Evaluate Vantage

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Arcus sets the hopes for Tigit in lung cancer

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As biopharma awaits Roche's pivotal Skyscraper-01 data Arcus gives its investors some more tea leaves to read.

Another set of quarterly financials from Arcus Biosciences has brought forth more promises about the group's Tigit study Arc-7. Though there is still little detail, the most important disclosure is that a third interim analysis has now taken place, and the dataset appears to be improving.

This will serve as an important catalyst for investors, who will now await actual data from Arc-7 in the second half – after Roche's own Tigit yields results from the similarly designed registrational Skyscraper-01 trial, whose success some are starting to question. Arcus's pronouncements on Arc-7's three analyses are opaque, but they have nevertheless set a clear benchmark that the company must meet to avoid disappointment.

Some might be frustrated at this dribbling out of information, and at the fact that Arcus has not held a publicly accessible investor webcast since last November. That coincided with Gilead licensing in the anti-Tigit MAb in question, domvanalimab, and seemingly imposing tight control over data disclosure.

Secrecy

Frustratingly, much secrecy surrounds not only domvanalimab but also Roche and Merck & Co's respective Tigit contenders tiragolumab and vibostolimab.

Arc-7 tests domvanalimab on top of Arcus's anti-PD-1 zimberelimab in first-line NSCLC with ≥50% PD-L1 expression. At its first interim analysis last June ORR was said to be "encouraging", while at the second look, which triggered Gilead's opt-in, the combo was "differentiated" versus zimberelimab monotherapy, which importantly was described as having "activity similar to other marketed anti-PD-1 antibodies in the setting".

Yesterday brought news that in a third analysis ORR for the Tigit/PD-1 doublet increased and separated further from zimberelimab. Response duration was measured for the first time, and this too showed improvement over zimberelimab, which was still showing activity consistent with marketed anti-PD-1s.

The last point is key to setting expectations. Merck's Keytruda as monotherapy in first-line NSCLC has shown ORR of 40-45% in ≥50% PD-L1 expressers in the Keynote-042 and 024 trials. Thus, for the domvanalimab combo to be differentiated and increasingly separating from PD-1 therapy the ORR should be well above 50%, and perhaps around 60%.

A separate question is whether this will be competitive against rival Tigits. Tiragolumab's phase 2 Cityscape study showed a 66% ORR in combination with Tecentriq in this set of patients, so this will set another

benchmark.

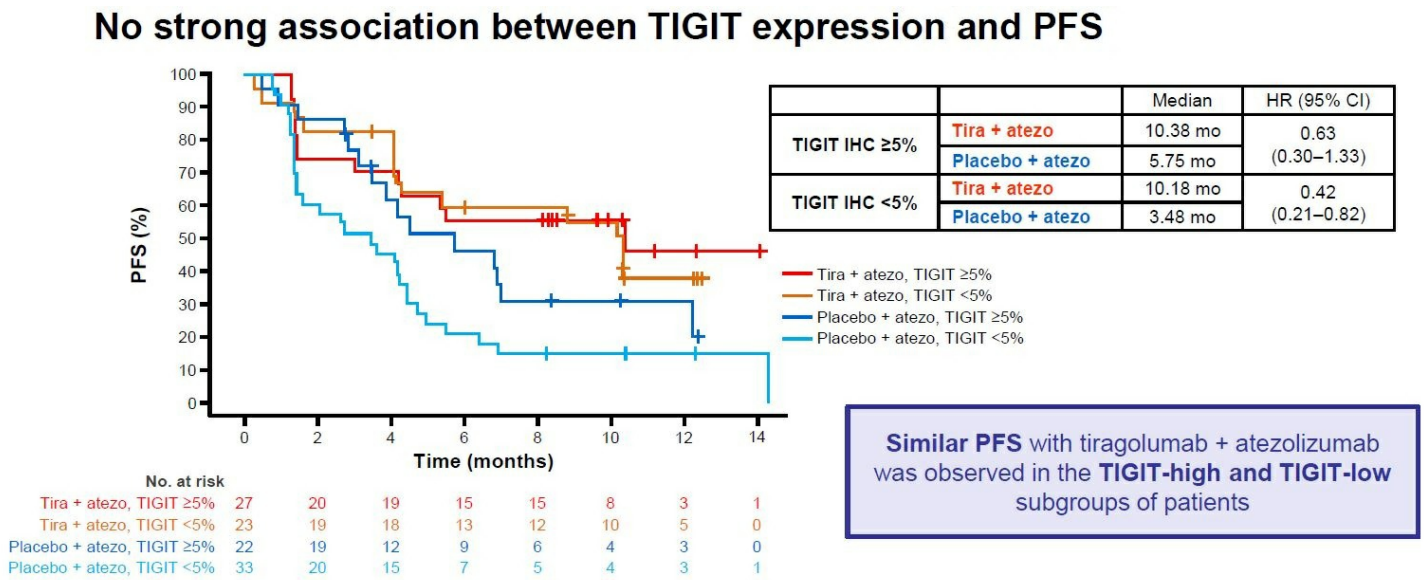
Selected studies in 1st-line NSCLC				
Company	Roche		Arcus/Gilead	Merck & Co
PD-(L)1 + Tigit combo	Tecentriq + tiragolumab		Zimberelimab + domvanalimab	Keytruda + vibostolimab
Trial	Cityscape	Skyscraper-01	Arc-7	Keyvibe-003
PD-L1 expression	≥1%	"High"	≥50%	≥1%
ORR	66% vs 24% in ≥50% PD-L1	Secondary endpoint	Increasingly separating vs PD-1 monoRx	Secondary endpoint
mPFS	HR=0.30 in ≥50% PD-L1	Co-primary endpoint	Co-primary endpoint	Co-primary in ≥1% PD-L1 Co-primary in ≥50% PD-L1
mOS	HR=0.23 in ≥50% PD-L1	Co-primary endpoint	Secondary endpoint	Co-primary in ≥50% PD-L1 Co-primary in ≥1% PD-L1 Co-primary in 1-49% PD-L1
Source: company presentations, Asco, Esmo & World Lung.				

Importantly, it also sets a benchmark for Roche's own pivotal Skyscraper-01 trial, which is due to read out by the mid-year. The comparator here is also Tecentriq monotherapy, and some analysts have been pointing out that looking to Cityscape to handicap Skyscraper-01 is flawed, since Tecentriq appeared to underperform in the former trial.

Then the monotherapy yielded ORR of just 24%, and median PFS of around four months – significantly lower than the 38% and eight months seen in the Impower-110 study, also in ≥50% PD-L1 expressers.

Moreover, a fairly obscure presentation from the 2020 World Lung conference showed that median PFS for tiragolumab plus Tecentriq was around 10 months irrespective of whether patients were Tigit-low or high. Summing up the argument of the tiragolumab naysayers, Wells Fargo's Mohit Bansal yesterday wrote: "The fact there was virtually no difference makes us cautious of Tigit's contribution."

Some time after Arc-7 and Skyscraper-01 read out Merck's own contribution to the Tigit/PD-(L)1 combo debate will come in the form of data from the Keyvibe-003 trial of Keytruda plus vibostolimab. Though this study begun over a year ago absolutely no data from it have yet been revealed.



Analysis of Roche's Cityscape trial. Source: Dr Byoung Chul Cho & WCLC.