Evaluate Vantage

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Triple meeting – Mirati gets an edge over Amgen

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Mirati's Kras inhibitor looks better than Amgen's on efficacy, but toxicity worries prevent a knockout punch.

In the battle of the Kras inhibitors Mirati yesterday struck a blow against its big biotech rival, Amgen. In data presented at the Triple meeting, Mirati's adagrasib showed a 45% overall response rate in non-small cell lung cancer, numerically better than the 35% ORR previously seen with Amgen's sotorasib.

However, it might be too soon for Mirati investors to break out the bubbly: the data are not a knockout, and though Mirati has now revealed its filing plans Amgen is ahead in the race to get approval. With questions also over adverse events with adagrasib it is probably too soon to call a winner in Kras.

This stance was echoed by Dr Pasi Jänne of the Dana-Farber Cancer Institute and lead investigator of the Krystal-1 trial of adagrasib, the subject of yesterday's presentation at the EORTC-NCI-AACR symposium.

When asked during a Mirati investor event yesterday whether the difference between adagrasib and sotorasib was clinically meaningful, Dr Jänne replied: "It's hard to read on response rate alone." He added that longer follow-up was needed to gather data on, for example, progression-free survival and durability of response.

Mirati bulls clearly did not share his caution: the group's stock was up as much as 15% this morning, but Amgen fell 2%.

Both adagrasib and sotorasib target Kras G12C mutations, which occur in around 14% of NSCLC and 3-4% of colorectal cancers. Mirati said yesterday that it plans to file for accelerated approval of adagrasib in second/third-line NSCLC in the second half of 2021.

Meanwhile, Amgen has not given concrete timelines, but recently hinted that filing of sotorasib might be imminent. Mizuho analysts think a submission in the first half of next year "doesn't seem unreasonable", while Leerink puts Amgen six to nine months ahead of Mirati.

Efficacy edge

Amgen might be in the lead, and its size should give it an edge when it comes to marketing. But adagrasib does look to have an efficacy advantage, at least based on the data so far. The Triple meeting featured pooled results from phase I and II cohorts in Krystal-1, in both NSCLC and colorectal cancer.

In NSCLC the overall response rate with adagrasib was 45% – or 43% if only the 14-patient phase I cohort was taken into account. Although cross-trial comparisons should be treated with caution, this is above the 35% ORR

in NSCLC recently reported with a 960mg once-daily dose of sotorasib in the phase I portion of the Codebreak-100 study (*Esmo 2020 – Kras cools off, September 20, 2020*).

Notably, Amgen has also said that its phase II data are consistent with the phase I results, without giving any concrete details.

Cross-trial comparison of Amgen and Mirati data so far		
Company	**Mirati**	**Amgen**
Project	Adagrasib/MRTX849	Sotorasib/AMG 510
Trial	Krystal-1	Codebreak-100
Target dose	600mg twice daily	960mg once daily
NSCLC	23/51 PRs (45% ORR)	12/34 PRs (35% ORR)
Colorectal cancer	3/18 PRs (17% ORR)	3/25 PRs (12% ORR)
Grade 3/4 TEAEs	30% (n=110)	19% (n=59)
Source: Triple meeting, NEJM, Esmo & company announcements. PR=partial remissions, all confirmed; ORR=overall response rate.		

Leerink believes that both the adagrasib and sotorasib data are strong enough for accelerated approval in NSCLC, but that in colorectal cancer only the former is worthy of this green light.

Still, all this needs to be weighed up against an increase in adverse events seen with Mirati's project. The most worrying was QT prolongation, which carries a risk of sudden cardiac death; this occurred in 14% of adagrasib-treated patients, but was not seen at all with sotorasib.

Mirati executives stressed that no arrhythmias had been seen, and said QT prolongation was manageable. Leerink pointed to Astrazeneca's Tagrisso and Xalkori as examples of successful drugs with similar QT effects.

Adagrasib was also linked with a high rate of nausea and diarrhoea: 51% and 54% respectively, compared with 10% and 25% respectively with the Amgen agent. The Mirati execs said these issues tended to occur early in treatment, and reduced in frequency and severity over time without the need for dose reduction.

The toxicity concerns were not enough to put off Mirati's backers, who have now pushed the group's market cap to a staggering $9bn.

The company also has a Kras G12D inhibitor, MRTX1133, in preclinical development, with animal data on this project featuring at the Triple meeting. Mirati plans to file an IND in the first half of next year. Still, the bull case for Mirati is all about adagrasib, and it just got slightly stronger.