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No plain sailing for Novartis’s PD-1 plan

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Getting the Swiss firm’s Beigene-derived anti-PD-1 MAb across the US finish line is proving harder than expected.

Over a year after ditching its own anti-PD-1 MAb spartalizumab in favour of Beigene’s tislelizumab, Novartis still cannot get the latter across the US regulatory finish line. Last week the FDA delayed a decision in oesophageal cancer, and today came the news that a lung cancer filing would not be pursued with tislelizumab monotherapy.

Though there are other factors at play here than the US non-approvability of an asset originated in China – an issue that hit Lilly/Innovent’s sintilimab at a blistering adcom in February – the markets are jittery about such a possibility. When tislelizumab’s July 12 Pdufa date was missed Beigene fell 5%.

Beigene accepts that some of its trials might be “a little more weighted towards China” than competitors’. But it has long argued that it can tick the US regulatory boxes, and its chief medical officer for solid tumours, Mark Lanasa, told *Evaluate Vantage* at Asco that most of its tislelizumab studies were “global. We should still meet the bar for multi-regional trials.”

The project’s first US indication was to have been second-line oesophageal squamous cell carcinoma, a setting where Bristol Myers Squibb’s Opdivo and Merck & Co’s Keytruda are already approved. Last week, however, Beigene said the FDA had been unable to carry out Chinese facility inspections owing to Covid-related travel restrictions.

The agency’s action date was thus deferred without a new Pdufa date being set. The filing is based on the global Rationale-302 trial; a separate global trial of a front-line chemo combo, Rationale-306, was toplined positive for overall survival in April, and “we’re hopeful that the FDA will be interested in that dataset as well”, Mr Lanasa had told *Vantage*.

Broader indication

The setback for Lilly/Innovent’s sintilimab concerned a broader indication, NSCLC, and here too Novartis’s plans have changed following what the group today called “FDA feedback”.

Until recently the plan had been to position tislelizumab initially as a second-line therapy, backed by the Rationale-303 study. However, in its second-quarter update Novartis said a US filing as monotherapy here would no longer be undertaken, and on an analyst call it added that the FDA said Rationale-303, run in central and south America, China and Eastern Europe, did not adequately reflect the US population and standard of

care.

In the EU the plan is different, a second-line NSCLC filing having been accepted by the EMA along with applications for three other settings, in April. Mr Lanasa said there were still sufficient numbers of immuno-oncology-naive patients in the EU to make second-line NSCLC viable for tislelizumab.

First-line NSCLC, the use in which sintilimab was knocked back, is now the domain of combinations. Here, Beigene is banking for instance on the Advantig-302 trial of tislelizumab plus the anti-Tigit MAb ociperlimab, which has Keytruda as comparator and also includes an ociperlimab-only cohort; this looks at PD-L1 ≥50% expressers, Mr Lanasa said, the same setting in which Roche's tiragolumab failed in Skyscraper-01.

Selected indications for tislelizumab (trademarked Baizean in China)				
		Regulatory status		
Study	**Setting**	**EU**	**US**	**China**
Rationale-301	1st-line hepatocellular carcinoma	–	Filing planned 2023	–
Rationale-302	2nd-line oesophageal sq cell carcinoma	Filing accepted Apr 2022	July 12 Pdufa date deferred	Approved Apr 2022
Rationale-303	2nd-line NSCLC	Filing accepted Apr 2022	Filing plan abandoned	Approved Jan 2022
Rationale-304	1st-line non-sq NSCLC	Filing accepted Apr 2022 (NB China study)	–	Approved Jun 2021
Rationale-305	1st-line PD-L1 +ve gastric/GEJ adeno	–	Filing due 2023	Filing accepted 21 Jun 2022
Rationale-306	1st-line oesophageal sq cell carcinoma	–	Filing planned 2023	–
Rationale-307	1st-line sq NSCLC	Filing accepted Apr 2022 (NB China study)	–	Approved Jan 2021
Rationale-309	1st-line nasopharyngeal cancer	–	Filing due H2 2022	Approved Jun 2022
Rationale-312	1st-line SCLC	–	Filing due 2024 (NB China study)	–
Rationale-203	3rd-line classical Hodgkin's lymphoma	–	–	Approved Dec2019
Rationale-204	2nd-line PD-L1+ve urothelial carcinoma	–	–	Approved Apr 2020
Rationale-208	2nd-line liver cancer	–	–	Approved Jun 2021
Rationale-209	2nd-line MSI-H/dMMR solid tumours	–	–	Approved Mar 2022
Source: Beigene & Evaluate Vantage.				

Other pipeline moves disclosed today by Novartis include the decision to seek partners for CPK850, CSJ117 and LJN452 following an annual portfolio review.

CSJ117, an anti-TSLP MAb for asthma, was notable for sharing its mechanism with Amgen/Astrazeneca's recently launched Tezspire, and there might have been commercial concerns that the market for these asthma biologicals could not sustain more than one drug. Keymed, Biosion, and companies developing inhibitors of the related IL7R-α, will take note.

Meanwhile, in 2020 Novartis sold the Nash project LLF580, an FGF21 stimulator, to Boston Pharmaceuticals, instead putting LJN452, a combo including the FXR agonist tropifexor, at the heart of its strategy in the elusive liver disease.

LJN452 now appears to have bitten the dust, and instead Novartis's clinical Nash pipeline comprises just one asset, FIA586, which is in phase 1 and is described only as having an undisclosed anti-inflammatory mechanism.

Assets to be partnered, following Novartis annual portfolio review				
Project	**Indication**	**Mechanism**	**Ph2 trial**	**Note**
CPK850	Retinitis pigmentosa	RLBP 1 gene therapy	NCT03374657	Reneuron stem cell therapy failed in Jan 2022
CSJ117	Asthma	Anti-TSLP MAb	NCT04410523	Same MoA as Amgen/Astra Tezspire; Keymed's CM326 is in ph1/2; Biosion's BSI045B is in ph1
LJN452 (tropifexor + licogliflozin)	Nash	FXR agonist + SGLT1/2 inhibitor	NCT04065841	Was Novartis's Nash focus after LLF580/BOS-580 was licensed to Boston Pharmaceuticals
Source: Novartis Q2 2022 report.				