CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

Section Editor: Tanios S. Bekaii-Saab, MD

The Emerging Role of KRAS G12C Inhibitors in the Treatment of Locally Advanced or Metastatic Colorectal Cancer

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H&O How common are *KRAS* G12C mutations in locally advanced or metastatic colorectal cancer?

KC *RAS* mutations overall are quite common in colorectal cancer (CRC) and affect nearly 50% of patients. *KRAS* G12C mutations are much less common, with several cohort studies putting the prevalence at somewhere between 2.8% and 3.2%. *KRAS* G12C mutations are more common in females than in males. Although *KRAS* G12C–mutated CRC represents only a small subtype of CRC, it is still a clinically important one.

H&O What is the standard treatment for patients with advanced *RAS*-mutated CRC?

KC When we see a patient with metastatic or unresectable CRC that has a *RAS* mutation of any sort, we stick to a basic cytotoxic regimen, such as leucovorin, 5-fluorouracil (5-FU), and oxaliplatin (FOLFOX) or leucovorin, 5-FU, and irinotecan (FOLFIRI). We usually combine this regimen with a vascular endothelial growth factor (VEGF) inhibitor, such as bevacizumab. The presence of *RAS* mutations is a negative predictive biomarker for anti–epidermal growth factor receptor (EGFR) therapy, so we do not use cetuximab (Erbitux, Lilly) or panitumumab (Vectibix, Amgen) in combination with chemotherapy in these patients. We are also working towards being able to target the *KRAS* G12C mutation in eligible patients.

H&O What KRAS G12C inhibitors are in development?

KC The 2 KRAS G12C inhibitors that are furthest along in development are sotorasib (Lumakras, Amgen) and adagrasib. Sotorasib has US Food and Drug Administration (FDA) approval for use in non–small cell lung cancer (NSCLC), and adagrasib has breakthrough therapy designation in NSCLC. Neither one is approved for use in CRC. In addition, researchers are developing agents called G12X inhibitors, in which G12X refers to additional mutations besides G12C, such as G12D. If these agents prove to be effective, they have the potential to be used in more patients.

H&O Are there any meaningful differences between sotorasib and adagrasib?

KC Both sotorasib and adagrasib are irreversible KRAS G12C inhibitors that selectively bind to KRAS G12C in its inactive, guanosine diphosphate (GDP)–bound state. Some slight differences between the agents exist. For example, adagrasib has a longer half-life than sotorasib, at 23 hours vs 5 hours, respectively. In addition, adagrasib may be better at penetrating the central nervous system than sotorasib. Although the agents have not been compared head to head, some slight pharmacodynamic and pharmacokinetic differences exist between them.

H&O Could you describe the design of CodeBreaK 100, and discuss the results in patients with CRC?

KC CodeBreaK 100 was a single-arm, phase 2 study for patients with any kind of advanced solid tumor with a *KRAS* G12C mutation. This study included 62 patients with CRC that had progressed after the use of 5-FU, oxaliplatin, and irinotecan. Patients received sotorasib at 960 mg per day until progression of disease, the development of unacceptable side effects, withdrawal of consent, or death. The primary endpoint was objective response by blinded independent central review. A total of 6 patients experienced an objective response, for an objective response rate of 9.7% (95% CI, 3.6-19.9). All responses were partial, with no complete responses. The disease control rate was high, at approximately 82%. The median time to treatment response was a couple of months, so it did not take long for these patients to respond to treatment. The disappointing finding was that the duration of response was relatively low, at approximately 4.2 months. So this agent can work, but it does not have the duration of response we would like to see. The study did show that sotorasib was fairly well tolerated, with 10% of patients experiencing a grade 3 adverse event and 2% of patients experiencing a grade 4 adverse event. The most common grade 3 adverse event was diarrhea, and the single grade 4 adverse event was an increase in blood creatine phosphokinase.

H&O Could you describe the design of the ongoing KRYSTAL-1 trial?

KC The KRYSTAL-1 trial, which Weiss presented at the 2021 European Society for Medical Oncology (ESMO) annual meeting, produced exciting results. In this phase 1/2 basket trial, which enrolled patients with advanced solid tumors with a *KRAS* G12C mutation, patients with CRC received adagrasib either as monotherapy or in combination with cetuximab. Among the 45 patients who received adagrasib monotherapy who were evaluable for clinical activity, the response rate was approximately 22%. We do not like to do cross-trial comparisons, but this was a bit higher than the 9.7% response rate we saw in CodeBreaK 100. The disease control rate in this trial also was high, at 87%. The median duration of response was 4.2 months and the time to treatment response was 5.6 months. The rate of grade 3 or 4 adverse events among all 46 patients who received adagrasib monotherapy was 30%, and included diarrhea and other gastrointestinal side effects.

When adagrasib was combined with cetuximab, the response rate nearly doubled among the 28 patients with CRC who were evaluable for clinical activity, to 43%. In addition, the disease control rate went up to 100%. The time to treatment response among the 32 patients who received adagrasib plus cetuximab was a bit shorter than with adagrasib monotherapy, at 1.3 months, and the rate of grade 3 or 4 adverse events was 16%. These data were exciting because they showed for the first time that KRAS G12C inhibitors can be combined with anti-EGFR therapy. As a result, additional studies of this combination are in the works.

> Ongoing studies are looking at combining more than one targeted agent to overcome resistance.

H&O What other trials are being launched?

KC CodeBreaK 300 is a randomized phase 3 study that is comparing sotorasib and panitumumab vs the investigator's choice of chemotherapy in previously treated participants with *KRAS* G12C–mutated CRC (NCT05198934). Patients in the investigator's choice arm will receive either trifluridine and tipiracil (Lonsurf, Taiho Oncology) or regorafenib (Stivarga, Bayer HealthCare), which are the treatments we typically use in patients with previously treated metastatic CRC who do not have KRAS G12C as a target. The primary endpoint for this trial, which is still recruiting patients, is progression-free survival (PFS). The estimated enrollment is 153 patients.

Also recruiting patients is the randomized, phase 3 KRYSTAL-10 study of adagrasib and cetuximab vs chemotherapy as second-line treatment in advanced CRC that is *KRAS* G12C–mutated (NCT04793958). This study is larger than CodeBreaK 300, with an estimated enrollment of 420 patients. Patients in the chemotherapy group receive either FOLFOX or FOLFIRI, whichever they did not receive in the first-line setting. The primary endpoints for KRYSTAL-10 are overall survival and PFS.

Regarding patients with *KRAS* G12X mutations, preclinical data were presented at the 2022 annual meeting of the American Association for Cancer Research (AACR) on RMC-6236. This agent is referred to as a RAS multi(ON) inhibitor because it targets multiple active, or "on," forms of RAS. Because the agent showed encouraging activity in the preclinical space, Revolution

Medicines is enrolling patients in a phase 1 study to look at the agent in patients with advanced solid tumors that have any *KRAS* G12X mutation except for *KRAS* G12C (NCT05379985). The study has a planned enrollment of 141 patients, including patients with CRC. I am looking forward to the results of this study.

H&O How common is resistance to KRAS G12C inhibitors?

KC Regarding primary resistance, some of the early studies of KRAS G12C inhibition in CRC showed relatively low response rates, at least with monotherapy. Something in the tumor is preventing it from being targeted effectively, although we do not know what that is yet. As for acquired resistance, we have seen that the duration of response is relatively short even among those whose tumors do respond, with most of these agents working for a median of approximately 4 months.

Resistance is very common with targeted therapy in oncology, and a big challenge for us is to determine what is driving primary resistance, which has the potential to help us get more patients to respond at the outset, and to address acquired resistance in those patients whose tumors stop responding. A relevant study by Awad and colleagues that was published last year in *The New England Journal of Medicine* looked at a group of 38 patients with *KRAS* G12C–mutated solid tumors—including 10 patients with CRC—who were treated with adagrasib and later developed resistance. The authors found that they could identify the mechanism of acquired resistance to adagrasib in nearly half of these patients. Eighteen percent of the patients, most of them with CRC, had more than one resistance mechanism. To make acquired resistance even more complicated, the mechanisms varied greatly, with secondary *RAS* mutations, tumor suppressor gene mutations, and new fusions popping up. One patient with lung cancer even had adenocarcinoma that transformed to squamous cell carcinoma.

H&O What therapeutic strategies can be used to delay or overcome acquired resistance?

KC The finding that multiple resistance patterns are emerging tells us that we need a multipronged approach to overcoming acquired resistance. Ongoing studies are looking at combining more than one targeted agent to overcome resistance. For example, the phase 1 KRYSTAL-14 trial is looking at the addition of the SOS1 pan-KRAS inhibitor BI 1701963 to adagrasib in approximately 100 patients with advanced solid tumors that are *KRAS* G12C–mutated (NCT04975256). Another phase 1 study called KRYSTAL-2 is looking at the addition of the SHP2 inhibitor *TNO155* to adagrasib in approximately 86 patients with advanced solid tumors that are *KRAS* G12C–mutated (NCT04330664). In addition, several vaccines are in development.

The combination approach to addressing acquired resistance requires serial biopsies. Fortunately, we can now perform liquid biopsies to detect these mechanisms of resistance, which will be easier on patients than performing multiple tumor biopsies. One key is having patients continue to enroll in clinical trials so we can move the field forward.

H&O How can biomarkers be used to predict which patients are most likely to respond to KRAS G12C inhibition in the first place?

KC I think that liquid biopsies are going to be extremely important in trying to figure out from the beginning which patients are likely to benefit from a specific targeted agent. We also need to look at various mutations in the context of each other. We are very happy to detect a *KRAS* G12C mutation because it is targetable, but we also need to look at the other mutations found concomitantly in a patient's tumors because some of them can disrupt the action of KRAS G12C inhibitors. Liquid biopsy is going to be key in looking for any co-mutations that may be present. We also need to determine which of these other mutations are drivers and which ones are passengers.

Disclosure

Dr Ciombor has served as a consultant for or on the advisory board of Merck, Pfizer, Lilly/Loxo, Seagen, Personalis, and Replimune, and has received research grants from BMS, Array, Incyte, Daiichi Sankyo, NuCana, AbbVie, Merck, Pfizer/Calithera, Genentech, and Seagen.

Suggested Readings

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