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Hot Topic

KRAS: From undruggable to a druggable Cancer Target

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ABSTRACT

RAS is the most frequently mutated oncogene in human cancers, with mutations in about 30% of all cancers. *RAS* exists in three different isoforms (*K-RAS*, *H-RAS* and *N-RAS*) with high sequence homology. *K-RAS* is the most commonly mutated *RAS* isoform. The Ras protein is a membrane bound protein with inherent GTPase activity and is activated by numerous extracellular stimuli, cycling between an inactive (GDP-bound) and active (GTP-bound) form. When bound to GTP, it is switched "on" and activates intracellular signaling pathways, critical for cell proliferation and angiogenesis. Mutated *RAS* is constitutively activated and persistently turned "on" thereby enhancing downstream signaling and leading to tumorigenesis. Various attempts to inhibit Kras in the past were unsuccessful. Recently, several small molecules (AMG510, MRTX849, JNJ-74699157, and LY3499446) have been developed to specifically target *K-RAS G12C*. Additionally, various other approaches including, SHP2, SOS1 and eIF4 inhibition, have been utilized to abrogate tumor growth in *K-RAS* mutant cells, resulting in a renewed interest in this pathway. In this review article, we provide an overview on the role of *K-RAS* in tumorigenesis, past approaches to inhibiting Kras, and current and future prospects for targeting Kras.

Introduction

Ras is a membrane-bound protein that possesses inherent GTPase (guanosine triphosphatases) activity and is expressed in all humans [1]. When activated, it can "switch on" downstream pathways, which ultimately turn on genes that are involved in various physiological processes, including cell growth, differentiation, and survival. It was initially identified in the 1960s by Harvey and Kirsten as a retroviral oncogene when sarcomas were induced in rodents from a murine leukemogenic virus preparation; hence it's named- Kirsten rat sarcoma 2 viral oncogene homolog [2,3]. In the early 1980s, a mutated *K-RAS* oncogene was identified in a tumor biopsy of a 66-year-old male with squamous cell lung carcinoma [4]. This mutation was not identified in patient's white cells and in normal bronchial and parenchymal tissue, demonstrating the significance of somatic mutations in tumorigenesis. Subsequently, it was found that somatic *K-RAS* mutations are present in approximately 30% of all human cancers, commonly in lung, pancreas, colorectal, and cholangiocarcinoma [5–12]. In this review, we discuss Kras signaling, it's role in tumorigenesis and why this target has been considered "undruggable" historically. We also outline some strategies for targeting *K-RAS* mutant cancers by discussing promising new agents against Kras, including specific G12C inhibitors, SHP2 inhibitors, SOS1 inhibitors, and conclude by summarizing ongoing trials.

Ras family members

Ras structure and function

There are two copies of *K-RAS,* namely *K-RAS1* and *K-RAS2*[13]. *K-RAS1* and *K-RAS2* are located on chromosome 6p11-12 and 12p11.1-12.1 respectively [14,15]. *K-RAS1* is a pseudo-gene [13]. Activating *K-RAS2* mutations have been identified in various human cancers. *K-RAS2* is simply referred to as *K-RAS*. The *K-RAS* gene consists of 6 exons spread over 35 kb of genomic DNA [16]. The structure of the *K-RAS* gene is depicted in Fig. 1. *K-RAS* is alternatively spliced to form *K-RAS 4A* and *K-RAS 4B*. The term *K-RAS* is generally used to indicate *K-RAS 4B* [17]. The Ras protein includes three closely related 21-kDa isoforms, H (Harvey rat sarcoma virus oncogene), N (human neuroblastoma) and K-ras (Kirsten rat sarcoma virus oncogene) [1]. Ras has three major domains: the G-domain, the C-terminal and the C-terminal CAAX box [18,19]. The G-domain, containing switch I and switch II loops, is a highly conserved domain and is responsible for GDP-GTP exchange [6,18]. The C-terminal including the CAAX box demonstrates a significant variation between *RAS* family members, and is required for post-translational modification [6,20]. Ras proteins bind with GDP (guanosine diphosphate) and GTP (guanosine triphosphate) with great affinity [21]. They act as "molecular switches" and cycle between the GDP-bound (inactive) and GTP-bound (active) forms. In the active

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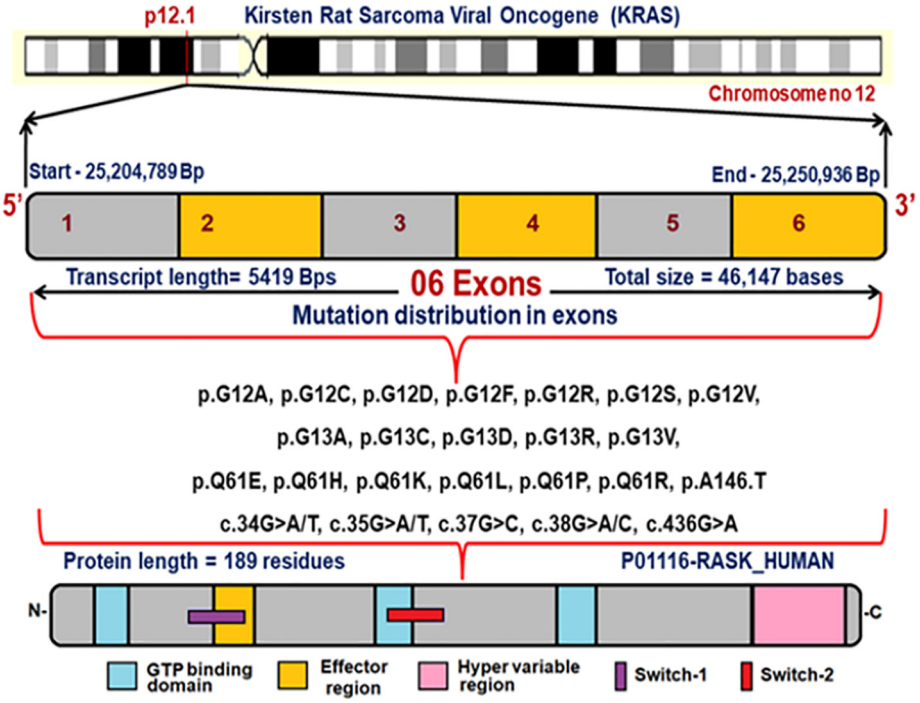

Fig. 1. Structure of *K-RAS* gene with associated mutations and their protein domains. Reproduced with permission from Ramakrishnan V et al. Effects of *KRAS* Gene Mutations in Gynecological Malignancies. Investigations in Gynecology Research & Womens Health.

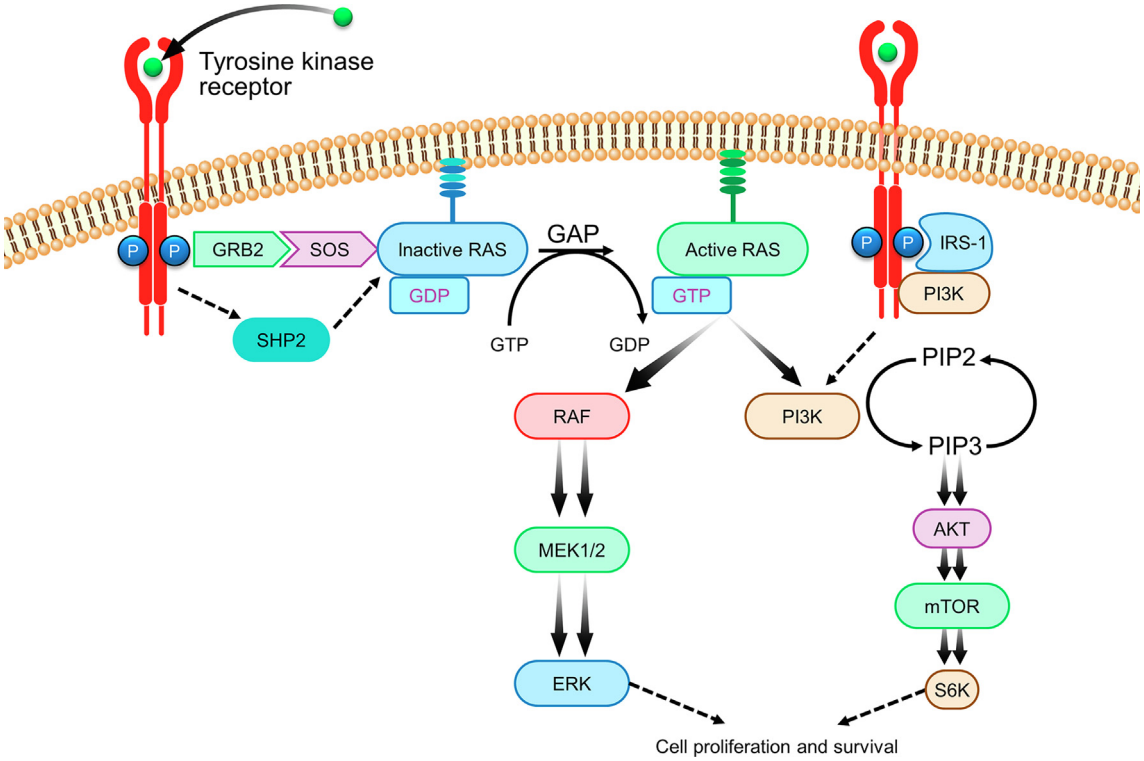

Fig. 2. Simplified scheme of Mitogen Activation Protein Kinase activation and signaling cascade.

state, they transmit signals from the cell membrane to the nucleus, leading to activation of transcription factors which lead to the regulation of cell growth and differentiation (Fig. 2) [22].

Ras signaling

Ras signaling begins when a ligand binds to an upstream receptor, such as a tyrosine kinase receptor. Almost all of the receptor tyrosine kinases are monomers [23]. A well-known pathway involves the interaction of epidermal growth factor (EGF) to its receptor (EGFR) [24]. Binding of EGF to EGFR induces dimerization of the receptor, followed by auto-phosphorylation [19,25]. The phosphorylated receptor binds to an adaptor protein Grb2 (Growth factor receptor-bound protein 2). This complex recruits son of sevenless (SOS) to the plasma membrane [23].

Table 1
Prevalence of *K-RAS* mutations in human cancers.

Tumor Type	Frequency of *K-RAS* mutation
Pancreatic adenocarcinoma (61,62)	≥ 80%
Colorectal cancer (11,55–57)	30–50%
Non-small cell lung cancer (49)	
Adenocarcinoma	30%
Squamous cell carcinoma	5%
Cholangiocarcinoma (63)	
Extrahepatic	45–54%
Intrahepatic	10–15%
Multiple myeloma (64,65)	21–33%
Uterine endometrial (66, 88)	
Endometrioid	21–26%
Serous	2%
Gastric cancer (67–69)	3–13%
Testicular cancer (70–72)	9–16%
Cervical adenocarcinoma (73,74)	7–18%
Diffuse Large B-cell lymphoma (75)	1.6%
Esophageal (66, 76–78)	
Adenocarcinoma	3.8–17%
Squamous cell carcinoma	0–12%
Breast Cancer (79,80)	8–13%
Acute Myeloid Leukemia (81–83)	5–23%
Chronic Lymphocytic Leukemia (84,85)	0.7–7%
Bladder Cancer (86)	4%
Cutaneous malignant melanoma (87)	< 1%

Once recruited to the plasma membrane, SOS is capable of displacing GDP from Ras, allowing Ras-GTP interaction. Ras can also regulate SOS activity suggesting that the pathway could be bidirectional [26–28]. The binding of GTP to Ras induces changes in switch I and switch II loops of the G-domain, thereby activating Ras.

Hydrolysis of GTP to GDP inactivates Ras. Ras inherently has low GTPase activity. The intrinsic GTPase activity is stimulated further by GTPase Activating Proteins (GAPs) such as p120-GAP and NF1 (neurofibromin) [29–31]. This keeps Ras in the inactive form and prevents its persistent activation. In addition to p120 and NF1, numerous other Ras GTPases have been identified [32–34]. GAP represents a notable class of tumor suppressor genes. Normally, Ras signaling is transient. Mechanistically, inactivation of the Ras GAPs will persistently activate Ras and its effectors leading to malignant transformation. The most extensively studied tumor suppressor gene is NF1-GAP. Germline mutation of the NF1 gene predisposes to variety of tumors, including gliomas, neurofibromas, pheochromocytoema and leukemia [35–37]. Additionally, recent studies have demonstrated a high frequency of somatic NF1 mutations in a variety of sporadic tumors, including lung adenocarcinoma, leukemia, ovarian, multiple myeloma, glioblastoma and melanoma [38–40].

There are a number of effector molecules that an activated Ras can act upon including Raf, PI3K [6]. The Raf family is the best characterized Ras effector and the one with the strongest role in human cancer. Raf (Rapidly Accelerated Fibrosarcoma) protein is a serine/threonine kinase initially isolated in avian retrovirus and murine sarcoma virus [41]. It consists of three subtypes, A-raf, B-raf and Raf-1 (C-raf). Binding of GTP to Ras promotes recruitment of Raf to the cell membrane, dimerization of Raf and phosphorylation. Additionally, many factors that are not completely understood are involved in the proper activation of Raf [5,42]. Activated Raf phosphorylates MEK (Mitogen Activated Protein Kinase), which in turn, phosphorylates ERK (extracellular-signal-regulated kinase). *B-RAF* is frequently mutated in human cancers, including melanoma, thyroid malignancy and hairy cell leukemia [43–45]. When compared with *A-RAF* and *C-RAF*, *B-RAF* has a higher basal kinase activity and is easily activated by *RAS* [46,47].

The second best characterized Ras effector is Phosphoinositide 3′-kinase (*PI3-K*), which is activated by numerous mechanisms. One of the mechanisms involves binding of extracellular growth factor to its receptor tyrosine kinase, leading to dimerization of the receptor monomer followed by auto-phosphorylation. Insulin Receptor Substrate-1 (IRS-1) then binds to the catalytic site of the phosphorylated dimer. Once bound to the dimer, IRS-1 serves as a binding and an activation site for PI3-K. A totally different mechanism of PI3-K activation involves direct binding of PI3-K with GTP-bound Ras. The activated PI3-K then migrates to the inner aspect of cell membrane leading to phosphorylation of phosphatidylinositol bisphosphate (PIP2) to phosphatidylinositol (3,4,5) trisphosphate (PIP3), which then activates a protein kinase AKT [48]. This ultimately activates mTOR. mTOR then activates the translation factor S6K. By binding to the larger ribosomal subunit, S6K induces translation of mRNA into protein. All the essential steps of the RAS-RAF and PI3-K signaling pathway are illustrated in Fig. 2.

K-RAS mutations in human tumors

K-RAS mutation subtypes

Various mutant forms of *K-RAS* are now recognized and are divided into three broad categories based on the mutated codon: G12 (mutation at codon 12), G13 (mutation at codon 13), and Q61 (mutation at codon 61).

The prevalence of *K-RAS* mutations in non-small cell lung cancer (NSCLC) is about 30% in adenocarcinoma and 5% in squamous cell carcinoma [49]. About 97% of *K-RAS* mutations in NSCLC occurs at exons 2 and 3 (G12, G13, and Q61) [50]. Also, they usually do not exist concomitantly with other sensitizing mutations, such as *EGFR, B-RAF* and *ALK* rearrangement [51]. *G12C* is the most common mutation subtype, accounting for about 40% of all *K-RAS* mutations followed by *G12V* [52–54].

In colorectal cancer, *K-RAS* mutations occur in about 30–50% of cases [11,55–57]. *G12D* and *G12V* are the two most common mutation subtypes [58,59]. Additionally, *K-RAS* mutations have also been identified in colorectal adenoma [60]. The prevalence of *K-RAS* mutations in pancreatic carcinoma is the highest with various studies showing the prevalence rate well above 80% with *G12D* being the most common subtype [61,62]. In cholangiocarcinoma, the prevalence of *K-RAS* mutation varies from 10% to 15% for intrahepatic cholangiocarcinoma and from 45% to 54% for extrahepatic cholangiocarcinoma [63]. *K-RAS* mutations are also found in various hematological malignancies (multiple myeloma, acute myeloid leukemia, and diffuse large B-cell lymphoma), other gastrointestinal malignancies (esophageal adenocarcinoma, gastric cancer), uterine carcinoma, and cervical adenocarcinoma [64–88]. The frequency of *K-RAS* mutations in various tumor types is summarized in Table 1.

Predictive and prognostic value of K-RAS mutations

Prognostic value

The prognostic value of *K-RAS* mutations in various tumor types remains unclear. In NSCLC, *K-RAS* mutant NSCLC patients were considered to have a worse prognosis [89]. However, various studies have demonstrated conflicting results [10,90–92]. *Mascaux* and colleagues performed a systematic review of 5216 stage I-IV patients in forty-three studies from 1990 to 2003 [10]. The study demonstrated a worse survival outcome in patients with *K-RAS* mutations or p21 expression compared to those without these aberrations (HR, 1.35 [95% CI 1.16–1.56]). Moreover, the study revealed no significant impact of *K-RAS* mutations on survival for squamous histology and for the stage I and stage I-III cohorts. On the contrary, a pooled analysis utilizing the Lung Adjuvant Cisplatin Evaluation (LACE) database of 3,533 patients with stage I-III disease, demonstrated no difference in overall survival in patients with *K-RAS* mutant versus *K-RAS* wild-type NSCLC [90]. A more recent study by *Pan* and colleagues utilizing 41 studies from 2005 to 2015 with 13,103 patients, showed worse overall survival (HR, 1.56 [95% CI 1.39–1.76]) and disease free survival (HR, 1.57 [95% CI 1.17–2.09]) with *K-RAS* mutation in patients with early-stage resected

NSCLC [92].

In colon cancer, *K-RAS* mutations may confer poor prognosis but the data are not consistent for localized disease. While many studies demonstrated a negative impact of *K-RAS* mutations on survival [93–97], including those with localized disease [93,95,97], *Roth* and colleagues demonstrated that *K-RAS* mutations did not affect survival in stage II or III colon cancer [98]. Furthermore, the RASCAL-II study demonstrated that out of the 12 possible mutations on codon 12 or 13 of the *K-RAS* gene, only one mutation on codon 12, *G12V* (glycine to valine), was associated with inferior survival [99].

In pancreatic cancer, studies have demonstrated conflicting results on the prognostic value of *K-RAS* mutations on survival [100–102]. A study conducted by *Bournet* and colleagues involving 219 patients with locally advanced or metastatic pancreatic adenocarcinoma, demonstrated no difference in survival between *K-RAS* mutant and *K-RAS* wild-type tumors [103]. The study however showed that the *G12D* (glycine to aspartic acid) mutation had worse prognosis when compared with other mutation subtypes and *K-RAS* wild type. Additionally, coexistence of *CDKN2* aberrations and *K-RAS* mutation appeared to confer the worst prognosis [104].

In summary, the prognosis conferred by *K-RAS* mutations may differ based on the specific mutation and tumor type. This may, in part, explain the conflicting results from different studies. More studies examining mutation subtypes are needed to assess the real prognostic value of *K-RAS* mutations in tumors.

Predictive value

The predictive value of *K-RAS* mutations in NSCLC has been evaluated in multiple trials [105,106]. These trials have demonstrated similar response rates between the *K-RAS* mutant and *K-RAS* wild-type NSCLC. However, data suggest that *K-RAS* mutations may be a negative predictor of response to EGFR tyrosine kinase inhibitors in the minority of patients with concomitant *K-RAS* and sensitizing *EGFR* mutations [107–109]. The situation with immune checkpoint inhibitors is more complex. While there are conflicting individual studies on the outcome of *K-RAS* mutant NSCLC patients treated with PD-1/PD-L1 inhibitors, a recent meta-analysis of three prospective studies (CheckMate 057, POPLAR and OAK trial), demonstrated that patients with *K-RAS* mutant NSCLC had a superior survival compared to *K-RAS* wild type patients [110]. However, subset analyses suggest that patients with concomitant *STK11/LKB1* gene alterations may be less responsive to PD-1/PD-L1 inhibitors [111].

For colorectal cancer, *K-RAS* mutations are a major predictor of lack of response to therapy with monoclonal antibodies targeting EGFR (panitumumab, cetuximab) [112–115]. In addition, patients with *K-RAS G13D* mutations have an inferior response to chemotherapy as compared to those with other *K-RAS* mutation subtypes or those with *K-RAS* wild-type tumors [116,117]. There is a lack of data on the predictive value of *K-RAS* mutations on response to therapy as majority of pancreatic cancers harbor *K-RAS* mutations.

Rationale for targeting Kras in cancer therapy

Three factors support the hypothesis that Kras is a valid therapeutic target. First, *K-RAS* plays a distinct role in tumorigenesis. A study by *Janseen* and colleagues, in their transgenic mouse model, demonstrated that the transfection of oncogenic *K-RAS V12G* in epithelial cells of the large and small intestine led to the development of intestinal lesions including, invasive adenocarcinomas indicating a clear role of *K-RAS* in tumorigenesis [118]. Additionally, various mouse models have demonstrated the formation of frank tumors with the activation of oncogenic *K-RAS* [119,120]. Second, *K-RAS* mutant cancer cells are *K-RAS* dependent. Preclinical abrogation of mutant *K-RAS* inhibits tumor growth. A study by *Collins* and colleagues in a mouse model demonstrated that both primary and metastatic pancreatic adenocarcinoma lesions rely on constant Kras activity [121]. This notion is further supported by preclinical studies in different tumor types [122,123]. Third, *K-RAS* mutant cancers represent about 30% of all human cancers as previously mentioned. Taken together, these factors make a compelling argument for targeting Kras for cancer therapy.

Historical approaches to Kras targeting for cancer therapy

The most successful approach to inhibiting oncogenic kinases has been the development of inhibitors that compete with ATP binding to the kinase domain. Kras utilizes GTP rather than ATP as a phosphate donor for signaling. Because of the tight binding of GTP (a thousand-fold tighter than ATP) to Kras, this approach has not been feasible, based on current technology.

Thus, a number of approaches have been utilized, as outlined below

Direct inhibition of Kras

Direct inhibition of Kras has been a goal of cancer drug development for several decades. SCH-53239 was the first small non-nucleotide molecule which was designed to prevent GDP to GTP nucleotide transition by binding with Ras protein and thereby preventing Ras activation [124]. Additionally, a water-soluble analog SCH-54292, which was able to bind to the switch II region of the Ras molecule, was developed [125]. However, the development of these compounds was dropped because of lack of potency.

Inhibition of RAS protein expression

Antisense oligonucleotides

Antisense oligonucleotides bind to their complimentary mRNAs at a specific strand and thereby inhibit mRNA translation and ultimately the protein synthesis [126]. With this approach, a study by *Gray* and colleagues demonstrated a 90% reduction in Ras protein expression after targeting the 5′-flanking region of *H-RAS* in NIH-3T3 cells transformed by the *H-RAS* oncogene [127]. ISIS 2503 is an oligonucleotide that targets the 5′-untranslated region of human *H-RAS* mRNA and thereby reduces mRNA expression [128]. *Cunningham et al* conducted a phase I study utilizing this compound in 23 patients with solid tumors [129]. The compound was well tolerated. None of the patients achieved an objective response and only four patients (17%) had disease stability for 2 months or more. To evaluate the clinical activity of single agent ISIS 2503, a phase II study was conducted in sixteen patients with refractory colorectal cancer [130]. None of the patients achieved an objective response. Only one patient achieved disease stability after two cycles of treatment. Additionally, phase I and II studies were also conducted with this compound in combination with gemcitabine. In a phase I study of 27 patients with advanced cancer, the combination of ISIS 2503 and gemcitabine was well tolerated; partial response was noted in a single patient and disease stability in 5 patients [128]. This combination was further evaluated in a phase II study in 48 patients with unresectable or metastatic pancreatic adenocarcinoma [131]. At a median follow-up of 12.6 months, the study reported a 6-month survival rate of 57.5%, median survival of 6.6 months and a response rate of 10.4%. Further development of this agent was discontinued because of minimal efficacy.

Inhibition of K-RAS processing

Farnesyltransferase inhibitors

Prenylation is a post-translational addition of either a farnesyl (farnesylation) or geranylgeranyl (geranylgeranylation) moiety to the carboxyl terminus of Ras proteins that help in membrane localization. This is a rate limiting step in the post-translational modification of Kras [132]. Farnesyltransferase inhibitors were expected to block Ras farnesylation, thus preventing membrane localization and inhibiting Ras-mediated cellular proliferation. Various trials, utilizing a variety of

farnesyltransferase inhibitors, including tipifarnib (R115777), and lonafarnib (SCH 66336) were conducted in different tumor types [133–136]. A phase II trial of tipifarnib was conducted by *Adjei et al* in forty-four patients with stage IIIB or stage IV NSCLC [133]. There were no objective responses, the disease stability rate was 16%, median time to progression was 2.7 months and median OS was 7.7 months. Additionally, various phase II studies of single agent tipifarnib failed to show any objective responses in various solid tumors [136,137]. Also, a phase III study of tipifarnib failed to improve survival over best supportive care in advanced colorectal cancer [138]. A phase III study of tipifarnib in patients with advanced pancreatic adenocarcinoma randomized 688 patients to receive gemcitabine and tipifarnib or gemcitabine and placebo [139]. The study demonstrated no survival benefit with the addition of tipifarnib (median OS was 193 days and 182 days in the combination arm and gemcitabine arm respectively). In a phase III Intergroup study, 144 AML patients in remission were randomized to either receive tipifarnib or observation [140]. The study demonstrated no improvement in DFS with tipifarnib maintenance therapy.

Likewise, phase II trials of lonafarnib conducted in metastatic colorectal cancer and urothelial cancer showed no objective responses [134,135]. Additionally, a combination of lonafarnib and paclitaxel in a phase II trial of 33 patients with advanced NSCLC demonstrated a partial response of 10% and a disease stability rate of 38% [141]. Based on the results of this trial, a phase III trial of lonafarnib in combination with carboplatin-paclitaxel versus carboplatin-paclitaxel and placebo was initiated in patients with NSCLC (NCT00050336). But the study was terminated because of inadequate activity at interim analysis. These studies failed to demonstrate any benefit likely because Kras can be alternatively prenylated through geranylgeranylation [142].

Hras on the other hand is dependent solely on farnesylation for post translational modification, and the farnesyltransferase inhibitors will be expected to show activity. In support of this hypothesis, tipifarnib has recently being shown to have activity in patients with *H-RAS* mutant head and neck cancer, in a phase II study which demonstrated an overall response rate (ORR) of 56% and a median duration of response of 8.3 months [143].

Geranylgeranyltransferase inhibitors

Based on data indicating that Kras may be prenylated through geranylgeranylation, geranylgeranyltransferase inhibitors were evaluated in the clinic. GGTI-2418, a geranylgeranyl transferase inhibitor, was utilized in a phase I study, in 14 patients with advanced solid tumors [144]. The drug was well tolerated and no dose limiting toxicity was noted. However, no objective response was noted and the development of this class of agents was abandoned because of lack of efficacy.

Targeting downstream RAS effectors

RAF kinase inhibitors

Because of the multiple unsuccessful attempts at direct inhibition, subsequent approaches focused on the inhibition of downstream signaling of Kras.

Raf is the first protein that is phosphorylated by activated Ras in the mitogen-activated protein kinase pathway. Sorafenib (BAY 43-9006) was the first compound initially developed to specifically target Raf. It is currently approved for numerous cancers including hepatocellular carcinoma, gastrointestinal stromal tumor, renal cell carcinoma and thyroid cancer [145–147]. It is, however, not a specific or potent Raf kinase inhibitor and its antitumor activity is due to inhibition of several other receptor tyrosine kinases [148]. For instance, in pancreatic cancer, where the prevalence of *K-RAS* mutation is high, sorafenib when used in combination with chemotherapy did not demonstrate any significant clinical activity [149,150]. Subsequently, various potent inhibitors of B-Raf (dabrafenib, vemurafenib and encorafenib) were introduced and are now approved for numerous tumor types with a *B-RAF* mutation (particularly *B-RAF V600E*), including melanoma, NSCLC, anaplastic thyroid and colon cancer [151–153]. Mechanistically, these agents should be effective in *K-RAS* mutant cancers as Raf is downstream of Ras, and these agents are specific inhibitors of B-Raf unlike sorafenib. However, B-raf inhibition paradoxically activates ERK signaling in wild-type *B-RAF* cells [154]. In *K-RAS* mutant cells, B-raf inhibition activates upstream proteins leading to ERK activation through an alternative pathway. One of the mechanisms by which this happens is through C-Raf activation [155]. In support of these data, the C-Raf activation cascade has been noted in *B-RAF* wild type cells and not in *B-RAF* mutant cells [156]. Currently, there are no active clinical trials utilizing single-agent *B-RAF* inhibitors in *K-RAS* mutant solid tumors.

MEK inhibitors

MEK inhibitors when used in conjunction with *B-RAF* inhibitors are superior to *B-RAF* inhibitors alone in *B-RAF* mutant cancers. Currently, three *MEK* inhibitors, trametinib, cobimetinib and binimetinib, are approved in combination with *B-RAF* inhibitors for patients with *B-RAF* mutant melanoma, NSCLC and colon cancer (along with cetuximab) [157–159].

Single agent MEK inhibition has shown disappointing results in various tumor types. A phase II study, of an oral *MEK* inhibitor (CI-1040), demonstrated minimal efficacy with no complete and partial responses among 67 patients with NSCLC, breast, colon and pancreatic cancer [160]. In another phase II trial, 84 patients with NSCLC, who had received one or two prior lines of treatment, were randomized to either receive pemetrexed or selumetinib (AZD6244, a *MEK* inhibitor) [161]. The study demonstrated no significant difference in progression-free survival between the two arms.

Inhibition of MEK induces PI3K activation leading to activation of EGFR [162]. Based on these data, various trials have utilized *MEK* inhibitors in combination with EGFR inhibitors. Phase II studies of selumetinib combined with erlotinib failed to show activity in previously treated NSCLC [163] and pancreatic carcinoma [164].

The combination of MEK inhibitors and chemotherapy has also been evaluated for *K-RAS* mutant NSCLC. A number of phase II studies were performed [165–168] culminating in the phase III SELECT-1 trial which randomized patients with *K-RAS* mutant advanced NSCLC with disease progression after first-line treatment to either selumetinib plus docetaxel or placebo plus docetaxel [169]. Median PFS was 3.9 months with selumetinib plus docetaxel therapy versus 2.8 months in placebo plus docetaxel (HR, 0.93 [95% CI 0.77–1.12]; $P = 0.44$). In summary, MEK inhibition either alone or in combination is not an effective therapy for *K-RAS* mutant cancers.

ERK inhibitors

Since ERK is the final downstream kinase of the MAP Kinase pathway, it has been hypothesized that *ERK* inhibition may be effective in *K-RAS* mutant tumors. This hypothesis is supported by preclinical data [170]. Various *ERK* inhibitors, including, LY3214496, BVD-523, MK-8353 and KO-947, are in early phase of clinical development either alone or in combination (NCT02857270, NCT-01781429, NCT02972034, NCT03745989, NCT03051035). The dose escalation portion of a phase I trial of LY3214496 in patients with *K-RAS, N-RAS* or *B-RAF* mutant advanced or metastatic cancer has been reported [171]. No concerning toxicities were noted. The study is now in the second phase, where LY3214496 is utilized either alone or in combination with abemaciclib or nab-paclitaxel plus gemcitabine in various tumor types (NCT02857270).

CDK4/6 inhibitors

Abemaciclib is a cyclin-dependent kinase (CDK 4/6) inhibitor currently approved in combination with hormonal therapy for patients with advanced or metastatic hormone receptor positive and HER-

Table 2
Completed phase II or phase III studies of downstream Kras signaling inhibition in tumors with high prevalence of *K-RAS* mutations.

Study	Tumor type	Study design/ Phase	Sample Size	Intervention	ORR (%)	Median PFS (months)	Median OS (months)
GISCAD study *Cascinu et al* (151)	Pancreatic adenocarcinoma	Open-label Randomized Phase II	114	Gemcitabine/cisplatin plus sorafenib versus Gemcitabine/ cisplatin	3.4 vs. 3.6	4.3 vs. 4.5	7.5 vs. 8.3
Kindler et al (152)	Pancreatic adenocarcinoma	Open-label Single arm Phase II	17	Gemcitabine plus sorafenib	0	3.2	4.0
Rinehart et al (162)	CRC, NSCLC, breast, pancreatic cancer	Open-label Single arm Phase II	67	CI-1040	0	4.4*	NRe
Hainsworth et al (163)	NSCLC	Open-label Randomized Phase II	84	Selumetinib (AZD6244) versus pemetrexed	5 vs. 5	2.2 vs. 3.0	NRe
Carter et al (165)	NSCLC	Randomized Phase II	79	K-RAS wild-type: erlotinib versus erlotinib plus selumetinib	5 vs. 12	2.4 vs. 2.1	6.3 vs. 12.9
				K-RAS mutant: selumetinib versus selumetinib plus erlotinib	0 vs. 10	4.0 vs. 2.3	10.5 vs. 21.8
Blumenschein et al (176)	NSCLC K-RAS, NRAS, BRAF, or MEK1 mutant	Open-label Randomized Phase II	134	Trametinib versus docetaxel	12 vs. 12	2.8 vs. 2.6	8 vs. NR
SELECT-1 *Janne et al* (171)	NSCLC K-RAS mutant	Randomized Double Blind Phase III	510	Selumetinib plus docetaxel versus placebo plus docetaxel	20.1 vs. 13.7	3.9 vs. 2.8	8.7 vs. 7.9
Ko et al (166)	PDAC	Non-randomized Single arm Phase II	46	Selumetinib plus erlotinib	0	1.9	7.3
Infante et al (170)	Pancreatic adenocarcinoma	Double-blind Randomized Phase II	160	Trametinib plus gemcitabine versus placebo plus gemcitabine	22 vs. 18	3.8 vs. 3.5	8.4 vs. 6.7
JUNIPER *Goldman et al* (175)	NSCLC K-RAS mutant	Open-label Randomized Phase III	453	Abemaciclib versus erlotinib	8.9 vs. 2.7	3.6 vs. 1.9	7.4 vs. 7.8

ORR, Objective Response Rate; PFS, Progression Free Survival; OS, Overall Survival; CRC, colorectal carcinoma; NSCLC, non-small cell lung cancer; NRe, not reported; * median duration of stable disease; NR, Not Reached; PDAC, pancreatic ductal adenocarcinoma.

negative breast cancer. In a mouse tumor model that recapitulates human NSCLC, *Puyol* and colleagues demonstrated that CDK4 inhibition can induce selective death of *K-RAS* mutant cancer cells [172]. In a phase III open-label trial, patients with stage IV, *K-RAS* mutant NSCLC after having disease progression on platinum-doublet were randomized to abemaciclib or erlotinib. ORR was 8.9% in the abemaciclib arm versus 2.7% in the erlotinib arm ($P = 0.01$) [173]. Likewise, median PFS was 3.6 months with abemaciclib versus 1.9 months with erlotinib (HR, 0.58; 95% CI 0.47–0.72). However, despite having a better response rate and PFS, abemaciclib did not improve overall survival (median OS with abemaciclib was 7.4 months versus 7.8 months with erlotinib).

The results of the above mentioned studies are summarized in Table 2 [149,150,160,161,163,164,168,169,173,174]. In addition, various ongoing trials that have targeted downstream Kras effectors or utilized indirect Kras inhibition approaches are summarized in table 3.

Covalent Kras G12C inhibitors

Kras has been considered "undruggable" despite decades of extensive attempts to develop an effective anti-Ras therapy, as described above. Recent studies have identified small molecules that can selectively target and inactivate the *K-RAS G12C* mutant variant [175–180]. *K-RAS G12C* results from a missense mutation (glycine-to-cysteine substitution) at codon 12. This leads to impairment of GAP mediated hydrolysis of GTP to GDP, thereby locking the Kras protein in a hyperexcitable state.

K-RAS G12C is the most common mutant variant in NSCLC accounting for about 40% of all *K-RAS* mutant tumors and about 13% of all lung adenocarcinoma [52,54,181]. Additionally, it is present in about 3% of colorectal cancer cases and a small subset of patients with pancreatic, endometrial and urothelial cancers [66,182]. The frequency of different *K-RAS* mutations in various tumor types is shown in Fig. 3 [183].

Ostrem and colleagues developed a series of compounds that could target the mutant Kras G12C protein by covalently binding to the mutant cysteine residue [175]. With this approach, they were able to selectively target the mutant cells and spare the normal ones. Additionally, they found that these inhibitors were binding to a new allosteric binding pocket, the switch-II pocket (S-IIP). This pocket extends from the mutant cysteine residue into a pocket comprising mainly of the switch II region. By targeting this specific pocket, these compounds displace glycine 60 towards the switch I region leading to conformational disruption of GTP bound Ras and thereby preventing further downstream signaling. However, the initial lead compound developed by Ostrem and colleagues (compound 12) had poor pharmacologic properties [176,177].

Consequently, ARS853, which had more than 600-fold improved engagement with Kras G12C over compound 12, was discovered [176,177]. Two studies, by *Lito et al* and *Patricelli et al*, demonstrated reduction in GTP-bound Kras levels in *K-RAS G12C* mutant cancer cell lines after treatment with ARS853 [176,177]. Additionally, they also showed that ARS833 bound preferentially to the GDP-bound state of Kras G12C. Since this compound was selectively inhibiting GDP-bound Kras, there was a significant concern about its efficacy in vivo. Consequently, *Janes* and colleagues identified a compound, ARS-1260, which selectively targets the switch II pocket and also inhibits Kras in the GTP-bound state [178]. They demonstrated that ARS-1260 covalently inhibits Kras G12C activity in vitro, and exhibited antitumor activity in subcutaneous xenograft models bearing *K-RAS G12C* but not *G12V* mutations.

Subsequently, *Canon* and colleagues demonstrated the activity of AMG 510 in *K-RAS G12C* mouse xenografts [179]. Similar preclinical studies of another Kras G12C inhibitor, MRTX849 have been published

Table 3
Ongoing trials targeting Kras downstream signaling in *K-RAS* mutant solid tumors.

Site of action	Study/Clinical Trial Identifier	Tumor Type	Mutation profile	Phase/Study Design	Intervention	Recruitment status	Estimated Enrollment
PI3K	NCT04073680	Solid tumor	PIK3CA or K-RAS	Ib/II Open-label	Serabelisib and Canagliflozin	Not yet recruiting	60
RAF	NCT02974725	NSCLC, melanoma	K-RAS or BRAF (NSCLC), N-RAS (melanoma)	Ib Open-label	LXH254 with LTT462 or trametinib or ribociclib	Recruiting	195
RAF	NCT04249843	Solid tumor	B-RAF, K-RAS, N-RAS	Ia/Ib Open-label	BGB-3245	Recruiting	69
RAF MEK	NCT03681483	NSCLC	K-RAS	I Open-label	RO5126766	Recruiting	31
MEK	NCT03704688	NSCLC	K-RAS	I Open-label	Trametinib and ponatinib	Recruiting	37
MEK	NCT04132505	Pancreatic adenocarcinoma	K-RAS	I Open-label	Binimetinib and hydroxychloroquine	Recruiting	39
MEK	NCT03299088	NSCLC	K-RAS	Ib Open-label	Trametinib and pembrolizumab	Recruiting	42
MEK	NCT02613650	Colorectal	H-RAS, N-RAS or K-RAS	Ib Open-label	MEK162 and mFOLFIRI	Recruiting	30
MEK	NCT03981614	Colorectal	K-RAS or N-RAS	II Randomized Open-label	Binimetinib plus palbociclib versus TAS-102 (trifluridine and tipiracil)	Recruiting	112
MEK	SELECT-1 NCT01933932	NSCLC	K-RAS	III Randomized Double-blind	Selumetinib plus docetaxel versus docetaxel plus placebo	Active, not recruiting	510
MEK	M14LTK NCT02230553	NSCLC	K-RAS mutant and PIK3CA wild-type	I/II Open-label	Trametinib and lapatinib	Recruiting	30
MEK	NCT03990077	NSCLC	K-RAS	I Open-label	HL-085 and docetaxel	Not yet recruiting	27
MEK	M14AFS NCT02450656	NSCLC	K-RAS mutant and PIK3CA wild-type	I/II Randomized Open-label	Selumetinib plus afatinib versus docetaxel	Recruiting	320
MEK	MEKiAUTO NCT04214418	Pancreatic adenocarcinoma colorectal	K-RAS	I/II Open-label	Cobimetinib, hydroxychloroquine and atezolizumab	Not yet recruiting	175
MEK	NCT03170206	NSCLC	K-RAS	I/II Open-label	Binimetinib and palbociclib	Recruiting	72
MEK	NCT02079740	Solid tumor	K-RAS or N-RAS	Ib/II Open-label	Trametinib and navitoclax	Recruiting	130
MEK	NCT03637491	Solid tumor	K-RAS or N-RAS	Ib/II Open-label Randomized	Binimetinib and avelumab or binimetinib, avelumab and talazoparib or binimetinib and talazoparib	Recruiting	122
ERK	NCT02857270	Melanoma, NSCLC, colorectal, pancreatic adenocarcinoma	BRAF or RAS NSCLC, BRAF or NRAS melanoma, BRAF colorectal	I Open-label	LY3214996 alone and in combination with abemaciclib, nab-paclitaxel and gemcitabine or cetuximab and encorafenib	Recruiting	272
ERK	NCT04145297	GI malignancy	KRAS, NRAS, HRAS, BRAF non-V600, MEK, ERK	I Open-label	Ulixertinib (BVD-523) and hydroxychloroquine	Recruiting	12
ERK	NCT03051035	Solid tumor	BRAF, KRAS, NRAS or HRAS in non-squamous histology	I Open-label	KO-947 alone	Active but not recruiting	100
ERK	NCT03415126	Solid tumor	BRAF mutant melanoma, N-RAS or H-RAS mutant solid tumors, K-RAS mutant CRC, K-RAS mutant NSCLC	I Open-label	ASN007	Active but not recruiting	49
mTOR	NCT03520842	Non-squamous NSCLC	K-RAS	II Open-label	Regorafenib and methotrexate	Recruiting	18

NSCLC, non-small cell lung cancer.

[180].

A phase I study of AMG 510 was presented at the European Society for Medical Oncology (ESMO) annual meeting and at the World Lung Cancer Conference in 2019, by *Govindan* and colleagues [184]. A total of 76 patients with *K-RAS G12C* mutant solid tumors were enrolled in the study. There was no dose limiting toxicity. Most of the patients (34.2%) had grade 1 or grade 2 treatment-related adverse events. 6 patients had grade 3 adverse events, which included anemia and diarrhea. The recommended phase II dose was 960 mg once daily. Among NSCLC cohort (n = 23), the ORR was 48% and disease control rate (DCR) was 96%. In the colorectal cancer cohort (n = 29), the ORR was 3% and the DCR was 79%. There are two other phase I trials (NCT03600883, NCT04185883), which are actively recruiting patients with *K-RAS G12C* mutant solid malignancies. These trials will also assess the safety and feasibility of various therapeutic agents in combination with AMG510, including a PD-1 inhibitor, MEK inhibitor, a SHP2 allosteric inhibitor, and a pan-ErbB tyrosine kinase inhibitor. Additionally, a phase III trial is scheduled to start accrual this summer in patients with previously treated locally advanced and unresectable or metastatic *K-RAS G12C* mutant NSCLC with randomization to AMG510 or docetaxel (NTC04303780). The clinical activity of AMG 510 in colorectal cancer is minimal to modest compared to the activity in NSCLC,

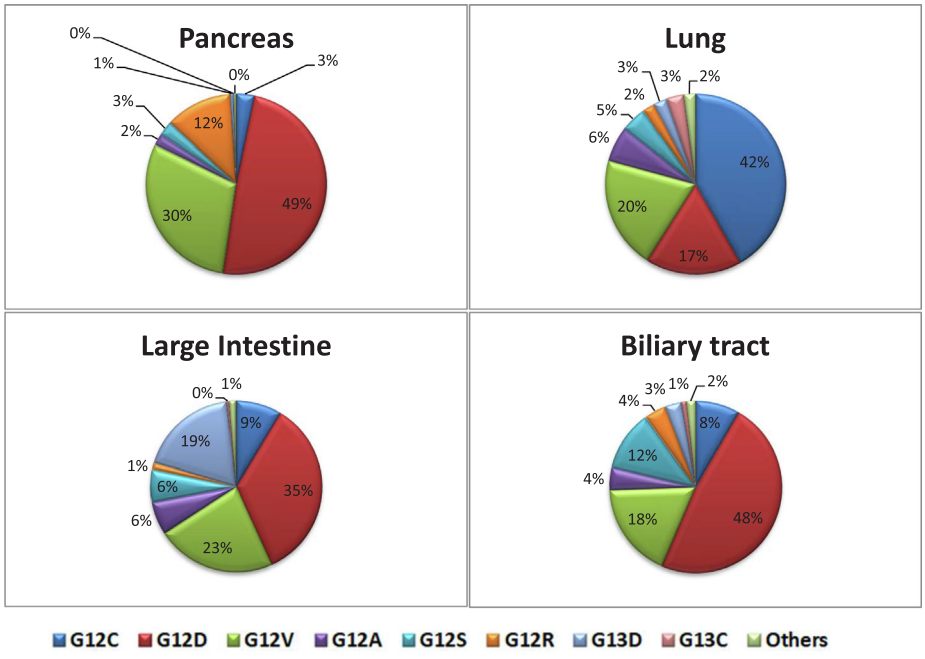

Fig. 3. *K-RAS* mutation frequency in different tumor types.

suggesting that signaling networks in colorectal cancer are different from NSCLC. As an example, Braf inhibition in *BRAF V600E* mutation is much more effective in NSCLC compared to colorectal cancer, where bypass signaling in EGFR abrogates the effect of Braf inhibition. Thus, concurrent inhibition of EGFR is needed to achieve impressive responses after Braf inhibition. This same mechanism seems to be present in *K-RAS G12C* mutant colorectal cancer, as demonstrated by *Amodio* and colleagues [185].

Studies with another Kras G12C inhibitor are also ongoing. A phase 1/2 multiple expansion study of MRTX849 is currently accruing patients (NCT03785249). In this trial, patients with advanced, unresectable or metastatic solid tumors with a *K-RAS G12C* mutation will be enrolled to access the safety, pharmacokinetics, tolerability and clinical activity of MRTX849. This trial will also evaluate the safety of the combination of MRTX849 with other therapeutic agents, including, a PD-1 inhibitor in patients with NSCLC and cetuximab in patients with colorectal cancer. Another phase 1/2 study will be opening in the near future utilizing a combination of MRTX849 and TNO155 in patients with KRAS G12C mutant cancer (NCT04330664). TNO155 is a SHP2 inhibitor and will be discussed in detail below. Two other *K-RAS* G12C inhibitors, ARS-3248/JNJ-74699157, and LY3499446 are under investigation (NCT04006301, NCT04165031). Table 4 summarizes all the active trials in *K-RAS* mutant solid tumors which utilize novel direct inhibitors of Kras.

PAN K-RAS inhibitors

SOS1 inhibitors

BI-3406 is an orally bioavailable drug designed to inhibit the son of sevenless 1 (SOS1) protein. *Hofmann* and colleagues have demonstrated that this Boehringer-Ingelheim drug only inhibits SOS1, and not SOS2 [186]. They further demonstrated that in *K-RAS*-mutant cancer, including G12 and G13. By inhibiting SOS1, BI-3406 reduced GTP-KRAS levels thereby restricting tumor cell proliferation. BI 1701963, which is a BI-3406 analog, is in phase I trials, either alone or in combination with Trametinib in patients with *K-RAS* mutant solid tumors (NCT04111458).

SHP2 inhibitors

SHP2, a protein tyrosine phosphatase (PTPN11), relays stimulatory signals from various membrane receptor tyrosine kinases to the MAPK kinase signaling pathway [187]. *Chen* and colleagues initially developed SHP099, a selective and orally bioavailable allosteric inhibitor of SHP2, and demonstrated its antitumor activity in receptor tyrosine kinase-driven cancers in patient derived tumor xenograft models [188]. Later, *Mainardi* and colleagues demonstrated an importance of SHP2 inhibition in controlling *K-RAS* mutant tumor growth by MEK inhibition [189]. They demonstrated that MEK inhibition can reduce phosphorylated ERK in cell lines of three tumor types (NSCLC, pancreatic cancer and colon cancer). Furthermore, they found that ERK levels slowly started rising along with a rise in SHP2 levels suggesting the activation of a feedback loop involving receptor tyrosine kinase. Additionally, when they simultaneously blocked SHP2 and MEK, they found a strong synergy between a SHP2 inhibitor and a MEK inhibitor in all three cells lines, and the strongest effect was observed in NSCLC cell lines. In addition, they demonstrated that the PTPN11-knockout cells demonstrated lower baseline RAS-GTP levels and had an increased sensitivity to MEK inhibitor. Based on these preclinical data, it is reasonable to utilize SHP inhibitor in *K-RAS* mutant tumor. There are two SHP 2 inhibitors, namely, RMC 4630 and TNO155, in early phase of development, (NCT03634982, NCT03989115, NCT04000529, NCT03114319, NCT04330664).

Transcription regulator eIF4 inhibitors

Protein synthesis is catalyzed by eukaryotic translational initiation factor 4 (eIF4) which is responsible for recruitment of the 5′-untranslated segment of the mRNA to the ribosomal subunit [190]. eIF4A, a component of eIF4 complex, is an ATPase/RNA helicases and its specific role in this process is mRNA unwinding to facilitate ribosome binding [190]. Since this protein complex is an essential component of the translation initiation of multiple oncogenic pathways, including *K-RAS*, targeting this protein in *K-RAS* mutant cancer cases can potentially control tumor growth and proliferation. eFT226 is a first in class selective inhibitor of eIF4A. *Thompson* and colleagues have demonstrated antitumor activity of this compound in a preclinical study in B-

Table 4
Ongoing clinical trials of novel Kras inhibitors in *K-RAS* mutant solid tumors.

Site of action	Study/Clinical Trial Identifier	Tumor Type	Mutation profile	Phase/Study Design	Intervention	Recruitment status	Estimated Enrollment
K-RAS G12C	CodeBreak 101 NCT04185883	Solid tumor	K-RAS G12C	Ib Open-label	AMG 510 alone and in combination with MEK, PD-1, SHP2 or ErbB inhibitor	Recruiting	250
K-RAS G12C	CodeBreak 200 NCT04303780	NSCLC	K-RAS G12C	III Randomized Open-label	AMG 510 plus Docetaxel versus Docetaxel	Not yet recruiting	650
K-RAS G12C	CodeBreak 100 NCT04303780	Solid tumor	K-RAS G12C	I/II Open-label	AMG 510 alone and in combination with PD-1 inhibitor	Recruiting	533
K-RAS G12C	NCT03785249	Solid tumor	K-RAS G12C	I/II Open-label	MRTX849 alone	Recruiting	200
K-RAS G12C	NCT04330664	Solid tumor	K-RAS G12C	I/II Open-label	MRTX849 in combination with TNO155	Recruiting	148
K-RAS G12C	NCT04165031	Solid tumor	K-RAS G12C	I/II Open-label	LY3499446 alone or in combination with abemaciclib, cetuximab, erlotinib, docetaxel	Recruiting	230
K-RAS G12C	NCT04006301	Solid Tumor	K-RAS G12C	I Open-label	JNJ-74699157 alone	Recruiting	140
SOS1	NCT04111458	Solid tumor	K-RAS	I Open-label	BI 1,701,963 alone and in combination with trametinib	Recruiting	140
SHP2	NCT03634982	Solid tumor	RTK, K-RAS G12, BRAF class 3, NF1 LOF	I Open-label	RMC-4630 alone	Recruiting	240
SHP2	NCT03989115	Solid tumor	K-RAS, BRAF class 3, NF1 LOF	Ib/II Open-label	RMC-4630 in combination with cobimetinib	Recruiting	144
SHP2	NCT03114319	Solid tumor	EGFR NSCLC, K-RAS G12C NSCLC, CRC, Esophageal SCC, HN SCC, RAS/RAF wild-type other solid tumor	I Open-label	TNO155 alone	Recruiting	135
SHP2	NCT04000529	NSCLC, CRC, HNSCC	wild-type (dose escalation); K-RAS G12C NSCLC, K-RAS wild-type NSCLC, K-RAS codon 12, 13, or 61 for CRC (dose escalation)	Ib Open-label	TNO155 in combination with spartalizumab or ribociclib	Recruiting	126
mRNA based vaccine	NCT03948763	NSCLC, CRC, pancreatic adenocarcinoma	K-RAS G12D, G12V, G13D, G12C	I Open-label	mRNA-5671/V941 alone and in combination with pembrolizumab	Recruiting	100
eIF4	NCT04092673	Solid tumor	HER2, ERBB3, FGFR1, FGFR2, K-RAS	I/II Open-label	eFT226 (Zotatifin) alone	Recruiting	45

CRC, colorectal carcinoma; NSCLC, non-small cell lung cancer.

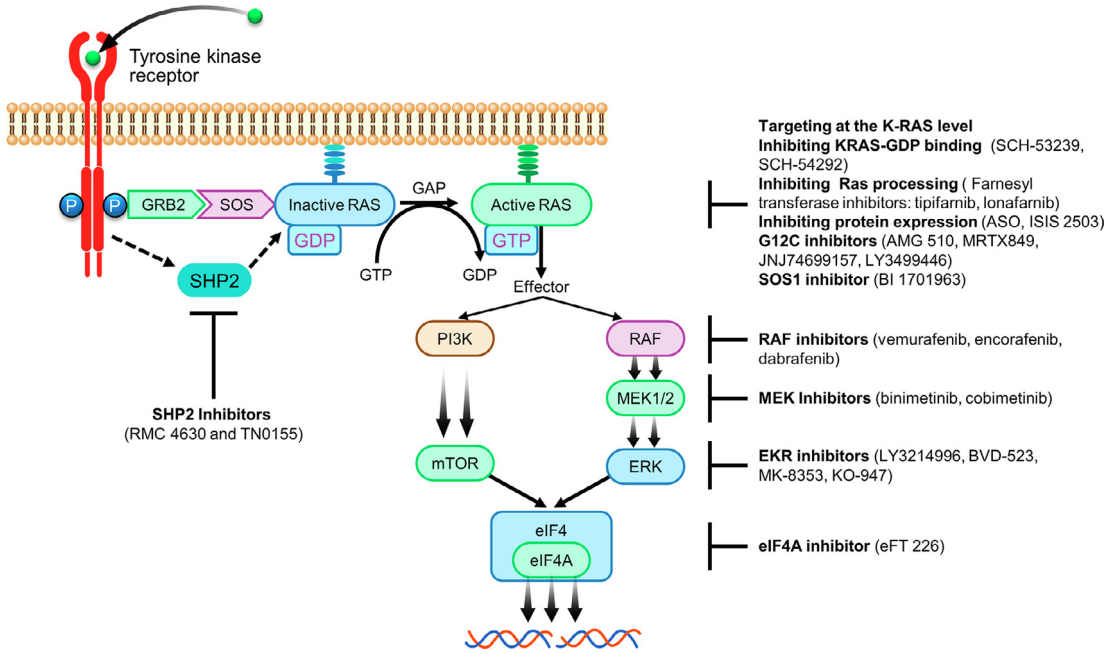

Fig. 4. Various drugs targeting at different levels on Kras pathway.

cell lymphoma where there is a PI3K/AKT/mTOR pathway aberrancy [191]. Additionally, *Thompson* and colleagues have demonstrated in vivo tumor growth inhibition in solid tumor xenograft models with FGFR1/2 or HER2 amplifications, including NSCLC, breast and colorectal cancers [192]. A phase I trial of eFT 226 (zotatifin) is currently recruiting patients with *HER2, ERBB3, FGFR1, FGFR2* and *K-RAS* mutant solid tumors (NCT 04092673). Various drugs targeting at different levels on Kras pathway is depicted in Fig. 4.

Other agents in late preclinical development

Recently, mRNA-based vaccination is being utilized to investigate specific immune responses against cancer cells. Mutanome is a distinct set of somatic mutations unique to an individual's tumor. As majority of these mutations are unique to each individual, *Sahin et al* investigated the concept of individualized mutanome vaccines by implementing an RNA-based neo-epitope approach in patients with stage III or IV melanoma [193]. After identifying non-synonymous mutations in 13 patients, an RNA vaccine was engineered encoding 10 selected mutations per patient, which was then injected intranodally. Following vaccination, all patients developed T-cell responses and two of the five patients with metastatic disease achieved an objective response. This study unlocked a novel path for a more personalized treatment and has drawn significant attention. A phase I trial of mRNA-5671/V941 (that encodes antigen for *K-RAS G12D*, *G12V, G12C* and *G13D*) as monotherapy and in combination with pembrolizumab in patients with solid tumors with four prevalent *K-RAS* mutations is currently underway (NCT03948763). The mRNA-5671/V941 vaccine is intended to target majority of the *K-RAS* mutations that occur in solid tumors.

Additionally, a novel short inhibitory peptide, KRpep-2d, is recently identified using a T7 phage display technique. KRpep-2d is a 19-mer cyclic peptide which is able to non-covalently and selectively inhibit Kras G12D activity with high potency [194,195]. It acts as an allosteric inhibitor by binding near the switch II pocket [196]. This molecule is still in its infancy but is likely to enter clinical trial in near future for *K-RAS G12D* mutant tumors.

Conclusion

While *K-RAS* has been seen as an attractive target for cancer therapy, all approaches taken to inhibit *K-RAS* either directly or indirectly through inhibiting post translational modification or downstream signaling to date have been ineffective. Advances in genomics and molecular biology, however, have for the first time suggested that direct inhibition of *K-RAS* may be possible. An identification of a targetable binding pocket (S-IIP) in *K-RAS G12C* recently resulted in a renewed interest in targeting *K-RAS* via *G12C* inhibition. The covalent Kras G12C inhibitors have provided the first clinical evidence of the ability to inhibit a class of *K-RAS* mutant tumors. This initial success has rekindled interest in Kras inhibition, with a number of other approaches including SHP2, SOS1 and eIF4 inhibition being tested in the clinic. These newer approaches, if successful would abrogate the activity of all mutant isoforms of *K-RAS*. Thus, we are for the first time at the cusp of successfully drugging this hitherto undruggable target.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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