Esmo 2021 – colorectal cancer could be Mirati’s golden ticket

Madeleine Armstrong

Adagrasib looks better than Amgen’s Lumakras, which could explain why Mirati has been dragging its heels in lung cancer.

2021 has not been a great year for Mirati, but things could be about to get better. The group, which has fallen behind with its Kras inhibitor adagrasib in lung cancer, looks to have stolen a march on its competitor Amgen in a potential new use, colorectal cancer.

Data revealed in an Esmo late-breaking abstract today showed a decent response rate with adagrasib monotherapy, and efficacy became even more impressive when the project was combined with Merck KGaA/Lilly’s EGFR inhibitor Erbitux. The results might provide a reason for Mirati’s tardiness in lung cancer, as the group could be hoping to add colorectal cancer to a filing planned for later this year.

That submission had originally been expected to cover NSCLC alone. Perhaps this issue will be addressed at Mirati’s investor meeting on Monday, which will also include a long-awaited update from the NSCLC cohort of the phase 1/2 Krystal-1 trial (Mirati fiddles as its share price burns, August 12, 2021).

Better than Lumakras?

In the meantime, though, Mirati bulls will be celebrating Krystal-1's colorectal cancer data, which involved patients with Kras G12C mutations who had previously received an average of three lines of therapy.

With adagrasib monotherapy there was a 22% overall response rate. One of these responses remains unconfirmed but, with the usual caveats about cross-trial comparisons, this far exceeds the 7% response rate with Lumakras monotherapy in the Codebreak-100 study.

Indeed, the result with adagrasib alone was not far off the 27% ORR with Lumakras in combination with Amgen’s EGFR inhibitor Vectibix in its analagous phase 1/2 study, Codebreak-101, unveiled in an Esmo poster on Thursday. All but one of seven responses have now been confirmed, Amgen said during a conference call to discuss the data.

But it was the adagrasib plus Erbitux arm of Krystal-1 that really impressed, with a 43% ORR, according to the abstract.
Cross-trial comparison of Kras inhibitors in colorectal cancer

<table>
<thead>
<tr>
<th>Project (company)</th>
<th>Adagrasib (Mirati)</th>
<th>Lumakras (Amgen)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
<td><strong>Krystal-1</strong></td>
<td><strong>Codebreak-100</strong></td>
</tr>
<tr>
<td><strong>Cut-off</strong></td>
<td>25 May 2021</td>
<td>9 Jul 2021</td>
</tr>
<tr>
<td></td>
<td>Adagrasib mono</td>
<td>Adagrasib + Erbitux</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>22% (10/45)*</td>
<td>43% (12/28)**</td>
</tr>
<tr>
<td><strong>TRAEs</strong></td>
<td>91%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Grade 3/4 TRAEs</strong></td>
<td>30%</td>
<td>16%</td>
</tr>
</tbody>
</table>

*Includes 1 unconfirmed PR; **Includes 2 unconfirmed PRs; ***Includes 3 unconfirmed PRs, but Amgen said that at a later data cut all 1 were now confirmed; ^No grade 5 AEs seen; ^^No grade 4 AEs seen.

ORR=overall response rate; TRAE=treatment-related adverse event. Source: Esmo abstract LBA6, poster 434P & Amgen presentation.

Still, there are reasons for caution, notably around toxicity, where adagrasib looked markedly worse than Lumakras.

Investors will no doubt be watching Sunday’s Esmo presentation on Krystal-1 for more info on specific adverse events with adagrasib. At last year’s Triple Meeting QT prolongation was flagged as a particular worry; high rates of nausea and diarrhoea were also seen with the Mirati project (Triple meeting – Mirati gets an edge over Amgen, October 26, 2020).

Vectibix is far from a clean drug either, though, with a black box warning for skin toxicities and infusion reactions. Skin problems were most commonly seen in Codebreak-101, although rates of nausea and diarrhoea were also fairly high, at 26% and 23% respectively.

Going earlier

It has long been clear that Lumakras monotherapy has no future in colorectal cancer, but the Esmo data suggest that combos could provide a way forward for Amgen. The group plans to start a phase 3 study of Lumakras plus Vectibix in third-line or later patients in the fourth quarter.

Meanwhile, Cardiff Oncology also hopes to hit Kras-mutated cancer with its PLK1 inhibitor onvansertib. The most recent data cut showed a 38% ORR in combination with Avastin, including unconfirmed responses; however, confirmed rates have waned of late.

But adagrasib might have done enough to get a monotherapy nod, and Mirati already has an eye on earlier lines of therapy: the Krystal-10 study, of adagrasib plus Erbitux in second-line colorectal cancer, started this year.

More from Evaluate Vantage

Evaluate HQ
44-(0)20-7377-0800
Evaluate Americas
+1-617-573-9450
Evaluate APAC
+81-(0)80-1164-4754

© Copyright 2021 Evaluate Ltd.