KRAS G12C—An Emerging Biomarker and Novel Investigational Target in NSCLC

AMGEN®
Oncology

Agenda

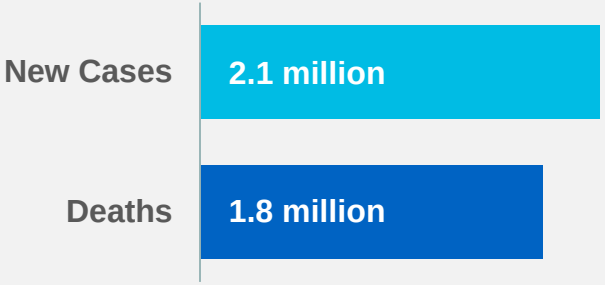
1. Review the evolving NSCLC landscape, including actionable and emerging biomarkers
2. Raise awareness that *KRAS G12C* is the most prevalent emerging molecular target in NSCLC and define patient and tumor characteristics
3. Discuss clinical guideline recommendations for molecular testing at diagnosis of NSCLC

NSCLC, non-small cell lung cancer; KRAS, Kirsten rat sarcoma.

AMGEN Oncology

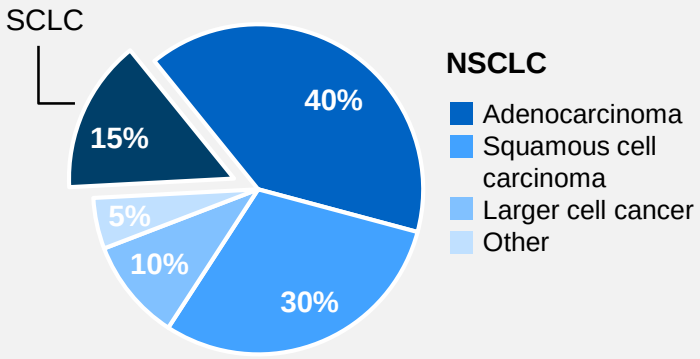
Lung Cancer Is the Leading Cause of Cancer Death[1]

Global Statistics



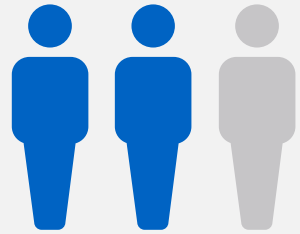
2.1 million new cases and **1.8 million deaths** due to lung cancer were estimated in 2018, representing **18.4% of cancer-related mortality**[1]

Histological Subtypes



NSCLC accounts for **80%–85%** of all lung cancer cases with adenocarcinoma being the most common subtype[2-5]

Late Diagnosis



Most NSCLC patients (**66%**) are diagnosed with advanced or metastatic disease[6]

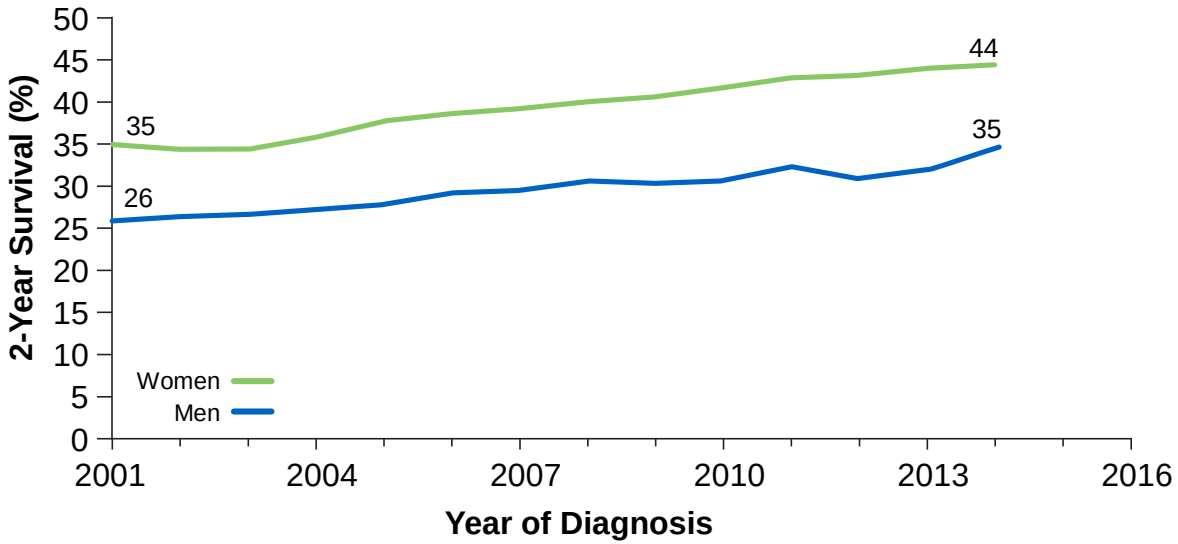
NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

1. Bray F, et al. *CA Cancer Clin*. 2018;68:394-424. **2.** American Cancer Society. https://www.cancer.org/cancer/lung-cancer/about/what-is.html. Accessed August 23, 2020. **3.** Howlader N, et al. SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. https://seer.cancer.gov/csr/1975_2017/. Accessed August 18, 2020. **4.** Román M, et al. *Mol Cancer*. 2018;17:33. **5.** Duma N, et al. *Mayo Clin Proc.* 2019;94:1623-1640. **6.** Ahmadzada T, et al. *J Clin Med.* 2018;7:153.

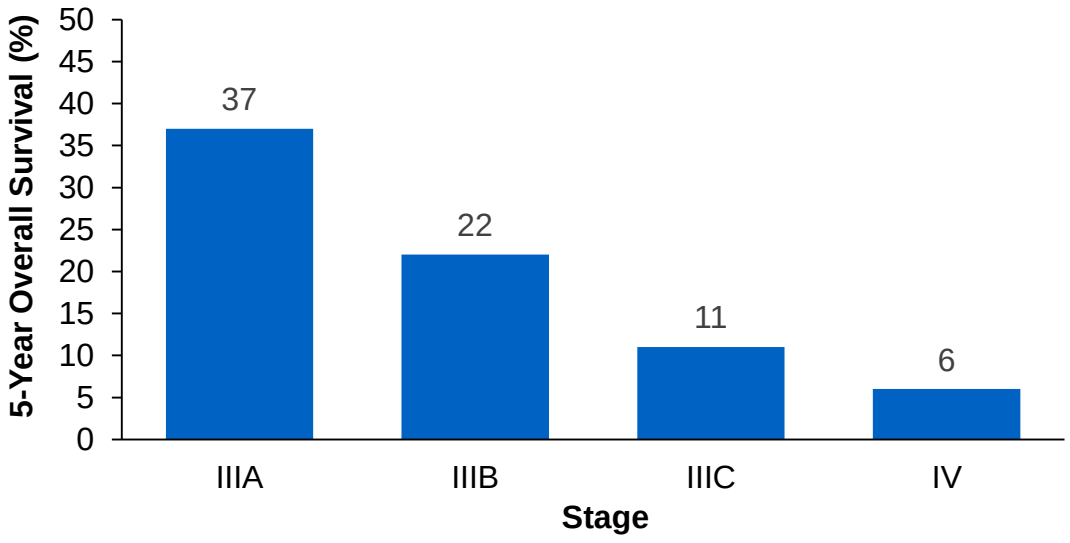
AMGEN Oncology

Despite Recent Treatment Advancements, Opportunities Remain to Improve Outcomes for Patients With NSCLC[1-5]

2-Year Survival by Year of NSCLC Diagnosis[1]



5-Year OS in Patients With Late-Stage NSCLC[5] (1999-2010)



Survival rates for patients with NSCLC are improving; however, 5-year survival is only 6% for patients with metastatic disease[1,5]

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

1. Howlader N, et al. *N Engl J Med.* 2020;383:640-649. **2.** Morabito A. *BMC Med.* 2018;16:24. **3.** Santos ES, et al. *Expert Rev Anticancer Ther.* 2020;20:221-228. **4.** Nadler E, et al. *Clin Lung Cancer.* 2018;19:360-370. **5.** Chansky K, et al. *J Thorac Oncol*. 2017;12:1109-1121.

AMGEN Oncology

NSCLC Is a Heterogeneous Disease With an Increasing Number of Actionable and Emerging Biomarkers[1,2]

Actionable Biomarkers in NSCLC[3-7]

- Sensitizing *EGFR* Mutations
- *ALK* Rearrangements
- *ROS1* Rearrangements
- *BRAF* V600E Point Mutation
- *RET* Rearrangements
- *NTRK* Gene Fusions
- *MET* Exon 14 Skipping Mutations

→ **FDA-Approved Targeted Therapy**

- PD-L1 Expression
- TMB

→ **FDA-Approved Immunotherapy**

Emerging Biomarkers Currently Under Investigation in NSCLC[4,8]

- *KRAS* Mutations
- *MET* Amplifications
- *ERBB2 (HER2)* Alterations

→ **Targeted Therapy Under Investigation**

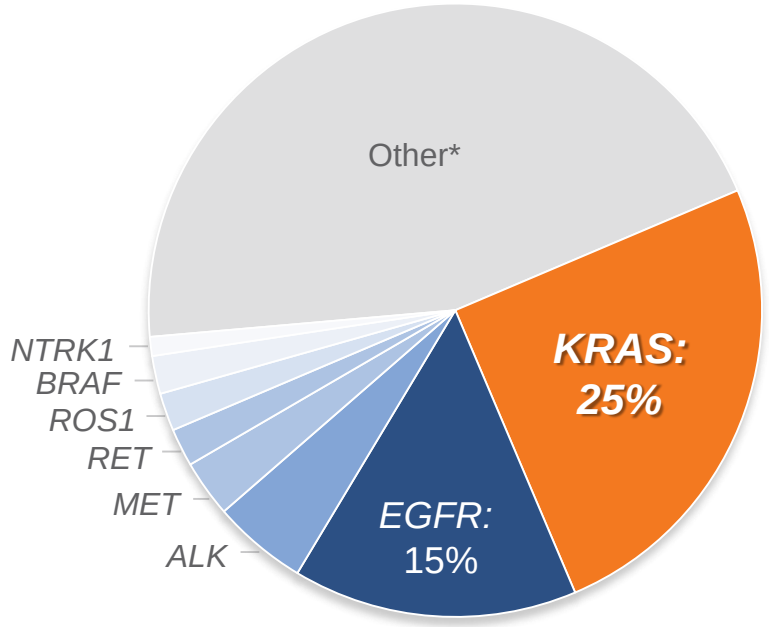
Greater understanding of NSCLC heterogeneity has driven personalized approaches to patient management[2]

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

1. Skoulidis F, et al. *Nat Rev Cancer.* 2019;19:495-509. **2.** Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. **3.** American Cancer Society. https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell/targeted-therapies.html. Accessed August 24, 2020. **4.** Pakkala S, et al. *JCI Insight.* 2018;3:e120858. **5.** Food and Drug Administration. https://www.fda.gov. Accessed August 21, 2020. **6.** Food and Drug Administration. https://www.fda.gov. Accessed August 21, 2020. **7.** Food and Drug Administration. https://www.fda.gov. Accessed August 19, 2020. **8.** Nagasaka M, et al. *Cancer Treat Rev.* 2020;84:101974.

AMGEN Oncology

KRAS G12C Is the Most Prevalent Emerging Molecular Target in NSCLC[1,2]



KRAS is one of the most prevalent driver mutations in lung adenocarcinomas[1]

KRAS G12C in NSCLC

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]

Identifying driver mutations in NSCLC allows for the potential for personalized medicine[1]

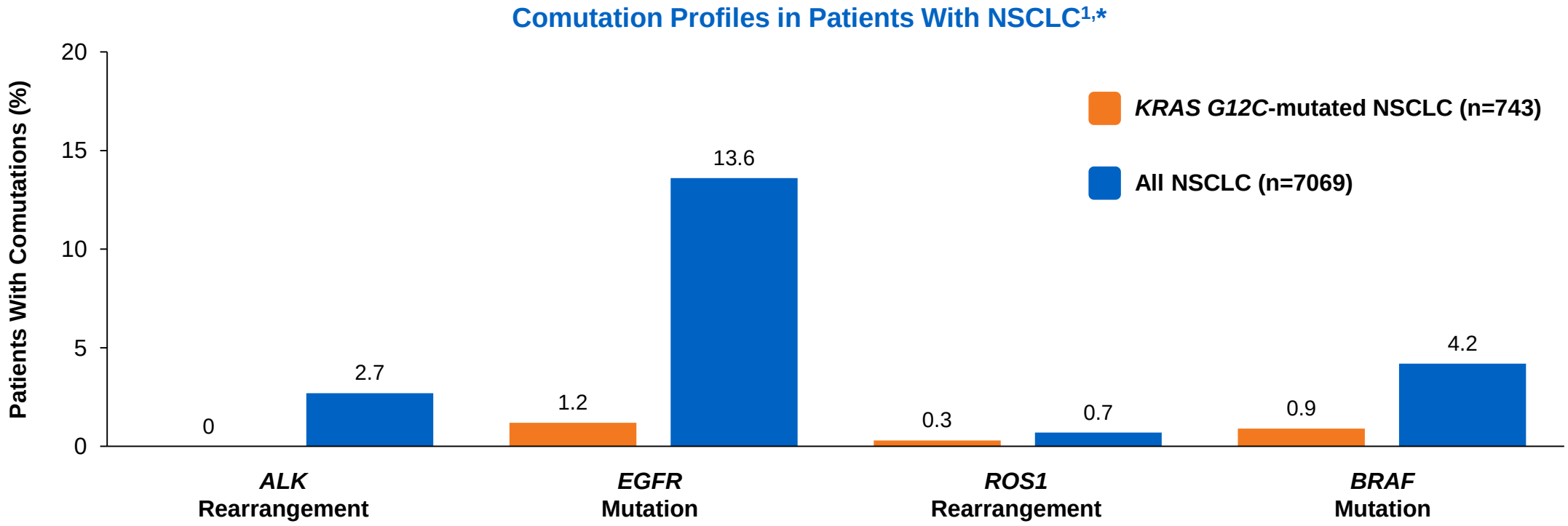
*"Other" includes HER2, PIK3CA, MEK1, and patients with no driver mutation detected, but does not include TMB or MSI-H.[1]

ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; HER2; human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma; MEK1, mitogen-activated protein kinase kinase 1; MET, mesenchymal-to-epithelial transition; MSI-H, microsatellite instability-high; NSCLC, non-small cell lung cancer; NTRK1, neurotrophic tyrosine receptor kinase 1; PIK3CA, phosphoinositide 3-kinase, catalytic, alpha polypeptide; RET, rearranged during transfection; ROS1, c-ros oncogene 1; TMB, tumor mutational burden.

1. Pakkala S, et al. *JCI Insight.* 2018;3:e120858. **2.** Data on file, Amgen; 2020.

AMGEN Oncology

The *KRAS G12C* Mutation Rarely Overlaps With Actionable Driver Mutations[1]



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 mutations[1,2]

*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. **2.** American Cancer Society. https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell/targeted-therapies.html. Accessed August 24, 2020.

AMGEN® Oncology

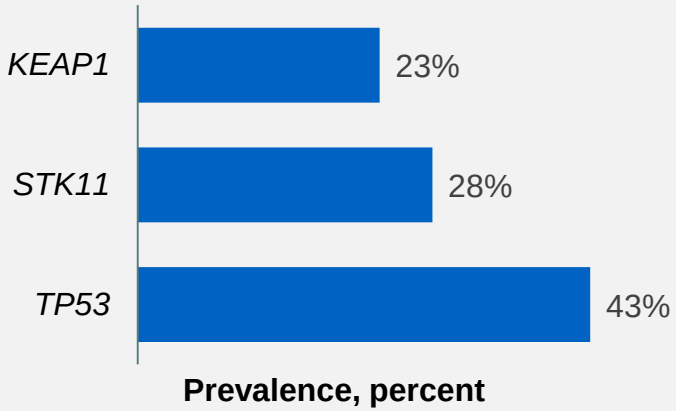
KRAS G12C-Mutated NSCLC Tumors Are Heterogeneous[1]

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[2-4]

Comutations Contribute to the Heterogeneity of *KRAS G12C* Tumors

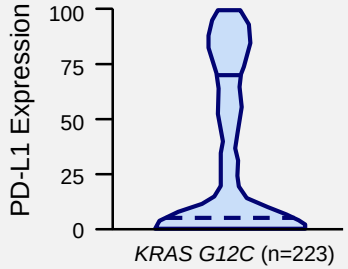
Patterns of Co-occurring Mutations in *KRAS G12C*-mutated NSCLC



TP53, STK11, and *KEAP1* mutations occur frequently in *KRAS G12C*-mutated NSCLC[1]

KRAS G12C Tumors Demonstrate Varying Levels of PD-L1 Expression

PD-L1 Expression in Patients With *KRAS G12C*



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%)[1]

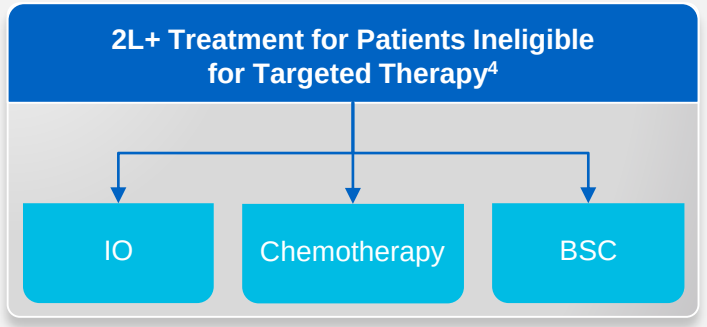
KEAP1, kelch-like ECH-associated protein 1; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; STK11, serine/threonine kinase 11; TP53, tumor protein p53.

1. Arbour KC, et al. Presented at: The American Society of Clinical Oncology; June 2020; Virtual Meeting. Abstract 9596. **2.** Aggarwal S, et al. Presented at: The European Society for Medical Oncology; September 2020; Virtual Congress. **3.** Arbour KC, et al. *Clin Cancer Res*. 2018;24:334-340. **4.** Ahmadzada T, et al. *J Clin Med.* 2018;7:153.

AMGEN Oncology

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

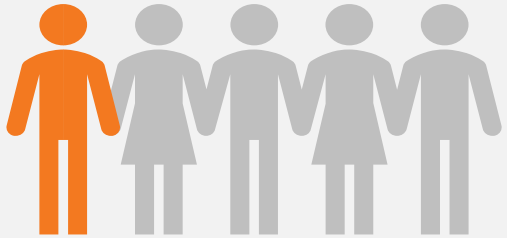
There are no currently approved therapies specifically targeting the *KRAS G12C* mutation[3]



Platinum-based chemotherapies and immunotherapy are the most common treatments[2]

1 in 5

advanced NSCLC patients with *KRAS G12C* mutations do not receive systemic therapy[1]



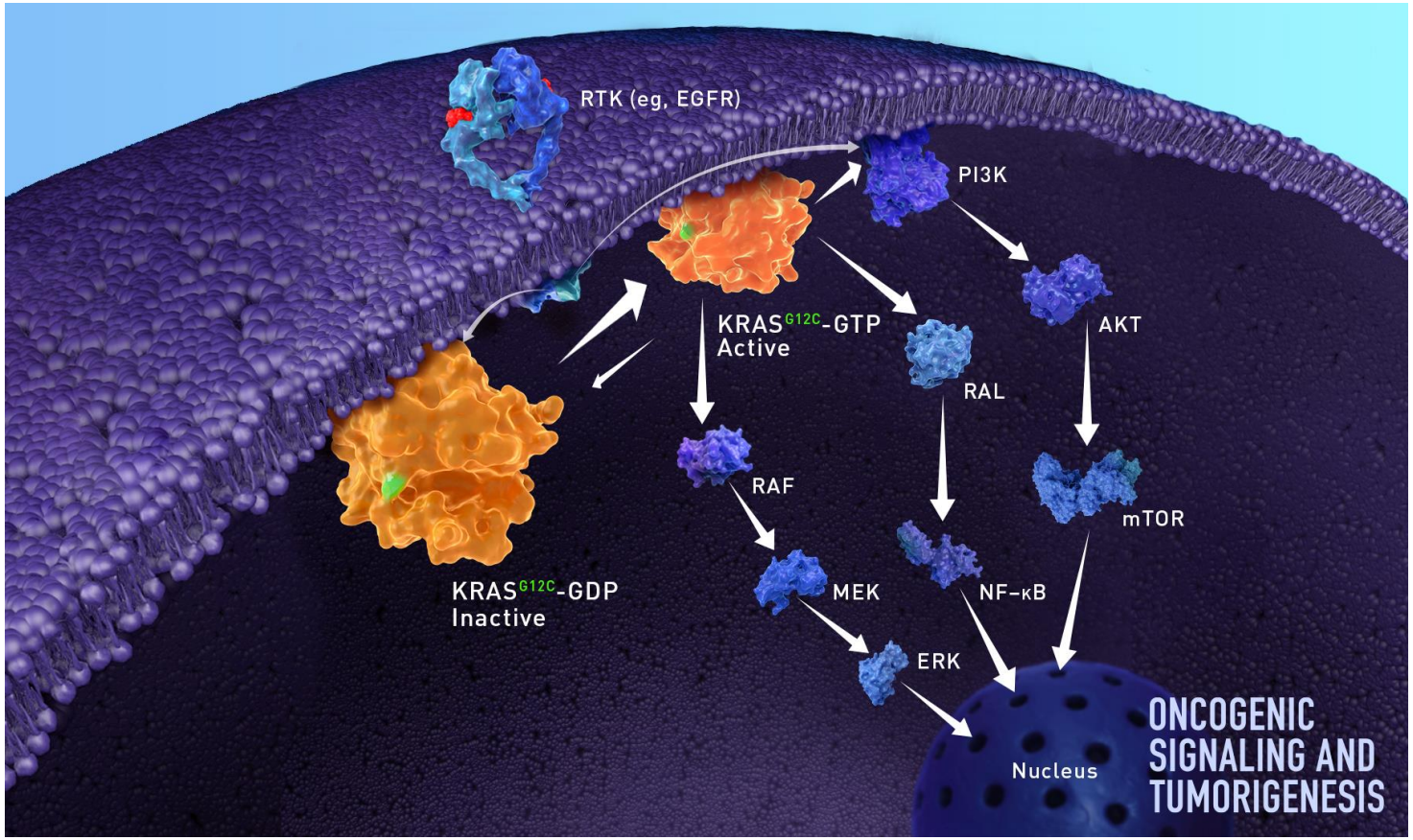
Patients may only receive best supportive care, potentially due to more advanced disease, comorbidities, and poor performance status[5,6]

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. **2.** Aggarwal S, et al. Presented at: The European Society for Medical Oncology; September 2020; Virtual Congress. **3.** Ahmadzada T, et al. *J Clin Med.* 2018;7:153. **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. **5.** Kitazawa H, et al. *Sci Rep*. 2019;9:19872. **6.** Ruppert A-M, et al. *JTO Clin Res Rep*. 2020. doi:10.1016/j.jtocrr.2020.100052.

AMGEN® Oncology

KRAS G12C Drives Cancer Cell Growth and Survival[1-5]



- **The KRAS pathway regulates cellular proliferation, differentiation, and survival[1,2,6]**
- ***KRAS G12C* is a single point mutation at codon 12, which causes the glycine to be substituted with a cysteine[7,8]**
- **The *KRAS G12C* mutation favors the active form of the KRAS mutant protein, supporting tumorigenesis[1,3]**

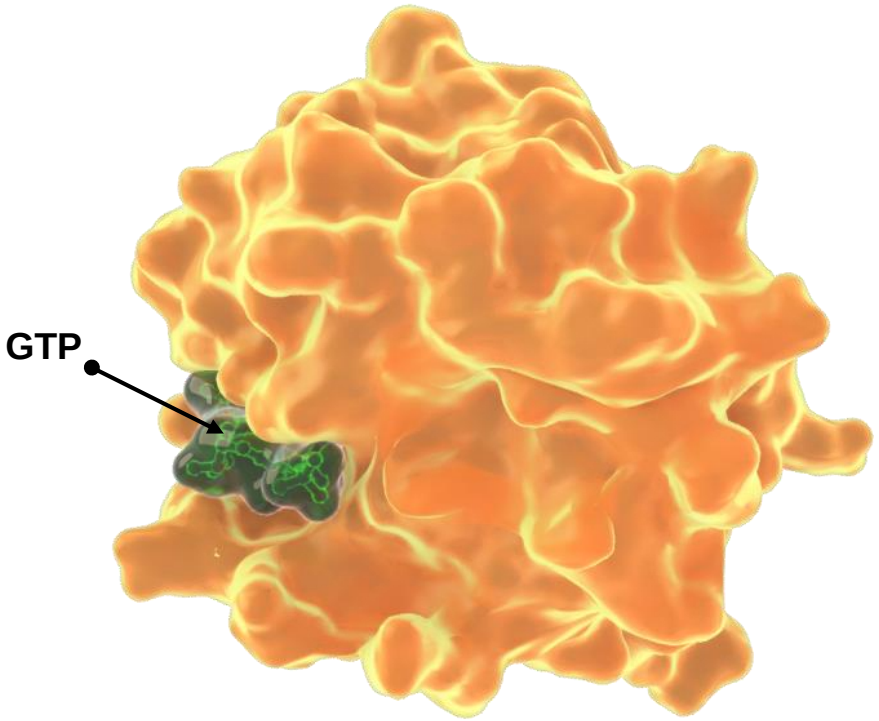
AKT, protein kinase B; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer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

1. Ryan MB, et al. *Nat Rev Clin Oncol.* 2018;15:709-720. **2.** Simanshu DK, et al. *Cell.* 2017;170:17-33. **3.** Neel NF, et al. *Genes Cancer*. 2011;2:275-287. **4.** Ahmadzada T, et al. *J Clin Med*. 2018;7:153. **5.** Ferrer I, et al. *Lung Cancer*. 2018;124:53-64. **6.** Barbacid M. *Annu Rev Biochem*. 1987;56:779-827. **7.** Cox AD, et al. *Nat Rev Drug Discov*. 2014;13:828-851. **8.** Ihle NT, et al. *J Natl Cancer Inst.* 2012;104:228-239.

AMGEN® Oncology

Despite Nearly Four Decades of Scientific Efforts, Targeting KRAS Has Been One of Cancer Research's Toughest Challenges[1]

Wild-Type KRAS



Lack of surface pockets
makes tight binding of small molecules difficult[1]

Competitive inhibition is challenging
due to the high affinity binding of GTP to KRAS[1]

Nonselective binding to wild-type KRAS
can inhibit wild-type KRAS and adversely affect normal cellular signaling[2]

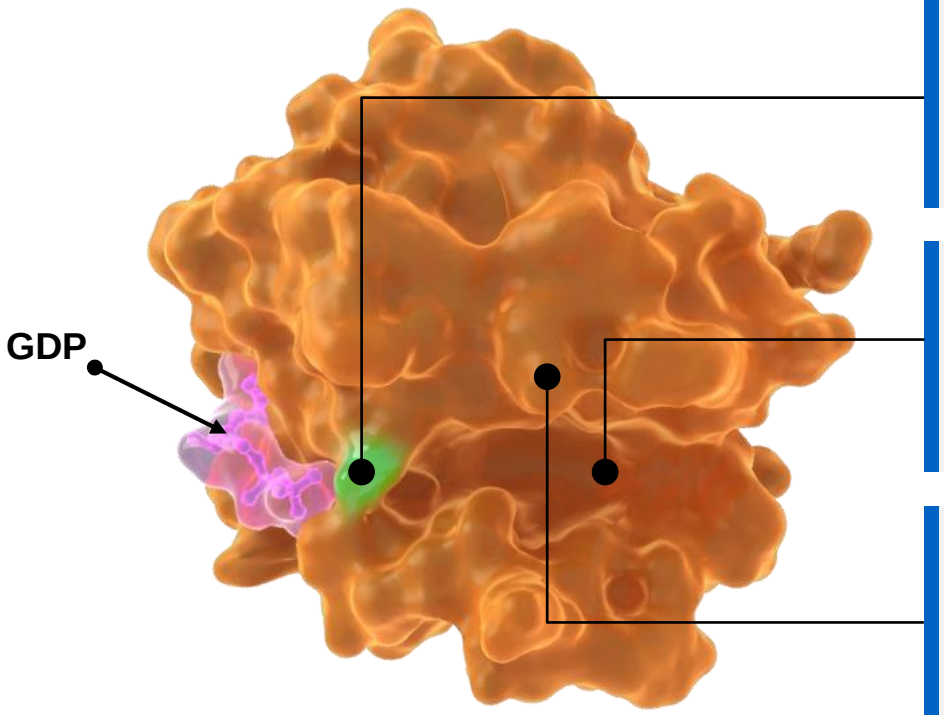
GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma.

1. Cox AD, et al. *Nat Rev Drug Discov*. 2014;13:828-851. **2.** Ryan MB, et al. *Nat Rev Clin Oncol*. 2018;15:709-720.

AMGEN Oncology

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

Mutant KRAS^{G12C}



Cysteine 12
may allow for potential irreversible covalent binding[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]

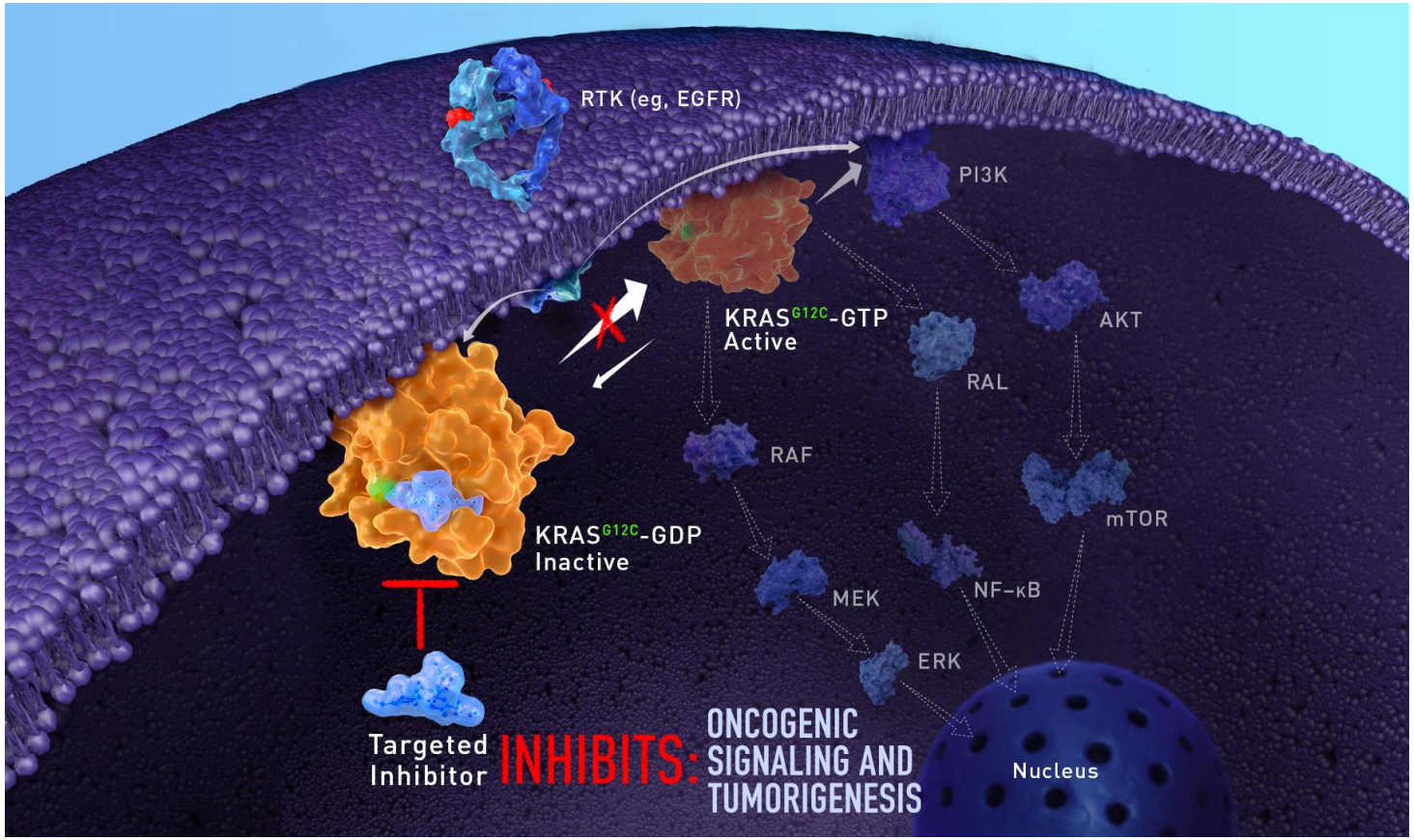
H95 Residue
may provide a site to stabilize drug-protein interaction[1]

GDP, guanosine diphosphate; KRAS, Kirsten rat sarcoma.

1. Canon J, et al. *Nature*. 2019;575:217-223. **2.** Ostrem JML, et al. *Nat Rev Drug Discov*. 2016;15:771-785. **3.** Lanman BA, et al. Presented at: The American Association for Cancer Research; March 29–April 3, 2019; Atlanta, GA. Abstract 4455. **4.** Saiki AY, et al. Presented at: The American Association for Cancer Research; March 29–April 3, 2019; Atlanta, GA. Abstract 4484.

AMGEN
Oncology

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-κB, 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.

1. Canon J, et al. *Nature.* 2019;575:217-223. **2.** Ryan MB, et al. *Nat Rev Clin Oncol.* 2018;15:709-720. **3.** Simanshu DK, et al. *Cell.* 2017;170:17-33. **4.** Neel NF, et al. *Genes Cancer.* 2011;2:275-287. **5.** Ahmadzada T, et al. *J Clin Med.* 2018;7:153. doi:10.3390/jcm7060153. **6.** Ferrer I, et al. *Lung Cancer.* 2018;124:53-64. **7.** Cox AD, et al. *Nat Rev Drug Discov.* 2014;13:828-851. **8.** Ostrem JML, et al. *Nat Rev Drug Discov.* 2016;15:771-785.

AMGEN® Oncology

Molecular Testing at Diagnosis Is Essential to Assessing Treatment Options in Patients With Advanced NSCLC[1-3]

Clinical guidelines recommend molecular testing in advanced NSCLC[2,4,5]

Comprehensive molecular testing allows for **selection of appropriate targeted therapies**[2]

Identification of biomarkers at diagnosis of advanced NSCLC can guide selection of appropriate treatments and improve patient care[1,3]

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

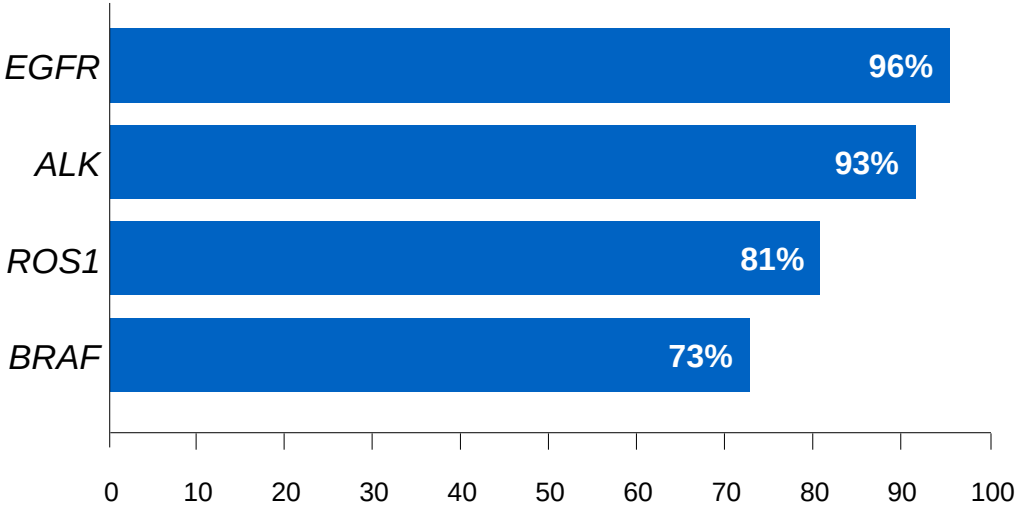
1. Pakkala S, et al. *JCI Insight.* 2018;3:e120858. **2.** Lindeman NI, et al. *J Thorac Oncol*. 2018;13:323-358. **3.** Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. **4.** Kalemkerian GP, et al. *J Clin Oncol*. 2018;36:911-919. **5.** Gregg JP, et al. *Transl Lung Cancer Res*. 2019;8:286-301.

AMGEN Oncology

There Remains a Need to Improve Molecular Testing Rates in NSCLC[1,2]

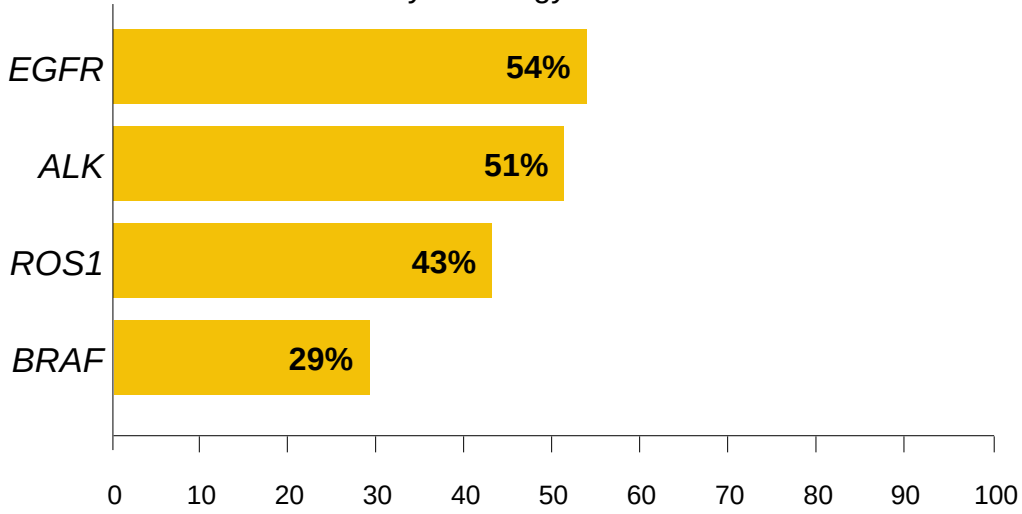
Reported Rates of Biomarker Testing

90% Academic and Government Institutions[1,*]



Respondents Requesting Molecular Testing for a Given Biomarker, %

Community Oncology Practices[2,†]



Respondents Requesting Molecular Testing for a Given Biomarker, %

Only the minimum necessary biomarkers recommended in guidelines at the time of survey initiation are shown.[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)[2,†]

*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.

1. Smeltzer MP, et al. *J Thorac Oncol*. 2020;S1556-0864(20)30383-X. **2.** Gierman HJ, et al. *J Clin Oncol.* 2019;37:1585. **3.** Kalemkerian GP, et al. *J Clin Oncol.* 2018;36:911-919. **4.** Lindeman NI, et al. *J Thorac Oncol.* 2018;13:323-358.

AMGEN Oncology

KRAS Testing in NSCLC Is Recommended by Clinical Guidelines[1-3]

CAP/IASLC/AMP Guidelines for NSCLC[1]	ASCO Guidelines for NSCLC[2]	NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC[3]
Single-gene or expanded panel *KRAS* testing recommended	Expanded panel *KRAS* testing recommended	Single-gene or expanded panel *KRAS* testing may be useful*

Consider including *KRAS* in your NSCLC biomarker panel

*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."

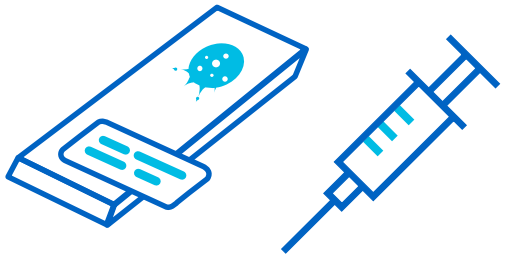
AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; IASLC, International Association for the Study of Lung Cancer; KRAS, Kirsten rat sarcoma; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.

1. Lindeman NI, et al. *J Thorac Oncol.* 2018;13:323-358. **2.** Kalemkerian GP, et al. *J Clin Oncol.* 2018;36:911-919. **3.** 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.

AMGEN® Oncology

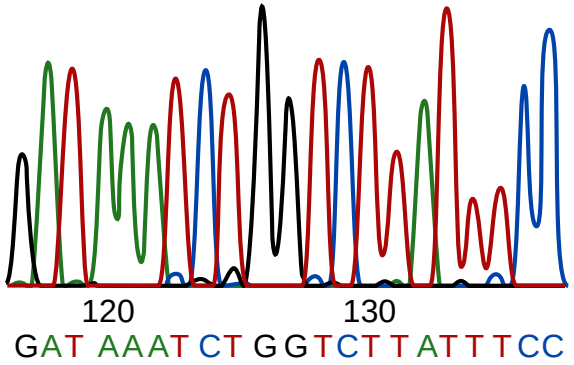
The *KRAS G12C* Mutation Can Be Detected With Established Molecular Testing Platforms[1,2]

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® CDx, Oncomine™ Dx Target Test, Guardant360® CDx*)[1,4-7]

You may already have *KRAS G12C* results for your patients with NSCLC[1,4-7]

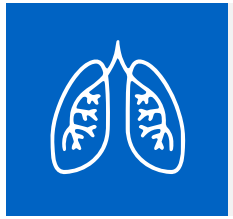
*Tests listed include FDA-approved companion diagnostic tests in NSCLC that can detect *KRAS* mutations as of August 2020.[8] The tests identified herein are examples of tests that are currently in use and are provided for educational and informational purposes only. This is not a comprehensive list, 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.

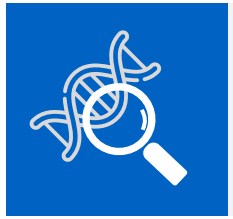
1. Lindeman NI, et al. *J Thorac Oncol.* 2018;13:323-358. **2.** Kalemkerian GP, et al. *J Clin Oncol.* 2018;36:911-919. **3.** Leighl NB, et al. *Clin Cancer Res*. 2019;25:4691-4700. **4.** Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. **5.** Foundation Medicine. https://assets.ctfassets.net/w98cd481qyp0/41rJj28gFwtxCwHQxopaEb/5031613e71b07962785e434e396b1429/P170019.S016.Label.Technical_Info.pdf. Accessed August 21, 2020. **6.** Oncomine Dx Target Test. https://www.thermofisher.com/order/catalog/product/A32451#/A32451. Accessed August 26, 2020. **7.** Guardant360®. https://guardant360.com/wp-content/uploads/2020/05/gene-list.png. Accessed August 19, 2020. **8.** FDA. https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Accessed August 26, 2020.

AMGEN Oncology

Summary



NSCLC is a heterogeneous disease characterized by multiple molecular alterations that can inform treatment options[1-3]



KRAS G12C is one of the most prevalent driver mutations in NSCLC, occurring in ~1 in 8 of patients, comparable to EGFR mutations[3,4]

$KRAS^{G12C}$ inhibition may represent an important therapeutic approach in NSCLC that is currently under investigation[5]

Guidelines recommend molecular testing in advanced NSCLC; including testing for emerging biomarkers like *KRAS* mutations[2,6,7]

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

1. Skoulidis F, et al. *Nat Rev Cancer.* 2019;19:495-509. **2.** Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. **3.** Pakkala S, et al. *JCI Insight.* 2018;3:e120858. **4.** Data on file, Amgen; 2020. **5.** Canon J, et al. *Nature.* 2019;575:217-223. **6.** Lindeman NI, et al. *J Thorac Oncol*. 2018;13:323-358. **7.** Kalemkerian GP, et al. *J Clin Oncol*. 2018;36:911-919.

AMGEN Oncology