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RAS signaling in carcinogenesis, cancer therapy and resistance mechanisms

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Abstract
Variants in the RAS family (HRAS, NRAS and KRAS) are among the most common mutations found in cancer. About 19% patients with cancer harbor RAS mutations, which are typically associated with poor clinical outcomes. Over the past four decades, KRAS has long been considered an undruggable target due to the absence of suitable small-molecule binding sites within its mutant isoforms. However, recent advancements in drug design have made RAS-targeting therapies viable, particularly with the approval of direct $KRAS^{G12C}$ inhibitors, such as sotorasib and adagrasib, for treating non-small cell lung cancer (NSCLC) with $KRAS^{G12C}$ mutations. Other KRAS-mutant inhibitors targeting $KRAS^{G12D}$ are currently being developed for use in the clinic, particularly for treating highly refractory malignancies like pancreatic cancer. Herein, we provide an overview of RAS signaling, further detailing the roles of the RAS signaling pathway in carcinogenesis. This includes a summary of RAS mutations in human cancers and an emphasis on therapeutic approaches, as well as de *novo*, acquired, and adaptive resistance in various malignancies.

Introduction to RAS: Its structure and mutations in cancer

RAS was firstly identified as a virus-encoded gene by Jennifer Harvey and her colleagues in 1964 [1]. It was regarded as an oncogene, being one of the most frequently mutated genes in human cancer [2, 3]. Mutationally activated RAS is present in approximately one in five human cancers.

The RAS gene family includes three members: HRAS, NRAS, and KRAS [4]. Indeed, RAS proteins are implicated in a variety of biological responses, including cell proliferation, migration, growth arrest, senescence, differentiation, apoptosis, and survival [2]. Cancer cells with RAS mutations display more aggressive phenotypes [5]. As a result, patients with RAS mutations are more likely to experience poor prognosis and shorter survival compared to those with wild-type (WT) RAS [6, 7].

Alterations in components of the RAS signaling pathway, especially the RAS proteins that serve as central mediators, have significant consequences in various cancers, particularly in NSCLC, colorectal cancer (CRC), and pancreatic ductal adenocarcinoma (PDAC) [8]. Over the past four decades, significant efforts from both academia and industry have been directed toward developing drugs targeting RAS proteins for cancer therapy [9]. This decades-long difficulties for drug design are due to several factors: (1) Inhibitors must selectively target the dynamic conformational changes that RAS undergoes as it cycles between the GTP-bound (RAS (ON)) state and the GDP-bound (RAS (OFF)) state, each characterized by distinct structural features; (2) RAS proteins exhibit a strong affinity for GTP, compounded by the

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high intracellular concentrations of GTP; (3) RAS proteins lack deep small-molecule binding pockets, making them challenging pharmacological targets; (4) On-target toxicity may arise from inhibition of WT KRAS or simultaneous targeting of downstream pathways, including RAF/MEK/ERK and PI3K/AKT/mTOR; (5) Downstream pathway inhibitors can lead to a paradoxical increase in RAS signaling due to the release of negative feedback; (6) The sequestration of the KRAS-GTP complex by effector proteins [10–13]. The groundbreaking discovery of compounds and the subsequent development of covalent allosteric inhibitors, which irreversibly bind to cysteine 12 and occupy a cryptic induced pocket in the switch II region of GDP-bound KRAS, effectively trap the oncoprotein in its inactive conformation, allowing for effective inhibition of $KRAS^{G12C}$ [14]. In 2021, the clinically available $KRAS^{G12C}$ inhibitors sotorasib (AMG 510) [15] and adagrasib (MRTX849) [16] were approved for a specific subset of patients with NSCLC. As of 2024, sotorasib has demonstrated promising clinical activity and tolerable safety in PDAC, while adagrasib has shown similar positive outcomes in CRC [17, 18].

RAS structures: insights into hotspot mutations

As previously noted, the RAS family comprises three genes—KRAS, NRAS, and HRAS—that encode isoforms with highly conserved sequences and structural homology. Each isoform includes a G domain (residues 1–166) and a C-terminal hypervariable region (HVR) (residues 166–188/189), both essential for RAS function (Fig. 1A). The G domain, which contains the switch I (residues 30–40), switch II (residues 60–76), and P-loop (residues 10–17) regions, is crucial for binding downstream effectors, thus facilitating signal transduction [19]. Notably, the three isoforms primarily vary in their HVR, which determines their unique cellular localization and distinct activities [20].

In all three RAS isoforms—KRAS, HRAS, and NRAS—the primary mutational hotspots are located at amino acid residues G12, G13, and Q61. These mutations compromise RAS's intrinsic GTPase activity and enhance GEF-mediated nucleotide exchange, resulting in a persistently active, GTP-bound state that promotes oncogenic signaling [21–23]. Thus, we focused our analysis on the three-dimensional structures of KRAS, HRAS, and NRAS proteins, with specific attention to these prevalent mutational hotspots (Fig. 1B).

RAS mutation frequencies in human cancers

RAS isoform mutations exhibit selectivity across various cancers. Specifically, KRAS mutations are most commonly found in solid tumors, particularly in PDAC, CRC, lung adenocarcinoma (LUAD), uterine corpus endometrial carcinoma (UCEC), stomach adenocarcinoma (STAD), and testicular germ cell tumors (TGCT). HRAS mutations are primarily observed in pheochromocytoma and paraganglioma (PCPG), thymoma (THYM), head and neck squamous cell carcinoma (HNSC), bladder urothelial carcinoma (BLCA), thyroid carcinoma (THCA), skin cutaneous melanoma (SKCM), and UCEC. In contrast, NRAS mutations are predominantly found in SKCM and hematological malignancies, such as acute myeloid leukemia (AML) (data available through the cBioPortal for Cancer Genomics) (Fig. 2A-C). Therefore, it is essential for researchers to conduct comprehensive studies on various human tumor types, focusing on the differences in RAS mutations from developmental or evolutionary perspectives. In general, some RAS gene mutations result in the production of oncoproteins that drive cancer, while others may be benign [24]. The most notable mutational hotspots in all three RAS isoforms (HRAS, KRAS, and NRAS) are found at three amino acid residues: G12, G13, and Q61. Despite the identification of numerous mutation sites and varying frequencies across different cancer types, KRAS mutations predominantly (about 80%) show a preference for the G12 hotspot. In contrast, approximately 60% of NRAS mutations occur at the Q61 site. The mutational frequency of the three hotspot residues in HRAS is relatively similar, accounting for about 20–30% of mutations [25] (Fig. 2D).

RAS mutant subtypes in human cancers

RAS alterations have been identified as oncogenic drivers in several cancer types, including PDAC, CRC, LUAD, and melanoma [28–31]. The distribution of RAS mutations varies among different cancer types, with $KRAS^{G12X}$ mutations accounting for 91% of KRAS mutations in PDAC, 85% in LUAD, and 68% in CRC (Fig. 3A). Mutations at G12 in KRAS are the most common, followed by alterations at G13. Both $KRAS^{G12X}$ and $KRAS^{G13X}$ mutations disrupt the cycle between the GTP-bound active state and the GDP-bound inactive state, favoring the GTP-bound active state [32–34]. The KRAS mutant subtypes are primarily classified as $KRAS^{G12D}$, $KRAS^{G12V}$, $KRAS^{G12C}$, $KRAS^{G12R}$, $KRAS^{G12A}$, and $KRAS^{G13D}$ mutations, along with KRAS wild-type amplification [35, 36] (Fig. 3B). In contrast, the NRAS mutant subtypes include $NRAS^{Q61R}$, $NRAS^{Q61K}$, $NRAS^{Q61L}$, and $NRAS^{Q61H}$ alterations (Fig. 3B). The $KRAS^{G12C}$ mutation is the most common mutant subtype in LUAD, while $KRAS^{G12D}$ is the most prevalent allele in PDAC, where $KRAS^{G12C}$ is rarely observed (Fig. 3B). Additionally, $NRAS^{Q61R}$ is the most common mutant subtype found in melanoma (Fig. 3C). Indeed, the codons and frequencies of RAS mutations vary by tissue type.

Together, the analysis of RAS protein data provides significant insights into the functional diversity within the RAS family, which includes the main types: HRAS,

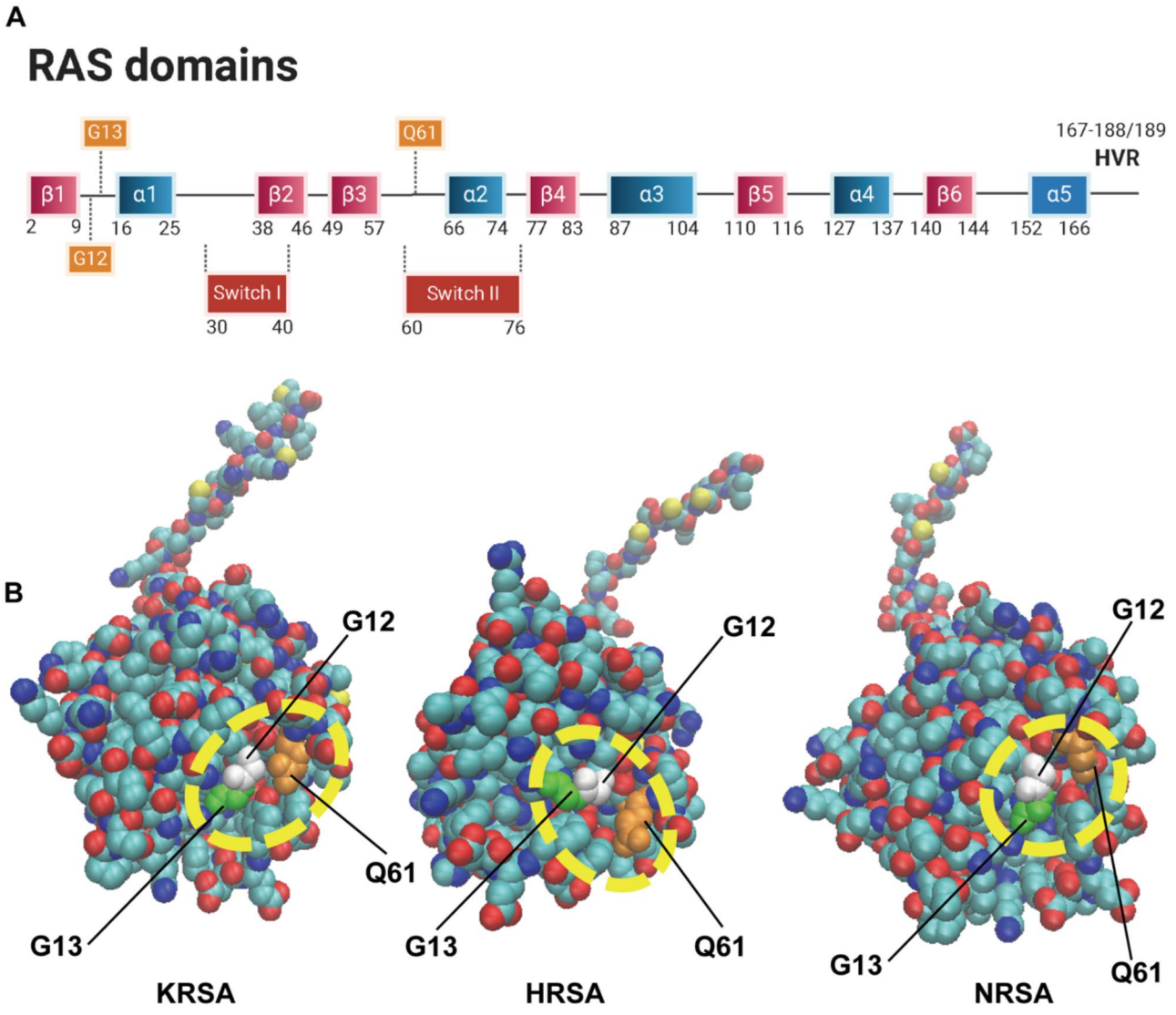

Fig. 1 Structure of RAS. (**A**) The RAS protein structure includes the effector lobe (residues 1–86), the allosteric lobe (residues 87–165), and the HVR (residues 167–188/189). Within the effector lobe, the switch I (residues 30–40) and switch II (residues 60–76) regions are essential for binding downstream effectors and interacting with GEFs or GAPs. The HVR domain facilitates membrane attachment, playing a critical role in defining RAS's cellular localization. (**B**) KRAS, HRAS, and NRAS are shown in surface representation, highlighting key mutational hotspots. The position of residue G12 is displayed in white, G13 in green, and Q61 in orange. HVR: hypervariable region

KRAS, and NRAS. Each of these types consists of subtypes that exhibit distinct mutations and biochemical properties, influencing their roles in cellular signaling and oncogenesis. Understanding the differences between these family members and their subtypes can aid in developing more targeted therapeutic approaches, potentially improving the efficacy of treatments designed to inhibit RAS-driven signaling pathways.

Activation and signaling cascade

The RAS–RAF–MEK–ERK (MAPK) signaling pathway is typically activated by various factors, including cytokines, cytokine receptors, hormones, protein kinases, transcription factors, and others [37]. The canonical pathway consists of a RTK linked to the RAS–RAF–MEK–ERK cascade, in which the RAS family (KRAS, NRAS, and HRAS) acts as GDP–GTP-regulated binary on-off switches (switch 1 and switch 2) during signal transduction [38]. Both switch regions undergo conformational changes, with the switch 2 state being particularly critical for the eventual development of RAS inhibitors (Fig. 4).

This switch is regulated by GEFs, which stimulate the conversion of the inactive GDP-bound form to the active GTP-bound form, and GAPs, which facilitate the conversion back to the inactive GDP-bound form [38, 39].

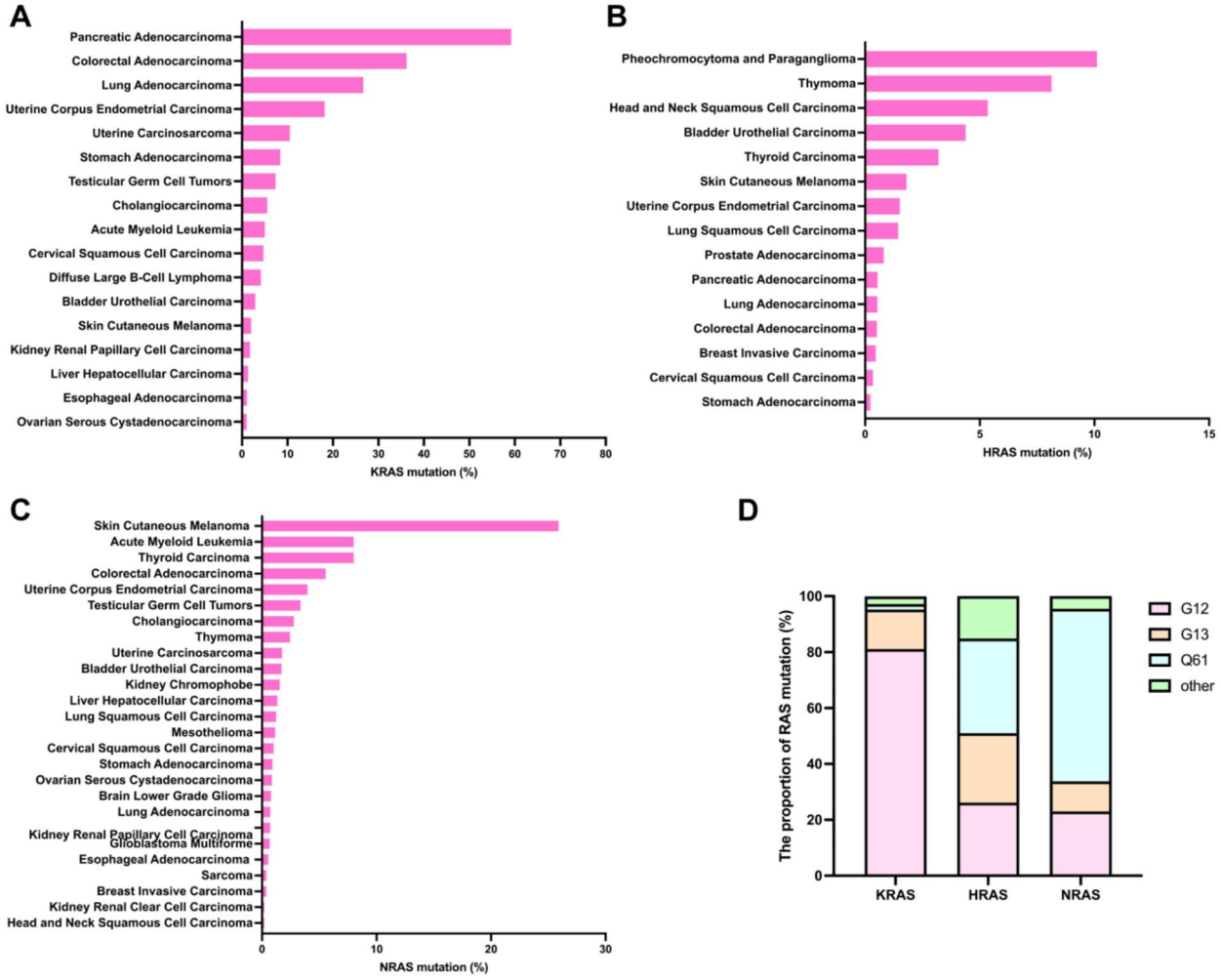

Fig. 2 The frequency of RAS mutations varies across different cancer types and is notably concentrated at the G12, G13, and Q61 residues in the exons of RAS oncogenes. (**A**) KRAS mutations are most prevalent in pancreatic ductal adenocarcinoma, followed by colorectal cancer and lung adenocarcinoma. (**B**) HRAS mutations are primarily observed in pheochromocytoma and paraganglioma, thymoma, and head and neck squamous cell carcinoma. (**C**) NRAS mutations are mainly found in skin cutaneous melanoma, acute myeloid leukemia, and thyroid carcinoma. (**D**) The prevalence of G12, G13, and Q61 mutations in the exons of KRAS, HRAS, and NRAS isoforms is highlighted. The data shown in graphs (**A**), (**B**), and (**C**) are sourced from the cBioPortal TCGA (available via the cBioPortal for Cancer Genomics), while the data in graph (**D**) were derived from recent studies utilizing the COSMIC or cBioPortal databases [3, 26, 27]

GEFs and GAPs are typically multidomain proteins that are regulated by extracellular signals [40]. RAS activation must be tightly regulated, as aberrant activation of RAS is linked to numerous human cancers [41]. The RAS-GEF family includes RAS-GRF, RAS-GRP, and SOS. The RAS-GRF protein is responsible for Ca^{2+} influx and calmodulin-dependent activation of RAS, primarily expressed in the central nervous system (CNS). In contrast, RAS-GRP is predominantly expressed in hematopoietic cells and stimulates RAS proteins downstream of non-receptor tyrosine kinases [35]. SOS is a widely distributed RAS-GEF, and its activation of RAS is critical for various biological processes, including cell growth [42, 43]. SOS1 and SOS2 (SOS1/2), activated by RTKs and cytokine receptors, bind to the SH3 domains of the adapter protein GRB2 through C-terminal proline-rich motifs [44]. GRB2 can simultaneously bind to the SOS1-activating non-receptor protein tyrosine phosphatase SHP2 via its SH2 domain, enabling precise cooperation with the RAS-GEF SOS to activate RAS. Subsequently, active RAS recruits and interacts with downstream effector proteins, particularly RAF, which phosphorylates and activates MEK1 and/or MEK2. This activation leads to the phosphorylation of various cytosolic and nuclear proteins, including transcription factors. Additionally, active RAS-GTP can interact with the downstream effector PI3K, thereby transducing signals to regulate biological processes [45, 46]. Therefore, the RAS–RAF–MEK–ERK and RAS–PI3K–AKT–mTORC pathways serve as fundamental signaling pathways of RAS [25, 46]. Other important

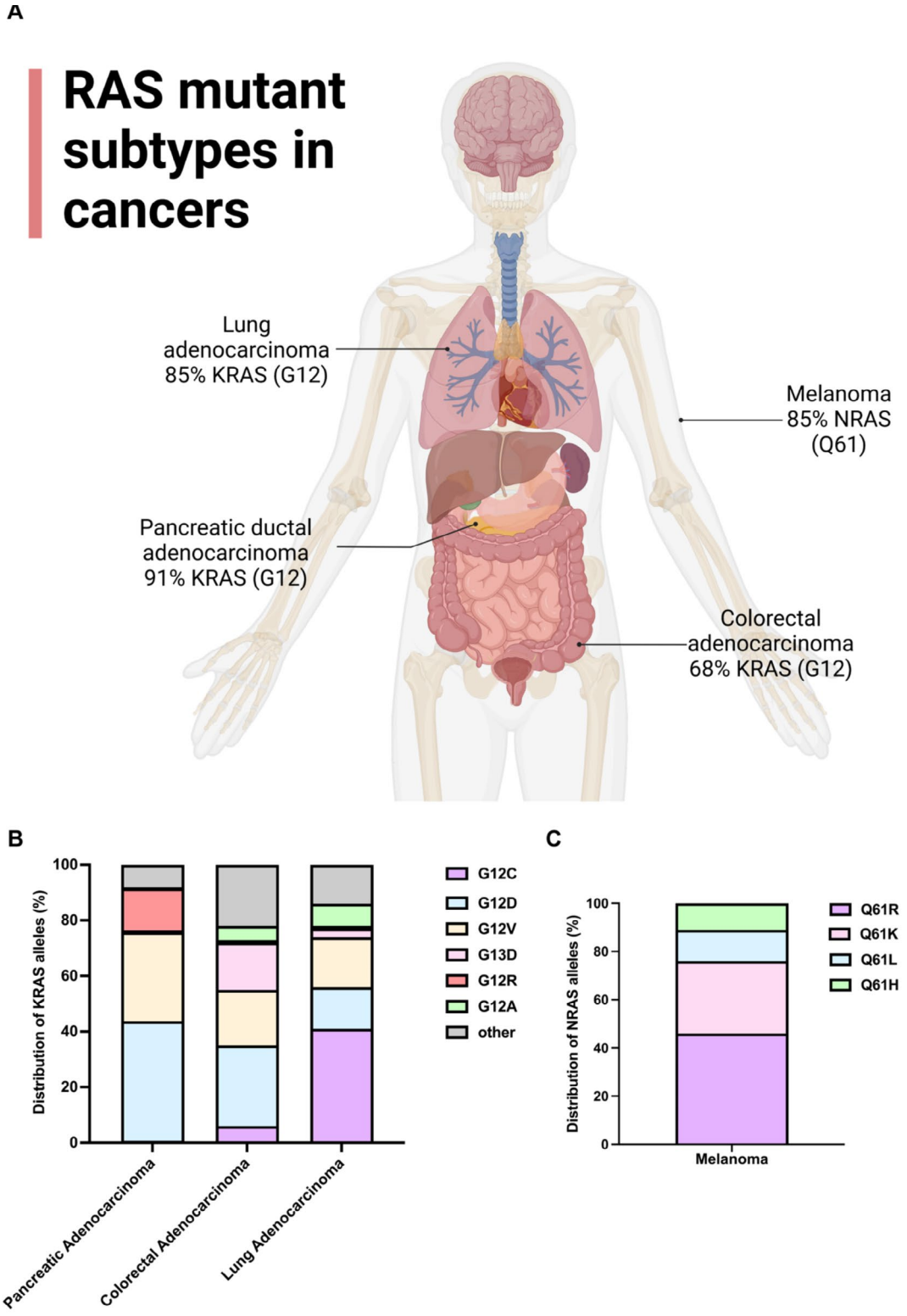

Fig. 3 RAS mutant subtypes in pancreatic ductal adenocarcinoma, colorectal cancer, lung adenocarcinoma, and melanoma. (**A**) The most common RAS mutant subtypes found in PDAC, CRC, LUAD, and melanoma include: PDAC: $KRAS^{G12D}$; CRC: $KRAS^{G12V}$; LUAD: $KRAS^{G12C}$; Melanoma: $NRAS^{Q61R}$; (**B**) The prevalence and types of KRAS mutations in codons 12 and 13 across pancreatic cancer, colorectal cancer, and lung adenocarcinoma show a significant frequency of $KRAS^{G12D}$ and $KRAS^{G12V}$ mutations, with $KRAS^{G12C}$ being less common. (**C**) The frequency and types of NRAS mutations in codon 61 in melanoma predominantly include $NRAS^{Q61R}$, along with other alterations such as $NRAS^{Q61K}$, $NRAS^{Q61L}$, and $NRAS^{Q61H}$. PDAC: pancreatic ductal adenocarcinoma; CRC: colorectal cancer; LUAD: lung adenocarcinoma

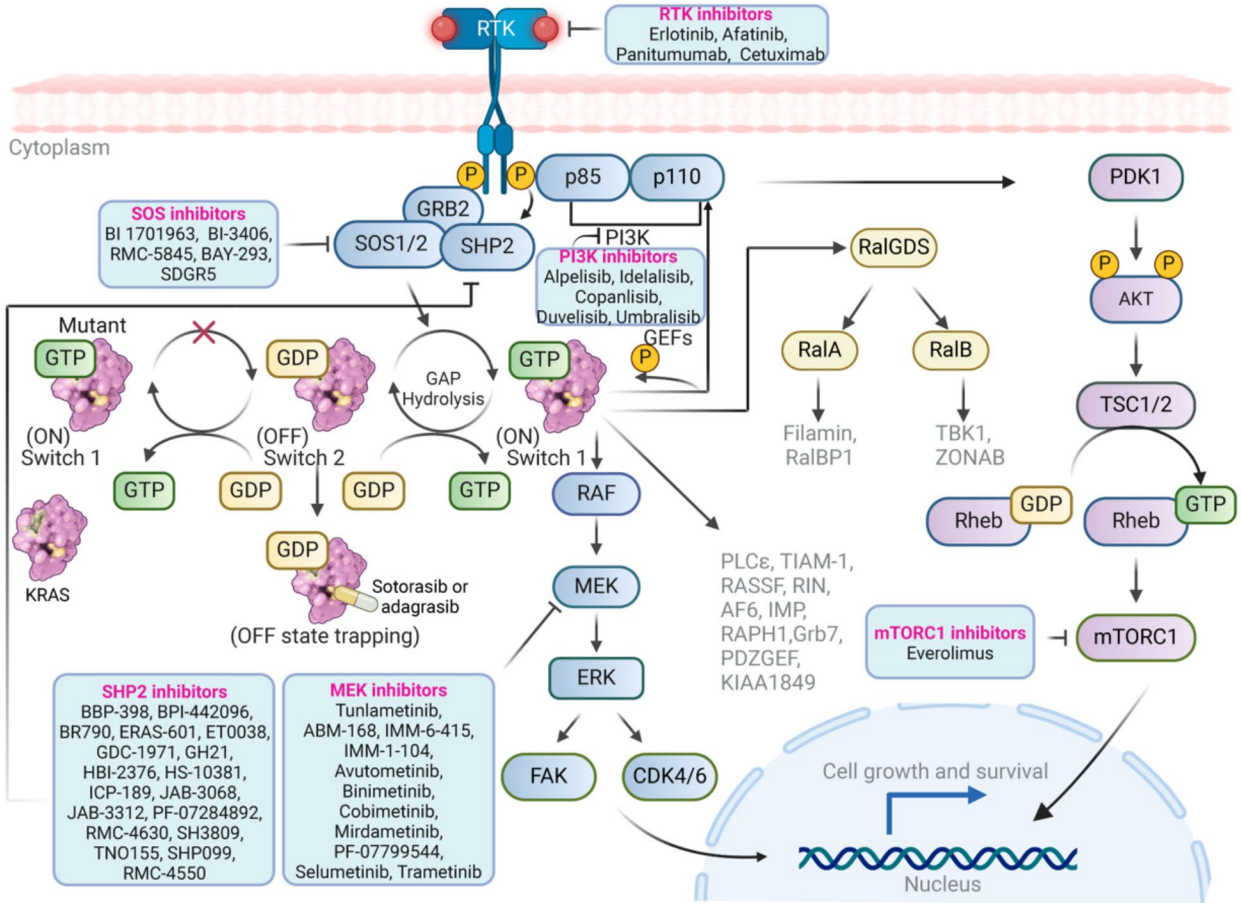

Fig. 4 An overview of the various RAS signal transduction pathways and therapeutic approaches for RAS-mutant tumors. Activation of RTKs promotes the exchange of GDP for GTP in RAS, thereby activating RAS. GTP-bound RAS binds to and activates the effector RAF, which initiates the MAPK signaling cascades. Targeting RTKs can reduce the activation of RAS populations. Inhibition of SOS or SHP2 decreases the GDP–GTP exchange rate, leading to a reduction in the GTP-bound RAS population. Another effector, p110, activates the PI3K signaling cascades. Both the MAPK and PI3K signaling cascades can be inhibited at each kinase tier. ERK: Extracellular signal-regulated kinase; FAK: Focal adhesion kinase; GEFs: Guanine nucleotide exchange factors; MEK: Mitogen-activated protein kinase kinase; PDK1: 3-Phosphoinositide Dependent Protein Kinase-1; PI3K: Phosphatidylinositol 3-kinase; RAF: Rapidly accelerated fibrosarcoma; RalGDS: Ral guanine nucleotide dissociation stimulator; RAS: Rat sarcoma virus; RTK: Receptor tyrosine kinase; SH3: SRC homology 3 domain; SOS: Son of sevenless

RAS effectors include RalGDS, PLCε, and the Rho guanine nucleotide exchange factor TIAM1, among others (Fig. 4). All of these effectors are associated with cell proliferation, differentiation, cell cycle regulation, metabolic changes, and cell survival [47].

In conclusion, the activation of the RAS signaling cascade is a pivotal process in regulating cell proliferation, differentiation, and survival. Upon activation, RAS proteins trigger a complex network of downstream pathways, including the MAPK and PI3K pathways, which play crucial roles in cellular responses to external stimuli. Dysregulation of RAS signaling, particularly through mutations in RAS genes, is a common driver of oncogenesis, leading to uncontrolled cell growth and tumor development. A deeper understanding of RAS activation mechanisms and its signaling cascades provides important opportunities for developing targeted therapies aimed at inhibiting aberrant RAS activity, especially in cancers driven by RAS mutations.

Role in carcinogenesis

Metabolic programming is crucial for RAS-induced cell proliferation and carcinogenesis. RAS signaling enhances nutrient flux in cancer by participating in central carbon metabolism and increasing glucose uptake and glycolysis, thereby providing a competitive advantage to cancer cells [48]. It also promotes multiple branching biosynthetic pathways and regulates overall mitochondrial function by inducing mitophagy, which can delay tumor progression associated with damaged mitochondria [35]. In oncogenic KRAS-induced cancer growth, glycolytic ATP generation is essential for survival under hypoxic conditions, while aerobic glycolysis is likely important for providing glycolytic intermediates necessary for nucleotide and

phospholipid synthesis. Additionally, KRAS promotes the glutamine-fueled tricarboxylic acid (TCA) cycle, leading to the production of ATP, ROS, NADPH, amino acids, nucleotides, and lipids. This process is crucial for RAS-induced tumorigenicity, as it supplies substrates to the TCA cycle from amino acids and other sources, such as fatty acid oxidation [48]. Additionally, RAS signaling contributes to oncogenesis and tumor progression by inducing fatty acid oxidation, which mediates pro-tumorigenic M2 macrophage polarization [49].

Upstream of the RAS signaling pathways are primarily composed of cell surface receptors, such as the EGFR and human ERBB2, which receive external signals and transmit these signals through KRAS. This biological process primarily promotes cell proliferation and migration [50, 51].

As mentioned earlier, KRAS functions as a switch for GDP-GTP regulation, controlling the cytoplasmic signaling network and various normal cellular processes. Two splice variants of KRAS, KRAS4A and KRAS4B, have been identified, both of which are essential for tumor initiation and likely have specific roles in the tumor microenvironment. For example, KRAS4B is typically expressed at higher levels and is found in both stem and progenitor cells, while the expression of KRAS4A increases tumor cell adaptation to stressors, such as hypoxia [52]. However, recent studies have shown that KRAS4A is widely expressed, and tumors can adapt to express KRAS4A through splicing during times of stress. These findings prompt a renewed focus on the role of KRAS4A in tumorigenesis and shift the perspective on KRAS inhibition, as KRAS4A now requires careful consideration [26, 53]. It is reported that KRAS4A and KRAS4B differ only in their C-terminal membrane-targeting region [53]. The unique membrane-anchoring mechanisms of KRAS4A and KRAS4B suggest variations in their dynamics of association with the cell membrane. Recent studies have uncovered isoform-specific interactions between KRAS4A and the RAS effectors Sin1 and hexokinase I [54, 55]. These isoform-specific interactions are likely attributed to the distinct localization of KRAS4A and KRAS4B in separate membrane environments, mediated by their unique HVRs [56]. Researchers also demonstrated the contrasting activation patterns of downstream signaling pathways between the two KRAS isoforms, attributable to their divergent HVRs [56]. Furthermore, the presence of hotspot oncogenic mutations at positions 12, 13, and 61 in both KRAS4A and KRAS4B poses a significant challenge for targeted therapies due to variations in their structures and functions [56]. Therefore, future studies should focus on delineate the distinct signaling properties of KRAS4A and KRAS4B to develop novel therapeutic strategies that effectively target both splice variants.

The downstream signaling pathways mediated by KRAS have been discussed previously. In the RAS-RAF-MEK-ERK pathway, KRAS-GTP is typically activated by various extracellular stimuli, including growth factors, hormones, cytokines, and environmental stresses. Following RAS activation, the serine/threonine kinases of RAF are recruited to the cell membrane, where their C-terminal catalytic domain binds to MEK1/2 and phosphorylates multiple serine residues on these two proteins. MEK1/2 are dual-specificity kinases that phosphorylate both tyrosine and threonine/serine residues, leading to the activation of ERK1/2. The activation of the RAS-RAF-MEK-ERK cascade plays a crucial role in promoting cancer cell proliferation, survival, migration, and angiogenesis [57]. In another pathway, the PI3K-AKT-mTOR pathway, RTKs, cytokine receptors, integrins, and GPCRs activate KRAS-GTP, which then binds to and activates PI3K. Activation of PI3K stimulates the phosphorylation of its phospholipid substrate, PIP2, to produce PIP3. This lipid interacts with AKT, promoting its phosphorylation and activation by PDK1. The activation of AKT subsequently activates mTOR, thereby regulating cell growth, survival, and metabolism [58, 59] (Fig. 4).

Clinical implications of RAS mutations in different cancer types

As mentioned above, the widespread prevalence of activating RAS mutations across various malignancies has been recognized. Among these, KRAS is the most frequently altered, followed by NRAS and HRAS. For instance, KRAS mutations occur in approximately 59.24% of pancreatic cancers, 36.2% of colorectal cancers, and 26.68% of LUAD [12] (Table 1). In clinical settings, RAS mutational status is associated with various clinicopathological characteristics, prognosis, and treatment efficacy (Table 1).

NSCLC

In LUAD, activating missense KRAS mutations are typically mutually exclusive with other clinically recognized driver mutations, such as those in EGFR and ALK [60, 61]. An early study of LUAD patients indicated that the presence of KRAS point mutations in codon 12 serves as an unfavorable prognostic factor [62]. One study found that patients with LUAD harboring the $KRAS^{G12C}$ mutation were more frequently associated with invasive mucinous adenocarcinoma and solid predominant tumors. These patients also had increased lymphovascular invasion, higher programmed death-ligand 1 (PD-L1) expression, and exhibited a potentially aggressive phenotype correlated with early and locoregional recurrence [63]. Regarding prognostic value, it was also shown that $KRAS^{G12C}$ is an independent prognostic factor in stage I tumors and part-solid lesions [63]. Similarly, a recent

Table 1 Clinicopathological features, prognosis and treatment efficacy of patients with RAS mutations

Tumor type	The most common RAS mutation	Mutation rate	Clinicopathologic features	Prognosis & Treatment efficacy	References
LUAD	KRAS	26.68%	More mucinous type; frequent poorly- differentiated grade; solid pattern tumors preference; female sex (controversial)	Unfavorable prognostic factor (controversial); a negative predictor of response to TKIs (controversial); a positive predictor of response to ICIs	[60–76]
PDAC	KRAS	59.24%	Limits antitumor immunity	A worse prognosis; predictive for the efficacy of erlotinib (controvisal)	[77–85]
CRC	KRAS	36.2%	Villous histology preference; advanced adenomas; older age; more common in lung and brain metastases	A worse prognosis; poor clinical outcomes from TKIs treatment; a negative predictor of response to ICIs	[86–97]
Melanoma	NRAS	25.9%	Presence of mitoses; lower TIL grade; anatomic site other than scalp/necks; advanced stages	Poorer melanoma-specific survival; poor clinical outcomes from ICIs treatment	[98–101]
Thyroid cancer	HRAS	8.13%	Poor or undifferentiated	Poor prognosis	[102]
Cholangiocarcinoma	KRAS	5.56%	Higher M1 macrophage activation; higher interferon-γ expression; the development of extrahepatic metastasis	Worse overall survival; the resistance to FGFR inhibitors; affecting the responsiveness to interferon immune signals	[34, 103, 104]
CMML	NRAS	8%	A high risk of progression	Resistance after HMA therapy	[105]

**Abbreviations* LUAD: Lung adenocarcinoma; PDAC: Pancreatic ductal adenocarcinoma; TKIs: Tyrosine kinase inhibitors; ICIs: Immune checkpoint inhibitors; CRC: Colorectal cancer; TIL: Tumor-infiltrating lymphocyte; FGFR: Fibroblast growth factor receptor; CMML: Chronic myelomonocytic leukemia; HMA: Hypomethylating agent. The data involved in the most common RAS mutation as well as mutation rate are from the cBioportal TCGA (available via the cBioPortal for Cancer Genomics)

observational study indicated that detectable $KRAS^{G12C}$ is considered a marker of poor prognosis in lung cancer [64]. Although $KRAS^{G12D}$-mutant lung adenocarcinoma also exhibits similar clinical features to $KRAS^{G12C}$, such as a higher prevalence in males, former or current smokers, radiologically solid tumors, and invasive mucinous adenocarcinoma [65]; In terms of prognosis, $KRAS^{non-G12D}$ mutations appear to be worse prognostic factors, particularly in stage I tumors. In contrast, $KRAS^{G12D}$ mutations do not seem to be associated with clinical outcomes in resected stage I-III LUAD [65]. However, some studies have reported conflicting results. Evidence suggests that a significant number of KRAS-mutant lung cancers occur in never smokers, and there is a higher frequency of $KRAS^{G12C}$ mutations in women [66]. Pooled analyses of early-stage resected NSCLC suggest that KRAS mutation status is not a significant prognostic factor [67]. Mucinous adenocarcinomas with KRAS mutations were also found to be more frequently located in the lower lung lobes, exhibiting a lower frequency of nuclear atypia and a reduced proportion of geminin-positive cells [68]. Notably, KRAS mutations have been considered indicators of resistance to therapy with EGFR tyrosine kinase inhibitors (TKIs), such as erlotinib, as well as to conventional chemotherapy in NSCLC [69–72]. Dissenting reports showed the negative impact of KRAS mutations on the response to EGFR-TKIs. Therefore, the current evidence is not enough to use the KRAS mutation statues to recommend the selection of patients for anti-EGFR treatment in NSCLC. Additionally, KRAS mutations have been observed in the progression of other EGFR-TKIs, albeit with a low prevalence of approximately 1% [73]. However, a subgroup analysis of OS indicated that immune checkpoint inhibitors (ICIs), such as nivolumab, were favored among patients with RAS mutation-positive status [74]. Furthermore, several studies have reported similar findings, particularly among patients with co-existing PD-L1 expression of 50% or higher [75, 76]. However, these findings require further validation before they can be incorporated into routine patient management.

PDAC

In PDAC, two studies have reported that the $KRAS^{G12V}$ mutation (not $KRAS^{G12D}$) detected in plasma and serum is associated with poor survival, partly due to a high circulating proportion of regulatory T cells (Tregs) [77, 78]. However, more studies have shown that KRAS mutations, particularly the G12D mutation subtype in circulating tumor DNA (ctDNA), are independent predictors of poor prognosis and could also serve as early biomarkers of treatment response [79–82]. However, some studies present conflicting results. One study suggested that KRAS mutation status is more predictive than prognostic in advanced pancreatic cancer, suggesting that KRAS mutation status may be more useful for predicting how a patient will respond to treatment rather than determining their overall prognosis or survival outcome [83], other studies have suggested that KRAS WT status provides a significant advantage in OS for patients with PDAC treated with gemcitabine/nimotuzumab or gemcitabine/erlotinib, compared to those with KRAS

mutations [84, 85]. Therefore, before a definitive conclusion can be reached regarding the impact of KRAS mutations on prognosis in PDAC, further research and additional investigations are required.

CRC

In CRC, RAS mutations are associated with more aggressive biological behaviors compared to their WT counterparts. These include a higher prevalence in mucinous tumor types, an increased tendency for lung metastases, and a preference for primary tumors to occur on the right side [86]. As a result, a study observed that KRAS mutations were independently associated with tumor location, and patients harboring KRAS or NRAS mutations in CRC demonstrated shorter OS [87]. Additionally, the metastatic potential of CRC varies with the presence of RAS mutations; these mutations are more frequently found in lung and brain metastases, whereas RAS WT CRC shows a significantly higher cumulative incidence of liver metastases [88, 89]. It is important to note that in patients with colorectal liver metastases, RAS mutations are independently associated with worse recurrence-free survival (RFS) and OS following repeat hepatectomy (RH) [90–92]. Notably, KRAS WT status predicts survival and is associated with an early radiological response to anti-EGFR therapies, such as cetuximab and panitumumab [93–95]. Reportedly, in a colorectal cancer mouse model, KRAS mutations are associated with suppressed Th1/cytotoxic immunity. Specifically, $KRAS^{G12D}$–mediated repression of IRF2 contributes to the resistance of colorectal cancer to anti–PD-1 therapy [96, 97]. Therefore, whether RAS mutational status should be considered prior to initiating ICI treatment requires further investigation.

Other malignancies

RAS mutational status also correlates with clinicopathological features in various other cancer types, including melanoma, thyroid cancer, cholangiocarcinoma, myeloid leukemia, and women's cancers. In melanoma, NRAS mutations are associated with the presence of mitoses, lower tumor-infiltrating lymphocyte (TIL) grade, locations in the extremities (such as brisk lesions) rather than on the scalp or neck, advanced American Joint Committee on Cancer (AJCC) stages, and poorer melanoma-specific survival [98–100]. A recent study reported that NRAS-mutant cutaneous melanoma is associated with a worse prognosis compared to WT melanoma when treated with ICIs. It also showed an increased recurrence in both primary and relapsed cases, although OS was similar between the subgroups [101]. In thyroid cancer, RAS mutations are indicative of aggressive biological behavior, including poor differentiation or undifferentiated characteristics, and are associated with a poorer prognosis [102]. In cholangiocarcinoma, KRAS and NRAS mutations are associated with a pattern indicative of a more immune-inflamed microenvironment, characterized by higher M1 macrophage activation and increased interferon-γ expression compared to WT tumors [34]. Additionally, RAS mutations mediate resistance to FGFR inhibitors in FGFR2 fusion-positive cholangiocarcinoma [103]. KRAS mutations are also linked to aggressive behavior in intrahepatic cholangiocarcinoma (ICC), including the development of extrahepatic metastasis. These mutations affect the responsiveness of tumor cells to interferon immune signals and are associated with poor prognosis following surgical resection [104]. In chronic myelomonocytic leukemia (CMML), mutations in the RAS pathway are associated with a high risk of disease progression and resistance following treatment with hypomethylating agents (HMAs), the current standard of care for this condition [105]. In female cancers like ovarian cancer, activating KRAS mutations are frequently found in low-grade ovarian carcinomas, those at less advanced clinical stages, and in the mucinous histological subtype [106]. These findings indicate that patients with RAS mutations exhibit unique clinicopathological characteristics and have varying treatment responses depending on the specific tumor type and targeted therapies employed.

RAS proteins with alterations at codons 12, 13, or 61 result in a locked state of the enzyme in its GTP-bound, activated form, which is considered oncogenic [107]. However, recent studies indicate that each RAS mutation exhibits functional differences [108]. For example, the mutational status of KRAS is widely recognized as a predictor of resistance to therapy with EGFR antibodies, such as cetuximab [109–111]. However, retrospective analyses show that patients with KRAS codon 13 mutations, unlike those with codon 12 mutations, may benefit from cetuximab therapy [112]. Furthermore, in the colonic epithelium, the expression of $KRAS^{G12D}$, but not $NRAS^{G12D}$, stimulated hyperproliferation [113]. The expression of $NRAS^{Q61R}$ in melanocytes induced the development of melanomas, whereas the expression of $NRAS^{G12D}$ in these cells did not promote melanoma formation [108]. Therefore, both the specific isoform and the codon mutation should be taken into account when designing strategies to target RAS-driven cancers.

In summary, the clinical implications of RAS mutations can vary depending on the specific mutation and tumor type, which partly explains the conflicting results observed in different studies. Further research examining various mutant types is needed to evaluate the true clinical significance of RAS mutations in tumors.

RAS suppression strategies

Targeting RAS directly

For patients with RAS-mutant cancers, directly inhibiting RAS is a desirable treatment approach. The timeline of RAS inhibitor discovery is illustrated in Fig. 5. We also emphasize the recent development of various RAS inhibitors in this field, including mutant-specific RAS ($KRAS^{G12C}$) switch-II covalent inhibitors, therapies targeting $KRAS^{G12D}$, pan/multi-RAS/KRAS inhibitors, and immune therapies (Fig. 6).

From the RAS discovery to the clinical development of $KRAS^{G12C}$ inhibitors

In mouse development, KRAS is essential, whereas HRAS and NRAS are not required [114, 115]. As shown in Fig. 5, research on the direct inhibition of KRAS mutations can be traced back to the period from 1964 to 1978, when retroviral isolates were observed and subsequently identified to carry *ras* oncogenes [1, 116–118]. In the spring of 1982, the laboratories of Robert Weinberg, Michael Wigler, and Mariano Barbacid reported the molecular cloning of a human transforming gene from bladder carcinoma cell lines [119–121]. By the autumn of 1982, the nucleotide sequences of the HRAS and KRAS oncogenes were published, marking a shift in the field toward the recently isolated human oncogenes. NRAS was subsequently identified in 1983 [4]. Then, in 1995, one of the earliest examples of rational drug design based on *ras* oncogene research emerged with the development of peptidomimetic inhibitors of mammalian

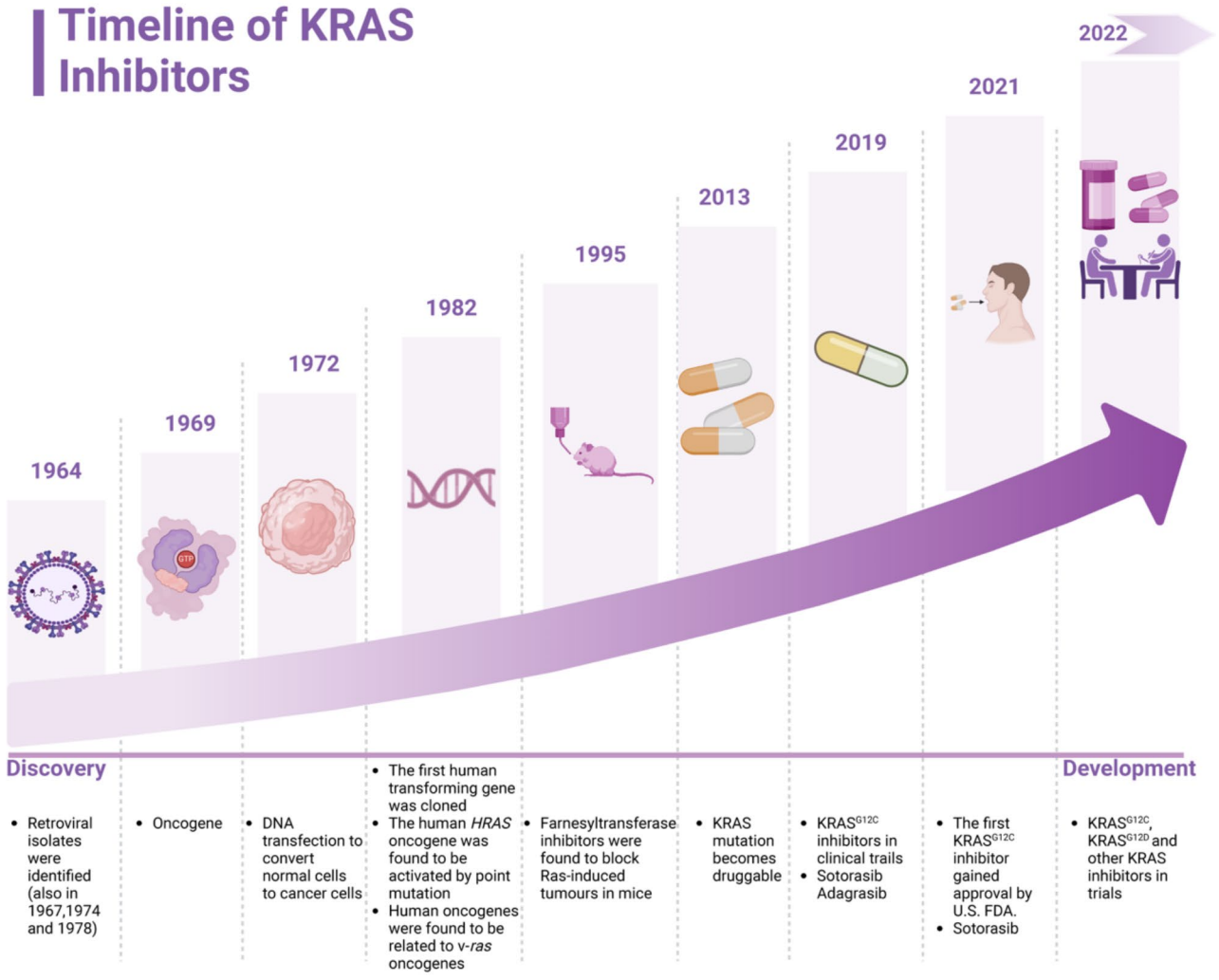

Fig. 5 The timeline from the discovery of RAS to the development of KRAS inhibitors is as follows. 1964 to 1978: The ras oncogenes were identified; 1982: The nucleotide sequences of the HRAS and KRAS oncogenes were published; 1983: NRAS was identified; 1995 to 2013: RAS was historically considered "undruggable."; 2021: The first $KRAS^{G12C}$ inhibitor received approval from the Food and Drug Administration (FDA). Recently, numerous preclinical and clinical studies have focused on RAS inhibitors and their associated resistance mechanisms

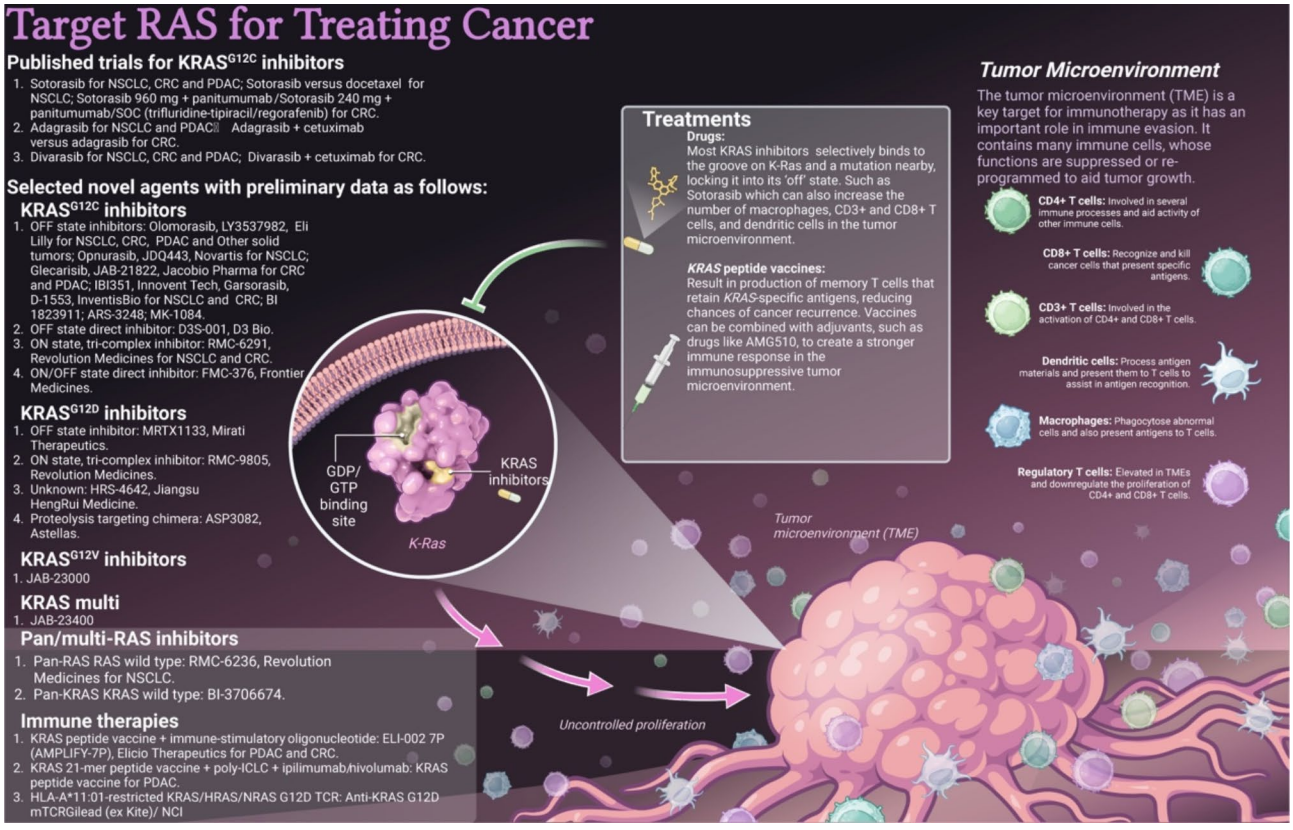

Fig. 6 Therapeutic approaches to target RAS in cancer. This includes various strategies to target RAS mutations, particularly: $KRAS^{G12C\ Inhibitors}$: Data from clinical trials demonstrate their efficacy; $KRAS^{G12D}$ Inhibitors: Targeting this specific mutation to provide therapeutic benefit; $KRAS^{G12V}$ Inhibitors: Developing agents to inhibit this variant effectively; Multi-KRAS Inhibitors: Agents designed to target multiple KRAS mutations simultaneously; Pan/Multi-RAS Inhibitors: Broader inhibitors that target various RAS isoforms and mutations; Immune Therapies: Approaches that harness the immune system to target RAS-driven tumors. These diverse therapeutic strategies aim to improve outcomes for patients with RAS-mutant cancers

farnesyltransferase (FT). These inhibitors were found to block RAS-induced tumors in mice [122, 123]. However, targeting RAS farnesylation is not ideal, as many other proteins are also farnesylated. Nevertheless, tipifarnib, a farnesyltransferase inhibitor (FTI), has shown encouraging clinical activity for hematological malignancies, particularly in relapsed or refractory peripheral T-cell lymphoma (PTCL), and is currently being evaluated in clinical trials (NCT02464228) [124]. In solid tumors, such as NSCLC, tipifarnib has been identified as one of the most effective drugs in preventing relapse to targeted therapies, including EGFR-TKIs (such as erlotinib or osimertinib), the $KRAS^{G12C}$ inhibitor (sotorasib), ALK-EML4 inhibitors (such as lorlatinib), and $BRAF^{V600E}$ inhibitors (such as dabrafenib) [125]. These findings pave the way for the combination of FTIs and targeted therapies.

Small molecule inhibitors targeting RAS have faced challenges due to the lack of an adequate binding pocket, leading to several decades of effort in drug discovery. In 2013, the laboratory of K. Shokat made a significant breakthrough in targeting KRAS [126]. They screened for $KRAS^{G12C}$-specific small molecules that irreversibly bind to the cysteine at the mutation site and selectively target the $KRAS^{G12C}$-GDP inactive state [126]. Therefore, inhibitors of this type do not affect RAS signaling in non-malignant cells, theoretically resulting in a low risk of on-target, off-tumor toxicities [126–128]. In 2019, sotorasib became the first clinical $KRAS^{G12C}$ inhibitor to enter trials for advanced solid tumors [129]. As illustrated in Fig. 3B, $KRAS^{G12C}$ mutations primarily occur in NSCLC and CRC. Following the success of clinical trials, such as the CodeBreaK100 study and the phase 1/1b KRYSTAL-1 study in NSCLC and CRC, the U.S. FDA granted accelerated approval for sotorasib in May 2021 and for adagrasib in December 2022 [16, 130–132]. Recent results from the CodeBreak 200 study, a randomized, open-label, phase 3 trial, demonstrated a modest progression-free survival (PFS) benefit of sotorasib compared to docetaxel (5.6 months versus 4.5 months, $p=0.0017$), meeting its primary endpoint. However, OS, which was a key secondary endpoint, did not show improvement for patients with previously treated metastatic NSCLC [15]. The U.S. FDA review raised concerns about potential biases, necessitating a new confirmatory phase 3 study to secure full regulatory approval [12]. Although $KRAS^{G12C}$ mutations

are infrequent (approximately 1–2% of cases), recent data showed that advanced pancreatic cancer treated with sotorasib demonstrated a PFS of 4.0 months, an OS of 6.9 months, and an objective response rate (ORR) of 21%. In contrast, adagrasib suggested slightly higher response rates, with a PFS of 5.4 months, an OS of 8.0 months, and an ORR of 33% [18, 133]. The differences in response rates may be attributed to potential biases, such as the limited number of patients enrolled in the studies. Notably, in these settings, patients were heavily pretreated, with a median of 2–3 prior lines of therapy. Based on these data, both sotorasib and adagrasib have been included as approved agents in the National Comprehensive Cancer Network (NCCN) guidelines for PDAC.

Recent data on the newer $KRAS^{G12C}$ selective inhibitor divarasib, which was designed for high potency and selectivity in solid tumors, demonstrated confirmed responses with a PFS of 13.1 months in NSCLC and 5.6 months in CRC [134]. Additionally, a 36% partial response rate (PCR) was observed in PDAC with the use of divarasib [134]. Increased drug potency observed with single-agent divarasib and adagrasib compared to sotorasib is reflected in slightly higher objective response rates (ORRs) and longer PFS, despite the small number of patients enrolled in the studies. Recent data on novel G12C inhibitors in NSCLC, CRC, and PDAC are also promising. For instance, Opnurasib demonstrated an ORR of 42% and a disease control rate (DCR) of 93% in NSCLC ($n=24$; NCT04699188). IBI351 showed an ORR of 46.6% and a DCR of 90.5% in NSCLC ($n=116$; NCT05005234) and an ORR of 47.5% and DCR of 85% in CRC ($n=40$; NCT05005234). Additionally, Olomorasib achieved an ORR of 42% and a DCR of 92% ($n=24$; NCT04956640), while Glecarisib exhibited an ORR of 42% and a DCR of 93.5% in PDAC ($n=31$; NCT05002270). Notably, Glecarisib also demonstrated significant anti-tumor activity in CRC, with an ORR of 33.3% and a DCR of 90.9% ($n=33$; NCT05002270) (Fig. 6).

Preliminary data from Phase I/II trials indicate that garsorasib, which has high oral bioavailability and CNS penetration, demonstrates promising antitumor activity in NSCLC patients with brain metastases [135]. Notably, 33–42% of patients with $KRAS^{G12C}$-mutated NSCLC are initially diagnosed with CNS metastases [136, 137]. Adagrasib is the only $KRAS^{G12C}$ inhibitor with reported activity data in untreated CNS metastases, demonstrating a CNS ORR of 42% and a PFS of 5.4 months ($n=19$). The CNS failure rate was 37% (7 out of 19 patients), with only two patients experiencing CNS progression in the KRYSTAL-1 trial [138]. Therefore, Adagrasib may currently be the first choice for patients with $KRAS^{G12C}$-mutant NSCLC. However, Phase 3 studies will be necessary to provide further guidance for clinical practice.

Next batter up! From targeting $KRAS^{G12D}$ and pan-RAS inhibitors to emerging therapeutics

As mentioned earlier, $KRAS^{G12C}$ mutations represent only a subset of KRAS mutations, primarily found in LUAD. To effectively target KRAS mutations, it is essential to develop strategies against other prevalent specific mutations, such as $KRAS^{G12D}$. With the emergence of allele-specific $KRAS^{G12C}$ inhibitors, there is a growing focus on $KRAS^{G12D}$ inhibitors, pan/multi-RAS/KRAS inhibitors, and novel immunotherapies, including KRAS peptides and vaccines, which are currently being tested in patients and entering clinical trials [139–142] (Fig. 6).

Targeting $KRAS^{G12C}$ is achievable by designing a reactive warhead that forms an irreversible covalent bond with the mutant cysteine-12 residue [143, 144]. Due to the absence of reactive cysteines in the active site of $KRAS^{G12D}$ mutations, alternative approaches are being developed for these inhibitors. Since KRAS transitions between a GTP-bound ON state and a GDP-bound OFF state, developing inhibitors for specific mutations requires evaluating which state to target. MRTX1133 is the first noncovalent, potent, and selective inhibitor for $KRAS^{G12D}$ in its OFF state. It binds to the switch II pocket, inhibiting nucleotide exchange and preventing protein-protein interactions with the effector RAF [145]. Although MRTX1133 does not form a covalent bond, it demonstrates significant anti-cancer properties and is set to enter clinical trials in June 2024 (NCT05737706). In contrast, RMC-9805, a selective and orally bioavailable $KRAS^{G12D}$ (ON) inhibitor, first establishes a noncovalent bond between $KRAS^{G12D}$ and cyclophilin A, which subsequently allows a "cool" nonreactive covalent warhead to slowly bind to the mutant aspartate. RMC-9805 has also entered clinical trials in September 2023 (NCT06040541). Additionally, the $KRAS^{G12D}$ degrader ASP3082 is currently in Phase 1 clinical trials (NCT05382559). This degrader works by binding $KRAS^{G12D}$ to an E3 ligase, leading to the degradation of the protein. Another $KRAS^{G12D}$ inhibitor, HRS-4642, forms a salt bridge with KRAS's Asp12 [146]. Although HRS-4642 exhibits similar binding affinity for both GDP-bound and GTP-bound $KRAS^{G12D}$, crystallographic studies reveal the structural basis of inhibitor binding, which induces changes in the switch II pocket of $KRAS^{G12D}$ [146]. Recent data from the Phase 1 clinical trials of HRS-4642 in China (NCT05533463) demonstrate encouraging efficacy in NSCLC, showing a 10% ORR and a 90% DCR ($n=10$) [12]. Further studies are necessary to identify the factors that predict responses to $KRAS^{G12D}$ inhibitors and to determine which combination therapies are likely to be effective for different cancer types. Additionally, with the advancement of allele-specific KRAS inhibitors, it is essential to conduct head-to-head comparisons

between KRAS alleles to better characterize the allele-specific effects on tumor biology [33].

Selectivity for KRAS was achieved through direct and/or indirect constraints imposed by the evolutionary divergence among RAS isoforms in three residues within the G domain [147]. Therefore, developing pan-RAS/KRAS inhibitors that preferentially target the inactive state of RAS/KRAS is crucial to prevent reactivation through nucleotide exchange. These pan-RAS inhibitors can address mutations across all RAS isoforms, thereby potentially benefiting the largest patient population. RMC-6236 is a potent, orally bioavailable multi-RAS (ON) inhibitor, selective for the active RAS (ON) form of both wild-type and mutant variants of the canonical RAS isoforms (HRAS, NRAS, and KRAS). It is currently undergoing Phase 1 clinical trials (NCT05379985). Recent reports indicate encouraging clinical activity signals in NSCLC with an ORR of 38% and a DCR of 85% (n=40), as well as in PDAC with an ORR of 20% and a DCR of 87% (n=46) [12]. However, pan-RAS inhibitors may carry a higher risk of toxicity, as they inhibit signaling through wild-type KRAS, NRAS, and HRAS isoforms. Consequently, it is rational to develop a new class of pan-KRAS inhibitors (also referred to as pan-KRAS-selective inhibitors) that target most wild-type and mutant KRAS isoforms while sparing NRAS and HRAS. The first pan-KRAS-selective inhibitor, BI-2865, along with its close analogue BI-2493, selectively binds to KRAS through an interaction with His 95, one of the four amino acids in the switch II binding pocket that vary among isoforms [148]. BI-3,706,674 is a pan-KRAS OFF state inhibitor that is currently undergoing Phase 1 clinical trials, although no published data are available yet (NCT06056024). Therapeutic nucleic acid-based approaches, including small interfering RNAs (siRNA), also hold promise for developing drugs targeting KRAS. One such clinical drug candidate, AZD4785, is a potent 2′-4′ constrained ethyl-modified antisense oligonucleotide inhibitor that selectively targets KRAS. It has the ability to target al.l mutant isoforms of KRAS, offering significant therapeutic potential across various tumor types [149].

Multiple immunotherapeutic strategies for targeting RAS are emerging. Earlier data indicated that mutant RAS peptide vaccines can induce host T cell responses, with potentially improved survival observed in a small single-arm study [150]. In 2016, a case was reported involving a CRC patient who received cytotoxic T cells targeting mutant $KRAS^{G12D}$, resulting in significant tumor regression [151]. Recently, researchers reported a case of a patient with progressive metastatic pancreatic cancer who achieved objective tumor regression after receiving T-cell receptor (TCR) gene therapy targeting the $KRAS^{G12D}$ driver mutation [152]. More recently, data from the Phase 1 AMPLIFY-201 trial in CRC and pancreatic cancer demonstrated that the lymph-node-targeted mutant KRAS-specific amphiphile vaccine (ELI-002 2P) was safe and induced significant T cell responses. Specifically, 84% of patients exhibited mutant KRAS-specific T cell responses, with 21 out of 25 patients showing responses (59% of whom had both CD4+and CD8+T cells) [142]. Additionally, the median RFS was reported to be 16.33 months [142]. Seven amphiphile-modified KRAS and NRAS peptides—G12D, G12R, G12V, G12A, G12C, G12S, and G13D (Amph-Peptides 7P)—are currently being investigated in a Phase 1/2 study, verified in July 2024 (NCT05726864). Similarly, several clinical trials are underway in Phase 1, including a KRAS peptide vaccine (NCT05013216) and an anti-$KRAS^{G12D}$ mTCR (NCT03745326).

As we know, after Phase 3 studies, drugs may advance to clinical use and inform therapeutic decisions. Accordingly, Table 2 outlines ongoing Phase 3 studies based on lines of therapy. Currently, only $KRAS^{G12C}$ inhibitors are in Phase 3 trials, which could potentially alter first-line therapy for NSCLC and second-line therapy for CRC in the future.

Finally, we summarize $KRAS^{G12C}$ inhibitors in Phase 1/2 clinical trials in Table 3, along with other inhibitors, including $KRAS^{G12D}$ inhibitors, pan-RAS/RAS wild-type inhibitors, pan-RAS inhibitors, and immune therapies currently in clinical trials, as outlined in Table 4.

Targeting upstream and downstream proteins

As illustrated in Fig. 4, the RAS signaling pathway consists of several upstream regulators and downstream effectors. Modifying one of these critical factors can serve as an indirect approach to inhibit RAS activation.

Targeting upstream mediators

The strategies include inhibiting upstream regulators, attenuating the SOS-RAS interaction, targeting the GN binding site, and repressing SHP2, as depicted in Fig. 4.

The upstream regulators of the RAS pathway include RTKs, such as the EGFR. erlotinib and afatinib are first-line EGFR-TKIs used to treat NSCLC patients with EGFR mutations. Additionally, cetuximab and panitumumab are EGFR monoclonal antibodies approved for use in metastatic CRC [153], while necitumumab is utilized for the treatment of squamous cell lung cancer [154]. Acquired KRAS mutations are widely recognized as a common mechanism of resistance to EGFR inhibitors in CRC [155], However, a study based on retrospective analyses found that KRAS codon 13 mutations may actually be associated with responsiveness to cetuximab therapy [112]. Recently, several novel drugs, including Amivantamab, Sunvozertinib, and Poziotinib, have emerged to target EGFR exon 20 insertion mutations in NSCLC

Table 2 $KRAS^{G12C}$ inhibitors in phase 3 clinical trials based on lines of therapy

Therapy lines	Tumor type	Stages	KRAS inhibitor	Trial details	Treatment arms
First-line	NSCLC (PD-L1 < 1%)	Advanced Stage IIIB/C/ IV	Sotorasib (OFF state inhibitor)	CodeBreaK 202 NCT05920356 *n* = 750	Carboplatin/pemetrexed/sotorasib versus carboplatin/pemetrexed/pembrolizumab
	NSCLC (PD-L1 TPS ≥ 50%)	Unresectable, locally advanced or metastatic non squamous	Adagrasib (OFF state inhibitor)	KRYSTAL-7 (phase 3) NCT04613596 *n* = 806	Pembrolizumab/adagrasib versus pembrolizumab
	NSCLC A: PD-L1 TPS ≥ 50% B: PD-L1 TPS 0–100%	Untreated advanced	Olomorasib (LY3537982) (OFF state inhibitor)	SUNRAY-01 NCT06119581 *n* = 1,016	A: Olomorasib/pembrolizumab versus pembrolizumab B: Olomorasib/platinum/pemetrexed/ pembrolizumab versus platinum/ pemetrexed/pembrolizumab
Second line	CRC	Metastatic	Sotorasib (OFF state inhibitor)	CodeBreaK301 NCT06252649 *n* = 450	FOLFIRI/sotorasib/panitumumab versus FOLFIRI ± bevacizumab
		Advanced	Adagrasib (OFF state inhibitor)	KRYSTAL-10 NCT04793958 *n* = 420	Adagrasib/cetuximab versus FOLFOX or FOLFIRI
Previously treated	NSCLC	Advanced	Adagrasib (OFF state inhibitor)	KRYSTAL-12 NCT04685135 *n* = 450	Adagrasib versus docetaxel
		Locally advanced or metastatic	Opnurasib (JDQ443) (OFF state inhibitor)	KontRASt-02 NCT05132075 *n* = 360	JDQ443 versus docetaxel

**Abbreviations* NSCLC: non-small cell lung cancer; CRC: colorectal cancer

[156–158]. Among these, Amivantamab, a bispecific antibody that directly targets both EGFR and the MET receptor, has received FDA approval based on the results of the CHRYSALIS clinical trial [159]. It is essential to understand how intrinsic and acquired KRAS mutations influence the antitumor activity of these emerging therapeutic approaches in clinical settings. Identifying these effects will help optimize treatment strategies and improve patient outcomes.

As noted earlier, SOS is a key member of the GEFs that catalyzes the conversion of RAS-GDP to RAS-GTP. Consequently, the development of inhibitors targeting the SOS-RAS interaction is receiving growing attention. A combination of fragment screening and high-throughput screening led to the identification of a small-molecule compound, BAY-293, which effectively disrupts the KRAS-SOS1 interaction. This disruption inhibits the reloading of KRAS with GTP, resulting in significant antiproliferative activity [160]. Additionally, BI-3406 is a highly potent and selective small-molecule SOS1 inhibitor that is orally bioavailable. It prevents the KRAS–SOS1 interaction by binding to the catalytic domain of SOS1, effectively limiting cellular proliferation [161]. Notably, BI-3406 increases the sensitivity of KRAS-mutant cancers to MEK inhibitors by preventing the feedback reactivation that often occurs with MEK inhibition [161]. Consequently, a recent report indicated that combining BI-3406 with adagrasib appears to be a promising strategy for overcoming both intrinsic and acquired resistance to $KRAS^{G12C}$ inhibitors [162]. The first inhibitor, BI-1,701,963, prevents the reactivation of KRAS and is currently undergoing clinical trials (NCT04111458).

The GN pocket appears to be an ideal target for drug design; however, the sub-nanomolar affinity of GTP and GDP for RAS, combined with their high intracellular concentrations, poses significant challenges for developing inhibitors that target this site. SML-8-73-1 is a GDP analogue specifically designed to interact with the GN-binding pocket of $KRAS^{G12C}$. Its prodrug derivative, SML-10-70-1, has demonstrated antiproliferative effects in both H23 and H358 cell lines (which are dependent on the G12C mutation and KRAS) as well as in A549 cells (which harbor a G12S mutation and are KRAS-independent) [128, 163]. Another small molecule KRAS agonist, KRA-533, activates KRAS by binding to the GTP/GDP-binding pocket, thereby preventing the cleavage of GTP into GDP [164]. KRA-533 effectively suppresses malignant growth by promoting apoptosis and autophagic cell death [164].

SHP2, encoded by the PTPN11 gene, is a non-receptor protein tyrosine phosphatase that plays a crucial role in signal transduction, promoting SOS1-mediated RAS-GTP loading. SHP099 is a moderately potent, selective, and orally bioavailable small-molecule inhibitor of SHP2. It effectively inhibits the proliferation of cancer cells both in vitro and in vivo by suppressing SHP2 activity [165]. SHP394 is an orally efficacious inhibitor of SHP2, designed to improve potency and enhance

Table 3 $KRAS^{G12C}$ inhibitors in phase 1/2 clinical trials

Phase	KRAS inhibitor	Trial details	Tumor type and No. of patients	Reported data
1/2	Sotorasib (OFF state inhibitor)	CodeBreaK 100 NCT03600883	NSCLC (*n* = 174) (131)	ORR: 37.1%; DCR: 80.6%; mPFS: 6.8 mo; mOS: 12.5 mo
			CRC (*n* = 62) (132)	ORR: 9.7%; DCR: 82.3%; mPFS: 4.0 mo; mOS: 10.6 mo
			PDAC (*n* = 38) (18)	ORR: 21%; DCR: 84%; mPFS: 4.0 mo; mOS: 6.9 mo
1/2	Adagrasib (OFF state inhibitor)	KRYSTAL-1 NCT03785249	NSCLC (*n* = 116) (16)	ORR: 42.9%; DCR: 50.5%; mPFS: 6.5 mo; mOS:12.6 mo
			CRC (*n* = 44 for adagrasib; 32 for adagrasib + cetuximab) (153)	**Adagrasib** ORR: 19%; mPFS: 5.6 mo; mOS: 19.8 mo **Adagrasib + cetuximab** ORR: 46%; mPFS: 6.9 mo; mOS: 13.4 mo:
			PDAC (*n* = 21); biliary tract cancers (*n* = 12) (133)	**PDAC** ORR: 33.3%; mPFS: 5.4 mo; mOS: 8.0 mo **biliary tract cancers** ORR: 41.7%; mPFS: 8.6 mo; mOS: 15.1 mo
1	Divarasib (OFF state inhibitor)	NCT04449874	NSCLC (*n* = 60); CRC (*n* = 55); PDAC (*n* = 7) (134)	**NSCLC** ORR: 53.4%; mPFS: 13.1 mo **CRC** ORR: 29.1%; mPFS: 5.6 mo **PDAC** ORR: 42.8%
1b	Divarasib + cetuximab	NCT04449874	CRC (*n* = 24 for KRASi-naive patients; *n* = 5 for Prior KRAS G12Ci) (154)	**KRASi-naive patients** ORR: 62.5%; mPFS: 8.1 mo **Prior KRAS G12Ci** 3 (60.0%)–PR; 2 (40.0%)–SD
1	Olomorasib (LY3537982; Eli Lilly) (OFF state inhibitor)	NCT04956640	NSCLC (*n* = 14); CRC (*n* = 32); PDAC(12) (*n* = 24); Other solid tumors (*n* = 11) (12)	**NSCLC** KRAS G12Ci naive: ORR 60% KRAS G12Ci treated: ORR 0% **CRC** ORR 9% **PDAC** ORR: 42% **Other solid tumors** ORR 36%
1/2	Opnurasib (JDQ443; Novartis) (OFF state inhibitor)	KontRASt-01 NCT04699188	NSCLC (*n* = 24) (12)	ORR 42%
1/2	Glecarisib (JAB-21822; Jacobio Pharma) (OFF state inhibitor)	NCT05002270	CRC (*n* = 33); PDAC (*n* = 31) (12)	**CRC** ORR 33.3% **PDAC** ORR 42%
2	IBI351 (Innovent Tech) (OFF state inhibitor)	NCT05005234 NCT05497336	NSCLC (*n* = 116); CRC (*n* = 40) (12)	**NSCLC** ORR: 46.6%; mPFS: 8.3 mo **CRC** ORR: 47.5%
1/2	Garsorasib (D-1553 InventisBio) (OFF state inhibitor)	NCT04585035	NSCLC (*n* = 74); CRC (*n* = 20) (12)	**NSCLC** ORR: 40.5% mPFS: 8.2 mo **CRC** ORR: 20.8%; mPFS: 7.6 mo
1	D3S-001 (D3 Bio) (OFF state inhibitor)	NCT05410145	No data	No data

Table 3 (continued)

Phase	KRAS inhibitor	Trial details	Tumor type and No. of patients	Reported data
1/2	FMC-376 (Frontier Medicines) ON/OFF state direct inhibitor	NCT06244771	No data	No data
1	RMC-6291 (Revolution Medicines) (On state inhibitor)	NCT05462717	NSCLC ($n=17$); CRC ($n=20$) (12)	**NSCLC** KRASi G12Ci naive: ORR 43%; KRASi treated: ORR 50% **CRC** ORR 40%

**Abbreviations* NSCLC: non-small cell lung cancer; CRC: colorectal cancer; PDAC: pancreatic ductal adenocarcinoma; mo: month; ORR: objective response rate; PFS: progression free survival; OS: overall survival

Table 4 Other inhibitors in clinical trials

Type of inhibitor	Phase	Inhibitor	Trial details	Tumor type and No. of patients	Reported data
$KRAS^{G12D}$	1/2	MRTX1133 (Mirati Therapeutics) (OFF state inhibitor)	NCT05737706	No data	No data
	1	RMC-9805 (Revolution Medicines) (ON state, tri-complex inhibitor)	NCT06040541	No data	No data
	1	HRS-4642 (Jiangsu HengRui Medicine) (Unknown)	NCT05533463	NSCLC ($n=10$); other solid tumors ($n=8$) (12)	**NSCLC** ORR: 10% **Other solid tumors** ORR: 0%
	1	ASP3082 (Astellas) (PROTAC)	NCT05382559	No data	No data
Pan-RAS/RAS wild-type inhibitor	1	RMC-6236 (Revolution Medicines) (ON state; tri-complex inhibitor inhibitor)	NCT05379985	NSCLC ($n=40$); PDAC ($n=46$) (12)	**NSCLC** ORR: 38% **PDAC** ORR: 20%
Pan-RAS inhibitor	1	BI-3,706,674 (OFF state inhibitor)	NCT06056024	No data	No data
Immune therapies	1/2	ELI-002 7P (AMPLIFY-7P) (Elicio Therapeutics) ($KRAS^{G12D/G12R/G12V/G12A/G12C/G12S/G13D}$ peptide vaccine + immune-stimulatory oligonucleotide)	NCT05726864	Adjuvant treatment biomarker reduction PDAC/CRC ($n=19$); Clearance of minimal residual disease ($n=4$); Polyfunctional mKRAS-specific T cell responses ($n=15$) (142)	**PDAC/CRC–adjuvant treatment** Biomarker reduction: 79% (15/19) **Clearance of minimal residual disease** 21% (4/19) **Polyfunctional mKRAS-specific T cell responses** 80% (12/15)
	1	KRAS peptide vaccine ($KRAS^{G12D/G12R/G12V/G12A/G12C/G13D}$ 21-mer peptide vaccine + poly-ICLC + ipilimumab/ nivolumab)	NCT05013216	Adjuvant treatment positive ($n=11$); mKRAS-specific T cell response ($n=11$) (12)	mKRAS-specific T cell response: 73% (8/11)
	1	Anti-RAS^{G12D} mTCR Gilead (ex Kite)/ NCI (KRAS/HRAS/NRAS ^{G12D}; HLA-A*11:01-restricted KRAS/ $HRAS/NRAS^{G12D}$ TCR)	NCT03745326	No data	No data

**Abbreviations* NSCLC: non-small cell lung cancer; PDAC: pancreatic ductal adenocarcinoma; mo: month; ORR: objective response rate

pharmacokinetic properties [166]. Additionally, RMC 4550, a potent and selective allosteric inhibitor of SHP2, represents a promising therapeutic strategy [167]. Recently, TNO155, a highly potent, selective, and first-in-class SHP2 inhibitor, has entered clinical development [168] (NCT03114319). RMC 4630 and JAB-3068, both SHP2 inhibitors, are currently undergoing clinical trials (NCT03634982, NCT05054725, NCT04916236, and NCT03989115 for RMC 4630; NCT03565003, NCT03518554, and NCT04721223 for JAB-3068). As the data from these trials have not yet been published, it will be worthwhile to monitor future developments!

Targeting downstream effectors

RAS mediates oncogenic transformation through the activation of downstream signaling pathways. As illustrated in Fig. 4, the primary downstream pathways include RAF/MEK/ERK and PI3K/AKT/mTOR. Inhibiting these effectors can effectively block oncogenic RAS signaling. Strategies targeting these pathways involve RAF inhibition, MEK inhibition, ERK inhibition, and PI3K-AKT-mTOR inhibition.

ARAF, BRAF, and CRAF comprise the RAF kinase family, all of which share a common upstream activator, RAS [169]. ZM336372 was the first small-molecule, ATP-competitive RAF inhibitor developed, targeting CRAF in cancer [170], However, among the first-generation RAF inhibitors, only Sorafenib progressed to clinical use and received FDA approval for treating advanced renal cell carcinoma (RCC) [171], and WT BRAF hepatocellular carcinoma [172]. Despite its multi-kinase profile, Sorafenib exhibits limited efficacy against BRAF-V600E mutations in cells [173]. This development resulted in the creation of BRAF-V600E inhibitors, with vemurafenib being the first RAF inhibitor to enter clinical trials. It received FDA approval in 2011 for treating patients with BRAF-V600E metastatic melanoma [174, 175]. Following this, dabrafenib was approved in 2013 for melanoma patients with BRAF-V600E/K mutations [176, 177]. In KRAS-mutant and RAS/RAF wild-type tumors, dabrafenib and vemurafenib activate the MAPK pathway instead of suppressing signaling [178, 179]. The underlying mechanism involves BRAF inhibitors driving RAS-dependent BRAF binding to CRAF, thereby activating MEK-ERK signaling [180]. Consequently, targeting both BRAF and CRAF appears essential. LXH-254 is an inhibitor that effectively targets this pathway and has shown efficacy against NRAS-mutant NSCLC cells [181]. However, LXH254 exhibits reduced activity against ARAF and may induce paradoxical activation of MAPK signaling, similar to the effects observed with dabrafenib [182]. Thus, the development of pan-RAF inhibitors is essential. Belvarafenib, a potent inhibitor of BRAF V600E, as well as wild-type CRAF, BRAF, and ARAF, binds to both protomers of a RAF dimer, thereby demonstrating clinical activity in BRAF- and NRAS-mutant melanoma cells without inducing paradoxical MAPK activation in RAS-mutant cells. However, mutations in the ARAF isoform have been identified as a potential driver of resistance to Belvarafenib [183, 184]. These resistance data support the hypothesis that novel therapeutic strategies should focus on combination approaches or the inhibition of all RAS isoforms to effectively disrupt compensatory mechanisms and achieve significant antineoplastic effects. Lifirafenib (BGB-283), an investigational reversible inhibitor of key RAF family kinases (BRAF- V600E, wild-type ARAF, BRAF, CRAF) and EGFR, has demonstrated clinical activity in solid tumors harboring BRAF and KRAS/NRAS mutations and is currently undergoing clinical trials [185] (NCT02610361). Preclinical studies also suggest that lifirafenib enhances the antitumor activity of MEK inhibitors in KRAS-mutant tumors [186]. Other RAF inhibitors, including PLX8394 and DAY101, are currently undergoing evaluation in clinical trials (NCT02428712 and NCT03429803, respectively).

MEK inhibitors, such as Trametinib, Cobimetinib, and Binimetinib, have been approved for the treatment of patients with advanced melanoma harboring the BRAF V600E/K mutation [187–189]. Binimetinib has demonstrated activity in patients with NRAS-mutated melanoma [190, 191]. However, MEK inhibitors, such as Trametinib and Selumetinib, have not improved survival in patients with KRAS-mutant advanced NSCLC [192, 193]. Similarly, Trametinib showed no survival benefit in patients with untreated metastatic pancreatic cancer, regardless of KRAS mutation status [194]. The underlying mechanism is CRAF-mediated MEK activation [195]. Thus, the concept of co-targeting MEK and CRAF has emerged; RAF/MEK inhibitor combinations have shown synergistic efficacy in KRAS-mutant tumor cells [196]. These findings provide the rationale for ongoing clinical trials of combination RAF and MEK inhibitors for KRAS-mutant malignancies.

Reactivation of ERK signaling is recognized as a common driver of resistance following BRAF and MEK-targeted therapies [197]. Therefore, ERK inhibitors represent an attractive downstream target. SCH772984 is a specific inhibitor of ERK1/2 activity and has demonstrated robust efficacy in BRAF-, KRAS-, and NRAS-mutant cancer cells [197]. BVD-523 (ulixertinib), a reversible ATP-competitive ERK1/2 inhibitor with high potency and selectivity, has exhibited dose-dependent growth inhibition and tumor regression. It also demonstrated anti-tumor activity in cases of acquired resistance to single-agent and combination BRAF/MEK-targeted therapies [198]. Notably, clinical trials evaluating BVD-523 are currently underway (NCT01781429, NCT02296242, and NCT02608229) [198]. The recent

discovery of AZD0364, a potent and selective oral inhibitor of ERK1/2, has shown promising antitumor activity in both monotherapy and combination therapy in preclinical models, particularly in NSCLC [199, 200]. Future clinical trials will be necessary to evaluate its clinical activity. It is worth noting that cancer cells exhibit susceptibility to the hyperactivation of ERK pathway activity [201]. Depending on the cell type and stimulus, ERK activity can mediate various antiproliferative processes, including apoptosis, autophagy, and senescence, both in vitro and in vivo [201–203]. Gaining insight into these mechanisms is crucial for developing potential therapeutic strategies for cancer. Conversely, the scaffold protein SH3 and multiple ankyrin repeat domain 3 (SHANK3) acts as a RAS interactor, binding to active KRAS, including its mutant forms. SHANK3 competes with RAF, thereby limiting oncogenic KRAS downstream signaling and maintaining MAPK/ERK activity at an optimal level [204]. Recent data highlights SHANK3 depletion surpasses the threshold, leading to MAPK/ERK signaling hyperactivation and MAPK/ERK-dependent cell death in KRAS-mutant cancers [204]. Therefore, inhibiting the SHANK3-KRAS interaction also offers an alternative approach for selectively killing KRAS-mutant cancer cells by inducing excessive signaling.

As previously mentioned and shown in Fig. 4, PI3Ks consist of three classes (I–III). Among these, Class I PI3Ks are heterodimers composed of a catalytic subunit (p110) and a regulatory subunit (p85). Class I PI3Ks can be activated by GTP-bound RAS, subsequently phosphorylating PIP2 to PIP3, which allows the recruitment of AKT and activation of mTOR. Targeting isoform-specific p110 is more specific and provides a better toxicity profile. The first PI3K inhibitor, alpelisib, is a p110α-specific inhibitor and has demonstrated clinical activity in PIK3CA-activating mutant solid tumors [205]. In contrast, since p110δ and p110γ are exclusively expressed in leukocytes, inhibitors targeting these isoforms have gained approval for the treatment of hematological tumors [26]. From 2014 to 2021, four PI3K inhibitors received FDA approval. Idelalisib, the first PI3K inhibitor, was approved for relapsed B-cell malignancies in 2014. This was followed by the approval of copanlisib, a pan-class I inhibitor, in 2017; duvelisib, a dual PI3K p110δ/p110γ inhibitor, in 2018; and umbralisib, a PI3Kδ and casein kinase-1ε inhibitor, in 2021 [206].

Everolimus, an allosteric mTOR inhibitor and a derivative of rapamycin, is orally administered and has been approved by the FDA for the treatment of various solid tumors, including RCC and pancreatic neuroendocrine tumors (NETs) [207].

Thus, inhibitors targeting upstream and downstream mediators in the RAS signaling pathway can be developed in combination with RAS inhibitors to extend durable benefits for patients.

Resistance mechanisms of RAS inhibitors

Primary resistance

Patients with $KRAS^{G12C}$-mutant NSCLC have shown varying clinical outcomes with treatment using the $KRAS^{G12C}$ inhibitor sotorasib. Specifically, among 172 efficacy-evaluable patients, 62 (36%) experienced early progression (PFS < 3 months), while 40 (23%) achieved long-term clinical benefit (PFS > 12 months), according to recently published data from the 2-year analysis of the CodeBreaK 100 trial [208]. As illustrated in Figs. 7A and 84% of patients with KEAP1 mutations exhibited early disease progression. Additionally, these patients were more prone to harboring ROS1 single-nucleotide variants and secondary RAS mutations [208]. Among 56 patients with $KRAS^{G12C}$-mutant NSCLC, early progression with sotorasib was observed across PD-L1 expression levels [208]. From Fig. 7A, it is evident that elevated PD-L1 expression correlates with a higher probability of early progression. However, the limited sample size necessitates further large-scale studies to validate these findings. Notably, patients with KEAP1 mutations exhibited a significant enrichment of early progression, independent of their STK11 mutation status. In contrast, other mutations did not show a significant association with early progression when compared to long-term benefits [208]. In a real-world cohort of patients with $KRAS^{G12C}$-mutant NSCLC treated with sotorasib, KEAP1 mutations were significantly associated with resistance to therapy [209]. Recent emerging data indicate that patients with NSCLC harboring $KRAS^{G12C}$ mutations, along with co-occurring genomic alterations in KEAP1, SMARCA4, or CDKN2A, experience inferior clinical outcomes when treated with sotorasib or adagrasib monotherapy [13, 131, 208]. This may be attributed to the fact that patients with KEAP1, SMARCA4, or CDKN2A mutations are more likely to experience early disease progression, with PFS of 3 months or less [13]. Additionally, the ORRs in these patients were lower than those observed in patients with WT KEAP1, SMARCA4, or CDKN2A [13] (Fig. 7B). Although patients with PDAC commonly harbor the $KRAS^{G12D}$ mutation, the underlying mechanisms of resistance share similarities with those seen in $KRAS^{G12C}$-mutant tumors. Recent data from patients with $KRAS^{G12D}$ treated with MRTX1133 suggest that the loss of tumor suppressor genes such as PTEN, KEAP1, NF1, TP53, and RB1 may confer partial resistance to this drug [210]. However, the associations of STK11 mutations and DNA damage repair (DDR) gene alterations (including BRCA1/2, ATM, ATR, CHEK1/2, PALB2, RAD50/51/51B/51 C/51D) with ORRs were found to be positive [13] (Fig. 7B). There was a significant trend

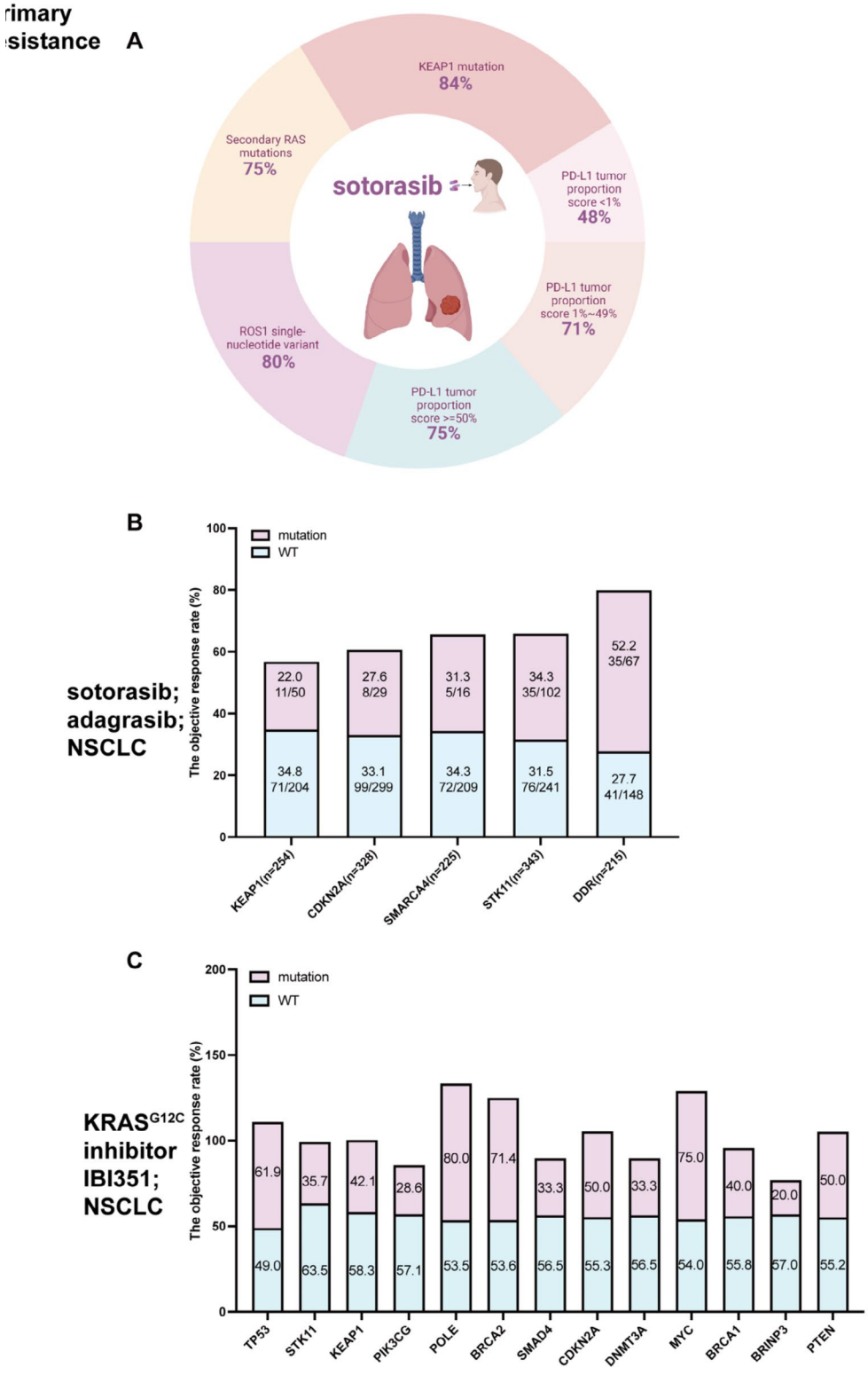

Fig. 7 Primary resistance to KRAS^{G12C} inhibitors. (**A**) The primary resistance mechanisms identified include KEAP1 co-mutations, ROS1 single-nucleotide variants, secondary RAS mutations, and a high PD-L1 tumor proportion score (TPS) [208]. (**B**) Co-alterations in KEAP1, SMARCA4, and CDKN2A have been associated with lower objective response rates, while co-alterations involving STK11 and DNA damage response (DDR) genes have been linked to better objective responses [13]. (**C**) Co-alterations in TP53, STK11, KEAP1, PIK3CG, POLE, BRCA2, SMAD4, CDKN2A, DNMT3A, MYC, BRCA1, BRINP3, and PTEN have been linked to either improved or reduced objective response rates [211]

toward higher ORRs associated with mutations in DDR genes; however, no significant differences were observed between the ORRs of STK11 WT and STK11 mutant patients. Another recent report indicates that $KRAS^{G12C}$ mutations co-occurring with STK11 are associated with lower response rates to IBI351, a potent covalent and irreversible inhibitor of $KRAS^{G12C}$ [211] (Fig. 7C), inconsistent with the results from the study by Negrao et al.., which evaluated sotorasib and adagrasib monotherapy [13]. However, both reports did not find significant differences in ORRs between STK11 WT and STK11 mutant patients. $KRAS^{G12C}$ allele-specific inhibitors are the first FDA-approved therapeutics for RAS-mutant tumors. Notably, a recent study reported that RMC-7977, a highly selective inhibitor targeting the active GTP-bound forms of KRAS, HRAS, and NRAS, with affinity for both mutant and WT variants, has demonstrated broad and significant anti-tumor activity in PDAC. However, resistance to RMC-7977 in PDAC has been observed, primarily driven by MYC alterations and the activation of the YAP-TAZ-TEAD pathways [212]. These findings, however, were inconsistent with the results presented in Fig. 7C, which focused on patients with $KRAS^{G12C}$-mutant NSCLC [211]. This disparity suggests that the mechanisms of resistance may differ between tumor types, highlighting the importance of understanding context-specific pathways in developing effective therapeutic strategies for KRAS-mutant cancers.

Importantly, STK11, SMARCA4, and KEAP1 not only impact the efficacy of KRAS inhibitors but also contribute to poor responses to ICIs due to a "cold" immune microenvironment, which lacks the necessary immune activation for ICIs to be effective. Skoulidis et al. identified STK11/LKB1 alterations as the most common genomic drivers of primary resistance to PD-1 axis inhibitors in KRAS-mutant LUAD [213]. STK11 and KEAP1 mutations are among the most frequently mutated genes in LUAD. These mutations are associated with lower ORRs to IBI351 in $KRAS^{G12C}$-mutant NSCLC and also contribute to resistance to ICIs in patients with KRAS-mutant LUAD [214]. Moreover, Marinelli et al. reported that co-occurring alterations in KEAP1, PBRM1, SMARCA4, and STK11 were associated with reduced efficacy of immunotherapy, even in patients with high tumor mutational burden (TMB), which is generally regarded as a marker predictive of enhanced response to immunotherapy [215, 216]. However, although tumors with KEAP1/TP53 double mutations often exhibit high TMB, they tend to respond less effectively to immunotherapy compared to tumors with only TP53 mutations, despite the elevated TMB [217]. This reinforces the complexity of predicting immunotherapy responses based solely on mutational profiles like tumor mutational burden (TMB). It is possible that the "quality" of coexisting mutations within a tumor (e.g., KEAP1, STK11, TP53) may be more predictive of response than the "quantity" of alterations represented by TMB. However, well-powered prospective studies are needed to ascertain whether prioritizing the specific identity of genomic alterations is more beneficial than merely focusing on the total number of nonsynonymous mutations, regardless of their nature.

Notably, despite the higher ORRs associated with mutations in DDR genes (BRCA1/2, ATM, ATR, CHEK1/2, PALB2, RAD50/51/51B/51 C/51D) as depicted in Fig. 7B, the ORR in patients with BRCA1 mutations was lower than that of BRCA1 WT patients, as shown in Fig. 7C. Furthermore, all genes illustrated in Fig. 7C showed no significant differences in ORRs between WT and mutant groups. These conflicting results warrant further validation in future investigations. Recently published data on the $KRAS^{G12C}$ inhibitor Divarasib demonstrated that preexisting mutations in RAS genes contribute to primary resistance mechanisms [134]. This finding is consistent with the results observed in studies of sotorasib, as reported by Dy et al. [208]. Although the specific mechanisms of resistance mediated by co-occurring mutations remain unclear and addressing this type of resistance is challenging, these mutations may serve as valuable biomarkers for predicting responses to treatment. Additionally, they could be beneficial for patient stratification and therapy intensification in future randomized clinical trials.

Acquired and adaptive resistance and corresponding combination therapy

Recently, multiple mechanisms have been identified that confer resistance to current KRAS inhibitors. A case report revealed that resistance is driven by the enrichment of clonal populations, KRAS-independent downstream signaling, and diverse remodeling of the tumor microenvironment [218]. Notably, Awad et al.. have reported that various genomic and histologic mechanisms also drive resistance to covalent $KRAS^{G12C}$ inhibitors. For example, genomic mechanisms include acquired KRAS alterations (such as G12D/R/V/W, G13D, Q61H, R68S, H95D/Q/R, Y96C, and $KRAS^{G12C}$ amplification), acquired bypass mechanisms of resistance (such as MET amplification), and activating mutations in NRAS, BRAF, MAP2K1, EGFR, and RET. Additionally, oncogenic fusions and loss-of-function mutations in tumor suppressor genes, including PTEN, have been implicated in resistance [219] (Fig. 8A). As illustrated in Fig. 8A-B, the most common form of acquired resistance involves upstream RTKs, including MET, HER2, RET, ALK, and EGFR, through amplifications, fusions, or mutations. This is followed by mutations in KRAS alleles (such as G12S, G13D, and Q61H) occurring in either the cis or trans configuration [219–222]. Although it has been

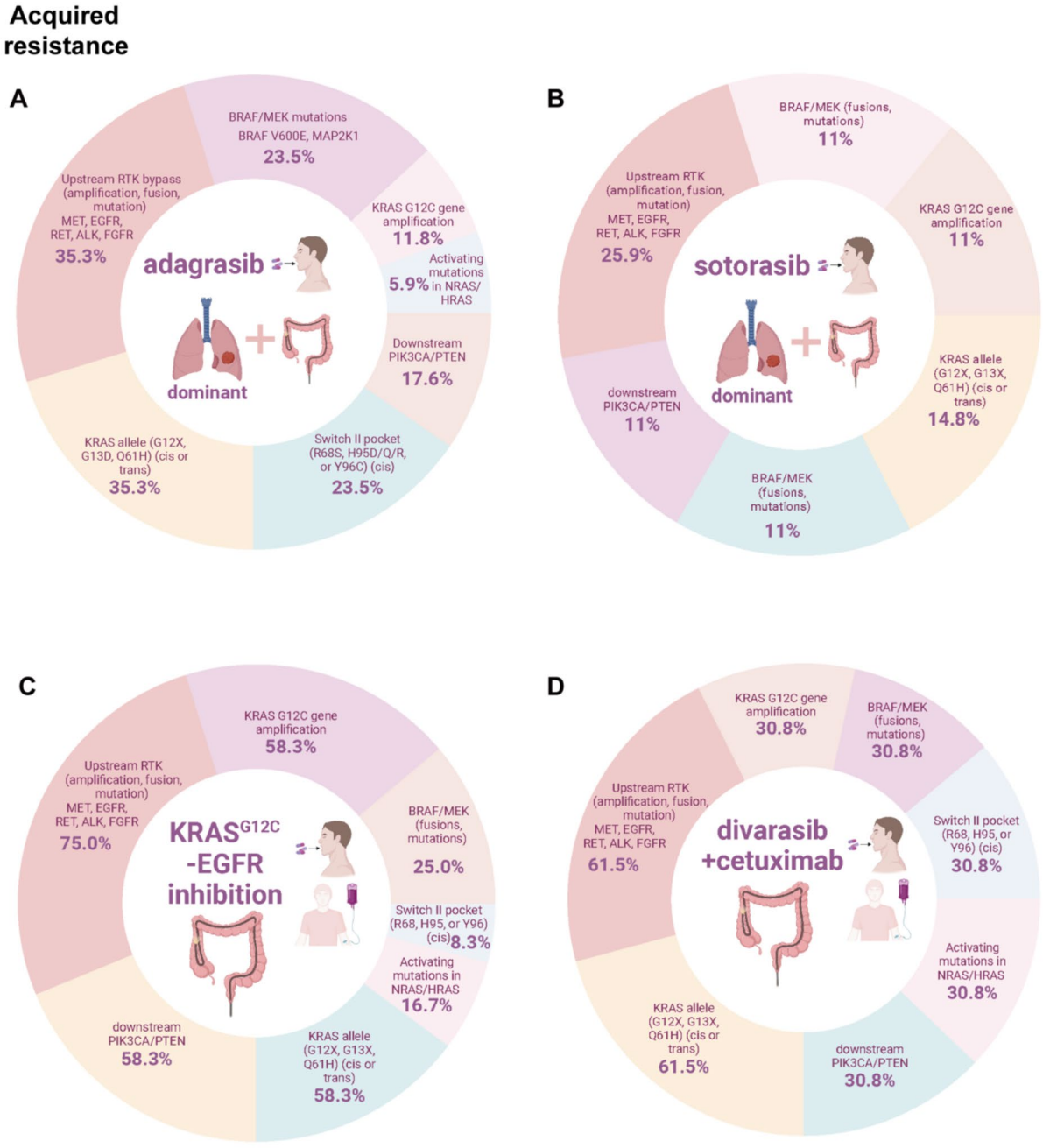

Fig. 8 Acquired mechanisms of resistance to KRAS^{G12C} inhibitors. (**A**-**D**) Frequency of acquired resistance mutations in MAPK pathway genes, as documented in references [219–222]

reported that CRC cells exhibit higher basal RTK activation compared to NSCLC cells, and that EGFR signaling plays a key role in mediating resistance to KRAS^{G12C} inhibitors [223], this understanding provides a crucial mechanistic foundation for developing EGFR antibodies in combination with KRAS^{G12C} inhibitors. Such combinations could potentially overcome resistance to these inhibitors [220, 224]. However, Fig. 8C and D also demonstrate that acquired resistance primarily arises from alterations in upstream RTKs, with subsequent mutations in KRAS alleles (such as G12S, G13D, and Q61H) occurring in either cis or trans configurations [220, 222]. Similarly, in July 2024, Dilly et al. demonstrated that mutations in PIK3CA and KRAS, as well as amplifications of KRAS^{G12C}, MYC, MET, EGFR, and CDK6, emerged as mechanisms of acquired resistance to adagrasib or sotorasib in patients with KRAS^{G12C}-mutant PDAC [225]. Additionally, the study found that amplifications

of KRAS, YAP1, MYC, and Cdk6/Abcb1a/b were associated with resistance to MRTX1133 [225]. These findings underscore the complexity of resistance mechanisms in KRAS-mutant tumors and the need for strategies that can address these diverse alterations to enhance treatment efficacy.

Additionally, researchers have identified adaptive feedback reactivation of WT RAS-MAPK signaling as a key mechanism of adaptive resistance to KRAS inhibitors (Fig. 9). This highlights the potential importance of vertical combination strategies to effectively overcome resistance [226, 227]. In the presence of mutant KRAS, feedback inhibition typically limits the activity of upstream RTKs and WT RAS isoforms. When treating the KRAS 'off' state, suppression of the MAPK pathway leads to the loss of this feedback inhibition, resulting in the upregulation of RTKs and a shift of RAS into an 'on' state, mediated by SOS and SHP2, which activates WT RAS isoforms. This rebound signaling can significantly limit the effectiveness of drug treatment (Fig. 9). For instance, recent published data have shown that co-targeting SOS1 enhances the antitumor effects of adagrasib by overcoming both intrinsic and acquired resistance [162]. The HER family inhibitors afatinib and cetuximab, along with the PI3Kα inhibitor BYL-719, demonstrated a combinatorial effect with MRTX1133 [210]. In contrast, inhibitors targeting SHP2, SOS1, mTOR, and CDK4/6 did not show this synergistic effect [210]. This suggests that specific pathways may interact more effectively with $KRAS^{G12D}$-targeted therapies, highlighting potential combination strategies for enhanced therapeutic efficacy. These findings are consistent with published reports suggesting that the inhibition of mutant KRAS can lead to feedback compensation, promoting the expression of ERBB receptors. This mechanism may contribute to acquired resistance to MRTX1133 treatment, highlighting the complexity of resistance pathways that can arise in response to targeted therapies [228]. In July 2024, investigators reported the mechanistically critical role of ERK in resistance to KRAS-ERK MAPK targeted therapies. This study highlighted how ERK signaling can mediate resistance mechanisms, suggesting that despite targeting KRAS directly, the downstream effects on ERK may allow cancer cells to adapt and survive treatment [229]. Understanding this relationship could lead to more effective combination therapies that simultaneously inhibit ERK alongside KRAS to overcome resistance and improve patient outcomes. Of note, the previously

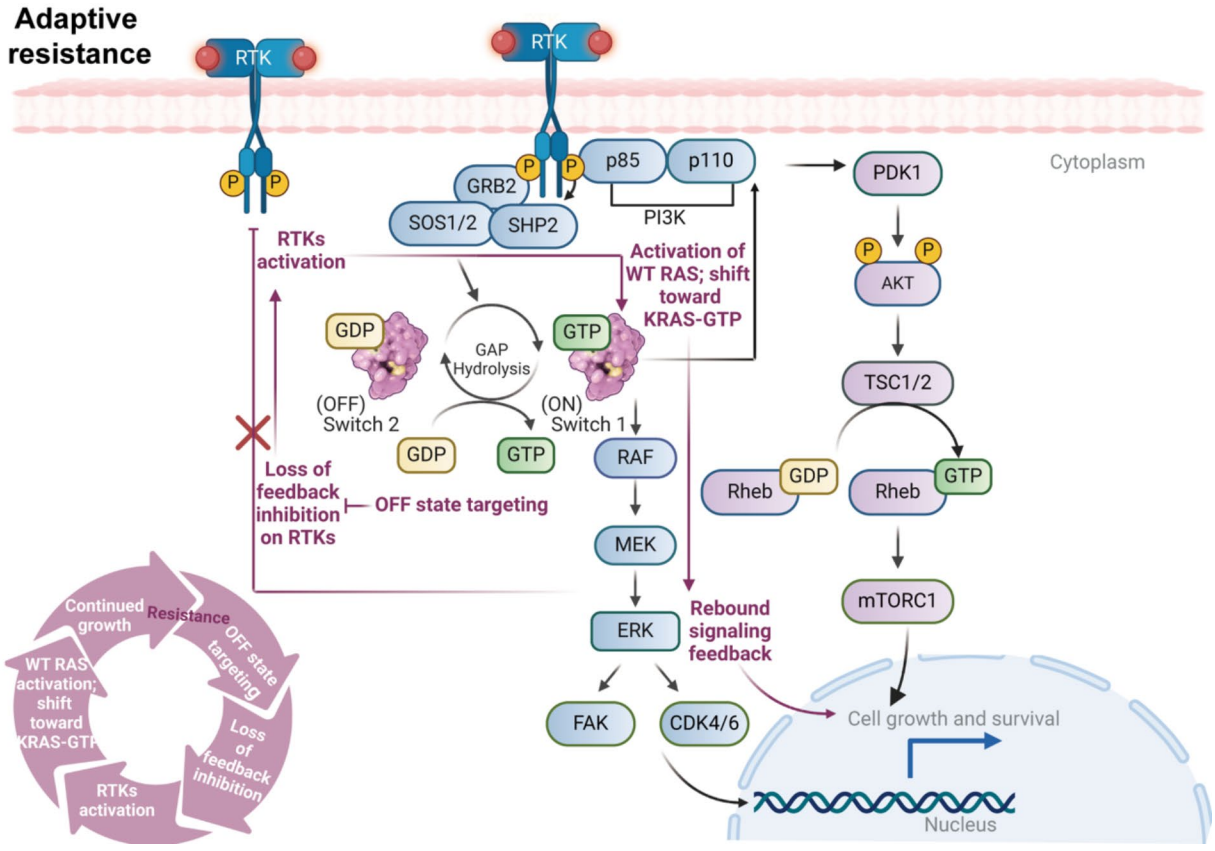

Fig. 9 Adaptive mechanisms of resistance to KRAS inhibitors. Adaptive mechanisms of resistance. This figure illustrates the various ways in which cancer cells develop resistance to treatment, highlighting both specific mutations and broader adaptive responses

mentioned RMC-7977 could provide significant therapeutic benefits by not only targeting mutant RAS-driven signaling but also inhibiting the activity of WT isoforms that may contribute to tumor growth and adaptive feedback resistance mechanisms [212]. The efficacy of this inhibitor highlights its potential for offering more effective treatment options in RAS-mutant cancers.

In addition to genetic alterations and adaptive mechanisms of resistance to KRAS inhibitors, histological mechanisms play a significant role in the process of histologic transformation in cancers, including those driven by KRAS mutations [219]. Histologic transformation refers to the change in the type of cancer cells, which can lead to more aggressive tumor behavior and resistance to therapies. Published data in 2024 indicate that adeno-to-squamous transition, the presence of mucinous histological features, and focal adhesion kinase (FAK)-YAP signaling play significant roles in driving resistance to KRAS inhibition [230–232]. Therefore, combination strategies that involve RAS inhibitors with MYC inhibition or targeting the Hippo signaling pathways in PDAC may soon be translated into clinical practice. These approaches aim to address the various resistance mechanisms that co-evolve alongside RAS inhibition. To overcome resistance, combination therapy strategies target both acquired genetic mutations and adaptive resistance to KRAS inhibitors. These strategies address upstream RTKs, secondary RAS mutations, WT RAS isoforms, and downstream effector pathways such as RAF–MEK and PI3K–AKT. By simultaneously inhibiting these various components, combination therapies aim to improve treatment efficacy and counteract resistance mechanisms. These data collectively support the advancement of multiple combination therapy strategies to effectively address the challenges posed by resistance to RAS inhibition. By simultaneously targeting RAS and related pathways, such as MYC and Hippo signaling, clinicians may enhance therapeutic effectiveness and improve outcomes for patients with KRAS-driven tumors. This comprehensive approach reflects a growing understanding of the intricate relationships between genetic alterations, histological changes, and signaling pathways in cancer biology. Given the multifactorial nature of this resistance, there is a clear need to explore more cost-effective combination therapies and alternative treatment strategies.

Importantly, the insights gained from these studies provide critical mechanistic evidence supporting the principles of personalized medicine. By identifying specific resistance mechanisms within individual tumors, clinicians can develop tailored treatment strategies that directly target these pathways, optimizing therapeutic outcomes for patients. This approach encourages the creation of rational, mechanism-driven combination therapies aimed at overcoming resistance and improving the efficacy of KRAS-targeted treatments. Ultimately, integrating these findings into clinical practice could significantly enhance outcomes for patients with KRAS-driven cancers, particularly in difficult cases such as PDAC. Emphasizing personalized and adaptive treatment strategies will be essential in addressing the evolving nature of cancer resistance and achieving greater therapeutic success.

Finally, it is important to note that the therapeutic vulnerabilities in KRAS-mutated and KRAS WT cancers differ significantly. For KRAS-mutant cancers, specific therapies targeting the $KRAS^{G12C}$ mutation, such as Sotorasib and Adagrasib, have exploited the unique properties of the mutant protein. As stated above, inhibiting pathways that are essential for the survival of KRAS-mutant tumors, such as the MAPK/ERK and PI3K/AKT pathways, can lead to tumor cell death. Importantly, recent study suggests that argininosuccinate synthase 1 (ASS1) deficiency, driven by mutant KRAS, promotes DNA synthesis and creates a reliance on SLC7A1, highlighting dietary arginine restriction and SLC7A1 inhibition as promising therapeutic approaches in KRAS-mutant NSCLC [233]. Likewise, A recent report identified the EPHA2-PARD3 axis as a vulnerability in KRAS-mutant CRC [234]. Novel clinical approaches are leveraging the fact that mutant KRAS peptides are naturally processed and presented in tumors by the major histocompatibility complex (MHC) [235]. While cancers with WT KRAS may rely on other pathways, such as EGFR or HER2, making them susceptible to targeted therapies against these receptors. Besides, utilizing combinations of chemotherapy, targeted agents, and immunotherapies can exploit the unique signaling pathways activated in WT cancers. A single-institution cohort of 795 cases of exocrine pancreatic cancer revealed that 43.8% of KRAS WT cases exhibited evidence of an alternative driver of the MAPK pathway, including BRAF mutations, in-frame deletions, and RTK fusions. In contrast, 56.2% of cases did not show a clear MAPK driver alteration; however, 29.3% of these MAPK-negative KRAS WT cases displayed activating alterations in other oncogenic drivers, such as GNAS, MYC, PIK3CA, and CTNNB1. Additionally, the study demonstrated the potent efficacy of pan-RAF and MEK inhibition in patient-derived organoid models with BRAF in-frame deletions [236]. This indicates that identifying additional genetic alterations in WT KRAS tumors can uncover specific vulnerabilities, facilitating personalized treatment strategies. Moreover, WT KRAS cancers may be more sensitive to therapies that target the tumor microenvironment, including anti-angiogenic agents.

Understanding the therapeutic vulnerabilities of both KRAS-mutated and WT cancers is crucial for developing effective treatment strategies. Tailoring therapies to the

unique characteristics of each tumor type can improve patient outcomes and enhance the efficacy of cancer treatments.

Conclusion

The RAS signaling pathway plays a pivotal role in carcinogenesis, underscoring the critical need for a comprehensive understanding of RAS biology to develop innovative therapeutic strategies. Extensive research efforts have been directed towards RAS inhibitors in both clinical and preclinical settings. Among these, the FDA-approved allele-specific $KRAS^{G12C}$ inhibitors have notably transformed the treatment paradigm for RAS-driven tumors [16, 130–132, 237]. Despite these exciting advancements, the low clinical response rate to a monotherapy approach across all RAS-mutant cancers remains a significant challenge, compounded by the emergence of resistance mechanisms. Consequently, a diverse array of strategies targeting specific RAS-mutant subsets is under development. Understanding and addressing resistance mechanisms have become pivotal topics in current research. One promising direction involves the combination of different inhibitors to overcome resistance, offering a more robust and sustained therapeutic response [238]. Despite the notable advancements in combination therapies, the optimal therapeutic approach has yet to be definitively identified. Nonetheless, large-scale clinical trials of RAS-targeted therapies are showing promising efficacy in several highly refractory malignancies, including NSCLC, CRC, and PDAC. As we move forward, it is crucial to recognize both the potential opportunities and the challenges that lie ahead in refining and optimizing these therapies for broader clinical use.

Abbreviations

AJCC	American Joint Committee on Cancer
AML	Acute Myelocytic Leukemia
ASS1	Argininosuccinate Synthase 1
BLCA	Bladder Urothelial Carcinoma
CMML	Chronic Myelomonocytic Leukemia
CNS	Central Nervous System
CRC	Colorectal Cancer
DCR	Disease Control Rate
EGFR-TKIs	Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors
FAK	Focal Adhesion Kinase
FDA	Food and Drug Administration
FT	Farnesyltransferase
FTI	Farnesyltransferase Inhibitor
HMA	Hypomethylating Agent
HNSC	Head and Neck Squamous Cell Carcinoma
HVR	Hypervariable Region
ICC	Intrahepatic Cholangiocarcinoma
ICI	Immune Checkpoint Inhibitors
LUAD	Lung Adenocarcinoma
MET	Mesenchymal-Epithelial Transition
NCCN	National Comprehensive Cancer Network guidelines
NETs	Neuroendrocrine Tumours
NSCLC	Non–Small Cell Lung Cancer
ORRs	Objective Response Rates
OS	Overall Survival
PCPG	Pheochromocytoma and Paraganglioma
PCR	Partial Response Rate
PDAC	Pancreatic Ductal Adenocarcinoma
PFS	Progression-Free Survival
PTCL	Peripheral T-Cell Lymphoma
RCC	Renal Cell Carcinoma
RFS	Recurrence-Free Survival
RH	Repeat Hepatectomy
SKCM	Skin Cutaneous Melanoma
siRNA	Small interfering RNAs
STAD	Stomach Adenocarcinoma
TCA	Tricarboxylic Acid
TCR	T-Cell Receptors
TGCT	Testicular Germ Cell Tumors
THCA	Thyroid Carcinoma
THYM	Thymoma
TIL	Tumor-Infiltrating Lymphocyte
TMB	Tumor Mutational Burden
UCEC	Uterine Corpus Endometrial Carcinoma
WT	Wild- Type

Supplementary Information

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Supplementary Material 1: Additional Table 1. Common abbreviations for gene names and metabolites.

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Author contributions

YXJ worked in conceptualization and writing—original manuscript preparation; WH helped in conceptualization, reviewing, and editing. All authors read and approved the fnal manuscript.

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Data availability

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

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References

1. Harvey JJ. An unidentified virus which causes the rapid production of tumours in mice. Nature. 1964;204:1104–5. https://pubmed.ncbi.nlm.nih.gov/14243400
2. Bos JL. ras oncogenes in human cancer: a review. Cancer Res. 1989;49(17):4682–9. https://pubmed.ncbi.nlm.nih.gov/2547513
3. Prior IA, Hood FE, Hartley JL. The frequency of Ras mutations in cancer. Cancer Res. 2020;80(14):2969–74. https://pubmed.ncbi.nlm.nih.gov/32209560

4. Malumbres M, Barbacid M. RAS oncogenes: the first 30 years. Nat Rev Cancer. 2003;3(6):459–65. https://pubmed.ncbi.nlm.nih.gov/12778136
5. Guerrero S, Casanova I, Farré L, Mazo A, Capellà G, Mangues R. K-ras codon 12 mutation induces higher level of resistance to apoptosis and predisposition to anchorage-independent growth than codon 13 mutation or proto-oncogene overexpression. Cancer Res. 2000;60(23):6750–6. https://pubmed.ncbi.nlm.nih.gov/11118062
6. Jakob JA, Bassett RL, Ng CS, Curry JL, Joseph RW, Alvarado GC et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. Cancer. 2012;118(16):4014–23. https://pubmed.ncbi.nlm.nih.gov/22180178
7. Foltran L, De Maglio G, Pella N, Ermacora P, Aprile G, Masiero E et al. Prognostic role of KRAS, NRAS, BRAF and PIK3CA mutations in advanced colorectal cancer. Future Oncol. 2015;11(4):629–40. https://pubmed.ncbi.nlm.nih.gov/25686118
8. Jiang J, Jiang L, Maldonato BJ, Wang Y, Holderfield M, Aronchik I et al. Translational and therapeutic evaluation of RAS-GTP inhibition by RMC-6236 in RAS-driven cancers. Cancer Discov. 2024;14(6):994–1017. https://pubmed.ncbi.nlm.nih.gov/38593348
9. Hymowitz SG, Malek S. Targeting the MAPK pathway in RAS mutant cancers. Cold Spring Harb Perspect Med. 2018;8(11):a031492. https://pubmed.ncbi.nlm.nih.gov/29440321
10. Ryan MB, Corcoran RB. Therapeutic strategies to target RAS-mutant cancers. Nat Rev Clin Oncol. 2018;15(11):709–20. https://pubmed.ncbi.nlm.nih.gov/30275515
11. Hunter JC, Manandhar A, Carrasco MA, Gurbani D, Gondi S, Westover KD. Biochemical and structural analysis of common cancer-associated KRAS mutations. Mol Cancer Res. 2015;13(9):1325–35. https://pubmed.ncbi.nlm.nih.gov/26037647
12. Singhal A, Li BT, O'Reilly EM. Targeting KRAS in cancer. Nat Med. 2024;30(4):969–83. https://pubmed.ncbi.nlm.nih.gov/38637634
13. Negrao MV, Araujo HA, Lamberti G, Cooper AJ, Akhave NS, Zhou T et al. Comutations and KRASG12C inhibitor efficacy in advanced NSCLC. Cancer Discov. 2023;13(7):1556–71. https://pubmed.ncbi.nlm.nih.gov/37068173
14. Canon J, Rex K, Saiki AY, Mohr C, Cooke K, Bagal D et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature. 2019;575(7781):217–23. https://pubmed.ncbi.nlm.nih.gov/31666701
15. de Langen AJ, Johnson ML, Mazieres J, Dingemans AMC, Mountzios G, Pless M et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRASG12C mutation: a randomised, open-label, phase 3 trial. Lancet. 2023;401(10378):733–46. https://pubmed.ncbi.nlm.nih.gov/36764316
16. Jänne PA, Riely GJ, Gadgeel SM, Heist RS, Ou SHI, Pacheco JM et al. Adagrasib in non-small-cell lung cancer harboring a KRASG12C mutation. N Engl J Med. 2022;387(2):120–31. https://pubmed.ncbi.nlm.nih.gov/35658005
17. Yaeger R, Uboha NV, Pelster MS, Bekaii-Saab TS, Barve M, Saltzman J et al. Efficacy and safety of Adagrasib plus Cetuximab in patients with KRASG12C-mutated metastatic colorectal cancer. Cancer Discov. 2024;14(6):982–93. https://pubmed.ncbi.nlm.nih.gov/38587856
18. Strickler JH, Satake H, George TJ, Yaeger R, Hollebecque A, Garrido-Laguna I et al. Sotorasib in KRAS p.G12C-mutated advanced pancreatic cancer. N Engl J Med. 2023;388(1):33–43. https://pubmed.ncbi.nlm.nih.gov/36546651
19. Vetter IR, Wittinghofer A. The guanine nucleotide-binding switch in three dimensions. Science. 2001;294(5545):1299–304. https://pubmed.ncbi.nlm.nih.gov/11701921
20. Schöpel M, Potheraveedu VN, Al-Harthy T, Abdel-Jalil R, Heumann R, Stoll R. The small GTPases Ras and Rheb studied by multidimensional NMR spectroscopy: structure and function. Biol Chem. 2017;398(5–6):577–88. https://pubmed.ncbi.nlm.nih.gov/28475102
21. Fetics SK, Guterres H, Kearney BM, Buhrman G, Ma B, Nussinov R et al. Allosteric effects of the oncogenic RasQ61L mutant on Raf-RBD. Structure. 2015;23(3):505–16. https://pubmed.ncbi.nlm.nih.gov/25684575
22. Xu S, Long BN, Boris GH, Chen A, Ni S, Kennedy MA. Structural insight into the rearrangement of the switch I region in GTP-bound G12A K-Ras. Acta Crystallogr Sect Struct Biol. 2017;73(Pt 12):970–84. https://pubmed.ncbi.nlm.nih.gov/29199977
23. Lu S, Banerjee A, Jang H, Zhang J, Gaponenko V, Nussinov R. GTP binding and oncogenic mutations may attenuate hypervariable region (HVR)-catalytic domain interactions in small GTPase K-Ras4B, exposing the effector binding site. J Biol Chem. 2015;290(48):28887–900. https://pubmed.ncbi.nlm.nih.gov/26453300
24. Tang D, Kroemer G, Kang R. Oncogenic KRAS blockade therapy: renewed enthusiasm and persistent challenges. Mol Cancer. 2021;20(1):128. https://pubmed.ncbi.nlm.nih.gov/34607583
25. Chen K, Zhang Y, Qian L, Wang P. Emerging strategies to target RAS signaling in human cancer therapy. J Hematol Oncol. 2021;14(1):116. https://pubmed.ncbi.nlm.nih.gov/34301278
26. Moore AR, Rosenberg SC, McCormick F, Malek S. RAS-targeted therapies: is the undruggable drugged? Nat Rev Drug Discov. 2020;19(8):533–52. https://pubmed.ncbi.nlm.nih.gov/32528145
27. Murugan AK, Grieco M, Tsuchida N. RAS mutations in human cancers: roles in precision medicine. Semin Cancer Biol. 2019;59:23–35. https://pubmed.ncbi.nlm.nih.gov/31255772
28. Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Drugging the undruggable RAS: mission possible? Nat Rev Drug Discov. 2014;13(11):828–51. https://pubmed.ncbi.nlm.nih.gov/25323927
29. Integrated genomic characterization of pancreatic ductal adenocarcinoma. Cancer Cell. 2017;32(2):185–203. https://pubmed.ncbi.nlm.nih.gov/28810144
30. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014;511(7511):543–50. https://pubmed.ncbi.nlm.nih.gov/25079552
31. Keam SJ. Tunlametinib: first approval. Drugs. 2024;84(8):1005–10. https://pubmed.ncbi.nlm.nih.gov/39034326
32. Duan X, Zhang T, Feng L, de Silva N, Greenspun B, Wang X et al. A pancreatic cancer organoid platform identifies an inhibitor specific to mutant KRAS. Cell Stem Cell. 2024;31(1):71–88. https://pubmed.ncbi.nlm.nih.gov/38151022
33. Zeissig MN, Ashwood LM, Kondrashova O, Sutherland KD. Next batter up! Targeting cancers with KRAS-G12D mutations. Trends Cancer. 2023;9(11):955–67. https://pubmed.ncbi.nlm.nih.gov/37591766
34. DiPeri TP, Zhao M, Evans KW, Varadarajan K, Moss T, Scott S et al. KRAS allelic variants in biliary tract cancers. J Hepatol. 2024;80(2):322–34. https://pubmed.ncbi.nlm.nih.gov/37972659
35. Zhu C, Guan X, Zhang X, Luan X, Song Z, Cheng X et al. Targeting KRAS mutant cancers: from druggable therapy to drug resistance. Mol Cancer. 2022;21(1):159. https://pubmed.ncbi.nlm.nih.gov/35922812
36. Hofmann MH, Gerlach D, Misale S, Petronczki M, Kraut N. Expanding the reach of precision oncology by drugging all KRAS mutants. Cancer Discov. 2022;12(4):924–37. https://pubmed.ncbi.nlm.nih.gov/35046095
37. Park HB, Baek KH. E3 ligases and deubiquitinating enzymes regulating the MAPK signaling pathway in cancers. Biochim Biophys Acta Rev Cancer. 2022;1877(3):188736. https://pubmed.ncbi.nlm.nih.gov/35589008
38. Simanshu DK, Nissley DV, McCormick F. RAS proteins and their regulators in human disease. Cell. 2017;170(1):17–33. https://pubmed.ncbi.nlm.nih.gov/28666118
39. Pantsar T. The current understanding of KRAS protein structure and dynamics. Comput Struct Biotechnol J. 2020;18:189–98. https://pubmed.ncbi.nlm.nih.gov/31988705
40. Bos JL, Rehmann H, Wittinghofer A. GEFs and GAPs: critical elements in the control of small G proteins. Cell. 2007;129(5):865–77. https://pubmed.ncbi.nlm.nih.gov/17540168
41. Stephen AG, Esposito D, Bagni RK, McCormick F. Dragging ras back in the ring. Cancer Cell. 2014;25(3):272–81. https://pubmed.ncbi.nlm.nih.gov/24651010
42. Findlay GM, Pawson T. How is SOS activated? Let us count the ways. Nat Struct Mol Biol. 2008;15(6):538–40. https://pubmed.ncbi.nlm.nih.gov/18523461
43. McCormick F. Signal transduction. How receptors turn Ras on. Nature. 1993;363(6424):15–6. https://pubmed.ncbi.nlm.nih.gov/8479530
44. Christensen SM, Tu HL, Jun JE, Alvarez S, Triplet MG, Iwig JS et al. One-way membrane trafficking of SOS in receptor-triggered Ras activation. Nat Struct Mol Biol. 2016;23(9):838–46. https://pubmed.ncbi.nlm.nih.gov/27501536
45. Pacold ME, Suire S, Perisic O, Lara-Gonzalez S, Davis CT, Walker EH et al. Crystal structure and functional analysis of Ras binding to its effector phosphoinositide 3-kinase gamma. Cell. 2000;103(6):931–43. https://pubmed.ncbi.nlm.nih.gov/11136978
46. Krygowska AA, Castellano E. PI3K: a crucial piece in the RAS signaling puzzle. Cold Spring Harb Perspect Med. 2018;8(6):a031450. https://pubmed.ncbi.nlm.nih.gov/28847905
47. Reck M, Carbone DP, Garassino M, Barlesi F. Targeting KRAS in non-small-cell lung cancer: recent progress and new approaches. Ann Oncol. 2021;32(9):1101–10. https://pubmed.ncbi.nlm.nih.gov/34089836
48. Weinberg F, Hamanaka R, Wheaton WW, Weinberg S, Joseph J, Lopez M et al. Mitochondrial metabolism and ROS generation are essential for

Kras-mediated tumorigenicity. Proc Natl Acad Sci U S A. 2010;107(19):8788–93. https://pubmed.ncbi.nlm.nih.gov/20421486
49. Dai E, Han L, Liu J, Xie Y, Kroemer G, Klionsky DJ et al. Autophagy-dependent ferroptosis drives tumor-associated macrophage polarization via release and uptake of oncogenic KRAS protein. Autophagy. 2020;16(11):2069–83. https://pubmed.ncbi.nlm.nih.gov/31920150
50. Pao W, Girard N. New driver mutations in non-small-cell lung cancer. Lancet Oncol. 2011;12(2):175–80. https://pubmed.ncbi.nlm.nih.gov/21277552
51. Mangiapane LR, Nicotra A, Turdo A, Gaggianesi M, Bianca P, Di Franco S et al. PI3K-driven HER2 expression is a potential therapeutic target in colorectal cancer stem cells. Gut. 2022;71(1):119–28. https://pubmed.ncbi.nlm.nih.gov/33436496
52. Fang Z, Marshall CB, Nishikawa T, Gossert AD, Jansen JM, Jahnke W et al. Inhibition of K-RAS4B by a unique mechanism of action: stabilizing membrane-dependent occlusion of the effector-binding site. Cell Chem Biol. 2018;25(11):1327–36. https://pubmed.ncbi.nlm.nih.gov/30122370
53. Tsai FD, Lopes MS, Zhou M, Court H, Ponce O, Fiordalisi JJ et al. K-Ras4A splice variant is widely expressed in cancer and uses a hybrid membrane-targeting motif. Proc Natl Acad Sci U S A. 2015;112(3):779–84. https://pubmed.ncbi.nlm.nih.gov/25561545
54. Amendola CR, Mahaffey JP, Parker SJ, Ahearn IM, Chen WC, Zhou M et al. KRAS4A directly regulates hexokinase 1. Nature. 2019;576(7787):482–6. https://pubmed.ncbi.nlm.nih.gov/31827279
55. Castel P, Dharmaiah S, Sale MJ, Messing S, Rizzuto G, Cuevas-Navarro A et al. RAS interaction with Sin1 is dispensable for mTORC2 assembly and activity. Proc Natl Acad Sci U S A. 2021;118(33):e2103261118. https://pubmed.ncbi.nlm.nih.gov/34380736
56. Whitley MJ, Tran TH, Rigby M, Yi M, Dharmaiah S, Waybright TJ et al. Comparative analysis of KRAS4a and KRAS4b splice variants reveals distinctive structural and functional properties. Sci Adv. 2024;10(7):eadj4137. https://pubmed.ncbi.nlm.nih.gov/38354232
57. Martinelli E, Morgillo F, Troiani T, Ciardiello F. Cancer resistance to therapies against the EGFR-RAS-RAF pathway: The role of MEK. Cancer Treat Rev. 2017;53:61–9. https://pubmed.ncbi.nlm.nih.gov/28073102
58. Fresno Vara JA, Casado E, de Castro J, Cejas P, Belda-Iniesta C, González-Barón M. PI3K/Akt signalling pathway and cancer. Cancer Treat Rev. 2004;30(2):193–204. https://pubmed.ncbi.nlm.nih.gov/15023437
59. Hoxhaj G, Manning BD. The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. Nat Rev Cancer. 2020;20(2):74–88. https://pubmed.ncbi.nlm.nih.gov/31686003
60. Gainor JF, Varghese AM, Ou SHI, Kabraji S, Awad MM, Katayama R et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. Clin Cancer Res. 2013;19(15):4273–81. https://pubmed.ncbi.nlm.nih.gov/23729361
61. Vokes NI, Galan Cobo A, Fernandez-Chas M, Molkentine D, Treviño S, Druker V et al. ATM mutations associate with distinct co-mutational patterns and therapeutic vulnerabilities in NSCLC. Clin Cancer Res. 2023;29(23):4958–72. https://pubmed.ncbi.nlm.nih.gov/37733794
62. Slebos RJ, Kibbelaar RE, Dalesio O, Kooistra A, Stam J, Meijer CJ et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. N Engl J Med. 1990;323(9):561–5. https://pubmed.ncbi.nlm.nih.gov/2199829
63. Cao H, Ma Z, Li Y, Zhang Y, Chen H. Prognostic value of KRAS G12C mutation in lung adenocarcinoma stratified by stages and radiological features. J Thorac Cardiovasc Surg. 2023;166(6):e479–99. https://pubmed.ncbi.nlm.nih.gov/37142051
64. Ernst SM, van Marion R, Atmodimedjo PN, de Jonge E, Mathijssen RHJ, Paats MS et al. Clinical utility of circulating tumor DNA in patients with advanced KRASG12C-mutated NSCLC treated with Sotorasib. J Thorac Oncol. 2024;19(7):e29–30. https://pubmed.ncbi.nlm.nih.gov/38615940
65. Cao H, Ma Z, Huang Q, Han H, Li Y, Zhang Y et al. Clinicopathologic features, concurrent genomic alterations, and clinical outcomes of patients with KRAS G12D mutations in resected lung adenocarcinoma. Eur J Cancer. 2024;202:113985. https://pubmed.ncbi.nlm.nih.gov/38452722
66. Dogan S, Shen R, Ang DC, Johnson ML, D'Angelo SP, Paik PK et al. Molecular epidemiology of EGFR and KRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smoking-related KRAS-mutant cancers. Clin Cancer Res. 2012;18(22):6169–77. https://pubmed.ncbi.nlm.nih.gov/23014527
67. Shepherd FA, Domerg C, Hainaut P, Jänne PA, Pignon JP, Graziano S et al. Pooled analysis of the prognostic and predictive effects of KRAS mutation status and KRAS mutation subtype in early-stage resected non-small-cell lung cancer in four trials of adjuvant chemotherapy. J Clin Oncol. 2013;31(17):2173–81. https://pubmed.ncbi.nlm.nih.gov/23630215
68. Ichinokawa H, Ishii G, Nagai K, Kawase A, Yoshida J, Nishimura M et al. Distinct clinicopathologic characteristics of lung mucinous adenocarcinoma with KRAS mutation. Hum Pathol. 2013;44(12):2636–42. https://pubmed.ncbi.nlm.nih.gov/24119562
69. Douillard JY, Shepherd FA, Hirsh V, Mok T, Socinski MA, Gervais R et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol. 2010;28(5):744–52. https://pubmed.ncbi.nlm.nih.gov/20038723
70. Zhu CQ, da Cunha Santos G, Ding K, Sakurada A, Cutz JC, Liu N et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol. 2008;26(26):4268–75. https://pubmed.ncbi.nlm.nih.gov/18626007
71. Massarelli E, Varella-Garcia M, Tang X, Xavier AC, Ozburn NC, Liu DD et al. KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. Clin Cancer Res. 2007;13(10):2890–6. https://pubmed.ncbi.nlm.nih.gov/17504988
72. Hames ML, Chen H, Iams W, Aston J, Lovly CM, Horn L. Correlation between KRAS mutation status and response to chemotherapy in patients with advanced non-small cell lung cancer☆. Lung Cancer. 2016;92:29–34. https://pubmed.ncbi.nlm.nih.gov/26775593
73. Serna-Blasco R, Sánchez-Herrero E, Sanz-Moreno S, Rodriguez-Festa A, García-Veros E, Casarrubios M et al. KRAS p.G12C mutation occurs in 1% of EGFR-mutated advanced non-small-cell lung cancer patients progressing on a first-line treatment with a tyrosine kinase inhibitor. ESMO Open. 2021;6(5):100279. https://pubmed.ncbi.nlm.nih.gov/34607284
74. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE et al. Nivolumab versus Docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627–39. https://pubmed.ncbi.nlm.nih.gov/26412456
75. Sun L, Hsu M, Cohen RB, Langer CJ, Mamtani R, Aggarwal C. Association between KRAS variant status and outcomes with first-line immune checkpoint inhibitor-based therapy in patients with advanced non-small-cell lung cancer. JAMA Oncol. 2021;7(6):937–9. https://pubmed.ncbi.nlm.nih.gov/33856403
76. Jeanson A, Tomasini P, Souquet-Bressand M, Brandone N, Boucekine M, Grangeon M et al. Efficacy of immune checkpoint inhibitors in KRAS-mutant non-small cell lung cancer (NSCLC). J Thorac Oncol. 2019;14(6):1095–101. https://pubmed.ncbi.nlm.nih.gov/30738221
77. Cheng H, Luo G, Jin K, Fan Z, Huang Q, Gong Y et al. Kras mutation correlating with circulating regulatory T cells predicts the prognosis of advanced pancreatic cancer patients. Cancer Med. 2020;9(6):2153–9. https://pubmed.ncbi.nlm.nih.gov/32017404
78. Ako S, Nouso K, Kinugasa H, Dohi C, Matushita H, Mizukawa S et al. Utility of serum DNA as a marker for KRAS mutations in pancreatic cancer tissue. Pancreatology. 2017;17(2):285–90. https://pubmed.ncbi.nlm.nih.gov/28139399
79. Bournet B, Muscari F, Buscail C, Assenat E, Barthet M, Hammel P et al. KRAS G12D mutation subtype is a prognostic factor for advanced pancreatic adenocarcinoma. Clin Transl Gastroenterol. 2016;7(3):e157. https://pubmed.ncbi.nlm.nih.gov/27010960
80. Heinemann V, Vehling-Kaiser U, Waldschmidt D, Kettner E, Märten A, Winkelmann C et al. Gemcitabine plus erlotinib followed by capecitabine versus capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomised phase 3 trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO-PK0104). Gut. 2013;62(5):751–9. https://pubmed.ncbi.nlm.nih.gov/22773551
81. Till JE, McDaniel L, Chang C, Long Q, Pfeiffer SM, Lyman JP et al. Circulating KRAS G12D but not G12V is associated with survival in metastatic pancreatic ductal adenocarcinoma. Nat Commun. 2024;15(1):5763. https://pubmed.ncbi.nlm.nih.gov/38982051
82. Qian ZR, Rubinson DA, Nowak JA, Morales-Oyarvide V, Dunne RF, Kozak MM et al. Association of alterations in main driver genes with outcomes of patients with resected pancreatic ductal adenocarcinoma. JAMA Oncol. 2018;4(3):e173420. https://pubmed.ncbi.nlm.nih.gov/29098284
83. Haas M, Ormanns S, Baechmann S, Remold A, Kruger S, Westphalen CB et al. Extended RAS analysis and correlation with overall survival in advanced pancreatic cancer. Br J Cancer. 2017;116(11):1462–9. https://pubmed.ncbi.nlm.nih.gov/28449008
84. Schultheis B, Reuter D, Ebert MP, Siveke J, Kerkhoff A, Berdel WE et al. Gemcitabine combined with the monoclonal antibody nimotuzumab is an

active first-line regimen in KRAS wildtype patients with locally advanced or metastatic pancreatic cancer: a multicenter, randomized phase IIb study. Ann Oncol. 2017;28(10):2429–35. https://pubmed.ncbi.nlm.nih.gov/28961832
85. Boeck S, Jung A, Laubender RP, Neumann J, Egg R, Goritschan C et al. KRAS mutation status is not predictive for objective response to anti-EGFR treatment with erlotinib in patients with advanced pancreatic cancer. J Gastroenterol. 2013;48(4):544–8. https://pubmed.ncbi.nlm.nih.gov/23435671
86. Morris VK, Lucas FAS, Overman MJ, Eng C, Morelli MP, Jiang ZQ et al. Clinicopathologic characteristics and gene expression analyses of non-KRAS 12/13, RAS-mutated metastatic colorectal cancer. Ann Oncol. 2014;25(10):2008–14. https://pubmed.ncbi.nlm.nih.gov/25009008
87. Guo TA, Wu YC, Tan C, Jin YT, Sheng WQ, Cai SJ et al. Clinicopathologic features and prognostic value of KRAS, NRAS and BRAF mutations and DNA mismatch repair status: a single-center retrospective study of 1,834 Chinese patients with stage I-IV colorectal cancer. Int J Cancer. 2019;145(6):1625–34. https://pubmed.ncbi.nlm.nih.gov/31162857
88. Tie J, Lipton L, Desai J, Gibbs P, Jorissen RN, Christie M et al. KRAS mutation is associated with lung metastasis in patients with curatively resected colorectal cancer. Clin Cancer Res. 2011;17(5):1122–30. https://pubmed.ncbi.nlm.nih.gov/21239505
89. Yaeger R, Cowell E, Chou JF, Gewirtz AN, Borsu L, Vakiani E et al. RAS mutations affect pattern of metastatic spread and increase propensity for brain metastasis in colorectal cancer. Cancer. 2015;121(8):1195–203. https://pubmed.ncbi.nlm.nih.gov/25491172
90. Sasaki K, Margonis GA, Wilson A, Kim Y, Buettner S, Andreatos N et al. Prognostic implication of KRAS status after hepatectomy for colorectal liver metastases varies according to primary colorectal tumor location. Ann Surg Oncol. 2016;23(11):3736–43. https://pubmed.ncbi.nlm.nih.gov/27352204
91. Margonis GA, Spolverato G, Kim Y, Karagkounis G, Choti MA, Pawlik TM. Effect of KRAS mutation on long-term outcomes of patients undergoing hepatic resection for colorectal liver metastases. Ann Surg Oncol. 2015;22(13):4158–65. https://pubmed.ncbi.nlm.nih.gov/26077912
92. Denbo JW, Yamashita S, Passot G, Egger M, Chun YS, Kopetz SE et al. RAS mutation is associated with decreased survival in patients undergoing repeat hepatectomy for colorectal liver metastases. J Gastrointest Surg. 2017;21(1):68–77. https://pubmed.ncbi.nlm.nih.gov/27334313
93. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med. 2013;369(11):1023–34. https://pubmed.ncbi.nlm.nih.gov/24024839
94. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26(10):1626–34. https://pubmed.ncbi.nlm.nih.gov/18316791
95. De Roock W, Piessevaux H, De Schutter J, Janssens M, De Hertogh G, Personeni N et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol. 2008;19(3):508–15. https://pubmed.ncbi.nlm.nih.gov/17998284
96. Liao W, Overman MJ, Boutin AT, Shang X, Zhao D, Dey P et al. KRAS-IRF2 axis drives immune suppression and immune therapy resistance in colorectal cancer. Cancer Cell. 2019;35(4):559–72. https://pubmed.ncbi.nlm.nih.gov/30905761
97. Lal N, White BS, Goussous G, Pickles O, Mason MJ, Beggs AD et al. KRAS mutation and consensus molecular subtypes 2 and 3 are independently associated with reduced immune infiltration and reactivity in colorectal cancer. Clin Cancer Res. 2018;24(1):224–33. https://pubmed.ncbi.nlm.nih.gov/29061646
98. Thomas NE, Edmiston SN, Alexander A, Groben PA, Parrish E, Kricker A et al. Association between NRAS and BRAF mutational status and melanoma-specific survival among patients with higher-risk primary melanoma. JAMA Oncol. 2015;1(3):359–68. https://pubmed.ncbi.nlm.nih.gov/26146664
99. Devitt B, Liu W, Salemi R, Wolfe R, Kelly J, Tzen CY et al. Clinical outcome and pathological features associated with NRAS mutation in cutaneous melanoma. Pigment Cell Melanoma Res. 2011;24(4):666–72. https://pubmed.ncbi.nlm.nih.gov/21615881
100. Ellerhorst JA, Greene VR, Ekmekcioglu S, Warneke CL, Johnson MM, Cooke CP et al. Clinical correlates of NRAS and BRAF mutations in primary human melanoma. Clin Cancer Res. 2011;17(2):229–35. https://pubmed.ncbi.nlm.nih.gov/20975100
101. Wohlfeil SA, Kranzmann L, Weiß C, von Wasielewski I, Klespe KC, Kähler KC et al. Influence of adjuvant therapies on organ-specific recurrence of cutaneous melanoma: a multicenter study on 1383 patients of the prospective DeCOG registry ADOReg. Int J Cancer. 2024; https://pubmed.ncbi.nlm.nih.gov/38975881
102. Garcia-Rostan G, Zhao H, Camp RL, Pollan M, Herrero A, Pardo J et al. ras mutations are associated with aggressive tumor phenotypes and poor prognosis in thyroid cancer. J Clin Oncol. 2003;21(17):3226–35. https://pubmed.ncbi.nlm.nih.gov/12947056
103. DiPeri TP, Zhao M, Evans KW, Varadarajan K, Moss T, Scott S et al. Convergent MAPK pathway alterations mediate acquired resistance to FGFR inhibitors in FGFR2 fusion-positive cholangiocarcinoma. J Hepatol. 2024;80(2):322–34. https://pubmed.ncbi.nlm.nih.gov/37972659
104. Tanaka M, Kunita A, Yamagishi M, Katoh H, Ishikawa S, Yamamoto H et al. KRAS mutation in intrahepatic cholangiocarcinoma: Linkage with metastasis-free survival and reduced E-cadherin expression. Liver Int. 2022;42(10):2329–40. https://pubmed.ncbi.nlm.nih.gov/35833881
105. Montalban-Bravo G, Thongon N, Rodriguez-Sevilla JJ, Ma F, Ganan-Gomez I, Yang H et al. Targeting MCL1-driven anti-apoptotic pathways overcomes blast progression after hypomethylating agent failure in chronic myelomonocytic leukemia. Cell Rep Med. 2024;5(6):101585. https://pubmed.ncbi.nlm.nih.gov/38781960
106. Nodin B, Zendehrokh N, Sundström M, Jirström K. Clinicopathological correlates and prognostic significance of KRAS mutation status in a pooled prospective cohort of epithelial ovarian cancer. Diagn Pathol. 2013;8:106. https://pubmed.ncbi.nlm.nih.gov/23800114
107. Holderfield M, Lee BJ, Jiang J, Tomlinson A, Seamon KJ, Mira A et al. Concurrent inhibition of oncogenic and wild-type RAS-GTP for cancer therapy. Nature. 2024;629(8013):919–26. https://pubmed.ncbi.nlm.nih.gov/38589574
108. Burd CE, Liu W, Huynh MV, Waqas MA, Gillahan JE, Clark KS et al. Mutation-specific RAS oncogenicity explains NRAS codon 61 selection in melanoma. Cancer Discov. 2014;4(12):1418–29. https://pubmed.ncbi.nlm.nih.gov/25252692
109. Lièvre A, Bachet JB, Le Corre D, Boige V, Landi B, Emile JF et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res. 2006;66(8):3992–5. https://pubmed.ncbi.nlm.nih.gov/16618717
110. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008;359(17):1757–65. https://pubmed.ncbi.nlm.nih.gov/18946061
111. Lièvre A, Bachet JB, Boige V, Cayre A, Le Corre D, Buc E et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol. 2008;26(3):374–9. https://pubmed.ncbi.nlm.nih.gov/18202412
112. Tejpar S, Celik I, Schlichting M, Sartorius U, Bokemeyer C, Van Cutsem E. Association of KRAS G13D tumor mutations with outcome in patients with metastatic colorectal cancer treated with first-line chemotherapy with or without cetuximab. J Clin Oncol. 2012;30(29):3570–7. https://pubmed.ncbi.nlm.nih.gov/22734028
113. Haigis KM, Kendall KR, Wang Y, Cheung A, Haigis MC, Glickman JN et al. Differential effects of oncogenic K-Ras and N-Ras on proliferation, differentiation and tumor progression in the colon. Nat Genet. 2008;40(5):600–8. https://pubmed.ncbi.nlm.nih.gov/18372904
114. Johnson L, Greenbaum D, Cichowski K, Mercer K, Murphy E, Schmitt E et al. K-ras is an essential gene in the mouse with partial functional overlap with N-ras. Genes Dev. 1997;11(19):2468–81. https://pubmed.ncbi.nlm.nih.gov/9334313
115. Nakamura K, Ichise H, Nakao K, Hatta T, Otani H, Sakagami H et al. Partial functional overlap of the three ras genes in mouse embryonic development. Oncogene. 2008;27(21):2961–8. https://pubmed.ncbi.nlm.nih.gov/18059342
116. Kirsten WH, Mayer LA. Morphologic responses to a murine erythroblastosis virus. J Natl Cancer Inst. 1967;39(2):311–35. https://pubmed.ncbi.nlm.nih.gov/18623947
117. Peters RL, Rabstein LS, VanVleck R, Kelloff GJ, Huebner RJ. Naturally occurring sarcoma virus of the BALB/cCr mouse. J Natl Cancer Inst. 1974;53(6):1725–9. https://pubmed.ncbi.nlm.nih.gov/4373578
118. Rasheed S, Gardner MB, Huebner RJ. In vitro isolation of stable rat sarcoma viruses. Proc Natl Acad Sci U S A. 1978;75(6):2972–6. https://pubmed.ncbi.nlm.nih.gov/208081
119. Shih C, Weinberg RA. Isolation of a transforming sequence from a human bladder carcinoma cell line. Cell. 1982;29(1):161–9. https://pubmed.ncbi.nlm.nih.gov/6286138
120. Goldfarb M, Shimizu K, Perucho M, Wigler M. Isolation and preliminary characterization of a human transforming gene from T24 bladder carcinoma cells. Nature. 1982;296(5856):404–9. https://pubmed.ncbi.nlm.nih.gov/7063039

121. Pulciani S, Santos E, Lauver AV, Long LK, Robbins KC, Barbacid M. Oncogenes in human tumor cell lines: molecular cloning of a transforming gene from human bladder carcinoma cells. Proc Natl Acad Sci U S A. 1982;79(9):2845–9. https://pubmed.ncbi.nlm.nih.gov/6953433
122. Nagasu T, Yoshimatsu K, Rowell C, Lewis MD, Garcia AM. Inhibition of human tumor xenograft growth by treatment with the farnesyl transferase inhibitor B956. Cancer Res. 1995;55(22):5310–4. https://pubmed.ncbi.nlm.nih.gov/7585593
123. Kohl NE, Omer CA, Conner MW, Anthony NJ, Davide JP, deSolms SJ et al. Inhibition of farnesyltransferase induces regression of mammary and salivary carcinomas in ras transgenic mice. Nat Med. 1995;1(8):792–7. https://pubmed.ncbi.nlm.nih.gov/7585182
124. Witzig TE, Sokol L, Kim WS, de la Cruz F, Garcia-Sancho M, Advani AM et al. RH,. Phase 2 trial of the farnesyltransferase inhibitor Tipifarnib for relapsed/refractory peripheral T cell lymphoma. Blood Adv. 2024;8(17):4581–92. https://pubmed.ncbi.nlm.nih.gov/38991123
125. Figarol S, Delahaye C, Gence R, Doussine A, Cerapio JP, Brachais M et al. Farnesyltransferase inhibition overcomes oncogene-addicted non-small cell lung cancer adaptive resistance to targeted therapies. Nat Commun. 2024;15(1):5345. https://pubmed.ncbi.nlm.nih.gov/38937474
126. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature. 2013;503(7477):548–51. https://pubmed.ncbi.nlm.nih.gov/24256730
127. O'Bryan JP. Pharmacological targeting of RAS: recent success with direct inhibitors. Pharmacol Res. 2019;139:503–11. https://pubmed.ncbi.nlm.nih.gov/30366101
128. Lim SM, Westover KD, Ficarro SB, Harrison RA, Choi HG, Pacold ME et al. Therapeutic targeting of oncogenic K-Ras by a covalent catalytic site inhibitor. Angew Chem Int Ed. 2014;53(1):199–204. https://pubmed.ncbi.nlm.nih.gov/24259466
129. Fakih M, O'Neil B, Price TJ, Falchook GS, Hong DS. Phase 1 study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of AMG 510, a novel small molecule KRAS G12C inhibitor, in advanced solid tumors. J Clin Oncol. 2019;37(15suppl):3003–3003.
130. Hong DS, Fakih MG, Strickler JH, Desai J, Durm GA, Shapiro GI et al. KRASG12C inhibition with Sotorasib in advanced solid tumors. N Engl J Med. 2020;383(13):1207–17. https://pubmed.ncbi.nlm.nih.gov/32955176
131. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J et al. Sotorasib for lung cancers with KRAS p.G12C mutation. N Engl J Med. 2021;384(25):2371–81. https://pubmed.ncbi.nlm.nih.gov/34096690
132. Fakih MG, Kopetz S, Kuboki Y, Kim TW, Munster PN, Krauss JC et al. Sotorasib for previously treated colorectal cancers with KRASG12C mutation (CodeBreaK100): a prespecified analysis of a single-arm, phase 2 trial. Lancet Oncol. 2022;23(1):115–24. https://pubmed.ncbi.nlm.nih.gov/34919824
133. Bekaii-Saab TS, Yaeger R, Spira AI, Pelster MS, Sabari JK, Hafez N et al. Adagrasib in advanced solid tumors harboring a KRASG12C mutation. J Clin Oncol. 2023;41(25):4097–106. https://pubmed.ncbi.nlm.nih.gov/37099736
134. Sacher A, LoRusso P, Patel MR, Miller WH, Garralda E, Forster MD et al. Single-agent Divarasib (GDC-6036) in solid tumors with a KRAS G12C mutation. N Engl J Med. 2023;389(8):710–21. https://pubmed.ncbi.nlm.nih.gov/37611121
135. Li Z, Song Z, Zhao Y, Wang P, Jiang L, Gong Y et al. D-1553 (Garsorasib), a potent and selective inhibitor of KRASG12C in patients with NSCLC: phase 1 study results. J Thorac Oncol. 2023;18(7):940–51. https://pubmed.ncbi.nlm.nih.gov/36948246
136. Cui W, Franchini F, Alexander M, Officer A, Wong HL, IJzerman M et al. Real world outcomes in KRAS G12C mutation positive non-small cell lung cancer. Lung Cancer. 2020;146:310–7. https://pubmed.ncbi.nlm.nih.gov/32619782
137. Wu MY, Zhang EW, Strickland MR, Mendoza DP, Lipkin L, Lennerz JK et al. Clinical and imaging features of non-small cell lung cancer with G12C KRAS mutation. Cancers. 2021;13(14):3572. https://pubmed.ncbi.nlm.nih.gov/34298783
138. Negrao MV, Spira AI, Heist RS, Jänne PA, Pacheco JM, Weiss J et al. Intracranial efficacy of Adagrasib in patients from the KRYSTAL-1 trial with KRASG12C-mutated non-small-cell lung cancer who have untreated CNS metastases. J Clin Oncol. 2023;41(28):4472–7. https://pubmed.ncbi.nlm.nih.gov/37327468
139. Flores-Gómez AA, Drosten M. HRS-4642: the next piece of the puzzle to keep KRAS in check. Cancer Cell. 2024;42(7):1157–9. https://pubmed.ncbi.nlm.nih.gov/38981436
140. Zhou C, Li C, Luo L, Li X, Jia K, He N et al. Anti-tumor efficacy of HRS-4642 and its potential combination with proteasome inhibition in KRAS G12D-mutant cancer. Cancer Cell. 2024;42(7):1286–300. https://pubmed.ncbi.nlm.nih.gov/38942026
141. Wang X, Wang W, Zou S, Xu Z, Cao D, Zhang S et al. Combination therapy of KRAS G12V mRNA vaccine and pembrolizumab: clinical benefit in patients with advanced solid tumors. Cell Res. 2024;661–4. https://pubmed.ncbi.nlm.nih.gov/38914844
142. Pant S, Wainberg ZA, Weekes CD, Furqan M, Kasi PM, Devoe CE et al. Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: the phase 1 AMPLIFY-201 trial. Nat Med. 2024;30(2):531–42. https://pubmed.ncbi.nlm.nih.gov/38195752
143. Lanman BA, Allen JR, Allen JG, Amegadzie AK, Ashton KS, Booker SK et al. Discovery of a covalent inhibitor of KRASG12C (AMG 510) for the treatment of solid tumors. J Med Chem. 2020;63(1):52–65. https://pubmed.ncbi.nlm.nih.gov/31820981
144. Fell JB, Fischer JP, Baer BR, Blake JF, Bouhana K, Briere DM et al. Identification of the clinical development candidate MRTX849, a covalent KRASG12C inhibitor for the treatment of cancer. J Med Chem. 2020;63(13):6679–93. https://pubmed.ncbi.nlm.nih.gov/32250617
145. Wang X, Allen S, Blake JF, Bowcut V, Briere DM, Calinisan A et al. Identification of MRTX1133, a noncovalent, potent, and selective KRASG12D inhibitor. J Med Chem. 2022;65(4):3123–33. https://pubmed.ncbi.nlm.nih.gov/34889605
146. Mao Z, Xiao H, Shen P, Yang Y, Xue J, Yang Y et al. KRAS(G12D) can be targeted by potent inhibitors via formation of salt bridge. Cell Discov. 2022;8(1):5. https://pubmed.ncbi.nlm.nih.gov/35075146
147. Kim D, Herdeis L, Rudolph D, Zhao Y, Böttcher J, Vides A et al. Pan-KRAS inhibitor disables oncogenic signalling and tumour growth. Nature. 2023;619(7968):160–6. https://pubmed.ncbi.nlm.nih.gov/37258666
148. Corcoran RB. A single inhibitor for all KRAS mutations. Nat Cancer. 2023;4(8):1060–2. https://pubmed.ncbi.nlm.nih.gov/37620420
149. Ross SJ, Revenko AS, Hanson LL, Ellston R, Staniszewska A, Whalley N et al. Targeting KRAS-dependent tumors with AZD4785, a high-affinity therapeutic antisense oligonucleotide inhibitor of KRAS. Sci Transl Med. 2017;9(394):eaao4188. https://pubmed.ncbi.nlm.nih.gov/28615361
150. Wedén S, Klemp M, Gladhaug IP, Møller M, Eriksen JA, Gaudernack G et al. Long-term follow-up of patients with resected pancreatic cancer following vaccination against mutant K-ras. Int J Cancer. 2011;128(5):1120–8. https://pubmed.ncbi.nlm.nih.gov/20473937
151. Tran E, Robbins PF, Lu YC, Prickett TD, Gartner JJ, Jia L et al. T-Cell transfer therapy targeting mutant KRAS in cancer. N Engl J Med. 2016;375(23):2255–62. https://pubmed.ncbi.nlm.nih.gov/27959684
152. Leidner R, Sanjuan Silva N, Huang H, Sprott D, Zheng C, Shih YP et al. Neoantigen T-Cell receptor gene therapy in pancreatic cancer. N Engl J Med. 2022;386(22):2112–9. https://pubmed.ncbi.nlm.nih.gov/35648703
153. Ayati A, Moghimi S, Salarinejad S, Safavi M, Pouramiri B, Foroumadi A. A review on progression of epidermal growth factor receptor (EGFR) inhibitors as an efficient approach in cancer targeted therapy. Bioorganic Chem. 2020;99:103811. https://pubmed.ncbi.nlm.nih.gov/32278207
154. Paz-Ares L, Socinski MA, Shahidi J, Hozak RR, Soldatenkova V, Kurek R et al. Correlation of EGFR-expression with safety and efficacy outcomes in SQUIRE: a randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin plus necitumumab versus gemcitabine-cisplatin alone in the first-line treatment of patients with stage IV squamous non-small-cell lung cancer. Ann Oncol. 2016;27(8):1573–9. https://pubmed.ncbi.nlm.nih.gov/27207107
155. Misale S, Yaeger R, Hobor S, Scala E, Janakiraman M, Liska D et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. Nature. 2012;486(7404):532–6. https://pubmed.ncbi.nlm.nih.gov/22722830
156. Park K, Haura EB, Leighl NB, Mitchell P, Shu CA, Girard N et al. Amivantamab in EGFR Exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: initial results from the CHRYSALIS phase I study. J Clin Oncol. 2021;39(30):3391–402. https://pubmed.ncbi.nlm.nih.gov/34339292
157. Wang M, Yang JCH, Mitchell PL, Fang J, Camidge DR, Nian W et al. Sunvozertinib, a selective EGFR inhibitor for previously treated non-small cell lung cancer with EGFR Exon 20 insertion mutations. Cancer Discov. 2022;12(7):1676–89. https://pubmed.ncbi.nlm.nih.gov/35404393
158. Elamin YY, Robichaux JP, Carter BW, Altan M, Tran H, Gibbons DL et al. Poziotinib for EGFR exon 20-mutant NSCLC: clinical efficacy, resistance mechanisms, and impact of insertion location on drug sensitivity. Cancer Cell. 2022;40(7):754–67. https://pubmed.ncbi.nlm.nih.gov/35820397
159. Chon K, Larkins E, Chatterjee S, Mishra-Kalyani PS, Aungst S, Wearne E et al. FDA approval summary: Amivantamab for the treatment of patients with non-small cell lung cancer with EGFR Exon 20 insertion mutations. Clin Cancer Res. 2023;29(17):3262–6. https://pubmed.ncbi.nlm.nih.gov/37022784

160. Hillig RC, Sautier B, Schroeder J, Moosmayer D, Hilpmann A, Stegmann CM et al. Discovery of potent SOS1 inhibitors that block RAS activation via disruption of the RAS-SOS1 interaction. Proc Natl Acad Sci U S A. 2019;116(7):2551–60. https://pubmed.ncbi.nlm.nih.gov/30683722
161. Hofmann MH, Gmachl M, Ramharter J, Savarese F, Gerlach D, Marszalek JR et al. BI-3406, a potent and selective SOS1-KRAS interaction inhibitor, is effective in KRAS-driven cancers through combined MEK inhibition. Cancer Discov. 2021;11(1):142–57. https://pubmed.ncbi.nlm.nih.gov/32816843
162. Thatikonda V, Lyu H, Jurado S, Kostyrko K, Bristow CA, Albrecht C et al. Co-targeting SOS1 enhances the antitumor effects of KRASG12C inhibitors by addressing intrinsic and acquired resistance. Nat Cancer. 2024;1352–70. https://pubmed.ncbi.nlm.nih.gov/39103541
163. Hunter JC, Gurbani D, Ficarro SB, Carrasco MA, Lim SM, Choi HG et al. In situ selectivity profiling and crystal structure of SML-8-73-1, an active site inhibitor of oncogenic K-Ras G12C. Proc Natl Acad Sci U S A. 2014;111(24):8895–900. https://pubmed.ncbi.nlm.nih.gov/24889603
164. Xu K, Park D, Magis AT, Zhang J, Zhou W, Sica GL et al. Small molecule KRAS agonist for mutant KRAS cancer therapy. Mol Cancer. 2019;18(1):85. https://pubmed.ncbi.nlm.nih.gov/30971271
165. Chen YNP, LaMarche MJ, Chan HM, Fekkes P, Garcia-Fortanet J, Acker MG et al. Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases. Nature. 2016;535(7610):148–52. https://pubmed.ncbi.nlm.nih.gov/27362227
166. Sarver P, Acker M, Bagdanoff JT, Chen Z, Chen YN, Chan H et al. 6-Amino-3-methylpyrimidinones as potent, selective, and orally efficacious SHP2 inhibitors. J Med Chem. 2019;62(4):1793–802. https://pubmed.ncbi.nlm.nih.gov/30688459
167. Nichols RJ, Haderk F, Stahlhut C, Schulze CJ, Hemmati G, Wildes D et al. RAS nucleotide cycling underlies the SHP2 phosphatase dependence of mutant BRAF-, NF1- and RAS-driven cancers. Nat Cell Biol. 2018;20(9):1064–73. https://pubmed.ncbi.nlm.nih.gov/30104724
168. LaMarche MJ, Acker M, Argintaru A, Bauer D, Boisclair J, Chan H et al. Identification of TNO155, an allosteric SHP2 inhibitor for the treatment of cancer. J Med Chem. 2020;63(22):13578–94. https://pubmed.ncbi.nlm.nih.gov/32910655
169. Karoulia Z, Gavathiotis E, Poulikakos PI. New perspectives for targeting RAF kinase in human cancer. Nat Rev Cancer. 2017;17(11):676–91. https://pubmed.ncbi.nlm.nih.gov/28984291
170. Hall-Jackson CA, Eyers PA, Cohen P, Goedert M, Boyle FT, Hewitt N et al. Paradoxical activation of Raf by a novel Raf inhibitor. Chem Biol. 1999;6(8):559–68. https://pubmed.ncbi.nlm.nih.gov/10421767
171. Lyons JF, Wilhelm S, Hibner B, Bollag G. Discovery of a novel Raf kinase inhibitor. Endocr Relat Cancer. 2001;8(3):219–25. https://pubmed.ncbi.nlm.nih.gov/11566613
172. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356(2):125–34. https://pubmed.ncbi.nlm.nih.gov/17215530
173. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90. https://pubmed.ncbi.nlm.nih.gov/18650514
174. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507–16. https://pubmed.ncbi.nlm.nih.gov/21639808
175. Bollag G, Hirth P, Tsai J, Zhang J, Ibrahim PN, Cho H et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature. 2010;467(7315):596–9. https://pubmed.ncbi.nlm.nih.gov/20823850
176. Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet. 2012;379(9829):1893–901. https://pubmed.ncbi.nlm.nih.gov/22608338
177. Ballantyne AD, Garnock-Jones KP. Dabrafenib: first global approval. Drugs. 2013;73(12):1367–76. https://pubmed.ncbi.nlm.nih.gov/23881668
178. Hatzivassiliou G, Song K, Yen I, Brandhuber BJ, Anderson DJ, Alvarado R et al. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. Nature. 2010;464(7287):431–5. https://pubmed.ncbi.nlm.nih.gov/20130576
179. Poulikakos PI, Zhang C, Bollag G, Shokat KM, Rosen N. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. Nature. 2010;464(7287):427–30. https://pubmed.ncbi.nlm.nih.gov/20179705
180. Heidorn SJ, Milagre C, Whittaker S, Nourry A, Niculescu-Duvas I, Dhomen N et al. Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. Cell. 2010;140(2):209–21. https://pubmed.ncbi.nlm.nih.gov/20141835
181. Park S, Kim TM, Cho SY, Kim S, Oh Y, Kim M et al. Combined blockade of polo-like kinase and pan-RAF is effective against NRAS-mutant non-small cell lung cancer cells. Cancer Lett. 2020;495:135–44. https://pubmed.ncbi.nlm.nih.gov/32979462
182. Monaco KA, Delach S, Yuan J, Mishina Y, Fordjour P, Labrot E et al. LXH254, a potent and selective ARAF-sparing inhibitor of BRAF and CRAF for the treatment of MAPK-driven tumors. Clin Cancer Res. 2021;27(7):2061–73. https://pubmed.ncbi.nlm.nih.gov/33355204
183. ARAF mutations limit response to RAF dimer inhibition. Cancer Discov. 2021;11(7):1610. https://pubmed.ncbi.nlm.nih.gov/33990346
184. Yen I, Shanahan F, Lee J, Hong YS, Shin SJ, Moore AR et al. ARAF mutations confer resistance to the RAF inhibitor belvarafenib in melanoma. Nature. 2021;594(7863):418–23. https://pubmed.ncbi.nlm.nih.gov/33953400
185. Desai J, Gan H, Barrow C, Jameson M, Atkinson V, Haydon A et al. Phase I, open-label, dose-escalation/dose-expansion study of Lifirafenib (BGB-283), an RAF family kinase inhibitor, in patients with solid tumors. J Clin Oncol. 2020;38(19):2140–50. https://pubmed.ncbi.nlm.nih.gov/32182156
186. Yuan X, Tang Z, Du R, Yao Z, Cheung SH, Zhang X et al. RAF dimer inhibition enhances the antitumor activity of MEK inhibitors in K-RAS mutant tumors. Mol Oncol. 2020;14(8):1833–49. https://pubmed.ncbi.nlm.nih.gov/32336014
187. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012;367(2):107–14. https://pubmed.ncbi.nlm.nih.gov/22663011
188. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):603–15. https://pubmed.ncbi.nlm.nih.gov/29573941
189. Ascierto PA, McArthur GA, Dréno B, Atkinson V, Liszkay G, Di Giacomo AM et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016;17(9):1248–60. https://pubmed.ncbi.nlm.nih.gov/27480103
190. Dummer R, Schadendorf D, Ascierto PA, Arance A, Dutriaux C, Di Giacomo AM et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(4):435–45. https://pubmed.ncbi.nlm.nih.gov/28284557
191. Ascierto PA, Schadendorf D, Berking C, Agarwala SS, van Herpen CM, Queirolo P et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. Lancet Oncol. 2013;14(3):249–56. https://pubmed.ncbi.nlm.nih.gov/23414587
192. Jänne PA, van den Heuvel MM, Barlesi F, Cobo M, Mazieres J, Crinò L et al. Selumetinib plus Docetaxel compared with Docetaxel alone and progression-free survival in patients with KRAS-mutant advanced non-small cell lung cancer: the SELECT-1 randomized clinical trial. JAMA. 2017;317(18):1844–53. https://pubmed.ncbi.nlm.nih.gov/28492898
193. Blumenschein GR, Smit EF, Planchard D, Kim DW, Cadranel J, De Pas T et al. A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC)†. Ann Oncol. 2015;26(5):894–901. https://pubmed.ncbi.nlm.nih.gov/25722381
194. Infante JR, Somer BG, Park JO, Li CP, Scheulen ME, Kasubhai SM et al. A randomised, double-blind, placebo-controlled trial of trametinib, an oral MEK inhibitor, in combination with gemcitabine for patients with untreated metastatic adenocarcinoma of the pancreas. Eur J Cancer. 2014;50(12):2072–81. https://pubmed.ncbi.nlm.nih.gov/24915778
195. Lito P, Saborowski A, Yue J, Solomon M, Joseph E, Gadal S et al. Disruption of CRAF-mediated MEK activation is required for effective MEK inhibition in KRAS mutant tumors. Cancer Cell. 2014;25(5):697–710. https://pubmed.ncbi.nlm.nih.gov/24746704
196. Yen I, Shanahan F, Merchant M, Orr C, Hunsaker T, Durk M et al. Pharmacological induction of RAS-GTP confers RAF inhibitor sensitivity in KRAS mutant tumors. Cancer Cell. 2018;34(4):611–25. https://pubmed.ncbi.nlm.nih.gov/30300582
197. Morris EJ, Jha S, Restaino CR, Dayananth P, Zhu H, Cooper A et al. Discovery of a novel ERK inhibitor with activity in models of acquired resistance to BRAF and MEK inhibitors. Cancer Discov. 2013;3(7):742–50. https://pubmed.ncbi.nlm.nih.gov/23614898

198. Germann UA, Furey BF, Markland W, Hoover RR, Aronov AM, Roix JJ et al. Targeting the MAPK signaling pathway in cancer: promising preclinical activity with the novel selective ERK1/2 Inhibitor BVD-523 (Ulixertinib). Mol Cancer Ther. 2017;16(11):2351–63. https://pubmed.ncbi.nlm.nih.gov/28939558
199. Flemington V, Davies EJ, Robinson D, Sandin LC, Delpuech O, Zhang P et al. AZD0364 Is a potent and selective ERK1/2 inhibitor that enhances antitumor activity in KRAS-mutant tumor models when combined with the MEK inhibitor, Selumetinib. Mol Cancer Ther. 2021;20(2):238–49. https://pubmed.ncbi.nlm.nih.gov/33273059
200. Ward RA, Anderton MJ, Bethel P, Breed J, Cook C, Davies EJ et al. Discovery of a potent and selective oral inhibitor of ERK1/2 (AZD0364) that is efficacious in both monotherapy and combination therapy in models of non small cell lung cancer (NSCLC). J Med Chem. 2019;62(24):11004–18. https://pubmed.ncbi.nlm.nih.gov/31710489
201. Timofeev O, Giron P, Lawo S, Pichler M, Noeparast M. ERK pathway agonism for cancer therapy: evidence, insights, and a target discovery framework. NPJ Precis Oncol. 2024;8(1):70. https://pubmed.ncbi.nlm.nih.gov/38485987
202. Sugiura R, Satoh R, Takasaki T. ERK: a double-edged sword in cancer. ERK-dependent apoptosis as a potential therapeutic strategy for cancer. Cells. 2021;10(10):2509. https://pubmed.ncbi.nlm.nih.gov/34685488
203. Yue J, López JM. Understanding MAPK signaling pathways in apoptosis. Int J Mol Sci. 2020;21(7):234. https://pubmed.ncbi.nlm.nih.gov/32231094
204. Lilja J, Kaivola J, Conway JRW, Vuorio J, Parkkola H, Roivas P et al. SHANK3 depletion leads to ERK signalling overdose and cell death in KRAS-mutant cancers. Nat Commun. 2024;15(1):8002. https://pubmed.ncbi.nlm.nih.gov/39266533
205. Verret B, Cortes J, Bachelot T, Andre F, Arnedos M. Efficacy of PI3K inhibitors in advanced breast cancer. Ann Oncol. 2019;30(Suppl_10):x12–20. https://pubmed.ncbi.nlm.nih.gov/31859349
206. Skånland SS, Okkenhaug K, Davids MS. PI3K inhibitors in hematology: when one door closes… Clin Cancer Res. 2024;30(17):3667–75. https://pubmed.ncbi.nlm.nih.gov/38967552
207. Janku F, Yap TA, Meric-Bernstam F. Targeting the PI3K pathway in cancer: are we making headway? Nat Rev Clin Oncol. 2018;15(5):273–91. https://pubmed.ncbi.nlm.nih.gov/29508857
208. Dy GK, Govindan R, Velcheti V, Falchook GS, Italiano A, Wolf J et al. Long-term outcomes and molecular correlates of Sotorasib efficacy in patients with pretreated KRAS G12C-mutated non-small-cell lung cancer: 2-year analysis of CodeBreaK 100. J Clin Oncol. 2023;41(18):3311–7. https://pubmed.ncbi.nlm.nih.gov/37098232
209. Thummalapalli R, Bernstein E, Herzberg B, Li BT, Iqbal A, Preeshagul I et al. Clinical and genomic features of response and toxicity to Sotorasib in a real-world cohort of patients with advanced KRAS G12C-mutant non-small cell lung cancer. JCO Precis Oncol. 2023;7:e2300030. https://pubmed.ncbi.nlm.nih.gov/37384866
210. Hallin J, Bowcut V, Calinisan A, Briere DM, Hargis L, Engstrom LD et al. Anti-tumor efficacy of a potent and selective non-covalent KRASG12D inhibitor. Nat Med. 2022;28(10):2171–82. https://pubmed.ncbi.nlm.nih.gov/36216931
211. Zhou Q, Meng X, Sun L, Huang D, Yang N, Yu Y et al. Efficacy and safety of KRAS G12C inhibitor IBI351 monotherapy in patients with advanced non-small cell lung cancer: results from a phase 2 pivotal study. J Thorac Oncol. 2024;S1556-0864(24):00762–7. https://pubmed.ncbi.nlm.nih.gov/39127176
212. Wasko UN, Jiang J, Dalton TC, Curiel-Garcia A, Edwards AC, Wang Y et al. Tumour-selective activity of RAS-GTP inhibition in pancreatic cancer. Nature. 2024;629(8013):927–36. https://pubmed.ncbi.nlm.nih.gov/38588697
213. Skoulidis F, Goldberg ME, Greenawalt DM, Hellmann MD, Awad MM, Gainor JF et al. STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. Cancer Discov. 2018;8(7):822–35. https://pubmed.ncbi.nlm.nih.gov/29773717
214. Ricciuti B, Arbour KC, Lin JJ, Vajdi A, Vokes N, Hong L et al. Diminished efficacy of programmed death-(Ligand)1 inhibition in STK11- and KEAP1-mutant lung adenocarcinoma is affected by KRAS mutation status. J Thorac Oncol. 2022;17(3):399–410. https://pubmed.ncbi.nlm.nih.gov/34740862
215. Marinelli D, Mazzotta M, Scalera S, Terrenato I, Sperati F, D'Ambrosio L et al. KEAP1-driven co-mutations in lung adenocarcinoma unresponsive to immunotherapy despite high tumor mutational burden. Ann Oncol. 2020;31(12):1746–54. https://pubmed.ncbi.nlm.nih.gov/32866624
216. Scalera S, Ricciuti B, Mazzotta M, Calonaci N, Alessi JV, Cipriani L et al. Clonal KEAP1 mutations with loss of heterozygosity share reduced immunotherapy efficacy and low immune cell infiltration in lung adenocarcinoma. Ann Oncol. 2023;34(3):275–88. https://pubmed.ncbi.nlm.nih.gov/36526124
217. Scalera S, Mazzotta M, Corleone G, Sperati F, Terrenato I, Krasniqi E et al. KEAP1 and TP53 frame genomic, evolutionary, and immunologic subtypes of lung adenocarcinoma with different sensitivity to immunotherapy. J Thorac Oncol. 2021;16(12):2065–77. https://pubmed.ncbi.nlm.nih.gov/34450259
218. Tsai YS, Woodcock MG, Azam SH, Thorne LB, Kanchi KL, Parker JS et al. Rapid idiosyncratic mechanisms of clinical resistance to KRAS G12C inhibition. J Clin Invest. 2022;132(4):e155523. https://pubmed.ncbi.nlm.nih.gov/34990404
219. Awad MM, Liu S, Rybkin II, Arbour KC, Dilly J, Zhu VW et al. Acquired resistance to KRASG12C inhibition in cancer. N Engl J Med. 2021;384(25):2382–93. https://pubmed.ncbi.nlm.nih.gov/34161704
220. Desai J, Alonso G, Kim SH, Cervantes A, Karasic T, Medina L et al. Divarasib plus cetuximab in KRAS G12C-positive colorectal cancer: a phase 1b trial. Nat Med. 2024;30(1):271–8. https://pubmed.ncbi.nlm.nih.gov/38052910
221. Zhao Y, Murciano-Goroff YR, Xue JY, Ang A, Lucas J, Mai TT et al. Diverse alterations associated with resistance to KRAS(G12C) inhibition. Nature. 2021;599(7886):679–83. https://pubmed.ncbi.nlm.nih.gov/34759319
222. Yaeger R, Mezzadra R, Sinopoli J, Bian Y, Marasco M, Kaplun E et al. Molecular characterization of acquired resistance to KRASG12C-EGFR inhibition in colorectal cancer. Cancer Discov. 2023;13(1):41–55. https://pubmed.ncbi.nlm.nih.gov/36355783
223. Amodio V, Yaeger R, Arcella P, Cancelliere C, Lamba S, Lorenzato A et al. EGFR blockade reverts resistance to KRASG12C inhibition in colorectal cancer. Cancer Discov. 2020;10(8):1129–39. https://pubmed.ncbi.nlm.nih.gov/32430388
224. Yaeger R, Weiss J, Pelster MS, Spira AI, Barve M, Ou SHI et al. Adagrasib with or without cetuximab in colorectal cancer with mutated KRAS G12C. N Engl J Med. 2023;388(1):44–54. https://pubmed.ncbi.nlm.nih.gov/36546659
225. Dilly J, Hoffman MT, Abbassi L, Li Z, Paradiso F, Parent BD et al. Mechanisms of resistance to oncogenic KRAS inhibition in pancreatic cancer. Cancer Discov. 2024; https://pubmed.ncbi.nlm.nih.gov/38975874
226. Ryan MB, Coker O, Sorokin A, Fella K, Barnes H, Wong E et al. KRASG12C-independent feedback activation of wild-type RAS constrains KRASG12C inhibitor efficacy. Cell Rep. 2022;39(12):110993. https://pubmed.ncbi.nlm.nih.gov/35732135
227. Ryan MB, Fece de la Cruz F, Phat S, Myers DT, Wong E, Shahzade HA et al. Vertical pathway inhibition overcomes adaptive feedback resistance to KRASG12C inhibition. Clin Cancer Res Off J Am Assoc Cancer Res. 2020;26(7):1633–43. https://pubmed.ncbi.nlm.nih.gov/31776128
228. Gulay KCM, Zhang X, Pantazopoulou V, Patel J, Esparza E, Pran Babu DS et al. Dual inhibition of KRASG12D and Pan-ERBB is synergistic in pancreatic ductal adenocarcinoma. Cancer Res. 2023;83(18):3001–12. https://pubmed.ncbi.nlm.nih.gov/37378556
229. Klomp JA, Klomp JE, Stalnecker CA, Bryant KL, Edwards AC, Drizyte-Miller K et al. Defining the KRAS- and ERK-dependent transcriptome in KRAS-mutant cancers. Science. 2024;384(6700):eadk0775. https://pubmed.ncbi.nlm.nih.gov/38843331
230. Tong X, Patel AS, Kim E, Li H, Chen Y, Li S et al. Adeno-to-squamous transition drives resistance to KRAS inhibition in LKB1 mutant lung cancer. Cancer Cell. 2024;42(3):413–28. https://pubmed.ncbi.nlm.nih.gov/38402609
231. Hu F, Lito P. Insights into how adeno-squamous transition drives KRAS inhibitor resistance. Cancer Cell. 2024;42(3):330–2. https://pubmed.ncbi.nlm.nih.gov/38471455
232. Haderk F, Chou YT, Cech L, Fernández-Méndez C, Yu J, Olivas V et al. Focal adhesion kinase-YAP signaling axis drives drug-tolerant persister cells and residual disease in lung cancer. Nat Commun. 2024;15(1):3741. https://pubmed.ncbi.nlm.nih.gov/38702301
233. Gai X, Liu Y, Lan X, Chen L, Yuan T, Xu J et al. Oncogenic KRAS induces arginine auxotrophy and confers a therapeutic vulnerability to SLC7A1 inhibition in non-small cell lung cancer. Cancer Res. 2024;84(12):1963–77. https://pubmed.ncbi.nlm.nih.gov/38502865
234. Gunji D, Narumi R, Muraoka S, Isoyama J, Ikemoto N, Ishida M et al. Integrative analysis of cancer dependency data and comprehensive phosphoproteomics data revealed the EPHA2-PARD3 axis as a cancer vulnerability in KRAS-mutant colorectal cancer. Mol Omics. 2023;19(8):624–39. https://pubmed.ncbi.nlm.nih.gov/37232035
235. Cheng NC, Vonderheide RH. Immune vulnerabilities of mutant KRAS in pancreatic cancer. Trends Cancer. 2023;9(11):928–36. https://pubmed.ncbi.nlm.nih.gov/37524642
236. Singh H, Keller RB, Kapner KS, Dilly J, Raghavan S, Yuan C et al. Oncogenic drivers and therapeutic vulnerabilities in KRAS wild-type pancreatic cancer. Clin Cancer Res. 2023;29(22):4627–43. https://pubmed.ncbi.nlm.nih.gov/37463056

237. Li Z, Dang X, Huang D, Jin S, Li W, Shi J et al. Garsorasib in patients with KRASG12C-mutated non-small-cell lung cancer in China: an open-label, multicentre, single-arm, phase 2 trial. Lancet Respir Med. 2024;12(8):589–98. https://pubmed.ncbi.nlm.nih.gov/38870979
238. Kitai H, Choi PH, Yang YC, Boyer JA, Whaley A, Pancholi P et al. Combined inhibition of KRASG12C and mTORC1 kinase is synergistic in non-small cell lung cancer. Nat Commun. 2024;15(1):6076. https://pubmed.ncbi.nlm.nih.gov/39025835

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