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Review Article

Targeting KRAS^{G12C-} Mutated Advanced Colorectal Cancer: Research and Clinical Developments

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Abstract

The detection of mutations in the KRAS gene has gained increasing importance in the treatment of colorectal cancer, carrying significant prognostic and therapeutic implications. Nonetheless, the development of drugs targeting KRAS mutations encountered obstacles until the recent advent of KRASG12C inhibitors, notably sotorasib (AMG510) and adagrasib (MRTX849). Although both agents have demonstrated safety and promising efficacy in preclinical studies and early phase trials, not all tumor types carrying the KRASG12C mutation exhibit favorable responses to monotherapy approaches. Specifically, in colorectal cancer (CRC), patients experience lesser benefits compared to those with non-small cell lung cancer (NSCLC), largely attributed to swift treatment-induced resistance driven by increased epidermal growth factor receptor (EGFR) signaling. Consequently, combination therapy trials involving EGFR inhibitors are currently in progress. This review aims to scrutinize available clinical trial data on KRASG12C inhibitors in KRASG12C-mutated CRC, delve into potential mechanisms of resistance to monotherapy, explore reasons behind the reduced efficacy of available agents in CRC compared to NSCLC, and delineate future directions for these promising new drugs.

Introduction

KRAS mutations are found in approximately 45% of colorectal cancer (CRC) and are associated with resistance to targeted therapies such as anti-epidermal growth factor receptor (EGFR) inhibitors.**[**1**] [**2**]**. The KRASG12C mutation is found in 14% of non-small cell lung cancer (NSCLC), 3% of CRC, and 1–3% of other solid tumors **[**3**]**. Patients with metastatic KRASG12C-mutant CRC progress quickly on standard of care chemotherapy regimens and may have shorter overall survival (OS) compared to those with non-KRASG12C mutations **[**4**]**.

After overcoming several challenges in drug development, sotorasib and adagrasib (developed by Amgen and Mirati Therapeutics, respectively) are the two KRASG12C inhibitors with the most promising clinical activity in solid tumors.**[**5**] [**6**]**

Targeting KRASG12C with sotorasib and adagrasib in mice bearing KRASG12C-mutant NSCLC tumors reduced the phosphorylation of ERK and led to significant tumor regression **[**7, 8**]**. A Phase 1 clinical trial evaluating the safety and efficacy of sotorasib has demonstrated a tolerable safety profile as well as promising antitumor activity in patients with KRASG12C mutant solid tumors. **[**9, 10**]** Based on the significant clinical activity in patients with NSCLC in the CodeBreak100 trial, sotorasib was approved by the FDA for patients with locally advanced or metastatic NSCLC harboring the KRASG12C mutation who had progressed on prior systemic therapy **[**11**]** Similarly, based on data from a Phase 2 KRYSTAL-1 trial, adagrasib was approved in Europe for the same indications in NSCLC and is currently under review by the FDA.**[**12**]** Herein, this review focuses on the current development of direct KRASG12C inhibitors and alternative strategies for targeting KRAS, particularly in CRC where the effect of monotherapy appears to be limited.

Monotherapy with Sotorasib or Adagrasib in KRASG12C-Mutated Tumors

- **Sotorasib (AMG510)**

In the first in human phase 1 study, sotorasib was evaluated with a dose-escalation design in patients with refractory KRASG12C-mutated solid tumors (NCT 03600883) **[**13**]**. Doses were escalated from 160mg daily to 960mg daily. No dose limiting toxicities were noted in the escalation phase. The 960mg oral dose was selected for further development based on its safety and pharmacokinetics. Additional expansion cohorts of NSCLC, CRC, and other solid tumors with KRASG12C mutation were enrolled to include a total of 129 patients. Most patients enrolled in the study were NSCLC (59), followed by CRC (42) and other tumors (28). A total of 73 patients (56.6%) had treatment-related adverse events; only 15 (11.6%) patients experienced grade 3 or 4 events. Notable activity was noted in the NSCLC group with an objective response rate (ORR) of 32.2% and a disease control rate (DCR) of 88.1%. Median progression free survival (PFS) in this group was 6.3 months. Clinical activity was more modest in the CRC and other solid tumor groups. In the CRC cohort, the ORR was 7.1% and the DCR was 73.8%. The median PFS in this group was 4 months. Responses were also documented in the other solid tumors group, including patients with pancreatic, endometrial, and appendiceal cancers as well as one patient with melanoma.

The phase 2 CodeBreak 100 (NCT03600883) **[**14**]** trial studied sotorasib in patients with metastatic KRASG12C-mutant CRC who had progressed on prior fluoropyrimidine, oxaliplatin, and irinotecan

treatment, using the phase 1 dosing of 960mg daily **[**15**]**. The ORR was 9.7% and the DCR was 82.3%. The median PFS in this group was 4 months, similar to the phase 1 trial. The adverse events profile was also similar with 7 (12%) patients experiencing a grade 3 or 4 event. A phase 2 trial also studied sotorasib in patients with KRASG12C-mutant advanced NSCLC who had progressed on prior platinum-based chemotherapy and programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) therapy. A total of 124 patients were evaluated for response, which resulted in an ORR of 37.1% with 4 (3.2%) patients who achieved a complete response. The DCR was 80.6%, the median PFS was 6.8 months, and the OS was 12.5 months **[**16**]**.

- **Adagrasib (MRTX849)**

The KRYSTAL-1 study (NCT03785249) **[**17**]** is a phase 1/2 study investigating adagrasib in patients with advanced or metastatic solid tumors harboring a KRASG12C mutation. Patients were all previously treated with chemotherapy, anti-PD-1/PD-L1 therapy, or both. The phase 1/1b dose expansion phase established a dose of 600mg twice daily. Of the 25 patients enrolled, 2 patients had CRC who received the phase 2 dose and were evaluable. One patient achieved a partial response with a duration of response of 4.2 months. Of the 15 patients with NSCLC, the median PFS was 11.1 months and median OS was not reached. The ORR was 53.3%. A total of 36% of patients experienced a grade 3–4 treatment-related adverse event with fatigue being the most common (15%) at the phase 2 dose **[**28**]**. The phase 2 portion of this trial is ongoing. Interim analysis in August 2020 reported the data on 79 patients with pretreated NSCLC who received adagrasib at 600mg twice daily. Among the 51 evaluable patients (including those from the phase 1/1b cohort), the ORR was 45%. The DCR was 96%. **[**18**]** Updated analysis of monotherapy in CRC patients in May 2021 included 45 evaluable patients with an ORR of 22% and a DCR of 87%. Median PFS was 5.6 months **[**19**]**.

- **Differences Between Sotorasib and Adagrasib**

In addition to the maturing clinical data on sotorasib and adagrasib, there are several differences between the two agents. Both drugs share a chemical backbone and target the same S-IIP region of KRAS, but differences in chemical structure led to a mean half-maximum inhibitory concentration (IC50) of 47.9 nM for sotorasib and 89.9 nM for adagrasib. The half-life of adagrasib at 24.7 hours is also considerably longer than sotorasib, which is reported to be 5.5 hours **[**20, 21**]**. In mouse models, sotorasib had an oral

bioavailability of 22–40% compared to 62.9% with adagrasib **[**22**]**.

Pre-clinical models also demonstrate different affinities for on-target resistance mutations between the two agents, as discussed below **[**23**]**. While the clinical implications of these differences are not yet clear in human trials, there will likely be distinct characteristics of each drug with unique applications in select patient populations.

Mechanisms of Resistance to KRASG12C Inhibitors

Despite the early clinical data suggesting activity of the KRASG12C inhibitors in various cancer types, responses appear to be limited when used as monotherapy. There are several key mechanisms of resistance that have been identified in pathways both upstream and downstream of KRAS **[**24**]**. Pre-clinical models of resistant KRASG12C-mutant cancer, secondary KRAS mutations were the most common. Specific mutations such as G13D, R68M, and A59S/T appeared to confer resistance to sotorasib while remaining sensitive to adagrasib. The Q99L alteration was resistant to adagrasib but sensitive to sotorasib.**[**25**]** However, the most common mutation was Y96D/S, and this mutation conferred the strongest resistance against both sotorasib and adagrasib.Citation33 Low allele frequency hotspot mutations in KRAS, NRAS, MRAS, and BRAF were also able to confer resistance. Single-cell sequencing identified that many cells with these secondary mutations still harbor KRASG12C, suggesting that ongoing inhibitor activity does not need to be disrupted to manifest resistance.**[**26**]** An additional escape mechanism is the production of new KRASG12C protein in the GTP-bound state, which does not interact with existing inhibitors, thus avoiding inactivation. **[**27**]**

Combination with Anti-EGFR Therapy to Improve Response of KRASG12C Inhibitors in CRC

In order to potentiate the effect of KRASG12C inhibitors and suppress early mechanisms of resistance, a combination approach of sotorasib or adagrasib with EGFR inhibitors such as panitumumab or cetuximab is an approach that is currently being tested. Preclinical work demonstrates that cetuximab sensitizes KRASG12C-mutated CRC cell lines to sotorasib and leads to sustained down-regulation of phosphorylated MEK and ERK proteins, which ultimately causes arrest of cell proliferation and cell death. This has been subsequently tested in patient-derived organoids and xenograft models, both showing resistance with single-

agent therapy (either KRASG12C or anti-EGFR inhibition alone) versus significant synergistic effect when used in combination.[28]

Trials are already ongoing with sotorasib and adagrasib combined with panitumumab and cetuximab, respectively. Code Break 101 is an umbrella phase 1b trial studying sotorasib in combination with various agents, including panitumumab. As of April 2021, 26 patients have been treated with this combination with a promising ORR (confirmed and unconfirmed) of 33%.[29, 30] So far, no unexpected adverse events outside of those known for sotorasib and panitumumab have been seen. Similarly, the KRYSTAL-1 umbrella trial also had a cohort of patients who received adagrasib in combination with cetuximab and 32 patients have been enrolled as of July 2021. Among the 28 evaluable patients, the confirmed and unconfirmed ORR was 43% with a DCR of 100%. Again, the adverse events have been limited to those expected from the individual agents, with only 16% experiencing grade 3–4 toxicity [31]. These preliminary results are promising and further data from these trials are eagerly awaited as more patients are enrolled. Larger, confirmatory randomized trials in the second- and third-line settings are being conducted to further define the role of these combinations in metastatic colorectal cancer.

Future Directions

Beyond early phase trials with the aforementioned combinations, randomized Phase 3 trials will be necessary to establish the efficacy of both sotorasib and adagrasib and move them forward as standard of care. Efforts are already underway. For instance, KRYSTAL-10 (NCT04793958) [33]

is an open-label, randomized phase 3 trial comparing adagrasib plus cetuximab versus chemotherapy in the second-line setting for patients with KRASG12C metastatic CRC. NCT05198934 [34] is a phase 3 multicenter, randomized trial of sotorasib and panitumumab versus investigator's choice (trifluridine and tipiracil or regorafenib) in previously treated metastatic KRASG12C-mutant CRC. In NSCLC, CodeBreak200 (NCT04303780) [35] is a randomized phase 3 trial comparing sotorasib with docetaxel in previously treated patients with locally advance or metastatic disease. Other planned trials will study sotorasib as first-line therapy for those with KRASG12C-mutant metastatic disease (NCT04933695) as well as using sotorasib in conjunction with chemotherapy in the neoadjuvant setting for stage IIA-IIIB KRASG12C-mutant NSCLC (NCT05118854).

Beyond KRASG12C inhibition, there still remains limited options for patients harboring other KRAS mutations found in the remaining 97% of KRAS-mutant CRC. However, there are agents on the horizon targeting mutational subtypes G12F, G12V, and G12R with RMC-6236 and G12D with MRTX1133.

Conclusion

After extensive drug development efforts, targeted agents for a subset of KRAS-mutant cancers have emerged. Early phase 1/2 trials indicate that sotorasib and adagrasib are safe and effective in clinical settings. While KRASG12C-mutant NSCLC demonstrates the most robust and enduring response to treatment, KRASG12C-mutant CRC patients also exhibit some therapeutic benefit. Despite limited response duration, patients who have undergone multiple lines of therapy find meaningful relief from well-tolerated targeted agents. Nevertheless, the development of KRASG12C inhibitors in CRC is in its infancy, necessitating further data from combination therapies, larger randomized trials, and the exploration of novel inhibitors targeting other, more prevalent KRAS mutations.

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