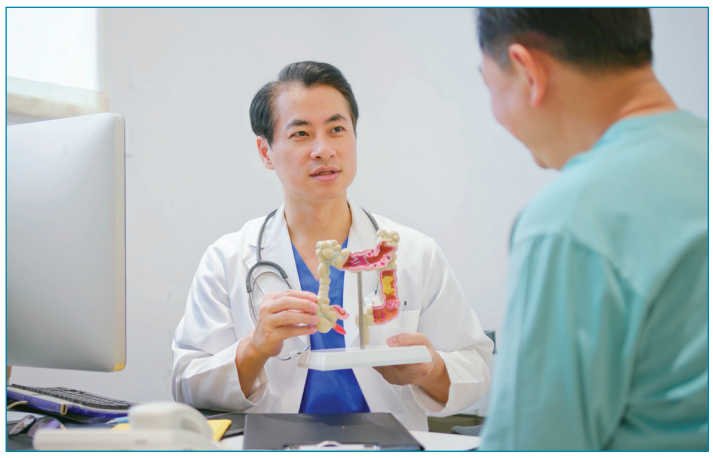
New Treatment for Metastatic Colorectal Cancer With Mutated KRAS G12C

BY CATLIN NALLEY

Metastatic colorectal cancer patients with mutated KRAS G12C who received the KRAS inhibitor sotorasib in combination with panitumumab, a monoclonal antibody, had a longer progression-free survival compared to their counterparts who underwent standard treatment. Data from the Phase III, multicenter, open-label, randomized CodeBreaK 300 trial (NCT05198934) were recently published in the *New England Journal of Medicine* (2023; doi: 10.1056/NEJMoa2308795).

"This is the first Phase III clinical trial to show a benefit over standard of care in patients with the KRAS G12C mutation whose cancer progressed after receiving standard chemotherapy," said Marwan Fakih, MD, Professor in the Department of Medical Oncology & Therapeutics Research and the Judy & Bernard Briskin Distinguished Director of Clinical Research at City of Hope. He is lead author of the study and principal investigator of the clinical trial at City of Hope.



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"The efficacy results from our study are promising in this population with unmet needs and should set a new standard of care for metastatic colorectal cancer patients with KRAS G12C mutation who progressed following prior standard treatments," he stated.

Trial Background & Design

KRAS G12C, a mutation that occurs in approximately 3-4 percent of patients with metastatic colorectal cancer, is often associated with worse outcomes. "In patients with disease that is refractory to initial therapies (fluoropyrimidine-based chemotherapy with or without bevacizumab), the standard late-line treatments—trifluridine/tipiracil or regorafenib—have shown limited efficacy (objective response, 1-2%; median progression-free survival, ≤2.0 months) but at the cost of toxic effects," according to Fakih and colleagues. They noted there are currently no targeted therapies driven by a positive-selection biomarker approved specifically for the treatment of patients with KRAS-mutated colorectal cancer.

Recognizing the need to identify novel therapeutic options for this patient population, the researchers conducted the CodeBreak 300 trial, which builds on positive results from a Phase II trial of sotorasib in combination with panitumumab.

In the current study, the researchers evaluated the efficacy and safety of two different doses of sotorasib—960 mg and 240 mg—plus panitumumab versus the investigator's choice of standard therapy—trifluridine/tipiracil or regorafenib—in chemorefractory metastatic colorectal cancer patients with KRAS G12C mutation.

Investigators enrolled metastatic colorectal cancer patients with mutated KRAS G12C who had not received prior KRAS G12C inhibitor treatment. Eligibility criteria included the following: disease progression or recurrence after receiving at least one previous line of therapy for metastatic disease; a KRAS G12C mutation confirmed by prospective central molecular testing; measurable disease according to RECIST, version 1.1; ECOG performance status score of 0, 1, or 2; and adequate organ function.

"The previous line of therapy for metastatic disease must have included fluoropyrimidine, oxaliplatin, and irinotecan unless the patient had unacceptable side effects, in which case the patient was eligible to receive trifluridine/tipiracil or regorafenib as the next line of therapy, if deemed appropriate by the investigator and if approved by the medical monitor," explained Fakih and team.

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Patients were randomized 1:1:1 to receive sotorasib (960 mg once daily) plus panitumumab, sotorasib (240 mg once daily) plus panitumumab, or the investigator's choice of standard care therapy. The researchers stratified randomization by previous use of antiangiogenic therapy, the time from initial diagnosis of metastatic disease to randomization (≥18 months or <18 months), and ECOG performance status score (0 or 1 vs. 2).

> "CodeBreaK 300 establishes sotorasib 960 mg daily in combination with panitumumab 6mg/kg IV every 2 weeks as the new standard third-line therapy for KRAS G12C metastatic colorectal cancers that have progressed following fluoropyrimidines, oxaliplatin, and irinotecan."
>
> —Marwan Fakih, MD, at City of Hope

Progression-free survival—defined as the time from randomization to disease progression—was the primary endpoint of this analysis. Secondary endpoints included overall survival, objective response, duration of response, time to response, disease control, safety, quality of life, and pharmacokinetics.

Research Findings

Between April 19, 2022, and March 14, 2023, the investigators screened 219 patients at 76 sites across 12 countries. Of these patients, 160 from Europe (65.6%), Asia (22.5%), North America (10.6%), and other regions (1.2%) were eligible and randomly assigned to one of the three treatment groups: sotorasib (960 mg once daily) plus panitumumab (53 patients), sotorasib (240 mg once daily) plus panitumumab (53 patients), or the investigator's choice of standard-care therapy (54 patients).

Among the patients in the standard-care cohort, 37 received trifluridine/tipiracil and 14 were treated with regorafenib. Three of the patients in this group did not receive the assigned treatment and were not included in the safety analysis.

Study authors reported that patient characteristics were generally well-balanced across the three treatment arms. Overall, the median age was 62 years and 49.4 percent of the patients were men. The breakdown of ECOG performance status score was as follows: 0 (60%), 1 (36.9%), and 2 (3.1%). Fifteen percent of patients received one previous line of therapy and 85 percent underwent two or more prior therapies.

After a median follow-up of 7.8 months, the median progression-free survival was 5.6 months among patients in the sotorasib 960 mg

group and 3.9 months in those who were administered sotorasib 240 mg. Comparatively, the progression-free survival for patients in the standard-care arm was 2.2 months.

"The median progression-free survival of 5.6 months represents more than doubling of reported progression-free survival with standard-of-care approaches with trifluridine/tipiracil and regorafenib," Fakih noted during a discussion with *Oncology Times*.

"Keep in mind that, in unselected patient populations with metastatic colorectal cancer, the median progression-free survival on second-line treatments is approximately 6 months," he emphasized. "To see a median progression-free survival of 5.6 months in a poor prognosis population with KRAS G12C represents a new milestone for third-line therapy in this population."

Investigators reported that the objective response was 26.4 percent, 5.7 percent, and 0 percent in the 960 mg sotorasib/panitumumab, 240 mg sotorasib/panitumumab, and standard-care groups, respectively.

As of the data cutoff, 55 patients (34.4%) had died and overall survival data is still maturing, according to the study authors. "The hazard ratio in the 960 mg sotorasib/panitumumab group as compared with the standard-care group was 0.77 (95% CI: 0.40-1.45)," they stated. "The hazard ratio in the 240 mg sotorasib-panitumumab group as compared with the standard-care group was 0.91 (95% CI: 0.48-1.71)."

In terms of safety, Grade 3 or higher treatment-related adverse events were observed in 35.8 percent, 30.2 percent, and 43.1 percent of patients in the 960 mg sotorasib/panitumumab, 240 mg sotorasib/panitumumab, and standard-care groups, respectively. The most common adverse events reported among patients treated with the combination of sotorasib and panitumumab were skin-related toxic effects and hypomagnesemia, according to the investigators.

Data showed the pharmacokinetic properties of sotorasib and panitumumab were consistent with those seen in previous studies. Additionally, the study authors observed similar exposures with the two sotorasib dose levels. "No pharmacokinetic drug-drug interactions were observed between sotorasib and panitumumab," they reported.

When discussing limitations of this research, Fakih and colleagues acknowledged that this trial is not designed or powered to detect a significant difference among the groups in overall survival. As mentioned, "overall survival data is maturing and longer follow-up is needed to determine the effects of treatment on this endpoint." Additionally, the investigators noted that the trial population was largely comprised of White and Asian patients, with limited representation of Black patients with colorectal cancer.

"In this Phase III trial of a KRAS G12C inhibitor plus an anti-EGFR antibody in patients with chemorefractory metastatic colorectal cancer, both doses of sotorasib (960 mg and 240 mg) plus panitumumab resulted in significantly longer progression-free survival and a higher incidence of response than standard care," Fakih and colleagues summarized. "Adverse events associated with sotorasib–panitumumab at both doses were as expected, with no new safety concerns and the occurrence of few discontinuations related to adverse events."

Discussion & Next Steps

This Phase III trial confirmed that the combination of sotorasib 960 mg daily with panitumumab or sotorasib 240 mg daily with panitumumab is superior to the standard-of-care regorafenib or trifluridine in terms of progression-free survival in patients with KRAS G12C who had previously progressed on standard treatments, according to Fakih.

"Since progression-free survival was the primary endpoint of this study, [it] is deemed positive," he said. "While both sotorasib arms were superior to standard of care, the higher dose of sotorasib was particularly efficacious with an overall response rate of 26.4 percent and a median progression-free survival of 5.6 months."

Findings from this study are clinically meaningful and, in Fakih's opinion, "CodeBreaK 300 establishes sotorasib 960 mg daily in combination with panitumumab 6 mg/kg IV every 2 weeks as the new standard third-line therapy for KRAS G12C metastatic colorectal cancers that have progressed following fluoropyrimidines, oxaliplatin, and irinotecan," he said, while noting this dose level is in line with current NCCN guidelines.

When discussing next steps, Fakih told *Oncology Times*, "The combination of sotorasib and panitumumab has been combined safely with FOLFIRI and associated with robust activity in this population. That data provides further rationale for moving sotorasib and panitumumab in combination with systemic chemotherapy in earlier lines of treatment.

"KRAS G12C inhibitors combined with EGFR inhibitors should be investigated with systemic therapy in future clinical trials in earlier lines of treatment," he continued. "Such combinations may prove synergistic and may accentuate the clinical benefits over what is seen with sequential therapy." OT

Catlin Nalley is a contributing writer.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to

1. Compare progression-free survival and overall response rate in the three treatment arms of the phase III CodeBreaK 300 clinical trial.
2. Identify safety issues related to the use of sotorasib plus panitumumab.

Disclosure: All authors, faculty, staff, and planners have no relevant financial relationships with any ineligible organizations regarding this educational activity.