Advances in targeting KRAS mutations: A promising approach for the treatment of non-small cell lung cancer (Review)

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Abstract. Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations are among the most frequent oncogenic drivers in cancer, particularly in non-small cell lung cancer (NSCLC). KRAS was previously considered an 'undruggable' target due to the protein's smooth molecular surface and the absence of obvious drug binding sites. However, the development of selective KRAS G12C inhibitors, such as sotorasib and adagrasib, together with progress in immunotherapy, have demonstrated potential clinical activity. Further understanding of the complex signaling networks driven by KRAS has revealed new opportunities to target this pathway directly or through rational combination strategies. The present review explored KRAS-targeted therapies and immunotherapies, including limitations, resistance mechanisms and the efficacy of combination regimens. Although there has been notable progress, concerns regarding optimal therapy combinations, resistance management and early treatment strategies remain. The present review demonstrated the need for continued research to address these challenges and improve outcomes for patients with KRAS-mutated NSCLC.

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1. Introduction

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related mortalities globally and accounts for ~85% of all lung cancer cases (1). Among the molecular subtypes of NSCLC, Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations are one of the most commonly identified oncogenic drivers. These mutations are commonly prevalent in lung adenocarcinoma (LUAD) and are strongly linked with smoking and environmental carcinogens (2). KRAS is a member of the rat sarcoma viral (RAS) oncogene family and accounts for the majority of RAS-related mutations encountered in human cancer. KRAS alterations account for ~85% of all RAS mutations (3). The prevalence of KRAS mutations varies across cancer types, with the highest frequencies found in pancreatic (88%), colorectal (45-50%) and lung cancer (31-35%) (4). KRAS mutations are present in ~30% of LUAD cases in Western populations and ~10% of in Asian populations (5,6).

The KRAS proto-oncogene encodes a small guanine triphosphate (GTPase) that acts as a binary switch in signal transductions of multiple receptor tyrosine kinases, such as mesenchymal-epithelial transition (MET), epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), thus regulating cellular functions such as proliferation, differentiation and survival. KRAS is a clonal transforming oncogene and is a key oncogenic driver across multiple solid tumors (7-9).

Structurally, KRAS is a 21-kDa GTPase composed of a conserved G-domain and two dynamic regulatory regions, Switch I and Switch II, which control its active (GTP-bound) and inactive (GDP-bound) states. The Switch II pocket (SII-P) forms the allosteric site targeted by KRAS G12C inhibitors, while C-terminal farnesylation enables its anchoring to the plasma membrane (10,11).

The prevailing outlook on the poor prognosis and limited treatment options for NSCLC has significantly shifted over the last 2 decades due to the development of targeted therapy, molecular profiling and immunotherapy (12,13). Although several preclinical and clinical studies have investigated RAS inhibitors, no authorized treatments directly inhibit mutant

variants of KRAS or its downstream signaling (14,15). These novel KRAS inhibitors are currently being investigated in combination with other therapies, which may significantly improve the treatment of KRAS-mutated NSCLC. Targeted therapy and immunotherapy have shown promising results in treating NSCLC, therefore the present review explored novel treatment strategies and their efficacy in targeting the KRAS mutation in NSCLC.

2. KRAS signaling pathways

KRAS is a key proto-oncogene that encodes a small GTPase that controls cell survival, differentiation and proliferation by acting as a molecular switch in important cellular signaling cascades (3). The GTPase cycles between an inactive GDP-bound and an active GTP-bound state. Activation is promoted by guanine nucleotide exchange factors (GEFs), which stimulate GDP-GTP exchange, such as SOS1 and the GTPase-activating proteins (GAPs); for example, neurofibromin 1 is a GAP that accelerates GTP hydrolysis to inactivate KRAS (14,16).

Multiple downstream effectors of KRAS, primarily, are part of the RAF-MEK-ERK signaling pathway. Activated KRAS-GTP recruits RAF kinases to the membrane, which promotes RAF dimerization and activation. RAF phosphorylates MEK1/2, leading to activation of ERK1/2. Upon activation, nuclear translocation of ERK occurs and targets transcription factors, including E26 transformation-specific family, serum response factor and ribosomal S6 kinase, to influence cell proliferation, differentiation and migration. Furthermore, KRAS stimulates phosphoinositide 3-kinase (PI3K), leading to AKT activation that promotes cell survival, metabolism and growth. KRAS also activates RalGEFs, which regulate cytoskeleton remodeling, membrane dynamics and vesicle trafficking (Fig. 1) (14,16,17). In its wild-type state, KRAS participates in normal cell signaling but does not directly suppress immune responses. KRAS mutations; however, it inhibits T-cell activity by stimulating an immunosuppressive tumor microenvironment (TME) through the induction of cytokine-(such as IL-6) and chemokine-(such as IL-8) driven inflammation and immune evasion, and increase programmed cell death-1 ligand (PD-L1) expression levels via activation of the MAPK and PI3K-AKT pathways, resulting in immune escape (14,18).

3. Clinical significance of KRAS mutations in NSCLC

KRAS mutations are clinically significant in NSCLC due to their frequency, prognostic implications and impact on treatment decisions (19,20). Point mutations commonly deregulate the KRAS gene, resulting in an inherently active GTP-bound phase and activating downstream oncogenic signaling pathways (21-23). KRAS mutation frequency is lower (~5%) in squamous NSCLC and higher (20-40%) in LUAD (24). Furthermore, these mutations are more prevalent in Western populations compared with Asian populations (26 vs. 11%) and in smokers compared with non-smokers (30 vs. 11%); the presence of KRAS mutations in NSCLC is closely associated with smoking (25). Furthermore, KRAS mutations are more common in female and younger patients, according to a pooled study of resected NSCLC tumors; however, only the association with younger patients was significant in the multivariate analysis (P=0.044) conducted (26,27). The previous study by Shepherd *et al* (27) on the frequency of KRAS mutations did not include any analysis specific to histology or race. Smoking is suggested to leave a particular molecular mark on KRAS gene since point mutations (G12C and G12V) are often detected in former or current smokers; by contrast, transitional mutations (G12D) are more common in non-smokers (28,29). Furthermore, compared with individuals who have never smoked, smokers often have substantially more complicated KRAS-mutant tumors with a more considerable mutational burden and a higher probability of significant co-occurring mutations in tumor protein P53 (TP53) or serine/threonine kinase 11 (STK11) (30).

Co-mutations, including STK11/LKB1, may influence the prognosis of KRAS-mutant NSCLC. For example, ERK1/2 phosphorylation is more significant in tumors with KRAS G12C mutations compared with those with KRAS G12D mutations, and this enhanced MAPK signaling can be further amplified in the presence of STK11/LKB1 loss, contributing to more aggressive tumor biology. Supporting this, a previous study employing animal models driven by KRAS mutations showed that the MEK inhibitor selumetinib was more effective in KRAS G12C tumors compared with KRAS G12D tumors (31). As a result, various KRAS mutations may induce signal transduction cascades differently, resulting in unique drug sensitivity profiles (32). Regarding co-occurring mutations, LUAD is typically associated with KRAS single-driver mutations, accounting for 95-99% of KRAS-mutant cases, while double mutants (EGFR/ALK/BRAF and KRAS) are rare, occurring in <1% of cases (33-35).

4. Targeting KRAS mutations in NSCLC

Approximately one-third of patients with LUAD have a KRAS mutation; despite significant advancements in the discovery and development of targeted therapeutics for molecular subtypes of LUAD (36), no authorized medication currently targets any KRAS mutation directly (37). For the past 40 years, significant efforts have been made to develop medicines for KRAS. These investigations have targeted the KRAS protein and its membrane location, interactions between proteins, post-translational modifications, and downstream signaling pathways; however, these methods have not shown promising outcomes in clinical trials (38,39).

Direct targeting of KRAS. Since KRAS has a restricted number of active binding sites, complicated biochemistry (40) and a high affinity for GTP (41), direct targeting of the protein was thought to be complex until ~5 years ago (42). Developments in crystallography and computer modeling (43) have identified small compounds that directly bind to the inactive GDP-bound conformation of KRAS G12C within the SII-P, thereby locking the protein in its inactive state and preventing downstream signaling (44). However, the binding affinity of these early-stage drugs would need to be substantially increased before they can be used as effective treatments. These early compounds demonstrated that RAS is principally druggable; however, they lacked sufficient potency and pharmacological

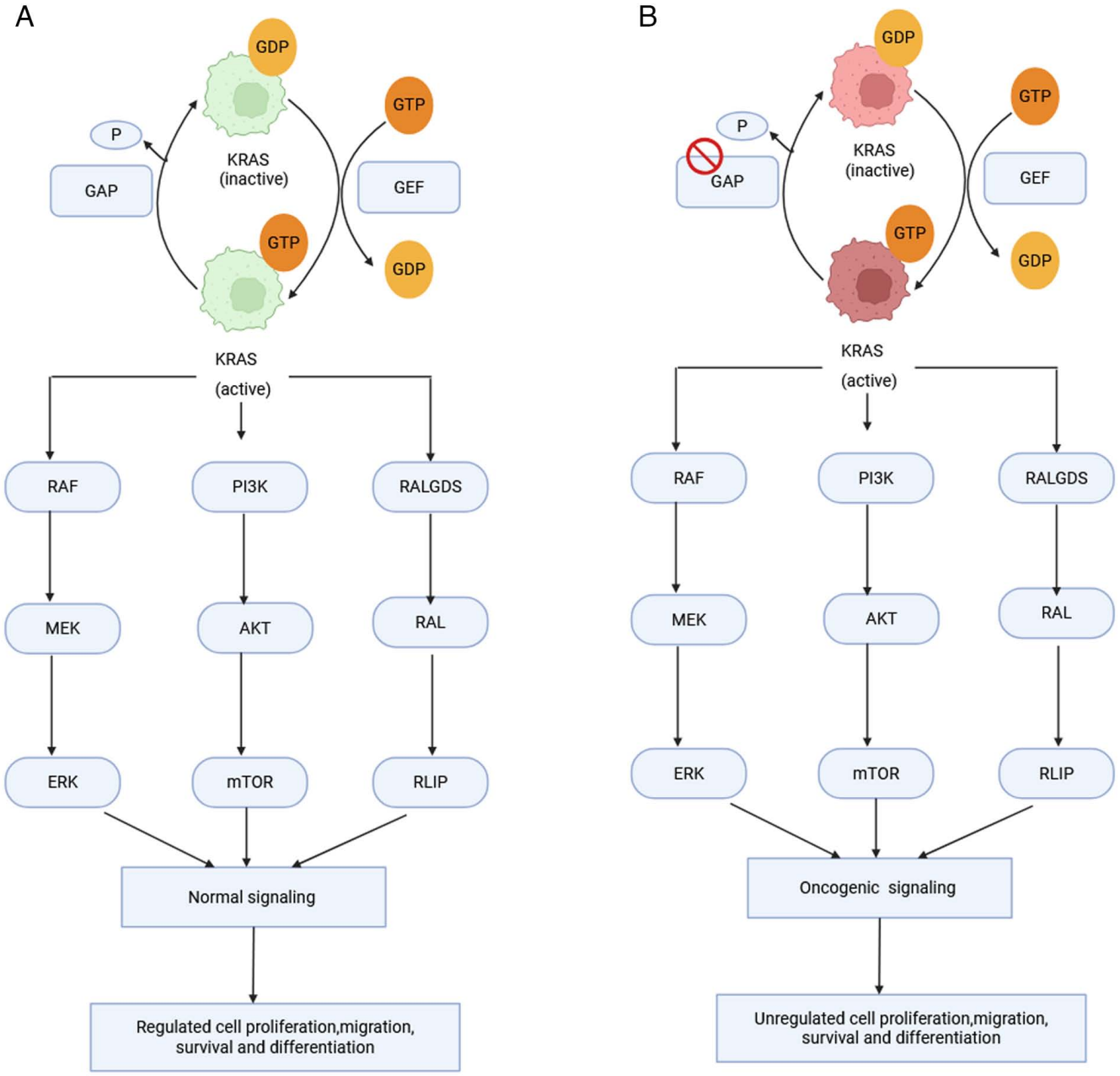

Figure 1. (A) Normal KRAS signaling. KRAS exists in a normal balance between its inactive form bound to GDP and the active form bound to GTP. It balances the activation of several downstream pathways, including RAF/MEK/ERK, RAL/RLIP and PI3K/AKT/mTOR, which execute regulated cellular features such as proliferation, migration, survival and differentiation. (B) Oncogenic KRAS signaling. Mutations disrupt the normal function of GTPase-activating proteins that hydrolyze GTP to GDP, resulting in constitutively active KRAS. Constitutive activation thus propagates a sustained drive for downstream signaling that promotes cell proliferation, migration, survival and differentiation, which are associated with oncogenic signaling. KRAS, Kirsten rat sarcoma viral oncogene homolog; GAP, GTPase activating proteins; GEF, guanine nucleotide exchange factors; RLIP, RalA binding protein 1.

properties to achieve clinical efficacy and often lacked the precision required to target mutant KRAS effectively (45)

Indirect targeting of KRAS: History, challenges and emerging approaches. Prior to the advent of direct KRAS inhibitors, indirect strategies were investigated, such as by blocking KRAS post-translational modifications, preventing its anchoring to the cell membrane or disrupting the downstream signaling pathways it controls (46-48). Early analyses focused on farnesyl transferase inhibitors, salirasib and tipifarnib being tested to prevent membrane anchoring of KRAS. Although the preclinical activity was promising, the clinical efficacy of salirasib and tipifarnib in NSCLC was limited due to compensatory prenylation with geranylgeranyl transferase. In a phase II trial of salirasib in KRAS-mutant LUAD, no objective responses were observed, although 30-40% of patients achieved temporary disease stabilization at 10 weeks (49,50).

Blockage of the downstream KRAS signaling has also been investigated. Small molecules that target ERK and MEK decrease effector phosphorylation and block RAF interactions in preclinical models (45,51). Despite this, MEK inhibitor clinical trials as monotherapy have been ineffective. In a phase II study of previously treated patients with KRAS-mutant NSCLC, FAK inhibition with defactinib alone

had limited clinical activity [median progression-free survival (PFS), 45 days], and activity was not associated with TP53 or CDKN2A status (52).

These studies highlight the primary limitations of indirect KRAS targeting: Biochemical redundancy, adaptive feedback loops and toxicity due to effects on essential signaling pathways (53). Post-prenylation processing enzymes such as Ras-converting enzyme 1 and isoprenylcysteine carboxyl methyltransferase remain potential targets, but inhibitors lack specificity and risk broad systemic toxicity (54). However, these limitations are being overcome through the development of pragmatic strategies. Combined inhibition of farnesyl- and geranylgeranyl transferase has been reported as a promising approach in models of pancreatic cancer, although it has not been tested in LUAD (55). Epidemiological studies suggest that oral bisphosphonate use is associated with a decreased risk of lung cancer in non-smoker postmenopausal women (56) and a case report described regression of hepatic metastases in primary lung adenocarcinoma following zoledronic acid monotherapy (57). Preclinical models indicate that these vulnerabilities are subtype-specific: Mesenchymal-like KRAS-mutant NSCLC is sensitive to combined FGFR-MEK inhibition, whereas epithelial-like tumors preferentially respond to ERBB-MEK blockade (58). Such biomarker-led combination strategies provide novel avenues for indirect targeting. Collectively, these indirect approaches illustrate the innovative nature of previous efforts to target KRAS and the associated limitations, and demonstrate the importance of investigations on direct interventions in the current therapeutic landscape.

5. Advances in treating KRAS mutations in NSCLC

KRAS G12C-specific inhibitors. The mutant KRAS G12C protein shows decreased GAP-stimulated GTPase activity from biochemical analyses, consistent with earlier G12X mutants (excluding G12P). In contrast with other mutated KRAS proteins, the mutation KRAS G12C maintains periodic intrinsic GTPase function and alternates among the active KRAS-GTP and inactive KRAS-GDP states (59,60). Structural analysis demonstrated that the KRAS Cys12 mutation is proximal to a newly identified allosteric site, the SII-P, which is transiently accessible in the GDP-bound state. This finding allowed the design of covalent inhibitors to bind Cys12 irreversibly, trapping KRAS G12C in its inactive state and ablating downstream signaling (61,62). The first therapies to target this SII-P were sotorasib, adagrasib and, more recently, garsorasib (D-1553). These KRAS G12C inhibitors all bind covalently to the SII-P but differ in their binding kinetics and molecular interactions (63). Adagrasib exhibits higher conformational mobility, allowing more sustained binding to KRAS-G12C, while garsorasib has shown promising clinical activity in NSCLC and colorectal cancer (64,65). Structural scaffold differences between KRAS G12C inhibitors, such as sotorasib and adagrasib, are likely responsible for the different pharmacodynamic profiles and tissue penetration.

Although the SII-P is the most-validated and extensively targeted allosteric site, it is not the sole structural determinant of KRAS inhibitor binding; other regions of KRAS also influence drug design and activity. KRAS contains key structural regions, including the Switch I and Switch II domains and a hypervariable region that regulates membrane attachment. The switch I region can be indirectly modulated by inhibiting SOS1-KRAS interactions using SOS1 inhibitors (such as BI-3406 and BI-1701963). The nucleotide binding pocket has been the focus of investigation with nucleotide competitive analogs and membrane localization disrupted with FTase inhibitors through the hypervariable region (66-68). These findings underscore that KRAS contains several structural features beyond the SII-P that may be exploited therapeutically.

The first KRAS G12C inhibitor studied in a clinical trial for an advanced solid tumor was sotorasib. The initial investigation was a CodeBreaK 100 phase I/II basket trial to determine the safety and beneficial effects of sotorasib in patients with advanced tumors with a KRAS G12C mutation, particularly those who previously received standard treatment. Based on the clinical trial outcome, sotorasib received approval from the Food and Drug Administration (FDA) in 2021 to treat advanced-stage NSCLC (69,70). In a cohort of 126 patients with KRAS G12C mutation NSCLC, the objective response rate (ORR) was 37.1%, with 3.2% exhibiting a complete response (CR). The median overall survival (OS) was 12.5 months, median PFS was 6.8 months, and adverse events were seen in 69.8% of patients (71). Another study found a 42.9% confirmed ORR for 116 patients with KRAS G12C mutated NSCLC. the median OS was 12.6 months and the median PFS and response duration were 6.5 and 8.5 months, respectively (72). In a subsequent phase III trial comparing sotorasib and docetaxel, sotorasib increased PFS [PFS, 5.6 months vs. 4.5 months for docetaxel, hazard ratio (HR)=0.66, P=0.0017] in patients with NSCLC who had previously received chemotherapy (73). The IFCT-2102 Lung KG12Ci study, a nationwide study conducted in France, included 458 patients with metastatic or advanced KRAS G12C-mutated non-squamous NSCLC across 76 centers. The median age was 65.8 years and 43.4% of the patients were female. The majority (95.4%) were current or former smokers and 38.0% had brain metastases at the initiation of sotorasib therapy. The key efficacy endpoints were a median real-world PFS of 3.5 months and a median real-world OS of 8.3 months (median follow-up was 15.8 and 16.4 months, respectively). The real-world ORR was 35.5% and the disease control rate (DCR) was 63.7%. In the subgroup of patients with brain metastases, the intracranial real-world ORR was 20.1% and the intracranial real-world DCR was 66.9%. From a safety perspective, sotorasib was considered to be tolerable. However, 16.5% of patients discontinued their therapy because of adverse events, while 5.2% of patients experienced grade 3-4 hepatotoxicity (74).

Sotorasib changed the treatment landscape for KRAS G12C-mutant NSCLC by providing improved clinical outcomes compared with standard second-line therapies, such as docetaxel, docetaxel-ramucirumab and immune checkpoint inhibitor (ICI) monotherapy. Nevertheless, the intracranial efficacy of sotorasib is low, particularly in patients with brain metastases, and survival benefits are limited due to the acquisition of resistance; thus, there is an urgent need for mechanism-based combination approaches and next-generation inhibitors. The clinical decision to use sotorasib should

be made with caution, particularly for patients with KRAS G12C-mutant NSCLC with central nervous system (CNS) involvement or a high disease burden.

Another KRAS G12C inhibitor with a positive clinical record is adagrasib. The phase I/IB KRYSTAL-1 study of adagrasib demonstrated a favorable safety profile and a median PFS of 11.1 months (75). KRYSTAL-12 (trial no. NCT04685135), a phase III study of adagrasib vs. docetaxel in patients with previously treated KRAS G12C-mutated NSCLC, demonstrated that 94.0% of patients who received adagrasib and 86.4% of patients who received chemotherapy had treatment-related adverse events (TRAEs). Grade ≥3 TRAEs occurred in 47.0% of patients who received adagrasib and 45.7% of patients who received docetaxel. These patients would have received immunotherapy before receiving adagrasib (76).

The KRAS G12C inhibitor garsorasib showed strong efficacy and tolerable safety in a phase II trial (trial no. NCT05383898) of 123 Chinese patients with pre-treated KRAS G12C-mutated NSCLC. All participants (median age, 64; 88% male) were administered 600 mg garsorasib twice daily and achieved an ORR of 50% (1 CR and 60 partial responses) and a DCR of 89%. With a median follow-up of 12.3 months, the median PFS was 9.1 months and the median OS was 14.1 months, the longest reported in commercialized KRAS G12C inhibitors. TRAEs were seen in 95% of patients, with grade ≥3 events (50%) mainly comprising hepatic enzymes (AST elevation, 17%; ALT, 15%) and gastrointestinal symptoms (nausea/vomiting, 2%); most toxicities were dose-modifiable (77,78). Garsorasib has demonstrated promising clinical activity with high response rates, durable responses and prolonged OS in patients with previously treated KRAS G12C-mutant NSCLC, and has shown superior outcomes compared with existing inhibitors, in certain contexts as aforementioned. However, widespread use and future studies with a larger sample size are necessary to collect more data on CNS activity, long-term survival and comparative effectiveness. Presently, the use of garsorasib may be considered post-chemotherapy and ICI therapy, particularly in patients with healthy liver function who can be closely monitored. Further to the aforementioned studies, numerous other clinical trials (Table I) are currently under investigation to identify therapies with increased efficacy of KRAS G12C inhibitors.

Clinical resistance continues to present a notable barrier and commonly involves allosteric sites such as the SII-P. Second-site mutations on or around the SII-P change pocket geometry and/or local dynamic structures that directly disrupt inhibitor binding (79). For example, Y96D eliminates hydrogen bonding in the pocket, A59T, and G13D disrupts the conformational state essential for drug interaction (80). Furthermore, bypass mechanisms of resistance, including upstream mechanisms by amplifying the HER2 gene, can induce KRAS activation and reduce dependence on SII-P inhibition (81). Taken together, these findings show that the structural confirmation of the SII-P influences inhibitor binding affinity, and demonstrates how mutations in this region can lead to resistance. This close association between the structure and function of KRAS underscores the importance of combining strategies or developing next-generation inhibitors to overcome these challenges, including resistance.

Combining KRAS G12C inhibitors with ICIs is supported by synergistic immunogenicity: Blocking KRAS can increase tumor antigen presentation and T-cell infiltration, while ICIs counteract immune suppression (62,82). The KRYSTAL-7 trial (trial no. NCT04613596) is a phase III study assessing first-line adagrasib in combination with pembrolizumab compared with monotherapy pembrolizumab in patients with advanced NSCLC with a KRAS G12C mutation. In patients with a PD-L1 tumor proportion score ≥50%, the confirmed ORR was 63% [32/51 patients; 95% confidence interval (CI), 48-76%]. The DCR in the same subgroup was 84% (43/51 patients; 95% CI, 71-93%). The median PFS at a median follow-up of 10.1 months was not achieved (95% CI, 8.2 months to not evaluable). The TRAEs reported among the 148 patients evaluated for safety led to permanent discontinuation of adagrasib in 6% (n=9) and pembrolizumab in 11% (n=16) of patients with TRAEs; 4% (n=6) of patients discontinued both agents due to TRAEs (83). The phase Ib 100/101 CodeBreaK study tested sotorasib in combination with pembrolizumab or atezolizumab in patients with metastatic KRAS G12C NSCLC. Although the combination demonstrated clinical activity (ORR, ~29%), numerous patients experienced severe grade 3-4 hepatotoxicity when starting both drugs concomitantly. A 'sotorasib lead-in' dose introduction strategy markedly ameliorated severe liver toxicity and reduced discontinuation of treatment, underscoring the relevance of dosage sequence to enhance tolerability (84). Presently, the ongoing Krascendo-170 trial (trial no. NCT05789082) is evaluating divarasib in combination with pembrolizumab sequentially, to determine whether the treatment dose can be maximized without losing an optimal balance between efficacy and toxicity in frontline KRAS G12C-mutated NSCLC.

Combining KRAS G12C inhibitors with ICIs may potentially improve efficacy, particularly in patients with PD-L1-high tumors. Adagrasib has potential as a frontline combination therapy, requiring clarification of the optimal order and timing for administration. Future clinical plans should individualize treatment according to tumor biology and immune status, guided by direct comparison trials initiated through biomarker-informed pathways.

The toxicities of KRAS G12C inhibitors (sotorasib and adagrasib) are clinically relevant, although frequently manageable with individualized approaches. In a prospective biomarker study, 75% of patients with a history of immune-related hepatitis from prior immunotherapy subsequently developed severe hepatotoxicity with sotorasib (85). Nevertheless, attempts at dose reduction and rechallenge were made in over half of cases, and long-term rechallenge was successful in some patients using corticosteroids. Similarly, gastrointestinal AEs (such as diarrhea, nausea and vomiting) may be controlled with supportive medications (such as antiemetics, antidiarrheals, hydration and dietary changes), and therapy is typically held or dose adjusted for grade ≥3 events in the case of adagrasib. Liver toxicity may be managed with regular liver enzyme monitoring and prompt dose modification. These results highlight that while toxicities may restrict dosing, personalized immunosuppression and dose adjustment interventions can sustain therapeutic benefit in appropriate patients (86,87).

KRAS G12C inhibitors have presented a new era for NSCLC treatment through direct targeting of KRAS, as both sotorasib and adagrasib have shown significant clinical activity, and as

Table I. Ongoing clinical trials for KRAS G12C inhibitors in KRAS mutant NSCLC.

A, Sotorasib

Trial no.	Regimen	Primary objective/s	Trial phase
NCT03600883	Sotorasib	Evaluate the safety and tolerability	I/II
NCT05118854	Sotorasib + platinum doublet	Evaluate the efficacy and determine the safety, tolerability and RP2D	II
NCT05180422	Sotorasib + MVASI	Evaluate the safety and tolerability	I/II
NCT06068153	Sotorasib + lenvatinib/tarloxotinib	Evaluate the ORR	II
NCT05074810	Sotorasib + avutometinib ± defactinib	Assess the safety and efficacy	I/II
NCT06249282	Sotorasib + carfilzomib	Determine the MTD and RP2D	I

B, Adagrasib

Trial no.	Regimen	Primary objective/s	Trial phase
NCT03785249	Adagrasib	Evaluate the safety effects and clinical activity	I/II
NCT04613596	Adagrasib + pembrolizumab	Assess the safety and efficacy	II/III
NCT05609578	Adagrasib + pemetrexed	Evaluate the clinical efficacy	II
NCT05840510	Adagrasib + nab-sirolimus	Evaluate the safety, MTD and/or RP2D	I
NCT05375994	Adagrasib + avutometinib	Assess the safety and efficacy	I/II

C, Other

Trial no.	Regimen	Primary objective/s	Trial phase
NCT06300177	Garsorasib	Assess the safety and tolerability identify the MTD and RP2D	Phase I/II
NCT06497556	Divarasib	Assess the safety and efficacy	III
NCT05276726	Glecirasib	Evaluate the safety and tolerability, drug levels and clinical activity	I/II
NCT04956640	Olomorasib	Assess the safety and efficacy	I/II

KRAS, Kirsten rat sarcoma viral oncogene homolog; RP2D, recommended phase II dose; ORR, objective response rate; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer.

well as the more recent therapy, garsorasib. However, modest survival benefits, low intracranial activity and a resistance mechanism remain significant limitations. Continued work with rational combinations, tailored sequencing with immunotherapy, toxicity-mitigation approaches and the emergence of next-generation inhibitors are necessary to sustain long-term responses and provide further treatment options for patients with KRAS G12C tumors.

Emerging strategies for targeting non-G12C KRAS mutations in NSCLC. The lack of effective targeted treatment for patients with non-G12C KRAS mutations in NSCLC is a notable clinical issue, particularly considering the recent FDA approval of KRAS G12C inhibitors. In contrast to G12C inhibitors, which covalently trap the G12C-specific cysteine residue, non-G12C mutations require alternative treatment strategies. Immune profiling studies show that non-G12C mutations are often associated with increased rates of PD-L1 negativity and STK11 co-mutations, which are both predictors of poor response to ICIs (88-90).

By targeting pan-KRAS inhibition, TME modulation and upstream and downstream signaling pathways, emerging strategies aim to overcome limitations such as allele-specific resistance, pathway redundancy, and adaptive signaling escape. Pan-RAS and RAS-GTP inhibitors are being further developed, as they have demonstrated activity against other KRAS mutations beyond G12C (88). The non-covalent inhibitors MRTX1133 and HRS-4642 disrupt KRAS G12D interactions with SOS1 or RAF1, resulting in downstream MEK-ERK inhibition. MRTX1133 (trial no. NCT05737706) has progressed to phase I clinical trials, and HRS-4642 is in phase I/II trials (91), showing preclinical tumor growth inhibition *in vitro* and *in vivo* (92).

Although tumor mutational burden (TMB) and PD-L1 expression levels are comparable in G12C and non-G12C subgroups, clinical responses in non-G12C variants are unsatisfactory (93). These tumors are frequently associated with co-mutations such as STK11, which shape an immune-cold microenvironment, contributing to poor response to ICIs (90).

Despite novel targeted approaches, the therapeutic landscape for non-G12C mutations of KRAS remains limited.

Due to the constraints of targeted approaches, immunotherapy has become an essential alternative and complementary treatment option, especially for KRAS-mutant NSCLC. Furthermore, novel approaches such as combination regimens with KRAS pathway inhibitors and ICIs are being explored, based on data that KRAS mutations alter the immune microenvironment and response to ICIs (89). These strategies highlight the need for novel immunotherapeutic regimens and rational combinations to improve outcomes for patients with non-G12C KRAS mutations. Although emerging KRAS G12C inhibitors show potential, patients with non-G12C KRAS mutations in NSCLC have limited options for targeted therapy and respond poorly to immunotherapy because of co-mutations and a cold tumor immune microenvironment. Novel non-covalent KRAS inhibitors and combination approaches targeting signaling pathways and immune modulation are emerging as promising treatment options; however, further development of therapies targeted at specific molecular and immune mechanisms is necessary to improve outcomes for this complex cohort.

Current immunotherapies in KRAS-mutated NSCLC. ICIs, combined with platinum-based chemotherapy or alone, are the conventional first-line treatment for patients with advanced KRAS mutation-positive NSCLC (94). Smoking has been associated with elevated TMB in addition to the immune-related characteristics of KRAS-mutant tumors. Increased TMB may correlate with an improved response to ICIs (95,96). Mazieres *et al* (97) retrospectively analyzed NSCLC cases with different oncogenic driver mutations and reported that increased PD-L1 expression levels were observed in KRAS-mutant tumors, which also showed superior responses to ICIs compared with that of other oncogenic driver mutations such as EGFR, ALK, ROS1 and RET alterations. However, most phase III ICI trials in NSCLC did not stratify patients by KRAS subtype, and only a few included post-hoc analyses (98,99). Although KRAS G12C inhibitors have shown benefit, other KRAS mutations still lack targeted options. Table II summarizes key immunotherapy trials in KRAS-mutant NSCLC.

The KEYNOTE-042 study is a phase III trial comparing pembrolizumab to platinum-based chemotherapy as a first-line treatment for patients with PD-L1-positive advanced NSCLC. KRAS mutations, including NRAS mutations, were found in 22.9% (9.6% KRAS G12C) of 301 patients; these patients exhibited increased levels of tissue TMB and PD-L1 expression. In KRAS-mutant cohorts, pembrolizumab treatment showed a significantly improved outcomes, with an OS hazard ratio of 0.42 (95% CI, 0.22-0.81) and a PFS hazard ratio of 0.51 (95% CI, 0.29-0.87) compared with KRAS wild-type tumors (100). The KEYNOTE-189 study, which examined the efficacies of first-line platinum-based chemotherapy alone or combined with pembrolizumab in advanced-stage NSCLC, reported that 12.8% of the 289 patients (95% CI, 10.1-15.6%) had a KRAS G12C mutation, while 30.8% (95% CI, 22.9-38.8%) reported any KRAS mutation. Furthermore, tumors with any KRAS mutation had elevated tissue TMB and PD-L1 levels. Pembrolizumab-based treatment showed higher clinical outcomes regardless of KRAS status than chemotherapy alone in PFS, OS and ORR (101). These trials indicate that KRAS-mutated NSCLC, particularly KRAS G12C, have an enhanced response to pembrolizumab and immunotherapy due to high-level expression of PD-L1 and TMB. Pembrolizumab, alone or combined with chemotherapy, could result in survival and progression-free benefits for these patients vs. chemotherapy alone.

A retrospective study conducted in China showed that immunotherapy-based treatment in patients with KRAS-mutant NSCLC showed improved results compared with that of chemotherapy alone. The immunotherapy regimens used in this cohort were PD-1/PD-L1 inhibitors either alone or in combination with chemotherapy. Overall, the median OS was 22.9 months (95% CI, 14.1-31.7) and PFS was 9.4 months (95% CI, 6.6-12.1). Immunotherapy regimens had a median OS of 45.2 vs. 11.3 months (P=1.81E-5) and a median PFS of 10.5 vs. 8.2 months (P=0.706) compared with chemotherapy. The first line therapy cohort demonstrated a median OS and median PFS of 33.5 vs. 16.1 months (P=0.010) and 32.2 vs. 6.9 months (P=0.00038), respectively. In the second line therapy cohort, median OS was not reached vs. 9.23 months (P=0.026) and median PFS was 10.8 vs. 5.5 months (P=0.010). Immunotherapy improved the median OS compared with that of chemotherapy for both patients with KRAS G12C tumors and those with non-KRAS G12C tumors, according to subgroup analysis (G12C, 25.2 vs. 9.1 months, P=0.0037; non-G12C, not reached vs. 25.7 months, P=0.020). In addition, concurrent KRAS/TP53 mutants also showed an improved median OS with immunotherapy-based regimens compared to those who received chemotherapy (33.5 vs. 11.8 months; P=0.036). These findings suggest that immunotherapy is beneficial for OS relative to chemotherapy in patients with late-stage KRAS-mutant NSCLC, regardless of the treatment line or KRAS mutation subtype (102).

Recent studies have provided novel insights into the role of immunotherapy in KRAS-mutant NSCLC. A retrospective analysis was conducted in Italy with a cohort of 143 patients with advanced NSCLC and KRAS mutations received ICIs, with or without chemotherapy. The most frequent KRAS mutation was G12C (41%), followed by G12V (23.7%) and G12D (11.8%); ≥50% of the patients received ICIs as monotherapy, while the rest had it in combination with chemotherapy, mainly as a first-line therapy. The OS or PFS among the KRAS subgroups showed no significant differences. By contrast, patients with KRAS Q61, 13X and G12C mutations had a relatively longer OS (46.5, 31.8 and 28.7 months, respectively) of the KRAS subgroups analyzed. The KRAS G12D cohort showed the most improved response to treatment with an (ORR) of 73%, largely driven by patients with stable disease (40%), which was greater for chemoimmunotherapy. The median duration of response (DOR) was 7.4 months overall, with the longest DOR at 10.2 months seen in G12V. Co-mutations were also assessed: STK11 was present in 24% of cases and TP53 in 29%. Patients with STK11 co-mutations tended towards more prolonged OS (39.7 months) compared with those without STK11 co-mutations (26.1 months). By contrast, TP53 co-mutations were associated with a shorter OS (19.1 months), although the analysis did not reach statistical significance. Notably, bone metastases were associated with lower survival and almost doubled the risk of death (HR, 2.81;

Table II. Overview of immunotherapy clinical trials in KRAS-mutant NSCLC.

Trial name	Phase	Treatment	Key findings	Trial no.	(Refs.)
KEYNOTE-042	III	Pembrolizumab	KRAS-mutation patients with PD-L1 ≥50%, OS was 20 months (pembrolizumab) vs. 12.2 months (chemotherapy).	NCT02220894	(141)
CheckMate-057	III	Nivolumab vs. docetaxel	KRAS-mutant NSCLC, mOS was 12.2 months for nivolumab vs. 9.4 months for docetaxel.	NCT01673867	(142)
KEYNOTE-189	III	Pembrolizumab + platinum	KRAS-mutant NSCLC, mOS was 22 months (pembrolizumab + chemo) vs. 10.6 months (chemotherapy alone).	NCT02578680	(143)
IMPower150	III	Atezolizumab + bevacizumab + chemotherapy	KRAS-mutant subgroup, OS was 19.2 months (ABCP) vs. 14.7 months (BCP).	NCT02366143	(144)
KRYSTAL-7	II	Adagrasib + pembrolizumab	KRAS G12C Mutation NSCLC, showed an ORR of 59% and DCR of 81%; however, 27-30% had grade ≥3 liver toxicity.	NCT04613596	(145)
CONTACT-01	III	Atezolizumab + cabozantinib vs docetaxel	KRAS-mutant NSCLC, no PFS/OS benefit.	NCT04471428	(146)

KRAS, Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death-1 ligand; DCR, disease control rate; ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; BCP, bevacizumab + carboplatin + paclitaxel; mOS, median overall survival.

P<0.001) (103). However, the analysis was retrospective, single institution-based, underpowered and the treatment strategies were heterogeneous, which limited the strength and external validity of the results. Furthermore, the negative association between STK11 co-mutations and improved survival is in contrast to numerous previous findings (104,105) and may be a cohort-specific artifact. Therefore, the aforementioned study requires further validation in larger, homogeneously treated cohorts.

A multicenter retrospective study compared first-line programmed cell death protein 1 (PD-1)/PD-L1 inhibitors (n=78) vs. platinum-based chemotherapy (n=29) in metastatic KRAS-mutant NSCLC. The PFS was significantly longer in the immunotherapy group (7.9 vs. 6.0 months; P=0.030), although there were no differences in the median OS (16.2 vs. 19.2 months; P>0.05). Positive PD-L1 status was associated with an improved PFS, whereas increased CRP, CEA and NLR levels were associated with poor outcomes. It was also suggested that PD-1/PD-L1 inhibitors may achieve more robust disease control, particularly in PD-L1-positive patients, using inflammatory parameters such as C-reactive protein (CRP), Carcinoembryonic antigen (CEA), and neutrophil-to-lymphocyte ratio (NLR) as potential prognostic values (106).

Immunotherapy, particularly in combination with chemotherapy, markedly prolongs survival for advanced KRAS-mutant NSCLC over chemotherapy alone; this is greater among patients with PD-L1-positive tumors or high tumor mutational burden. KRAS G12C is the predominant subtype and exhibits notable responsiveness to ICIs, providing evidence for ICIs-based chemoimmunotherapy as the optimal first-line treatment.

6. Clinical impact of KRAS co-mutations (STK11, TP53 and KEAP1)

Co-mutations in STK11, TP53 and KEAP1 determine the characteristic phenotype of the TME and clinical prognosis for KRAS-mutant NSCLC. KRAS/TP53 tumors have an immune-inflamed profile with high TMB (10-12 mutations/Mb), high PD-L1 expression (≥50%) and dense $CD8^+$ T-cell infiltration, which supports an improved response to ICIs (107). In a pooled analysis of 713 patients, KRAS/TP53 cases had significantly higher benefit from ICIs compared with chemotherapy, with an OS HR of 0.71 (95% CI, 0.55-0.92) and interaction HR of 0.53-0.56 favoring immunotherapy (108,109). Thus, KRAS/TP53 cases had significantly higher benefit from ICIs when compared with that of chemotherapy.

By contrast, KRAS/STK11 tumors are more consistently characterized by non-inflamed immune-cold with low PD-L1 expression (<10%), minimal $CD8^+$ cell infiltration and a TMB of 4-6 mutations/Mb. Poor responses to ICIs and chemoimmunotherapy suggest the clinical manifestation of this (110). Numerous studies have shown that an STK11 co-mutation is associated with worse PFS and OS relative to KRAS-only or KRAS/TP53 disease, which often translates to the level of benefit derived from chemotherapy alone (111-113). These mutations also significantly correlated with worse PFS (4.2 months vs. 11.0 months; HR, 2.2; P < 0.01) and OS (9.8 months vs. NR; HR 2.6; P<0.01). Although there are conflicting data as to their effects on KRAS G12C inhibitor efficacy, with some studies showing reduced responses and others reporting similar outcomes regardless of STK11 status, the prognosis for patients with KRAS/STK11 co-mutations

remains poor (114-116). This highlights the necessity for novel single and combination strategies in KRAS/STK11 disease, as standard chemo-immuno-oncology regimens offer limited benefit.

KRAS/KEAP1 tumors are the most aggressive subtype and possess infrequent broad resistance to chemotherapy, ICIs and KRAS-targeting agents. KEAP1/NFE2L2 mutations are associated with an inferior prognosis to platinum-pemetrexed and ICI regimens, as a pooled analysis reported an HR of 1.96 (95% CI, 1.33-2.92) for shorter survival (117). In the KRYSTAL-1 study, patients with KEAP1 co-mutation had a significantly shorter median PFS (4.1 months) and OS (5.4 months) when treated with adagrasib in comparison with their wild-type counterparts (9.9 and 19.0 months, respectively) (114). Functional validation also demonstrates that KEAP1 deletion significantly elevates IC_{50} of KRAS G12C inhibitors in H358 cells (118). Since KRAS/KEAP1 tumors are resistant to multiple drugs, KRAS/KEAP1 tumors warrant prioritization for clinical trials and experimental strategies beyond current standard therapies.

Together, this emphasizes the need for co-mutation profiling in treatment algorithms, as patients with KRAS/TP53 tumors may be more responsive to frontline ICI therapy; by contrast, patients with KRAS/STK11 and KRAS/KEAP1 tumors represent aggressive, immune-refractory subsets warranting alternative or combination strategies.

7. Mechanisms of resistance to anti-KRAS therapies

Although targeted medicines provide a notable response after treatment initiation, a large proportion of tumors eventually resist targeted medications because of intertumoral heterogeneity, where pre-existing resistance subclones survive treatment and expand, driving tumor evolution toward resistance (119). Secondary mutations in the KRAS gene also cause resistance to specific inhibitors of the G12C mutation. Mutations such as Y96D, A59T and G13D result in changes to the KRAS protein structure that prevent inhibitors, including sotorasib and adagrasib, from engaging with their target. Such mutations frequently occur in the SII-P, a key area for drug binding (120,121).

Concurrent mutations or alterations in driver oncogenes, including TP53 and STK11/LKB1, are also involved in resistance. It has been reported that tumors in which KRAS and STK11 are mutant are less sensitive to immune checkpoint blockade and KRAS-targeted agents, potentially due to the activation of compensatory survival signaling pathways (122,123). Second, distant activation of alternative signaling cascades exists that may mediate escape from KRAS inhibition. MET amplification is the most extensively known bypass mechanism, allowing downstream activation of the PI3K-AKT-mTOR signaling in the presence of KRAS inhibition (79,124). Other reported bypass routes include RET fusions and wild-type RAS activation (121,123). These alterations enable tumor cells to maintain proliferative signaling despite KRAS blockade. Aside from developing secondary mutations, reactivation of wild-type KRAS or other RAS family members can resurrect signaling downstream of the pathway. This reactivation undermines the efficacy of KRAS G12C inhibitors and leads to therapeutic failure (121).

Tumor cells can also acquire resistance via nongenetic means unrelated to new mutations. Cancer cells are kept alive under drug pressure by cellular plasticity, stress-response signaling and reprogramming of signal networks. For example, activation of integrin β4 and paxillin pathways, among others, can stimulate AKT signaling, contributing to a drug-tolerant persistent cell phenotype (125,126). Finally, modifications in the TME are significantly associated with therapy resistance. As such, hypoxia and TME nutrient deprivation can induce adaptive stress responses in cancer cells, leading to improved survival and resistance to targeted therapies (127). Patients receiving KRAS inhibitors also had worse prognoses when they had oxidative stress response-related alterations, such as KEAP1 mutations (71). Table III summarizes the various resistance mechanisms to KRAS-targeted therapies in NSCLC, including genetic factors, signaling pathways and TME-associated modifications associated with treatment resistance.

8. Future directions

Multiplex screening via next-generation sequencing (NGS) is recommended for adequate patient selection in the European Society for Medical Oncology clinical practice guidelines (4,128). KRAS G12C inhibitors are a key treatment option for patients who are not eligible for standard first-line therapies. For example, co-mutations, including STK11 and KRAS G12C, are associated with inferior responses to ICIs, indicating that KRAS G12C inhibitors may be preferential as first-line treatment in those settings. Another potential strategy is to use chemotherapy or ICIs in combination with KRAS G12C inhibitors (129-131).

The development of resistance to conventional therapies is a notable problem that has led to a paradigm shift toward multitargeted therapies and improvements in drug delivery systems for improved patient prognostic results. KRAS mutations are considered actionable, particularly for G12C subtype for which direct inhibitors are now available. Personalization of therapy is essential because KRAS mutations are heterogeneous and exert diverse effects on treatment response (132-134). Additional investigation is warranted for KRAS G12D and G12V mutations, which represents 38% of KRAS-mutant LUAD cases, as these variants currently lack effective targeted therapies. Furthermore, emerging pan-KRAS inhibitors should be further explored as potential treatment strategies (135).

Emerging strategies for KRAS-mutant NSCLC are increasingly shaped by advanced bioinformatic and genomic tools that enable personalized therapy. Artificial intelligence (AI) is increasingly shaping the drug discovery process, notably with its rapid expansion induced by drug repurposing strategies. Machine learning model coupled with molecular docking has demonstrated that the FDA-approved drugs, including afatinib, neratinib and zanubrutinib, are likely to be effective against KRAS G12C. This method demonstrates how AI can identify novel therapeutic opportunities and is particularly useful for hard-to-target alleles such as KRAS G12D, where direct inhibitors remain limited (89).

Table III. Mechanisms of resistance to KRAS-targeted therapies in NSCLC with genetic alterations.

Resistance type	Mechanism	Examples	Clinical impact
Genetic alterations	Secondary KRAS mutations	Y96D, A59T and G13D	Impaired drug binding, direct resistance.
	Co-occurring oncogenic mutations	TP53, STK11 KEAP1, MET amplification and BRAF mutations	Activation of bypass signaling pathways.
	Alternative pathway activation	EGFR, MET amplification and RET fusion	Escape from KRAS inhibition.
Non-genetic adaptations	Adaptive signaling rewiring	Integrin β4 and paxillin-mediated AKT activation	Tolerant phenotype leading to acquired resistance.
	Tumor microenvironment stress responses	Hypoxia and nutrient deprivation	Enhances survival under therapeutic pressure.
Tumor heterogeneity	Intratumoral clonal diversity	Mixed KRAS subtypes within a single tumor	Emergence of resistance subpopulation.
Immune escape	Alterations in immune profile	Low PD-L1 expression and STK11 co-mutations	Reduced efficacy of immune checkpoint inhibitors.

KRAS, Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer; TP53, tumor protein P53; STK11, serine/threonine kinase 11; KEAP1, Kelch-like ECH-associated protein 1; EGFR, epidermal growth factor receptor; MET, mesenchymal epithelial transition factor; RET, rearranged during transfection; PD-L1, programmed cell death-1 ligand.

Neoantigen prediction algorithms represent another avenue of research. Mutant KRAS peptides have demonstrated potent T-cell responses, which is relevant for STK11 co-mutated or high TMB tumors. Such subsets are frequently resistant to ICIs monotherapy, and the options of personalizing a vaccine or establishing adoptive T-cell therapy constitute a rational approach for these populations (136,137).

Single-cell RNA sequencing (scRNA-seq) has also been applied to KRAS-induced tumors, and a tumor-associated epidermal subpopulation that depended on the oncogene BMI-1 has been identified, which contributes to tumor growth and treatment resistance. Treatment approaches targeting this subpopulation with small-molecule inhibitor PTC596 inhibited tumor growth in preclinical models, demonstrating how scRNA-seq could detect resistant subclones and guide targeted therapy (138).

Finally, CRISPR-based therapies are also broadening treatment choices. High-fidelity Cas9 editing has shown that KRAS G12C and G12D mutations can be corrected in organoid or xenograft models with reduced tumor growth (139). In addition, genome-wide CRISPR screens have identified synthetic lethal relationships that might be exploited for rational combination strategies or resistance to KRAS inhibitors by targeting TEA domain transcription factor, CDK4 and Wee1-like protein kinase dependencies (140). Together, these approaches represent the innovative customized therapy for KRAS-mutation lung cancer; however, these CRISPR-based and synthetic-lethal strategies still face key limitations, such as off-target effects and uncertain clinical translation, additional research is required to overcome these limitations and improve patient outcomes.

9. Conclusion

KRAS has emerged as a viable target for therapeutic inhibition in lung cancer, overcoming the previous challenges associated with a limited understanding of KRAS biology and protein biochemistry. Technological progress has deepened understanding of RAS biology, including the discovery of novel druggable pockets and the usefulness of molecular subtyping. Among the current investigational treatments, small-molecule inhibitors targeting the KRAS G12C mutation have demonstrated promising results. However, molecular heterogeneity and resistance mechanisms remain concerns, thus requiring additional translational research. Combination strategies, such as immuno-targeted therapy, are increasingly popular to maximize KRAS inhibition. The current challenges and strategies in KRAS-mutated NSCLC research are overcoming resistance to ICIs and KRAS inhibitors, discovering predictive biomarkers, expanding targeted therapies to additional KRAS mutations and optimizing diagnostic accuracy using NGS analysis of patient plasma and tissue samples. Furthermore, worldwide accessibility to novel agents remains essential. These efforts will help to improve the quality of life and survival of patients with NSCLC.

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US prepared the original draft. HK reviewed the manuscript. JS, YZ and ZD reviewed and edited the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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