Evaluate Vantage

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Agenus investors wake up to inevitability

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The stock crashed on Friday as balstilimab's US filing was pulled – an event that had been entirely foreseeable.

Ever since Merck & Co's Keynote-826 cervical cancer study of Keytruda read out positively in September an FDA rejection had been staring Agenus in the face, as *Evaluate Vantage* had stressed at the time.

Yet when the inevitable train crash happened on Friday – Agenus confirmed that it was withdrawing its accelerated approval filing for balstilimab in this cancer – its stock fell 22%. Perhaps some investors had been betting on not selling the shares until just before the December 16 Pdufa date, in which case the withdrawal would have come as an early shock.

Then again, maybe Agenus shareholders just refused to accept facts. Either way the company is now in serious difficulties. True, balstilimab monotherapy was never going to be a huge part of Agenus's business, but the group needed a single-agent approval in any setting just to get it to market, before focusing on more lucrative labels in combination with either of the group's two novel anti-CTLA-4 MAbs.

"Technicality"

On Friday Agenus's chief executive, Garo Armen, attacked the FDA, claiming that its recommendation that Agenus pull balstilimab's filing was based on a "technicality", and that such regulatory action was "unreasonable".

In reality, however, the agency had acted in accordance with standard practice. The matter centres on the approval of Keytruda, four months ahead of schedule, on a formal basis, in second-line cervical cancer, the same indication for which Agenus was seeking an accelerated green light.

Keytruda's accelerated approval for this use had been based on remission rates in the uncontrolled Keynote-158 trial, in 2018. The randomised Keynote-826, though in the first-line setting, was a confirmatory study, so its subsequent positive readout backed a front-line label, granted on October 13, as well as formalising second-line use.

And, with Keytruda on the market with a full, second-line approval, it was no longer appropriate for the agency to consider approving a rival on the basis of remission rates under an accelerated procedure. The fact that Merck had generated no randomised second-line data appears to be the technicality here, but this matters little: front-line trials are often used to convert second-line accelerated approvals into full green lights.

PD-L1 negatives?

Mr Armen also argued that in uncontrolled trials balstilimab had shown some activity in PD-L1-negative patients (8% ORR) whereas Keytruda had shown none. However the numbers here were so small that the FDA refused to consider reviewing balstilimab only in PD-L1 non-expressing cervical cancer.

In fact, the situation was threatening to become more complex still, with Sanofi and Regeneron on September 28 revealing the filing of Libtayo for second-line cervical cancer. Notably this was based on survival data from a controlled trial, Empower-Cervical 1, where Libtayo showed an overall survival benefit versus chemo alone.

The FDA has set January 30 as the action date for this Libtayo filing. In the meantime Agenus has discontinued Brava, a potentially confirmatory phase 3 cervical cancer study, and it now has until its November 9 third-quarter call to come up with a new plan for getting balstilimab combos to market.

All these developments are also relevant for Iovance, whose TIL project lifileucel had impressed in an uncontrolled trial in cervical cancer that was thought likely to lead to an accelerated approval filing. That said, Iovance probably has bigger problems that it must sort out first.

Selected immunotherapies in cervical cancer

Project	Setting	Trial	Result
Keytruda (Merck & Co)	2nd-line	Keynote-158 cohort E	14% ORR (9 PRs, 2 CRs)
	1st-line (chemo combo, +/- Avastin)	Keynote-826 (all-comers)	mOS 24.4 vs 16.5 mth (HR=0.67, p<0.001)
		Keynote-826 (PD-L1 ≥1%)	mOS NR vs 16.3 mth (HR=0.64, p<0.001)
Libtayo (Sanofi/Regeneron)	2nd-line	Empower-Cervical-1	mOS 12.o vs 8.5 mth (HR=0.69, p<0.001)
Balstilimab (Agenus)	2nd-line	NCT03495882	14% ORR (24 PRs, 3 CRs)
	2nd-line (confirmatory)	Brava	Trial discontinued
Bintrafusp alfa (Merck KGaA)	2nd-line	Intr@pid Cervical 017	Uncontrolled trial, ends Apr 2022

Source: Esmo, Evaluate Pharma & prescribing information.