# Treatment Strategies for KRAS-Mutated Non-Small-Cell Lung Cancer

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Activating mutations in Kirsten rat sarcoma viral oncogene homologue (KRAS) are highly prevalent in solid tumours and are frequently found in 35% of lung, 45% of colorectal, and up to 90% of pancreatic cancers. Mutated KRAS is a prognostic factor for disease-free survival (DFS) and overall survival (OS) in NSCLC and is associated with a more aggressive clinical phenotype, highlighting the need for KRAS-targeted therapy. Once considered undruggable due to its smooth shallow surface, a breakthrough showed that the activated G12C-mutated KRAS isozyme can be directly inhibited via a newly identified switch II pocket. This discovery led to the development of a new class of selective small-molecule inhibitors against the KRAS G12C isoform. Sotorasib and adagrasib are approved in locally advanced or metastatic NSCLC patients who have received at least one prior systemic therapy.

KRAS G12C mutation NSCLC IMAs sotorasib Drug Resistance Mechanisms adagrasib Combination Therapies

## 1. Introduction

Kirsten rat sarcoma viral oncogene homologue (KRAS) is the best-known oncogene with the highest mutation rate among all cancers. KRAS was first detected in 1982 in lung cancer cells, located on the short arm of chromosome 12 (12p11.1–12p12.1) [1]. It is a member of the RAS family of GTPase signal transducer proteins, which hydrolyse guanosine triphosphate (GTP) to guanosine diphosphate (GDP) and includes the Harvey rat sarcoma viral oncogene (HRAS) and neuroblastoma rat sarcoma viral oncogene (NRAS). RAS proteins are molecular switches that, under normal physiological conditions, cycle between the inactive GDP-bound state and the active GTP-bound state to transduce extracellular signals to the interior of the cell. RAS proteins interact to form functional clusters on membranes and efficiently recruit downstream effectors [2]. Structurally, KRAS is divided into an effector-binding lobe, an allosteric lobe, and a carboxy-terminal region responsible for membrane anchoring. The effector lobe comprises the P loop and the switch I/switch II loop regions. The cycling between the inactive and active form causes a conformational change in the switch I and II regions [3], which plays a critical role in KRAS downstream signalling through mediating protein–protein interactions with effector proteins that include RAF1 in the MAPK pathway or PI3K in the PI3K–AKT pathway. Thus, activated KRAS regulates several cellular processes such as differentiation, proliferation, and apoptosis [4].

KRAS mutations are an early event in lung tumorigenesis, associated with a history of smoking [5][6], a high mutation burden, and elevated markers of immune evasion (PD-L1 and PD-L2) [7]. KRAS-driven tumours shift their metabolism towards a more anabolic profile by upregulating the expression of multiple rate-limiting enzymes involved in key metabolic processes essential for survival. This metabolic reprogramming promotes glycolysis and lactate production [8][9] through increased glucose transporter 1 (GLUT1) expression and rate-limiting glycolytic enzymes, including hexokinases, phosphofructokinase 1 (PFK1), and lactate dehydrogenase A (LDHA) [9]. KRAS-driven tumours produce key lipid mediators establishing an immunosuppressive tumour microenvironment (TME) and utilise exogenous lipids produced by the TME such as fatty acids (FAs), prostaglandins, and other lipid mediators that sustain tumour growth and metastasis.

Mutated KRAS was notoriously challenging to target and even “undruggable” due to its smooth, spheric structural biology, and a lack of drug-binding pockets, which limited therapeutic interventions. Four decades of research finally culminated in the first major breakthrough in the race to target KRAS-driven cancers. In 2013, a seminal breakthrough by the Shokat lab showed that the activated KRAS isozyme, caused by the G12C mutation in the KRAS gene, can be directly inhibited via a newly identified switch II pocket [10]. This discovery has led to the development of a new class of selective small-molecule inhibitors against the KRAS G12C isoform. In vitro, preclinical and clinical trial data demonstrated antitumor activity and clinical efficacy. Sotorasib (Lumakras, Amgen) monotherapy was approved in 2021 as a second-line treatment in KRAS G12C-driven, locally advanced, or metastatic non-small-cell lung cancer (NSCLC).

# 2. KRAS a Therapeutic Target in Treatment Resistant Lung Adenocarcinomas (LUAD)

## 2.1. Histological Patterns Associated with Driver Mutations in Lung Cancer

Lung cancers, particularly lung adenocarcinomas (LUADs), are heterogenous and include various histological subtypes and molecular alterations that impact chemosensitivity as well as overall survival [11]. LUADs consist of non-mucinous adenocarcinomas and invasive mucinous adenocarcinomas (IMAs), representing approximately 90% and 10% of cases, respectively [12]. Invasive non-mucinous carcinomas are further subdivided into five histological patterns: lepidic, acinar, papillary, micropapillary, and solid [13]. These are strongly associated with prognosis, with lepidic having the most favourable, acinar and papillary having intermediate, and solid and micropapillary patterns having the worst prognosis [14].

The prognosis of IMAs in the lung on the other hand is less well characterised, with several studies demonstrating conflicting results [12][14]. Associations between histology and driver mutations have also been made. EGFR mutations are associated with lepidic predominant LUADs [15], ALK and ROS rearrangements with cribriform pattern and signet-ring features [16][17], and KRAS mutations showing a strong association with IMAs [18].

## 2.2. Associations between KRAS Mutations and Invasive Mucinous Lung Adenocarcinomas

The invasive mucinous adenocarcinomas (IMAs) of the lung are rare, representing 3–10% of LUAD cases [12]. IMAs have goblet cell morphology, with abundant intracytoplasmic mucin [13]. These tumours develop through distinct genetic pathways that differ from those of non-mucinous LUADs. KRAS mutations have a strong association with IMAs, with a prevalence of 60% [18]. Conversely, features seen in non-mucinous LUADs such as TP53 mutations, high tumour mutational burden (TMB), and targetable mutations such as EGFR, ALK, and BRAF v600E are rarely seen [19]. In addition to having distinct genetic features, IMAs differ in response to conventional treatments, even though they are treated similarly to non-mucinous LUADs. For example, patients receiving non-TKI platinum-based chemotherapy with stage IV IMAs have similar overall survival (OS) to untreated IMA patients [20]. Reduced repose rates to chemotherapy are also seen in other cancers with mucinous histology such as mucinous colorectal carcinomas and mucinous ovarian carcinomas [21].

The reduced sensitivity of IMAs to chemotherapy has not been fully elucidated but may be due to the viscous nature of mucus, which may hinder drug delivery, reducing therapeutic efficacy [22]. Additionally, mucinous carcinomas may have poorer vasculature, also leading to the decreased delivery of drugs [23]. Mucins are heavily glycosylated proteins, responsible for the gel-like, cohesive, and adhesive nature of mucus. There are 21 mucin-related genes whose expression and functions vary between tissues. Within lung cancer, MUC2 and MUC5A are the most common [24].

## 2.3. Novel Therapeutic Delivery Approaches to Target KRAS-Mutated NSCLC

Patients with IMAs have been shown to have lower rates of partial response to chemotherapy than those with non-mucinous LUADs [20]. One potential explanation for these lower response rates is poor drug delivery through the abundant viscous mucin present in this subtype of LUADs. The development of drugs that can penetrate this mucin barrier, therefore, may be a fruitful therapeutic approach.

Advances in nanomedicine have generated a broad range of engineered nanoparticles (NPs) for drug delivery applications, which are designed to promote drug transport across cell membranes and to deliver drugs in a controlled and targeted manner. The ability of a drug to penetrate mucin relies on its small size and a neutral highly hydrophilic surface [25]. NPs are synthetic particles of <100nm, and therefore they represent an attractive method to penetrate mucin [26]. NP Liposomes are composed of an outer phospholipid bilayer surrounding an aqueous core, which allows for the transport of both hydrophilic and lipophilic drugs, as well as drugs with a wide range of size and charge [27]. They are biodegradable and biocompatible and present low immunogenicity; however, they tend to degrade rapidly and adhere together [28]. Polyethylene glycol (PEG), a hydrophilic and non-ionic polymer, when coated on the surface of NPs, confers more stability and allows rapid diffusion through mucin by reducing particle adhesions to the mucin fibres found in the mucus mesh [29]. PEG has become popular with research groups engineering mucous-penetrating drug carriers [29]. CALYPSO, a Phase III study, compared carboplatin–PEGylated liposomal doxorubicin with carboplatin–paclitaxel in patients with ovarian cancer. Treatment led to delayed progression and similar overall survival compared with the carboplatin–paclitaxel group [30].

Targeted NP-containing docetaxel (BIND-014) has also been studied as a second-line therapy for patients with KRAS-positive or squamous cell NSCLC [31]. BIND-014 is approximately 100 nm in size and is composed of docetaxel encapsulated in a polymer core made of hydrophobic poly(lactide) surrounded by a hydrophilic poly(ethylene glycol) conjugated with a small molecule of PSMA-targeting ligands [31]. In a Phase I study, (NCT02283320) BIND-014 was well tolerated, with predictable and manageable toxicity and tumour shrinkage at doses below the conventional docetaxel formulation dose [31].

Additionally, liposomes can be used to deliver therapeutic agents to inhibit specific oncogenes. Ozeplasmid (Reqorsa), a non-viral lipid nanoparticle, encapsulates a plasmid with TUSC2, a tumour-suppressor gene, and in combination with osimertinib is currently in Phase I and II clinical trials (NCT04486833) in advanced lung cancer patients who progressed on osimertinib (Acclaim-1). Ozeplasmid has recently been approved by a safety review committee (SRC), according to Genprex, Inc. (Austin, TX, USA) [32], confirming its favourable safety profile. The final enrolment for this clinical trial is expected to be completed in the first quarter of 2023. Other NPs currently being investigated in LUADs include magnetic, polymer, liposomes, solid lipid, metal, and viral NPs and are summarised elsewhere [33].

# 3. Therapeutic Options for KRAS Mutated NSCLC

## 3.1. Targeting KRAS

KRAS can be targeted indirectly by the inhibition of upstream regulators such as SOS or downstream targets such as MEK or PI3K. A Phase I clinical trial NCT04111458 is currently examining the efficacy of SOS inhibitor (BI1701963) monotherapy and its combination with MEK inhibitor trametinib.

The direct targeting of KRAS has proven challenging due to its picomolar affinity for GTP, the lack of suitable pockets for high-affinity small-molecule binding, and its high mutation rate [34]. However, in recent years, the understanding of KRAS has significantly increased with a resurgence of publicly available KRAS structures and increased computational capacity, enabling molecular dynamic (MD) simulations to study the dynamics of KRAS protein in more detail at the atomistic level [35].

The breakthrough discovery by the Shokat laboratory identified a new allosteric binding site on KRAS known as its ‘switch II pocket’(S-IIP) [10]. This demonstrated the possibility to inhibit inactive KRAS G12C with covalent binders, identified by screening a library of roughly 500 fragment-like disulphides [10]. This led to the development of twelve KRAS G12C-directed inhibitors, all tested in clinical trials and two approved for use in the clinic.

## 3.2. Direct Inhibitors of KRAS G12C

### 3.2.1. Sotorasib (AMG510)

Amgen’s KRAS G12C covalent inhibitor research program identified and developed the clinical candidate drug sotorasib, which entered clinical trial in August 2018 CodeBreaK100 (Phase I) (NCT03600883) [36][37]. Sotorasib

binds to the cysteine of the switch II region (S-IIP), keeping KRAS in its inactive GDP-bound form, inhibiting KRAS signalling, and suppressing the MAPK pathway. This compound was the first to show the benefit of KRAS G12C inhibitor treatment on disease progression in patients, demonstrating a 37.1% response rate, a progression-free survival of 6.8 months, and a median overall survival of 12.5 months in a Phase II clinical trial of 126 patients with advanced NSCLC CodeBreaK100 (Phase II) [37]. Sotorasib was the first KRAS inhibitor to receive FDA approval on 28 May 2021 [38][39]. Qiagen therascreen KRAS RGQ PCR kit and Guardant360 CDx were also approved for use to screen for the G12C mutation in a person's tumour tissue or blood, respectively. Ongoing clinical trials are investigating sotorasib as monotherapy or in combination with various anticancer agents in patients with advanced or metastatic solid tumours.

### 3.2.2. Adagrasib (MRTX849)

Adagrasib (MRTX849), developed by Mirati Therapeutics, is another direct small molecule that targets KRAS G12C and entered the KRYSTAL-1 clinical trial in January 2019 (NCT03785249) [40]. The FDA recently approved adagrasib for accelerated approval. Adagrasib also binds to the cysteine of the S-IIP-inhibiting KRAS-dependent signalling including the suppression of the MAPK pathway [41]. In a panel of human KRAS G12C cell line (CDX) and patient-derived xenograft (PDX) models, Hallin et al. demonstrated tumour regression exceeding 30% volume reduction from baseline in 17 out of 26 models (65%) at approximately three weeks of treatment [42]. Riely et al. demonstrated that patients with STK-11 co-mutations who typically have a relatively poor response to immune checkpoint inhibitors had an ORR of 64%. Interestingly, these patients had a minimal expression of CD4 and CD8 transcripts at baseline, and after treatment with adagrasib, these transcripts increased, suggesting a potential immune response to therapy [43]. Ongoing clinical trials are investigating adagrasib as monotherapy or in combination with other anticancer agents in patients with advanced or metastatic solid tumours.

### 3.2.3. Other Direct KRAS G12C Inhibitors

LY3499446 (Eli Lily) entered a clinical trial in November 2019 (NCT04165031) but was terminated due to unexpected toxicity. Toxicity can still be an issue despite the mutant-specific nature of inhibitors and may be due to off-target effects on other cysteine-containing proteins.

Newer inhibitors in early-phase testing include GDC-6036 (Genentech), which is being investigated in a Phase I clinical trial as monotherapy and in combination with other anticancer therapies in patients with advanced/metastatic solid tumours with a KRAS G12C mutation (NCT04449874). D-1553, developed by InvestisBio, entered clinical trials in October 2020 as monotherapy (NCT04585035). JDQ443 (Novartis Pharmaceuticals) is being examined in a Phase I/II clinical trial as monotherapy and in combination with TNO155 (SHP2 inhibitor) and/or spartalizumab (anti-PD1 antibody) in patients with advanced or metastatic solid tumours with the KRAS G12C mutation (NCT04699188). BI 1,823,911 (Boehringer Ingelheim) is a small-molecule KRAS G12C inhibitor that entered clinical trials in July 2021 (NCT04973163). JAB-21822 (Jacobio) is currently being investigated in several clinical trials as monotherapy or in combination with Cetuximab (EGFR mAb) or JAB-3312 (SHP2 inhibitor). YL-15293 (Shanghai YinLi) is being examined as monotherapy in a clinical trial (NCT05119933).

Finally, RMC-6291 (Revolution Medicine) is currently under investigation as monotherapy in a clinical trial (NCT05462717).

#### 3.2.4. Beyond KRAS G12C Inhibitors

Mirati Therapeutics developed a small-molecule MRTX-1133 that selectively targets the KRAS G12D allele [44] and has received IND clearance by the US FDA (Jan 2023), enabling Phase I initiation for a first-in-class oral inhibitor. KRAS G12D inhibitors will benefit never smokers with NSCLC for whom the mutation rate is 55.7% and could be a game-changer in PDAC and colorectal carcinoma, where the mutation rates are 67.6% and 39%, respectively.

Proteolysis-targeting chimeras (PROTACs) are bifunctional molecules that bind to both the target of interest and an E3-ligase protein, connected by a linker, degrading the protein of interest via the cellular proteasomal degradation machinery [45]. PROTACs have emerged as a new class of targeted therapy, and several groups have developed specific KRAS G12C PROTACs incorporating specific inhibitors such as ARS1620 [46] or MRTX849 [47]. Boehringer Ingelheim reported on a direct pan-KRAS inhibitor and direct pan-KRAS PROTAC that inhibits all the major KRAS mutants while sparing HRAS and NRAS [48].

Other targeted strategies include a combination of SOS inhibitor BI1701963 and MEK inhibitor trametinib (NCT04111458) [49]. This ensures both the upstream inhibition of the binding of SOS (GEF) to KRAS and the downstream inhibition of MEK, which effectively shuts downs the signalling of the MAPK pathway.

# 4. Resisting KRAS Targeted Therapy

## 4.1. Resistance to KRAS G12C-Targeted Therapy

KRAS G12C inhibitors have demonstrated impressive activity and response rates. However, similar to other targeted therapies, these inhibitors are also plagued by both intrinsic and acquired resistance mechanisms, which limits their efficacy and duration of response in patients. These mechanisms are outlined below and are all-encompassing often with several emerging in parallel within a tumour.

#### 4.1.1. Intrinsic Resistance

KRAS activation stimulates signalling through both the MEK and PI3K pathways, with both pathways providing a bypass escape mechanism for the other when either is individually targeted [50]. Researchers previously identified a synergistic antiproliferative response to the combined treatment of NSCLC cell lines with PI3K–mTOR and MEK inhibitors [51]. Additionally, studies have demonstrated that KRAS G12C inhibitors suppress MAPK signalling for a short duration, with the reactivation of the signalling pathway often observed within 24 to 72 h of treatment in cell lines and mice xenograft models [52]. This signalling rebound is a result of the compensatory activation of receptor tyrosine kinases (RTKs), which is cell-type-specific. Epithelial cells typically activated ERBB signalling, while mesenchymal cells activated FGFR or AXL signalling [52]. Co-targeted approaches inhibiting RTKs and mutant KRAS may be more effective than single-agent KRAS inhibitors.

### 4.1.2. Acquired Resistance

First reports have emerged that have elucidated the mechanisms of clinical resistance through the evaluation of genetic alterations in biopsies and the circulating tumour DNA from the KRYSTAL-1 trial (NCT03785249) [53][54]. Koga et al. identified secondary KRAS mutations causing resistance to sotorasib and adagrasib via the testing of 142 Ba/F3 clones that were resistant to either inhibitor [55]. Other examples of KRAS resistance are through the activation of bypass signalling pathways enabling the continued signalling of the MAPK and/or PI3K pathways, even with the total inhibition of KRAS [56].

A study by Tanaka et al. identified ten distinct resistance alterations that emerged in a patient treated with adagrasib [53]. All 10 alterations converged on the activation of RAS–MAPK signalling, suggesting a central common mechanism of acquired resistance [53]. RAS reactivation occurred via the activation of the NRAS isoform, KRAS-activating mutations in trans (G13D and G12V), the potential loss of KRAS G12C through a mutational switch to a different KRAS mutation in cis, and a novel secondary alteration in KRAS (Y96D) that alters drug binding. KRAS Y96D also confers resistance to other KRAS G12C-selective inhibitors in clinical development [53]. Similar to EGFR inhibition, a histologic transformation from lung adenocarcinoma to squamous cell carcinoma was also observed. Interestingly, these data suggest that adagrasib treatment results in the evolution of a diverse set of adaptive mechanisms in KRAS G12C-mutated cancers, instead of the dominant adaptive mechanisms seen with other targeted therapies. Thus, monitoring for the emergence of drug resistance is more complicated.

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