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Update: KRAS Inhibition in Cancer Management

Anthony A. Stephenson¹, Katie L. Bailey^{1,2}, Crystal M. Krause^{1,3}, Kelsey Klute⁴, Michael A. Hollingsworth^{5,6}, Mark A. Carlson^{1,2,3,7}

¹Department of Surgery, University of Nebraska Medical Center, Omaha NE 68198, USA

²VA Medical Center, Omaha NE 68105, USA

³Center for Advanced Surgical Technology, University of Nebraska Medical Center, Omaha NE 68198, USA

⁴Department of Internal Medicine, Division of Oncology & Hematology, University of Nebraska Medical Center, Omaha NE 68198, USA

⁵Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha NE 68198, USA

⁶Fred & Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha NE 68198, USA

⁷Department of Genetics, Cell Biology and Anatomy, University of Nebraska Medical Center, Omaha NE 68198, USA

Correspondence:

Mark A. Carlson

macarlso@unmc.edu

001-402-559-4581

Abstract

With >20% prevalence across all human tumors, mutant KRAS has been a primary target of oncological drug development for nearly 40 years. Until recently, attempts at pharmacologic inhibition of this protein did not lead to any clinically-approved inhibitors; as a result, KRAS had been deemed “undruggable”. However, during the past decade there has been a surge of direct and indirect KRAS inhibitors in clinical trials. This update article will summarize the recent data on these drugs, including (1) small molecule inhibitors targeting the *KRAS*^{G12C} mutant (2) RNA therapeutics targeting *KRAS*^{G12D}, (3) mRNA vaccines targeting a variety of KRAS mutants, (4) pan-KRAS inhibition targeting SOS1, an upstream activator of KRAS, and (5) adoptive T-cell therapy targeting the G12D and G12V mutants. These nascent treatments may bring new anti-cancer options against a key oncologic regulator which formerly had been considered undruggable.

Introduction

The KRAS protein was discovered in extracts of virally-transformed cells in 1979.¹ Within a few years, the *KRAS* genetic sequence was published,² human genes homologous to the viral genes were identified,^{3,4} the oncogenicity of Ras mutants in human tumors was demonstrated,⁵⁻⁷ and a high frequency of KRAS mutation was detected in human cancers.⁸⁻¹¹ Thereafter, mutant KRAS became a target for cancer therapy.¹² Members of the Ras family (which includes *KRAS*, *HRAS*, and *NRAS*) are among the frequently mutated genes in cancer, with a prevalence of ~25% in all human tumors¹³. Specifically, *KRAS* (for Kirsten Rat Sarcoma virus) mutants are involved with oncogenesis in 90% of pancreatic cancers, 30-40% of colorectal cancers (CRC), and 5-20% of lung cancers^{14,15}. The GTPase function of the KRAS protein acts as powerful “master” switch in major cellular pathways, including RAF/MAPK and PI3K/Akt, which regulate essential cellular functions such as proliferation, differentiation, survival, immunological responses, and stromal integrity (Fig. 1). Activated KRAS mutants^{16,17} (and, to a lesser extent, amplification of wild-type KRAS¹⁸⁻²⁰) dysregulate these systems, promoting tumor proliferation and protecting from anti-tumor mechanisms. Despite years of attempts to produce a pharmacologic inhibitor of KRAS or its mutants, no approved therapy has made it to the clinic; KRAS was deemed to be “undruggable”.^{12,21,22}

The past decade has seen a resurgence in the development of pharmacologic KRAS inhibitors. The intent of this update is to outline the various inhibitor mechanisms and the current experimental therapeutics that are in clinical trials, including: (1) small-molecule direct inhibitors of the KRAS G12C mutant; (2) small interfering RNA (siRNA) targeting the KRAS G12D mutant; (3) An mRNA vaccine targeting common oncogenic KRAS mutations; (4) A pan-KRAS

inhibitor working through GEF blockade; and (5) adoptive T-cell therapy against tumors with KRAS G12D or G12V mutations.

KRAS Biology and Signaling

There are three isoforms of the 21 kDa Ras protein: HRAS (Harvey Rat Sarcoma), NRAS (Neuroblastoma Ras), and KRAS.¹³ There are two copies of the *KRAS* gene: *KRAS1* and *KRAS2*; the latter (simply referred to as *KRAS*) is the proto-oncogene.¹³ KRAS has six exons, which can be alternatively spliced into two transcripts, *KRAS4A* and *KRAS4B*; the latter is translated into the KRAS protein of interest.²³ KRAS has three primary domains, including the G-domain (residues 1-166), which contains a highly conserved GDP-GTP binding region with two biologically-relevant “Switch” loops (I and II).²⁴ The other two domains (C-terminal domain and the CAAX motif), are more variable and participate in post-translational modifications and membrane trafficking.

KRAS activation occurs when this protein binds to GTP, producing a conformational change in KRAS, which then results in a series of protein-protein interactions at the plasma membrane, followed by propagation of signaling to downstream effectors, including the MAPK and PI3K/Akt pathways, which results in upregulation of cellular survival and proliferation (Fig. 1), along with other effects. Displacement of GDP by GTP to produce this active state is facilitated by Guanine Nucleotide Exchange Factors (GEFs). Hydrolysis of the bound GTP to GDP switches KRAS back to the inactive state; this inactivation is catalyzed by GTPase-Activating Proteins (GAPs). The reversible binding and exchange of the guanine nucleotides

within the G-domain produces the molecular switch function of KRAS, in which KRAS-GTP is “on” (signal propagation) and KRAS-GDP is “off” (no signal propagation).

Most KRAS-activating mutations in cancer are single nucleotide substitutions at codons 12, 13, and 61.¹⁴ Codons 12 and 13 account for nearly 90% of KRAS-driven cancers. The single amino acid substitution of glycine at position 12 (G12) produces steric interference with GAP binding to the Switch-II pocket of KRAS, thus preventing catalytic hydrolysis of GTP, which results in constitutive activation of KRAS.¹⁴ Inhibition of GTP binding to KRAS mutants with a small molecule appeared to be a natural anti-cancer approach; however, this strategy proved difficult due to the protein’s relatively smooth surface and shallow binding pockets, along with its picomolar affinity for GTP.^{21,25} Research focus in this area gradually shifted to other participants in pathways influenced by mutant KRAS.²⁶

The RAF-MAPK pathway became a primary main target due to its regulation of cell cycle progression and mitotic activation.²⁷ Inhibition of BRAF, MEK, or ERK was found to have clinical efficacy in a small subset of cancer patients, but was not efficacious in KRAS-mutant cancers.^{14,28} This inhibitor resistance was due to the fact that *(i)* KRAS drives oncogenesis through multiple different pathways, while downstream inhibitors are only specific to the RAF/MAPK pathway, and *(ii)* tumor cells develop bypass mechanisms that allow for the RAF/MAPK pathway to remain constitutively activated while specific participants remain inhibited.²⁹ While this former circumstance can be overcome by the direct inhibition of mutant KRAS, the latter circumstance theoretically could compensate for direct KRAS inhibition, thereby decreasing its anticancer efficacy.³⁰ Some clinical trials currently underway are attempting to impair these bypass mechanisms through simultaneous targeting of multiple participants in a given pathway (vertical polytherapy).³¹

Direct Inhibitors

The KRAS G12C mutation is the most common mutation in non-small cell lung cancer, with a prevalence of approximately 10-11%; this mutation also is present in 3-4% of colorectal adenocarcinomas and 1-3% of other solid tumors.³² Drug discovery efforts found that quinazolinone-based entities could dock into a “cryptic pocket” (associated with residues H95/Y96/Q99) and covalently bind to the cysteine residue at position 12,²⁵ thus locking KRAS in the GDP-bound state and blocking constitutive activation. The proof-of-concept drug to exploit this cryptic pocket in experimental tumor models was ARS-1620, which then led to AMG 510.^{25,33}

Sotorasib (AMG 510)

Amgen’s experimental therapeutic sotorasib (AMG 510) has a structure which exploits the cryptic groove associated with the KRAS His95 residue, producing a 10-fold increase in binding potency over ARS-1620 in mutant cell lines.³⁴ Treatment of cell lines expressing KRAS G12C with sotorasib decreased phosphorylation of ERK, Akt, and S6 and increased Caspase-3 cleavage, with inhibition of cellular proliferation and survival.³⁵ Sotorasib had minimal to no effect on cell lines that did not express KRAS G12C. In murine *KRAS*^{G12C} solid tumor models, sotorasib treatment along with PD-1 inhibition produced durable (112 day) tumor regression. Of note, mice lacking competent T cells had regression but not a durable “cure”,³⁵ implying an important role of immune response in these models.

In 2018, sotorasib became the first direct KRAS inhibitor to enter clinical testing.³⁶ In a phase 1 dose escalation and expansion trial involving 129 patients with advanced, heavily-pretreated solid tumor patients with demonstrated *KRAS*^{G12C} mutation,³⁷ daily oral administration of sotorasib resulted in treatment-related adverse events in 57% of patients (most commonly diarrhea, fatigue, and nausea; 11.6% grade 3-4), but no treatment-related deaths. Objective response and disease control rates were 32% and 88% in patients with NSCLC and 32% and 74% in patients with colorectal cancer, respectively. Median duration of response was 10.9 months and 5.4 months in NSCLC and colorectal cancer, respectively. Other clinical trials are underway (Table 1), including: (1) a phase 1 study of combined treatment with sotorasib and other chemotherapeutics (including other components of the KRAS pathway or immune checkpoint inhibition) in advanced solid tumors with KRAS G12C (NCT04185883); (2) a phase 1/2 study of sotorasib mono- and combined therapy in solid tumors with the G12 C mutation (NCT03600883); and (3) a phase 3 study of sotorasib vs. docetaxel in the treatment of NSCLC with the G12C mutation (NCT04303780). The clinical outcome of combined therapy with AMG sotorasib and immune checkpoint inhibition will be particularly interesting, considering the preclinical efficacy of this combination in the above murine models,³⁵ which underlines the topical importance of anti-cancer T-cell activity.³⁸

MRTX849

Mirati Therapeutics' MRTX849 is another direct KRAS inhibitor that with potential efficacy in the treatment of KRAS G12C mutant cancers. Similar to sotorasib , MRTX849 (adagrasib) forms a covalent bond with the cysteine substituted at position 12, locking KRAS in

its inactive state.³⁹ MRTX849 has been shown to specifically inhibit KRAS G12C in mutant cell lines, while preserving function of wild-type KRAS in non-cancerous cells; in addition, this inhibitor had durable efficacy against KRAS G12C tumor xenografts in nude mice (55 days of complete regression).⁴⁰

MRTX849 is being evaluated as monotherapy or in various combinations in a phase I/II clinical trial of advanced solid tumor patients (NCT03785249), with some partial responses reported.⁴¹ As of August 2020, 79 patients with NSCLC were treated in the study;⁴² the most common treatment-related adverse events include nausea, diarrhea, vomiting and fatigue. The only grade 3-4 serious adverse event was hyponatremia, which occurred in 3% of patients. Among 14 evaluable patients, the objective response rate was 43% with 4/6 patients having an ongoing response of greater than 11 months. The recommended phase 2 dose was identified as 600 mg twice daily.

Another phase I/II clinical trial is studying MRTX849 in combination with TNO155 (NCT04330664; Table 1); the latter is an inhibitor of SHP2 (Src homology region 2 domain-containing phosphatase-2, also known as PTPN11 or PTP-1D). SHP2 is a tyrosine-protein phosphatase that promotes RTK-KRAS signaling in KRAS-driven cancers^{20,43,44} through a variety of mechanisms, including GEF complexation (Fig.1).⁴⁵ Combined inhibition of mutant KRAS and SHP2 may have synergistic effects in KRAS-driven cancer (another example of vertical polytherapy).

Other Direct KRAS Inhibitors

Two novel KRAS G12C inhibitors, LY349446 (Eli Lilly and Company,) and JNJ-74699157 (Johnson & Johnson/ Janssen Research & Development,) also entered phase I clinical trials in patients with advanced solid tumors at the end of 2019 (NCT04165031 and NCT04006301, respectively).⁴⁶

pan-KRAS inhibition

Another approach to disrupt KRAS signaling is through inhibition of SOS1 (Son Of Sevenless 1), a GEF that promotes KRAS activation. SOS1 facilitation of the GDP-GTP switch on KRAS is increased through growth factor signaling and tyrosine kinase activity, working through the mediator protein Grb2 (Fig. 1). BI 1701963 is a small molecule that binds SOS1 and prevents interaction with KRAS-GDP, thus preventing the switching-on of KRAS.⁴⁷⁻⁴⁹ As a pan-KRAS inhibitor and the first in clinical trials (NCT04111458), BI 170963 potentially could be used in nearly 15% of all cancers (i.e., those in which a KRAS mutation plays a major role). There is interest in combining BI 1701963 with other KRAS pathway inhibitors,⁴⁹ such as trametinib (a MEK inhibitor with clinical efficacy against melanoma with *BRAF*^{V600E/K}).⁵⁰ The downfall of inhibiting of pan-KRAS inhibition, however, is the effect on wild-type KRAS in normal cells;⁴⁸ data on this potential issue should be available upon completion of the ongoing Phase 1 trial (NCT04111458; Table 1).

RNA Therapeutics

Therapy with RNA interference (RNAi) involves the delivery of small interfering RNA (siRNA; <30 base pair length) to cells expressing a complementary mRNA template, which then complex to form double stranded RNA. As dsRNA typically is found only in virally infected cells, a mechanism has evolved to digest and silence intracellular dsRNA (i.e., dsRNA is perceived as foreign genetic material). RNAi therapy takes advantage of this defense mechanism by targeting siRNA to mRNA that code for disease-relevant proteins, thus decreasing or preventing translation of the targeted protein (“knockdown”). In 2018, the first RNAi-based drug (patisiran) was approved for the treatment of transthyretin amyloidosis.⁵¹ Unfortunately, therapy with RNAi remains limited by pharmacokinetic issues, including a short serum half-life of siRNA, inefficient delivery of the siRNA to the tumor, and intracellular digestion of these sequences once delivered.⁵² While most of the small molecule inhibitors of the KRAS protein target the G12C mutation that primarily is found in NSCLC and colorectal cancer, RNAi therapy has focused primarily on the G12D mutation, a predominant driver of pancreatic ductal adenocarcinoma (PDAC). The substitution of aspartate at the glycine-12 position has a prevalence of nearly 30% of all PDAC patients, and is associated with a worse overall survival compared to other *KRAS* mutations seen in PDAC.²³

AZD4785

AZD4785 was the first RNA therapeutic targeting mutant KRAS to reach clinical trials in cancer patients (NCT03101839). This entity is an antisense oligonucleotide (i.e., not an siRNA) which utilizes a mechanism similar to RNAi, though the route of degradation is different.⁵³ AZD4785 demonstrated anti-tumor efficacy in KRAS-mutant cell- and patient-derived

xenografts within nude mice, and was capable of targeting multiple isoforms of mutant KRAS.⁵⁴ In the phase 1 trial, however, 15/28 subjects did not complete the 6-month observation period secondary to death or early decision to withdraw. It is not clear whether further clinical study with AZD4785 will be undertaken.⁵⁵

iExosomes

Exosomes are extracellular signaling vesicles (30-150 nm diameter) utilized by multiple cell types, and can carry a wide range of molecules; exosomes can participate in the maintenance, progression, and metastasis of cancer cells.⁵⁶ Exosomal delivery of therapeutics has been studied in a range of diseases, including cancer.⁵⁷ iExosomes are engineered exosomes⁵⁸ which contain KRAS G12D siRNA and possess a transmembrane signaling ligand CD47. The latter binds to SIRP-alpha on phagocytes and thereby inhibits phagocytosis,⁵⁸ thus prolonging exosome half-life. iExosomes demonstrated enhanced pancreatic tumor uptake compared to liposomes and other nanoparticles utilized for RNAi delivery, knocked down KRAS G12D in murine tumors models to nearly undetectable levels after 30 days of treatment, and also prolonged survival in these models.^{58,59} iExosome delivery of KRAS G12D siRNA is in a phase I clinical trial for patients with metastatic PDAC (NCT03608631).

LODER™

The LODER™ (Local Drug EluteR) devices consists of a biodegradable polymeric matrix containing KRAS G12D siRNA.⁶⁰ This matrix can be manually embedded/injected into

the tumor, and then provides a sustained local release of siRNA for approximately four months.⁶⁰ A Phase I/II clinical trial of 15 patients with locally advanced PDAC studied LODER™ administered in combination with standard chemotherapeutics (NCT01188785) demonstrated a 60% partial response and 40% no progression. There were some apparent drug-related adverse effects including pancytopenia and colonic obstruction, as well as procedure-related adverse effects such as cholangitis.⁶¹ The LODER matrix is currently in a phase II clinical trial in combination with chemotherapy for locally advanced PDAC (NCT01676259); patient accrual is expected to be completed in December 2020. The original study design would have compared standard chemotherapy with and without LODER™, but after an interim analysis this design was revised so that all patients would receive LODER™,⁶² suggesting some efficacy has been observed. Of note, LODER™ was designed for treatment of local disease, and would not be suitable for metastatic cancer,⁶³ in contrast to systemic treatments such as the above iExosome therapy.

Immunotherapy

Current efforts to enhance immune attack of KRAS-driven tumors focus on cytotoxic (T-cell mediated) mechanisms, whether through augmentation of native T-cell response with a KRAS tumor vaccine or by infusion of engineered, expanded T-cells that attack KRAS tumor cells.

mRNA Vaccine

Moderna and Merck are collaborating on a vaccine (mRNA-5671/V941) that would target common KRAS mutations.⁶⁴ For decades it has been known that that presentation of mutant KRAS peptides in patients can induce a specific T-cell immune response which kills KRAS-mutant tumor cells but not normal cells,⁶⁵⁻⁶⁹ implying that KRAS appears on the cell surface during processing. However, past trials of KRAS vaccines so far have not demonstrated adequate anti-tumor immune responses or efficacy;⁷⁰ active investigation into a KRAS vaccine therefore continues. The above mRNA vaccine consists of mutant KRAS mRNA housed in lipid nanoparticles, which is taken up by antigen presenting cells. The APCs would translate the KRAS mRNA and present the resultant protein with the major histocompatibility complex, thus eliciting a T-cell mediated response against tumor cells that express the KRAS mutant protein. With sequences specific for KRAS mutations G12C, G12D, G12V, and G13D, mRNA-5671 potentially can target ~83% of all KRAS-driven tumors.⁷¹ Similar to RNAi therapeutics, the vaccine is dependent on a delivery system that must protect the nucleotides from degradation while engaging the APCs.⁷² The mRNA-5671 vaccine currently is in a phase I clinical (with or without the PD-1 inhibitor pembrolizumab) in patients with KRAS Mutant NSCLC, colorectal cancer, or PDAC (NCT03948763). Combination of this mRNA vaccine with a PD-1 inhibitor (another immunotherapeutic, but with a different mechanism) may prove beneficial in the upregulation of T-cell response against tumors expressing mutant KRAS, hopefully providing clinically impactful anti-tumor activity.

ACT with Engineered mTCR

Human T lymphocytes can be modified with murine T cell receptors (mTCRs; derived from transgenic HLA mice) that are engineered to recognize human tumor epitopes with HLA restriction; infusion of these modified T cells results in specific killing of cells with the targeted epitope.⁷³ Anti-tumor treatment with such engineered T cells is an example of Adoptive Cellular Therapy (ACT), alternatively known as adoptive T-cell therapy, or adoptive immunotherapy. In early clinical trials of ACT with engineered mTCRs, toxicity secondary to destruction of normal tissue was noted.^{74,75} This toxicity is a reflection of the fact that many tumor antigens are also expressed to a variable degree in normal tissue.⁷⁶ In a case report of a patient with metastatic colorectal cancer, treatment with autologous *ex vivo*-expanded Tumor-Infiltrating Lymphocytes (TILs) that specifically targeted the KRAS G12D mutant produced regression of metastatic lung lesions,⁷⁷ which suggested that adoptive transfer of T cells targeting the KRAS mutant could have anti-tumor efficacy with less risk of toxicity. Currently, ACT with mTCRs specific for the KRAS G12D and G12V mutants is being evaluated in phase I/II clinical trials involving patients with metastatic or unresectable cancer (NCT03745326; NCT03190941). Therapy with T lymphocytes expressing engineered Chimeric Antigen Receptors (CAR-T)⁷⁸ specific for KRAS mutants has not yet reached the clinical trial stage.

Conclusion

The KRAS oncogene contributes to approximately 125,000 cancer patient deaths per year in the US.¹⁴ Previous attempts to inhibit KRAS yielded no approved direct inhibitor therapies, and the protein was deemed “undruggable”. However, persistent efforts to develop such an inhibitor has produced some promising candidates which now are in clinical trials. These

candidate drugs utilize an array of mechanistic approaches to decrease KRAS activity, including blockade of critical binding sites on the mutant protein itself, inhibition of other proteins critical for KRAS signal transduction, degradation of mutant KRAS mRNA, vaccines against mutant KRAS, and adoptive T-cell therapy. Preliminary data suggest that KRAS inhibitors (such as sotorasib and adagrasib) have acceptable toxicity profiles and promising clinical activity in patients with advanced solid tumors harboring KRASG12C mutations. Additional novel KRAS inhibitors in preclinical testing (not discussed here) will likely enter clinical trials in the near future. There now is renewed hope that a specific inhibitor for mutant KRAS will become available. As an archetype of precision medicine, such an inhibitor would be intended for the patient whose tumor possessed the specific mutation targeted by the inhibitor. Such treatment should be both efficacious and well-tolerated.

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Figure 1.

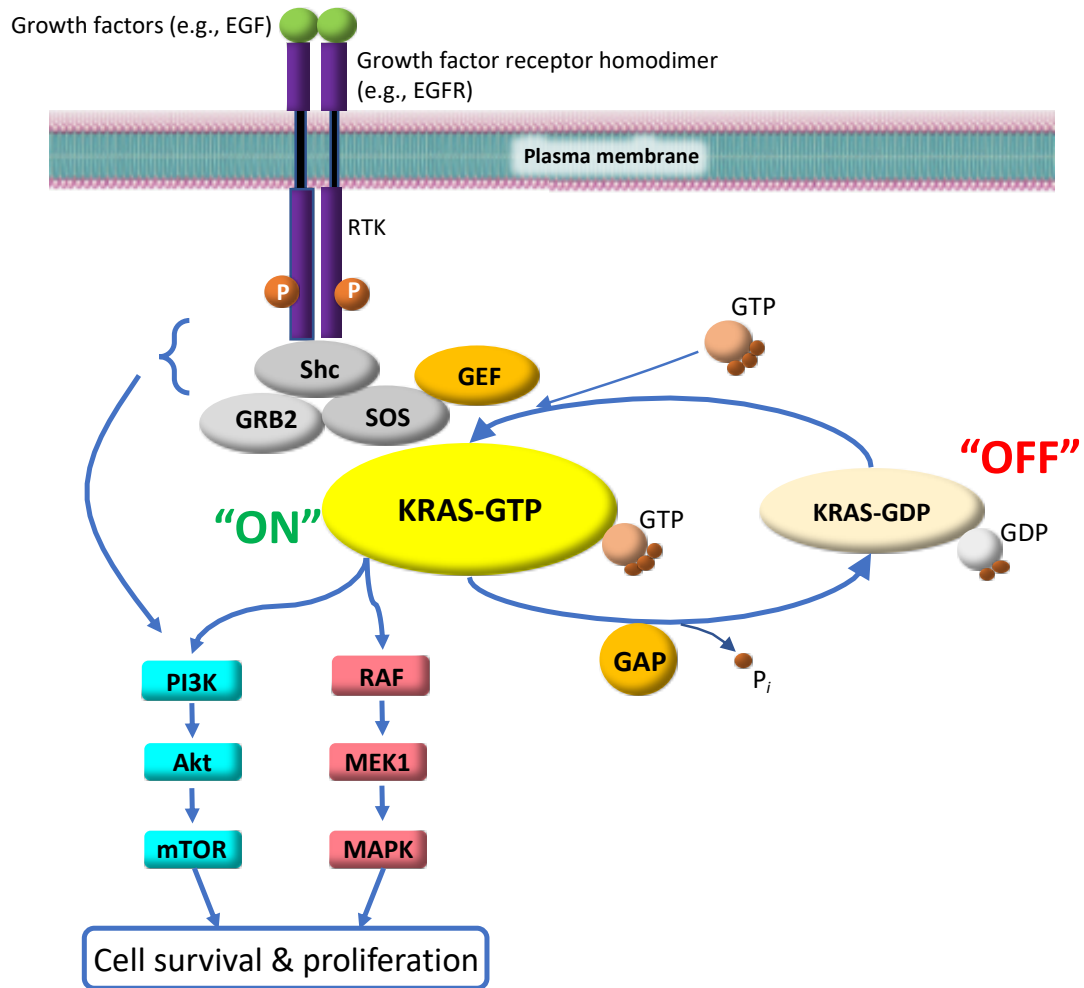


Fig. 1. KRAS activation and effector network. Akt: Ak strain Transforming (aka PKB, Protein Kinase B); EGF: Epidermal Growth Factor; EGFR: Epidermal Growth Factor Receptor; GAP: GTPase-activating protein; Grb2: Growth factor receptor-bound protein 2; GEF: Guanine Nucleotide Exchange Factor; GDP: guanosine-5'-diphosphate; GTP: guanosine-5'-triphosphate; KRAS: Kirsten Rat Sarcoma; MAPK: Mitogen-Activated Protein Kinase (aka ERK or Extracellularly Regulated Kinase); MEK1: MAPK/ERK Kinase (aka MAPKK or MAP2K); mTOR: Mammalian Target of Rapamycin; P_i: inorganic Phosphate; PI3K: Phosphatidylinositol-3 Kinase; RAF: Rapidly Accelerated Fibrosarcoma; RTK: Receptor Tyrosine Kinase; Shc: Src

Homology and Collagen; SoS: Son of Sevenless. Figure was composited from multiple sources.^{23,79-89}

Table 1. Drugs currently in clinical trials for KRAS cancers.

Drug	Company	Mechanism	CLINICAL TRIAL(S)
AMG 510 (Sotorasib)	Amgen	G12C Inhibitor	NCT04303780: A Phase 3 Multicenter, Randomized, Open Label, Active-controlled, Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C NCT04185883: A Phase 1b, Protocol Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 (pINN) Sotorasib Monotherapy and in Combination With Other Anti-cancer Therapies in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation (CodeBreak 101) NCT03600883 : A Phase 1, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 (pINN Sotorasib) in Subjects of Chinese Descent With Advanced/Metastatic Solid Tumors With KRAS p.G12CMutation (CodeBreak 105)
MRTX849	Mirati Therapeutics	G12C Inhibitor	NCT04330664: A Phase 1/2 Trial of MRTX849 in Combination With TNO155 in Patients With Advanced Solid Tumors With KRAS G12C Mutation NCT03785249: A Phase 1/2 Multiple Expansion Cohort Trial of MRTX849 in Patients With Advanced Solid Tumors With KRAS G12C Mutation KRYSTAL-1
JNJ-74699157	J&J and Wellspring Biosciences	G12C Inhibitor	NCT0400630: A First-in-Human Study of the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Antitumor Activity of JNJ-74699157 in Participants With Advanced Solid Tumors Harboring the KRAS G12C Mutation
LY3944996	Eli Lilly and Company	G12C Inhibitor	NCT04165031: A Phase 1/2 Study of LY3499446 Administered to Patients With Advanced Solid Tumors With KRAS G12C Mutation
iExosomes	Codiak Biosciences	siRNA-G12D	NCT03608631: Phase I Study of Mesenchymal Stromal Cells-Derived Exosomes With KrasG12D siRNA for Metastatic Pancreas Cancer Patients Harboring KrasG12D Mutation
LODER	Silenseed ltd	siRNA-G12D	NCT01188785: Phase 2 Study Evaluating the Efficacy, Safety, Tolerability and PK of siG12-LODER in the Treatment of Patients With Unresectable LAPC When Used in Conjunction With Standard Chemotherapy (Gemcitabine+Nab-Paclitaxel) Versus Chemotherapy Alone
mRNA 5671	Moderna	RNA Vaccine G12D,G12C, G12V, G13D	NCT03948763: A Phase 1, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/V941 as a Monotherapy and in Combination With Pembrolizumab in Participants With KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma
BI 1701963	Boehringer Ingelheim	SOS1 Inhibitor	NCT04111458: A Phase I Open-label Dose Escalation Trial of BI 1701963 as Monotherapy and in Combination With Trametinib in Patients With KRAS99 Mutated Advanced or Metastatic Solid Tumours
mTCR	National Cancer Institute	Adoptive T-Cell Therapy G12D, G12V	NCT03745326: A Phase I/II Study Administering Peripheral Blood Lymphocytes Transduced With a Murine T-Cell Receptor Recognizing the G12D Variant of Mutated RAS in HLA-A*11:01 Patients

			NCT03190941: A Phase I/II Study Administering Peripheral Blood Lymphocytes Transduced With a Murine T-Cell Receptor Recognizing the G12V Variant of Mutated RAS in HLA-A*11:01 Patients
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