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Asco 2023 – Regeneron nips at Bristol's heels in Lag3

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Fianlimab continues to look like biopharma's leading Lag3 asset, with activity in a new melanoma setting to boot.

With interest in the Lag3 mechanism recently piqued by lung cancer data on Immutep's eftilagimod alpha, Regeneron is working hard to stay ahead of the pursuing pack. And data just unveiled in an Asco abstract confirm the leading activity of its contender, fianlimab.

That molecule's Libtayo combo had already impressed at last year's Esmo meeting, with 64% ORR in front-line melanoma beating Bristol Myers Squibb's Opdualag across trials. But the Asco data are intriguing for another reason: fianlimab plus Libtayo appears active in melanoma patients who have already progressed on PD-(L)1 blockade in the perioperative setting.

In earlier iterations of this dataset "we couldn't believe how good the results were", Israel Lowy, Regeneron's senior vice-president of oncology translational and clinical sciences, tells *Evaluate Vantage*. And now his optimism is holding up: "I don't know why our efficacy is better than Bristol's, but we'll take it."

Small but important

True, the additional results comprise a small subset of just 13 of the 98 patients in the fianlimab phase 1 study in question.

But this is nevertheless an important group, as all 13 had received anti-PD-(L)1 in the neoadjuvant or adjuvant setting but subsequently relapsed. Yet eight of the 13 responded to fianlimab plus Libtayo, including one complete remission, with an estimated median PFS of 11.8 months, according to a just unveiled abstract that will likely be updated further at Asco.

At Esmo Regeneron reported a 64% ORR among 80 purely first-line melanoma subjects, and not only is this seen holding up across all 98, "we're seeing the same high level of efficacy" in the relapsed patients, says Lowy. Median PFS across the trial stands at 15.3 months; though this is lower than Esmo's 24 months that number looked unreliable, and in any case on a cross-trial basis the data look better than the 10.1 months on Opdualag's label.

Apart from differences between MAb design, one fact that could explain Regeneron's efficacy is that fianlimab has been dosed up to 1.6g every three weeks, with the only relevant added tox being "low-grade and easily managed" adrenal insufficiency. In contrast, the dose of Bristol's anti-Lag3 relatlimab in the Opdualag combo is

160mg every four weeks.

Fianlimab + Libtayo in 1st-line melanoma		
	All patients	Patients progressed on PD-(L)1 exposed in (neo)adj setting
Number enrolled	98	13
ORR	61.2%	61.5%
mPFS	15.3mth	11.8mth
Discontinuations due to TRAEs	16.3%	NA
Source: Asco abstract with 1 Nov 2022 cutoff.		

It is hard to find a comparator for the PD-(L)1-relapsed data, but Lowy says: “We’re providing data that says ... you can get a fresh benefit. It’s as if you had reset, and you were functionally PD-(L)1 naive.” And it does have to be the combo: fianlimab monotherapy, a separate cohort of the phase 1 trial, has not yielded meaningful activity, in line with the preclinical science and with others’ experience.

Fixed dose?

Two phase 3 melanoma studies of fianlimab plus Libtayo, one front line and the other in the adjuvant setting, are under way against Merck & Co’s Keytruda, and should yield data in 2025. There are also phase 2/3 trials in first-line NSCLC adding fianlimab on top of Libtayo (in PD-L1 ≥50% expressers) and on top of Libtayo and chemo.

If pivotal studies yield a registrational dataset a further consideration will be how to combine fianlimab and Libtayo. Bristol notably launched relatlimab plus Opdivo as part of the Opdualag fixed-dose combo, and Lowy says Regeneron “would anticipate having such a fixed-dose formulation available at the time of launch. There are multiple advantages.”

With numerous other competitors on its heels, not least Merck’s own favezelimab, it is key for Regeneron to keep posting sector-leading data. One thing Lowy is sure about is that fianlimab, a straight MAb, will be better than the sorts of Lag3 x PD-1 bispecifics being investigated for instance by Macrogenics (tebotelimab) and Roche (RO7247669).

“We’ve thought about that,” he says. “If you’re targeting two different antigens on the same cell surface you have to figure out what the right balance of affinities is, and you’re always stuck with one combination there. [For Lag3 x PD-1] we haven’t been convinced preclinically that the data made sense.”

Regeneron is due to present the fianlimab data at Asco on Monday 5 June.