

Fruquintinib in the FRESCO-2 Trial



Arvind N. Dasari, MD

Associate professor in the Department of Gastrointestinal Medical Oncology in the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston



Cathy Eng, MD

David H. Johnson Chair in Surgical and Medical Oncology, professor of medicine (hematology and oncology), coleader of the Gastrointestinal Cancer Research Program, codirector of gastrointestinal oncology, and director of the Young Adults Program at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee, and cochair of the National Cancer Institute Gastrointestinal Steering Committee

Can you briefly describe the results of the FRESCO-2 trial?

DASARI: The FRESCO-2 trial [NCT04322539] was a global, randomized phase 3 study that assessed fruquintinib [Elunate], which is a highly selective and potent inhibitor of VEGF receptors 1, 2, and 3.¹ The trial enrolled patients with heavily pretreated metastatic, refractory colorectal cancer who were randomly assigned 2:1 to fruquintinib vs placebo, with both arms getting the best supportive care. The primary end point was overall survival (OS). The study did meet that primary end point, with an HR of 0.66, and that resulted in an improvement in OS from about 4.8 months in the placebo arm to about 7.4 months in the fruquintinib arm.

Progression-free survival [PFS] was one of the key secondary end points of the trial, and there was a statistically and clinically significant improvement in the PFS, with an HR of around 0.32. In addition to this, the drug was very well tolerated overall. There were easily manageable adverse effects [AEs]. In fact, the dose intensity in the placebo arm and the treatment arm [was] comparable. All this put together suggests that fruquintinib is well tolerated and provides meaningful survival benefits for these patients, who desperately need new treatment options.

ENG: We helped design this international trial, but there was a prior [phase 3 study called] FRESCO [NCT02314819], conducted in China, that was in the third-line setting.² [The fact that] practice patterns [in China] are not similar to ours here in the United States with the continuation of

Phase 3 randomized trial evaluating fruquintinib vs placebo in patients with metastatic colorectal cancer

Dose

5-mg capsule or matched placebo orally once daily on days 1-21 in a 28-day cycle plus best supportive care

Efficacy Outcomes in the FRESCO-2 Trial

Outcome	Fruquintinib (n = 461)
Median overall survival	7.4 months (95% CI, 6.7-8.2)
Patients alive at 9 months	41% (95% CI, 36%-46%)
Median progression-free survival	3.7 months (95% CI, 3.5-3.8)
Median duration of response	10.7 months (95% CI, 3.9-not estimable)
Disease control rate	56%

Adverse Effects in FRESCO-2

Adverse effect	Grade 3/4 adverse effect in fruquintinib (n = 286) arm
Hypertension	n = 62 (14%)
Asthenia	n = 35 (8%)
Hand-foot syndrome	n = 29 (6%)

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bevacizumab [Avastin] was a large part of the impetus for creating a separate trial.

Although our trial was not specifically for the third-line [setting], I do kindly remind people that we wanted to be inclusive. Some people will criticize [the fact] that we allowed a placebo arm. The reality is, there was no other standard of care once you've received trifluridine/tipiracil [Lonsurf]. [The only alternative we could offer] would be regorafenib (Stivarga) as a potential option. That is one advantage to the trials; you got to see the benefit of the drug overall. The median lines of therapy was 4 in the final publication. It's important to keep in mind that although the HR was 0.66, that's a 34% reduced risk of death if you're on fruquintinib.

From a patient perspective, because it is an oral, single agent, it provides increased convenience, which reduces financial stress because [patients receiving it spend] less time away from work and less time in the chair for infusions. Because it's tolerated well, it is advantageous for the patient overall regarding the quality of life. We're both familiar with regorafenib and trifluridine/tipiracil, which had the disadvantage of myelosuppression. Regorafenib has associated toxicities that we have to think about when considering patients with metastatic colorectal cancer. It has its limitations because of the hand-foot skin reaction and the [elevated] liver function tests.

DASARI: There was a formal quality-of-life analysis of FRESKO-2 done. Those data were presented earlier this year [and] confirmed that quality of life is preserved overall. The time to deterioration was better with fruquintinib compared with placebo.³

If fruquintinib is approved, how will it impact the standard of care?

DASARI: We've been getting a lot of inquiries from patients and providers alike who reviewed the data. I've been impressed, and I am eagerly awaiting the potential approval, given the efficacy and the good AE profile that we just discussed. I think it will be a standard of care for patients with metastatic colorectal cancer. There is a body of evidence from FRESKO and FRESKO-2 showing the activity of this drug in the third line and as a fourth-line therapy. Looking beyond just this approval, given that this drug has [impressive] efficacy and is well tolerated, there's a lot of discussion and excitement around expanding its role into early lines of therapy and combining it with other agents, which has been challenging with regorafenib so far.

ENG: For our patient population with surgically unresectable disease, we have limited treatment. We've not had a new drug that's been approved after trifluridine/tipiracil. We need to find additional treatment options for microsatellite instability [MSI]-stable patients. There's a lot of interest in the new drugs for KRAS G12C, although that's a rare patient population, and MSI-high patients, once again, another rare patient population, and HER2, another rare patient population. For the average MSI-stable patient, we need treatment options. This just gives another opportunity to them, with good quality, improved OS. By improving the OS, it improves their own personal quality of life as well as their ability to potentially participate in another clinical trial.

Are there any AEs that clinicians should be on the lookout for?

ENG: Hypertension, [but it is] easily controlled with medications. The one thing that we want people to be

aware of is that you can get hand-foot skin syndrome like [you might with] capecitabine, but not as severe, [and] blisters like you may see with regorafenib. It's not a hand-foot skin reaction, but a hand-foot skin syndrome. We just want people to be aware, to stay in contact with their doctor, and [to] notify their doctor if things aren't well controlled. If you look at the data regarding serious AEs from FRESKO-2, less than 1% of all patients withdrew from the trial due to any potential toxicity.

What are some current unmet needs in the space?

DASARI: We need more treatment options. We are making some headway for a small subset of patients defined by molecular alterations. All these alterations put together probably account for maybe 10% or 15% of the entire patient population. Even then, in most of these subsets, there is eventual development of resistance to these targeted therapies. We desperately need new therapies for these patients that are effective and well tolerated. Fruquintinib fits that bill for an all-comer patient population. It's well tolerated, [and it] has [improved] efficacy. That's the most exciting takeaway from all this work. ■

References

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