Targeting *KRAS*-Mutant Non–Small-Cell Lung Cancer: One Mutation at a Time, With a Focus on *KRAS G12C* Mutations

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INTRODUCTION

Lung cancer represents 11.6% of all cancers globally, with more than 2 million new cases worldwide in 2018.[1] Across all disease stages, non–small-cell lung cancer (NSCLC) has an overall 5-year relative survival rate of 23%; for metastatic NSCLC, the same rate is 6% in the United States.[2] Various subgroups of metastatic NSCLC, such as *KRAS*-mutated NSCLC, are typically associated with poorer survival.[3]

Advances in the understanding of NSCLC oncogenic drivers have led to the development of targeted therapies for several molecular subsets of lung adenocarcinoma, contributing to an improvement in patient outcomes and survival.[4-6] Although *KRAS* mutations are observed in approximately one-third of patients with lung adenocarcinoma in Western populations,[7] no approved targeted therapies exist for this important molecular subset.

OVERVIEW OF *KRAS* IN NSCLC

Introduction and Prevalence of *KRAS* Mutations

RAS genes encode small membrane-bound guanine nucleotide-binding proteins (G proteins), including NRAS, HRAS, and KRAS.[8,9] These spherical proteins have a relatively smooth molecular surface without readily accessible binding pockets and have high affinity for guanosine diphosphate (GDP) and guanosine triphosphate (GTP).[10,11] RAS proteins have a slow dissociation rate from the GDP-bound state. Guanine nucleotide exchange factors (GEFs), such as son-of-sevenless (SOS), promote conversion from the inactive GDP-bound state to the active GTP-bound state (Fig 1).[10,12] Similarly, GTPase-activating proteins accelerate conversion back to the inactive state when they are recruited to the plasma membrane in direct proximity to RAS.[10]

KRAS proteins are highly homologous (90%) with other RAS proteins in the G or catalytic domain sequence.[13] The G domain binds guanine nucleotides, activating signal transduction. It includes four main regions in the inactive GDP-bound (Fig 2A) and the active GTP-bound protein (Fig 2B): amino acid residues 10-17 (the phosphate-binding loop), 30-40 (switch I), 60-76 (switch II), and 116-120 and 145-147 (the base-binding loops).[8,9,13] In contrast, the C-terminus, which incorporates farnesyl or prenyl groups, is a hypervariable region. The sequence divergence between different RAS proteins contributes to differential post-translational processing, subcellular trafficking, cellular localization, and subsequent response to therapy.[13] There is approximately 8% sequence homology in the C-terminus between KRAS and the other RAS proteins.[8,13] In common with the other RAS proteins, KRAS proteins are binary switches, cycling between active GTP-bound and inactive GDP-bound states in normal cells during signal transduction to regulate downstream signaling pathways.[9,10] This results in conformational changes in the switch I and II regions (Fig 2), enabling GTP-bound KRAS to interact with and activate proteins regulating effector pathways.[9,13,14] In the active state, KRAS relays upstream signals from cell surface receptors to a number of downstream pathways, including RAF/MEK/ERK, PI3K/AKT/mTOR, RALGDS/RAL, and TIAM1/RAC, that control normal cell function and proliferation (Fig 1).[8,13,15]

KRAS mutations greatly diminish GTP hydrolysis, thereby leading to increased GTP-bound mutant KRAS in the active state. Constitutively active KRAS then initiates downstream signaling and leads to uncontrolled cell proliferation and survival.[16] As a result, *KRAS* mutations are oncogenic drivers associated with numerous human cancers, including lung cancer.[10] The mechanisms through which distinct *KRAS* mutations lead to RAS activation are not thoroughly understood and might differ by allelotype.[12] This has made targeting RAS and KRAS extremely challenging in the clinic.[9,11,17]

Across all cancers, the most common *RAS* mutations are *KRAS* mutations (85%), with *NRAS* (12%) and *HRAS* (3%) much less frequent. Globally, *KRAS* mutations are associated with approximately 1 million cancer-related deaths annually.[10] Oncogenic *KRAS* mutations occur at codons 12 and 13 (ie, within the phosphate-binding loop) and at codon 61 (ie, within switch II) of the G domain. The most common mutation is at codon 12 and accounts for 80% of all *KRAS* mutations.[9,18] Single-base substitution mutations at

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To provide an overview of the epidemiology and prognostic and predictive value of *KRAS* mutations in non–small-cell lung cancer (NSCLC), summarizing current treatment approaches and highlighting unmet needs.

Knowledge Generated

Specific *RAS* mutations can render RAS proteins constitutively active, resulting in uncontrolled cell proliferation. *KRAS*-mutated NSCLC is heterogeneous. *KRAS G12C* is the most prevalent of the *KRAS* mutations. *KRAS* mutations, particularly *KRAS G12C*, are indicative of poor overall survival, with comutational status also affecting prognosis. Therapies targeting KRAS are beginning to show clinical potential, most notably with $KRAS^{G12C}$ inhibitors. Strategies for $KRAS^{G12C}$ inhibition are discussed.

Relevance

In Western populations, *KRAS* mutations are one of the most common oncogenic drivers in NSCLC, with *KRAS G12C* mutation representing nearly half of *KRAS* mutations. KRAS inhibition offers potential for targeted treatment of NSCLC; $KRAS^{G12C}$ inhibitors are under clinical development and may represent an effective therapeutic option for patients with NSCLC.

position 12 lead to stabilization of KRAS-GTP binding, resulting in structural changes in KRAS and consequently constitutively activated KRAS (GTP-bound state).[9,19] For example, the *KRAS G12C* mutation is a single point mutation with a glycine-to-cysteine substitution at codon 12. The cysteine 12 residue is located close to the nucleotide-binding pocket and switches I and II. The glycine-to-cysteine substitution has an effect on GEF binding and downstream signaling, leading to cell proliferation and survival.[13]

In NSCLC, *KRAS* is one of the most frequently mutated oncogenes. According to a large genomic study of human lung tumors, *KRAS* mutations are more commonly observed in the subtype of adenocarcinoma than in squamous cell carcinoma or large cell carcinoma, with a mutation frequency of 32.6% in adenocarcinoma.[20] The incidence of *KRAS* mutations is between 8% and 24% in large clinical trials[21] and between 27% and 32% in a series of patients with adenocarcinoma.[7,22] The majority of *KRAS* mutations are found in current and former smokers[23];

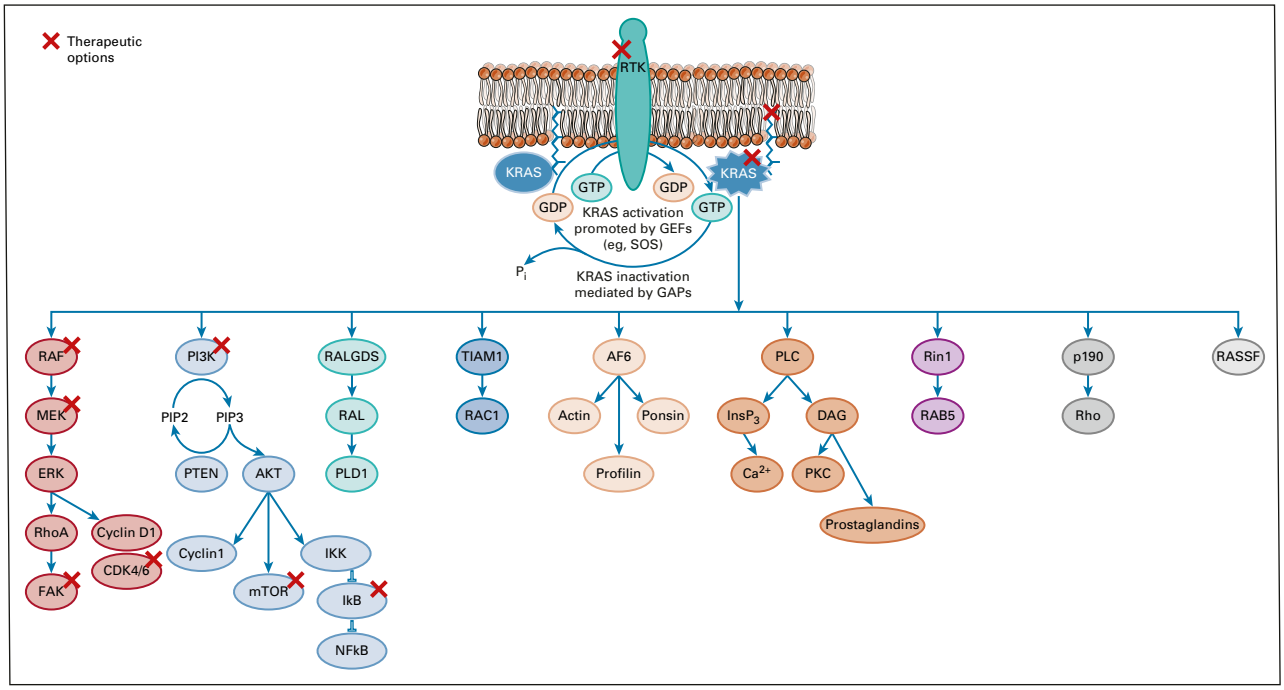

FIG 1. Overview of the process of phosphorylation of the KRAS protein and the downstream effector pathways and potential therapeutic targets for inhibitors of KRAS activity. GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factors; GTP, guanosine triphosphate; SOS, son-of-sevenless.

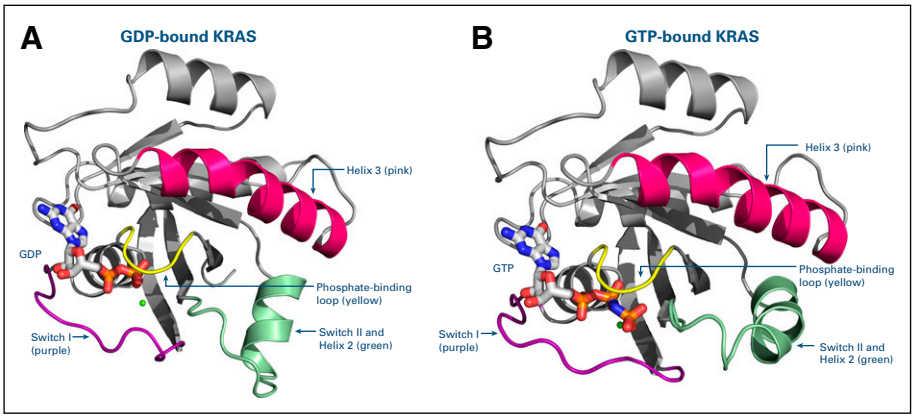

FIG 2. Structure of the KRAS protein in (A) guanosine diphosphate (GDP)–bound state and (B) guanosine triphosphate (GTP)–bound state, with the four main regions highlighted.

however, *KRAS G12D* is also found in never-smokers.[24] In Western populations, approximately one-quarter to one-third of patients with NSCLC have a *KRAS* mutation.[25-27] The overall incidence of *KRAS* mutation is lower (approximately 5%-10%) in Indian,[28,29] Chinese,[30-32] and Iranian populations.[33] Across Western populations with NSCLC, the prevalence of the *KRAS G12C* mutation is approximately 12%-14% (40%-50% of all *KRAS* mutations).[8,19,22,25-27,34] *KRAS G12V* mutations account for approximately 20%-25% of *KRAS* mutations in NSCLC,[19,22] and others include *KRAS G12D*, *KRAS G12A*, and *KRAS G12S* (Table 1).[19,35] The proportion of *KRAS G12C*–mutated subtypes is slightly lower (32%-34%) across large databases of Asian populations.[31,36] *KRAS G12C* and *KRAS G12D* mutations are approximately equally distributed across disease stage in patients with NSCLC.[27] Of note, in *KRAS G12C*–mutant tumors, *KRAS G12C* was a truncal mutation in the majority of patients with NSCLC, suggesting that it is likely a driver mutation in most of these patients.[35]

TABLE 1. Percentage of *KRAS* Mutations in Lung Adenocarcinoma as Assessed by Conventional Molecular Techniques and Next-Generation Sequencing[19,35]

Mutation	Frequency of Mutation in Lung Adenocarcinoma Across Data Sets, Range (%)
G12C	41.4-55.3
G12A	6.1-12.1
G13C	6.4-12.1
G12V	10.6-26.5
G12D	6.1-12.1
Q61L	1.7-2.0
Q61H	4.3[a]
G12R	1.7[a]
G12S	2.1-4.1
G13D	3.5-8.5
K88	2.0[a]

[a]Only reported in a single data set.

The clinicopathological features of NSCLC with *KRAS* mutations are discussed in Appendix 1 (online only).

Relationship Between *KRAS* Mutation and Other Oncogenic Mutations, PD-L1 Expression, and Tumor Mutational Burden

Concurrent alterations in the expression of at least one other gene (tumor suppressor genes: *CDKN2A*, *KEAP1*, *STK11*, *TP53*; KRAS downstream effector genes: *PIK3CA*, *BRAF*, *AKT1*) exist in approximately half of patients with *KRAS* mutations (Appendix 2, online only, includes a discussion of additional coalterations). The most common comutations are *TP53* (approximately 40%) and *STK11* (12%-20%).[26,27,37] Furthermore, approximately one-quarter of patients with *KRAS* mutations have more than one concurrent genetic alteration,[26] which depends on the underlying *KRAS* mutation. For example, *KRAS G12C* mutations tend to co-occur with *ERBB2* amplifications and *ERBB4* mutations, *KRAS G12V* mutations co-occur with *PTEN* mutations, and *KRAS G12D* mutations co-occur with *PDGFRA* mutations.[26] The presence of comutations tends to indicate a highly aggressive subgroup (Table 2); comutations may also have negative overall impact on response to treatment (Appendix 2). In contrast, *KRAS* mutations are generally mutually exclusive with other driver oncogenes in NSCLC, such as *EGFR*, *ALK*, and *ROS1* mutations in the treatment-naïve setting, and occur relatively infrequently in combination with *BRAF* mutations.[7,22,27]

KRAS-mutated NSCLC tumor cells are associated with higher PD-L1 expression levels than wild-type cells.[38,39] It is possible that the increased PD-L1 expression is due to concurrent *TP53* mutation[40] or smoking status.[41] The upregulation of PD-L1 appears to be via activation of phosphorylated extracellular signal–regulated kinase (ERK) signaling.[42] The extent of PD-L1 expression appears to be related to the *KRAS* mutation subtype.[38] *KRAS G12D*, *KRAS G12V*, and *KRAS G13C* mutations are associated with a higher proportion of PD-L1–positive versus *KRAS G12A* and *KRAS G12C* mutations, which are associated with a higher proportion of PD-L1–negative tumors.[43] However, others have reported that *KRAS G12C* is

associated with PD-L1 positivity, yet at low levels of expression.[27] Preliminary data also suggest that the distribution of PD-L1 levels is higher in patients with *KRAS* mutations versus those with wild-type disease.[44]

Finally, patients with *KRAS*-mutated NSCLC have a higher tumor mutational burden (TMB) than those with wild-type disease.[39,44] Even when adjusted for smoking status, the relationship between *KRAS*-mutant disease and TMB was maintained; these factors, taken together, may contribute to the positive response to immune checkpoint inhibitors targeting PD-L1 in patients with *KRAS* mutations.[39]

Current Treatment Options for Patients With *KRAS* Mutations: Clinical Outcomes

KRAS status and response to chemotherapy. *KRAS* mutations appear to be predictive for treatment outcome and can be associated with chemotherapy resistance.[45-49] For example, in vitro studies demonstrated that different *KRAS* mutations led to differences in sensitivity to cytotoxic chemotherapeutic agents,[50] highlighting the need to consider *KRAS* mutations at the subgroup level. When compared with wild-type cells, *KRAS G12C* mutation was associated with reduced cisplatin sensitivity in vitro and in vivo.[48,50] However, in patients with early-stage NSCLC from the Lung Adjuvant Cisplatin Evaluation (LACE)–Bio database, few biomarkers appeared to have prognostic or predictive effect, with the possible exception of a subset of *KRAS* mutations.[51] Patients with codon 12 *KRAS* mutations and those with wild-type disease appeared to derive no benefit from adjuvant chemotherapy.[52] In contrast, those with codon 13 *KRAS* mutations had significantly worse overall and disease-free survival.[52] More recent data have demonstrated a similar overall response to chemotherapy (approximately 20%) in patients with *KRAS G12C* tumors and those with wild-type disease in the locally advanced or metastatic setting.[44]

KRAS status and response to targeted therapy. A meta-analysis from 2008 identified an association between *KRAS* mutations and lack of response to EGFR–tyrosine kinase inhibitors (TKIs; predominantly gefitinib).[53] This association remained when potentially confounding factors such as ethnicity, investigational treatment (erlotinib *v* gefitinib), and previous treatment were taken into account.[53] This finding results from the mutual exclusivity of *EGFR* mutations with *KRAS* mutations in NSCLC (Appendix 3, online only). In a single-center analysis, no patient with *KRAS*-mutated disease responded to gefitinib or erlotinib compared with 35.7% of patients with *KRAS* wild-type disease achieving a complete or partial response.[54] Similarly, in a pooled analysis of four trials comparing EGFR-TKI with placebo and including 968 patients with advanced disease, *KRAS* mutation was associated with an extremely low overall response rate (1.3%).[55]

KRAS status and response to immunotherapy. *KRAS* mutation status tended to be associated with beneficial

TABLE 2. Association Between *KRAS* Mutations and *KRAS G12C* Mutations and Survival

Reference	Subgroup (reference group)
Worse overall survival	
El Osta et al, 2019[22]	*KRAS* mutation (*KRAS* WT)[a]
	KRAS comutation (no comutation [multivariate analysis])[a]
	KRAS comutation with *STK11* (no *STK11* comutation)[a]
Svaton et al, 2016[115]	*KRAS* mutation (*KRAS* WT)[b]
	KRAS G12C (*KRAS* WT)[a]
	KRAS G12C (other *KRAS* mutations)
Nadal et al, 2014[34]	*KRAS* mutation (*KRAS* WT)[c]
	KRAS G12C (*KRAS* WT)[c]
Aredo et al, 2019[27]	Distant disease stage (local disease)[c]
	STK11 comutations (no *STK11* comutations)[a]
	KRAS G12D mutation[a]
	Every 1-year increase in age[a]
Izar et al, 2014[116]	*KRAS* mutation (*KRAS* WT, *EGFR* mutant, *KRAS*/*EGFR* WT/WT)[c]
Improved overall survival	
Izar et al, 2014[116]	*KRAS G12C, KRAS G12V* (other *KRAS* mutations)[a]
Zer et al, 2016[55]	*KRAS G12C* (other *KRAS* mutations)[b]

Abbreviation: WT, wild-type.
[a]$P < .05$.
[b]$P \leq .01$ versus reference group.
[c]$P \leq .001$.

outcome with immune checkpoint inhibitors such as pembrolizumab, with prolonged progression-free survival (PFS) in *KRAS*-mutated advanced NSCLC (14.7 months) versus wild-type disease (3.5 months).[40] It is possible that comutations with STK11/LKB1 affect the response to immunotherapy.[56,57] In a retrospective study, PD-L1 expression seemed to be more relevant for predicting efficacy of immune checkpoint inhibitors in *KRAS*-mutant NSCLC (approximately 87% current or former smokers) than in patients with other types of NSCLC.[43] However, the benefits of immune checkpoint inhibitors may not extend to all *KRAS*-mutated subgroups. In one study, there was a trend toward improved outcomes after immune checkpoint inhibitors in patients with *KRAS G12A* or *KRAS G12V* mutations compared with *KRAS G12C* mutations; however, this was not statistically significant.[43] More recently, in a study enrolling PD-L1–positive patients, pembrolizumab monotherapy did not significantly improve outcomes compared with chemotherapy for patients with wild-type disease.[44] However, pembrolizumab monotherapy did improve PFS and overall survival in patients with *KRAS*-mutant disease, particularly in the *KRAS G12C* subgroup.[44] Median PFS in patients with *KRAS G12C* tumors was 15 months versus 6 months in those with wild-type disease and 12 months in those with any *KRAS* mutation; overall survival was not reached in the *KRAS G12C* subgroup versus 15 months in those with wild-type disease and 12 months in those with any *KRAS* mutation.[44] The addition of chemotherapy to pembrolizumab eliminated the differential effect of *KRAS* mutations on pembrolizumab activity.[58] PFS and overall survival were improved by the combination versus chemotherapy alone in those with wild-type and mutant disease.[58]

Considering the heterogeneity of responses by *KRAS*-mutated subtypes of NSCLC to currently available therapies, developing agents that effectively target and inhibit specific KRAS subtypes is key to improving outcomes for patients with *KRAS*-mutated NSCLC.

STRATEGIES FOR KRAS INHIBITION

Inhibition of KRAS Protein Activity

Early attempts to inhibit RAS proteins focused on decreasing RAS activation by identifying molecules preferentially binding to the RAS-GTP pocket.[11,13] As the first RAS protein identified and sequenced, early focus was mostly directed toward HRAS protein inhibition. However, KRAS was subsequently found to be of more clinical relevance and has become the target of renewed research efforts.[10] Nonetheless, attempts to directly inhibit formation of the GTP-bound protein have been unsuccessful because of the high binding affinity of RAS proteins for GTP and the lack of accessible binding pockets on RAS proteins large enough to allow small-molecule binding (Table 3[13,59-66]). Furthermore, given the ubiquitous nature of KRAS proteins and their influence on multiple downstream pathways, it was reasoned that arbitrarily inhibiting wild-type and mutant KRAS proteins would likely be associated with unacceptable toxicity.[9]

An alternative approach to the direct inhibition of KRAS proteins involves interfering with the peripheral association of KRAS with the lipid membrane compartments (Fig 1).[9] Early research demonstrated that RAS protein isoprenylation was required for peripheral association with plasma and internal membranes and for subsequent oncogenic transformation.[67] This led to the development of farnesyl transferase inhibitors, which were found to inhibit tumor growth of *HRAS* mutant cancers, and subsequently demonstrated activity against *KRAS*-mutant cancer in vitro[68] and in murine models.[69] However, clinical trials evaluating farnesyl transferase inhibitors in *KRAS*-mutated lung cancers have produced disappointing results.[8] It appears that the presence of alternative prenylation pathways, via geranylgeranyltransferase type 1, allows for the continued association of KRAS, but not HRAS, with the cell membrane. This difference may account for the different outcomes of farnesyl transferase inhibitors in *RAS*-mutant cancers.[70] Furthermore, it has led to exploration of combined farnesyl transferase and geranylgeranyl transferase type 1 inhibition.[13] Other attempts to inhibit the association of KRAS with the cell membrane have been unsuccessful to date. For example, salirasib (*trans*-farnesylthiosalicyclic acid) was found to have preclinical activity but had no demonstrable activity in the first phase II study in patients with *KRAS*-mutant lung cancer.[59] Salirasib has not been further developed.[59] Other research has focused on inhibition of phosphodiesterase delta, a chaperone protein involved in association of KRAS with lipid membrane compartment.[71] Despite the interest in targeting membrane association of KRAS, this approach may be relatively nonspecific and is unlikely to discriminate between the association of mutant and wild-type proteins, leading to potential toxicity concerns.[13]

Preclinical studies found that GEF SOS1 inhibition completely inhibits the RAS/RAF/MEK/ERK pathway in cells with wild-type *KRAS* and reduces phospho-ERK activity by 50% in *KRAS*-mutant cell lines regardless of the allelotype.[72] Combinations with $KRAS^{G12C}$ inhibitors are synergistic; however, clinical efficacy and tolerability have not yet been explored.[72]

Downstream Inhibition of Key KRAS Pathway Mediators

KRAS proteins have an integral role in regulating numerous downstream effector pathways. Of these, the RAF/MEK/ERK and PI3K/AKT/mTOR pathways are arguably the most important in *KRAS*-mutated cancers and offer multiple potential opportunities for targeted therapy in *RAS*-mutated cancer (Fig 1).

The importance of feedback mechanisms across pathways in *RAS*-mutated cancer is highlighted by the failure of RAF inhibition in this subgroup and the paradoxical activation of

TABLE 3. Overview of Unsuccessful Strategies to Target *KRAS* Mutations in NSCLC

Mechanism of Action	Reason for Lack of Apparent Success
Inhibit KRAS protein binding	
Small molecule antagonist to KRAS-GTP protein[13]	High picomolar affinity of RAS for GTP and high cellular concentration of GTP; difficult for successful competition for the nucleotide-binding pocket
Disrupt binding of KRAS protein to a GEF catalyst of nucleotide exchange[63]	Not sufficiently potent
Disrupt membrane binding of KRAS	
Farnesyl transferase inhibitor[13]	Geranyl-geranylation provides an alternative mechanism to farnesylation for activation of KRAS proteins
Competitive inhibition of attachment of GTP-bound protein to plasma membrane[59]	Not sufficiently potent to warrant further investigation
Inhibit KRAS signaling of downstream effector pathways	
MEK inhibition as monotherapy[13,60] and in combination with chemotherapy[61,62]	Upregulation of compensatory effector pathways, dose-limiting toxicities, and development of resistance
BRAF inhibition as monotherapy[64]	Paradoxical ERK signal activation
Dual BRAF and ERK1/2 inhibitors[64]	Importance of BRAF and ERK targets in normal cells
Inhibition of FAKi[65]	Combination therapy may be required
Direct inhibitors of KRAS proteins	
Noncovalently bind to RAS proteins and inhibit RAS/RAF complex formation[66]	Not sufficiently potent; off-target activity could be problematic

Abbreviations: GEF, guanine nucleotide exchange factors; GTP, guanosine triphosphate; NSCLC, non–small-cell lung cancer.

the RAF/MEK/ERK pathway in cells expressing wild-type BRAF.[13,64] Currently available RAF inhibitors tend to inhibit selected RAF dimers. However, next-generation RAF inhibitors, considered pan-RAF inhibitors, appear not to cause paradoxical activation of the RAF/MEK/ERK pathway and, thus, may be more effective in *RAS*-mutated disease.[64] Similarly, MEK inhibition was considered a potential therapeutic target.[73] However, to date, monotherapy with MEK inhibitors has not demonstrated clinical activity because of increased upstream signaling mediated via ERBB3 and FGFR1 leading to ERK signaling activation.[13,74,75] Consequently, MEK inhibitors were evaluated in combination regimens, with early results indicating MEK inhibition may be synergistic with docetaxel in *KRAS*-mutated NSCLC.[76] However, this was not borne out with a randomized comparative study.[61] Finally, ERK inhibition has been investigated as a strategy.[13] Although not specifically in NSCLC, results of an in vitro analysis suggested the ERK node may be the rate-limiting step in the RAF/MEK/ERK pathway. Direct ERK inhibition may prevent relief of negative feedback leading to ERK hyperactivation, which is observed with RAF/MEK inhibitors, and may prove a useful therapeutic approach.[77] However, it is suggested that resistance will likely occur because of single amino acid mutations in the ERK DFG motif after exposure to ERK inhibition.[78]

Similarly, it appears that pan-PI3K inhibitors and dual PI3K/mTOR inhibitors inhibit growth of NSCLC cell lines in vitro. However, limited efficacy has been observed in clinical trials due to feedback mechanisms.[79,80]

Cyclin-dependent kinase 4/6 inhibitors, such as abemaciclib, have been reported to inhibit cell growth in vitro. Early results were encouraging in patients with *KRAS*-mutated NSCLC[81,82]; however, a phase III study comparing abemaciclib with erlotinib in previously treated patients failed to demonstrate efficacy.[83]

The focal adhesion kinase (FAK) pathway is another signaling axis for *KRAS*-mutated NSCLC. FAK is a master regulator of cell adhesion during cell motility and invasion, and several FAK inhibitors are under development.[84] Preclinical models have demonstrated that *KRAS*-mutant cells with alterations in *TP53* or *CDKN2A* are sensitive to FAK inhibition.[85] In patients with *KRAS*-mutated NSCLC, the FAK inhibitor defactinib was reported to have modest clinical activity; however, efficacy was not associated with comutation (*TP53* or *CDKN2A*) status.[65]

Small-molecule inhibitors of PARP impair the stabilization and restart of stalled DNA replication forks, trapping PARP on chromatin to achieve its cytotoxic effect. The combination with WEE1 inhibitors is associated with killing of 25%-40% of *KRAS*-mutant NSCLC cells,[86] although clinical efficacy in *KRAS*-mutated disease is yet to be determined.

To overcome the increased upstream signaling observed when a single downstream effector pathway is targeted in *KRAS*-mutated cancer, combination therapy targeting multiple downstream pathways may be required.[13,79] Combinations of MEK inhibitors and EGFR inhibitors have demonstrated growth inhibition of *KRAS*-mutated NSCLC cell lines in vitro and tumor regression in vivo in

KRAS-mutated lung cancers, but in clinical trials the combination was associated with unacceptable toxicity without any clinical benefit.[87] Combinations including PI3K inhibitors have proven effective against *KRAS*-mutated cell lines[88,89] and in *KRAS*-mutated murine lung cancers[90] and were initially considered as a potential approach for the treatment of *KRAS*-mutated NSCLC. However, combinations of MEK and PI3K inhibitors appear to be associated with unacceptable toxicity, and further clinical evaluation appears unlikely.[79] In contrast, the combination of P13K inhibition with *KRAS*^{G12C} inhibition may offer a more acceptable therapeutic window in patients with *KRAS G12C*–mutated NSCLC.[79]

Finally, the Src homology 2 domain-containing PTP2 (SHP2) protein is required for RAS/ERK pathway activation, with evidence implicating SHP2 as an oncogenic driver.[91] Inhibition of SHP2 is ineffective against *KRAS*-mutated cancer cell lines in vitro, but in vivo evidence suggests a role for SHP2 inhibition under growth factor–limiting conditions.[92] Combined with MEK inhibition, SHP2 inhibition may have therapeutic potential in *KRAS*-mutated NSCLC.[92]

Synthetic lethal interaction partners of RAS are potentially important because they represent genes that act as modifiers of known oncogenes but have no effect on their wild-type counterparts.[93] Metabolic synthetic lethality appears a possible approach,[94-96] with SLC7A11 suppression being highly selective for *KRAS* mutant versus wild-type cell lines in vitro and leading to tumor regression in animal models.[95] Another potential partner includes *CDKN1A*.[97] The heterogeneity of mutant KRAS proteins likely extends to heterogeneity in synthetic lethality partners.[97] Collateral genetic dependencies specific to mutant KRAS proteins may also be relevant to understand, and therapies targeting these dependencies may enhance KRAS^{G12C} inhibition.[81]

Direct Inhibitors of Mutant KRAS

The lack of success with direct targeting of KRAS proteins, downstream inhibition of KRAS effector pathways, and other strategies contributed to a focus on developing mutation-specific KRAS inhibitors.[11,15] Given the crucial role of KRAS proteins in normal physiology, KRAS inhibition has potential for substantial toxicity.[19] Inhibition of mutant KRAS proteins, however, should limit toxicity in healthy tissue and thus provide a therapeutic advantage over inhibition of wild-type proteins or the effector pathways.[13]

The identification of a hidden pocket adjacent to switch II in GDP-bound KRAS[9] has renewed interest in direct targeting of KRAS mutant proteins (Fig 3).[63,98] Covalent binding of small molecules to KRAS mutant proteins appears to lead to changes in the switch I– or switch II–binding regions, interfering with the switch functions and affecting the binding of GEFs to the GDP-bound protein, thereby preventing conversion of the mutant protein to the GTP-bound active state.[98] These small-molecule inhibitors are KRAS mutant protein–specific, with initial focus on KRAS^{G12C} proteins. Cysteine 12 in KRAS^{G12C} protein offers the potential for disulfide covalent binding with small-molecule inhibitors, maintaining the mutant KRAS in its inactive GDP-bound state.[63,98] However, early KRAS^{G12C} inhibitors were not sufficiently potent or were too unstable for further development.[63] AMG 510 is the most clinically advanced of the covalent small-molecule inhibitors of KRAS^{G12C} mutant proteins.[99,100] AMG 510 selectively and irreversibly binds to cysteine 12 in a small pocket, the H95 groove, on the mutated KRAS^{G12C} protein.[101] AMG 510 has been shown to inhibit SOS-catalyzed nucleotide exchange in mutant KRAS^{G12C}, resulting in in vitro inhibition of KRAS signaling and impaired viability of *KRAS G12C*-mutated cell lines, but not wild-type cells.[102,103] Early phase I results support the tolerability and antitumor efficacy of a small-molecule inhibitor of KRAS^{G12C}, but caution in result interpretation is urged until survival advantages for direct inhibitors of mutant proteins are confirmed in large-scale randomized trials.[104] The benefit of direct KRAS^{G12C} inhibition is further supported by preliminary evidence that a second covalent inhibitor of KRAS^{G12C}, MRTX849, is associated with regression and objective responses in patients with *KRAS G12C*-mutated NSCLC.[105] Clinical trials are also underway evaluating other oral KRAS^{G12C} inhibitors, LY3499446 (ClinicalTrials.gov identifier: NCT04165031) and JNJ-74699157 (ClinicalTrials.gov identifier: NCT04006301), in patients with *KRAS G12C*-mutated advanced solid tumors, including NSCLC. Similarly, strategies to inhibit KRAS^{G12D} are also being developed and offer promise for future treatment options.[106]

Resistance to direct targeting of RAS proteins does occur and may be due to genetic alterations in the nucleotide exchange function or adaptive mechanisms in either downstream pathways or in newly expressed KRAS^{G12C}.[79,107-111] For

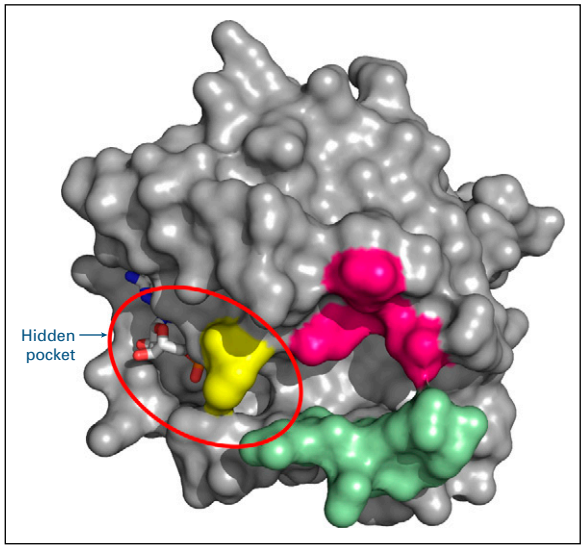

FIG 3. A three-dimensional representation of KRAS in the guanosine diphosphate–bound state showing the hidden pocket.

example, newly expressed $KRAS^{G12C}$ may stay in an active state (ie, resistant to inhibition) as a result of EGFR or AURK signaling pathways and mediated by PTPN11/SHP2 recruiting SOS1 to promote conversion to the active state.[111] Thus, combination therapies are likely to provide greater benefit than direct targeting of $KRAS^{G12C}$ alone. In addition, increased understanding of the biologic diversity underpinning *KRAS*-mutated NSCLC will allow for improved identification of patient subgroups most likely to benefit from a specific targeted treatment.[99] The presence of *STK11/LKBI* comutations, for example, appears to have an important role in the resistance of NSCLC to checkpoint inhibitors. Thus, combining checkpoint inhibitors with the evolving new direct inhibitors of mutant KRAS proteins may shift the balance away from an immune-suppressive tumor microenvironment to allow effective anti-tumor immunity[110] and provide a new improved approach to treating the disease.[99] The combination of KRAS and SHP2 inhibitors offers potential synergistic activity, as described above, and is worthy of being assessed clinically.[101,111] Furthermore, MEK inhibitors and SHP2 inhibitors were found to be synergistic in *KRAS*-mutant cancer cell lines, including NSCLC lines, making this combination also worthy of additional exploration.[92,112,113] The SHP2 inhibitors, TNO155 (Novartis) and RMC-4630 (Revolution Medicine), are currently in active phase I/II clinical trials as monotherapy (ClinicalTrials.gov identifiers: NCT03114319 and NCT03634982, respectively) and in combination with a $KRAS^{G12C}$ inhibitor (ClinicalTrials.gov identifiers: NCT04330664 and NCT04185883) and a MEK inhibitor (ClinicalTrials.gov identifier: NCT03989115), respectively. Similarly, combinations of KRAS inhibitors with inhibitors of the ErbB family including EGFR, PI3K, AKT, and MEK1/2 have been evaluated in vitro and are also of interest.[101] Triple-drug regimens are also explored, aimed to disrupt compensatory feedback loops to avoid the onset of resistance, while minimizing additive toxicities.[114]

In conclusion, the new class of $KRAS^{G12C}$ inhibitors is currently undergoing clinical assessment with promising early results. This represents a major breakthrough against a molecular subtype of NSCLC present in a significant proportion of patients with no currently available targeted treatment options. Extensive clinical and translational evaluation of AMG 510 and other KRAS inhibitors is being conducted in patients with *KRAS G12C* mutation in ongoing studies. Efforts to develop novel combination approaches building on AMG 510 are already being undertaken. These developments prompt the inclusion of *KRAS* testing in the molecular testing strategies for advanced lung adenocarcinoma.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Targeting *KRAS*-Mutant Non–Small-Cell Lung Cancer: One Mutation at a Time, With a Focus on *KRAS G12C* Mutations

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX 1

Clinicopathological Features of Non–Small-Cell Lung Cancer With *KRAS* Mutations

KRAS-mutated non–small-cell lung cancer (NSCLC) occurs with an equal sex distribution across men and women (Dacic S, et al: Mod Pathol 23:159-168, 2010). *KRAS* mutations are more frequent in patients with a current or previous smoking history, with 93% of patients with *KRAS* mutations being smokers,[22] although in one series up to 30% of patients with a *KRAS* mutation had never smoked.[36] In contrast, up to 73%[22,36] of patients with EGFR-mutant disease (Midha A, et al: Am J Cancer Res 5:2892-2911, 2015) had never smoked, contributing to EGFR-mutant disease occurring more frequently in women than men (Dacic S, et al: Mod Pathol 23:159-168, 2010; Midha A, et al: Am J Cancer Res 5:2892-2911, 2015; Hsiao SH, et al: Mol Clin Oncol 2:252-258, 2014). *KRAS* mutations occurred more frequently in older patients (Lee B, et al: Oncotarget 7:23874-23884, 2016). *KRAS*-mutant tumors are more likely to be large and poorly differentiated, with a solid pattern and of a mucinous type (Lee B, et al: Oncotarget 7:23874-23884, 2016; Kakegawa S, et al: Cancer 117: 4257-4266, 2011).

KRAS-mutated NSCLC appears to be heterogeneous; of the three prevalent *KRAS* mutations, *KRAS G12C* mutations are more likely than *KRAS G12D* and *KRAS G12V* mutations to be nonmucinous (Lee B, et al: Oncotarget 7:23874-23884, 2016). *KRAS G12C* mutations are significantly more likely to be present in women with *KRAS*-mutant lung cancer (43.4%) than in men (32.7%, $P < .01$); no significant difference was observed between women and men for other subtypes of *KRAS* mutations.[23] Some studies have reported that tobacco carcinogens appear to be associated with transverse mutations such as *KRAS G12C* mutations,[23] although this association has not always been reported to be significant (Kakegawa S, et al: Cancer 117:4257-4266, 2011). It appears that women are more susceptible to tobacco carcinogens, which may explain the higher incidence of *KRAS G12C* mutations in women.[23] Similarly, transversion mutations are more likely to be associated with disease with bronchioloalveolar features (Kakegawa S, et al: Cancer 117:4257-4266, 2011).

Finally, *KRAS G12C* mutation may be associated with poorer survival than other *KRAS* mutations, although results are not consistent across analyses (Table 2).[22,27,34,55,115,116]

APPENDIX 2

Effect of Comutations on Prognosis

Recent evidence suggests that mutations in genes (ie, *KEAP1/NFE2L2*) encoding proteins involved in the stress response pathway may represent a highly aggressive, rapidly progressing subgroup of non–small-cell lung cancer (NSCLC; Nadal E, et al: J Thorac Oncol 14: 1881-1883, 2019), regardless of smoking history, *EGFR* status, *ALK* status, and *KRAS* (Goeman F, et al: J Thorac Oncol 14:1924-1934, 2019). Deregulation of the KEAP1/NFE2L2 pathway appears to lead to resistance to various treatments (eg, tyrosine kinase inhibitors, immune checkpoint inhibitors) and rapid proliferation of cancer cells (Goeman F, et al: J Thorac Oncol 14:1924-1934, 2019). *KEAP1/NFE2L2* mutations co-occur with *KRAS* mutations but appear to be mutually exclusive with *TP53* mutations, a mutation leading to alteration in the DNA damage response machinery (Goeman F, et al: J Thorac Oncol 14:1924-1934, 2019). Survival results were worse in patients with *KRAS* and *STK11* mutation versus those with double wild-type disease,[22] or *KRAS*[26] or *STK11* mutations alone (Bange E et al: JCO Precis Oncol 10.1200/PO.18.00326). It is suggested that the *STK11* mutation alongside the *KRAS* mutation results in augmented downstream KRAS signaling and increased tumorigenesis (Bange E et al: JCO Precis Oncol 10.1200/PO.18.00326).

Effect of Comutations on Clinical Outcomes

Concurrent mutations may also have a negative overall impact on response to treatment. For example, the presence of concurrent *KEPA1/NEF2L2* mutations was associated with a shorter overall survival in patients with *KRAS* mutations treated with immune checkpoint inhibitor monotherapy (ie, nivolumab or pembrolizumab; Arbour KC, et al: Clin Cancer Res 24:334-340, 2018).

Similarly, in preliminary results *STK11/LKB1* mutations co-occurred with *KRAS* mutations in approximately one-third of 49 patients from a single study site.[56] Across 17 study sites and nearly 500 patients, *STK11/LKB1* mutations were associated with significantly shorter progression-free survival (PFS) and overall survival in patients treated with chemo-immunotherapy (ie, pemetrexed/carboplatin/pembrolizumab)[56] than those with *STK11/LKB1*–wild-type tumors (Skoulidis F, et al: J Clin Oncol 37, 2019 [suppl 15; abstr 102]). Similarly, PFS was shorter in those with *STK11/LKB1* and *KRAS* comutations from a group of 174 patients from a multicenter trial treated with immune checkpoint inhibitor monotherapy (ie, nivolumab).[57] In contrast, patients with *TP53* and *KRAS* comutations were more sensitive to nivolumab, with a PFS similar to those with only *KRAS* mutations.[57] Furthermore, patients from the Lung Adjuvant Cisplatin Evaluation (LACE) database receiving adjuvant chemotherapy with cisplatin and with *KRAS* and *TP53* comutations had approximately 2.5 times worse overall survival than patients with double wild-type disease (Shepherd FA, et al: J Clin Oncol 35:2018-2027, 2017). In contrast, *KRAS* mutation status was not predictive of survival after adjuvant therapy in the absence of a TP53 comutation.[52]

NF1 loss in *KRAS*-mutant disease is associated with focal adhesion kinase-1 hyperactivation and phosphoserine aminotransferase upregulation, enhancing tumor cell viability and having the potential to be associated with resistance to KRAS inhibitors (Wang X, et al: EMBO Mol Med 11:e9856 2019).

APPENDIX 3

Molecularly Driven Subgroups of Non–Small-Cell Lung Cancer: Testing and Treatment

Molecular testing, an essential first step in the diagnostic work-up of advanced-stage non–small-cell lung cancer (NSCLC), supports the selection of optimal targeted therapies for patients harboring certain driver mutations/gene rearrangements (Osmani L, et al: Semin Cancer Biol 52:103-109, 2018; Kalemkerian GP, et al: J Clin Oncol 36:911-919, 2018; Planchard D, et al: Ann Oncol 29:iv192-iv237, 2018; National Comprehensive Cancer Network: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf). Of patients with lung cancer who received personalized therapy matched to their mutational profile, nearly 80% had a clinical benefit,[4] with longer survival experienced by those receiving targeted therapy (Aisner DL, et al: Clin Cancer Res 24:1038-1047, 2018), underlining the importance of molecular testing and targeted treatment (Pennell NA, et al: Am Soc Clin Oncol Educ Book 39:531-542, 2019).

Currently, *EGFR*, *ALK*, and *ROS1* molecular testing is recommended for patients with advanced adenocarcinoma in most European countries and in the United States (Planchard D, et al: Ann Oncol 29: iv192-iv237, 2018; Lindeman NI, et al: J Thorac Oncol 13:323-358, 2018; Liebs S, et al: Cancer Med 8:3761-3769, 2019; Hanna N, et al: J Clin Oncol 35:3484-3515, 2017). As newer targeted therapies become available, testing for *BRAF V600E* mutations and NTRK-gene fusions is also recommended (Kalemkerian GP, et al: J Clin Oncol 36:911-919, 2018; Planchard D, et al: Ann Oncol 29:iv192-iv237, 2018; Lindeman NI, et al: J Thorac Oncol 13:323-358, 2018; Liebs S, et al: Cancer Med 8:3761-3769, 2019). In addition, agents targeting *MET*, *RET*, and *ERBB2* (*HER2*) have demonstrated promising efficacy and are anticipated to gain regulatory approval in the upcoming months. As the list of targetable alterations has grown, many institutions have adopted more comprehensive next-generation sequencing (NGS) panels to detect less common targetable alterations as well as avoid the need for repeat biopsies due to exhaustion of tissue from sequential testing.

In patients with NSCLC, *EGFR*, *ALK*, *ROS1*, and *BRAF* mutations are often mutually exclusive and tend not to overlap with *KRAS* and other driver mutations (Sholl LM, et al: J Thorac Oncol 10:768-777, 2015).

Molecular testing at the time of acquired resistance to targeted therapies is also recommended to select appropriate salvage therapy for certain driver mutations (Planchard D, et al: Ann Oncol 29:iv192-iv237, 2018; National Comprehensive Cancer Network: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf; Hanna N, et al: J Clin Oncol 35:3484-3515, 2017).

In addition to identifying the presence of oncogenic driver mutations, testing is also conducted to ascertain programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) receptor expression levels associated with NSCLC (Planchard D, et al: Ann Oncol 29:iv192-iv237, 2018; National Comprehensive Cancer Network: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf). Despite the significant clinical impact of conducting molecular testing, the uptake continues to be suboptimal in the routine clinical practice setting (Mason C, et al: J Clin Pathw 4:49-54, 2018).

Finally, *KRAS* testing should also be included as part of any expanded testing panel able to detect a wide range of mutations, such as NGS, and offered to all patients with advanced lung adenocarcinoma (Kalemkerian GP, et al: J Clin Oncol 36:911-919, 2018; National Comprehensive Cancer Network: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf; Lindeman NI, et al: J Thorac Oncol 13:323-358, 2018; Kim ES, et al: J Thorac Oncol 14:338-342, 2019). Outside of clinical trial scenarios, specific targeted therapies for patients with an identified *KRAS* mutation are not effective; hence, single-gene testing is not current practice (Kalemkerian GP, et al: J Clin Oncol 36:911-919, 2018).