Evaluate Vantage

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Reading Arcus’s Tigit tea leaves

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As data non-disclosure prompts sellside guesswork one indisputable fact stands out: Gilead has not opted in to Arcus’s domvanalimab.

Yesterday’s unveiling of the Arc-7 study of Arcus’s anti-Tigit MAb domvanalimab, one of 2021’s key biopharma catalysts, has left more questions than answers. No remission rate data were disclosed, and all investors know is that “internal thresholds” have been met, and that Arcus’s anti-PD-1 combo looks “like any of the other anti-PD-1s and anti-Tigits”.

Still, one fact is not in doubt: Gilead has chosen not to opt into a licensing deal for domvanalimab, something it would surely have done had the data been strong enough. Arcus stock, having nearly halved from a peak it hit in February, opened up 16% this morning, likely helped by the sellside interpreting management’s comments as positive.

The hope had been that Arc-7’s interim analysis would indicate whether domvanalimab was adding efficacy to PD-(L)1 blockade in front-line, highly PD-L1-positive (≥50%) NSCLC, and how this compared against rival datasets from Roche’s tiragolumab and Merck & Co’s vibostolimab.

None the wiser

Each of Arc-7’s three cohorts, Arcus's anti-PD-1 MAb zimberelimab, domvanalimab plus zimberelimab, or a triplet with the A2a and A2b receptor antagonist etrumadenant, is to “continue as planned”. But Arcus revealed nothing quantitative, arguing that it had blinded itself to Arc-7 – an open-label study – to preserve data integrity for a medical conference.

What it did say was that zimberelimab monotherapy was performing in line with marketed anti-PD-(L)1s, and that both combos yielded “encouraging” data that met “internal thresholds”. However, on an analyst call Arcus said the data were not mature enough to compare against Roche’s Cityscape trial, suggesting that the doublet is some way short of the 66% ORR Roche had shown with tiragolumab plus Tecentriq in PD-L1 ≥50% expressers.

Though Arcus’s ORR threshold had been thought to be around 50%, Evercore’s Umer Raffat said management’s “body language” suggested a figure just short of this for the doublet, but above it for the triplet, which was described as “truly differentiated”. Arcus said both combos separated from zimberelimab, but made no comment on how the triplet did versus the doublet.

Arcus said Gilead had decided not to opt in, but would instead make this call by the end of 2021, “following maturation of the Arc-7 data”.

Cross-trial comparison of Tigit blockade in 1st-line NSCLC			
	Roche	**Merck & Co**	**Arcus**
Anti-Tigit MAb	Tiragolumab	Vibostolimab	Domvanalimab
Study	Cityscape	MK-7684-001	Arc-7
Source	Asco 2020	Esmo 2020	Jun 2021 press release
PD-L1 expression	≥50%	≥1%	≥50%
Anti-PD-(L)1 monotherapy ORR	24%	NA*	In 35-40% range ("similar to marketed anti-PD-(L)1")
Anti-PD-(L)1 + Tigit ORR	66%	46%	"Encouraging, met internal threshold", perhaps slightly below 50%, "like any other" PD-1+Tigit
Anti-PD-(L)1 + Tigit + A2a/A2b ORR	NA	NA	"Encouraging, met internal threshold", perhaps above 50%, "truly differentiated"
*ORR=overall remission rate. *Merck's ph1 study has no Keytruda comparator, but Opdivo and Keytruda monotherapy have yielded ORRs of 37-45% in 1st-line, PD-L1 ≥50% NSCLC.*			

The Arc-7 result had been keenly awaited not only because of Gilead's possible opt-in, but also because domvanalimab is an Fc-inactivated antibody, and investors wanted to see what difference this approach made.

Most other anti-Tigit projects have functioning or even enhanced Fc regions, though Compugen has played up its Fc-silent contender, COM902. Until actual data are reported the matter remains unresolved, though proponents of Fc silencing will not be cheered by Arcus yesterday saying it was "very quickly" advancing its own Fc-active anti-Tigit, AB308.

The CD226 axis

Compugen's other claim to fame is its combination of Tigit with PVRIG blockade, via its anti-PVRIG MAb COM701. The thinking is that Tigit is part of the so-called CD226 axis that also includes PVRIG and a third protein, CD96/Tactile, and all three should be hit for maximal efficacy.

All this will be highly relevant to Glaxosmithkline, which last week paid $625m up front for rights to Iteos's Fc-active anti-Tigit MAb EOS-448. Glaxo has made much of already having an anti-PVRIG, SRF813, licensed last year from Surface Oncology, and an anti-CD96 MAb, GSK6097608, derived from a 2018 research collaboration with 23andme.

It is likely that Glaxo will pursue double and triple combos, though for now EOS-448 remains in a phase 1 monotherapy trial in which it has yielded one remission among 20 patients. At yesterday's investor event Glaxo's chief scientific officer, Hal Barron, said: "Tigit plus a PD-1 could be IO version 2.0."

He added that the antibody's "Fc portion has to be enabled. We will be informed not only by our own data but also by competitor data [as to] whether this Fc competency issue will end up differentiating." After Arcus's non-disclosure the debate continues.