Evaluate Vantage

September 01, 2022

Esmo 2022 – last-minute Kras entry takes centre stage

Jacob Plieth

Amgen’s confirmatory Codebreak-200 trial will feature as a surprising late-breaker at Esmo’s presidential session.

A common theme of the long-running battle of Kras inhibitors has been how frequently Mirati has been outplayed by Amgen. The latest act in the saga took place yesterday, when Amgen somehow managed to get data from its confirmatory Codebreak-200 study of Lumakras accepted as a late-breaker for the Esmo meeting, which starts in eight days’ time.

The deadline for late-breaker Esmo submissions was August 9, yet Amgen only toplined Codebreak-200 two days ago. True, Amgen will have had the results in house for some time before announcing, and if it additionally managed to use some of its connections to persuade Esmo to give it leeway then it has again played its hand well.

Esmo late-breaking titles went live on August 18, but one slot, LBA10, was noticeably left blank. Yesterday LBA10’s title appeared on the Esmo website: “sotorasib versus docetaxel for previously treated NSCLC with KRAS G12C mutation, Codebreak-200 phase 3 study” is due to be presented at 5.40pm European time at the meeting’s presidential symposium on September 12.

Amgen told *Evaluate Vantage* that it had submitted a "shell abstract" to the congress organisers in anticipation of having the data in time for Esmo. Its investors will welcome the group’s strong connections. It will not go unnoticed, for instance, that its senior vice-president of oncology, Jean-Charles Soria, worked at Gustave Roussy – which claims to be Europe’s leading cancer hospital – for 15 years, most recently as director general.

The scientific co-chair of the Esmo 2022 congress is Dr Fabrice André, a medical oncologist at Gustave Roussy. He had recently tweeted that Esmo 2022 would be a conference that would be remembered for 20 years.

> Without disclosing what will be presented, #ESMO22 will be for sure a conference that colleagues will remember 20 years after , given the wealth of innovation + new concepts on the clinical trials side
>
> — FabriceAndre (@FAndreMD) August 22, 2022

The question now, for Amgen as well as for Mirati, is how good the Codebreak-200 data are. All Amgen has said is that Lumakras showed “statistical significance and superiority over” docetaxel on the study’s primary endpoint of progression-free survival.

There is little precedent on what to expect, as Codebreak-200 tested patients who had failed one systemic treatment, likely PD-(L)1 blockade. Wells Fargo analysts reckon “good data” would be a six-month or greater PFS benefit for Lumakras, versus four months or less for the chemo.

However, they also note that Gilead's Trodelvy and Astrazeneca/Daiichi Sankyo's datopotamab are aiming to replace docetaxel in post-PD-(L)1 NSCLC patients, so combos will be key for Lumakras to gain traction. Amgen has not fared well here: World Lung data showed unexpected levels of liver toxicity for Lumakras plus PD-(L)1 blockade.

Esmo will separately feature the Codebreak-101 trial of Lumakras plus Vectibix in colorectal cancer, as well as a late-breaker on a cut from Mirati’s adagrasib’s Krystal-1 study in the same setting.

Selected Esmo 2022 abstracts on Kras

Project (company)	Study (use)	Note	Abstract
Lumakras (Amgen)	Codebreak-200 (2nd-line Kras G12C+ve NSCLC, vs docetaxel)	Confirmatory trial for accelerated approval, toplined positive for PFS	LBA10
Adagrasib (Mirati)	Krystal-1 (Kras G12C+ve colorectal cancer)	Colorectal cancer filing path is unclear	LBA24
Lumakras + Vectibix (Amgen)	Codebreak-101 (Kras G12C+ve colorectal cancer)	Had data at Esmo 2021, but World Lung 2022 data on Lumakras + PD-(L)1 blockade showed liver tox	315O
GDC-6036 (Roche)	Ph 1 (Kras G12C+ve solid tumours)	Field is getting crowded	459MO

Source: Esmo & company statements.

Mirati shareholders appeared to welcome the toplining of Codebreak-200, sending the stock up 9% yesterday, but in NSCLC the company has a problem.

Adagrasib’s US accelerated approval filing has a December 14 action date, but should the FDA grant Lumakras a full green light before then – on the basis of Codebreak-200 – it will be difficult for adagrasib to be approved on the basis of its surrogate endpoint of overall remission rate, as *Evaluate Vantage* has argued.

Still, Lumakras’s formal approval is by no means assured. That will depend on the size of the benefit in Codebreak-200, and on whether the FDA deems PFS to be an appropriate second-line endpoint. Nothing has been said about overall survival, which does appear in the trial’s secondary efficacy metrics.

Mirati and Amgen investors alike face a stressful few months.

This is an updated version of a story published earlier.