

# New KRYSTAL-1 Data Show 90% Intracranial Disease Control Rate in Patients With *KRAS* G12C–Mutated NSCLC and Untreated CNS Metastases

MARY CAFFREY

**DATA PUBLISHED IN LATE JUNE 2023** from the KRYSTAL-1 study (NCT03785249) of adagrasib (Krazati; Mirati Therapeutics) show that the selective *KRAS* G12C inhibitor produced durable intracranial (IC) activity in a small group of patients with *KRAS* G12C–mutated non–small cell lung cancer (NSCLC) with untreated central nervous system (CNS) metastases.<sup>1</sup>

The results, which were published in the *Journal of Clinical Oncology (JCO)*, are the first prospective evaluation of the *KRAS* G12C inhibitor in untreated CNS metastases. Mirati Therapeutics officials said in a statement that this is a “clinically meaningful” result in *KRAS* G12C–mutated NSCLC.<sup>2</sup> Study authors stated that CNS metastases are seen in 27% to 42% of patients who have this specific mutation at diagnosis, and that these patients are more likely to have higher rates of disease progression and worse outcomes.<sup>1</sup>

Adagrasib received accelerated FDA approval in December 2022 as a targeted therapy for patients with locally advanced or metastatic NSCLC with a *KRAS* G12C mutation who have had at least 1 prior systemic therapy.<sup>3</sup>

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—Alexander I. Spira, MD, PhD, FACP,  
CEO and clinical director,  
NEXT Oncology Virginia;  
physician and co-director,  
Virginia Cancer Specialists Research Institute

## Results

The authors of the *JCO* paper discussed results for 25 patients treated with a median of 1 prior systemic therapy; of them, 19 were radiographically evaluable per CNS RECIST v1.1. Results showed an IC objective response rate of 42% (95% CI, 20.3%–66.5%), and IC disease control rate of 90%.

“High concordance between IC and systemic activity was observed,” the authors wrote. Specifically, giving patients 600 mg of adagrasib twice a day produced a high rate of systemic activity (79%), with a low rate of CNS failure (37%).

“These results provide proof-of-concept for adagrasib’s ability to penetrate the CNS and provide CNS activity,” according to the Mirati statement.<sup>2</sup>

In addition, the *JCO* authors reported median IC progression-free survival of 5.4 months and median overall survival of 11.4 months, with few CNS adverse events and an overall safety profile consistent with prior reports on adagrasib.<sup>1</sup>

The authors noted that this contrasts with what has been the normal course for patients who develop CNS metastases in NSCLC, which is seen in approximately one-fourth of patients with *KRAS* G12C mutations. They wrote that until recently, “patients with *KRAS*-mutated NSCLC and untreated CNS

metastases have [had] limited treatment options and poor clinical outcomes,” and radiation therapy has been the norm, although this approach can cause necrosis and cognitive impairment.

More recently, investigators have turned their attention to targeted drugs with CNS penetration, such as EGFR or anaplastic lymphoma kinase inhibitors.

Other post hoc analyses that have evaluated both adagrasib and sotorasib (Lumakras, Amgen), another *KRAS* G12C inhibitor, required treatment of CNS metastases with radiation prior to enrollment, making it impossible to fully evaluate the effects of the *KRAS* G12C inhibitor on IC activity. Authors listed limitations as the small size of the group, limited follow-up period and exclusion of patients with poor performance status.

## Discussion With Investigator

Alexander I. Spira, MD, PhD, FACP, senior author on the KRYSTAL-1 trial, which led to adagrasib’s accelerated approval,<sup>4</sup> and second author on the CNS study, is CEO and clinical director, NEXT Oncology Virginia; and physician and co-director, Virginia Cancer Specialists Research Institute. He spoke with *Evidence-Based Oncology (EBO)* about the latest results.

The interview has been edited lightly for clarity.

**EBO:** Please discuss the results that appeared recently in the *Journal of Clinical Oncology* regarding intracranial activity in patients with *KRAS* G12C–mutated NSCLC who received adagrasib. How do these findings distinguish adagrasib from other available treatments for this patient group?

**SPIRA:** Very briefly, this is the first published series on patients with untreated brain metastases. There have been other studies, and there have been anecdotal reports. There are 2 drugs in the class—sotorasib and adagrasib—that are approved; there are others working their way up through clinical studies. But this is really the first published data set, [with] a small number of patients but a real number, who demonstrated intracranial activity, meaning metastases to the brain shrunk on treatment with a *KRAS* G12C inhibitor.

**EBO:** Since the FDA approved adagrasib, what has been the reception from clinicians in the field who treat this group of patients?

**SPIRA:** Both adagrasib and sotorasib have had uptake. It’s been probably a little bit less, I think, than people anticipated. Maybe not enough [physicians] are testing *KRAS* G12C. So, it’s been a little less than anticipated, but physicians are using these drugs, and they are part of our clinical toolbox.

**EBO:** That leads to the next question: Have you or your colleagues experienced any challenges with prior authorization, either for the approved therapy itself or for the testing to determine which patients might be eligible for treatment?

**SPIRA:** Not really now. The drugs are approved for the FDA-approved indication, and it always takes longer than we would like, and the manufacturers have good programs to help out. »



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But by and large, it's being used appropriately, and payers are paying for it. Testing is still lacking. Many more [physicians] are testing for these [mutations] now, more so than a few years ago. It's not on the payers' part, it's more on the physicians' part—we're just not testing as often as we should.

**EBO:** So this is more of a physician education issue than a payer issue?

**SPIRA:** Yes.

**EBO:** Several other trials for this therapy are ongoing. These include a phase 3 study as well as a phase 2 study for patients specifically who are older than 70 years or who have poor ECOG performance status—these are patients who are often left out of clinical trials. Can you discuss the rationale and/or progress for these studies?

**SPIRA:** There are a whole bunch of studies going on. One of the ones you mentioned [is] looking at showing that these drugs do work in [patients with] poor ECOG performance status [phase 2 ADEPPT,

NCT05673187]. That's always a question—not a huge scientific question. But it's also to show that if patients are not doing so well, these drugs do often work well enough that patients can benefit, and benefit pretty quickly.

There is a confirmatory study of adagrasib vs the standard of care, docetaxel [phase 3 KRYSTAL-12, NCT04685135]. As you know, adagrasib was fast-tracked, so [this is] a confirmatory study, which is completed, and we're just waiting for the results.

And lastly, there are some frontline studies coming as well, to demonstrate what happens when we try to move these drugs up [to treat] newly diagnosed patients, where we hope they will work better. Specifically, those are being done in combination with pembrolizumab [Keytruda, Merck; phase 3 KRYSTAL-7, NCT04613596].

**EBO:** There are quite a few combination studies that are ongoing. Can you say which ones look most promising? Or is it difficult to say?

**SPIRA:** I think we're most excited about the frontline studies [in patients who are newly diagnosed]. And

that's really where the money is right now because what we're trying to do is get these patients earlier. For the original KRYSTAL-1 study, for which the brain metastases study that you talked about today is a subset, the patients were very heavily pretreated. So we hope [to show] that you can bring these drugs up sooner and patients will benefit even more and do better. ♦

#### REFERENCES

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## FDA ACTIONS

### Trifluridine/Tipiracil Combo Is Approved in Pretreated mCRC

Kristi Rosa

**THE FDA HAS APPROVED** trifluridine and tipiracil (Lonsurf) plus bevacizumab (Avastin) for patients with metastatic colorectal cancer (mCRC) who were previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; a VEGF inhibitor; and an EGFR inhibitor, if they have RAS wild-type disease.<sup>1,2</sup>

The regulatory decision is supported by data from the phase 3 SUNLIGHT trial (NCT04737187), in which the combination significantly improved overall survival (OS) and progression-free survival (PFS) vs trifluridine/tipiracil alone in this population.<sup>3</sup>

The addition of bevacizumab to trifluridine/tipiracil resulted in a median OFS of 10.8 months (95% CI, 9.4-11.8) vs 7.5 months (95% CI, 6.3-8.6) with trifluridine/tipiracil alone, translating to a 39% reduction in the risk of death (HR, 0.61; 95% CI, 0.49-0.77; 1-sided *P* < .001).

Moreover, the median PFS in the investigative arm was 5.6 months (95% CI, 4.5-5.9) vs 2.4 months (95% CI, 2.1-3.2) in the control arm, translating to a 56% reduction in the risk of disease progression or death (HR, 0.44; 95% CI, 0.35-0.54; 1-sided *P* < .001).

The open-label, international randomized, phase 3 SUNLIGHT study enrolled patients with histologically confirmed mCRC with an

who had received no more than 2 previous treatments for advanced disease, including a fluoropyrimidine, irinotecan, and oxaliplatin.<sup>2</sup> Prior treatment with a VEGF inhibitor was optional, but prior EGFR inhibition was required for those with RAS wild-type disease.

Study participants were randomly assigned 1:1 to receive trifluridine/tipiracil at a twice daily dose of 35 mg/m<sup>2</sup> on days 1 to 5 and 8 to 12 every 28 days with (n = 246) or without (n = 246) bevacizumab, which was given at 5 mg/kg on days 1 and 15 every 2 weeks of every 4-week cycle. Treatment continued until progressive disease or intolerable toxicity.

The primary end point of the study was OS in the full analysis set. Secondary end points included PFS, disease control rate, objective response rate, safety, and quality of life.

The median age of the 492 patients who underwent randomization was 63 years. Approximately half (52%) of patients were male, and the majority (88%) were White. Regarding ECOG performance status, 46% had a status of 0 and 54% had a status of 1. Seventy-three percent of patients had a primary disease site of the colon, and 27% had disease in the rectum. Notably, 71% of patients had RAS-mutated disease.

In terms of prior treatment, 92% of patients received 2 prior lines for advanced disease. All

patients previously received fluoropyrimidine, 99.8% had prior irinotecan, and 98% received prior oxaliplatin. Moreover, 76% had prior exposure to VEGF treatment, and 94% of the 142 patients with RAS wild-type disease had a prior EGFR inhibitor.

Of the patients who received trifluridine/tipiracil plus bevacizumab, 39% were treated for at least 6 months and 14% were treated for at least 1 year.

The most common adverse events experienced by at least 20% of patients included neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased aspartate aminotransferase, increased alanine aminotransferase, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite. ♦

#### REFERENCES

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