CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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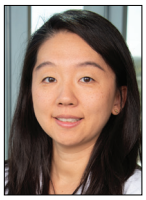
The Role of Antiangiogenesis Agents in Refractory Metastatic Colorectal Cancer



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H&O What are the standard treatment options for patients with refractory metastatic colorectal cancer (CRC)?

SK Patients with refractory metastatic CRC typically have already received chemotherapy with 5-fluorouracil or capecitabine plus oxaliplatin and irinotecan with bevacizumab, in addition to an epidermal growth factor receptor (EGFR) inhibitor for left-sided *RAS* wild-type cancer and targeted therapy for *BRAF* V600–mutated cancer.

We have limited options when it comes to treating patients with refractory metastatic CRC. The first option is the combination of the nucleoside analogue trifluridine and the thymidine phosphorylase inhibitor tipiracil (Lonsurf, Taiho Oncology); the tipiracil increases the availability of the trifluridine. Trifluridine/tipiracil received US Food and Drug Administration (FDA) approval in 2015 for the treatment of patients with advanced CRC that has not responded to other treatments.

The second option is regorafenib (Stivarga, Bayer HealthCare), which is approved for use in refractory metastatic CRC. Regorafenib is a small-molecule agent that works on multiple levels, targeting kinases, multiple vascular endothelial growth factor (VEGF) receptors, fibroblast growth factor (FGF) receptors, and platelet-derived growth factor (PDGF) receptors, among other targets. Regorafenib has been shown to improve OS, although the difference is small and better drugs are still needed.

Other options that are currently awaiting FDA approval include trifluridine/tipiracil plus bevacizumab and fruquintinib, which is another oral tyrosine kinase inhibitor.

H&O Could you discuss the design of the SUNLIGHT trial?

SK Dr Joseph Taberno presented the results of the SUNLIGHT trial at the 2023 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium. This open-label, randomized phase 3 study was designed to compare trifluridine/tipiracil plus bevacizumab vs trifluridine/tipiracil alone in patients with metastatic CRC who had received at least 2 prior lines of treatment and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Prior treatment consisted of a fluoropyrimidine, irinotecan, and oxaliplatin. Patients who were eligible for an anti-EGFR monoclonal antibody were required to have received that as well.

A total of 492 patients were randomly assigned in a 1:1 ratio to receive trifluridine/tipiracil at 35 mg/m^2 twice a day, given on days 1 to 5 and then days 8 to 12 every 28 days, either alone or in combination with bevacizumab at 5 mg/kg intravenously every 2 weeks. The primary endpoint was overall survival (OS).

H&O What were the results of the SUNLIGHT trial?

SK SUNLIGHT was a positive trial, with a statistically significant improvement in median OS in the experimental

arm vs the control arm, at 10.8 vs 7.5 months, respectively. When the investigators looked at median OS in prespecified subgroups, they found that benefit extended to all groups regardless of geographic location, age, *RAS* mutation status, right vs left disease, sex, age, and prior bevacizumab use. One note about the study is that the enrollment criteria required participants to have received a monoclonal antibody against VEGF, but only 76% of patients received prior VEGF inhibition. The reason for this discrepancy is unknown.

Median progression-free survival (PFS) was significantly higher in the experimental arm than in the control arm, at 5.6 vs 2.4 months. The response rate also was higher in the experimental arm than the control arm, at 6.3% vs 0.9%. A 6.3% response rate is low, but it is still meaningful because we do not expect to see a response in patients taking regorafenib or trifluridine/tipiracil on its own. The use of the experimental therapy vs the control therapy also increased the time to deterioration and the time to worsening to an ECOG performance status of 2 or higher.

Combination treatment did not lead to any new safety signals or an increase in adverse events (AEs) leading to study withdrawal, although it did lead to an increase in dose delays. AEs associated with trifluridine/tipiracil include neutropenia, nausea, anemia, fatigue, and diarrhea. There was a higher incidence of hypertension, nausea, and neutropenia in the combination group than in the control group.

Based on the results of this study, I expect to see FDA approval of trifluridine/tipiracil in combination with bevacizumab for patients with metastatic CRC.

H&O Could you discuss the role of regorafenib in refractory metastatic CRC?

SK Regorafenib is a small-molecule agent that inhibits kinases involved in cancer growth. It received FDA approval in 2012 for use in metastatic CRC that has progressed after all standard therapies, based on the results of the CORRECT trial. CORRECT was a randomized, placebo-controlled, phase 3 trial in refractory metastatic CRC. As with SUNLIGHT, patients had to have received a fluoropyrimidine, irinotecan, and oxaliplatin, plus EGFR inhibition if eligible. A total of 760 patients were randomly assigned in a 2:1 ratio to receive experimental treatment with regorafenib at 160 mg daily on a 3-weeks-on, 1-week-off schedule every 28 days vs placebo. Although the median OS was only slightly longer in the regorafenib arm than in the placebo arm, at 6.4 vs 5.0 months, respectively, the difference was statistically significant.

Regorafenib can be difficult to tolerate, with the most common AEs including hand-foot skin reactions, diarrhea, hypertension, and rash. Depending on the ECOG performance status of the patient, we may wish to start with a lower dose before escalating up.

The phase 3 CONCUR trial also compared regorafenib vs placebo in patients with treatment-refractory metastatic CRC in an Asian population that had received at least 2 previous lines of treatment or was unable to tolerate standard treatments. A total of 204 patients were randomized in a 2:1 ratio to receive regorafenib or placebo. After a median follow-up of 7.4 months, the median OS was longer with regorafenib than with placebo, at 8.8 vs 6.3 months, respectively. The fact that the regorafenib appeared to be a little more beneficial in CONCUR than in SUNLIGHT can be explained by the fact that the patients in CONCUR were less heavily pretreated and potentially had more favorable tumor biology.

> The FDA granted fast track designation to fruquintinib in 2020, so we are waiting to see if it gains approval.

H&O How should agents be sequenced in refractory metastatic CRC?

SK We do not know with certainty how to sequence these drugs. Some trials allowed for prior regorafenib or trifluridine/tipiracil, whereas others did not. Several retrospective studies have attempted to tease out whether it is better to start with regorafenib or with trifluridine/tipiracil, with the results suggesting that OS might be longer with regorafenib before trifluridine/tipiracil. One hypothesis is that regorafenib improves the action of later trifluridine/tipiracil by providing a chemosensitizing effect. Another hypothesis is that trifluridine/tipiracil benefits patients more later by giving them a break from chemotherapy. Although regorafenib is not easy to tolerate, it does not cause bone marrow suppression the way chemotherapy with trifluridine/tipiracil does. I would caution, however, that these are retrospective trials that have inherent bias. For example, it is possible that patients who receive regorafenib first may have a higher ECOG performance status. We may be able to get information regarding optimal sequencing from studies performed in Europe.

H&O Could you discuss the research on fruquintinib?

SK Fruquintinib is an oral tyrosine kinase inhibitor that targets the VEGF receptors 1, 2, and 3. The phase 3, randomized, double-blind, placebo-controlled FRESCO-2 trial compared fruquintinib plus best supportive care vs placebo plus best supportive care in refractory metastatic CRC. Patients were required to have received prior regorafenib or trifluridine/tipiracil in addition to all other standard therapies, which made the patients in FRESCO-2 more heavily pretreated than those in SUNLIGHT. Fruquintinib was given at 5 mg daily on a 3-weeks-on, 1-week-off schedule every 28 days vs placebo. A total of 691 patients were randomly assigned in a 2:1 ratio to fruquintinib or placebo.

In results that Dr Arvind Dasari presented at the 2023 annual meeting of the European Society for Medical Oncology, median OS was longer in the fruquintinib group than in the placebo group, at 7.4 vs 4.8 months. Fruquintinib also outperformed placebo in terms of PFS (3.1 vs 1.8 months, respectively) and the disease control rate (55.5% vs 16.1%, respectively). There was also a marginal benefit in response rate with fruquintinib vs placebo, at 1.5% vs 0%, respectively.

Fruquintinib seemed to be well tolerated overall, with the most common AEs including hypertension, fatigue, and hand-foot syndrome.

The FDA granted fast track designation to fruquintinib in 2020, and we are waiting to see if it gains approval. I have several patients with more marginal performance status who I think would benefit from this drug.

H&O Are any other agents showing promising early results in treating metastatic CRC?

SK Many of the agents that were previously investigated for use in refractory metastatic CRC were meant for a general population. The promising agents that are being investigated now are targeting specific patient characteristics or biomarkers. The goal is to find agents that will be effective in a certain subset of patients.

An important study that was presented at the ASCO Gastrointestinal Cancers Symposium this year looked at the second-generation cytotoxic T-lymphocyte–associated antigen 4 inhibitor botensilimab and the programmed death 1 inhibitor balstilimab. In this expanded phase 1a/1b study, Dr Anthony B. El-Khoueiry and colleagues studied the use of botensilimab/balstilimab in 59 patients with heavily pretreated, microsatellite stable CRC. They found that after a median follow-up of 6.4 months, the median OS was not reached among the patients who did not have any liver metastases. Although this represented a small group of patients, the results were impressive. Of the 16 patients who responded to treatment, 11 patients continued to have sustained response at the time of the presentation. The most common AE was diarrhea/colitis. Because these results were encouraging, a phase 2 trial of botensilimab/balstilimab is currently enrolling patients who have microsatellite stable CRC without any active liver metastases (NCT05608044). A global phase 3 trial is also being planned.

> Although results with CAR T-cell therapy have been poor in solid tumors, we expect to see better results as the technology is refined.

Researchers are also investigating agents that target KRAS. KRYSTAL-1 was a phase 1/2 trial, open-label, nonrandomized trial that evaluated the small-molecule inhibitor adagrasib as monotherapy or in combination with cetuximab in patients with previously treated metastatic CRC with a *KRAS* G12C mutation. The population was heavily pretreated, with 20% of patients having received prior regorafenib or trifluridine/tipiracil. In results published by Yaeger and colleagues in the *New England Journal of Medicine* this year, the response rate was higher in the 32 patients who received adagrasib/cetuximab than in the 44 who received adagrasib alone, at 46% vs 19%, respectively—a dramatic difference. The duration of response also was longer with adagrasib/cetuximab than with adagrasib alone, at 7.6 vs 4.3 months, although the study was not meant to produce statistically significant results. Finally, median PFS was longer with adagrasib/cetuximab than with monotherapy, at 6.9 vs 5.6 months, respectively. AEs included nausea, vomiting, and diarrhea, along with some elevation in liver enzymes.

KRAS G12C mutations occur in just 3% of patients with CRC, so this represents a small population, but these results with adagrasib/cetuximab are exciting because KRAS historically was thought to be undruggable. The next step is to target additional *KRAS* mutations, such as *KRAS* G12D, which would be important not only in CRC but in other gastrointestinal cancers,

such as pancreas cancer.

Finally, the chimeric antigen receptor (CAR) T-cell therapies are very exciting. With CAR T-cell therapy, we are able to personalize immunotherapy by reengineering a patient's T cells to be able to target the tumor-specific antigen of choice. The goal is to elicit a powerful immune response within the patient. However, we are still trying to understand which of the tumor-specific antigens are best to target. One trial that we are participating in here at the University of Colorado is targeting guanylyl cyclase C (GUCY2C; NCT05319314). Other trials are examining agents that target carcinoembryonic antigen (CEA) or mesothelin. Although results with CAR T-cell therapy have been poor in solid tumors, we expect to see better results as the technology is refined.

Disclosures

Dr Kim has received research funding from Merck and has received advisory board compensation from I-Mab and Merck.

Suggested Readings

Dasari NA, Lonardi S, Garcia-Carbonero R, et al. FRESCO-2: a global phase III multiregional clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer [ESMO abstract LBA25]. *Ann Oncol*. 2022;33(7)(suppl).

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Li J, Qin S, Xu R, et al; CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2015;16(6):619-629.

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Yaeger R, Weiss J, Pelster MS, et al. Adagrasib with or without cetuximab in colorectal cancer with mutated *KRAS* G12C. *N Engl J Med*. 2023;388(1):44-54.