Society for Medical Oncology; September 2020; Virtual Congress.
4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. v.6.2020. ©National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 3, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

---

Do not copy or distribute. © 2020 Amgen Inc. All rights reserved.
KRAS G12C Drives Cancer Cell Growth and Survival1-5

- The KRAS pathway regulates cellular proliferation, differentiation, and survival1,2,6
- KRAS G12C is a single point mutation at codon 12, which causes the glycine to be substituted with a cysteine7,8
- The KRAS G12C mutation favors the active form of the KRAS mutant protein, supporting tumorigenesis1,3

AKT, protein kinase B; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAL, Ras-like; RTK, receptor tyrosine kinase.

Despite Nearly Four Decades of Scientific Efforts, Targeting KRAS Has Been One of Cancer Research’s Toughest Challenges

Lack of surface pockets makes tight binding of small molecules difficult

Competitive inhibition is challenging due to the high affinity binding of GTP to KRAS

Nonselective binding to wild-type KRAS can inhibit wild-type KRAS and adversely affect normal cellular signaling

GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma.

Investigating the Structure of KRAS$^{G12C}$ Reveals Unique Features of the Mutant Protein$^1$

1. Cysteine 12 may allow for potential irreversible covalent binding$^2$

2. P2 Pocket is present in the inactive, GDP-bound form of KRAS$^{G12C}$ and provides a potential binding site for small molecules$^3,4$

3. H95 Residue may provide a site to stabilize drug-protein interaction$^1$

GDP, guanosine diphosphate; KRAS, Kirsten rat sarcoma.


Do not copy or distribute. © 2020 Amgen Inc. All rights reserved.
Inhibition of KRAS\(^{G12C}\) Represents an Important Therapeutic Approach in NSCLC and Is Currently Under Investigation\(^{1-7}\)

Targeted inhibitors could selectively lock the KRAS\(^{G12C}\) mutant protein in the inactive state, blocking oncogenic signaling without affecting wild-type KRAS signaling\(^{1,8}\)

AKT, protein kinase B; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; NF-\(\kappa\)B, nuclear factor kappa-light-chain-enhancer of activated B cells; NSCLC, non-small cell lung cancer; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAL, Ras-like; RTK, receptor tyrosine kinase.

Molecular Testing at Diagnosis Is Essential to Assessing Treatment Options in Patients With Advanced NSCLC

Clinical guidelines recommend molecular testing in advanced NSCLC\textsuperscript{2,4,5}

Comprehensive molecular testing allows for selection of appropriate targeted therapies\textsuperscript{2}

Identification of biomarkers at diagnosis of advanced NSCLC can guide selection of appropriate treatments and improve patient care\textsuperscript{1,3}

---

1L, first line; 2L, second line; IO, immunotherapy; mOS, median overall survival; NSCLC, non-small cell lung cancer.

There Remains a Need to Improve Molecular Testing Rates in NSCLC\textsuperscript{1,2}

### Reported Rates of Biomarker Testing

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>90% Academic and Government Institutions\textsuperscript{1,*}</th>
<th>Community Oncology Practices\textsuperscript{2,†}</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>96%</td>
<td>54%</td>
</tr>
<tr>
<td>ALK</td>
<td>93%</td>
<td>51%</td>
</tr>
<tr>
<td>ROS1</td>
<td>81%</td>
<td>43%</td>
</tr>
<tr>
<td>BRAF</td>
<td>73%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Only the minimum necessary biomarkers recommended in guidelines at the time of survey initiation are shown.\textsuperscript{3,4}

Between 2017 and 2019, only 22\% of patients in community oncology practices were tested for all 4 of the guideline-recommended biomarkers (N=1203)\textsuperscript{2,†}

---

\textsuperscript{1}IASLC international survey initiated in 2018 of HCPs from 102 countries (n=121 respondents from the US/Canada) involved in lung cancer care (N=2537): 43% academic, 47% government, 21% private, 5% other. 1 A retrospective study analyzing genomic testing patterns in patients with advanced NSCLC from 2017–2019. 2 ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; HCP, healthcare professional; IASLC, International Association for the Study of Lung Cancer; NSCLC, non-small cell lung cancer; ROS1, c-ros oncogene 1.


Do not copy or distribute. © 2020 Amgen Inc. All rights reserved.
KRAS Testing in NSCLC Is Recommended by Clinical Guidelines\(^1-3\)

**CAP/IASLC/AMP Guidelines for NSCLC\(^1\)**

Single-gene or expanded panel KRAS testing recommended

**ASCO Guidelines for NSCLC\(^2\)**

Expanded panel KRAS testing recommended

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines\(^\circledR\)) for NSCLC\(^3\)**

Single-gene or expanded panel KRAS testing may be useful*

---

*The NCCN Guidelines for NSCLC state that KRAS is a prognostic biomarker and also state, "Owing to the low probability of overlapping targetable alterations, the presence of a known activating mutation in KRAS identifies patients who are unlikely to benefit from further molecular testing."

AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; IASLC, International Association for the Study of Lung Cancer; KRAS, Kirsten rat sarcoma; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.


---

Consider including KRAS in your NSCLC biomarker panel

---

Do not copy or distribute. © 2020 Amgen Inc. All rights reserved.
The KRAS G12C Mutation Can Be Detected With Established Molecular Testing Platforms\(^1,2\)

**Sample Collection**

KRAS G12C can be detected using either **tissue or liquid biopsy** samples\(^3\)

**Testing Platform**

KRAS G12C can be detected by **single-gene testing** (eg, PCR) or by **expanded gene panels** (eg, NGS)\(^1,2\)

**Test Reports**

Many expanded panels already include **KRAS** mutations (eg, FoundationOne\(^\text{®}\) CDx, Oncomine\(^\text{™}\) Dx Target Test, Guardant360\(^\text{®}\) CDx\(^*\))\(^1,4-7\)

---

You may already have **KRAS G12C** results for your patients with NSCLC\(^1,4-7\)

---

\(^*\)Tests listed include FDA-approved companion diagnostic tests in NSCLC that can detect KRAS mutations as of August 2020.\(^4\) The tests identified herein are examples of tests that are currently in use and are provided for educational and informational purposes only. This is not a comprehensive list, nor an endorsement by Amgen to use any specific test, but rather a list of FDA-approved tests that are more widely known and commonly used. KRAS, Kirsten rat sarcoma; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction.

Summary

NSCLC is a heterogeneous disease characterized by multiple molecular alterations that can inform treatment options

**KRAS G12C** is one of the most prevalent driver mutations in NSCLC, occurring in ~1 in 8 of patients, comparable to EGFR mutations

**KRAS**$^{G12C}$ inhibition may represent an important therapeutic approach in NSCLC that is currently under investigation

Guidelines recommend molecular testing in advanced NSCLC; including testing for emerging biomarkers like **KRAS** mutations

---

EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer.


Do not copy or distribute. © 2020 Amgen Inc. All rights reserved.