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US FDA In No Hurry To Withdraw Amgen's Lumakras Despite Negative Adcomm Vote On Confirmatory Trial Results

by Sue Sutter

ODAC votes 10-2 that the progression-free survival data in CodeBreaK 200 cannot be reliably interpreted due to various study conduct issues; agency assures the committee that it is not currently proposing withdrawal and that multiple regulatory pathways are available for sotorasib, one of two KRAS G12C inhibitors on the market under accelerated approval.

The US Food and Drug Administration appears in no hurry to try to remove *Amgen, Inc.*'s accelerated approval lung cancer drug Lumakras (sotorasib) from the market despite an advisory committee's conclusion that the progression-free survival endpoint in the CodeBreaK 200 confirmatory trial could not be reliably interpreted.

On 5 October, the Oncologic Drugs Advisory Committee voted 10-2 that the primary endpoint in CodeBreaK 200, PFS by blinded independent central review (BICR), could not be reliably interpreted due to a variety of study conduct issues that may have biased the results.

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The FDA granted sotorasib accelerated approval in May 2021, making it the first KRAS G12C inhibitor to reach market. The approved indication is for treatment of patients with KRAS G12C-mutated non-small cell lung cancer who received at least one prior systemic therapy.

Notably, the FDA did not ask the committee whether the CodeBreaK 200 results could serve as the confirmatory evidence necessary to convert sotorasib's accelerated approval to regular approval, or about the totality of the evidence for the drug and its benefit-risk profile.

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Paz Vellanki, the FDA's cross-disciplinary team lad for the application, said that given "multiple regulatory pathways and the evolving therapeutic landscape," the FDA was not asking ODAC whether the CodeBreaK 200 results would support conversion to regular approval but, rather, to discuss the trial's results, multiple signals of potential bias, and if PFS per BICR could be reliably interpreted.

The narrowness of the question posed to the committee, coupled with FDA officials' repeated comments about regulatory pathways available to sotorasib, suggested the agency is not likely to seek the drug's market withdrawal as a "dangling" accelerated approval anytime soon.

Next Steps Don't Automatically Mean Withdrawal

In the FDA's opening remarks to the panel, Division of Oncology 2 Director Harpreet Singh discussed possible regulatory options if CodeBreaK 200 cannot be used to verify sotorasib's clinical benefit.

"If our concerns regarding study conduct supersede the narrow therapeutic effect of sotorasib relative to docetaxel," the comparator agent in CodeBreaK 200, "we would have an accelerated approval which has yet to be converted to a traditional or regular approval, and we would consider potential next steps within our regulatory framework," Singh said.

"FDA oncologists recognize the unmet need for patients with actionable mutations, such as KRAS G12C, as well as the evolving treatment paradigm," Singh said. "A decision to withdraw an accelerated approval is not automatic in the setting of a failed confirmatory trial. It is affected by many factors, all of which we will consider for sotorasib."

> ***Amgen is planning another randomized trial of sotorasib, known as CodeBreaK 202, in first-line NSCLC, which potentially could be used to confirm benefit.***

"We consider the nature of the failed trial, for example, if there is a detriment in survival," she said. "We consider the current therapeutic landscape at the time of the failed trial, not at the time of the initial accelerated approval. And certainly we consider a potential safety advantage of the drug granted accelerated approval."

Singh showed a slide listing several KRAS G12C inhibitors that are in development and have been publicly disclosed. "The FDA has a wide-angle view of the therapeutic landscape, including other

trials which may be ongoing or planned, and thus can reasonably assess areas of current or future unmet need," she said.

The most advanced among these other compounds is *Mirati Therapeutics, Inc.*'s Krazati (adagrasib), which received accelerated approval in December 2022 for the same indication as sotorasib. (Also see "*Keeping Track: US FDA Oncology Approvals For Ferring's Gene Therapy Adstiladrin And Mirati's Targeted Therapy Krazati*" - Pink Sheet, 18 Dec, 2022.)

Mirati is conducting a confirmatory trial similar to CodeBreaK 200, called KRYSTAL-12, Singh said. "Some key differences from CodeBreaK 200 included a 2:1 randomization schema and crossover after real-time BIRC was implemented from study start. This trial is ongoing, and the design certainly was influenced by external trial results and anticipated open-label bias."

Singh also noted that Amgen is planning another randomized trial of sotorasib in the first-line NSCLC setting. This trial, known as CodeBreaK 202, potentially could be used to confirm benefit, she said.

Hours Of Statistical Analyses

The FDA brought the Lumakras supplemental new drug application, which seeks conversion from accelerated to traditional approval, to ODAC due to agency concerns that interpretation of the PFS benefit seen in the open-label study may be complicated by study conduct issues that potentially biased the results. (Also see "*Amgen's Lumakras: FDA Flags 'Marginal' Efficacy Results, Potential Systemic Bias In Lung Cancer Trial*" - Pink Sheet, 3 Oct, 2023.)

The study demonstrated a statistically significant effect on the primary endpoint, with a 34% reduced risk of disease progression or death and a median PFS benefit of approximately five weeks compared with docetaxel. However, the agency described this five-week benefit as "marginal" and noted there was no overall survival advantage with sotorasib.

Among the potential biases identified by the agency were a high rate of early dropout in the comparator arm, high rates of discordance between investigator and BICR calls for progression, and potential violations of the imaging charter.

Both the sponsor and the FDA presented numerous sensitivity and tipping point analyses that relied upon different assumptions. Amgen asserted that the PFS benefit seen in CodeBreaK 200 was real and held up in the face of various analyses, while the FDA asserted its analyses raised questions about the reliability of the PFS results.

In the end, the majority of committee members said the various study conduct issues and potential biases identified by the agency made it difficult to interpret the PFS results.

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"No one expects a perfect RCT, but what we hope for is a small number of issues in trial conduct and an effect large enough to withstand the uncertainties caused by those issues," said Mark Conaway, professor in the Division of Translational Research and Applied Statistics at the University of Virginia. "For this trial, we seem to have the opposite – a large number of issues that cloud the interpretation of a small observed effect."

Adcomm chairman Ravi Madan, head of the Prostate Cancer Clinical Research Section at the National Cancer Institute, noted the panel heard "hours of statistical permutations discussed that could change interpretations." He said he voted in the negative due to the small size of the study, investigator conduct, and the "small five-week PFS benefit. I do think if the PFS benefit was much greater, this would have been a much shorter conversation."

"I think this drug is active," said Wiliam Gradishar, chief of hematology/oncology at Northwestern University. "It's certainly a more desirable drug I think on the whole than receiving docetaxel. That's demonstrated by the toxicity data, the patients' experience. But I too have the same issue with the integrity of the study and the assessments that were made."

"The difference in PFS between the arms … may have met what was desired by the trial, but clinical relevance is a different issue," Gradishar said. "And when the integrity of even that small difference is called into question despite the three hours of statistical gymnastics, I still have as many questions about whether there is anything more than a sort of a wash between the two treatment arms with respect to PFS."

Jorge Nieva, head of solid tumors at Keck School of Medicine of USC, was one of two panelists who said the PFS data could be reliability interpreted.

"I voted 'yes' because the study met its primary endpoint based on the intent-to-treat analysis, and ultimately we have to take the statistical plan as it is written and analyze things according to what was planned," Nieva said. "I think the *post hoc* analyses are informative, but they ultimately

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don't change the benefits that were in fact observed. And I don't think a type one error occurred here. Given the corroborating evidence, I have confidence that the drug does have a PFS benefit over the comparator in this case."

A Worthy Alternative To Docetaxel

Several panelists said they hope that sotorasib remains available to patients because the drug appears to have therapeutic activity, and as an oral agent it offers more convenience, with less toxicity, than intravenous chemotherapy.

> *"It is not our intent to immediately withdraw a drug that has a 'failed confirmatory trial.' It is under accelerated approval, and there are multiple pathways available to us. And we are not making this move to withdraw the drug from the market based on these results." – FDA's Harpreet Singh*

David Mitchell, the panel's consumer representative and a multiple myeloma patient, voted "no" but made clear it was in the context of the very narrow question posed.

"You didn't ask me if I, as a cancer patient for example, would like to have this drug available to me. Do I believe, even if they're roughly equal, the fact that it is a drug that's much easier than the control agent for patients? You didn't ask about what do you think [of the] risk-benefit. You didn't ask whether it should be converted to full approval. You asked a very narrow question about the conduct of the study. … And given the narrow framing of the question, the answer was clearly 'no.'"

Phillip Hoffman, professor of medicine in hematology/oncology at the University of Chicago, said that even in a worst-case scenario where there was no difference between sotorasib and docetaxel in terms of efficacy, "I still would hope that sotorasib could remain as an option for patients in that clinical setting. Because probably many of them, or if not most, would choose an oral targeted drug or the speed of activity and so on."

"I would hate to see the drug not continue to be available," Hoffman said.

"We do hear the conflict in your thought process around the vote about totality and the desire to keep sotorasib on market as an option for patients," Singh told panelists at the close of the meeting.

“It is not our intent to immediately withdraw a drug that has a ‘failed confirmatory trial.’ It is under accelerated approval, and there are multiple pathways available to us. And we are not making this move to withdraw the drug from the market based on these results. We have not indicated that, and we are taking again into account your discussion.”