Evaluate Vantage

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Arcus nears crunch time for Gilead opt-in

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The anti-Tigit MAb domvanalimab will generate key clinical results any day; will they be good enough for Gilead to opt in?

Since Roche triggered Tigit mania at the start of 2020 numerous antibodies blocking this immune target have entered clinical testing. Now the time has come for one of these, Arcus's domvanalimab, to prove its worth.

The data, from domvanalimab's phase 2 Arc-7 study in lung cancer, are especially important as they could determine whether Gilead opts in to a full partnership, netting Arcus a $200-275m payment plus up to $500m in regulatory milestones. At the heart of the issue lies domvanalimab's design as an Fc-inactivated MAb – an approach over whose benefit the jury is still out.

It will not go unnoticed that the two leading anti-Tigit MAbs, Roche's tiragolumab and Merck & Co's vibostolimab, are both conventional MAbs with competent Fc domains. Both are now in large mid to late-stage clinical programmes seeking to recruit thousands of patients.

Project	Domvanalimab
Company	Arcus
Market cap	$1.7bn
Product NPV	$1.5bn
% of market cap	85%
Event type	Readout of Arc-7 (zimberelimab +/- etrumadenant combo) trial
Indication	1st-line, PD-L1-expressing NSCLC
Date	Q2 2021
Trial ID	NCT04262856

Growing concern about Arcus's Fc-inactivated approach has largely centred over whether this will be sufficiently differentiated, according to the sellside.

Fears have been fuelled by a tie-up last month in which Bristol Myers Squibb licensed Agenus's Fc-enhanced anti-Tigit bispecific, AGEN1777, worth $200m up front. Bristol struck this deal in spite of having its own Tigit MAb, BMS-986207 – like domvanalimab an Fc-inactivated asset – in phase 1/2.

And neither has the advancement of Arcus's own Fc-enabled anti-Tigit MAb, AB380, into phase 1, helped sentiment. On the other hand, the effect of inactivating or boosting an antibody's Fc region is unclear, and Evercore's Umer Raffat recently stated: "Across IO ... I have yet to find an example of whether Fc being active or not actually made a difference."

Industry projects targeting Tigit			
Project	**Company**	**MAb type**	**Status & enrolment target**
Tiragolumab	Roche	IgG1, Fc active	Ph3 (6,567)
Vibostolimab	Merck & Co	IgG1, Fc active	Ph3 (3,090)
Ociperlimab	Beigene	IgG1, Fc active	Ph3 (2,096)
Domvanalimab	Arcus	IgG1, Fc silent	Ph2/3 (917)
BMS-986207	Bristol Myers Squibb	IgG1, Fc silent	Ph1/2 (334)
Etigilimab	Mereo	IgG1, Fc active	Ph1/2 (158)
IBI939	Innovent	?	Ph1 (332)
SGN-TGT	Seagen	IgG1, Fc enhanced	Ph1 (231)
AB308	Arcus	IgG1, Fc active	Ph1 (154)
COM902	Compugen	IgG4, Fc silent	Ph1 (45)
M6223	Merck KGaA	IgG1, Fc active	Ph1 (35)
EOS-448	Iteos	IgG1, Fc active	Ph1 (30)
AGEN1777 (bispecific)	Agenus/Bristol Myers Squibb	Fc enhanced	Preclinical
AGEN1327	Agenus	Fc enhanced	Preclinical
Source: Evaluate Pharma & company presentations.			

Still, Gilead must have liked domvanalimab when a year ago it signed a 10-year alliance with Arcus worth $175m in cash plus a $200m equity stake. This gave Gilead opt-in rights to Arcus's clinical assets, of which domvanalimab was earmarked as the most lucrative.

So what does the upcoming event need to show? Arc-7 is a study testing domvanalimab either as a doublet with Arcus's anti-PD-1 MAb zimberelimab, or as a triple combo with zimberelimab and etrumadenant, an adenosine A2a and A2b receptor antagonist. There is also a zimberelimab monotherapy arm, and the NSCLC patient population is front line, PD-L1 positive.

Obviously Gilead's criteria for opting in are not disclosed, and it is not even clear whether Arcus will release overall remission rate numbers at this point. Analysts have rumoured that Gilead might in any case not choose to opt in at this first interim readout, even if the data appear positive.

Baseline expectations?

Still, a good proxy are front-line NSCLC data generated so far by Roche and Merck. At Asco 2020 tiragolumab plus Tecentriq yielded an ORR of 37% in PD-L1 expressers, versus 21% for Tecentriq alone, but the effect in NSCLC expressing PD-L1 ≥50% was particularly striking: 66% versus 24%.

So tiragolumab appeared to be adding most efficacy in PD-L1-high patients, where PD-(L)1 blockade would be expected to be most potent, and it was somewhat concerning that Roche effectively admitted that anti-Tigit monotherapy was a non-starter.

The findings were backed up by Merck's Esmo dataset with vibostolimab, which combined with Keytruda in checkpoint-naive, PD-L1-expressing NSCLC yielded a 46% ORR. But there was virtually no activity either for vibostolimab monotherapy, or for the combo in checkpoint-refractory patients.

In Arc-7, some are suggesting that Gilead wants to see the combo give an ORR of at least 50%, plus clear separation from zimberelimab monotherapy. There is no baseline for zimberelimab, which has yielded no monotherapy data in first-line NSCLC yet; for comparison, Keytruda monotherapy yielded a 27% ORR in front-line PD-L1 expressers in the Keynote-042 trial.

While the bull case has Gilead opting straight in, the opposite scenario features abject failure of Arc-7. Then again, Arc-7 could yield positive data, but Gilead might still sit on the fence. Given that AB308 is now in the clinic, and Gilead could opt into this Fc-competent Tigit instead, that mid-case must be a possibility.

This story has been updated to correct the Fc characteristics of COM902.