Evaluate Vantage

September 13, 2022

Esmo 2022 – Regeneron stakes its Lag3 claim

Jacob Plieth

Fianlimab maintains its leading activity, but more Opdualag competition is not far behind.

Bristol Myers Squibb got to the market first with relatlimab, but competition in Lag3 blockade is slowly mounting. At Esmo Regeneron nailed its colours to the mast, claiming efficacy for its anti-Lag3 MAb fianlimab, combined with Libtayo, that on a cross-trial basis exceeded that of Bristol's Opdualag.

Notably this was in front-line melanoma, the indication in which Bristol markets Opdualag, a fixed-dose combo of relatlimab and Opdivo. Melanoma is well served by immuno-oncology, something acknowledged by the other most advanced Lag3 player, Merck & Co, which is instead running pivotal studies of favezelimab in Hodgkin's and colorectal cancers.

Like Bristol and Regeneron, Merck is combining its Lag3 offering with an in-house anti-PD-(L)1, namely Keytruda. This is the case with all earlier-stage assets too, Opdualag seemingly having set a blueprint for biopharma to follow in terms of building intellectual property protection.

Fianlimab

Regeneron's fianlimab had already shown promising signs of efficacy at 2021's Asco meeting, where an initial 33 PD-(L)1 inhibitor-naive melanoma patients given a Libtayo combo yielded a 64% overall remission rate by investigator review.

At Esmo over the weekend Regeneron updated efficacy in these and seven additional patients, as well as presenting data in a further 40 subjects in a separate treatment-naive melanoma cohort. Together these yielded a 64% ORR, which on a cross-trial basis beat the 43% in Bristol's registrational Relativity-047 trial, though this number had been assessed by more robust independent review.

Regeneron also provided an analysis estimating that median progression-free survival was 24 months, seemingly far superior to the 10.1 months in Opdualag's label. However, caution must be used here: the survival curve for fianlimab plus Libtayo is heavily censored, and with just a few more early events the median could easily halve.

But there is no denying that Regeneron has a promising pipeline project on its hands. Not long ago it started a pivotal front-line melanoma trial, and says it is planning a second in the adjuvant setting. The group also recently took control of Libtayo from its partner, Sanofi.

Cross-trial comparison in 1st-line melanoma					
Project	**Trial**	**ORR***	**mPFS**	**Grade ≥3 AEs^**	**AE-related discontinuation**
Opdualag vs Opdivo	Relativity-047	43% vs 33%	10.1mth vs 4.6mth (HR=0.75)	40%	18%
Fianlimab + Libtayo	NCT03005782	64%	24mth**	20%	15%
*Notes: *by independent review for Opdualag, and investigator-assessed for fianlimab; **cross-trial comparison not appropriate owing to extensive censoring of PFS curve; ^rate of treatment-related AEs leading to death was 0.8% for Opdualag, and 2.5% for fianlimab. Source: prescribing information & Esmo.*					

Merck had also reported initial favezelimab data at last year's Asco, in late-line microsatellite-stable colorectal cancer, where the activity it saw was mostly in PD-L1-positive patients.

Favezelimab plus Keytruda is now in phase 3 in relapsed PD-L1-positive colorectal cancer, and in relapsed/refractory Hodgkin lymphoma. As for melanoma, Merck is running the phase 1/2 Keymaker-U02 trial, whose "substudy 02C" recruits stage III melanoma patients who are candidates for neoadjuvant therapy, and one of the many combos it tests is favezelimab plus Keytruda.

Selected R&D projects with activity at Lag3		
Project	**Company**	**Status**
Anti-Lag3 MAbs		
Favezelimab (MK-4280)	Merck & Co	Ph3 Keytruda combo for r/r Hodgkin lymphoma
		Ph3 Keytruda combo for 2nd-line PD-L1+ve colorectal cancer
Fianlimab (REGN3767)	Regeneron	Ph3 Libtayo combo for 1st-line melanoma
INCAGN2385	Incyte	Ph2 retifanlimab combo
BI 754111	Boehringer Ingelheim	Ph2 BI 754091 combo
LBL-007	Beigene/Leads Biolabs	Ph1/2 tislelizumab combo
Encelimab (TSR-033)	GSK/Anaptysbio	Ph1 solid tumours
IBI110	Innovent Biologics	Various ph1 trials
Sym022	Symphogen	Various ph1 trials
HLX26	Shanghai Henlius/Fosun	Ph1 HLX10 combo
Anti-Lag3 x PD-1 bispecific MAbs		
Tebotelimab	Macrogenics/Zai Lab	Ph2/3 combos in Her2+ve gastric cancer
RO7247669/ RG6139	Roche	Ph2 vs Opdivo in squamous oesophageal carcinoma
EMB-02	Epimab Biotherapeutics	Ph1/2 solid tumours
FS118	F-star Therapeutics	Ph1/2
IBI323	Innovent Biologics	Ph1
Source: Evaluate Pharma & clinicaltrials.gov.		

Among competitors Immutep's ieramilimab is notable for having relied on another company to provide the PD-1 part of a combo – being the subject of a deal with Novartis. However, that PD-1 was spartalizumab, which the Swiss firm has since deprioritised in favour of the Beigene-derived tislelizumab.

The pipeline is notable also for including several projects that combine Lag3 with PD-1 blockade in a single, bispecific MAb. It includes Macrogenics' tebotelimab, and RG6139, an asset about which Roche has so far said relatively little.

And Esmo also featured a poster on another anti-Lag3 MAb, Incyte's INCAGN02385. This concerned a monotherapy trial in solid tumour patients in the salvage setting, and the company was unable to report anything beyond stable diseases.

Nevertheless, Incyte boasted of good tolerability, linear pharmacokinetics and promising receptor occupancy, on the basis of which it selected 350mg once every two weeks as the dose for mid-stage studies in combination with retifanlimab.