Evaluate Vantage

April 28, 2021

Amgen’s low-dose Kras curveball

Jacob Plieth

The company reveals that it will test a low dose of sotorasib, a move apparently requested by the US FDA.

August 16 remains a vital date in Amgen’s calendar, being the deadline by which the US FDA is to decide whether to approve the company’s Kras G12C inhibitor sotorasib. Amgen has reiterated that it is ready to launch the drug, now to be branded Lumakras, “upon approval”.

In the meantime, however, the group continues to tinker with its clinical programme, yesterday revealing plans to test how a once-daily 240mg Lumakras dose compares with the 960mg for which it is seeking approval. This immediately caused confusion and speculation among analysts: what had triggered this substudy?

One initial guess was that a low dose could be preferable for combinations with other agents. But on last night’s first-quarter call the company said the dose-comparison study did not “really have anything to do with combinations”. Indeed, it seemed to say that testing 240mg had been driven simply by curiosity.

Its vice-president of R&D, David Reese, said the company wanted to see if it could “potentially get by with efficacy at a lower dose and enhance patient experience”. 240mg was chosen based on modelling taking into account pharmacokinetics and “preclinical data regarding efficacy at different target coverage levels”, said Mr Reese.

Post-marketing requirement

But then, overnight, the story changed. This morning before the markets opened Amgen issued a brief statement clarifying that in fact it was the FDA that had proposed a requirement to conduct a randomised trial to compare 960mg “versus a lower daily dose”.

The most important message for the markets is that this requirement does not alter Lumakras’s initial approval timeline, or the running of a pivotal phase 3 study. The dose-comparison trial will be run alongside, and should yield results in 2022/23.

However, investors will be none the wiser as to why the US regulator would have asked Amgen to explore a low dose of a drug that at 960mg does not appear to have raised undue toxicity concerns (*World Lung 2020 – no advance on Amgen’s “consistent” Kras promise, January 29, 2021*).

That said, the FDA’s apparent willingness for this to be a post-approval requirement probably increases the chances of Lumakras being approved by August. This is most relevant for Mirati’s G12C competitor adagrasib, which will not be filed until the second half.

Selected Lumakras (sotorasib) studies		
Trial	**Description**	**Design**
Codebreak-100	Registrational ph2	533 Kras G12C mutant pts, uncontrolled; 2L NSCLC cohort is relevant for approval;
Codebreak-200	Confirmatory ph3	330 Kras G12C-mutant NSCLC pts, vs docetaxel; PFS primary endpoint
Codebreak substudy	Dose-comparison	960mg once-daily vs 240mg once-daily in NSCLC
Source: clinicaltrials.gov & Amgen statements.		

Lumakras's filing is based on the phase 2 Codebreak-100 trial in second-line NSCLC. A confirmatory phase 3 trial, Codebreak-200, versus docetaxel, has completed enrolment after its recruitment target was lowered from 650 to 330 subjects, which Amgen says will be enough to maintain statistical power to assess its progression-free survival primary endpoint.

As for combinations, the logical adding of Shp2 inhibition to direct anti-Kras activity is the subject of a tie-up with Revolution Medicines involving that company's RMC-4630. However, Amgen seems to be playing this down, and focusing more on the synergistic activity of Lumakras and Mek or EGFR blockade; combo data are due in the second half.

RMC-4630 is separately licensed to Sanofi, but at the recent AACR meeting showed disappointing monotherapy activity. Roche also is investigating this mechanistic combo, planning to test its Relay Therapeutics-originated Shp2 inhibitor RG6433 with its own Kras G12C blocker GDC-6036.

And yesterday Novartis, the most advanced Shp2 player, with TNO155, played up its combinatorial potential. Trials of TNO155 with Mirati's adagrasib, and with Novartis's in-house Kras G12C inhibitor JDQ443, are under way.