Expanding the Reach of Precision Oncology by Drugging All *KRAS* Mutants

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ABSTRACT *KRAS* is the most frequently mutated oncogene, harboring mutations in approximately one in seven cancers. Allele-specific KRAS^{G12C} inhibitors are currently changing the treatment paradigm for patients with *KRAS*^{G12C}-mutated non–small cell lung cancer and colorectal cancer. The success of addressing a previously elusive *KRAS* allele has fueled drug discovery efforts for all *KRAS* mutants. Pan-KRAS drugs have the potential to address broad patient populations, including *KRAS*^{G12D}-, *KRAS*^{G12V}-, *KRAS*^{G13D}-, *KRAS*^{G12R}-, and *KRAS*^{G12A}-mutant or *KRAS* wild-type–amplified cancers, as well as cancers with acquired resistance to KRAS^{G12C} inhibitors. Here, we review actively pursued allele-specific and pan-KRAS inhibition strategies and their potential utility.

Significance: Mutant-selective KRAS^{G12C} inhibitors target a fraction (approximately 13.6%) of all KRAS-driven cancers. A broad arsenal of KRAS drugs is needed to comprehensively conquer KRAS-driven cancers. Conceptually, we foresee two future classes of KRAS medicines: mutant-selective KRAS drugs targeting individual variant alleles and pan-KRAS therapeutics targeting a broad range of KRAS alterations.

INTRODUCTION

In 2020, an estimated 19.3 million new cancer cases occurred worldwide, including 1.8 million new cases in the United States alone (1, 2). Recent analyses have found that approximately one in seven of all human cancers harbor *KRAS* (Kirsten rat sarcoma virus) alterations, making it one of the top oncogenic drivers of human cancer (3–5). The KRAS protein is a small membrane-bound GTPase (GTP hydrolase), acting as a switch for a multitude of cellular signaling functions (Fig. 1A). The balance between nucleotide hydrolysis and exchange determines the levels of active KRAS in cells. Bound to GDP, KRAS is in an "OFF" state. Upon GDP to GTP exchange, usually in response to growth factors and facilitated by guanine-nucleotide exchange factors (GEF) such as SOS1/SOS2, KRAS cycles to its activated "ON" state. In this form, KRAS activates effector pathways, including the MAPK and PI3K pathways, to promote cellular proliferation and survival. KRAS returns to the OFF state when GTP is hydrolyzed to GDP, a process that is catalyzed by GTPase activating proteins (GAP) such as NF1 (6). In its oncogenic form, KRAS remains predominantly in the active ON state as GTP hydrolysis, by its intrinsic GTPase function and enzymes, such as GAPs, is impaired (7, 8). Previous assumptions of the constitutive activity of KRAS oncoproteins were reevaluated after evidence illustrating that KRAS^{G12C} is not permanently GTP bound and maintains a dependency on upstream receptor tyrosine kinase (RTK) signaling for GEF-mediated GTP reloading (9, 10). Recent studies using SHP2 and SOS1 inhibitors in KRAS-driven cancer cell lines, as well as biochemical studies of KRAS mutants in otherwise RAS-less mouse embryo fibroblasts, have shown that a range of KRAS oncoproteins cycle between their active and inactive states and remain dependent on nucleotide exchange for activation (11–13).

Targeting KRAS in cancer has been a central goal during the past four decades, and research and development efforts have intensified over the past 10 years, largely sparked by the seminal discovery by J. Ostrem, K. Shokat and colleagues (14) of compounds tethered to the cysteine of KRAS^{G12C}. The recent accelerated approval of the KRAS^{G12C} mutant-selective inhibitor sotorasib (AMG 510) for the treatment of patients with second-line *KRAS*^{G12C} mutation-positive non–small cell lung cancer (NSCLC) by the FDA on May 28, 2021, marks the first approved targeted therapy for tumors with any *KRAS* mutation (https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-lung-cancer-mutation-previously-considered-resistant-drug).

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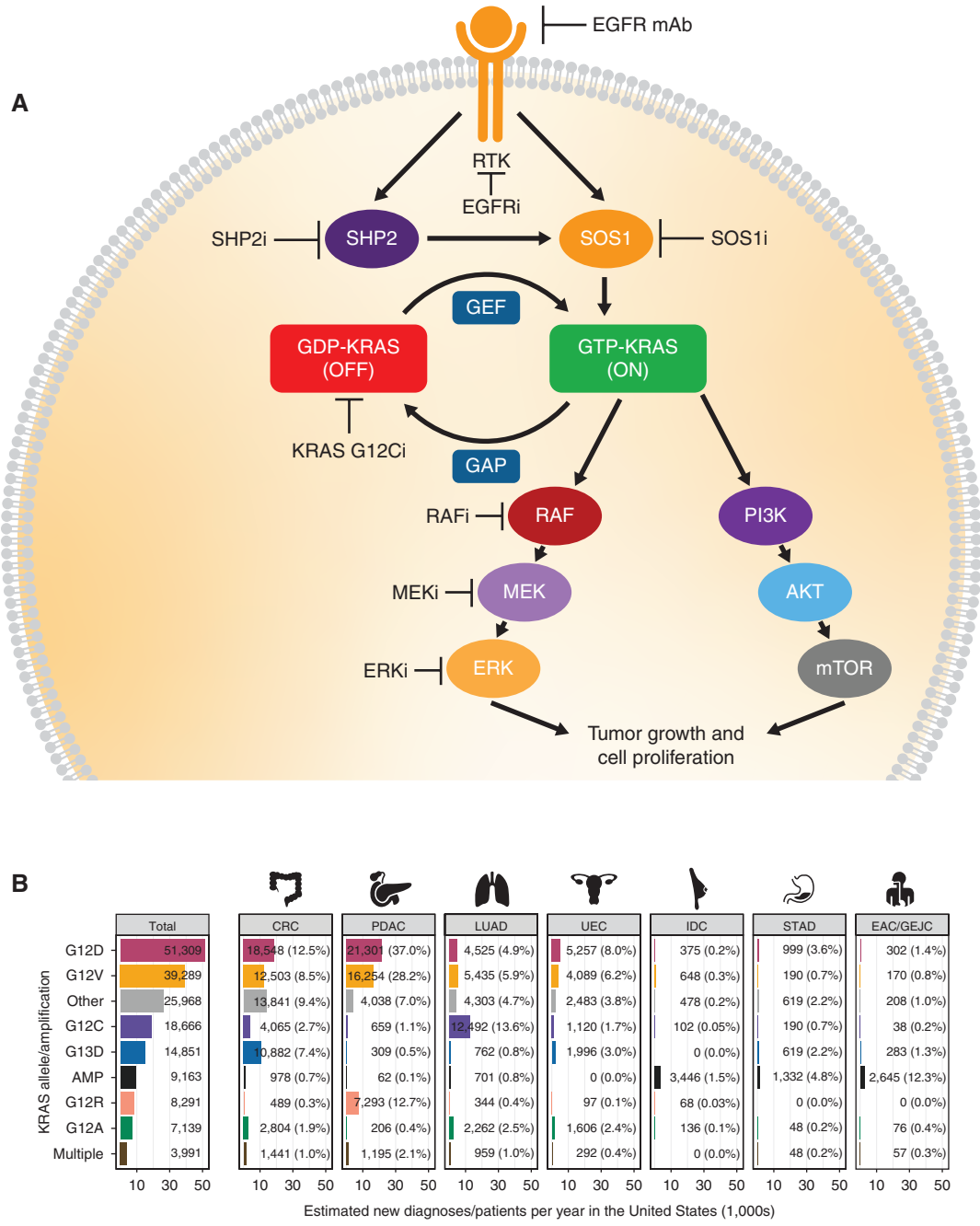

Figure 1. Overview of the RAS/MAPK signaling pathway and patient numbers/overall cohort prevalence for distinct *KRAS* alleles/amplification in seven cancer types. **A,** Schematic representation of KRAS cycling and signaling highlighting selected drug targets and inhibitors. **B,** Distribution of *KRAS* alleles/amplification and patient numbers in selected tumor types. Mutation and amplification rates for *KRAS* have been derived from the AACR GENIE 9.0 public database, whereas patient numbers for the respective tumor types have been extracted from the Cancer Facts & Figures 2000 report published by the American Cancer Society (2). The number of cases for lung adenocarcinoma was set to 40% of all lung cancers. In total, 81,996 distinct samples with mutation and copy number profiles were collapsed into unique patient samples and filtered for distinct alleles and amplification of *KRAS*. The top seven alleles/amplifications with the highest overall prevalence across tumor types are shown, whereas other mutations are grouped into the class "Other." The grouping "Multiple" contains all cases, for which different *KRAS* alterations have been observed in a single patient, for example, two different mutations or a mutation coupled with a *KRAS* amplification. The "Total" subpanel summarizes the patient numbers for the seven cancer types depicted and ranks the alterations based on overall numbers. Similarly, patient numbers are highlighted for each tumor type and each alteration. The percentages in parentheses reflect the proportion in relation to the full cohort (e.g., 13.6% of all patients with lung adenocarcinoma carry a $KRAS^{G12C}$ mutation). AMP, amplification; CRC, colorectal cancer; EAC/GEJC, esophageal adenocarcinoma/gastroesophageal junction cancer; IDC, invasive ductal carcinoma; LUAD, lung adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma; STAD, stomach adenocarcinoma; UEC, undifferentiated endometrial carcinoma.

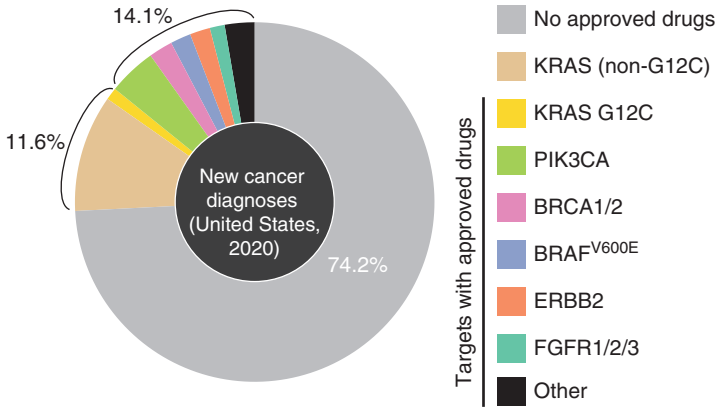

Figure 2. Percentage of patients who are eligible for FDA-approved precision medicine drugs out of all yearly 1.8 million new cancer cases in the United States. The top five target genes plus *KRAS*/*KRAS*^{G12C} with respect to patient cohort sizes and approved drugs are shown. Drugs against some of these target genes are approved in multiple indications (Supplementary Table S1). Of note, a small percentage of the KRAS segment is currently addressable by the recently approved KRAS^{G12C} inhibitor sotorasib (yellow); however, the larger portion of KRAS-driven cancer remains unserved (brown). The cohort size of patients benefiting from KRAS-targeting therapies has been derived from non-hematologic cancers mapping major cancer type cohort sizes with the fractions of *KRAS*-altered (mutated, amplified, multiple) patients in the respective types.

A second KRAS^{G12C} inhibitor, adagrasib (MRTX849), has recently received breakthrough therapy designation, and eight additional inhibitors have entered clinical studies. However, despite the success of KRAS^{G12C} mutant-selective inhibitors for G12C-driven NSCLCs, more than 85% of all *KRAS*-mutated cancers still lack effective therapies. The scope of this review is to highlight the unmet need for patients harboring *KRAS* mutations and the challenging goal of drugging all oncogenic KRAS variants across mutation and cancer types. This review also provides an update and outlook on the most promising therapeutic approaches toward generating pan-KRAS concepts aiming at bringing precision therapy options to a broad range of KRAS-driven cancers.

KRAS-DRIVEN CANCERS

KRAS mutations and/or *KRAS* wild-type amplifications are frequently found in colorectal cancer (United States ~45%, China ~49% of cases), pancreatic cancer (United States ~90%, China ~87% of cases), and NSCLC (subtype adenocarcinoma: United States ~35%, China ~13% of cases; see Fig. 1B for US data), with some differences across ethnicities/countries, especially in lung cancer, as previously described (ref. 15; https://doi.org/10.21203/rs.3.rs-916644/v1). In seven selected KRAS-driven cancer types in the United States (Fig. 1B), around 166,000 newly diagnosed tumors harbor a *KRAS* driver mutation, around 9,000 carry a *KRAS* wild-type amplification, and 4,000 patients show multiple *KRAS* alterations. Based on the analysis of the American Association for Cancer Research (AACR) project GENIE (release 9.0-public; ref. 5) data, we estimate up to 210,000 new annual diagnoses/patients showing alterations in *KRAS* in the United States across all non-hematologic cancers, weighted by their respective baseline incidence rates. The *KRAS* allelic distribution varies across tumor types, as shown in Fig. 1B, with G12C mutated in 13.6% of all lung adenocarcinomas, whereas *KRAS*^{G12D} and *KRAS*^{G12V} are the two most common alleles in colorectal and pancreatic cancer. *KRAS*^{G12D}, *KRAS*^{G12V}, and *KRAS*^{G12C} also represent the top three most frequently mutated alleles overall, found in over 51,000, 39,000, and 19,000 new cases in the selected seven tumor types (Fig. 1B), respectively, and together amount to 109,000 annual new diagnoses. Notably, other *KRAS* alleles such as G12R are mainly restricted to pancreatic cancer, whereas colorectal cancer also shows a significant fraction of non-G12D/V/C *KRAS* mutant alleles. Although *KRAS* mutations represent the most predominant aberration in many cancer types, others, such as breast invasive ductal carcinomas, stomach adenocarcinoma, and esophageal and gastroesophageal junction cancer, show recurrent *KRAS* wild-type amplifications. A subset of patients also harbors multiple *KRAS* alterations, including co-occurring multiallelic variants, such as *KRAS*^{G12C} and *KRAS*^{G13D}, as well as co-occurring *KRAS* mutations and amplifications.

The presence of *KRAS* mutations, especially the most common mutations at codon 12, is strongly associated with cellular *KRAS* dependency, as shown by functional genomic approaches across a large panel of human cell lines from different cancer types (16), suggesting *KRAS* mutations act as bona fide oncogenic driver events. It is apparent that mutations at other sites in *KRAS*, including codon 12, 13, 59, 61, 117, and 146 mutations, plus some atypical variants not currently included in standard guidelines in *KRAS* testing, also enhance its oncogenic potential (17).

To characterize the medical need and opportunity for drugging all KRAS variant oncoproteins, we compared the number of *KRAS*-mutant cancer cases with the patient population that can be matched with FDA-approved drugs (approved before April 1, 2021), based on genomic tumor mutations. Our calculation of prevalence of fully actionable mutations, based on AACR project GENIE (release 9.0-public), suggests that a total of 256,000 (14.1%) of patients with newly diagnosed cancer per year in the United States are eligible for treatment by FDA-approved genome-driven therapies (ref. 18; Supplementary Table S1). The top five patient populations in terms of size include cancers with alterations in *PIK3CA*, *BRCA1/2*, *BRAF*, *ERBB2*, and *FGFR1/2/3* (Fig. 2). A similar number of 14.6% of US patients are eligible for level 1 drugs based on the OncoKB precision oncology knowledge base (19). These data suggest that the number of *KRAS*-mutant/amplified cancer cases is almost comparable to the number of all cancers that are currently actionable based on a genome-driven precision medicine approach.

PROOF OF CONCEPT BY TARGETING KRAS^{G12C}

The development of compounds that covalently bind to cysteine 12 in GDP-KRAS^{G12C}, acting as inactive state-selective KRAS drugs, has rejuvenated interest in drugging this elusive key cancer driver (14, 20–22). In patients with

advanced NSCLC harboring *KRAS*^{G12C} mutations, sotorasib (AMG 510) and adagrasib (MRTX849) have demonstrated robust efficacy with objective response rates of 37% and 45% and disease control rates of 81% and 96%, respectively (20, 23–25). Sotorasib has recently received FDA approval for the treatment of patients with advanced *KRAS*^{G12C}-mutant NSCLC following at least one prior systemic therapy, based on data from the phase I/II CodeBreaK 100 study (24). Importantly, initial monotherapy response rates for both drugs in colorectal cancer are lower than in NSCLC. In colorectal cancer, RTK dependency and signaling rebound kinetics have been identified as potential mechanisms underlying resistance to KRAS^{G12C} inhibition (23, 26, 27). These data set an initial benchmark for response rates and response duration in monotherapy across cancer types, and learnings might be transferable to other KRAS inhibitors targeting other mutant variants. Multiple ongoing trials seek to augment responses to KRAS^{G12C} inhibitors in NSCLC, colorectal cancer, and other cancer types through rational combination strategies (28, 29), as further detailed below. Here again, data from combination trials will be instructive for patient populations beyond *KRAS*^{G12C}-mutated cancers.

All current clinical KRAS inhibitors target the GDP-bound OFF form. Revolution Medicines has described macrocyclic molecules that bind to the active state ON form of KRAS^{G12C} by acting as a molecular glue with cyclophilin A, a highly abundant immunophilin. The assembled tricomplex prevents KRAS^{G12C} (ON) from signaling via steric blockade of RAS effector signaling. An advanced compound, RMC-6291, shows sustained pathway inhibition following RTK activation, consistent with targeting the active form of KRAS^{G12C}. This activity is associated with profound antitumor activity and evidence of superior activity to KRAS^{G12C} (OFF) inhibitors in KRAS^{G12C}-driven preclinical models (30).

ALLELE-SELECTIVE INHIBITORS BEYOND KRAS^{G12C}

The next research frontier will be to discover effective therapeutic opportunities for all *KRAS* mutants. The druggability advantage of covalently targeting the nucleophilic cysteine residue has thus far not materialized for other amino acids (31) and hence it is questionable whether this strategy can be successfully applied to KRAS-mutant oncoproteins beyond KRAS^{G12C}. Noncovalent inhibitors may be a more promising path forward. Indeed, recently cyclic peptide scaffolds have been reported to bind to KRAS^{G12D} and inhibit its interaction with CRAF at high nanomolar concentrations, albeit currently lacking cellular activity (32). Recent reports at scientific meetings by Mirati Therapeutics and Boehringer Ingelheim have highlighted KRAS^{G12D} mutant-selective inhibitors. MRTX1133 and BI-KRASG12D1–3 can reversibly bind to KRAS^{G12D} and demonstrate selective inhibition of cell viability of *KRAS*^{G12D}-mutant, but not *KRAS* wild-type, tumor cells (ref. 18; https://ir.mirati.com/press-releases/press-release-details/2020/Mirati-Therapeutics-Reports-Investigational-Adagrasib-MRTX849-Preliminary-Data-Demonstrating-Tolerability-and-Durable-Anti-Tumor-Activity-as-well-as-Initial-MRTX1133-Preclinical-Data/default.aspx). Importantly, MRTX1133, BI-KRASG12D2 and BI-KRASG12D3 were also reported to be active against in KRAS^{G12D}-driven xenograft models (https://ir.mirati.com/press-releases/press-release-details/2020/Mirati-Therapeutics-Reports-Investigational-Adagrasib-MRTX849-Preliminary-Data-Demonstrating-Tolerability-and-Durable-Anti-Tumor-Activity-as-well-as-Initial-MRTX1133-Preclinical-Data/default.aspx and https://ras-drugdevelopment.com/speaker/marco-hofmann-2/). *KRAS*^{G12D}-mutated cancers represent a significant unmet need, with more than 2.5-fold the annual patient numbers of *KRAS*^{G12C}-mutated cancers, thus providing a strong impetus to drive further research efforts toward this target profile. Efforts based on the tricomplex technology for targeting either KRAS^{G12D} or KRAS^{G13C} oncoproteins are ongoing (Revolution Medicines, Corporate Overview, Q1–2021, https://ir.revmed.com/static-files/5ee2ba3e-dcdf-4780-94a7-ef35fe3df9f2). The feasibility to move beyond KRAS^{G12C}, KRAS^{G12D}, and KRAS^{G13C} with mutant-selective inhibitors or degraders remains to be determined.

INDIRECT THERAPEUTIC PAN-KRAS CONCEPTS

The global disease burden associated with *KRAS* mutations for different cancer types has spurred intense efforts to identify therapeutic concepts that can address a broad spectrum of *KRAS*-mutant cancers.

Several indirect pan-KRAS drugs are currently being developed by pharmaceutical companies that interfere with KRAS nucleotide exchange and activation by inhibiting SHP2 or the GEF SOS1 (Table 1). The rationale for pursuing SHP2 and SOS1 inhibitors as pan-KRAS inhibitors is grounded in the evidence that several (K)RAS oncoproteins, including KRAS^{G12C}, still cycle between an inactive and active state and rely on upstream activation and nucleotide exchange to exhibit their full transforming potential (9–13, 33, 34).

SHP2 inhibitors stabilize the auto-inhibited conformation of the enzyme and thereby disrupt SOS1-mediated nucleotide exchange of KRAS (11, 35, 36). In addition, SHP2 inhibition may also yield immunomodulatory effects in T cells and macrophages to elicit antitumor immune responses (37). Nine SHP2 inhibitors are currently being tested in the clinics as single agents as well as in combination with other pathway inhibitors. Three SHP2 inhibitors, RMC-4630, TNO155, and JAB-3068, have progressed to phase II clinical trials. In a phase I/II study (NCT03634982) with RMC-4630 that included patients with tumors harboring RAS node alterations (*KRAS*^{G12mut}, *KRAS*^{amp}, *NF1*^{LOF}, *BRAF*^{class3}), first clinical data demonstrated a disease control rate of 71% (5/7) with reduction in tumor volume reported in three (43%) and one confirmed objective response in patients with *KRAS*^{G12C}-mutant NSCLC (38). First clinical data in a phase I clinical study (NCT03114319) with the SHP2 inhibitor TNO155 showed sensitivity of some KRAS^{G12}-mutant tumors, especially KRAS^{G12C}-mutant NSCLC and *BRAF*/*NRAS* wild-type melanoma, but in the absence of partial responses (39).

Inhibitors of the GEF SOS1 block the interaction of SOS1 with KRAS-GDP, preventing nucleotide exchange and GTP loading of KRAS (12). BI 1701963 is currently the only SOS1 inhibitor being investigated in clinical trials. First preliminary clinical data from a dose escalation trial employing

Table 1. Mutant-specific KRAS inhibitors, pan-(K)RAS inhibitors, SHP2 inhibitors, and SOS1 inhibitors described in ClinicalTrials.gov or currently in advanced preclinical stages

Mutant-specific KRAS inhibitors

Programs (company)	IND	Target	Phase
Sotorasib/AMG 510 (Amgen)	In clinics	$KRAS^{G12C}$	Approved
Adagrasib/MRTX849 (Mirati)			
D-1553 (InventisBio)			
JDQ443 (Novartis)			
RG6330/GDC-6036 (Roche)			Clinical
LY3537982 (Eli Lilly)			
BI 1823911 (Boehringer Ingelheim)			
JAB-21822 (Jacobio)			
GFH925 (GenFleet)			
GH35 (Genhouse Bio)			
MRTX1133 (Mirati)	Preclinical or IND enabling studies	$KRAS^{G12D}$	Preclinical
KRASG12D1-3 (Boehringer Ingelheim)			
RAS(ON) G12D (Revolution Medicines)			
RAS(ON) G13C (Revolution Medicines)		$KRAS^{G13C}$	

SHP2 inhibitors

Programs (company)	IND	Phase
TNO155 (Novartis)	In clinics	Clinical
RMC-4630 (Revolution Medicines)		
JAB-3068 (Jacobio)		
JAB-3312 (Jacobio)		
RG-6433/RLY-1971 (Roche/Genentech)		
BBP-398 (BridgeBio/Navire)		
ERAS-601 (Erasca)		
PF-07284892/ARRY-558 (Pfizer)		
SH3809 (Nanjing Sanhome)		

Pan-(K)RAS inhibitors

Programs (company)	IND	Target	Phase
RSC-1255 (RasCal Therapeutics)	In clinics	Pan-RAS	Clinical
BI-pan-KRAS1-4 inhibitors (Boehringer Ingelheim)	Preclinical or IND enabling studies	Pan-KRAS: $KRAS^{G12D/V}$, KRAS wild-type	Preclinical
BI-pan-KRASdegrader1 (Boehringer Ingelheim)		Pan-KRAS: $KRAS^{G12C/D/V/A}$, $KRAS^{G13C}$, $KRAS^{A146T/P}$, $KRAS^{Q61E/P}$, KRAS wild-type	
RMC-6236 (Revolution Medicines)		Pan-RAS: $KRAS^{G12D/V}$, $KRAS^{G13D}$, $KRAS^{Q61K}$, RAS wild-type	

SOS1 inhibitors

Programs (company)	IND	Phase
BI 1701963 (Boehringer Ingelheim)	In clinics	Clinical
RMC-5845 (Revolution Medicines)	Preclinical or IND enabling studies	Preclinical
BAY-293 (Bayer)	Terminated/paused	
SDGR5 (Schrödinger/BMS)	Preclinical or IND enabling studies	
GH52 (Genhouse Bio)		
ERAS-9 (Erasca)		
SOS1i (Mirati)		

In clinics Preclinical or IND enabling studies Terminated/paused

NOTE: A selection of mutant specific KRAS inhibitors and pan-(K)RAS inhibitors is shown, focusing on those inhibitors, which are either studied in clinical trials or have been reported at scientific meetings. For SOS1 inhibitors, the focus is on compounds studied in clinical trials or reported in publications, at scientific meetings, or in press releases. Only clinical stage compounds are listed for SHP2 inhibitors. IND, Investigational New Drug Application.

continuous dosing of BI 1701963, a pan-KRAS SOS1 inhibitor, as monotherapy (NCT04111458) have been reported. BI 1701963 was generally well tolerated, with the maximum tolerated dose reached at 800 mg, and stable disease up to 18 weeks in 7 of 31 patients with solid tumors harboring *KRAS* mutations was demonstrated (40). The primary objective of this trial is to determine the monotherapy tolerability of BI 1701963, in order to define the recommended phase II dose for combination trials (40). Revolution Medicines (RMC-5845), Schrödinger (SDGR5), Genhouse Bio (GH52), Erasca (ERAS-9), and Mirati Therapeutics announced SOS1 inhibitors in their preclinical pipelines (Table 1).

As upstream activators of KRAS, both SOS1 inhibitors and SHP2 inhibitors hold particular promise in the combination setting, and they are being explored preclinically and clinically in combination studies aimed to interrogate whether vertical pathway blockade can "tighten the grip" on the KRAS/MAPK pathway and thereby increase the rates and duration of responses. SHP2 inhibitors and BI 1701963 are being combined with MEK inhibitors [NCT04294160, NCT03989115 (41), NCT04720976, NCT04111458, and NCT048357] to enhance MAPK pathway modulation and to suppress pathway reactivation elicited by the alleviation of negative feedback control (12, 42). SHP2 inhibitors are also being combined with ERK inhibitors (NCT04916236) and EGFR tyrosine kinase inhibitors (NCT03989115 and NCT03114319). Although initial reports described tumor reduction in 3 of 8 patients with *KRAS*-mutant colorectal cancer in the RMC4630 and the MEK inhibitor cobimetinib combination trial (ref. 41; NCT03989115), Revolution Medicines has subsequently announced the termination of this combination trial due to lack of efficacy (Revolution Medicines, Financial Updates, Q2–2021, https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-reports-second-quarter-financial-results). Ongoing SHP2/MEK inhibitor trials (Erasca, Jacobio Pharmaceuticals, and Novartis) and SOS1 inhibitor and MEK inhibitor combination trials (Boehringer Ingelheim) will provide more insights about the efficacy and tolerability of this combination in different patient populations.

As SOS1 inhibitors and SHP2 inhibitors shift the equilibrium of KRAS to the GDP-bound state, a strong rationale emerges to combine these indirect KRAS modulators with mutant-specific KRAS inhibitors, such as covalent $KRAS^{G12C}$ inhibitors that bind KRAS in its GDP-bound state. Preclinical data have demonstrated synergistic antiproliferative effects and enhanced antitumor efficacy for both the SHP2 inhibitor/$KRAS^{G12C}$ inhibitor combination (43) and the SOS1 inhibitor/$KRAS^{G12C}$ inhibitor combination (44, 45). In heterozygous KRAS-mutant tumor cells, RAS signaling can be supplemented and cross-regulated by RTK-WT RAS signaling. A combination of a mutant-specific KRAS inhibitor with either a SHP2 inhibitor or a SOS1 inhibitor could effectively block mutant KRAS and wild-type RAS signaling (12, 43, 45, 46). Based on the strong underlying scientific rationale and supportive preclinical data, SHP2 inhibitor and SOS1 inhibitor combinations with allele-specific $KRAS^{G12C}$ inhibitors are being tested in several ongoing clinical trials in patients with $KRAS^{G12C}$ mutation-positive NSCLC and colorectal cancer (NCT04330664, NCT04185883, NCT04699188, NCT04973163, and NCT04975256). The allele-selective nature of $KRAS^{G12C}$ inhibitors is anticipated to lead to improved tolerability for SHP2 and SOS1 inhibitor combinations compared with studies combining with MEK inhibitors.

Besides addressing *KRAS*-mutant tumors, the SHP2 inhibitor RMC-4630 is also being tested in a clinical study including patients with tumors carrying *KRAS* wild-type amplifications (NCT03989115). This positioning is supported by preclinical data demonstrating that targeting SOS1 or SHP2 can enhance the sensitivity of wild-type *KRAS*-amplified models to MEK inhibition (47). Based on their mode of action in suppressing nucleotide exchange, both SHP2 and SOS1 inhibitors are well poised to deliver therapeutic benefit in cancer settings that depend on RAS wild-type activity, including *KRAS* wild-type amplifications, *BRAF* class 3 mutations, and *NF1* loss-of-function mutations.

Combinations of pan-KRAS concepts with approved standard-of-care therapies, such as chemotherapy, are not yet being extensively studied but could be impactful in case of synergistic activities. In preclinical experiments, a combination of the topoisomerase I inhibitor irinotecan with a SOS1 inhibitor enhances formation of DNA double-strand breaks in a *KRAS*-mutated tumor model (45, 48). The mechanistic basis for this effect has not been elucidated yet but could be associated with the impact of SOS1 inhibition on cell cycle progression and DNA repair pathway choice. The combination of SOS1 inhibition and irinotecan is now being studied in a phase I clinical trial recruiting patients with *KRAS*-mutant colorectal cancer in China (NCT04627142).

Besides its role in cancer cell intrinsic mitogenic signaling, SHP2 mediates signaling through the immune checkpoint receptor PD-1 in T cells (49). As the PD-1/SHP2 signaling axis mediates the immune-suppressive effect of PD-1, several clinical trials are enrolling patients studying the combination of SHP2 inhibitors with PD-1 blocking antibodies (NCT04000529, NCT04720976, NCT04721223, and NCT04418661).

DIRECT THERAPEUTIC PAN-KRAS CONCEPTS

Using KRAS fragment screening and structure-based drug design, Boehringer Ingelheim has recently reported the discovery of direct pan-KRAS inhibitors and direct pan-KRAS proteolysis targeting chimeras (PROTAC), which are able to spare NRAS and HRAS (18). In a panel of cell lines, pan-KRAS inhibitors are active against a broad range of KRAS-driven cell lines, including $KRAS^{G12C}$-, $KRAS^{G12D}$-, $KRAS^{G12V}$-, and $KRAS^{G13D}$-driven cells, whereas *HRAS*- and *NRAS*-mutated cell lines did not exhibit sensitivity (18). Importantly, pan-KRAS inhibitors show selective activity also on a panel of cell lines that harbor *KRAS* amplifications, whereas *KRAS* wild-type cells with normal copy number remain unaffected (18).

A pan-KRAS probe compound BI-panKRAS3 demonstrates dose-dependent inhibition of KRAS-dependent signaling and yields antitumor efficacy in $KRAS^{G12D}$- and $KRAS^{G13D}$-mutated colorectal cancer models (18).

An emerging new class of medicines are PROTACs, which specifically degrade proteins via the cellular protein degradation machinery (50). These bifunctional molecules simultaneously engage a protein of interest and an E3 ligase, forming a ternary complex, enabling the E3 ligase to ubiquitinate and subsequently induce degradation of the target

protein (51). Covalent inhibitors that target KRAS^{G12C} in its GDP-bound OFF state have been successfully converted into PROTACs, but such covalent PROTACs are not catalytic, and it is unclear what advantages they possess beyond covalent KRAS^{G12C} inhibitors (52, 53). Although it may be technically more difficult to generate KRAS degraders based on the required physicochemical properties, degraders are in general more versatile in terms of target scope, as any functional binding site can be targeted. In principle, PROTACs also have the potential for a more rapid and sustained pathway blockade. In addition, by means of selecting a suitable E3-ligase, tissue selectivity can be built into the PROTAC design. Cellularly potent and selective KRAS PROTACs such as BI-KRAS-degrader1 were reported, which can degrade all major cycling KRAS mutants while sparing NRAS and HRAS (18). Mutant alleles that are strongly GTP hydrolysis impaired, including G12R and Q61R/K/L mutants, are less potently degraded by KRAS PROTACs targeting the GDP-bound form. Importantly, the role SOS1 plays in feedback reactivation can be translated across the KRAS inhibitor space with evidence of combinatorial activity with mutant-selective as well as pan-KRAS compounds (18). An open question is which of the drug classes will be less prone to developing acquired resistance, as also PROTACs are likely susceptible to resistance mechanisms of their own (51).

Gaining a broad *KRAS*-mutant coverage also appears feasible by means of different approaches of generating pan-RAS inhibitors that block all three RAS isoforms KRAS, NRAS, and HRAS. The pan-RAS strategy adopted by Boehringer Ingelheim focuses on switch I/II pocket inhibitors exemplified by the compound BI-2852 (54). Revolution Medicines has applied a cyclophilin-dependent molecular glue approach to discover RMC-6236, which has been described as a potent, orally available tricomplex RAS^{MULTI} (ON) inhibitor. RMC-6236 displays activity across a diverse spectrum of RAS-driven cell lines, whereas no activity is reported in KRAS-independent cell lines that are driven by a BRAF mutation. Single-agent antitumor activity has been reported in a range of KRAS^{G12D}- and KRAS^{G12V}-driven colorectal cancer and pancreatic ductal adenocarcinoma (PDAC) tumor models (55). It remains to be established whether concepts targeting all three RAS isoforms simultaneously will be compatible with achieving a therapeutic window in patients.

Inhibitors targeting the MAPK pathway components downstream of RAS, such as RAF, MEK, and ERK, are not addressed in this review in detail but can serve as combination partners of RAS inhibitors given supportive tolerability. Guo and colleagues (56) reported a phase Ib study of the MEK inhibitor VS-6766 (previously known as CH5126766 or RO5126766), which showed promising antitumor activity across a spectrum of *KRAS*-mutant tumors, including *KRAS*^{G12V} mutation-positive NSCLC. VS-6766 is an allosteric MEK inhibitor that also blocks RAF phosphorylation of MEK, leading to a reduction of feedback-driven pathway rebound, thus potentially conferring enhanced therapeutic activity compared with other MEK inhibitors (57). VS-6766 is currently studied in combination with the FAK inhibitor defactinib in *KRAS*-mutated NSCLC, yielding promising early responses with partial responses being observed in 2 patients with NSCLC with *KRAS*^{G12V}-mutated cancers (58).

TWO CLASSES OF KRAS MEDICINES

Conceptually, we expect the emergence of two major classes of KRAS medicines: KRAS drugs selectively targeting individual mutant variants and pan-KRAS concepts targeting a broad and diverse spectrum of *KRAS* alterations, covering mutations and amplification. Based on feasibility to generate small-molecule mutant-selective and pan-KRAS drugs, we could also see a range of spectrum-selective KRAS drugs, which balance the opportunities and risks associated with covering a narrower set of *KRAS* mutants.

The promise of mutant-selective KRAS drugs is manifold. Foremost, deep and durable target inhibition in a clearly defined patient population, a low risk of KRAS wild-type–mediated toxicity, and good combinability with other agents can be expected. Based on a wide therapeutic index, as seen for many of the current KRAS^{G12C} inhibitors, this drug class seems to be an obvious choice for early line settings in future clinical practice, alone or in combination with other targeted or immune-directed therapies. An open issue is clearly the feasibility of generating mutant-selective drugs beyond KRAS^{G12C} and perhaps KRAS^{G12D}. Importantly, there will be critical limitations of this approach in heterogeneous and drug-resistant tumors, as elaborated below. In contrast, pan-KRAS drugs and pan-RAS drugs face the still open issue of tolerability based on inhibition of wild-type (K)RAS. Data generated in the laboratory of Mariano Barbacid (CNIO, Spain), obtained in genetically modified murine models, indicate that ablation of the *Kras* locus in young mice does not result in immediate toxic effects but resulted in decreased viability starting at around 8 months of age (59). The effects on normal tissues of inhibiting or degrading wild-type KRAS in humans are yet to be interrogated. An important point in this context is the distinction between the likely toxicities associated with isoform-specific pan-KRAS inhibition compared with isoform-agnostic pan-RAS drugs that inhibit all three RAS isoforms, KRAS, HRAS, and NRAS. Barbacid's studies in mice indicate that in contrast to the late- and slow-onset effects obtained with genetic KRAS inactivation, the ablation of all RAS isoform expression causes death of adult mice within a few weeks of induction (60, 61). Therefore, it is highly likely that pan-RAS inhibitors will show a markedly higher level of toxicity than KRAS isoform-specific inhibitors. Pan-KRAS drugs have the potential to address a broad patient population; in particular, they could be positioned in early line settings where we lack mutant-selective KRAS drugs. Pan-KRAS inhibitors and degraders could also become the prime choice for cancers driven by wild-type *KRAS*, such as *KRAS* wild-type–amplified or cancers driven by loss of the NF1 tumor suppressor, as well as neurofibromatosis type 1 or its associated malignancies (34, 62, 63). Pan-KRAS drugs would have advantages versus mutant-selective KRAS drugs in heterogeneous cancers driven by multiple *KRAS* alterations at baseline or upon development of acquired resistance due to secondary *KRAS* on-target alterations (Fig. 3), with first examples emerging in the clinic (64–66). In the following section, these opportunities are further highlighted.

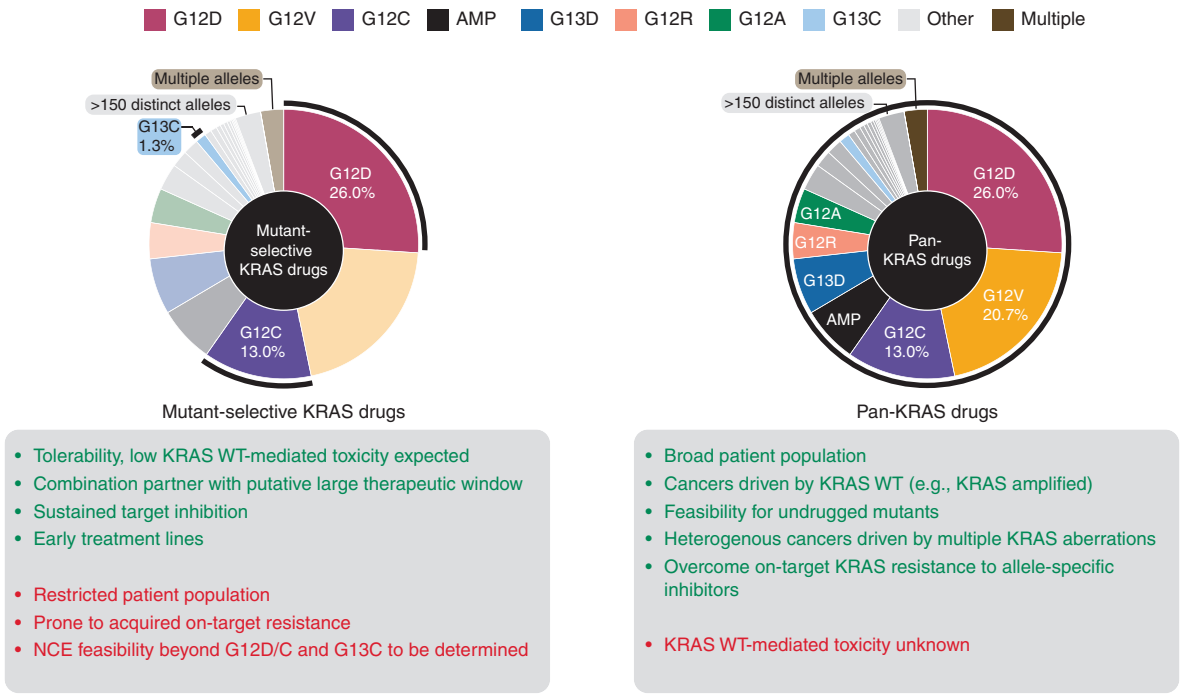

Figure 3. Distribution of KRAS alterations across all KRAS-driven tumors with a focus on putative benefits (green text) and drawbacks (red text) for mutant-selective and pan-KRAS drugs. The left pie chart shows *KRAS* alleles that are currently addressable or worked on in non-transparent colors (G12D, G12C, G13C), whereas transparent colors visualize mutated *KRAS* alleles, which remain elusive to targeted therapy so far. Alleles are color-coded as in Fig. 1, with a long tail of other alleles shown in gray. In total, around 200 distinct *KRAS* alleles/alterations are reported in the AACR GENIE database. The right pie chart shows all *KRAS* alterations putatively targetable by pan-KRAS drugs. NCE, New Chemical Entity; WT, wild-type.

PATIENT POPULATIONS ADDRESSABLE BY PAN-KRAS DRUGS

NSCLC

KRAS is the most prevalent cancer driver in lung adenocarcinoma, with more than 35% of patients harboring a *KRAS* mutation. *KRAS* mutations other than $KRAS^{G12C}$ represent more than half of all *KRAS* mutations in lung adenocarcinoma, with high prevalence of G12V, G12D, and G12A mutations. These mutant alleles all appear amenable to the pan-KRAS approaches described above, including pan-KRAS inhibitors and degraders, as well as SOS1 inhibitor/SHP2 inhibitor plus MEK inhibitor combinations. Similar to the $KRAS^{G12C}$ mutation, these mutations also rarely overlap with other actionable driver mutations, such as *EGFR* mutations and *ALK* rearrangements (5, 67). Non-G12C *KRAS*-mutant NSCLC tumors are distinct from $KRAS^{G12C}$-mutated lung cancers in terms of comutation of tumor suppressor genes. Although the frequency of *TP53* co-occurring mutations is comparable in non-G12C *KRAS*-mutated NSCLC (32%–35%), differences can be observed for the tumor suppressors *STK11/LKB1* (comutation rates: G12C, 23%; G12D, 14%) and *KEAP1* (comutation rates: G12C, 8%; G12D, 4%). Immune checkpoint inhibitors have been established as standard-of-care treatment for patients with NSCLC whose tumors express PD-L1 and lack *EGFR* mutations or *ALK* rearrangements, as a single agent or in combination with chemotherapy (68–70). However, response rates to single-agent immune checkpoint inhibitors overall are modest. Initial data suggest that a higher tumor mutational burden (TMB) occurs in the overall *KRAS*-mutant population, potentially resulting in improved response to immune checkpoint inhibition (71). This retrospective study showed that patients with NSCLC harboring a *KRAS* gene mutation accompanied by high expression levels of PD-L1 lived longer when they received immunotherapy alone, compared with patients without the mutation, whereas the survival difference was not seen in patients who received both chemotherapy and immunotherapy. Although these data are intriguing, validation in prospective randomized trials is pending (71). In *KRAS*-mutated NSCLC, the tumor microenvironment (TME) is frequently characterized by a lack or dysfunction of tumor-infiltrating lymphocytes (TIL), especially in the presence of co-occurring mutations in *STK11/LKB1* (refs. 72, 73). Preclinical studies suggest that sotorasib and adagrasib can induce a more proinflammatory and TIL-infiltrated TME in mouse models, translating into durable complete responses in combination with anti–PD-1 therapy (21, 74). Exploratory correlative analyses from the KRYSTAL-1 and CodeBreaK 100 trials in this context suggest higher response rates for single-agent adagrasib (64% vs. 45%) and sotorasib (50% vs. 39%) among patients whose tumors harbored an *STK11/LKB1* comutation versus the entire treatment cohort (24, 25). Although these early findings will need to be confirmed in larger combination trials with anti–PD-1 antibodies, they may offer an attractive approach for KRAS-targeted agents for this historically difficult-to-treat patient subgroup in a first-line setting (NCT04933695). Further studies are required to completely establish tumor

mutational burden and immune checkpoint inhibitor sensitivity among non-G12C *KRAS*-mutant subtypes. Early data suggest that the presence of *KRAS* alleles other than G12C mutations (75), especially in conjunction with a *TP53* comutation, may represent a negative predictive biomarkers for anti–PD-1/PD-L1 immune checkpoint inhibitors in patients with NSCLC (76). We expect the coming years in the field of *KRAS*-mutant NSCLC to be very insightful in particular because of the translation of learnings from the KRAS^{G12C} inhibitor field on combinations and comutations to non-G12C *KRAS*-mutated cancers.

Colorectal Cancer

KRAS mutations occur in approximately 45% of colorectal cancers, led in frequency by the G12D (13%), G12V (9%), and G13D (7%) alleles. Non-G12/13-type *KRAS* alleles occur with appreciable frequency at the A146 and Q61 position (3% and 2%, respectively). Besides its negative predictive role for response to anti-EGFR therapy, *KRAS* mutation status also has a negative prognostic impact in colorectal cancer and is associated with right-sidedness of tumor location (77). Emergence of KRAS amplification and acquisition of secondary KRAS mutations (G12C, G12D, G13D, and Q61H) was detected as one mechanism of acquired resistance in patients with metastatic colorectal cancer who relapsed on cetuximab or panitumumab treatment (78, 79). This finding suggests that a combination of an anti-EGFR therapy with a pan-KRAS inhibitor or a mutant-selective KRAS drug could be an effective second-line treatment to reverse KRAS-driven drug resistance. Learnings from the efficacy data obtained in colorectal cancer with sotorasib and adagrasib may be impactful also for non-G12C-type KRAS inhibitors. In *KRAS*^{G12C}-mutated colorectal cancer, sotorasib showed an initial objective response rate (ORR) of 7% (3 of 42 patients), whereas treatment with adagrasib yielded a preliminary response rate of 17% (3 of 18 patients; refs. 23, 26). This is reminiscent of the limited sensitivity of *BRAF*^{V600E} mutant colorectal cancer to single-agent vemurafenib, as a selective BRAF inhibitor, in comparison to other tumor types and could be a result of a rapid adaptive response that occurs in colorectal cancer. Recent studies showed that, similar to *BRAF*^{V600E}, *KRAS*^{G12C}-mutated colorectal cancers maintain sensitivity to upstream RTK signaling, particularly EGFR, and that EGFR reactivation restricts the efficacy of KRAS^{G12C} inhibition in colorectal cancer. The combination of KRAS^{G12C} and EGFR blockade overcomes this adaptive resistance, both in cell lines and in patient-derived xenograft models (27). Recent data suggest that the rationale to combine KRAS inhibitors with anti-EGFR agents in colorectal cancer translates into enhanced clinical efficacy. The combination of adagrasib plus cetuximab demonstrated a meaningful improvement over adagrasib monotherapy in a heavily pretreated patient population with *KRAS*^{G12C}-mutated colorectal cancer, resulting in a 43% ORR versus an ORR of 22% for the monotherapy (80). Data presented for the combination of sotorasib plus panitumumab versus sotorasib monotherapy in colorectal cancer point into a similar direction (81), although the data set for this combination is less mature. These data fuel future rational clinical combinations of KRAS-directed therapies in colorectal cancer, including a phase III study called KRYSTAL-10 combining adagrasib and cetuximab in second-line *KRAS*^{G12C}-mutated colorectal cancer (NCT04793958), and further emphasize the relevance of the underlying histologic and molecular context of each tumor type when developing KRAS blocking agents.

Other Gastrointestinal Cancers

KRAS alterations are the most frequently occurring somatic change in PDACs, with approximately 90% of cases. Learnings from *KRAS*^{G12C} inhibitors have been limited so far, with only case reports of responses, because *KRAS*^{G12D} and *KRAS*^{G12V} represent the majority of *KRAS* mutations occurring in about 65% of all PDAC cases, whereas G12C mutations are very rare with 1.1% (23, 26). Very recently, Mirati Therapeutics presented initial data on 10 *KRAS*^{G12C} mutant pancreatic cancer patients showing partial responses in 5 patients and a disease control rate of 100% (https://mirati.com/wp-content/uploads/ENA_Oct-2021_MRTX1133_vF.pdf). In addition to small molecule inhibitors, several strategies of KRAS inhibition have been investigated in PDAC, most notably using small interfering RNAs and inhibitory exosomes (82, 83), both in ongoing clinical trials. Emerging evidence suggests *KRAS* mutations constitute attractive targets for immune-based treatments in pancreatic cancer and beyond. One example is the mRNA vaccine mRNA-5671 that encodes neoepitopes for common KRAS mutations (G12C, G12D, G12V, and G13D; NCT03948763).

A second promising immunotherapeutic approach directed at *KRAS* mutations involves adoptive T-cell therapies and is extensively reviewed elsewhere (84). Recent preclinical studies have identified bispecific T-cell engager protein molecules that specifically bind to mutant RAS peptide neoepitopes (G12V, Q61H/L/R) complexed with HLA, inducing T-cell–mediated killing of target cancer cells expressing endogenous levels of the mutant RAS proteins and cognate HLA alleles (85). Although clinical translation of these immune-based treatments is in its early stage for epithelial cancers, a multipronged approach of cancer- and immune cell–directed therapies targeting multiple *KRAS* mutant alleles may become a reality in the foreseeable future.

Mutant-selective *KRAS*^{G12D} inhibitors as well as pan-KRAS concepts hold promise for affecting large segments of KRAS-driven PDAC. In addition to the initial promising data reported by Mirati on adagrasib in *KRAS*^{G12C} -mutated PDAC, a targeted approach against *NRG1* fusion– and *NTRK* fusion–positive PDAC has yielded early response rates of roughly 40% (86) and 75% (87), respectively, hinting at the possibility that also targeting KRAS-driven PDAC could be broadly effective as a monotherapy.

Based on their distinct structural properties that impinge on signaling, particular attention needs to be given to special *KRAS* mutants, such as *KRAS*^{G12R} (the third most predominant alteration in PDAC), *KRAS*^{A146T} (especially in colorectal cancer), and *KRAS*^{Q61H} mutations (88–90). The implication of these unusual variants is that specific KRAS variants can have tissue-specific oncogenic effects and exhibit allele-specific therapeutic vulnerabilities in downstream effector pathways. Although A146T and Q61H mutations in *KRAS* remain sensitive to pan-KRAS inhibitors and degraders targeting the OFF form of KRAS, this appears not the case for the *KRAS*^{G12R} mutant, which could require KRAS ON drugs.

The role of KRAS, when activated through canonical mutations, has been well established, as summarized above. A secondary means of KRAS activation in cancer is the focal high-level amplification of the *KRAS* gene, which is the fourth most prevalent *KRAS* alteration in cancer comparable in frequency to around 60% of the $KRAS^{G12C}$-mutated patient population. *KRAS* wild-type amplifications have been prominently observed in esophageal (12%), stomach (5%), and breast invasive ductal carcinomas (2%; Fig. 1B). Importantly, *KRAS*, *ERBB2*, and *FGFR2* amplifications are mutually exclusive in stomach cancer (91), with the latter two types of amplification subtypes already representing actionable alterations for precision medicine approaches (92, 93). The aggressive nature of these cancers, the paucity of current therapeutic strategies, and the fact that wild-type *KRAS* in an amplified state may reside preferentially in the GDP-bound, OFF form, with corresponding high susceptibility to inhibition by KRAS OFF drugs, render these tumors an attractive segment for developing pan-KRAS inhibitors and degraders.

Collectively, we see the potential to establish KRAS drugs as precision oncology approaches for a broad range of cancers and to ultimately replace chemotherapy as a standard of care in these KRAS-driven cancer types. As there is a lack of genetic overlap of *KRAS* aberrations with RTK-driven subtypes [e.g., in NSCLC (*EGFR*, *ALK*, *MET*, *ROS1*, *RET*, *BRAF*), colorectal cancer (*BRAF*), PDAC (*NRG1*), and gastric cancer (*ERBB2*, *FGFR2*)], KRAS-targeting drugs could be uniquely positioned in areas of particularly high unmet need.

FURTHER OPPORTUNITIES FOR PAN-KRAS DRUGS

Cancers Driven by Co-occurring KRAS Aberrations

Deep analysis of the AACR GENIE data revealed a subset of patients (approximately 2.8% of all KRAS-driven cancers) who harbor multiple *KRAS* alterations in a single biopsy specimen (Fig. 1B). These multiple alterations are less frequent in colorectal cancer and lung adenocarcinoma (about 1%) than in PDAC (2.1%), but given limited sequencing read coverage and putative low allelic frequencies, these numbers might be higher in patients. These heterogenous cancers carry either multiple forms of mutated *KRAS* or a mutated variant of *KRAS* in conjunction with a *KRAS* amplification. Allele-selective inhibitors would only target a portion of the tumor driven by a specific allele, whereas pan-KRAS inhibitors could be used to cover all distinct *KRAS* alterations, especially if these co-occur in the same tumor lesion.

Acquired Resistance to Mutant-Selective $KRAS^{G12C}$ Inhibitors

Although $KRAS^{G12C}$ inhibitors deliver clinical benefit, all patients who achieved an objective response ultimately progressed on treatment with sotorasib in a phase II study (24). Thus, acquired resistance limits the impact of $KRAS^{G12C}$ inhibitors, a conclusion that is likely to apply to other KRAS inhibitors. Two recent reports provide much-awaited first insights into the mechanisms underlying acquired resistance to the $KRAS^{G12C}$ inhibitors in the clinic (64, 65). The larger study interrogated genomic and histologic alterations using circulating free tumor DNA and/or tissue samples in 38 patients with disease progression on treatment with adagrasib after an initial clinical response (64). The analyzed cohort included 27 patients with NSCLC, 10 with colorectal cancer, and 1 with appendiceal cancer. One or more putative resistance mechanisms were identified in 17 patients (45%). Most of these patients (15 of 17) acquired molecular alterations leading to reactivation of RAS/MAPK signaling, albeit with the majority at low allelic frequencies while in most cases maintaining the $KRAS^{G12C}$-mutated allele. This striking convergence suggests that RAS/MAPK signaling restoration drives therapeutic resistance to $KRAS^{G12C}$ inhibitors in the clinic and highlights the strong addiction of $KRAS^{G12C}$-mutated tumors to RAS/MAPK signaling. Identified putative resistance mechanisms include on-target and beyond-target alterations (Fig. 4) and fall into six different classes: i) *KRAS* mutations in the switch II pocket that block inhibitor binding (secondary mutations in *KRAS* residues R68, H95, or Y96), ii) activating *KRAS* mutations (G12D, G12R, G12V, G13D, or Q61H) likely in a *trans* allele configuration, iii) *cis* allele conversion of the $KRAS^{G12C}$ codon mutation ($KRAS^{G12C} \rightarrow KRAS^{G12W}$), iv) $KRAS^{G12C}$ amplification, v) $KRAS^{G12C}$ bypass mutations in the RAS/MAPK/PI3K pathway (amplifications, mutations, or activating fusions of the genes encoding oncogenic RTKs *MET*, *EGFR*, *RET*, *ALK*, and *FGFR3*; activating mutations or fusions of the downstream effector kinases *BRAF*, *CRAF*, and *MEK1*; *NRAS* and *PI3K* mutations; and *PTEN* or *NF1* tumor suppressor mutations), and vi) cell state transformation from adenocarcinoma to squamous cell carcinoma histology (64, 94, 95). Importantly, 9 of 17 patients (53%) with detected putative resistance mechanisms harbored a least one acquired *KRAS* alteration. Furthermore, 7 of 17 patients (41%) acquired more than one putative resistance mechanism, a finding that appeared more prevalent in patients with colorectal cancer than NSCLC.

Differential preclinical profiling of sotorasib and adagrasib revealed specific secondary *KRAS* mutations that elicit resistance to one drug but maintain sensitivity to the other (64, 95); for example, $KRAS^{G12C}$ harboring additional mutations in the position H95, such as H95D/Q/R, abrogated the activity of adagrasib but remained vulnerable to sotorasib. This suggests that the sequential use of $KRAS^{G12C}$ inhibitors in patients, who are selected based on the appropriate KRAS resistance mutation, may be able to deliver clinical benefit. Alternatively, $KRAS^{G12C}$ inhibitors with a different mode of action to adagrasib and sotorasib have the potential to address secondary *KRAS* resistance mutations in the switch II pocket that cause cross-resistance to off-state inhibitors. This has been shown preclinically with the tricomplex $KRAS^{G12C}$ active state inhibitor RM-018 in cellular models expressing a $KRAS^{G12C\ Y96D}$ double-mutant variant (65). In addition, $KRAS^{G12C}$ active state inhibitors are expected to address adaptive changes of KRAS resulting in the production of new, active KRAS (10). Nevertheless, the acquisition of a diverse set of *KRAS* mutations in response to $KRAS^{G12C}$ inhibitor treatment across the cohort, as well as the subclonal intratumor heterogeneity of resistance mechanisms within many patients, poses a challenge for the development of allele-specific next-generation $KRAS^{G12C}$ inhibitors. In contrast, direct pan-KRAS inhibitors or degraders with potent activity against a set of activating *KRAS* mutations have the

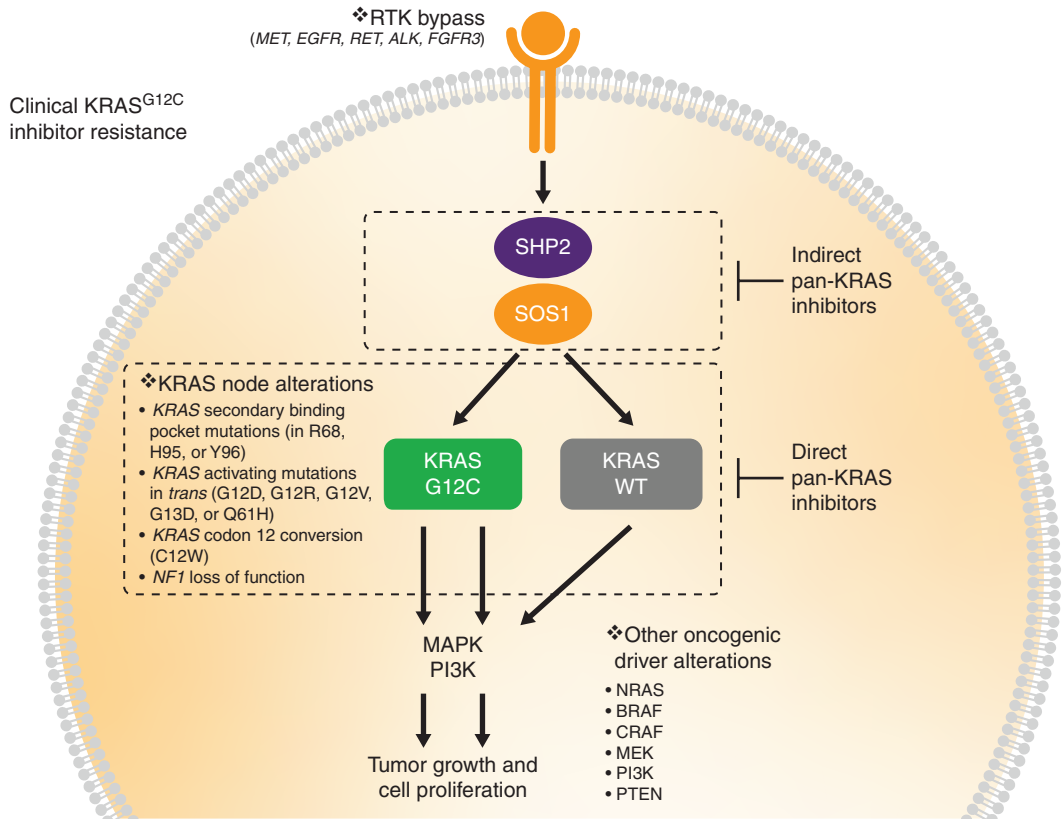

Figure 4. Putative acquired resistance mechanisms detected in KRAS^{G12C} inhibitor-resistant patients are shown in a schematic pathway diagram. The potential utility of direct and indirect pan-KRAS inhibitors in addressing resistance is indicated using dashed boxes.

potential to address KRAS inhibitor resistance mechanisms more broadly (Fig. 4; ref. 95). Furthermore, direct pan-KRAS agents, especially those with potent activity against wild-type KRAS, might be able to suppress upstream bypass resistance events, such as activating RTK alterations and NF1 loss-of-function mutations. The efficacy of pan-KRAS inhibitors could be augmented by vertical pathway combination with indirect pan-KRAS inhibitors, such as SHP2 or SOS1 inhibitors, that reduce KRAS-GTP loading of different KRAS variants, address adaptive feedback mechanisms (e.g., mediated by diverse RTKs upstream), and potentially dampen RTK alteration-driven resistance (refs. 11, 12, 36, 42, 96; Fig. 4).

Preclinical studies with models carrying molecularly defined and clinically relevant resistance mechanisms will be crucial to identify and prioritize KRAS-targeted monotherapies and combinations for clinical exploration to treat and possibly prevent acquired resistance to KRAS inhibitors. We anticipate that larger clinical data sets characterizing acquired resistance to KRAS^{G12C} inhibitors in NSCLC and colorectal cancer will soon become available. This will help to define the most recurrent mechanisms of resistance and the alterations that are responsible for driving clinically manifested tumor progression. The latter point is pertinent given the low allele frequency of putative resistance alterations detected in circulating tumor DNA (64–66). Importantly, additional clinical data may be able to address what drives therapy resistance in more than half of the patients (21 of 38), who harbored no identifiable molecular or histologic alterations upon progression on adagrasib (64). Insights gleaned from the most advanced clinical KRAS^{G12C} inhibitors, sotorasib and adagrasib, regarding acquired resistance in patient tumors and how to address it therapeutically will likely be instructive for the next generation of KRAS inhibitors.

CONCLUSION

Given that pan-KRAS concepts will address extensive unmet needs, a significant effort is now being applied within the pharmaceutical industry to move beyond KRAS^{G12C} inhibitors and discover new therapeutics with the ultimate goal to target all *KRAS* mutants. Exciting progress has already been reported for *KRAS*^{G12D} mutant-selective inhibitors as well as pan-KRAS inhibitors and degraders. We see allele-specific and pan-KRAS drugs as highly complementary therapeutic concepts that can be positioned to comprehensively conquer all KRAS cancers. It remains to be seen whether it will be possible to develop additional mutant-specific inhibitors, such as KRAS^{G12V} inhibitors or pan-mutant KRAS inhibitors, that spare wild-type KRAS. We are still at the beginning of drugging KRAS, and KRAS^{G12C} inhibitors represent the first chapter of the saga on cracking KRAS. Based on the intense efforts and rapid progress in the field, we see the beginning of the first "beyond KRAS^{G12C}" chapter becoming a reality. However, we expect many more

chapters need to be written before we have sufficient medicines against *KRAS*, the Everest of oncogenes (97), for patients with cancer driven by KRAS.

Authors' Disclosures

M.H. Hofmann reports grants from Austrian Research Promotion Agency (FFG) during the conduct of the study and is listed as inventor on several patent applications for SOS1 inhibitors and is a full-time employee of Boehringer Ingelheim Regional Center Vienna GmbH & Co KG. D. Gerlach reports grants from Austrian Research Promotion Agency (FFG) during the conduct of the study and is a full-time employee of Boehringer Ingelheim Regional Center Vienna GmbH & Co KG. S. Misale reports other support from Boehringer Ingelheim outside the submitted work. M. Petronczki reports grants from Austrian Research Promotion Agency (FFG) during the conduct of the study and is a full-time employee of Boehringer Ingelheim Regional Center Vienna GmbH & Co KG. N. Kraut reports grants from Austrian Research Promotion Agency (FFG) during the conduct of the study and is a full-time employee of Boehringer Ingelheim Regional Center Vienna GmbH & Co KG.

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