Evaluate Vantage

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World Lung 2020 – no advance on Amgen’s “consistent” Kras promise

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But the unveiling of sotorasib’s registrational dataset shows that bulls should be cautious of Mirati's numerical advantage.

Amgen has delivered on a promise that the results it used to file its Kras inhibitor sotorasib were consistent with an earlier disclosed phase I dataset. Investors who had been hoping for more, however, will be disappointed, as the latest data show the group’s Kras rival Mirati ahead on a numerical basis.

Accordingly, Amgen stock slipped yesterday afternoon, while Mirati crept up 5%. But this is a superficial interpretation of the two sets of results; Amgen has the larger dataset and a key safety advantage, has now reported the first ever complete responses to a Kras blocker, and crucially is ahead in the regulatory game.

Amgen had submitted a US filing for sotorasib for use in second-line, Kras G12C-mutated NSCLC, based on the phase II portion of the Codebreak-100 study. For its part Mirati plans to file its contender, adagrasib, in second/third-line NSCLC in the second half of this year, using data from the Krystal-1 trial.

The phase I portion of Codebreak-100 had yielded a 35% ORR at the target sotorasib dose, and revelation of the registrational phase II part had been set for Friday night at the World Lung conference’s presidential symposium. But a media embargo breach caused Amgen to put the phase II data into the public domain in market yesterday.

The headline results are a 37% ORR in 124 evaluable subjects, with three of the 43 remissions being complete, Amgen said. Median duration of response is 10 months, slightly below the 10.9 reported in phase I, and median progression-free survival, the first reported for a Kras inhibitor, of 6.8 months.

Evercore ISI analysts had expected an ORR of 30-35%, and response duration of above six months, so sotorasib has come out ahead. Mirati has not revealed response duration or PFS data, but an early estimate of the two metrics based on Kaplan-Meier curves seen with adagrasib had suggested 9.2 months and 6.8 months respectively.

Zeroing in

Apart from seeing Mirati’s absolute numerical advantage of a 45% ORR in a much smaller dataset, investors will zero in on two other metrics: safety, and activity in NSCLC patients whose tumours harbour an STK11 as well as Kras G12C mutation.

On the safety side Amgen has the upper hand. Mirati's last cut of pooled Krystal-1 data had shown a 30% rate of serious treatment-emergent adverse events (TEAEs), including a worrying 14% rate of QT prolongation, and 51% and 54% respective rates of nausea and diarrhoea (*Triple meeting – Mirati gets an edge over Amgen, October 26, 2020*).

Amgen's registrational data show a 21% rate of TEAEs, and 19% and 31% incidence of nausea and diarrhoea respectively; there has been no mention of QT prolongation, a side effect that carries risk of sudden cardiac death.

Meanwhile, STK11 co-mutation is emerging as an important additional battleground. While Kras G12C mutations occur in around 14% of NSCLC patients, some 30% of these are jointly driven by STK11, whose presence is associated with especially poor outcomes.

Last October Mirati boasted of a 64% ORR in STK11 co-mutants, albeit with a denominator of just 14 patients. Yesterday Amgen cited "encouraging" responses in subjects with this mutation, which Stat reported amounted to 14 remissions out of 35 patients.

No doubt the back-and-forth battle will continue. For now, Mirati investors should ask themselves precisely what their company's $10.3bn valuation prices in.

Cross-trial comparison of Amgen and Mirati data in NSCLC		
Company	Amgen	Mirati
Project	Sotorasib/AMG 510	Adagrasib/MRTX849
Trial	Codebreak-100 (registrational ph2)	Krystal-1 (pooled ph1 & registrational ph2)
Baseline	81% had progressed on Pt chemotherapy + anti-PD-(L)1; rest had progressed after one of these	Median 2 prior systemic treatments; 92% post anti-PD-(L)1
Target dose	960mg once daily	600mg twice daily
Overall response	37% (3 CRs, 43 PRs; n=124)	45% (23 PRs; n=51)
mDOR	10.0 mth	9.2 mth*
mPFS	6.8 mth	6.8 mth*
ORR in STK11/Kras G12C co-mutants	40% (14 PRs; n=35)	64% (9 PRs; n=14)
Grade 3/4 TEAEs	21% (n=126)	30% (n=110)
Specific TEAEs	Nausea (19%), diarrhoea (31%)	Nausea (51%), diarrhoea (54%), QT prolongation (14%)
*Source: 2020 World Lung meeting, 2020 Triple meeting, company announcements & Stat. *Preliminary estimate of Kaplan-Meier curves at Apr 2020.*		