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No fast way to eighth place for Incyte

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Retifanlimab gets knocked back by a US adcom. Could a rival now beat it to become the eighth anti-PD-(L)1 to reach the US market?

After yesterday's advisory panel setkback Macrogenics/Incyte's retifanlimab looks unlikely to become the eighth anti-PD-(L)1 MAb to get US approval. This is despite being filed in squamous carcinoma of the anal canal, a niche indication with no approved checkpoint blockers.

Of course the FDA is not bound by the adcom's advice, but if it follows through it might not be until after 2024 that retifanlimab can be approved, at least in this chosen first indication. By that time there might be several more anti-PD-(L)1 drugs on the US market, though whether this will actually make any difference to their pricing is anyone's guess.

2024 is now a key date because it is when retifanlimab's Pod1um-303 study is due to yield topline data. It was readout of this confirmatory phase 3 trial that the adcom yesterday suggested, by a 13-4 vote, the FDA should await rather than giving retifanlimab an accelerated green light on the strength of its uncontrolled Pod1um-202 trial, as sought by Incyte's BLA.

Remission rate doubts

Pod1um-202 had yielded a 13.8% remission rate, including one CR, among 94 retifanlimab-treated subjects with chemo-refractory squamous carcinoma of the anal canal. Not only does this seem like a low ORR, the adcom's briefing docs called into question its accuracy, saying only three of the 13 responding patients had a rectal mass as a target lesion, as well as criticising the study's statistical powering.

Pod1um-303, meanwhile, seeks to enrol 300 subjects, and compares a retifanlimab-chemo combo versus chemo alone. It has PFS as primary endpoint, with OS the key secondary, but clinicaltrials.gov cites October 2024 as its primary completion date.

Assuming that this readout is now the gating factor for retifanlimab's approval, which other anti-PD-(L)1 projects could beat it to the US market? Remarkably there are four other such agents already in the regulatory filing process, and one, Agenus's balstilimab, faces an FDA action date of December 16.

Lilly's Innovent-derived sintilimab has a 2022 Pdufa date, while two other China-originated assets, Junshi's toripalimab and Akeso's virtually unknown penpulimab, are seeking approval in nasopharyngeal carcinoma. Though toripalimab has yet to see its BLA filing completed, it is notable for possibly being the first test of whether the currently entrenched leaders can be undercut on price.

Who will be eighth* to the US market? Selected anti-PD-(L)1 MAbs**			
Project	**Company**	**Lead indication(s)**	**US status**
Retifanlimab	Incyte/Macrogenics	Chemo-refractory squamous carcinoma of the anal canal	Filed (24 Jun 2021 negative adcom vote, 25 Jul 2021 Pdufa date)
Balstilimab	Agenus	2nd-line cervical cancer	Filed (16 Dec 2021 Pdufa date)
Sintilimab	Lilly/Innovent	1st-line non-squam NSCLC (Alimta combo)	Filed (22 May 2022 Pdufa date)
Penpulimab	Akeso/Sino	Nasopharyngeal carcinoma	Filed 24 May 2021
Toripalimab	Coherus/Shanghai Junshi	3rd-line nasopharyngeal carcinoma	Rolling filing initiated 3 Mar 2021
Tislelizumab^	Novartis/Beigene	Lung & oesophageal cancers	First ex-China filing due 2021
Cosibelimab	Checkpoint (Fortress)	Cutaneous squamous cell carcinoma	Topline pivotal data Q4 2021
Sasanlimab^^	Pfizer	Non-muscle-invasive bladder cancer (BCG combo)	Ph3 trial ends Jun 2024
Zimberelimab	Arcus	1st-line PD-L1+ve NSCLC (+/- domvanalimab)	Ph3 trial ends Dec 2025
*Notes: *Keytruda, Opdivo, Tecentriq, Bavencio, Imfinzi, Libtayo & Jemperli are already approved; **all anti-PD-1 except cosibelimab, which is anti-PD-L1; ^Fc-enhanced MAb; ^^SC delivery. Source: company statements.*			

And they are not alone. Various other checkpoint blockers are in late-stage development, including Pfizer's subcutaneous sasanlimab and Checkpoint's cosibelimab, an asset whose maker has suggested it would seek to price at a 20-30% discount. Unless Incyte can find another indication for retifanlimab it might end up being not eighth but 15th across the US finish line.

Moreover, Stifel analysts point to Macrogenics' Mahogany trial, module A of which tests a retifanlimab plus Margenza combo in front-line, Her2/PD-L1-positive gastric/gastroesophageal junction cancer, but say it would have been easier to get this use on retifanlimab's label had both agents already secured monotherapy approvals.

This is the reason why, with numerous companies wanting an in-house anti-PD-(L)1 to serve as a backbone for other combos, initial monotherapy approvals are so important – even if they are sought in relatively insignificant indications.

Before yesterday's setback *Evaluate Pharma* sellside consensus saw retifanlimab generating just $53m of 2026 revenue, and perhaps the best news for Incyte is that for now the group does not need to pay Macrogenics a $40m approval milestone.