Evaluate Vantage

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Esmo 2018 – Accelerated approval looks more doubtful for Mirati

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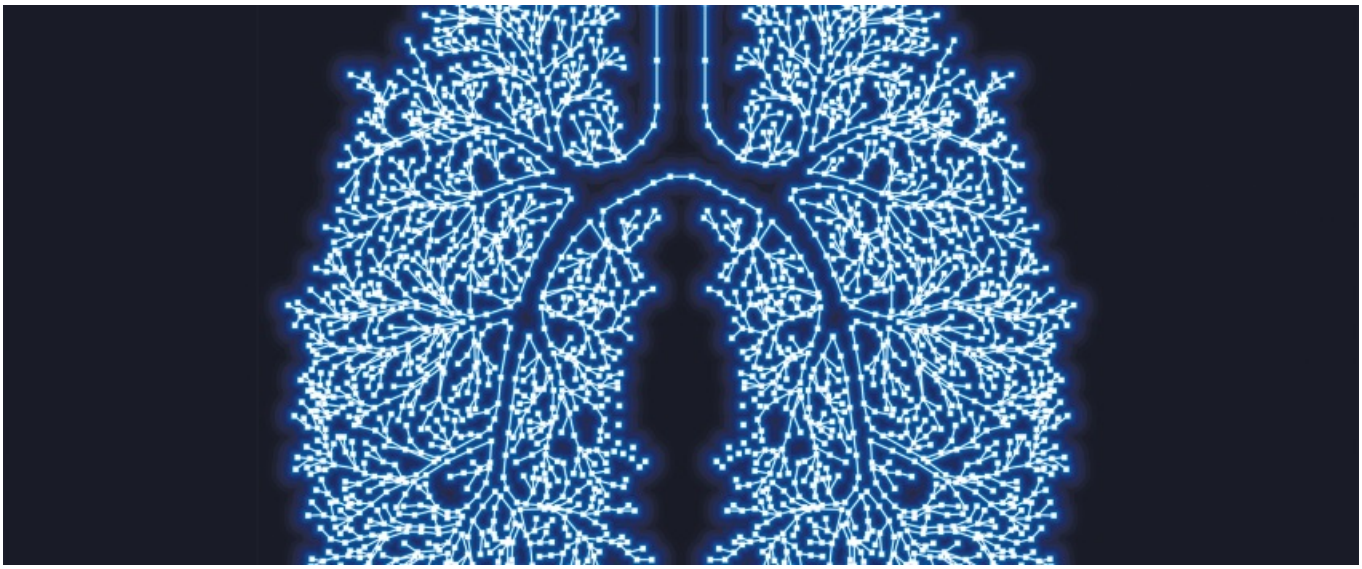

The company's stock slumped on disappointing data from its sitravatinib-Opdivo combo lung cancer study, and on news that the group will will need to carry out a randomised pivotal trial.

The path to launch for Mirati Therapeutics' sitravatinib just got a little more complicated and costly. Phase II data showed that a combination of the multi-kinase inhibitor and Bristol-Myers Squibb's Opdivo in lung cancer exceeded investor expectations, but only if you believe that all of the remissions presented by the company at the Esmo meeting yesterday are real.

However, Mirati accepts that nearly a third of these responses will never be confirmed. This was paired with news that accelerated US FDA approval would come only on positive response data from an interim analysis of a large randomised trial, expected around the end of 2020. Certainly, yesterday's Esmo data could not have built confidence in that outcome, and Mirati's shares closed down 15%.

Depends on how you count responses

The phase II trial was designed to evaluate Opdivo plus sitravatinib in non-squamous NSCLC patients who had progressed after treatment with a checkpoint inhibitor. Of 56 patients evaluable for response, nine had confirmed responses, either partial or complete, and two were unconfirmed but remain on trial awaiting confirmation.

Another five responses were "unconfirmed ... and will not be confirmed", the company took the unusual step of saying. Mirati nevertheless counted these five remissions, yielding a response rate of 29%, in excess of analyst expectations of at least 20%.

Removing these five patients from the analysis takes the response rate down to 20%, assuming that the other two unconfirmed responses are confirmed by trial investigators; if they are not, the nine confirmed responses amount to a rate of 16%.

It is not clear if these were the data being viewed by FDA officials at an end-of-phase II meeting, but Mirati executives further disappointed investors with news that the regulator would require a randomised phase III trial in second-line NSCLC after progression on a PD-(L)1/chemotherapy combination.

In this phase III study, which should be completed by the end of 2021, the comparator arm will be docetaxel,

and the primary endpoint will be overall survival. An interim analysis by the end of 2020, based on overall response rate, could be used for an accelerated review.

Single-agent docetaxel, the standard of care in second-line disease, has achieved a response rate of 5-6% in patients who have failed platinum-based chemotherapy, according to its label, although studies have found ORRs as high as 25%. This would be the benchmark for sitravatinib to beat to win accelerated approval.

Subject to change: sitravatinib's forecast					
		Sales forecasts ($m)			
Project	**Company**	**2021e**	**2022e**	**2023e**	**2024e**
Sitravatinib	Mirati Therapeutics	22	44	237	329
Source: EvaluatePharma.					

Both the phase II data and the phase III outlook disappointed investors. The H C Wainwright analyst Edward White wrote in August that a phase III trial to achieve accelerated approval would likely need to enrol 130 patients, with a post-approval confirmatory trial of 500-600 subjects.

This could push up the cost of achieving US approval immensely, while sitravatinib's launch date – now assumed to be 2021, according to *EvaluatePharma*'s consensus – could to be set back by a year or more.

In a call with investors, Mirati's chief executive, Charles Baum, played up the change in treatment protocols that are expected to create a growing population of patients who will progress on PD-(L)1/chemo combinations. He needs to hope that there are no practice-changing treatment strategies that emerge before the end of 2021 that render sitravatinib superfluous.