Editorial Commentary

KRAS and EGFR inhibitors: a new step in the management of colorectal cancer

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Nearly 20% of patients with cancers present activating RAS mutation. Kirsten rat sarcoma (KRAS) mutations are the most frequent alterations representing approximately 75% of RAS mutations (1). The *KRAS* gene is an oncogene encoding a G protein implicated in the regulation of cell division and cycle cell. The pathogenesis of colorectal cancer (CRC) is predominantly related to the chromosomal instability pathway notably the occurrence of mutations in the adenomatous polyposis coli (APC) in nearly 70% of cases. These mutations contribute to the activation of the Wnt signaling pathway which is the main pathway regulating colorectal tumorigenesis. The acquisition of other genetic and epigenetic mutations in p53, RAS and APC lead to the classic progression to adenocarcinoma (2). KRAS activating mutations appear later in the pathogenesis and contribute to permanent activation of KRAS dependent-pathways such as MAPK and PI3K-AKT signaling pathways involved in the proliferation and survival of tumor cells (3). KRAS activating mutations are present in 40% of patients with advanced CRC, and KRAS exon 2 mutations represent the vaster majority of KRAS mutations in CRC. $KRAS^{C12D}$ is the most frequent KRAS mutation found in almost 36% of patients followed by $KRAS^{G12V}$ found in 22%, and $KRAS^{G13D}$ present in 15% to 18% of patients. However, $KRAS^{G12C}$ represents approximately 3% of KRAS activating mutations in advanced CRC (4). It has been demonstrated that the occurrence of KRAS mutations was associated with worse survival outcomes notably progression-free survival (PFS), and is a significant negative predictive factor for epidermal growth factor receptor (EGFR) inhibitors (5).

Historically, KRAS mutations were considered as undruggable alterations. This fact was attributed to the structural and functional characteristics of KRAS. However, the advent of two irreversible selective $KRAS^{G12C}$ inhibitors (adagrasib formerly known as MRTX849, and sotorasib also known as AMG510) has changed the treatment paradigm of tumors harboring $KRAS^{G12C}$ mutation. The two agents were approved by the Food and Drug Administration (FDA) for the management of advanced non-small cell lung cancer (NSCLC) harboring $KRAS^{G12C}$ mutation. Sotorasib and adagrasib were associated with impressive objective response rate (ORR) of 36% and 43% respectively (6). However, when used as monotherapy, both agents were associated with lower efficacy in advanced CRC than NSCLC (10% with sotorasib and 22% with adagrasib) explaining the absence of FDA approval for both agents in CRC (7,8). To be noted that several selective inhibitors of $KRAS^{G12C}$ mutation are under clinical evaluation and development such as divarasib (GDC-6036), garsorasib (D-1553), opnurasib (JDQ443), LY537982.

The limited clinical activity of single-agent $KRAS^{G12C}$ selective inhibitor could be related to the upregulation of alternative pathways mediating resistance to selective KRAS

inhibition. It has been demonstrated that EGFR signaling pathway is the major mechanism of resistance to $KRAS^{G12C}$ inhibitors in CRC and that $KRAS^{G12C}$ inhibition led to RAS-MAPK signaling feedback reactivation (9,10). These findings suggest that adding EGFR inhibitors to selective KRAS inhibitors could overcome resistance to these selective inhibitors. This phenomenon was also seen in the case of BRAF mutations in CRC.

The CodeBreak 101 is a multicohort phase I/II trial evaluating sotorasib alone or in combination with other agents such as immunotherapy, targeted therapies (panitumumab), or chemotherapy in patients with solid tumors harboring $KRAS^{G12C}$ mutation (NCT04185883). In *Nature Medicine*, Kuboki and colleagues reported the results of the cohort of patients with advanced CRC with $KRAS^{G12C}$ mutation and refractory to chemotherapy and treated sotorasib and panitumumab in third-line setting. Overall, 48 patients received sotorasib at a dosage of 960 mg once a day and panitumumab 6 mg/kg every 2 weeks. Grade 3 or higher treatment-related adverse events (TRAEs) were reported in 27% of patients (13/48). Objective response was observed in 30% of patients in the dose-expansion cohort, and the disease control rate (DCR) rate was 92.5%. The median PFS and overall survival (OS) were 5.7 and 15.2 months respectively. The authors found several genomic co-alterations such as APC, TP53, SMAD4, PIK3CA, and EGFR (11). Recently, data of patients who received sotorasib and panitumumab as second-line treatment was released. Overall, 20 patients were enrolled in this cohort. Safety profile and objective response were comparable with the findings of Kuboki and colleagues in more chemo-refractory patients. However, median PFS was longer (8.3 months) (12). Furthermore, sotorasib was evaluated in combination with panitumumab and FOLFIRI in the subprotocol H of the CodeBreak 101 in patients who received at least one prior line for incurable disease. Grade 3 or higher TRAEs were reported in 46% of patients, and dermatological toxicity was the most common. Interestingly, this combination was associated with an ORR of 58% and a DCR of 94% in 31 evaluable patients (13).

The CodeBreak 300 is a randomized phase III that compared sotorasib in combination with panitumumab versus standard of core treatment (regorafenib or trifluridine-tipiracil) in patients with mCRC harboring $KRAS^{G12C}$ mutation and refractory to chemotherapy. Sotorasib was given at dosage of 240 mg or 960 mg once daily. The study met its primary endpoint of median PFS. In the 960 mg of sotorasib cohort, the median PFS was 5.6 versus 2.2 months in the control arm with a hazard ratio (HR) of 0.49, P=0.006. In the second cohort, the median PFS was 3.9 months and the HR was 0.58, P=0.03. Grade 3 or higher TRAEs occurred in at least 30% in all cohorts. Surprisingly, both cohorts of sotorasib were not compared (14). CodeBreak 300 was the first randomized phase III study to show that KRAS-targeted therapy in combination with EGFR inhibitor is superior to standard-of-care in third line treatment in advanced CRC.

The results were similar to those seen with adagrasib when combined with cetuximab, another EGFR-targeting monoclonal antibody. The KRYSTAL-1 trial is a phase I/II study evaluating adagrasib alone or in combination with cetuximab in patients with advanced CRC harboring $KRAS^{G12C}$ mutation and who did not previously receive a KRAS inhibitor. Overall, 44 patients received adagrasib as monotherapy and 32 patients in combination with cetuximab. As previously mentioned, adagrasib alone was associated with lower activity in advanced CRC with an ORR of 19% and a median PFS of 5.6 months. However, the combination was associated with an ORR of 46% and a median PFS of 6.9 months. To be noted that grade 3 or higher TRAEs occurred in 34% of patients treated with adagrasib alone and 16% in combination with cetuximab (8). Interestingly, adagrasib in combination with cetuximab was associated with higher clearance of $KRAS^{G12C}$ mutant allele using circulating tumor DNA than adagrasib alone after 2 cycles of treatment. These findings could explain the difference in terms of ORR. The combination of adagrasib and cetuximab is currently under investigation versus standard-of-care in second-line setting in the KRYSTAL-10 phase III trial that had completed recruitment (NCT04793958).

Divarasib, also known as GDC-6036, is a covalent inhibitor of $KRAS^{G12C}$ was evaluated as monotherapy in patients with metastatic solid cancers harboring $KRAS^{G12C}$ mutation in a phase I trial. Overall, 137 patients were enrolled, of whom 55 patients with CRC. The ORR was 29% among patients with CRC with a median PFS of 5.6 months. The safety profile was acceptable with grade 3 or higher TRAEs occurring in 12% of patients. Moreover, no dose-limiting toxicities were reported and no treatment-related deaths occurred (15). Divarasib was also combined with cetuximab in patients with CRC harboring $KRAS^{G12C}$ mutation in a phase Ib trial. The results from arm C (29 patients) of this study showed encouraging clinical activity of the combination. The ORR of 62.5% and a median PFS of 8.1 months in patients naïve from $KRAS^{G12C}$ inhibitors. Interestingly, among five patients who previously

Table 1 Trials of $KRAS^{G12C}$ inhibitors in combination with EGFR inhibitors

Study	Phase	Drugs	Nb of pts	ORR	mPFS	Grade ≥3 TRAEs
CodeBreak 101 [2024], (11)	I/II	Sotorasib + panitumumab	48	30%	5.7 m	27%
CodeBreak 101 [2023], (13)	I/II	Sotorasib + panitumumab + FOLFIRI	31	58%	Not mature	46%
CodeBreak 300 [2023], (14)	III	Sotorasib (960 or 240 mg) + panitumumab *vs.* SOC	53 *vs.* 53 *vs.* 54	26% *vs.* 5.7% *vs.* 0%	5.6 *vs.* 3.9 *vs.* 2.2 m	36% *vs.* 30% *vs.* 43%
KRYSTAL-1 [2023], (8)	I/II	Adagrasib + cetuximab	32	46%	6.9 m	16%
NCT04449874 [2024], (16)	Ib	Divarasib + cetuximab	29	62.5%	8.1 m	45%
NCT04585035 [2023], (17)	II	Garsorasib + cetuximab	29	45%	7.6 m	13%

EGFR, epidermal growth factor receptor; Nb, number; pts, patients; ORR, objective response rate; mPFS, median progression-free survival; TRAEs, treatment-related adverse events; m, months; FOLFIRI, folinic acid, 5-fluorouracil, irinotecan; SOC, standard of care.

received an anti $KRAS^{G12C}$ inhibitor, three patients showed partial response and two patients had stable disease as best response to therapy. Regarding toxicity profile, the combination was associated with 45% (13/29) of grade 3 or higher TRAEs (16).

Garsorasib, also named D-1553, is another selective inhibitor of $KRAS^{G12C}$. It has been investigated in a phase II trial in combination with cetuximab in mCRC harboring $KRAS^{G12C}$ mutation. The clinical response was similar than the combination with other KRAS inhibitors with an ORR of 45% and median PFS of 7.6 months. Moreover, grade 3 or higher TRAEs were reported in nearly 13% of patients. Cutaneous toxicity was the most frequent grade 3 or higher TRAE (17).

All available data suggest that combination of $KARS^{G12C}$ inhibitors with EGFR inhibitors resulted in improved clinical outcomes. However, the relatively low frequency of $KRAS^{G12C}$ mutations in advanced CRC in comparison with NSCLC, where it is the most frequent mutation, shed the light on the necessity of alternative strategies for the management of advanced CRC. These strategies could be the development of selective inhibitors of non-$KRAS^{G12C}$ mutation such as $KRAS^{G12D}$ or $KRAS^{G12V}$, the clinical development of pan-KRAS or pan-RAS inhibitors.

In fact, targeting $KRAS^{G12D}$ recognized important advances with the advent of several selective inhibitors that are in early-phase of development in patients with advanced CRC. MRTX1133 is a noncovalent selective inhibitor of $KRAS^{G12D}$ is under evaluation as single agent in a phase I/II trial (NCT05737706) in patients with $KRAS^{G12D}$-mutated solid tumors including CRC. Available preclinical data suggest a strong synergy between MRTX1133 and fluorouracil in pancreatic cancer and CRC and that cetuximab enhanced MRTX1133 efficacy in CRC. The combination of cetuximab and MRTX1133 could be a promising strategy in patients with CRC harboring $KRAS^{G12D}$ mutation (18,19). RMC-9805 is a covalent selective $KRAS^{G12D}$ inhibitor that showed tumor regression by inducing apoptosis in preclinical models of cancers harboring $KRAS^{G12D}$ mutation (20). It is under clinical evaluation in a phase I trial as single-agent in patients with $KRAS^{G12D}$-mutated solid cancers including CRC (NCT06040541). Pan-KRAS inhibitors are also under clinical development such as BI-2865, a noncovalent inhibitor that showed encouraging preclinical efficacy (21). BI-1701963 is another pan-KRAS inhibitor under clinical evaluation in combination with adagrasib (NCT04975265). The use of pan-RAS inhibitors, that could inhibit KRAS mutations as well as HRAS and NRAS mutations, could also be an alternative in patients with CRC. RMC-6236 is a pan-RAS inhibitor that is under clinical evaluation in a phase I/Ib trial (NCT05379985) of patients with solid tumors harboring $KRAS^{G12X}$ mutation (10 patients with CRC) and associated with encouraging clinical efficacy (22).

In conclusion, selective $KRAS^{G12C}$ inhibitors has shifted the treatment paradigm and gave us a hope for the treatment of patients with KRAS-mutant cancers. Growing evidence showed that combination of $KRAS^{G12C}$ inhibitors with EGFR inhibitors is associated with higher and durable responses in patients with advanced CRC (*Table 1*). Selective KRAS inhibitors, pan-KRAS or pan-RAS inhibitors are under clinical development and evaluation. Other strategies are also under investigation such as the combination of selective KRAS inhibitors and immune checkpoint

inhibitors. Moreover, the development of proteolysis targeting chimeras (PROTACs), mRNA vaccines targeting $KRAS^{G12D}$, $KRAS^{G12V}$, $KRAS^{G12C}$ and $KRAS^{G13D}$, adoptive T-cell receptors targeting $KRASD^{G12V}$ and $KRAS^{G12D}$ is ongoing and could dramatically change the management of patients with advanced CRC harboring KRAS mutations.

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Footnote

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