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Targeting KRAS in cancer

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RAS family variants—most of which involve *KRAS*—are the most commonly occurring hotspot mutations in human cancers and are associated with a poor prognosis. For almost four decades, KRAS has been considered undruggable, in part due to its structure, which lacks small-molecule binding sites. But recent developments in bioengineering, organic chemistry and related fields have provided the infrastructure to make direct KRAS targeting possible. The first successes occurred with allele-specific targeting of *KRAS* p.Gly12Cys (G12C) in non-small cell lung cancer, resulting in regulatory approval of two agents—sotorasib and adagrasib. Inhibitors targeting other variants beyond G12C have shown preliminary antitumor activity in highly refractory malignancies such as pancreatic cancer. Herein, we outline RAS pathobiology with a focus on *KRAS*, illustrate therapeutic approaches across a variety of malignancies, including emphasis on the 'on' and 'off' switch allele-specific and 'pan' RAS inhibitors, and review immunotherapeutic and other key combination RAS targeting strategies. We summarize mechanistic understanding of de novo and acquired resistance, review combination approaches, emerging technologies and drug development paradigms and outline a blueprint for the future of KRAS therapeutics with anticipated profound clinical impact.

RAS family proteins are key cellular 'relay switches', which integrate upstream signals from growth factor receptors and transmit signals into multiple effector pathways to drive cellular growth and proliferation[1,2]. More than 40 years ago, mutationally activated RAS was identified as a primary driver of oncogenesis across human cancers and almost one in five of all human cancers were shown to harbor a RAS alteration. Key intrinsic features of RAS have posed a decades-long hurdle for drug targeting. Firstly, RAS undergoes dynamic conformational changes, cycling between 'on' (GTP-bound) and 'off' (GDP-bound) states, each of which contain distinct structural features—and inhibitors must selectively modulate this balance (Fig. 1). Secondly, the strong affinity of RAS for GTP, combined with high intracellular concentrations of GTP, together renders the development of GTP-competitive inhibitors unfeasible. Thirdly, there is an absence of deep small-molecule binding pockets to serve as pharmacologic targets within RAS proteins[3,4]. Only recently, advances in medicinal chemistry and structural biology have converged to enable the breakthrough in targeted therapies against RAS.

KRAS represents the vast majority (>80%) of mutated RAS in solid tumors, and recurrent mutations within exon 2 codon 12 and 13, which act to maintain KRAS in the active 'on' state, have become a primary target in drug development. In 2013, the laboratory of Shokat and colleagues[5] used a novel disulfide tethering approach to identify compounds that bound covalently and selectively to KRAS G12C-GDP. These molecules bind to a newly discovered allosteric pocket near the cysteine residue, named the switch II pocket[6,7]. By requiring the mutant cysteine residue for binding, inhbitors of the *KRAS* variant with a p.Gly12Cys alteration (hereafter, KRAS G12C) specifically target the mutant protein while sparing KRAS wild-type protein. Historically, it was thought that KRAS oncoproteins were constitutively activated, 'locked' in an on state. There is an increasing mechanistic understanding that mutant *KRAS* continues to cycle, and indeed, the first clinical

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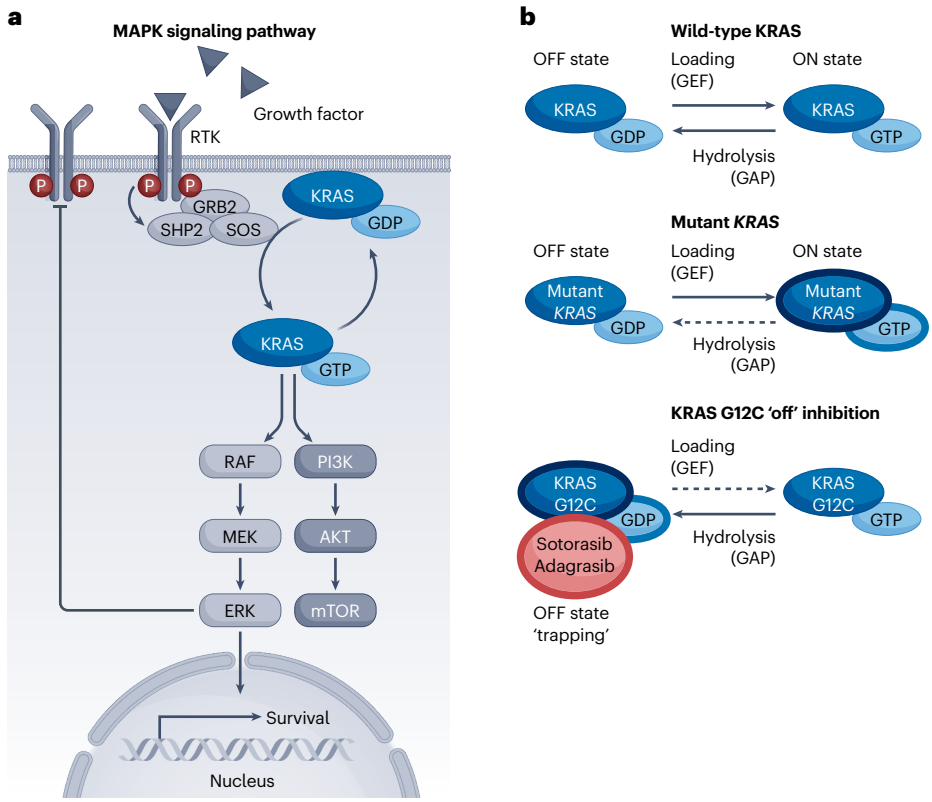

Fig. 1 | Regulation of KRAS and signal transduction pathways. a, KRAS transmits environmental signals from signaling ligands and growth factor receptors, into the RAS–RAF–MEK–ERK MAPK signaling and PI3K–AKT–mTOR pathway. KRAS is a small membrane-bound GTP hydrolase protein that cycles between 'on' (GTP-loaded) and 'off' (GDP-unloaded) states. This cycling between the 'on' and 'off' state depends on the activity of RAS-guanine nucleotide exchange factors (RAS-GEFs) and RAS-GTPase-activating proteins (RAS-GAPs). SOS1 and SOS2 are the major RAS-GEFs activated by upstream RTKs. SOS1-regulated GTP loading toward the RAS(on) state is mediated by the protein-tyrosine phosphatase SHP2. **b**, The level of active KRAS in cells is dictated by the balance between nucleotide hydrolysis and nucleotide loading. Active KRAS returns to the 'off' state when GTP is hydrolyzed to GDP, a process that is driven by GAPs as well as its intrinsic hydrolytic activity. *KRAS* mutations act to maintain KRAS in the active 'on' state, both by reducing the intrinsic GTPase ability of the protein and by preventing the activity of GAPs. Clinically approved KRAS G12C inhibitors, sotorasib and adagrasib, trap KRAS G12C in the inactive state, thereby blocking downstream signaling.

KRAS G12C inhibitors preferentially bind and 'trap' KRAS in its off state, exploiting this behavior. (Fig. 1)[8,9]. The drug specificity for 'on' versus 'off' states remains important for current drug development and selective differences between therapeutic agents. The first clinically available KRAS G12C inhibitors, sotorasib and adagrasib, have demonstrated promising clinical efficacy across multiple solid tumors and represent the first approved targeted therapies for tumors with any *KRAS* mutation[10,11].

Initial successes with KRAS G12C-mutant-selective inhibitors have been promising, nonetheless a series of hurdles to fully realize the potential of KRAS-directed therapies remain. KRAS serves as a convergent node within complex signaling pathways, and as such, KRAS and its broader signaling network adapt in response to therapeutic intervention. Emerging clinical data suggests that tumors frequently reactivate effector pathways via secondary genetic mutations. In addition, owing to adaptive feedback mechanisms, signaling pathways can rebound—thereby limiting the efficacy of therapeutic agents. Moreover, the heterogeneity of *KRAS* mutations across cancers, each potentially requiring a unique approach to effectively target, complicates the design of universally effective agents. A humbling fact is that with currently approved KRAS G12C inhibitors, only approximately 12% of *KRAS*-mutated tumors can be directly targeted[12]. In this Review, we aggregate data from recent clinical trials, examine emerging resistance mechanisms, and detail strategies to overcome therapy resistance. We highlight novel drug classes and combination strategies that aim to extend durable benefit for patients. Further, we explore the potential of KRAS-directed immunotherapeutic strategies. Together, these advances expand the therapeutic landscape for treating *KRAS*-mutant cancers.

Early clinical success and challenges with KRAS G12C inhibitors

Sotorasib and adagrasib, the first clinical KRAS G12C inhibitors, entered trials in non-small cell lung cancer (NSCLC), in which the prevalence of the *KRAS* G12C allele is approximately 12%—higher than others such as colorectal cancer (CRC) in which the frequency is around 3%. (Fig. 2)[13–15] The history of successful development of targeted therapies in NSCLC, with drugs targeting epidermal growth factor receptor (EGFR) mutations, ALK rearrangements, and others, established a precedent and a clear regulatory pathway for the development of new targeted agents in NSCLC. KRAS G12C inhibitors have subsequently shown efficacy in a range of solid tumors, with key studies highlighted below. Table 1 summarizes published, peer-reviewed clinical data from KRAS G12C inhibitors (adagrasib, sotorasib and divarasib) by tumor type[1]. Preliminary clinical data from additional KRAS inhibitors, drawn from recently presented abstracts or conference proceedings, are presented in Table 2.

NSCLC

The initial success of mutant-selective KRAS G12C inhibitors was demonstrated in patients with advanced NSCLC. In the CodeBreaK 100 study, sotorasib demonstrated an objective response rate (ORR) of 41.0% and progression-free survival (PFS) of 6.3 months in patients with

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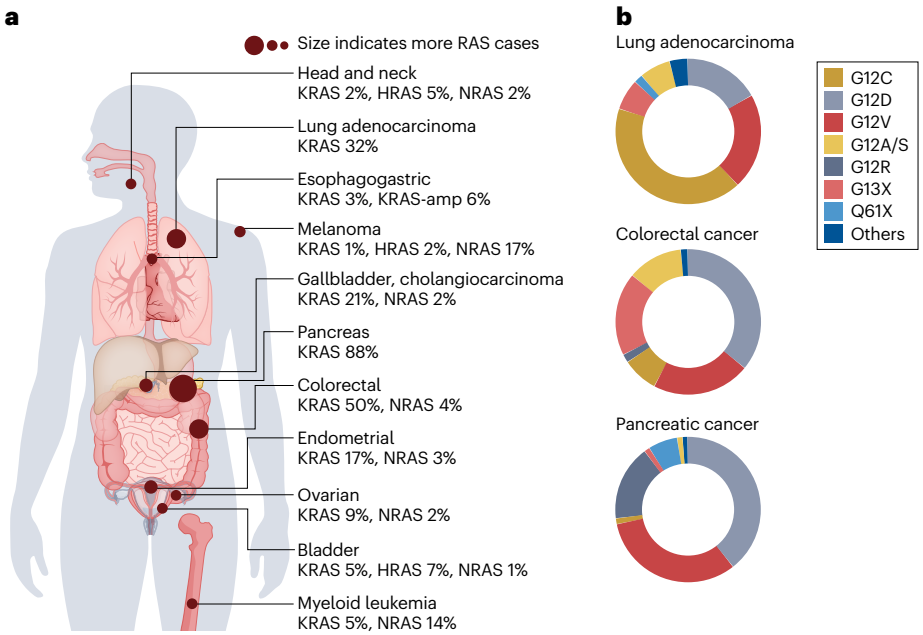

Fig. 2 | RAS mutations in cancer. a, Prevalence and distribution of RAS mutations across cancer types. **b**, Distribution of *KRAS* alleles in NSCLC, CRC and pancreatic cancer. Note that the allelic distribution varies significantly among cancer types, reflecting different underlying mutational processes (for example, G12C association with smoking) but also suggesting tissue-specific oncogenic signaling that varies between *KRAS* alleles[131,132]. Of note, *KRAS* G12D and *KRAS* G12V are the two most common alleles in CRC and PDAC, and some alleles remain unique to select histologies (*KRAS* G12R in PDAC). Data derived from ref. 13.

NSCLC[16,17]; similar results were reported from the phase 1/1b KRYSTAL-1 study, in which adagrasib demonstrated an ORR of 42.9% and a PFS of 6.5 months[18,19]. The US Food and Drug Administration granted accelerated approval for sotorasib in 2021 and adagrasib in 2022 for the treatment of NSCLC based on the results from these studies. Recent data from the randomized phase 3 CodeBreak 200 study in the setting of previously treated metastatic NSCLC demonstrated a modest benefit of sotorasib as compared with docetaxel. The primary endpoint of PFS was met (5.6 months versus 4.5 months) and a favorable ORR was reported (28.1% versus 13.2%); however, overall survival (OS), a key secondary endpoint, was not improved[20]. The Food and Drug Administration review raised concerns regarding potential biases within the trial design, including a high dropout rate in the docetaxel arm and inconsistencies in the assessment of progression status between arms, and a new confirmatory phase 3 study will be required to secure full regulatory approval[21].

Newer KRAS G12C selective inhibitors, which act through a similar mechanism but intend to improve upon first-in-class inhibitors (sotorasib and adagrasib) with respect to potency and selectivity, are currently in clinical trials (Table 2). The KRAS G12C inhibitor divarasib recently demonstrated an ORR of 53.4% and a PFS of 13.1 months in patients with NSCLC[22]. Preliminary data from olomorasib (LY3537982), opnurasib (JDQ443), IBI351 and garsorasib have also been reported, including activity in the context of disease progression on first-in-class inhibitors (Table 2)[23–27].

Of note, KRAS G12C inhibitors have demonstrated promising activity in treating NSCLC brain metastases, which affect approximately 40% of patients with *KRAS*-mutant NSCLC during their disease trajectory. Adagrasib is the only KRAS G12C inhibitor with data regarding activity in untreated brain metastases, with a central nervous system ORR of 42%, disease control rate (DCR) of 90%, and a PFS of 5.4 months ($n = 19$) in the KRYSTAL-1 trial[28]. The central nervous system activity of sotorasib remains unknown as patients with active, untreated brain metastases were excluded from initial studies; nevertheless, a post hoc analysis from CodeBreaK 100 showed that 16 (88%) patients had intracranial disease control and 2 patients had a complete response (CR)[29].

CRC

KRAS G12C inhibitors, as monotherapy, have shown efficacy in CRC, although less so relative to NSCLC. Several reasons for this discrepancy have been postulated, including adaptive feedback loops that activate upstream signaling in the context of single agents, as well as increased baseline receptor tyrosine kinase (RTK) expression and signaling[30–32]. A phase 2 clinical trial of sotorasib reported an ORR of 9.7% and a median PFS of 4.0 months, and in a phase 2 study of adagrasib, an ORR of 19% and a median PFS of 5.6 months was observed[33,34]. Recent data with divarasib in CRC demonstrated a single-agent ORR of 29.1% and a PFS of 5.6 months[22] (Table 1). Increased drug potency may underlie the slightly higher ORRs and longer PFS observed with single-agent divarasib and adagrasib as compared with sotorasib, although patient numbers are small.

Preclinical data demonstrating reactivation of the EGFR pathway in CRC as an adaptive response to KRAS G12C inhibition suggest that combined inhibition of KRAS G12C and EGFR can improve outcome and suppress feedback loops[30,32,35]. The limited success of mitogen-activated protein kinase (MAPK) blockade at a single node in CRC mirrors the experience with the BRAF inhibitor vemurafenib, where single-agent activity is limited by reactivation of RAS[36,37]. Indeed, combination EGFR and KRAS G12C blockade has improved clinical outcomes in CRC, with a combination of sotorasib and panitumumab (anti-EGFR) demonstrating an ORR of 26.4% and a median PFS of 5.6 months as compared with standard of care (trifluridine/tipiracil or regorafenib; ORR of 0%, PFS of 2.2 months) in the phase 3 CodeBreaK 300 trial[38]. Notably, a higher dose of sotorasib (960 mg compared to 240 mg) correlated with a longer PFS and higher response rate, suggesting that greater target occupancy and more complete signaling suppression may improve clinical impact in CRC[31,38]. For the related combination of adagrasib with the EGFR inhibitor cetuximab, an ORR of 46% and a PFS of 6.9 months were observed, significantly improving upon single-agent adagrasib activity[34]. In line with this, the combination of divarasib and cetuximab demonstrated an ORR of 62.5% and a PFS of 8.1 months[39] (Table 1). Interestingly, among five patients who had experienced disease progression on other KRAS G12C inhibitors before enrollment, three achieved a partial response (PR) and all five had disease control,

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Table 1 | Published trials for KRAS G12C inhibitors, reported by tumor type[a]

Clinical trial	Phase	Drug	Endpoints	Tumor type	No. of patients	Results
CodeBreaK 100	1/2	Sotorasib	Primary: ORR Secondary: DCR, PFS, OS, safety	NSCLC[19]	174	ORR: 41% (95% CI, 33.3–48.4%) DCR: 84% (95% CI, 77.3–88.9%) mPFS: 6.3 mo (95% CI, 5.3 to 8.2 mo) mOS: 12.5 mo (95% CI, 10.0 to 17.8 mo)
				CRC[33]	62	ORR: 9.7% (95% CI, 3.6–19.9%) DCR: 82.3% (95% CI, 70.5–90.8%) mPFS: 4.0 mo (95% CI, 2.8 to 4.2 mo) mOS: 10.6 mo (95% CI, 7.7 to 15.6 mo)
				PDAC[40]	38	ORR: 21% (95% CI, 10–37%) DCR: 84% mPFS: 4.0 mo (95% CI 2.8 to 5.6 mo) mOS: 6.9 mo (95% CI, 5.0 to 9.1 mo)
CodeBreaK 200	3	Sotorasib versus docetaxel	Primary: PFS Secondary: OS, ORR, DCR, TTR, DOR	NSCLC[20]	330	**Sotorasib** ORR: 28.1% (95% CI 21.5–35.4%) mPFS: 5.6 mo (95% CI, 4.3 to 7.8 mo) mOS: 10.6 mo (95% CI, 8.9 to 14.0 mo) **Docetaxel** ORR: 13.2% (95% CI 8.6–19.2%) mPFS: 4.5 mo (95% CI, 3.0 to 5.7 mo) mOS: 11.3 mo (95% CI, 9.0 to 14.9 mo)
CodeBreaK 300	3	Sotorasib 960 mg + panitumumab Sotorasib 240 mg + panitumumab SOC (trifluridine-tipiracil/ regorafenib)	Primary: PFS Secondary: OS, OR, DOR, TTR, DCR	CRC[38]	160	**Sotorasib 960 mg + panitumumab** ORR: 26.4% (95% CI, 15.3–40.3%) mPFS: 5.6 mo (95% CI, 4.2 to 6.3 mo) **Sotorasib 240 mg + panitumumab** ORR: 5.7% (95% CI, 1.2–15.7%) mPFS: 3.9 mo (95% CI, 3.7 to 5.8 mo) **SOC** ORR: 0% (95% CI, 0.0–6.6%) mPFS: 2.2 mo (95% CI, 1.9 to 3.9 mo)
KRYSTAL-1	1/2	Adagrasib	Primary: ORR Secondary: DCR, PFS, OS, 1-year survival	NSCLC[18]	116	ORR: 42.9% (95% CI, 33.5–52.6%) DCR: 50.5% mPFS: 6.5 mo (95% CI, 4.7 to 8.4 mo) mOS: 11.7 mo (95% CI, 9.2 mo to NE)
		Adagrasib + cetuximab versus adagrasib		CRC[34]	44,32	**Adagrasib + cetuximab** ORR: 46% (95% CI, 28–66%), PFS: 6.9 mo (95% CI, 5.4 to 8.1 mo) OS: 13.4 mo (95% CI, 9.5 to 20.1 mo) **Adagrasib** ORR: 19% (95% CI, 8–33%) mPFS: 5.6 mo (95% CI, 4.1 to 8.3 mo) mOS: 19.8 mo (95% CI, 12.5 to 23.0)
		Adagrasib		PDAC[41]	21	ORR: 33.3% (95% CI, 14.6–57.0%) DCR: 81.0% mPFS: 5.4 mo (95% CI 3.9 to 8.2 mo) mOS: 8.0 mo (95% CI 5.2 to 11.8 mo)
NCT04449874	1	Divarasib	Primary: safety	NSCLC[22]	60	ORR: 53.4% (95% CI: 39.9–66.7%) mPFS: 13.1 mo (95% CI, 8.8 mo to NE)
				CRC[22]	55	ORR: 29.1% (95% CI, 17.6–42.9%) mPFS: 5.6 mo (95% CI, 4.1 to 8.2 mo)
				PDAC[22]	7	ORR: 42.8% DCR: 100%
NCT04449874	1	Divarasib + cetuximab	Primary: safety	CRC[39]	29	KRASi-naive patients (n=24) ORR: 62.5% (95% CI: 40.6–81.2%) mPFS: 8.1 mo (95% CI: 5.5 to 12.3 mo) Prior KRAS G12Ci (n=5): 3 (60.0%)–PR, 2 (40.0%)–SD

[a]Data reported in peer-reviewed publications for sotorasib, adagrasib and divarasib, including in combination with EGFR inhibitors (cetuximab and panitumumab). DOR, duration of response; TTR, time to response. mo, months. NE, not evaluable

suggesting increased target suppression may overcome select mechanisms of resistance.

PDAC and other malignancies

In pancreatic adenocarcinoma (PDAC), where *KRAS* G12C mutations are infrequent (1–2% of cases), early data suggest encouraging single-agent activity for sotorasib, with an ORR of 21% and a PFS of 4.0 months—and adagrasib shows similar response rates[40–42] (Table 1). Of note, in both settings, patients were heavily pretreated with a median of 2–3 prior lines of therapy. Based on these data, both sotorasib and adagrasib are included in the National Comprehensive Cancer Network guidelines as approved agents for PDAC with *KRAS* G12C mutations. More recent data in PDAC with novel G12C inhibitors, including divarasib (ORR 43%, n = 7), olomorasib (ORR 42%, n = 24), glecirasib (ORR 42%, n = 31) and garsorasib (ORR 35%, n = 14) are also promising[22,23,43–45] (Table 1). Activity has also been observed in other gastrointestinal cancers, including biliary tract, appendiceal and gastroesophageal cancers, although data are limited in these settings.

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Table 2 | Selected novel agents with preliminary data

KRAS inhibitor	Trial/phase	Target	Mechanism	Reported data
KRAS G12C inhibitors				
Olomorasib LY3537982 Eli Lilly	NCT04956640 Phase 1[23,44]	KRAS G12C	OFF state inhibitor	NSCLC KRAS G12Ci naive (*n*=5): ORR 60%, DCR 80% KRAS G12Ci treated (*n*=9): ORR 0%, DCR 67% CRC, single agent (*n*=32) ORR 9%, DCR 84% Other solid tumors (*n*=11) ORR 36%, DCR 91% PDAC (*n*=24) ORR: 42%, DCR 92%
Opnurasib JDQ443 Novartis	KontRASt-01 NCT04699188 Phase 1/2[24]	KRAS G12C	OFF state inhibitor	NSCLC (*n*=24) ORR 42%, DCR 93%
Glecarisib JAB-21822 Jacobio Pharma	NCT05002270 Phase 1/2[45,81]	KRAS G12C	OFF state inhibitor	CRC (*n*=33) ORR 33.3%, DCR 90.9% PDAC (*n*=31) ORR 42%, DCR 93.5%
IBI351 Innovent Tech	NCT05005234 NCT05497336 Phase 2[26,27]	KRAS G12C	OFF state inhibitor	NSCLC (*n*=116) ORR: 46.6% (95% CI: 37.2–56.0%) DCR: 90.5% (95% CI: 83.7–95.2%), mPFS: 8.3 mo (95% CI: 5.6–10.4 mo) CRC (*n*=40) ORR: 47.5% (95% CI: 31.5–63.9%) DCR: 85.0% (95% CI: 70.2–94.3%)
Garsorasib D-1553 InventisBio	NCT04585035 Phase 1/2[25,130]	KRAS G12C	OFF state inhibitor	NSCLC (*n*=74) ORR: 40.5% (95% CI: 29.3–52.6%) DCR: 91.9% (95% CI: 83.2–97.0%) mPFS: 8.2 mo (7.5–NA) CRC (*n*=20) ORR: 20.8% (95% CI: 7.1–42.2%) DCR: 95.8% mPFS: 7.6 mo (95% CI, 2.9 to 9.5 mo)
RMC-6291 Revolution Medicines	NCT05462717 Phase 1[70]	KRAS G12C	ON state, tri-complex inhibitor	NSCLC KRASi G12Ci naive (*n*=7): ORR 43%, DCR 100% KRASi treated (*n*=10): ORR 50%, DCR 100% CRC (*n*=20) ORR 40%, DCR 80%
FMC-376 Frontier Medicines	NCT06244771 Phase 1/2	KRAS G12C	ON/OFF state direct inhibitor	No data
D3S-001 D3 Bio	NCT05410145 Phase 1	KRAS G12C	OFF state direct inhibitor	No data
KRAS G12D inhibitors				
MRTX1133 Mirati Therapeutics	NCT05737706 Phase 1/2	KRAS G12D	OFF state inhibitor	No data
RMC-9805 Revolution Medicines	NCT06040541 Phase 1	KRAS G12D	ON state, tri-complex inhibitor	No data
HRS-4642 Jiangsu HengRui Medicine	NCT05533463 Phase 1[66]	KRAS G12D	Unknown	NSCLC (*n*=10) ORR: 10%, DCR: 90% Other solid tumors (*n*=8) ORR: 0%, DCR: 62%
ASP3082 Astellas	NCT05382559 Phase 1	KRAS G12D	PROTAC	No data
Pan/multi-RAS inhibitors				
RMC-6236 Revolution Medicines	NCT05379985 Phase 1 (ref. 76)	Pan-RAS RAS wild type	RAS-multi, ON state, tri-complex inhibitor	NSCLC (*n*=40) ORR: 38%, DCR: 85% PDAC (*n*=46) ORR: 20%. DCR: 87%
BI-3706674	NCT06056024 Phase 1	Pan-KRAS KRAS wild type	Pan-KRAS, OFF state inhibitor	No data
Immune therapies				
ELI-002 7P (AMPLIFY-7P) Elicio Therapeutics	NCT05726864 Phase 1/2 (ref. 124)	KRAS G12D G12R, G12V, G12A, G12C, G12S, G13D	KRAS peptide vaccine+immune-stimulatory oligonucleotide	PDAC/CRC (*n*=19)–adjuvant treatment Biomarker reduction: 15/19 (79%) Clearance of minimal residual disease: 4/19 (21%)–*n*=2 pancreas, *n*=2 colorectal Polyfunctional mKRAS-specific T cell responses: 80% (*n*=12/15)

Table 2 (continued) | Selected novel agents with preliminary data

KRAS inhibitor	Trial/phase	Target	Mechanism	Reported data
KRAS peptide vaccine	NCT05013216 Phase 1 (ref. 125)	KRAS G12D G12R, G12V, G12A, G12C, G13D	KRAS 21-mer peptide vaccine+poly-ICLC+ipilimumab/ nivolumab	PDAC (n=11)–adjuvant treatment positive mKRAS-specific T cell response: 73% (n=8/11)
Anti-KRAS G12D mTCR Gilead (ex Kite)/ NCI	NCT03745326 Phase 1	KRAS/HRAS/NRAS G12D	HLA-A*11:01-restricted KRAS/ HRAS/NRAS G12D TCR	No data

RAS mutations occur at notable frequencies in gynecologic cancers (ovarian and endometrial), thyroid cancer and melanoma, among others (Fig. 2). Notably, targeted blockade within the MAPK pathway has yielded therapeutic successes in these diseases, including the combined use of BRAF and MEK inhibitors in *BRAF*-mutant melanoma and thyroid cancers as well as MEK inhibition in low-grade serous ovarian cancers, where MAPK pathway alterations are common[46–48]. Currently, clinical data for KRAS-directed treatments across these cancers are limited. As novel therapeutics target additional *KRAS* alleles and RAS isoforms (as detailed below), their potential to benefit these cancer types is promising.

Resistance mechanisms

Acquired resistance through genetic mechanisms

Recent clinical datasets, primarily from NSCLC and CRC, provide early insights into genetic mechanisms contributing to resistance to KRAS G12C inhibitors[39,49–52]. Strikingly, nearly all patients with identified resistance mutations acquire alterations that reestablish RAS–MAPK signaling, highlighting the strong addiction to RAS signaling among these cancers. These acquired resistance mutations can broadly be divided into several classes (Fig. 3a and Supplementary Table 1). Notably, many patients who develop resistance to KRAS G12C inhibitors harbor more than one resistance mechanism, with secondary mutations often occurring in sub-clonal tumor cell populations, highlighting the clinical challenge in surmounting the diversity of resistance mechanisms[39,49,51].

Developing effective inhibitors to overcome acquired resistance may necessitate drugs that simultaneously target multiple secondary alterations (for example, multi-RAS inhibitors, RAS degraders) or rely on binding outside the switch II pocket (RAS-ON inhibitors). Moreover, sequencing of therapies and thoughtful combinatorial strategies will become increasingly important. Genetic variants that emerge on exposure to KRAS G12X treatment will also inform the choice of subsequent therapy. Future studies that characterize the temporal evolution of G12C inhibitor resistance will underpin strategies to overcome resistance.

Genomic determinants of primary resistance

For individual patients, clinical outcomes with KRAS G12C inhibitor therapies vary widely. Of note, 36% of patients experienced either primary resistance or early disease progression (PFS < 3 months) on sotorasib therapy in recently published data from the 2-year analysis of the CodeBreaK 100 study in NSCLC[53]. In NSCLC, emerging data suggest that co-occurring genetic mutations in *KEAP1*, *SMARCA4* and *CDKN2A* are associated with inferior clinical outcomes to sotorasib therapy[54], with *KEAP1* mutations being associated with a lower response rate across datasets[19,53,55]. The biological mechanism of resistance mediated by these mutations remains to be explored, and moving forward, these genomic features will need to be defined across tumor types. Co-occurring mutations that predict for response will serve as markers for patient stratification and therapy intensification in randomized clinical trials.

Adaptive mechanisms of resistance

Notably, a large fraction of patients have no identifiable genetic alteration that explains primary or acquired resistance, suggesting that non-genetic mechanisms are responsible. Adaptive resistance describes the rapid reactivation of upstream RTKs, KRAS or their effector pathways as a consequence of feedback signaling mechanisms (Fig. 3b). In *KRAS* G12-mutant CRC, reactivation of MAPK signaling through EGFR is thought to be the dominant driver of downstream MAPK signaling, and recent clinical data, outlined above, support the use of combined blockade of EGFR and KRAS. However, whether targeting RTKs in other epithelial tumors will improve response remains under investigation. Recent preclinical data suggest that PDAC may behave similarly, with synergy observed between EGFR inhibition and KRAS p.Gly12Asp (G12D)-selective inhibition (MRTX1133) in xenograft models[56]. A cohort of the KRYSTAL-1 trial testing the combination of adagrasib and cetuximab in PDAC is ongoing (NCT03785249).

The identity of the activated upstream RTK may also vary between tissue types or between individual tumors; in PDAC *KRAS* G12D models, combining KRAS inhibition with pan-ERBB inhibition (rather than HER2 or EGFR inhibition) was highly synergistic, and even in *KRAS* G12C CRC models, KRAS G12C inhibition has been noted to differentially activate upstream RTKs[57,58]. Another possibility is that activation of wild-type RAS (KRAS, NRAS, HRAS), which bypasses mutant *KRAS* inhibition, may be a critical mediator of adaptive resistance. This latter mechanism has been observed to underline resistance to sotorasib in *KRAS* G12C-mutant NSCLC, CRC and PDAC cell lines[58]. Collectively, these findings suggest that that increased potency of *KRAS*-mutant-selective inhibitors alone will not be sufficient to overcome adaptive feedback, and other strategies will be needed in the clinic.

Emerging approaches include the combination of mutant *KRAS* inhibition and either upstream RTK targeting; targeting of convergent signaling nodes (for example, SHP2, SOS1 and MEK); or simultaneous targeting of wild-type RAS isoforms (Fig. 3). Several of these approaches are under active investigation.

Histologic/cell-state transformation as a resistance mechanism

Emerging data from lung adenocarcinomas exposed to KRAS G12C inhibition demonstrate that cell-state or lineage transitions may have a role in resistance to KRAS inhibition. In a recent study, lung adenocarcinoma was observed to transdifferentiate into an alveolar type-1-like state under KRAS inhibition, allowing cancer cells to evade treatment and survive[59]. Recent data refine this model by revealing the complex interplay between underlying genetics and cellular plasticity. Specifically in lung adenocarcinoma, the likelihood of adenosquamous transition under therapeutic pressure is genotype dependent, with a transition toward a squamous p40 immunohistochemistry positivity state occurring more frequently in *STK11*-mutated tumors at the time of therapy initiation. These findings mirror lineage transformation seen in response to tyrosine kinase inhibitor therapy in NSCLC[60,61].

A recurring emergent theme suggests that transition from epithelial-to-mesenchymal (EMT) states may confer *KRAS* independence in tumors. Fundamental early work identified a 'KRAS dependency' gene signature, which correlated epithelial differentiation status with sensitivity to KRAS knockdown, and with induction of mesenchymal-to-epithelial transformation (MET; for example, through *Zeb1* loss in PDAC) as restoring sensitivity[62]. Preclinical data support the observation that *KRAS* G12C-mutant cell lines with resistance to

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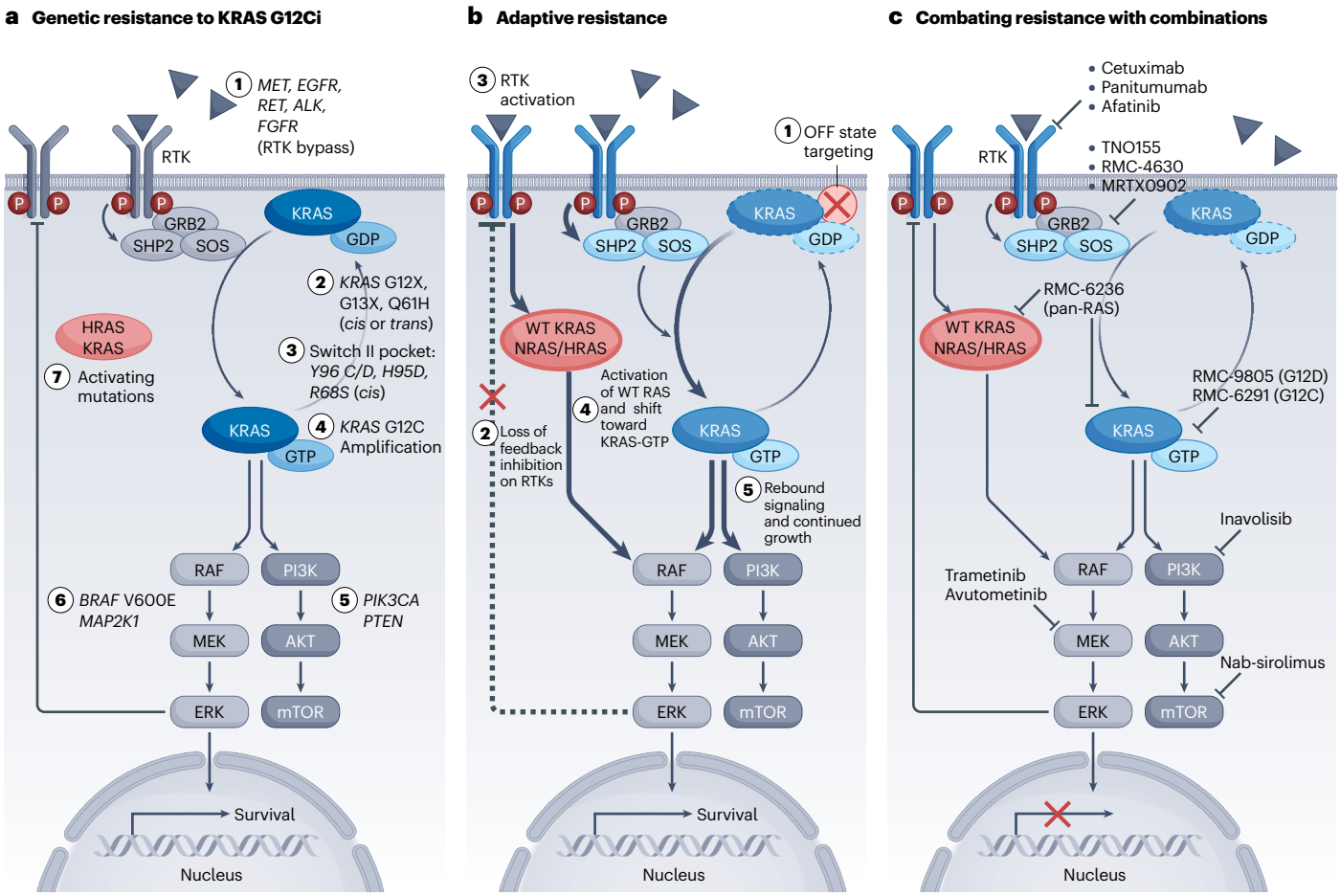

Fig. 3 | Overcoming resistance to RAS inhibitors with combination approaches. a, Acquired genetic resistance to KRAS G12C within MAPK components can be divided into several classes: (1) amplifications or mutations of upstream RTK (for example, EGFR and FGFR); (2) mutation of the *KRAS* G12C codon to another mutant variant (*cis* G12X) or secondary activating mutations on the *trans* (previously wild type) *KRAS* allele (G12D, G12R, G12V, G13D, Q61H); (3) KRAS switch II pocket mutations that block drug binding (R68, H95 or Y96); (4) *KRAS* G12C gene amplification or copy number gain; (5,6) activating mutations in downstream effectors pathways, such as *PIK3CA*, *BRAF* or *MEK*, that effectively bypass *KRAS* G12C; (7) activating mutations in *NRAS* or *HRAS*. Clinical resistance data from key studies are summarized in Supplementary Table 1 (refs. 39,49,50,52). **b**, Adaptive mechanisms of resistance. In the presence of mutant *KRAS*, feedback inhibition constrains the activity of upstream RTKs and wild-type (WT) RAS isoforms. Under treatment targeting the KRAS G12C 'off' state, MAPK pathway suppression results in loss of feedback inhibition, leading to upregulation of RTKs, a shift of RAS into an 'on state' mediated by SOS and SHP2, and activation of WT RAS isoforms. Rebound signaling feedback limits the efficacy of drug treatment. **c**, Addressing resistance with combination therapy. Combination strategies aim to limit both acquired genetic mutations and adaptive resistance to KRAS inhibitors by targeting upstream RTKs, secondary RAS mutations and WT RAS isoforms, or downstream effector pathways (RAF–MEK and PI3K–AKT).

sotorasib harbor increased activation of EMT programs with parallel activation of the PI3K pathway[63]. Interestingly, induction of EMT was a dominant mechanism of resistance in a rapid-autopsy case of a patient with lung adenocarcinoma who had relapse of disease while receiving sotorasib[64].

Given that a high percentage of tumors with clinical resistance to KRAS G12C inhibitors do not harbor clear secondary genomic alterations, these early data highlight potentially convergent transcriptional mechanisms to explain resistance. Moving forward, studies that integrate co-occurring genetic mutations and baseline transcriptional features of tumors will help guide understanding of the KRAS inhibitor response, predict patterns of acquired resistance and inform therapeutic choices in the clinic.

Novel strategies to inhibit KRAS

Building on the success of KRAS G12C inhibitors, newer therapeutics in development aim to extend their reach to additional *KRAS* alleles and to enhance efficacy, reduce toxicity and delay resistance. Novel KRAS-targeting drugs can be broadly split into two classes, each with its own advantages. The first class, mutation-selective inhibitors, are designed to target a single mutant gene or protein and are expected to have high potency, high (favorable) therapeutic index and favorable tolerability. The second class are pan-RAS/KRAS inhibitors, which target the full diversity of RAS alterations (mutations and amplifications) and have greater potential to address resistance—but are theoretically more likely to incur toxicity due to inhibition of wild-type RAS in normal tissues.

Mutation-selective inhibitors of KRAS

Several new drugs selective for specific KRAS-mutant proteins are currently in clinical phase development, and more are in late preclinical testing (Table 2). KRAS G12C inhibitors rely on the covalent interaction between the small-molecule inhibitor and the mutated cysteine residue. However, this strategy does not apply to other amino acids, and non-covalent inhibitors are one way to circumvent this challenge[65,66]. MRTX1133 is a non-covalent, selective KRAS G12D inhibitor, which binds to the switch II pocket of KRAS G12D. It has high selectivity over the wild-type allele, has been shown to successfully block key downstream

effectors of KRAS in vitro and leads to robust tumor regression in human patient-derived xenografts of NSCLC, PDAC and CRC and in mouse models[56,65,67,68]. A phase 1 study (NCT05737706) of MRTX1133 in *KRAS* G12D advanced solid tumors is underway.

Tri-complex inhibitors are another class of allele-specific and pan-allele targeting drugs that bind to RAS through a unique mechanism, serving as a molecular 'glue' with cyclophilin A. The assembled tri-complex prevents mutant *KRAS* from signaling via steric blockade. Tri-complex inhibitors, which were designed to bind the KRAS 'on' state, afford potential advantages. Firstly, tri-complex inhibitors can maintain pathway inhibition in the face of adaptive feedback from RTKs that may impel KRAS into an active state in response to the drug and, secondly, by binding through an alternate mechanism that overcomes a subset of acquired resistance alterations[69]. In the context of KRAS G12C inhibition with 'off' state inhibitors, secondary *KRAS* G12C p.Tyr96Asp (Y96D) (switch pocket) mutations sometimes emerge at the time of resistance. Interestingly, in engineered *KRAS* G12C/Y96D double-mutant cancer cell lines, RM-018—a KRAS G12C tri-complex inhibitor—maintained efficacy, demonstrating the ability of newer drugs to surmount mechanisms of genetic resistance to first-in-class therapies[51]. In line with preclinical data, RMC-6291, a related compound in clinical development, has demonstrated promising early clinical efficacy. In patients with NSCLC, 43% achieved a PR ($n = 17$), and in patients with CRC, 40% had a PR ($n = 20$)[70] (Table 2). Interestingly and importantly, among the ten patients with NSCLC who had previously been treated with a KRAS G12C 'off' state inhibitor, 50% achieved a PR and the DCR was 100%, suggesting the promise of this approach to overcome resistance. This class of selective inhibitors includes RMC-6291 (G12C) and RMC-9805 (G12D), which are currently in phase 1 studies (NCT05462717 and NCT06040541), as well as inhibitors against additional variants (p.Gly12Val (G12V), p.Gln61His (Q61H) and p.Gly13Cys (G13C)) planned to enter clinical development in 2024.

Several new agents in early development bind directly to the KRAS G12C 'on' state, without requiring an intermediate chaperone, and as above, afford similar potential advantages over 'off' state inhibitors, overcoming RTK-driven pathway rebound and addressing some secondary resistance alterations; these agents include BBO-8520 (phase 1 trial planned; ONKORAS-101) and FMC-376 (NCT06244771)[71,72] (Table 2).

Proteolysis targeting chimeric (PROTAC) technology drugs represent an emerging class of agents that induces degradation of a target protein using intrinsic cellular machinery. These drugs link a protein of interest with an E3 ligase, enabling ubiquitination and subsequent degradation through the cellular proteasome. ASP3082, a selective KRAS G12D degrader, is currently furthest along in clinical development. ASP3082 binds KRAS G12D and an undisclosed E3 ligase adaptor protein[73]. Activity was observed pre-clinically in in vivo systems, and a phase 1 study across solid tumors began in June 2022 (NCT05382559).

Pan-RAS/KRAS therapeutic approaches

Pan-RAS approaches, which inhibit all mutant and wild-type isoforms, have theoretical advantages over their allele-specific counterparts. First, the relative rarity of certain *KRAS* alleles (for example, Gln61, Gly13X and others) makes it impractical to generate an allele-specific inhibitor for each point mutation; therefore, pan-RAS/KRAS drugs expand the therapeutic potential of this drug class. Secondly, pan-targeting approaches have the potential to block compensatory activation of wild-type RAS isoforms, a mediator of resistance. Thirdly, pan-RAS/KRAS drugs are likely to prevent the emergence of at least one mode of acquired resistance (on-target mutations within *KRAS*), and thus may also have use in therapy sequencing after allele-selective approaches. The toxicity profile of inhibiting all RAS isoforms, including wild-type RAS, will be informed by ongoing clinical trials.

RMC-6236 is a tri-complex RAS 'on' state inhibitor with activity against mutant and wild-type KRAS, NRAS and HRAS and has demonstrated potent preclinical activity against tumors carrying various RAS genotypes, including cancer models resistant to first-generation KRAS G12C inhibitors with secondary *NRAS* mutations, amplification of wild-type *KRAS* and amplifications of RTKs[74,75]. Early data presented at the 2023 European Society of Medical Oncology congress reported clinical efficacy of this compound; among 40 patients with NSCLC, the ORR was 38% and the DCR was 85%, with 1 out of 40 exhibiting a CR. Among 46 patients with PDAC, the ORR was 20% (all PRs), and the DCR was 87% (Table 2)[76]. These preliminary data demonstrate an encouraging signal of clinical activity. Notably, antitumor responses were observed in tumors with G12D, G12V and p.Gly12Arg (G12R) mutations and several prior lines of therapy (median of three prior lines in patients with PDAC). To our knowledge, this agent is the first to show clinical activity in *KRAS* alleles that are frequently mutated in PDAC, a highly lethal and recalcitrant malignancy. The efficacy of RMC-6236 and other KRAS-directed treatments may be more pronounced in earlier lines of therapy, a hypothesis that will be evaluated in forthcoming clinical trials.

BI-2865 is a novel pan-KRAS inhibitor that selectively binds a spectrum of *KRAS* mutations and the wild-type KRAS protein, but notably spares other RAS family proteins, thereby potentially limiting the toxicity of RAS blockade in normal cells[77]. The selectivity of BI-2865 is based on binding to a residue within the switch II binding pocket (His95) that is present only in KRAS (and not NRAS or HRAS). Recent data demonstrate that BI-2865 can inhibit many of the common *KRAS* mutations seen in cancer, including G12D, G12V, G12C and p.Gly13Asp (G13D), as well as wild-type *KRAS*, which is amplified in many cancers, with potential to target approximately 95% of *KRAS* altered cancers overall[78]. Importantly, BI-2865 targets the inactive, GDP-bound state of KRAS, and its preclinical activity suggests that the majority of *KRAS* variants cycle sufficiently through the 'off' state for these inhibitors to exert activity. A phase 1 trial of BI-3706674, which is a similar compound and inhibits multiple versions of KRAS, is planned (NCT06056024)[79]. Pan-KRAS PROTAC degraders have also been described, such as ACBI3, which degrades all *KRAS* mutants; however, activity has yet to be reported in vivo and these compounds have not entered clinical development[80].

Overall, novel approaches aim to balance the benefit and toxicity of pan-RAS/KRAS drugs by combination with allele-selective KRAS inhibitors, thereby leveraging the high therapeutic index of selective drugs and simultaneously preventing adaptive pathway reactivation and escape through secondary mutations. A phase 1 study combining RMC-6291 (G12C ON) with RMC-6236 (pan-RAS) is now underway in solid tumors (NCT06128551).

Combination strategies targeting RAS

The RAS signaling pathway has several upstream and downstream mediators, which are attractive targets for combination therapies with RAS inhibitors. Given the benchmark activity of KRAS G12C inhibitors as monotherapy in NSCLC, CRC and other cancer types, combinations aim to address mechanisms of acquired genetic resistance and adaptive resistance to KRAS inhibition and thus extend durable benefit for patients (Fig. 3c). All combination strategies in early phase development are summarized with reported data in Supplementary Table 2, with ongoing phase 3 studies outlined in Table 3.

RTK inhibition

The RAS–MAPK pathway is susceptible to feedback reactivation at various levels, and thus combination strategies that target multiple nodes along the pathway have compelling rationale. The combination of EGFR inhibition and KRAS inhibition has demonstrated an early signal of clinical efficacy, particularly in CRC[34,38,39,81]. Relevant upstream RTKs mediating adaptive feedback are likely to be tumor or lineage specific. Based on preclinical studies demonstrating that HER2, HER3 and other RTK family members may drive continued growth signaling after KRAS inhibition, ongoing clinical trials are testing KRAS G12C selective inhibitors with the pan-ERBB inhibitor, afatinib[57,82]. Selected studies include

Table 3 | Ongoing phase 3 studies

KRAS inhibitor	Trial details	Combination class	Treatment arms	Tumor type
Sotorasib	CodeBreaK 202 NCT05920356 *n*=750	Chemotherapy	Carboplatin/pemetrexed/sotorasib versus carboplatin/pemetrexed/pembrolizumab	NSCLC; PD-L1<1% (first line)
	CodeBreaK301 NCT06252649 *n*=450	Chemotherapy	FOLFIRI/sotorasib/panitumumab versus FOLFIRI±bevacizumab	CRC (second line)
Adagrasib	KRYSTAL-7 (phase 2/3) NCT04613596 *n*=750	PD-1	Pembrolizumab/adagrasib versus pembrolizumab	NSCLC Phase 2: any PD-L1 tumor proportion score (TPS), first line Phase 3: PD-L1 TPS≥50%; first line Reported data in ref. 116: adagrasib/pembrolizumab, PD-L1 TPS>=50%, *n*=51: ORR 63%, DCR 84%
	KRYSTAL-12 NCT04685135 *n*=450		Adagrasib versus docetaxel	NSCLC (previously treated)
	KRYSTAL-10 NCT04793958 *n*=420	EGFR	Adagrasib/cetuximab versus FOLFOX or FOLFIRI	CRC (second line)
Opnurasib JDQ443	KontRASt-02 NCT05132075 *n*=360		JDQ443 versus docetaxel	NSCLC (previously treated)
Olomorasib LY3537982	SUNRAY-01 NCT06119581 *n*=1,016	PD-1 Chemotherapy	A: Olomorasib/pembrolizumab versus pembrolizumab B: Olomorasib/platinum/pemetrexed/pembrolizumab versus platinum/pemetrexed/pembrolizumab	NSCLC (first line) A: PD-L1 TPS≥50% B: PD-L1 TPS 0–100%

CodeBreaK 101 (sotorasib and afatinib; NCT04185883) and KRYSTAL-1 (adagrasib and afatinib; NCT03785249). Early data from CodeBreaK 101 support activity of combination sotorasib and afatinib, including in patients who had received prior sotorasib monotherapy, with 3 out of 5 previously treated patients achieving stable disease (SD), and 1 out of 5 achieving a PR[83].

SOS1 and SHP2 inhibitors

No single RTK dominates signaling upstream of KRAS across multiple tumors and, consequently, recent efforts have focused on identifying convergent nodes downstream of RTKs that may enable a unifying approach. SOS1 and SHP2 are signaling intermediates that are activated by RTKs. SOS1 triggers GTP loading of RAS through its nucleotide exchange activity, and SHP2, an adaptor phosphatase, directly activates SOS1 activity. Therefore, inhibition of both SOS1 and SHP2 maintains GDP-bound KRAS in an inactive form[84–87]. In preclinical models, the SHP2 inhibitors TNO155 and RMC-4630 demonstrate synergy with KRAS G12C selective inhibitors[84,87]. Recently reported data from early phase clinical trials demonstrate only modest activity of monotherapy in tumors with varied KRAS alterations. For example, in a phase 1 trial evaluating the SHP2 inhibitor TNO155, the best observed response was SD, observed in only 20% of patients (NCT03114319)[88–90].

Moving forward, combination of SOS1 or SHP2 inhibitors with other targeted therapies will be required to observe major clinical benefit. Indeed, published data from a recent phase 1 trial reveal a potentially novel approach whereby the allosteric SHP2 inhibitor PF-07284892 appeared to resensitize patients to oncogene-matched therapy (to which they had developed resistance). Five patients with a *BRAF* V600E, *KRAS* G12D or *ALK/ROS1* fusion, each of whom had experienced disease progression on oncogene-directed therapy, received PF-07284892 monotherapy. Following disease progression on PF-07284892, the matched targeted therapy (for example, encorafenib and cetuximab for *BRAF* V600E) was added to the regimen and, strikingly, four of five patients who received the combination experienced a PR—highlighting synergy between SHP2 and other targeted agents[91]. Further preliminary data also suggest a clinical benefit of combining SHP2 inhibition with KRAS G12C inhibition. In a phase 1/2a study, the combination of glecirasib (G12C inhibitor) with JAB-3312 (SHP2 inhibitor) demonstrated an ORR of 50% (14/28) and a DCR of 100% in patients with KRAS G12C inhibitor-naive NSCLC. In patients with NSCLC previously treated with a KRAS G12C inhibitor, the ORR was 14.3% (1/7), and the DCR was 57.1% (NCT05288205)[92]. Similar early clinical data have been reported for the combination of JDQ443 (opnurasib) with TNO155 and sotorasib with RMC-4630 (refs. 93,94; Supplementary Table 2)

Inhibition of SOS1 blocks its interaction with KRAS-GDP, preventing GTP loading of KRAS. To date, two SOS1 inhibitors, BI-1701963 and MRTX0902, have entered early-stage clinical development[87,95]. Similarly to the case for SHP2 inhibitors, limited monotherapy activity has been observed[94,96]. BI-1701963 is being evaluated in combination with a KRAS G12C inhibitor across cancer types (KRYSTAL-14: NCT04975256; CodeBreaK 101: NCT04185883). Several factors may distinguish SHP2 and SOS1 inhibition. SHP2 acts upstream of both SOS1 and SOS2 and thereby has potential to mediate substantial nucleotide exchange, compensatory activity of SOS2 or other guanine exchange factors, and potential to limit the effect of SOS1 inhibition alone. Pre-clinically, SHP2 inhibition has been associated with profound remodeling of the tumor microenvironment, with increased infiltration and activation of T cells and depletion of tumor-promoting myeloid cells that increase sensitivity to immune checkpoint blockade (ICB)[85]. Whether SHP2 or SOS1 blockade will have benefit in the context of KRAS 'on' state inhibition is an open question.

Downstream MAPK blockade

In theory, strategies that utilize downstream co-targeting may be more susceptible to parallel pathway reactivation. However, KRAS inhibition may not equally disrupt all effector arms, and this property can be exploited to develop rational combinations. In NSCLC, *KRAS* G12C-mutant resistant cell lines maintain activation of the PI3K–AKT–mTOR pathway, with dual pathway inhibition preventing resistance. Similarly, in CRC, compensatory hyperactivation of mTOR is a

vulnerability of G12C inhibitor-resistant cell lines[97,52]. Currently the combination of sotorasib and mTOR inhibitor everolimus is under investigation in the CodeBreaK 101 study in NSCLC (NCT0418588), divarasib with inavolisib (NCT04449874) and adagrasib with nab-sirolimus in solid tumors (NCT05840510).

MEK inhibitors have historically been disappointing as monotherapy; however, targeting MEK or RAF downstream of KRAS is currently under exploration. In the CodeBreaK 101 study, the combination of sotorasib and MEK inhibitor trametinib was evaluated in *KRAS* G12C-mutant NSCLC and CRC (NCT04185883). A DCR of 67% and 86% was observed in NSCLC ($n = 18$) and CRC ($n = 18$), respectively. This study included several patients with prior G12C-directed therapy. Notably, 34% of patients had grade 3 or higher toxicity and 24% of patients discontinued due to this toxicity, indicating that refinements of this approach will be necessary[98]. MEK inhibition paradoxically induces RAF–MEK complexes through feedback pathways and novel therapeutics disrupt this loop through multi-node inhibition[99]. Avutometinib (VS-6766) is a novel RAF/MEK clamp and is currently in phase 1 trials in combination with adagrasib (NCT05375994) and sotorasib (NCT05074810) in the setting of progression on prior KRAS-directed treatment, and with chemotherapy and defactinib (FAK inhibitor) in PDAC (NCT05669482).

Emerging combination strategies

Not all mechanisms of resistance emerge from canonical reactivation of MAPK signaling, and indeed resistance can be driven by rewiring of parallel signaling pathways that allows tumors to escape dependence on mutant *KRAS*. The Hippo pathway members YAP and TAZ have emerged as major regulators of resistance to KRAS inhibitors in recent preclinical studies[100–103]. YAP and TAZ bind to TEAD transcription factors to activate downstream transcription, and clinical responses have been observed in an ongoing trial testing the YAP/TEAD inhibitor VT3989 as a single agent—a first clinical proof of concept for blocking this pathway[104].

Cyclin-dependent kinases (CDKs) are a second potential synergistic target for KRAS inhibitors. The canonical MAPK pathway drives transcription of cyclin D1, leading to heterodimerization with CDK4/CDK6, and subsequent CDK-dependent RB phosphorylation and cell-cycle transition. In preclinical studies, combined inhibition of CDKs and KRAS halts cell-cycle progression[10,105]; moreover, this combination may lead to cancer cell stasis and to enhancement of immune-mediated surveillance of residual tumor cells, suggesting a non-autonomous mechanism of synergy[106]. Currently, various combinations are being clinically evaluated including sotorasib and CDK4/CDK6 inhibitor palbociclib (CodeBreaK 101), adagrasib and palbociclib (KRYSTAL-16) and JDQ443 and CDK4/6 inhibitor ribociclib (KontRASt-03; NCT04185883, NCT05178888 and NCT05358249).

Additional approaches are supported by recent preclinical data, including the co-targeting of metabolic scavenging pathways (for example, autophagy, macropinocytosis), mediators of the unfolded protein response (IRE1a), among others[107–109]. The future use of these drug classes will depend on whether these cellular behaviors are observed clinically in resistant tumors, and then whether these drugs should be used as the initial therapeutic approach or incorporated serially when acquired resistance emerges.

Combinations with ICB

Oncogenic KRAS is a central regulator of immunity and has long been known to promote an immunosuppressive signaling network in the cancer microenvironment through tumor cell expression of cytokines, recruitment of myeloid-derived suppressor cells, and suppression of $CD8^+$ T cell activity[110,111]. KRAS has also been shown to promote tumor cell expression of the immune checkpoint ligand PD-L1 (ref. 112). In line with this, preclinical studies have demonstrated that KRAS inhibition reverses immune suppression in models of NSCLC and PDAC, and moreover, T cells are required for durable responses to KRAS inhibition—suggesting that the adaptive immune response is activated to eliminate residual cancer cells[11,67,68]. Thus, a strong biological rationale exists for combining KRAS inhibitors with drugs that potentiate the immune system.

Several ongoing clinical trials are evaluating the combination of KRAS inhibitors with ICB. However, early data presented from the CodeBreaK 101 study raised concerns that combining sotorasib and ICB led to a high incidence of liver toxicity, and recent reports also suggest that prior anti-PD-1 therapy may predispose to hepatotoxicity and other toxicity with sotorasib, mirroring the experience with EGFR inhibitors in NSCLC[55,113,114]. In CodeBreaK 101, 58 patients with NSCLC were treated with the combination of sotorasib with either pembrolizumab or atezolizumab. An ORR of 29% (95% confidence interval (CI): 18–43%) and DCR of 83% (95% CI: 71–91%) were observed. In patients receiving concurrent sotorasib and pembrolizumab, grade 3–4 toxicity rates approached 80% ($n = 15/19$), but a lead-in dosing strategy for sotorasib partially mitigated these effects[115] (Supplementary Table 2). Recently, data from the KRYSTAL-7 study were reported for the combination of adagrasib and pembrolizumab in patients with NSCLC and PD-L1 expression on >50% of tumor cells, which promisingly showed an ORR of 63% and a DCR of 84% ($n = 51$) and did not result in a high level of grade 3–4 toxicity (10%), although patient numbers remain small (Table 3)[116]. At this time, it is unclear whether toxicity from ICB and RAS inhibition is a class effect or is specific to individual agents, and this is a critical issue to be informed by ongoing clinical trials (including NCT06119581).

Combinations with chemotherapy and front-line regimens

Chemotherapy remains a therapeutic mainstay for patients with *KRAS*-mutant NSCLC, CRC and PDAC; however, responses are incomplete and not durable. Combining chemotherapy and KRAS inhibitors may enhance efficacy by dual mechanisms and by intensifying selective pressure to minimize the emergence of resistance. In NSCLC, a major focus of investment over the next few years is the development of novel first-line combination approaches involving a KRAS G12C inhibitor plus chemotherapy, and with immunotherapy. This therapeutic paradigm has resulted in promising clinical activity and forms the basis of multiple randomized phase 3 trials comparing this combination to standard chemo-immunotherapy (NCT05920356 and NCT06119581; Table 3)[117,118]. Studies are also planned in CRC and PDAC to evaluate KRAS inhibitor and chemotherapy combinations[119] (NCT06252649; Supplementary Table 2).

Immunotherapeutic approaches to RAS targeting

Multiple immunotherapeutic approaches to targeting KRAS have been developed. Older strategies using peptide vaccines have shown induction of a host T cell response against mutant-specific *KRAS* alleles, with potentially improved relapse-free survival observed in small, mostly single-arm studies[120,121]. Researchers have reported individual cases of PRs with more modern approaches, including T cell antigen receptor (TCR) targeting of mutant *KRAS* G12D with human leukocyte antigen (HLA) dependency in metastatic CRC and PDAC[122,123]. Ongoing development challenges for TCR approaches include the ability to target select mutations, HLA restriction, potential for cytokine release syndrome, logistics, cost, scalability and feasibility considerations.

More recently, a novel lymph node targeting amphiphile platform technology (using an albumin-binding delivery system) has incorporated an 'off-the-shelf' peptide vaccine and an immune adjuvant in the form of a two-peptide vaccine (named ELI-002) against KRAS G12D and G12R. In a phase 1 trial of patients with CRC (stage 3 or 4) or PDAC (mostly stages 2–3) showing signs of minimum residual disease after standard therapy (evidenced by circulating tumor DNA (ctDNA)), direct mutant KRAS-specific T cell responses, both CD4 and CD8, were identified in 21/25 (84%) of patients following receipt of the vaccine. A preliminary efficacy signal correlated with T cell response[124]. A randomized

phase 2 trial utilizing a seven-peptide vaccine (G12D, G12R, G12V, G12A, G12C, G12S and G13D) is underway in resected PDAC (NCT05726864).

Similarly, Huff et al.[125] reported on a peptide KRAS vaccine (with an immune adjuvant) targeting G12V, G12D, G12C, G12R, G12A and G13D, along with ipilimumab and nivolumab in 11 patients with resected PDAC following completion of standard therapy. For the co-primary endpoint of immunogenicity, the study reported a median tenfold increase in interferon-producing KRAS-specific T cells in 8 out of 11 patients. Preliminarily, antigen-specific T cell response was associated with disease-free survival (median not reached versus 2.8 months, $P = 0.045$). Further, this approach is currently being evaluated in a safety cohort of 20 individuals at high risk for developing PDAC (NCT05013216).

Opportunity and future directions

A wealth of novel KRAS inhibitors are in preclinical and clinical development. This necessitates a focus on clinical evaluation of drug efficacy in ways that are operationally efficient, that maintain rigor and that can inform 'go' and 'no-go' decisions in a timely manner. Nevertheless, the drive to accelerate the development process to make these therapies accessible to patients must be carefully balanced against the need for methodologically sound and comprehensive clinical data. An illustrative example is from the CodeBreaK 200 study, where high dropout rates in the control arm, concerns about the interpretation of the timing of disease progression in this arm, and high crossover rates to sotorasib therapy ultimately complicated the interpretation of the final outcome, and has necessitated further trials[20,21,126]. These challenges are also exemplified when comparator arms of registration-intent trials vary due to rapidly evolving standards of care. The field will need to prioritize larger scale trials with OS as the primary endpoint to ensure that true efficacy is optimally captured. Although CodeBreaK 200 was not a definitive study, several additional trials comparing KRAS G12C inhibitors to standard-of-care chemotherapy are underway, both in NSCLC and CRC, and will offer additional data into the benefit of these drugs and optimal sequencing strategies (Table 3).

Moving forward, clinical studies must prioritize drug combinations to address the central problem of primary and acquired resistance. One approach is use of a master protocol design to evaluate multiple combination strategies in parallel, with real-time data evaluation to determine which arms have promising early signals and merit moving to an expansion phase (for example, CodeBreaK 101, KRYSTAL-1). Here, we further envision that ctDNA can be used in adaptive trial designs with dual purpose: first, as an early surrogate for timing of and depth of response to identify promising treatment strategies, and second, for proximate identification of resistance mechanisms that informs the selection of next-generation agents and relevant therapeutic combinations. Indeed, recent studies of KRAS inhibitors have demonstrated suppression of the baseline *KRAS* mutation in longitudinal ctDNA samples and has been used across studies to identify genetic mutations contributing to resistance[23,39,52]. Nevertheless, the utility of ctDNA dynamics remains to be optimized, with clinical implementation limited by varying degrees of tumor 'shedding' across different cancers and early-stage versus later-stage disease, lack of clarity on how depth of response correlates with clinical benefit, as well as the importance of timing of ctDNA collection related to therapeutic intervention. Moving forward, studies that define the value of ctDNA monitoring in the context of tissue-based profiling, radiographic assessment and patient outcomes will be crucial[127–129].

Although current clinical efforts have focused on defining combination strategies to address resistance to KRAS inhibitors, we acknowledge that the mechanisms of resistance are heterogeneous and diverge among patients and among diseases. Therefore, the feasibility of any single combination strategy to surmount acquired resistance remains unclear. As clinical trials move toward more complete target suppression with combination strategies, we caution that this approach may have the unintended consequence of forcing a higher rate of secondary resistance mutations—with a frequency of >90% seen in a recent combination study—which may limit future KRAS-directed therapies[39]. Orthogonal strategies, for example, the use of concurrent chemotherapy to debulk tumors and thereby limit opportunities for secondary mutations, are equally important to explore and are the focus of current clinical trials across tumor types (NCT04929223 and NCT05609578)[117,119].

Conclusions

We are now firmly in the era of highly effective targeting of RAS, a central biologic mediator of development and maintenance of the oncogenic state. Large-scale clinical development of RAS therapeutics has identified encouraging signals of efficacy in highly refractory malignancies, and observations to date highlight both opportunity and challenge ahead.

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Additional information

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