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REVIEW

Targeting KRAS^{G12C} in colorectal cancer: the beginning of a new era

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Available online XXX

RAS mutation is considered one of the most relevant oncogenic drivers in human cancers. Unfortunately, for more than three decades, RAS has been considered an undruggable target. Recently, the discovery of selective and potent KRAS^{G12C} inhibitors represented a light at the end of the tunnel. Indeed, sotorasib and adagrasib proved clinical activity in patients with refractory metastatic colorectal cancer harboring *KRAS*^{G12C} mutation; however, responses are lower than expected, suggesting the presence of intrinsic resistance. Consequently, novel combinatory strategies to disrupt the RAS signaling pathways are under clinical investigation. This review aims to discuss the current knowledge and novel routes of KRAS^{G12C} inhibition in metastatic colorectal cancer.

Key words: CRC, KRAS^{G12C}, target therapies, precision medicine

INTRODUCTION

Mutations in *RAS* genes are considered one of the most frequent oncogenic drivers in human malignancies, including colorectal cancer (CRC).[1] According to the model by Fearon and Vogelstein,[2] CRC development depends on the accumulation of an increasing number of genetic alterations. Of note, RAS oncogenic activation represents an early event in ∼30%-50% of CRC and has a crucial role in the malignant transformation of the colonic epithelium.[3]

The RAS family includes three oncogenes, *KRAS/NRAS/HRAS*, located in 12p.[1] Around 40% of metastatic CRCs (mCRC) exhibit *KRAS* mutations, typically in exon 2, and in codons 12 (near 80% of all *KRAS* mutations) and 13, and are less frequent in exons 3 (codons 59 and 61) and 4 (codons 117 and 146).[1,3,4] *NRAS* mutations are uncommon (5%-10% of CRC), and occur mostly in exons 3 (codon 61) and 2 (codons 12 and 13). For decades, different *KRAS* mutations were considered equal regarding lack of response to anti-epidermal growth factor receptor (EGFR), and a negative prognostic factor.[4,5] This assumption has rapidly changed and refined in the past few years, after the breakthrough discovery that it is possible to target KRAS^{G12C} selectively.[6-9]

The occurrence of *KRAS*^{G12C} mutation is rare, however, and is reported in ∼2%-4% of mCRC.[10] Different retrospective investigations evaluated the role of KRAS^{G12C} as a prognostic and predictive biomarker.[11-13] We recently reported the results of a real-life study including 111 patients with unresectable KRAS^{G12C}-mutant mCRC receiving a chemotherapy doublet or triplet-based regimen as first-line treatment.[11] We confirmed that the *KRAS*^{G12C} mutation depicts an aggressive disease with a disappointing response to standard treatments. Of note, only 62% and 36% of patients are fit to receive second or third lines of treatment after progression. Other groups demonstrated that patients carrying this mutation displayed a poorer outcome than other KRAS non-G12C mCRC.[12-14] Interestingly, KRAS^{G12C}-mutant CRC exhibits a distinct molecular profile.[14] Henry and colleagues[14] reported higher rates of basal EGFR activation, enrichment with *PIK3CA* mutation and a decreased immune expression profile.

In this scenario, after years of negative research, the discovery of KRAS^{G12C} inhibitors seemed to be a light at the end of the tunnel. Despite sotorasib and adagrasib demonstrating a safety profile and signals of anti-tumor activity in refractory KRAS^{G12C}-mutant mCRC, however, most patients are refractory, suggesting that more effective combinatory strategies are required. This concise review aims to summarize the available clinical data and discuss the novel lines of clinical research to render KRAS^{G12C} a real target.

METHODS

We carried out a manual revision of the literature by searching on PubMed, databases and abstracts from international conferences (e.g. ASCO, ESMO, ASCO GI and WGI). Papers published in peer-reviewed journals and conference abstracts of clinical trials regarding KRAS^{G12C} inhibition in

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mCRC in the English language up to September 2022 were selected.

KRAS signaling

RAS are small membrane-bound guanine nucleotide-binding proteins involved in different signaling pathways. Of note, RAS proteins play a crucial role in regulating cell growth, differentiation, motility and survival. They are involved in multiple aspects of tumor initiation, progression and resistance to target therapies.[5] In physiological conditions, RAS shifts between an active guanosine-5′-triphosphate (GTP)-bound state and an inactive guanosine diphosphate (GDP)-bound conformation.[9] The initiation of the RAS cascade is modulated by different receptor tyrosine kinases (RTKs), including EGFR, platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR).[3] The ligand binding to the extracellular domain of the RTK induces RTK dimerization and activation of intrinsic tyrosine kinase and autophosphorylation (Figure 1). The phosphorylated receptor interacts with the growth factor receptor-bound protein 2 (GRB2) and recruits the guanine nucleotide exchange factors (GEFs) to the plasma membrane. Subsequently, GEFs, such as Son of sevenless homolog (SOS), favor the GDP/GTP exchange, inducing a shift to the active conformational status. The RAS—GTP protein activates different pathways, including RAF—MEK—ERK, PI3K—AKT—mTOR and TIAM1—Rac—Rho/PAK, and nuclear

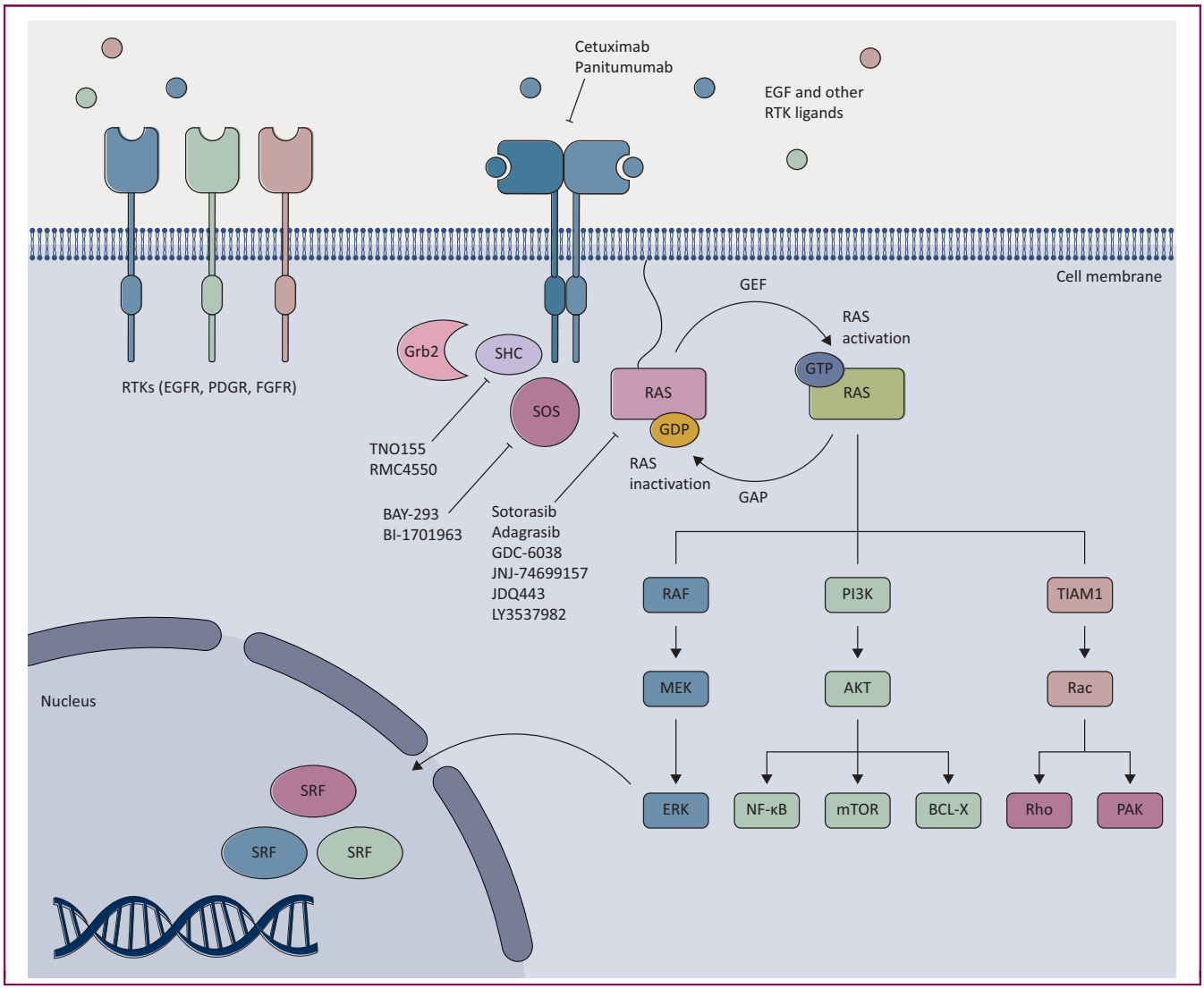

Figure 1. Ras signaling pathways. When ligands, such as epidermal growth factor (EGF), bind to the extracellular domain of a receptor tyrosine kinase (RTK), such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR), RTK dimerizes and activates a cascade of events. Son of sevenless (SOS), a guanine nucleotide exchange factor (GEF), is recruited via the adaptor proteins SH2-adaptor protein C (SHC) and growth factor receptor-bound protein 2 (Grb2). After exchanging guanosine diphosphate (GDP) with guanosine-5'-triphosphate (GTP), Ras is activated and dimerizes. The mitogen-activated protein kinase (MAPK) pathway is activated after Ras binds Raf, thereby promoting its dimerization and activation, Mitogen-activated protein kinase 1 and 2 (MEK1/2) and extracellular regulated kinase 1/2 (ERK1/2) activation. Active GTP-bound Ras also binds to phosphatidylinositol 3-kinase (PI3K), leading to phosphorylation of the serine/threonine kinase Akt that further activates mammalian target of rapamycin (mTOR) complex, nuclear factor (NF)-kB and B-cell lymphoma-extra large (BCL)-X. Thirdly, activation of TIAM1 drives Rac, Rho and PAK activation. As a result, many downstream serum response factors (SRF) and other transcription factors determine oncogenic transcription, cell cycle progression, growth, survival, metabolism, apoptosis inhibition, cell motility and migration. RAS activation ends after a shift from GTP-bound to a GDP-bound state that is mediated by RAS—GTPase-activating enzymes (RAS—GAPs).

transcription factors, involved in the homeostasis of several cellular processes, including cell metabolism, protein synthesis, cell proliferation, migration, motility and apoptosis. The RAS cycle is finally switched off by GTPase-activating proteins (GAPs) that induce GTP hydrolysis, forming inactive RAS—GDP.

KRAS^{G12C} from undruggable to a real target

Since the identification of *RAS* genes in 1982, for almost 30 years, KRAS has been considered an undruggable target. Several difficulties have been faced in the development of specific KRAS^{G12C} inhibitors. First, the affinity of KRAS and GTP is high at the picomolar level, whereas the concentration of GTP in cells is up to 0.5 micromolar. Second, due to the nearly spherical structure and lack of a deep hydrophobic pocket, it has been considered difficult to find a binding site for selective inhibitors.[15]

In 2013, Ostrem and colleagues[6] made a seminal discovery. The authors identified an allosteric pocket below the switch II region of mutant cysteine (named switch II) and subsequently developed a series of irreversible inhibitors. These compounds preferentially bound RAS in the GDP-bound conformation, impairing the exchange with GTP and thus preventing the signaling cascade activation. This mechanism of action could appear in contrast with the assumption that hotspot mutations determine the constitutive activation of RAS proteins. New evidence by Hunter and colleagues,[16] however, proved that specific *KRAS* mutations retain intrinsic and GAP-stimulated GTPase activity. Despite the preliminary results, compound 12, the first drug tested by Ostrem and colleagues,[6] showed inadequate pharmacological properties and low efficacy in blocking KRAS^{G12C}. This revolutionary discovery, however, rapidly led to the development of different and more potent inhibitors, moving from bench to bedside (Table 1).[7-9] ARS-1620 is the first KRAS^{G12C} small molecule inhibitor that exhibited antitumor activity *in vitro* and *in vivo* with promising therapeutic potential.[17] AMG 510 (sotorasib) is a next-generation inhibitor.[18] The substitution of the quinazoline nitrogen (N1) of ARS-1620 in AMG 510 allows the engagement with the histidine 95 of KRAS protein, determining a stronger binding and increased potency of AMG 510 by nearly 10-fold. In murine models, Canon and colleagues[18] elegantly demonstrated that treatment with AMG 510 led to impressive tumor regression. Adagrasib (MTRX849) is an irreversible KRAS^{G12C} inhibitor that demonstrated significant preclinical activity in different cell lines and patient-derived xenograft models from multiple tumor types.[19]

Clinical development of selective inhibitors targeting KRAS^{G12C}

The safety and antitumor activity of sotorasib was investigated in the phase I CodeBreaK 100 trial, enrolling patients with heavily pretreated *KRAS^{G12C}* tumors, including a cohort of 42 patients with pretreated mCRC.[20] In the mCRC subgroup, 3 patients (7.1%) had a partial response (PR), and 31 patients (71.8%) had stable disease (SD) as the best response; the median progression-free survival (mPFS) was 4.0 months (range, 0.0-11.1+ months). Treatment was feasible: diarrhea, fatigue and nausea were the most common events. In a phase II expansion cohort, the clinical activity of sotorasib was evaluated in 62 patients with refractory KRAS^{G12C}-mutant mCRC.[7] A total of 6 patients (10%) experienced a PR and 45 patients (73%) experienced an SD. mPFS was 4 months [95% confidence interval (CI) 2.8-4.2 months], and median overall survival (mOS) was 10.6 months (95% CI 7.7-15.6 months).

At the ESMO 2022 annual meeting, results of the KRYSTAL-1 trial investigating adagrasib as a single agent or in combination with cetuximab were presented.[21] In 43 patients receiving adagrasib monotherapy, overall response rate (ORR) was 19% (8/43), with a high disease control rate (DCR) of 86% (37/43). mPFS was 5.6 months (95% CI 4.1-8.3 months) and mOS 19.8 months (95% CI 12.5-23 months).

Amodio and colleagues[22] have shown that KRAS^{G12C}-mutant CRC is still dependent on EGFR signaling.

Table 1. Completed clinical trials targeting KRAS^{G12C}

Study name	Tumor type	Number of patients	Setting	Phase	Treatment arms	Results
CodeBreaK 100	KRAS^{G12C}-mutant advanced solid tumors	129 (42 Patients with mCRC)	Refractory	I	Sotorasib	mPFS: 4.0 months ORR: 7.1% (3/42)
CodeBreaK 100 (CRC expansion cohort)	KRAS^{G12C}-mutant mCRC	62	Refractory	II	Sotorasib	mPFS: 4 months mOS: 10.6 months ORR: 10% (6/62)
CodeBreaK 101	KRAS^{G12C}-mutant mCRC	30	Refractory	I	Sotorasib + Panitumumab	mPFS: 5.7 months ORR: 30% (12/40)
KRYSTAL-1	KRAS^{G12C}-mutant mCRC	42	Refractory	I	Adagrasib	mPFS:5.6 months mOS: 19.8 months ORR: 19% (8/43)
KRYSTAL-1	KRAS^{G12C}-mutant mCRC	28	Refractory	I	Adagrasib + Cetuximab	mPFS: 6.9 months mOS: 13.4 months ORR: 46% (13/28)
NCT04006301	KRAS^{G12C}-mutant advanced solid tumors	10 (4 Patients with mCRC)	Refractory	I	JNJ-74699157	ORR: 0%
NCT04449874	KRAS^{G12C}-mutant advanced solid tumors	498 (Including 43 patients with mCRC)	Refractory	I	GDC-6036	ORR: 20%

mCRC, metastatic colorectal cancer; mOS, median overall survival; mPFS, median progression free survival; ORR, overall response rate.

Table 2. Main pharmacokinetics characteristic and dose of KRAS^{G12C} inhibitors tested in phase I/II studies

Name	Sotorasib (AMG510)	Adagrasib (MRTX849)	JDQ443	GDC-6036	JNJ-74699157
Half-life (h)	5.5	23	N/A	15	6.8
Dose	960 mg q.d.	600 mg b.i.d	200 mg b.i.d.	400 mg q.d.	100 mg q.d.

b.i.d., twice a day; N/A, not available; q.d., every day.

Interestingly, in CRC, upstream activation of EGFR could reduce the efficacy of KRAS^{G12C} blockade. Thus, anti-EGFR monoclonal antibodies combined with KRAS^{G12C} inhibitors could represent a promising therapeutic strategy. In this regard, in the KRYSTAL-1 study, in 28 patients treated with cetuximab plus adagrasib, the ORR was 46% (13/28), DCR was 100% (28/28) and mPFS was 6.9 months (95% CI 5.4-8.1 months). The mOS was 13.4 months (95% CI 9.5-20.1 months).

It should be noted, however, that the 12-month OS rate was similar between monotherapy and combinatory treatment and that the mOS could be affected by the short follow-up and reduced number of patients.

Data from the dose expansion cohort of the phase Ib CodeBreaK 101 study investigating the combination of sotorasib plus panitumumab were also recently presented.[23] The ORR was 30% (12/40), with a DCR of 93% (95% CI 79.6% to 98.4%) and an mPFS of 5.7 months (95% CI 4.2-7.6 months).

A phase I trial was published, assessing the safety of JNJ-74699157, a novel KRAS^{G12C} inhibitor.[24] Unfortunately, the occurrence of dose-limiting skeletal muscle toxicities and the reduced efficacy at the 100 mg dose determined the early discontinuation of the study. The safety and clinical activity of GDC-6036, another high selective KRAS^{G12C} inhibitor, has been investigated in a phase I study.[25] A total of 43 patients with mCRC were enrolled, and no dose-limiting toxicities were observed. Among the patients assessable for the response, the confirmed ORR was 20% (8/41). Interestingly, a decrease in circulating tumor DNA levels was observed among responders. The main dose and pharmacokinetics characteristics of KRAS^{G12C} inhibitors tested in phase I/II clinical trials are reassumed in Table 2.

Other KRAS^{G12C} inhibitors are currently under different phases of clinical development (Table 3).

Other strategies to interfere with RAS signaling

Alongside the use of specific inhibitors, new approaches to disrupt the RAS signaling are under evaluation (Table 2).[26]

Interfering with KRAS cell membrane localization

The first step of RAS activation is represented by the location at the cell membrane and is finely regulated by post-enzymatic steps.[3,27] Above all, protein farnesylation by farnesyltransferase (FTase) or geranylgeranylation by geranylgeranyltransferase (GGTase) is required for the beginning of the RAS signaling cascade.

Different drugs that prevent the block of RAS farnesylation have been tested in preclinical models.[27] Despite a strong biological rationale, however, FTase inhibitors demonstrated limited antitumor activity in KRAS-mutant tumors.[28,29] One of the main mechanisms of primary resistance is represented by the compensatory activity of GGTase. Isoprenylcysteine carboxylmethyltransferase (ICMT) is an enzyme involved in the last step of the RAS prenylation process.[26,30] In *in vitro* and *in vivo* models, ICMT blockade resulted in reduced self-renewal/stemness of KRAS-mutant pancreatic and breast cancer cells. The current studies are still at preclinical levels, however, and the activity is still to be demonstrated in phase I studies.

Src homology region 2-containing protein tyrosine phosphatase 2 inhibitors

Src homology region 2-containing protein tyrosine phosphatase 2 (SHP2) is a downstream RTK non-receptor protein tyrosine phosphatase acting at the beginning of RAS—MAPK pathways.[31] It has been shown that adding SHP2 inhibition with RMC-4550 to KRAS^{G12C} inhibitors could potentiate the antitumor activity in preclinical models, preventing the activation of adaptive resistance signaling.[20,32]

SOS1 inhibitors

Another strategy to prevent the loading of GTP on RAS, and thus the activation of the protein, is constituted by the inhibition of SOS1. BAY-293 is a first-in-class potent SOS1 inhibitor that provided synergistic activity when combined with ARS-853 in preclinical KRAS^{G12C} cancer cell models.[33] A new SOS1 inhibitor, BI-1701963, is currently under evaluation as a single agent, or with the MEK inhibitor trametinib (NCT04111458) or in combination with adagrasib (NCT04975256). AZD4785 is an antisense oligonucleotide that favors mRNA degradation, reducing KRAS expression.[34] Despite promising preclinical results, the compound failed to demonstrate a reduction in KRAS expression and efficacy in a phase I study (NCT03101839).

Blocking KRAS downstream or parallel signaling pathways

Blocking KRAS downstream signaling pathways, such as the MAPK—RAF—ERK cascade, might represent a valid therapeutic option. In a phase I study, the MEK inhibitor pimasertib was combined with FOLFIRI as a second-line treatment of KRAS-mutant mCRC.[35] Unfortunately, dose escalation of pimasertib was limited by gastrointestinal and skin toxicity. Among 15 patients in the efficacy analysis group, 2 exhibited PR, 9 SD and 3 PD as the best response (one patient was non-assessable). Lifirafenib (BGB-283) is a novel, first-in-class, investigational RAF dimer inhibitor with potent, reversible inhibition of wild-type RAF, BRAF^{V600E} and KRAS.[36] Lifirafenib showed an acceptable safety profile in a phase I study, with signals of clinical activity in BRAF-mutant non-small-cell lung cancer (NSCLC), melanoma, low-grade ovarian cancer and thyroid

Table 3. Main on-going clinical trials investigating KRAS^{G12C} inhibition in metastatic colorectal cancer (mCRC)

Name	Tumor type	Setting	Phase	Treatment arms	Target accrual	Primary endpoints
CodeBreak 300 (NCT05198934)	KRAS^{G12C}-mutant mCRC	Refractory	III	Sotorasib + panitumumab versus investigator choice	153	PFS
CodeBreak 100 (NCT03600883)	KRAS^{G12C}-mutant advanced solid tumors	Refractory	I/II	Sotorasib	793	Safety; ORR
CodeBreak 101 (NCT04185883)	KRAS^{G12C}-mutant advanced solid tumors	Refractory	I/II	Sotorasib as single agent or in combination with different drugs (trametinib/trametinib + panitumumab/ afatinib/pembrolizumab/everolimus) FOLFIRI + panitumumab/palbociclib/ TNO155/MVASI® (bevacizumab-awwb) + FOLFOX or FOLFIRI/RMC-4630/AMG 404)	1054	Safety
KRYSTAL-10 (NCT04793958)	KRAS^{G12C}-mutant mCRC	Second line of treatment	III	Adragasib + cetuximab versus FOLFOX/ FOLFIRI	420	OS; PFS
KRYSTAL-01 (NCT03785249)	KRAS^{G12C}-mutant advanced solid tumors	Refractory	I	Adagrasib as single agent or in combination with other drugs (pembrolizumab; afatinib; cetuximab)	740	Safety; ORR
KRYSTAL-2 (NCT04330664)	KRAS^{G12C}-mutant advanced solid tumors	Refractory	I/II	Adagrasib + TNO155	86	Safety
KRYSTAL-14 (NCT04975256)	KRAS^{G12C}-mutant advanced solid tumors	Refractory	I	Adagrasib + BI 1701963	100	Safety
NCT05002270	KRAS^{G12C}-mutant advanced solid tumors	Refractory	I/II	JAB-21822as single agent or in combination with cetuximab	100	Safety; ORR; DOR
NCT04973163	KRAS^{G12C} mutant advanced solid tumors	Refractory	I	BI 1823911 single agent or in combination with BI 1701963	72	Safety; ORR
NCT04956640	KRAS^{G12C}-mutant advanced solid tumors	Refractory	I	LY3537982 as single agent or in combination with other drugs (abemaciclib; pembrolizumab; erlotinib; temuterkib; cetuxcimab; TNO155)	360	Safety
KontRASt-01 (NCT04699188)	KRAS^{G12C}-mutant advanced solid tumors	Refractory	I	JDQ443 as single agent or in combination with TNO155 or tislelizumab	420	Safety; ORR
NCT04449874	KRAS^{G12C}-mutant advanced solid tumors	Refractory	I	GDC-6036 as single agent or in combination with other drugs (atezolizumab; cetuximab; bevacizumab; erlotinib; GDC-1971; inavolisib)	498	Safety

DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

cancer, and KRAS-mutant endometrial carcinoma and NSCLC. Unfortunately, no activity was observed in patients with RAS-mutant mCRC.

Combinatory strategies targeting horizontal/parallel pathways represent a possible way to enhance efficacy. It is already known that KRAS may affect the cell cycle by modulating regulatory pathways.[37] In this regard, in the study by Hallin and colleagues,[19] the cyclin-dependent kinase 4/6 inhibitor palbociclib could revert the resistance to adagrasib. Recently, the results of a translational study investigating the combination of the MEK inhibitor binimetinib with palbociclib in a RAS-mutant CRC preclinical model and refractory patients were published.[38] In 18 derived xenograft models, the combined therapy induced sustained tumor regression. Therefore, these results were rapidly translated from bench to bedside, and six patients were enrolled in the safety run-in cohort. Treatment was well tolerated; one patient with a heavily pretreated KRAS^{G12D}-mutant CRC obtained a decrease in tumor markers and a PR.

Combination of KRAS^{G12C} inhibitors with immunotherapy

While immunotherapy has made a revolution in the therapeutic scenario of the hypermutated microsatellite instable (MSI-H) CRC, reduced activity has been observed in microsatellite stable (MSS) tumors.[39-41] Interestingly, robust evidence indicates that novel KRAS^{G12C} inhibitors could change the immunosuppressive tumor microenvironment (TME) composition, enhancing immunogenicity.[18,19] In murine models, treatment with sotorasib significantly increased intratumor CD8+ T lymphocytes, dendritic cells and macrophages, converting a cold TME into a pro-inflammatory and immunocompetent one.[18] Preliminary data of the phase I study assessing the safety of sotorasib plus pembrolizumab or atezolizumab for KRAS^{G12C}-mutant NSCLC patients were presented at the 2022 World Congress on Lung Cancer.[42] The main challenge for this treatment strategy was dose-limiting grade 3-4 hepatic toxicity. Further studies are needed to clarify if dual KRAS^{G12C} and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) blockade is feasible and well tolerated. Recently, Zhang and colleagues[43] elegantly demonstrated that ARS1620, a small molecule KRAS^{G12C} inhibitor, could generate attenuated major histocompatibility complex (MHC) class I peptide complexes. This neoantigen may represent a potential target for immune-based therapies to overcome primary and secondary resistance to KRAS^{G12C} inhibitors.

Acquired resistance to KRAS^{G12C} inhibitors

A major limitation to the efficacy of target therapies is represented by the insurgence of mechanisms of acquired

resistance. Recently, Awad and colleagues[44] published the results of a translational study assessing molecular and histologic alterations on tissue/blood samples in 38 patients with disease progression to adagrasib.

A cohort of 38 patients was included in the investigation: 27 with NSCLC, 10 with CRC and 1 with appendiceal cancer. Potential resistance mechanisms to adagrasib were observed in 17 out of 38 patients (45%), of whom 7 (18% of the cohort) had multiple coincident mechanisms. Most of the alterations involved the reactivation of RAS–MAPK signaling cascade, including *KRAS* mutations (G12D/R/V/W, G13D, Q61H, R68S, H95D/Q/R, Y96C), *NRAS*, *BRAF*, *MAP2K1* mutations and the amplification of the $KRAS^{G12C}$.

Other secondary resistance mechanisms included MET amplification, and gene fusions involving *ALK*, *RET*, *BRAF*, *RAF1* and *FGFR3*. Furthermore, a histologic transition from adenocarcinoma to squamous cell carcinoma was observed in two of nine patients with NSCLC. In a preclinical model of NSCLC, it has been shown that epithelial-to-mesenchymal transition induced by PI3K activation constituted a primary and acquired mechanism of resistance to sotorasib.[45] The triple blockade of $KRAS^{G12C}$, PI3K and SHP2 resulted in strong antitumor activity in mouse models of acquired resistance to sotorasib.

CONCLUSION

The presence of $KRAS^{G12C}$ mutation is rare in mCRC and identifies a subset of patients with aggressive disease and dismal efficacy of chemotherapy. In this scenario, after decades of dismal results, KRAS finally appears as a druggable target. Sotorasib and adagrasib were the first-in-class selective $KRAS^{G12C}$ inhibitors that proved antitumor activity in refractory mCRC patients. There is, however, a long road ahead. Data from phase I/II studies showed that only a subset of patients responded to $KRAS^{G12C}$ inhibitors, suggesting the presence of intrinsic resistance. This may partially depend on the high redundancy of KRAS signaling that determines the activation of various feedback mechanisms. Dual $KRAS^{G12C}$ and EGFR blockade appears to be a promising therapeutic strategy. Phase III randomized studies evaluating the combination of $KRAS^{G12C}$ inhibitors with anti-EGFR monoclonal antibodies versus standard of care are currently ongoing. Other strategies to disrupt the RAS cascade at different levels are currently under clinical evaluation. Due to the immunomodulatory properties of target therapies, there is a strong rationale for combining $KRAS^{G12C}$ blockade with immunotherapy. Further investigations are required to clarify the more effective combinatory strategy for patients with $KRAS^{G12C}$-mutant mCRC.

ACKNOWLEDGEMENTS

Gruppo Oncologico dell'Italia Meridionale (GOIM).

FUNDING

None declared.

DISCLOSURE

DC: travel support from Sanofi, Bristol Myers Squibb (BMS) and Merk-Serono. BAM: travel support from Sanofi, BMS, Novartis. EM: has served as advisor and speaker for Amgen, Bayer, Eisai, Incyte, Merck-Serono, Roche, Servier, Pierre Fabre and ESMO, travel grant AstraZeneca, Pierre Fabre.

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