Evaluate Vantage

February 08, 2022

Amgen hold-up gives Mirati a vital lifeline

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A possible timing crunch threatening Mirati’s delayed Kras inhibitor might not now happen.

Six months might not seem like much, but for Mirati every second of it will count. Readout of Amgen’s confirmatory lung cancer trial of Lumakras, yesterday delayed from the first to the second half of this year, buys vital breathing space for Mirati as it scrambles to get its rival adagrasib onto the market.

Since Mirati is a year behind Amgen, the possibility of Lumakras being formally approved, based on the confirmatory data, jeopardised adagrasib’s chances of gaining an accelerated label. Mirati earlier rejected the suggestion that there was a risk, but recent precedent shows the threat to be real; the group must now execute quickly.

When *Evaluate Vantage* two weeks asked Mirati’s chief executive, David Meek, whether Lumakras confirmatory data and full approval threatened adagrasib he stated: “No, we don’t think so. The FDA is well aware of the timelines of both programmes. We have breakthrough therapy designation [and] we were granted real-time oncology review, so we fully expect our approval.”

Still, investors need look no further than last October for an example of a very similar timing crunch. Then Agenus had to pull an accelerated filing under priority review for balstilimab in cervical cancer after the FDA granted Merck & Co’s Keytruda full approval, making a conditional green light for a similarly acting rival in the same setting unsustainable.

The timeline

For Mirati the timeline is crucial. Until yesterday’s delay Amgen had been due to reveal results of Lumakras’s confirmatory Codebreak-200 trial before the mid-year point, which is when Mirati expects adagrasib to be approved.

But even this Mirati expectation is extremely bullish: though the adagrasib NDA has been submitted it has yet to be reviewed and accepted, something Mirati expects imminently. If the FDA raises no questions, grants the filing priority review and accepts it now, a six-month cycle would put August as the action date for approval.

Thus Mirati is banking not only on flawless execution and priority review but also on a super-fast turnaround, as had happened for Lumakras, which was greenlit in the space of just three and a half months. However, a standard 10-month review is a possibility, and would put the adagrasib action date into November.

This bear case could see the FDA reviewing Lumakras's confirmatory dataset before adagrasib's Pdufa date,

even with Amgen’s delay.

Timeline of the duelling Kras G12C inhibitors in lung cancer		
	Lumakras (Amgen)	**Adagrasib (Mirati)**
Accelerated filing for 2L Kras G12C+ve NSCLC accepted	Feb 2021	Feb 2022*
Goal action date	Aug 2021	Aug/Nov 2022*^
Accelerated US approval	May 2021	Jul-Nov 2022*
Confirmatory study readout	Delayed from H1 to H2 2022 (Codebreak-200)*	H2 2023 (Krystal-12)*
Full US approval	2022/23*	2023/24*
*Note: *expected; ^Aug if priority review is granted, Nov if it is not. Source: company statements.*		

While Mirati has gained a valuable lifeline its investors will recall the crucial months it has already lost; adagrasib and Lumakras had been on similar timelines, with the former sometimes showing superior efficacy on a cross-trial basis, but while Amgen moved fast to get its asset before the regulator Mirati became embroiled in a C-suite overhaul.

How does Mirati now catch up? “We are coming in later, we are well aware of that,” said Mr Meek. But adagrasib is “a different agent, with a 24-hour half life, which enables near complete inhibition of mutant Kras G12C. Response rates across the board are higher with adagrasib relative to other G12C inhibitors.”

He also cited adagrasib’s CNS activity, and the project’s activity in colorectal cancer shows another point of departure from Lumakras. Still, the first filing is in NSCLC, while Mirati continues to “finetune” the colorectal cancer approval pathway with the FDA.

Interestingly, while Mr Meek denied the threat Amgen’s confirmatory data pose to adagrasib, he said they would “present challenges to follow-on Kras G12C inhibitors; they’re not going to be able to pursue the conditional marketing authorisation accelerated pathway, at least in second-line lung cancer.”

For Amgen a delay to Codebreak-200 matters much less than Lumakras’s 2021 sales, which some analysts yesterday saw as light. For Mirati to take advantage of the bullet it might just have dodged it cannot afford any further delays.