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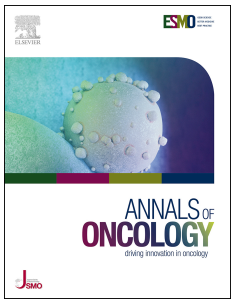

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Targeting *KRAS* in non–small cell lung cancer: recent progress and new approaches

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Highlights

- Better understanding of RAS signaling has led to development of promising directly blocking compounds in KRAS mutant tumors
- New drug candidates take advantage of the increased knowledge of KRAS mutation complex and relevant protein structures
- Increasing evidence continues to demonstrate the genomic heterogeneity in KRAS-mutated NSCLC
- Current efforts include understanding and overcoming resistance after treatment with KRASG12C inhibitors

Abstract (247 words)

Rat sarcoma (*RAS*) is the most frequently mutated oncogene in human cancer, with Kirsten rat sarcoma (*KRAS*) being the most commonly mutated *RAS* isoform. Overall, *KRAS* accounts for 85% of *RAS* mutations observed in human cancers and is present in 35% of lung adenocarcinomas. While the use of targeted therapies and immune checkpoint inhibitors (CPIs) has drastically changed the treatment landscape of advanced non–small cell lung cancer (NSCLC) in recent years, historic attempts to target *KRAS* (both direct and indirect approaches) have had little success, and no *KRAS*-specific targeted therapies have been approved to date for patients in this molecular subset of NSCLC. With the discovery by Ostrem, Shokat, and colleagues of the switch II pocket on the surface of the active and inactive forms of *KRAS,* we now have an improved understanding of the complex interactions involved in the *RAS* family of signaling proteins and has led to the development of a number of promising direct $KRAS^{G12C}$ inhibitors, such as sotorasib and adagrasib. In previously treated patients with $KRAS^{G12C}$-mutant NSCLC, clinical activity has been shown for both sotorasib or adagrasib monotherapy; these data suggest promising new treatment options are on the horizon. With the stage now set for a new era in the treatment of $KRAS^{G12C}$-mutated NSCLC, many questions remain to be answered in order to further elucidate the mechanisms of resistance, how best to use combination strategies, and if $KRAS^{G12C}$ inhibitors will have suitable activity in earlier lines of therapy for patients with advanced/metastatic NSCLC.

Key Words: KRAS, G12C, KRASG12C, non–small cell lung cancer

OVERVIEW OF *RAS/KRAS*-MUTANT LUNG CANCER

Rat sarcoma (*RAS*) is the most frequently mutated oncogene in human cancer [1, 2], with Kirsten rat sarcoma (*KRAS*) being the most commonly mutated *RAS* isoform [3] and a key clonal oncogenic driver. Overall, *KRAS* accounts for 85% of *RAS* mutations observed in human cancers [4]. The 3 human cancer types with the highest rate of *KRAS* mutations are pancreatic (88%), colorectal (45%-50%), and lung cancers (31%-35%) [5]. Despite decades of preclinical and clinical research aimed at identifying inhibitors of *RAS*, to date there are no approved therapies specifically inhibiting mutated forms of *KRAS* or its downstream signaling. However, a better understanding of the complex interactions involved in the RAS family of signaling proteins has led to the development of a number of promising compounds that directly block *KRAS* activity in patients with *KRAS*-mutant NSCLC and to the exploration of new combination approaches to inhibit *KRAS*. These new KRAS inhibitors, which are being investigated as monotherapies and also in combination with other therapies, have the potential to represent a significant advance in the treatment of *KRAS*-mutated NSCLC. Herein, we discuss the biology and history of targeting *KRAS* in lung cancer and provide an update on these emerging therapies.

KRAS *biology: structure, function, and downstream effector pathways*

KRAS encodes a membrane-bound guanosine triphosphatase (GTPase), which is inactive when bound to guanosine diphosphate (GDP) and active when bound to guanosine triphosphate (GTP)[6]. The cycling of RAS proteins to their active GTP-bound state is promoted by a guanine nucleotide exchange factor (GEF), such as son of sevenless isoform 1 (SOS1) protein [7, 8]. This active form of *KRAS* acts like a cellular switch that, when turned on by extracellular stimuli, can activate downstream signaling pathways responsible for fundamental cell processes [9] (Figure 1). Key effector pathways downstream of oncogenic *KRAS* include mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K), and Ras-like (Ral) GEF (RalGEF); all of these effectors are responsible for cell proliferation, cell cycle regulation, metabolic changes, cell survival, and cell differentiation [10]. The KRAS protein cycles between GTP- and GDP-bound states and has a resynthesis half-life of approximately 24 hours [11, 12].

KRAS can be dysregulated and lead to tumor growth, playing a key role in controlling interactions between cancer cells and the microenvironment, which ultimately affects therapeutic response [13]. Mutant *KRAS* cells have also been associated with decreased major histocompatibility class I (MHC I) expression, upregulation of programmed cell death–ligand 1 (PD-L1), and promotion of an immunosuppressive immune cell population in the tumor microenvironment (TME) [13] via the

recruitment, accumulation, and maintenance of myeloid-derived suppressor cells (MDSCs) to the TME [14]. Preclinical studies conducted on *KRAS* mutations in lung adenocarcinoma (LUAD), pancreatic, and colorectal cancer, suggest that these alterations occur early in the carcinogenesis process and promote cancer cell survival, invasion, and migration [15].

KRAS *mutations in lung cancer*

Point mutations represent a common dysregulation in the *KRAS* gene that leads to a constitutively active GTP-bound state, thereby triggering downstream oncogenic pathways [16-18]. Smoking has been strongly associated with *KRAS* mutations in lung cancer. *KRAS* mutations are more common in LUADs (20%-40%) and less common (~5%) in squamous NSCLC [19]. Such mutations are also more common in smokers versus nonsmokers (30% versus 11%) and in Western versus Asian populations (26% versus 11%) [20].

Genetic heterogeneity

KRAS mutations have been observed in up to 30% of patients with NSCLC [21] and occur primarily (>95%) at codons 12 and 13. A large study found that the most common codon variants in the protein were mutations from amino acid glycine (G) to cysteine (C) (or G12C variants), which accounted for 39% of *KRAS* mutations, followed by mutations from amino acid glycine (G) to valine (V) G12V (21%) and mutations from amino acid glycine (G) to aspartic acid (D) G12D (17%)[22]. Compared with other *KRAS* mutations, G12C is more common in women (P = 0.007) [22]. In addition, the distribution of mutations and codon variants in *KRAS* differs by smoking status. Smoking-associated $KRAS^{G12C}$ (41% of former and current smokers) or $KRAS^{G12V}$ mutations are associated with transversion mutations in the DNA, involving nucleotide changes from guanine (G) to thymine (T) or guanine (G) to cytosine (C). On the other hand, among never-smokers, the most common *KRAS* mutation was $KRAS^{G12D}$ (56%), a transition mutation involving nucleotide changes from guanine (G) to adenine (A) [22].

Prognostic implications of KRAS *mutations*

Data on the prognostic value of *KRAS* mutations in NSCLC are conflicting. Some reports suggest that patients with *KRAS* mutations have a poor prognosis, while other studies demonstrate that patients with wild-type (WT) *KRAS* and mutant *KRAS* have similar outcomes [23-26].

HISTORY OF TARGETING *KRAS* IN LUNG CANCER

Although great progress in discovering and developing targeted therapies for molecular subsets of LUAD has been made, no currently approved drugs specifically target any *KRAS* mutation, which occur in about one-third of patients with LUAD (see Figure 2) [21].

KRAS has been the subject of extensive drug development efforts for nearly 40 years. These efforts have included targeting the KRAS protein itself as well as its post-translational modifications, membrane localization, protein-protein interactions, and downstream signaling pathways. Most of these approaches have not proved successful in clinical studies [27] (see Table 1), because, as the discovery by Ostrem, Shokat and colleagues has demonstrated, the KRAS protein has a relatively shallow, smooth surface, with the exception of the GTP/GDP-binding pocket [6, 28, 29].

Direct targeting of KRAS

Until about 5 years ago, direct targeting of *KRAS* was seen as highly challenging due to the complexity of its biochemistry [30], the high affinity of GTP for *KRAS* [31], and its limited number of active binding sites [32]. Recent advances in computational modeling [33] and crystallography have led to the discovery of small molecules that bind directly to specific *RAS* conformations [34]. However, the binding affinity of these early-stage compounds needed to be significantly improved for them to work effectively as therapies. Although these compounds proved that *RAS* is a druggable target, they lacked potency and some lacked specificity for the mutated forms of *RAS* [35].

Indirect targeting of KRAS

Numerous other strategies for indirectly targeting *KRAS* were explored as well, including post-translational modifications, membrane localization, protein-protein interactions, and inhibition of downstream signaling pathways.

The farnesylation of RAS protein is required both for its normal physiologic function and for the transforming capacity of its oncogenic mutants. Over the last several decades, farnesyl transferase inhibitors (FTIs) were developed as anticancer agents to disrupt the farnesylation of oncogenic *RAS*. Some of these FTIs (e.g., tipifarnib and salirasib) have undergone clinical investigation but have not shown clinical efficacy in *KRAS*-mutant NSCLC [36, 37]. Mechanisms by mutant *KRAS* to combat

farnesylation and activate oncogenesis, such as alternative prenylation by geranylgeranyl transferases, have led to the failure of these studies [38].

Small molecules were also developed that inhibited the rapidly accelerated fibrosarcoma (RAF) association in cells and reduced the phosphorylation of downstream molecules, such as mitogen-activated protein kinase kinase (MEK) and extracellular regulated kinase (ERK) [35, 39]. While MEK has been hypothesized as a suitable target for downstream KRAS inhibition, the efficacy of MEK inhibitors as monotherapy in clinical trials has been modest. Selumetinib, an allosteric, selective inhibitor of MEK1/2, demonstrated preclinical activity in *KRAS*-mutated cancers [40]. However, in a randomized phase 2 trial in 87 pretreated patients with *KRAS*-mutated advanced NSCLC, which compared selumetinib + docetaxel with docetaxel + placebo, differences in overall survival (OS) were not statistically significant (9.4 versus 5.2 months; $P = 0.21$). Differences in other measures did reach statistical significance: objective response rate (ORR) in the selumetinib/docetaxel group was 37% versus 0% in the docetaxel/placebo group ($P < 0.0001$) and progression-free survival (PFS) was 5.3 versus 2.1 months ($P = 0.014$) [41]. In another study, 510 patients with *KRAS*-mutant advanced NSCLC were randomized to receive selumetinib + docetaxel or placebo + docetaxel as second-line therapy. This study failed to show an improvement in PFS ([HR, 0.93) [42].

Preclinical studies have demonstrated that *KRAS*-mutant NSCLC cell lines and xenografts with additional alterations in either the tumor protein P53 (TP53) or cyclin-dependent kinase inhibitor 2A (CDKN2A; INK4A/ARF) loci are sensitive to focal adhesion kinase (FAK) inhibition [43]. In a phase 2 study that investigated FAK inhibition in heavily pretreated patients with *KRAS*-mutant NSCLC, defactinib monotherapy demonstrated modest clinical activity (median PFS, 45 days) and efficacy was not associated with*TP53* and *CDKN2A* status [43].

Ongoing Efforts to Target *KRAS* in NSCLC

Seminal work conducted by Ostrem, Shokat and colleagues has paved the way the discovery of a new generation of direct inhibitors of $KRAS^{G12C}$. Their investigation of the crystal structure of the mutant protein bound to GDP revealed a new pocket beneath the effector binding switch II region, not apparent in previous models of *RAS*; the discovery of this new pocket allowed for the direct targeting of *KRAS* [34]. Numerous drug candidates have since been synthesized that take advantage of the increased understanding of mutant $KRAS^{G12C}$ protein structure and rely on covalent binding to cysteine.

Monotherapies

Sotorasib (AMG510) is a covalent $KRAS^{G12C}$ that irreversibly and selectively binds to the switch II pocket within mutant *KRAS*, locking it in the inactive GDP-bound state. Pharmacokinetic (PK) analyses of phase 1 data demonstrated that the half-life of sotorasib is approximately 5.5 hours [44]. Sotorasib monotherapy was evaluated in a phase 1/2 study (CodeBreak 100: NCT03600883; Table 2) in patients with previously treated, locally advanced or metastatic malignancies harboring a $KRAS^{G12C}$ mutation, with a primary endpoint of ORR. At the 960mg once daily dose continued until disease progression that was selected for phase 2 in patients with metastatic NSCLC (N=124), ORR was 37.1% and disease control rate (DCR) was 80.6% (Figure 3). In these patients with NSCLC, median duration of response was 10.0 months, median time to objective response was 1.4 months, and median progression-free survival (PFS) was 6.8 months for sotorasib. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 19.8% of patients (N=126) [45, 46]. TRAEs with sotorasib occurring in >5% of patients include GI toxicities such as diarrhea (4% grade 3), nausea, and vomiting, as well as hepatotoxicities such as alanine aminotransferase (ALT) increase (6.3% grade 3) and aspartate aminotransferase (AST) increase (5.6% grade 3). TRAEs led to treatment discontinuation in 7.1% of patients and to dose modification in 22.2% of patients. Sotorasib was granted breakthrough designation by the U.S. Food and Drug Administration (FDA) and a new drug application (NDA) was filed in December 2020. Furthermore, the global phase 3 trial, CodeBreak 200, comparing sotorasib with docetaxel in patients with $KRAS^{G12C}$-mutated NSCLC is ongoing.

Another $KRAS^{G12C}$ inhibitor in development is adagrasib (MRTX849), a covalent $KRAS^{G12C}$ inhibitor that irreversibly and selectively binds $KRAS^{G12C}$ in its inactive, GDP-bound state and also binds the switch II pocket (Table 2) [6]. In contrast to sotorasib, with a 5.5 hour half-life,, adagrasib was optimized and selected for certain PK properties, including oral bioavailability, long half-life (~24 hours), and extensive tissue distribution [47]. Adagrasib was evaluated in a recent phase 1/2 study (KRYSTAL-1; NCT03785249) in patients with NSCLC and $KRAS^{G12C}$ mutations who had received prior treatment with a programmed cell death protein 1/ programmed cell death–ligand 1 (PD-1/PD-L1) inhibitor administered either with or after chemotherapy (N=51). For those treated with single agent adagrasib (600 mg twice daily [BID]), ORR was 45% and DCR was 96% (Figure 3). The data was not mature at the time of cutoff, thus the duration of response has not yet been reported for adagrasib. Grade 3 or 4 TRAEs occurred in 30% of patients; commonly reported (>5%) grade 3 or 4 TRAEs included fatigue (6%) and increased AST/ALT (5%) [47]. TRAEs led to discontinuation of treatment in 4.5% of patients

[48]. Preclinical data indicate that adagrasib can penetrate the brain and cerebrospinal fluid and clinical data demonstrates the drug's antitumor activity against brain metastases [47].

GDC-6036/RG6330 is currently being evaluated for safety, PK, and preliminary activity in a phase 1 trial in patients with advanced or metastatic solid tumors harboring a *KRAS*^{G12C} mutation (NCT04449874; Table 2). Other compounds from AstraZeneca, Novartis, Jacobio, and InventisBio are in early phase 1 or preclinical development (Table 2). The development of two other KRAS^{G12C} inhibitors, JNJ-74699157 and LY-3499446, has been discontinued (NCT04006301 and NCT04165031; Table 2)[49].

Combination strategies for KRAS-mutant NSCLC

Combination therapy may further extend the benefit of KRAS^{G12C} inhibition by targeting more than one, or redundant, oncogenic pathways to prevent or delay resistance. Combination approaches for *KRAS* mutations in NSCLC are in development. Given the complexity of *KRAS*-mutant NSCLC, the frequency of co-mutations, and the bypass pathways involved in treatment resistance, combination therapy is a rational approach [6]. Many of the current KRAS inhibitors in development (Table 2) are also being evaluated in combination studies.

One interesting combination is *KRAS* inhibition combined with Src homology phosphatase 2 (SHP2) inhibition. SHP2 is activated in mutant cell lines after tyrosine kinase inhibitor (TKI) treatment. Recent studies have shown that SHP2 inhibition specifically suppresses the stemness of mutant, but not WT, *KRAS*-mutant NSCLC cells in vitro, and this suppression of stemness is promoted by TKI treatment [50]. Emerging data suggest that *KRAS*-mutant cancers are dependent on SHP2 and receptor tyrosine kinase (RTK); in particular, *KRAS*^{G12C} - and *KRAS*-mutant NSCLC has been found to be dependent on SHP2 activity *in vivo* [6]. Preclinical studies of adagrasib combined with SHP2 inhibition in several xenograft models of *KRAS*^{G12C}-mutant tumors have demonstrated greater activity for the combination compared with either agent alone [6]. Several ongoing clinical studies, both with sotorasib and adagrasib, are evaluating the combination of a KRAS^{G12C} inhibitor and a SHP2 inhibitor (NCT04330664 and NCT04185883).

Another approach focuses on combining KRAS inhibition with epidermal growth factor receptor (EGFR) TKIs, as the EGFR signaling pathway is often activated in tumor cells to bypass KRAS inhibition. This dual inhibition may thwart the tumor's ability to bypass KRAS inhibition and enhance outcomes observed with inhibiting either target alone. Several studies are currently evaluating this approach. A

phase 1/1b trial is investigating the treatment of NSCLC harboring a *KRAS* or *EGFR* mutation with the combination of MEK162, a MEK inhibitor, and erlotinib, an EGFR inhibitor (NCT01859026). The KRYSTAL-1 study includes an arm that will evaluate adagrasib in combination with afatinib, an EGFR/pan–human epidermal growth factor receptor 2 (HER2) inhibitor, in *KRAS*-mutated NSCLC. CodeBreak 101 also includes an arm that combines the $KRAS^{G12C}$ inhibitor sotorasib with a pan-ErbB inhibitor.

There is also interest in combining KRAS inhibition with a check-point inhibitor (CPI), the standard of care in advanced NSCLC [51]. In a $KRAS^{G12C}$ syngeneic tumor model, sotorasib as a single agent caused tumor regression in mice, but only one of 10 tumors remained completely regressed. Similarly, anti–PD-1 monotherapy achieved complete sustained regression in only one of 10 tumors [12]. However, combination therapy with sotorasib and an anti–PD-1 agent resulted in complete remission in nine of 10 mice [12]. Adagrasib plus anti–PD-1 therapy led to durable complete responses (DCRs; cures) in the majority of mice and a survival advantage relative to either agent as monotherapy [52]. In mouse models showing complete response, reintroduction of tumor cell inoculum failed to result in re-formation of tumor, demonstrating durable antitumor immunity for the combination. Clinical trials evaluating the combination of CPIs with the $KRAS^{G12C}$ inhibitor adagrasib or sotorasib or anti-PD-/L1 inhibitors in patients with $KRAS^{G12C}$-mutant NSCLC are ongoing (NCT03785249, NCT04185883, NCT03600883, NCT04613596).

SOS1 is another protein of interest in *KRAS*-mutant NSCLC. BI-3406 is a selective SOS1-*KRAS* interaction inhibitor that has shown efficacy in *KRAS*-driven cancers in preclinical studies. SOS1 inhibition suppresses growth of xenograft *KRAS*-mutant tumors and prevents adaptive resistance to MEK inhibition. When used in combination with a $KRAS^{G12C}$ or MEK inhibitor, BI-3406 increases the extent and duration of MAPK pathway inhibition and may more effectively deter adaptive resistance [12, 53].

Other ongoing studies seek to target *KRAS* via MEK inhibition, thus acting downstream of oncogenic *KRAS* signaling. One such study is evaluating VS-6766, a RAF-MEK inhibitor, in recurrent $KRAS^{G12V}$-mutant or other *KRAS*-mutant NSCLC as both monotherapy and in combination with defactinib, an oral small molecule that inhibits focal adhesion kinase (FAK; NCT04620330). In addition, CodeBreak 101 includes an arm evaluating the combination of sotorasib and a MEK inhibitor.

Yet other potential combination approaches to *KRAS* inhibition being studied include a *KRAS*^{G12C} inhibitor combined with chemotherapy, a mechanistic target of rapamycin (mTOR) inhibitor, and a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor (NCT04185883).

Co-mutations of special interest

Growing evidence suggests that *KRAS*-mutated NSCLC frequently may have genetic heterogeneity rather than only a single *KRAS* mutation [54]. In a recent study, the pattern of genetic co-mutations varied with different *KRAS* subtypes. These co-mutations or alterations included the *TP53* tumor suppressor gene (39%-42%); serine/threonine kinase 11 (*STK11;* 20%-29%); kelch-like ECH-associated protein 1 (KEAP1*;* 13%-27%); ataxia-telangiectasia mutated gene (*ATM*; 13%); hepatocyte growth factor (MET) receptor (15.4%); and Erb-B2 receptor tyrosine kinase 2 (*ERBB2*; 13.8%), found exclusively in *KRAS*^{G12C}-mutant tumors [54, 55]. It has been hypothesized that some of these co-mutations may hold prognostic and therapeutic significance in *KRAS*-mutant NSCLC [56]. *KRAS* mutations are typically considered mutually exclusive with other known activating driver mutations in NSCLC (e.g., *EGFR,* anaplastic lymphoma receptor tyrosine kinase [*ALK],* and proto-oncogene tyrosine-protein kinase ROS *[ROS1]*) [57].

TP53 is inactivated by mutations in more than 50% of NSCLC and appears to occur early in lung cancer progression [58]. Mutant *TP53* tumors demonstrate active inflammation and adaptive immune resistance. Furthermore, *TP53* expression correlates with PD-L1 positivity at both messenger ribonucleic acid (mRNA) and protein levels in patients with LUAD. Thus, increasing evidence suggests that *TP53* plays a crucial role in moderating the immune response [59]. Patients with *TP53/KRAS* co-mutations have been shown to have improved outcomes compared with those with WT *TP53* [60].

Approximately one-third of *KRAS*-mutant NSCLC harbor inactivating *STK11* mutations [54], which have been shown to be correlated with increased neutrophil counts, decreased PD-L1 expression, and downregulation of tumor-infiltrating lymphocytes (TILs) in preclinical models [61]. Loss of *STK11* and mutant *KRAS* has also been shown to be conducive to oncogenesis via mTOR-dependent upregulation of DNA methylation [62]. Several retrospective studies of patients with previously treated advanced NSCLC compared outcomes of patients with *KRAS* and *STK11* co-mutations with outcomes of patients with only an *STK11* mutation. In these studies, patients with the co-mutations had poorer outcomes [63-67]. In an analysis from IMpower150, *STK11* was shown to be a major driver of primary resistance to PD-1/PD-L1 checkpoint blockade in patients with *KRAS* mutations [64-66, 68]. In this study, median OS in patients with *KRAS*, *STK11,* and/or *KEAP1* mutations who received the combination of atezolizumab,

bevacizumab, and chemotherapy was 11.1 months, as compared with 8.67 months in those receiving the combination of bevacizumab and chemotherapy (HR for death, 0.50); PFS in the 2 groups was 6 and 3.35 months, respectively [64, 67].

An exploratory analysis from KRYSTAL-1 demonstrated that adagrasib had better efficacy in patients with *KRAS*^{G12C} and *STK11* co-mutations than in those with a *KRAS*^{G12C} mutation alone; ORR was 64% (9/14) in patients with *KRAS*^{G12C} and *STK11* co-mutations versus 33% (10/30) in patients with the *KRAS*^{G12C} mutation and WT *STK11* [47]. Tumors harboring *STK11* co-mutations exhibited increased immune response transcripts after treatment with adagrasib [48]; two of three patients this response after adagrasib treatment, suggesting that adagrasib recruits T cells into the tumor and may reverse *STK11*-mediated immune suppression. In this preliminary biomarker analysis, no apparent trend toward a higher ORR was observed with *KEAP1* or *TP53.*

In addition, in an exploratory biomarker analysis from CodeBreak100, different responses were observed in patient populations of special interest. *STK11/KEAP1* co-occurring mutational analyses showed a 23% ORR (3/13) for both *STK11* and *KEAP1* mutants, 50% ORR (11/22) for *STK11* mutant and *WT KEAP1*, 14% ORR for *WT STK11* and *KEAP1* mutant, and 42% ORR for WT *STK11* and WT *KEAP1*.

WHAT LIES AHEAD?

KRAS-mutant NSCLC occurs in about one-third of patients with LUAD, who represent the largest subset of patients with NSCLC for whom there is no approved targeted therapy [21]. Although progress has been made with sotorasib and adagrasib for patients with LUAD and KRAS^{G12C} mutations, many questions remain: What are the mechanisms of resistance to these inhibitors and can a better understanding of these resistance mechanisms inform patient selection or combination strategies? Will there be a role for KRAS inhibitors in the first line setting? Is it as monotherapy, or will a combination approach provide better patient outcomes? Will monotherapy data with KRAS^{G12C} inhibitors be sufficient to warrant use in the 1L NSCLC setting?

Current efforts to answer these questions are ongoing, and include studies focusing on resistance mechanisms, and efficacy in special patient populations to help guide the evaluation of the best

approach for integration of these novel targeted therapies into clinical practice [69]. Data from an initial study suggests multiple mechanisms of resistance are possible with $KRAS^{G12C}$ inhibitors, and no universal or predominant mechanism was seen unlike the tyrosine kinase inhibitors (TKIs) targeting EGFR and ALK. Mutations identified at resistance to adagrasib were often subclonal or in the context of multiple putative mechanisms. Examples included secondary *KRAS* mutations, MAPK pathway alterations, acquired genomic rearrangements, and histologic transformation. These data suggest there may not be a universal strategy for combinations at progression and a more personalized approach may be necessary.

As our understanding of the complex KRAS biology and the body of clinical evidence grows for KRAS-directed therapeutics, the place of these inhibitors in the treatment paradigm is expected to evolve. The current conventional approach calls for testing novel therapies in pretreated patients and then advance to earlier lines of therapy once the activity of a therapy is confirmed. However, questions remain regarding both patient selection and the potential efficacy of $KRAS^{G12C}$ inhibitors in the first-line setting. Current response rates in previously treated KRAS-mutant NSCLC observed with both sotorasib and adagrasib range from 37-45%. Based on data for other targeted therapies used in the frontline setting in oncogene-addicted tumors (e.g., EGFR-mutated NSCLC), some might expect that the response rates of this new class of $KRAS^{G12C}$ inhibitor may be higher in treatment-naive patients. However, we think this is unlikely, in part due to the genetic heterogeneity of KRAS mutated NSCLC compared to the relatively simpler underpinnings of RTK-driven tumors. The GTPase function of RAS and/or the signaling of the RAS pathway may be too complex as observed with the resistance mechanisms and, therefore, monotherapy activity in 1L NSCLC may be limited. One approach may be to select patients who are unsuitable for standard-of-care platinum-based therapy or use molecular testing as an enrichment strategy to select patients. For example, patients harboring co-mutations such as $KRAS^{G12C}$ with *STK11* respond poorly to single agent CPI therapy and may be candidates for $KRAS^{G12C}$ targeted therapy in the first-line setting based on preliminary data observed to-date (response rates of 50% [11/22] and 64% [9/14] for sotorasib and adagrasib, respectively). Another approach with the potential to move $KRAS^{G12C}$ inhibitors into the first-line setting, is to combine with a CPI +/- chemotherapy. However, the safety and feasibility of these combinations will need to be studied, and secondary analyses evaluating AEs observed relative to prior CPI treatment may inform feasibility.

There may also be a role for KRAS inhibition in the adjuvant or neoadjuvant setting, including in resectable disease. The ADAURA trial [70] demonstrated that targeted therapies may be an important

treatment option in earlier-stage NSCLC. Additionally, there is potential interest in exploring the combination of a KRAS inhibitor with radiation therapy in stage III tumors.

Numerous additional approaches aimed at inhibiting or degrading *KRAS* also show promise. Targeting tumors expressing mutant *KRAS* directly with vaccines or TILs is an ongoing area of exploration [71]. Other approaches involving targeted degradation of *KRAS* include designed ankyrin repeat proteins (DARPins) [72] and C12-directed covalent degrader molecules (PROTACs) [73].

After approximately four decades of research into targeted therapies for *KRAS*-driven tumors, the prospect of drugging the undruggable appears achievable. While the future of treatment for *KRAS*-mutant NSCLC looks promising, more work needs to be done to further optimize outcomes.

Table 1. Historical attempts to target *KRAS* in NSCLC

AKT, protein kinase B; BCL-2, B-cell lymphoma 2; CDK4, cyclin-dependent kinase 4; ERK, extracellular receptor kinase; HDAC, histone deacetylase; Hsp90, heat shock protein 90; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; MEK, mitogen-activated protein kinase kinase; MET, mesenchymal-epithelial transition; MT, mutant; mTOR: mammalian target of rapamycin; NF-kB: nuclear factor-kappa B; PDEδ, phosphodiesterase-δ; PI3K, phosphoinositide 3-kinase; RAF, mesenchymal-epithelial transition; RTK, receptor tyrosine kinase; SHP2, Src homology 2; siRNA, small interfering ribonucleic acid; TBK1, TANK-binding kinase 1.

Table 2. *KRAS*-targeting agents in clinical or preclinical development in NSCLC

[Figure captions]

Figure 1. Pathways of and potential combination treatment approaches to *KRAS mutations.*

Figure 2. Single oncogenic driver paradigm of LUAD molecular classification [21].

Figure 3. Best tumor change from baseline in NSCLC for (A) sotorasib [46] and (B) adagrasib [74] reported in phase 1/2 trials.

Figure 1.

AKT, gene on chromosome 14q32.32|14q32.32 that encodes protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; chemo, chemotherapy; EGFR, epidermal growth factor receptor; ERK, extracellular signal–regulated kinase; FAK, focal adhesion kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; 1L, first line; IO, immuno-oncology; KEAP1, kelch-like ECH-associated protein 1; *KRAS*, Kirsten rat sarcoma; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MHC, major histocompatibility complex; mTOR, mechanistic target of rapamycin; PD-1, programmed cell death protein 1; PD-L1, programmed cell death–ligand 1; PI3K, phosphatidylinositol-3-kinase; RAF, rapidly accelerated fibrosarcoma; RTKs, receptor tyrosine kinases; SHP2, Src homology phosphatase 2; SOS1, son of sevenless isoform 1; STK11, serine/threonine kinase 11; TCR, T cell receptor; TILs, tumor-infiltrating lymphocytes.

Figure 2.

ALK, anaplastic lymphoma kinase; *BRAF*, serine/threonine-protein kinase B-Raf; *EGFR*, epidermal growth factor receptor; *ERBB*, epidermal growth factor (EGF) family of receptor tyrosine kinases (RTKs); *FGFR*, fibroblast growth factor receptor; *HRAS*, Harvey rat sarcoma viral oncogene homolog; *KRAS*, Kirsten rat sarcoma; MAP2K, mitogen-activated protein kinase kinase; MET, hepatocyte growth factor receptor; NF1, neurofibromin 1; *NRAS*, neuroblastoma RAS viral oncogene homolog; RET, rearranged during transfection; RIT, *ras*-like protein in tissues; *ROS1*, proto-oncogene tyrosine-protein kinase ROS.

Figure 3.

3A **3B**

BID, twice daily; CR, complete response; NE, not evaluable; NSCLC, non–small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

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Author Contributions

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Conflict of interest

MR has reported honoraria and consultancy for Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, Merck, Mirati Therapeutics, Inc., Merck Sharp & Dohme, Novartis, Pfizer, Sanofi Aventis, and Roche, outside the submitted work.

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MG has reported advisory boards and speaking engagements for Janssen, Daichi Sankyo, Seattle Genetics, Inc., Sanofi-Aventis, Merck Sharp & Dohme, GlaxoSmithKline, Bayer, Takeda, Inivata, Incyte, Celgene, Pfizer, Roche, and Bristol-Myers Squibb, and has received research funding from Exelixis, MedImmune, Ipsen, Bayer, Bristol-Myers Squibb, Roche, Pfizer, Incyte, Tiziana Life Sciences, Clovis Oncology, Merck-Serono, Merck Sharp & Dohme, Spectrum Pharmaceuticals, Inc., and Blueprint Medicines, and has received nonfinancial support from Lilly and Merck Sharp & Dohme, outside the submitted work.

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Table 1. Historical attempts to target *KRAS* in NSCLC

Target/pathway	Drug/asset
RAF-MEK-ERK	Salirasib, trametinib, sorafenib
Farnesyl transferase	Tipifarnib, ionafarnib, salirasib
NF-κB	Bortezomib
RHOA-FAK	Defactinib
PI3K-AKT-mTOR	Ridaforolimus, sorafenib, copanlisib
HSP90 and MEK	AUY-922, selumetinib
MET	Pimasertib, ganetespib, onartuzumab
HDAC inhibition	Belinastat
DNA alkylation	KR-12
PDEδ	Deltasonamide 1 and 2
Geranylgeranyltransferase	GGTI-2418
KRAS siRNA	SGS6 siRNA, KRAS-siRNA NP
KRAS (vaccine)	mRNA-5671
SOS1	BI 1701963
KRAS degradation	PTD-RBD-VIF
RAS-mimetic	Rigosertib
Glutaminase	CB-839
BCL2 and MEK (synthetic lethality)	Navitoclax, trametinib
TBK1 and MEK (synthetic lethality)	Momelotinib, trametinib
CDK4 and MEK (synthetic lethality)	Palbociclib, PD-0325901, abemaciclib
SHP2 and MEK	SHP099, AZD6244

AKT, protein kinase B; BCL-2, B-cell lymphoma 2; CDK4, cyclin-dependent kinase 4; ERK, extracellular receptor kinase; HDAC, histone deacetylase; Hsp90, heat shock protein 90; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; MEK, mitogen-activated protein kinase kinase; MET, mesenchymal-epithelial transition; MT, mutant; mTOR: mammalian target of rapamycin; NF-kB: nuclear factor-kappa B; PDEδ, phosphodiesterase-δ; PI3K, phosphoinositide 3-kinase; RAF, mesenchymal-epithelial transition; RTK, receptor tyrosine kinase; SHP2, Src homology 2; siRNA, small interfering ribonucleic acid; TBK1, TANK-binding kinase 1.

Table 2. *KRAS*-targeting agents in clinical or preclinical development in NSCLC

Target	Manufacturer	Agent	Status	ClinicalTrials.gov identifier
KRAS^{G12C}	Mirati Therapeutics, Inc.	Adagrasib	Phase 1/2 Phase 1/2 Phase 2 Phase 3	NCT03785249 NCT04330664 NCT04613596 NCT04685135
KRAS^{G12C}	Amgen	Sotorasib	Phase 1b Phase 1/2 Phase 3	NCT04185883 NCT03600883 NCT04303780
KRAS^{G12C}	InventisBio	D-1553	Phase 1/2	NCT04585035
KRAS^{G12C}	Genentech	GDC-6036 / RG6330	Phase 1	NCT04449874
KRAS^{G12C}	AstraZeneca	AZD4625	Phase 1	Pending
KRAS^{G12C}	Novartis	JDQ443	Phase 1	NCT04699188
KRAS^{G12C}	Jacobio	JAB-21000	Preclinical	N/A
KRAS^{G12D}	Jacobio	JAB-22000	Preclinical	N/A
KRAS^{G12V}	Jacobio	JAB-2300	Preclinical	N/A
KRAS	BridgeBio	BBP-454	Preclinical	N/A
KRAS^{G12C}	Eli Lilly	LY3537982	Preclinical	N/A
KRAS^{G12C}	Eli Lilly	LY3499446	Discontinued	NCT04165031
KRAS^{G12C}	Janssen	JNJ-74699157	Discontinued	NCT04006301

KRAS, Kirsten rat sarcoma viral oncogene homolog; N/A, not applicable; NSCLC, non–small-cell lung cancer.