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Days of reckoning for immune checkpoint blockers

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Can a trial carried out in China back a US approval? Investors in anti-PD-(L)1 players will find out soon enough.

Innovent/Lilly's sintilimab faces a major catalyst on February 10. Its US advisory committee meeting, a rarity for an anti-PD-(L)1 antibody, represents a binary outcome not only for sintilimab but also for other me-too checkpoint MAbs whose makers are using data generated in China to back US approval.

The New Year will also soon see the FDA rule on a new use for Bristol Myers Squibb's Opdivo – in combination with relatlimab, an anti-Lag3 MAb seeking to become only the third approved type of checkpoint blocking mechanism. However, a much broader issue is the future of the low-cost anti-PD-(L)1 market, for which the the sintilimab adcom is crucial.

The question over sintilimab centres on recent proclamations by Richard Pazdur, the director of the FDA's Oncology Center of Excellence. Back in 2019 he had told *Biocentury* that anti-PD-(L)1 drugs developed by Chinese companies "could potentially be a great thing for everyone because we haven't seen the major western pharmaceutical companies moving on price".

With six PD-(L)1s available in the US at that time this was taken as a call for price competition, and several deals were struck to bring this about, most notably between Cstone and EQRx. However, in an *NEJM* piece last month entitled "the Wild West of checkpoint inhibitor development", Mr Pazdur seemed to have a change of heart, opining that US head-to-head studies would "probably be required" to back use in approved indications.

Bye bye, sintilimab?

If this is the case then sintilimab, a drug already marketed as Tyvyt in China, could be set for a long delay in the US. The indication sought by Innovent and Lilly is first-line non-squamous NSCLC as a chemo combo, a setting in which Keytruda's availability is backed by the Keynote-189 study.

But the corresponding sintilimab trial, Orient-11, was conducted entirely in China, and while it did show a survival benefit the comparator was not Keytruda but chemo alone. Wells Fargo analysts say the upcoming adcom is a litmus test of study requirement, while Bernstein has predicted the likely end of the low-cost oncology model, and reckons Lilly will walk away from sintilimab if a comparator study is required.

What does this mean for other US latecomers? Akeso/Sino's penpulimab has been filed for third-line

nasopharyngeal carcinoma on the back of remission rates seen in an uncontrolled China study. In the same indication Coherus has initiated a rolling BLA for toripalimab based on Polaris-02, a trial also conducted only in China.

Beigene/Novartis's tislelizumab is awaiting US approval for second-line oesophageal squamous cell carcinoma, and at least its supporting study, Rationale-302, comprised hospitals in the US and Europe in addition to China, Taiwan and South Korea.

Those tracking the success of US adcoms will note the pasting that Incyte/Macrogenics received last June at a panel meeting for retifanlimab. This resulted in a negative vote and a complete response letter, pushing the project's approval back by years.

Selected US regulatory catalysts for anti-PD-(L)1 agents

Drug	Company	Date	Regulatory action	Key supporting trials
Libtayo	Sanofi/Regeneron	Jan 30, 2022	Pdufa date for 2nd-line cervical cancer	OS benefit in Empower-Cervical-1 study
Tyvyt (sintilimab)	Lilly/Innovent	Feb 10, 2022	Adcom for 1st-line non-squam NSCLC (Alimta combo)*	OS benefit in Orient-11 study (China only)
Opdivo + relatlimab	Bristol Myers Squibb	Mar 19, 2022	Pdufa date for 1st-line melanoma	PFS benefit in Relativity-047 study
Keytruda	Merck & Co	Mar 28, 2022	Pdufa date for 2nd-line MSI-H/dMMR endometrial cancer	ORR in Keynote-158 study cohorts D & K
Annik (penpulimab)	Akeso/Sino	H1 2022**	Pdufa date for 3rd-line nasopharyngeal carcinoma	ORR in China-only study
Tuoyi (toripalimab)	Coherus/Shanghai Junshi	H1 2022**	Filing acceptance for 3rd-line nasopharyngeal carcinoma	ORR in Polaris-02 study (China only)
Opdivo + Yervoy or chemo	Bristol Myers Squibb	May 28, 2022	Pdufa for 1st-line oesophageal squamous cell carcinoma	OS benefit in Checkmate-648 study
Baizean (tislelizumab)	Novartis/Beigene	12 Jul, 2022	Pdufa for 2nd-line oesophageal squamous cell carcinoma	OS benefit in Rationale-302 study

*Note: *Pdufa date is Mar 22, 2022; **assumed. Source: Asco, Esmo & company filings.*

Meanwhile, the anti-Lag3 MAb relatlimab looks set for approval as an Opdivo combo, given the strength of the Relativity-047 study; the Pdufa date is March 19, with no adcom. Companies with mid-stage anti-Lag3 MAbs in development include Immutep/Novartis, Incyte, Merck & Co, Boehringer Ingelheim, Regeneron and Macrogenics.

Before that Sanofi/Regeneron's Libtayo faces a US approval decision for second-line cervical cancer, with a January 30 action date. Those who had seen Agenus's balstilimab set back in this setting will note that, while balstilimab was backed by uncontrolled remission data, Libtayo has shown a survival benefit in a controlled trial, Empower-Cervical 1.

Libtayo also provides an interesting marker for those fretting about the acceptability of China-only studies. Its US approval a year ago in front-line NSCLC was backed by Empower-Lung-1, a trial comprising not a single US hospital.

The latest Evaluate Vantage report on development and catalysts in the PD-(L)1 space is available as a free download.

This story has been amended to correct an error in the table.

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