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Iteos – and GSK – keep the faith

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With Tigit out of favour Belgium's Iteos reckons it could have the best possible PD-(L)1 combo, but does GSK share its optimism?

The air is fast escaping the Tigit bubble, though some hope remains that Roche's Skyscraper-01 trial could yet show a survival benefit, and Gilead has repeatedly played up its Arc-7 study. A much smaller Tigit player, Belgium's Iteos, is far from giving up either.

In Iteos's favour is that its GSK-partnered project, recently christened belrestotug, is being combined with Jemperli, whose surprising win over Merck & Co's Keytruda in the Perla trial in December passed virtually unnoticed. "We have one of the best PD-1s in our studies, and a Tigit that's differentiated," Michel Detheux, Iteos's chief executive, tells *Evaluate Vantage*.

A big question, however, is whether GSK appreciates this point. GSK and Iteos have collaborated on belrestotug since 2021, but that deal was struck by Hal Barron, who as chief science officer drove GSK's oncology strategy, but who left the company a year ago.

Since then questions have been raised as to whether cancer is even a focus for GSK, with Reuters reporting that Tony Wood, Barron's replacement, was "de-emphasising" oncology. Not so, claims Iteos.

"I've been able to build with Tony Wood the relationship I'd had with Hal Barron," Detheux says. When Detheux raised concerns about the Reuters interview he got a response from Wood "in the middle of the night. He told me: 'We are investing massively in specific programmes in oncology, and Tigit is a top priority.'"

And Iteos's finance chief, Matthew Gall, a member of the group steering Tigit work with GSK, tells *Vantage* that there is always the risk that a big pharma partner is not fully committed, but "that's not what we feel when we're in a room with GSK".

No exit

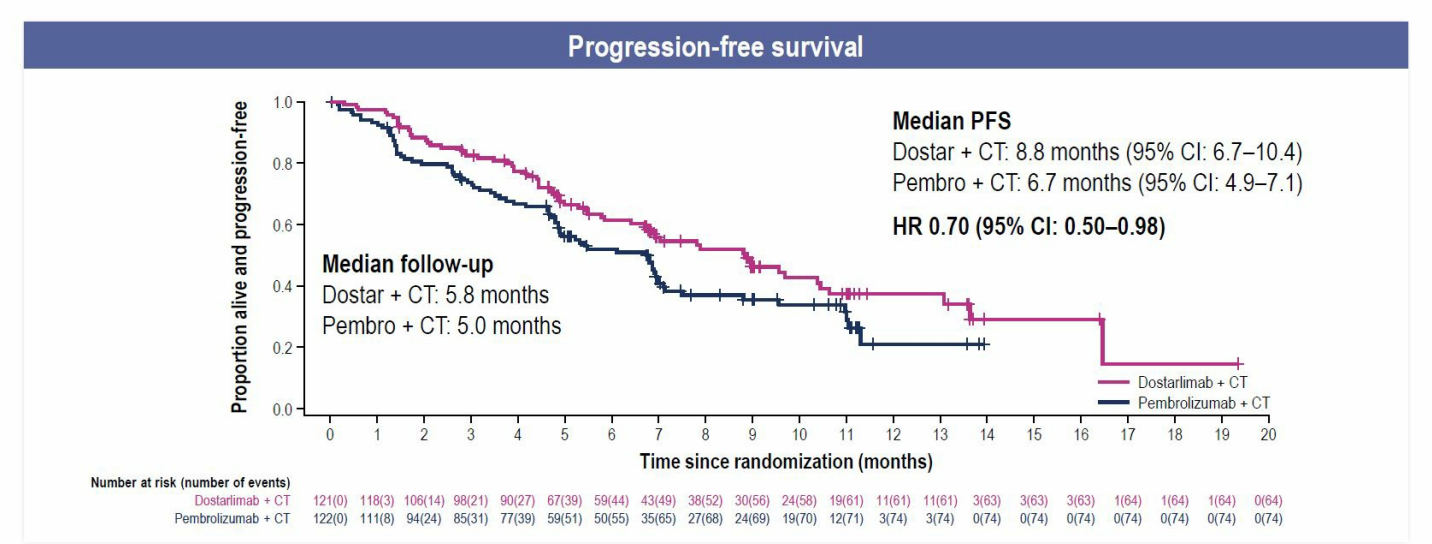
For its part GSK too denies the suggestion that it is exiting cancer. Wood "said he was just going to talk about [oncology] less", GSK's head of business development, Chris Sheldon, told last week's LSX Congress in London. "And I think those comments were interpreted as oncology being deprioritised; no, far from it."

Sheldon added that MAbs, including ADCs and T-cell engagers, remained a business development focus in immuno-oncology for GSK, and that it was more complex modalities like radiopharmaceuticals and cell therapies that would become a lower priority.

Still, since GSK and Iteos tied up things have hardly moved at breakneck speed. While rival anti-Tigit MAbs are the subject of 16 pivotal studies, and Roche and Merck have hugely expanded their programmes, belrestotug remains in mid-stage development, notwithstanding plans to start a phase 3 Jemperli combo trial this year.

This suggests an odd reluctance on the part of a big pharma company that, according to data quietly revealed last December, might have one of the best anti-PD-(L)1 MAbs on its hands.

At the Esmo Immuno-oncology congress Perla, a small first-line NSCLC trial pitting chemo combos of Jemperli versus Keytruda, met its aim of showing similar ORRs. However, Jemperli numerically beat Keytruda on ORR, 46% versus 37%, and on PFS too, yielding a 30% reduction in risk of progression or death versus the Merck drug; though Perla was not designed to show superiority the differences were striking.



Investigator-assessed PFS data in Perla. Source: Dr Solange Peters & Esmo Immuno-oncology congress.

As for the other half of the combo, Detheux says belrestotug is differentiated because it engages Fcγ receptors, promoting depletion of T regulatory cells, which damp down immune response. A belrestotug trial showing hints of monotherapy activity (5% ORR in 20 patients) demonstrated day-28 Treg reduction of around 80% from baseline across all doses tested.

Such considerations are important given that Roche looks like it has an underwhelming Tigit MAb and a good PD-L1, while conversely Gilead/Arcus have an active Tigit but a poor PD-1 MAb; for Merck's Tigit the jury is still out.

2023 catalyst

Of course, any suggestion of Iteos/GSK being best in class has yet to be tested clinically. For now the most important belrestotug study is '378, a Jemperli combo in first-line NSCLC patients with ≥50% PD-L1 expression, due to yield its first data around the year end. Though this is a phase 2 trial it has a Keytruda control arm, so the comparison – response and PFS data are expected in the first instance – will give an important pointer.

Detheux says the data will not inform the start of phase 3, which is in preparation already. Interestingly, he also rejects Merck's claim that studying PD-1 plus Tigit in ≥1% PD-L1 expressers, as the Keyvibe-003 study does, raises the odds of success; most PD-L1 1-49% expressers are treated not with Keytruda monotherapy but with chemo combo, he claims.

Ultimately, Detheux plays down the perception that Tigit as a mechanism has failed. Looking only at phase 2 and 3 he says "we've seen two positive readouts ... one that is inconclusive ... and two negative readouts in long shots. This is all we have today."

Roche's Skyscraper-01 data "will be impactful", the chief exec says. "But we are not going to define the future of our programme based on the readout. If the most advanced competitor derails that's not the worst situation for us if we're convinced that we are differentiated."

On Roche's first-quarter call the Swiss group's new head of pharmaceuticals, Teresa Graham, said the Tigit story was far from fully written, and it seems that Iteos agrees.

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