Evaluate Vantage

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Looking beyond Roche’s Tigit bombshell

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The failure of Skyscraper-01 calls into question Roche’s vast investment in Tigit blockade, but is there broader significance?

Boom! That was the sound of another immuno-oncology mechanism blowing up. In fairness, it would be premature to say with certainty that today’s failure of Roche’s tiragolumab in the Skyscraper-01 trial – one of 2022’s biggest catalysts – is the death knell for Tigit blockade, but it surely is not a good sign.

Judging by the market’s early reaction, investors in Arcus and Iteos, two players with large exposure to Tigit, fear that this mechanism will soon join IDO and IL-2 among immuno-oncology’s expensive flops. Here, *Evaluate Vantage* has tried to cut through the hubris and assess what is known and what is not, and what this all means.

What do we know?

In Skyscraper-01, in PD-L1-high front-line NSCLC patients, tiragolumab plus Tecentriq failed to beat Tecentriq in terms of progression-free survival, although there was a numerical benefit. Analysis of overall survival, the co-primary endpoint, is immature. This is the second pivotal trial in the Skyscraper programme to fail, with eight more yet to read out.

Were there any warning signs?

The failure of Skyscraper-02 was one, though this was easily dismissed given the intractable nature of SCLC. There were three other, bigger canaries in the coalmine, all from the Cityscape study that also tested Roche’s combo against Tecentriq in first-line NSCLC.

This did show tiragolumab adding efficacy in terms of remissions and PFS over Tecentriq, but only in high PD-L1 expressers; the effect was flattered by Tecentriq monotherapy underperforming versus the Impower-110 trial; and there was no link between efficacy and Tigit expression. Ultimately, these facts cast doubt over what Tigit blockade was bringing to the party.

So what was Roche thinking when it embarked on this massive programme?

When in January 2020 Roche quietly put tiragolumab into the first of 10 Skyscraper studies investors assumed that it must have had convincing data in house. However, beyond the subsequent Cityscape results, with the drawbacks outlined above, little else has emerged to back the enthusiasm for a programme that currently has an enrolment target of 8,365 patients.

Are there any positives?

The lack of statistical significance despite a numerical improvement suggests that Skyscraper-01 might have been underpowered, and the lack of a PFS benefit need not translate into a fail on overall survival. A setback in lung cancers does not necessarily mean that tiragolumab is a bust in other settings, and each anti-Tigit MAb works slightly differently.

How bad are the omens for other Tigit projects?

Full Skyscraper-01 data are needed before drawing firm conclusions, but things do not look great, especially as no other Tigit player has been able to rival Roche's earlier Cityscape dataset, or show meaningful single-agent activity. On the other hand, not all Tigit MAbs are alike, with differences in binding sites, IgG type and Fc functionality.

Clinical-stage projects targeting Tigit				
Project	**Company**	**MAb type**	**Key study**	**Total enrolment target**
Phase 3				
Tiragolumab	Roche	IgG1, Fc active	Skyscraper-01 (failed)	8,365
Vibostolimab	Merck & Co	IgG1, Fc active	Keyvibe-003	5,331
Ociperlimab	Novartis/ Beigene	IgG1, Fc active	NCT04866017	2,892
Domvanalimab	Gilead/ Arcus	IgG1, Fc silent	Arc-7 (ph2)	1,932
Phase 2				
EOS-448	Glaxosmithkline/ Iteos	IgG1, Fc active	NCT03739710	841
BMS-986207	Bristol Myers Squibb	IgG1, Fc silent	NCT05005273	657
Phase 1/2				
Etigilimab	Mereo (ex Oncomed; Celgene turned down option)	IgG1, Fc active	NCT04761198	158
AZD2936	Astrazeneca (ex Compugen)	IgG4, PD-1 bispecific	Artemide-01	147
Phase 1				
SGN-TGT	Seagen	IgG1, Fc enhanced	NCT04254107	397
JS006	Coherus/ Junshi	IgG4, incl Fc silent & active molecules	NCT05061628	384
IBI939	Innovent	?	NCT04353830	332
M6223	Merck KGaA	IgG1, Fc active	Javelin Bladder Medley	287
AB308	Arcus	IgG1, Fc active	NCT04772989	160
COM902	Compugen	IgG4, Fc silent	NCT04354246	90
AGEN1777	Bristol Myers Squibb/ Agenus	Fc enhanced bispecific	NCT05025085	75
Source: Evaluate Pharma & clinicaltrials.gov.				

Which companies are the most exposed?

Arcus, Iteos and Compugen offer nearly pure-play exposure to Tigit, and today opened off 29%, 19% and 3% respectively.

But it is also important to remember that several big biopharma business development departments will be feeling the heat. Gilead handed across $750m to Arcus last November, after Glaxo paid $625m for Iteos's EOS-448; later Novartis paid $300m for an option on Beigene's ociperlimab.

Among in-house assets Merck & Co has vibostolimab in the pivotal Keyvibe programme, some of whose studies mirror the design of the Skyscraper trials, and which is seeking to enrol 5,331 patients in total.

What data should investors look to next?

Before Roche reports full data from Skyscraper-01 investors will be able to scrutinise the failed Skyscraper-02 study, courtesy of an Asco late-breaker on June 5 (LBA8507). At a stroke this has been transformed into one of Asco's key presentations, given that it might shed light on this morning's failure and on Tigit blockade in general.

After that it will be the turn of the industry's next-biggest Tigit catalyst – data from Arcus/Gilead's domvanalimab in Arc-7, a first-line NSCLC study with a broadly similar design to Skyscraper-01 and Keyvibe-003. However, after three opaque updates it is anyone's guess how much data will actually be revealed.

Given the history of disastrous biz dev moves under Gilead's belt, that company's chief executive, Daniel O'Day, will today be sitting very nervously.