Evaluate Vantage

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By Jacob Plieth

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What now for low-cost PD-(L)1 competition?

BY JACOB PLIETH

Welcome to the third in a series of periodic Evaluate Vantage updates on developments in the PD-(L)1 inhibitor space, which focuses on the prospects for price competition in the US after sintilimab's strongly negative advisory committee meeting.

A 14-1 vote at a February 10 US adcom against sintilimab and in favour of additional trial(s) virtually assured the Innovent/Lilly drug's rejection by the FDA. Investors and healthcare systems can likely wave farewell to sintilimab's chances in the US, but the bigger question is whether this also scuppers the chances of other PD-(L)1 newcomers seeking to undercut the current US incumbents and bring about price competition at last.

Though the status quo looks set to remain in place for a while longer, and sintilimab's pivotal trial, carried out in China, was deemed not "generalisable" to the US population, this need not necessarily be the death knell for price competition. The case of the Innovent drug has some elements peculiar to it, and it seems that its developers dropped the ball in several key instances when they decided to bring a filing before the FDA. This report discusses what went wrong, and how follow-on projects might be able to avoid a similar fate.

Other regulatory developments since Vantage's last PD(L)anner report include several additional approvals, including one of the fastest FDA thumbs-up on record: Bristol's filing for Opdivo plus chemo as a treatment for neoadjuvant lung cancer was accepted for review on February 28, and received an FDA green light just four days later. This was thanks to Bristol's use of the real-time oncology review (RTOR) scheme, which streamlined data submission before the entire clinical application was submitted, and approval came over four months before its goal Pdufa date.

Less positive news came from Sanofi/Regeneron, which cancelled a follow-on US filing for Libtayo in second-line cervical cancer. Though some investors will have sensed in this echoes of last year's blow-up for Agenus's balstilimab, also in second-line cervical cancer, the two cases appear to be distinct. The balstilimab case concerns the unacceptability of a conditional filing once a rival is approved formally, while Libtayo's centres on a flawed study, whose design did not call for all patients to be analysed for PD-L1 expression.

As before, this report analyses recent regulatory trends beyond the US too, shining a light on the increasingly important market in China. Thanks to a recent green light for sugemalimab that country now boasts 12 approved anti-PD-(L)1 MAbs. One other awaits a regulatory decision, while five projects are in pivotal trials. Summary tables list these projects.

Meanwhile, regulatory developments in the EU and Japan tend to lag those in the US, and recent months have seen an interesting divergence from the US FDA in several approved indications. As before, we have tried to identify all the key upcoming regulatory catalysts, and summarise these for China as well as for the US, EU and Japan.

A PIVOTAL MOMENT FOR US PRICE DISCOUNTING?

Going into the February 10 advisory committee meeting on Lilly/Innovent's sintilimab in first-line lung cancer many had already written off this project's chances, given the savage briefing documents issued a few days earlier. Even Lilly itself accepted that it might have "misinterpreted" the FDA's guidance when it decided to pursue this filing a few years ago.

In the event there was no surprise, and on the question "Should additional clinical trial(s) demonstrating applicability to US patients and US medical care be required prior to a final regulatory decision?" the panellists voted 14-1 in favour. This vote against sintilimab's current dataset virtually assures a complete response letter and a formal FDA demand for a large, head-to-head study – to be followed, some analysts believe, by Lilly walking away from the deal.

This would be bad news not only for sintilimab, but for the idea that price competition might finally enter the US anti-PD-(L)1 market. Merck & Co's Keytruda has a stranglehold on several big uses, and is one of six PD-(L)1s available in the US, but despite this apparent choice the market has yet to see meaningful discounting. Sintilimab was the first of several me-too checkpoint MAbs whose makers are seeking to use data generated in China to back US approval, and to enter the US market at a discount.

That said, the good news for prospective new entrants is that sintilimab might not necessarily set a broad precedent. Indeed, much of the panellists' ire at the adcom was specifically directed at the way Lilly and Innovent had gone about the filing process, suggesting that other companies might avoid a similar fate if they engage the FDA early on and do as the agency says.

This became clear when Harpreet Singh, an FDA director of oncology, accused Lilly of being "incredibly misleading" in its characterisation of a 2020 meeting with the agency and the resulting guidance. This exchange went to the heart of how Orient-11, a first-line NSCLC trial of sintilimab conducted entirely in China, ended up backing a US filing.

Lilly and Innovent said Orient-11 had been designed to support approval in China, and they had had no discussion over its design with the FDA until after data were reported. It was only then – and after Richard Pazdur, the director of the FDA's Oncology Center of Excellence, apparently welcomed anti-PD-(L)1 drugs developed by Chinese companies as a means of lowering drug costs – that a US path forward emerged, and so a US filing was made.

DIDN'T MEET FLEXIBILITY CRITERIA

It is now abundantly clear that such a strategy will not do. Throughout the proceedings the agency stressed its flexibility regarding data generated outside the US but said Lilly/Innovent failed to meet any of the criteria to warrant such flexibility, and the lack of early FDA interaction was a major black mark.

This might have been an attempt to reconcile the mixed messages that had been emerging from Mr Pazdur. Back in 2019 Mr Pazdur 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".

However, in a December 2021 NEJM piece entitled "the Wild West of checkpoint inhibitor development", Mr Pazdur seemed to have had a change of heart, opining that US head-to-head studies would "probably be required" to back use in approved indications. This was followed by Lilly's admission that it might have misinterpreted FDA guidance.

So what did the adcom panellists criticise regarding the sintilimab case specifically? There were four key points: that Orient-11 might not be generalisable to the US population, that there were issues over lack of data integrity, that the trial had the wrong primary endpoint (progression-free survival), and that it used an outdated comparator (chemotherapy).

Lack of generalisability was relevant because Orient-11 was a single-country trial – not necessarily because it was conducted ex-US per se – and the FDA stressed the need for patient diversity. Data integrity came up at site inspections, where the FDA had found adverse event underreporting but "no evidence of fraud".

Lilly/Innovent argued that PFS was a better primary endpoint than OS because it avoided the confounding effect of subsequent therapies, but this cut little ice. Other anti-PD-(L)1 projects with China trials in major indications like first-line NSCLC that also rely on PFS therefore now look like non-starters for US approval.

This could include Cstone/EQRX's sugemalimab, Novartis/Beigene's tislelizumab and Coherus's toripalimab. However, the last two are pursuing a different approach: Coherus's US filing is in the niche use of nasopharyngeal carcinoma, and could thus pass FDA muster; tislelizumab has been filed for oesophageal cancer based on a global trial, and Novartis's near-term NSCLC strategy targets second-line use.

Mizuho's Salim Sayed reckons toripalimab, for one, has come out well from the adcom, and that it has a decent chance of securing US approval in nasopharyngeal carcinoma by its April Pdufa date. "What may matter more, though, is whether toripalimab, post-nasopharyngeal approval, gets picked up by NCCN guidelines for NSCLC, and if there is then subsequent uptake off-label," he wrote in a note to clients.

What are US anti-PD-(L)1 latecomers relying on?

Project	Company	Indication	Major US use?	US status	Supporting study	Study locations	Comparator	Key primary
Libtayo	Sanofi/ Regeneron	1L PD-L1 +ve (≥50%) NSCLC	Yes	Approved 22 Feb 2021	Empower-Lung-1	Ex-US	Chemo	OS & PFS
Tyvyt (sintilimab)	Lilly/ Innovent	1L non-squam NSCLC (Alimta combo)	Yes	Filed (22 Mar 2022 Pdufa date)	Orient-11	China	Chemo	PFS
Penpulimab	Akeso/ Sino	3L nasopharyngeal carcinoma	No	Filed 24 May 2021	NCT03866967	China	None	ORR
Toripalimab	Coherus/ Shanghai Junshi	3L (& 1L chemo combo) nasopharyngeal	No	Filed (Apr 2022 Pdufa date)	Polaris-02	China	None	ORR
					Jupiter-02	Asia	Chemo	PFS
		1L NSCLC (chemo combo)	Yes	Unclear if for FDA filing	Choice-01	China	Chemo	PFS
Tislelizumab	Novartis/ Beigene	2L oesophageal squamous cell carcinoma	?	Filed (12 Jul 2022 Pdufa date)	Rationale-302	Global	Chemo	OS
		1L non-squam NSCLC (chemo como)	Yes	FDA filing will target 2L	Rationale-304	China	Chemo	PFS
		1L squam NSCLC (chemo combo)	Yes	FDA filing will target 2L	Rationale-307	China	Chemo	PFS
Cosibelimab	Checkpoint (Fortress)	Cutaneous squamous cell carcinoma	?	Topline positive data Jan 2022	NCT03212404	Ex-US	None	ORR
		1L NSCLC (chemo combo)	Yes	Study started Dec 2021	Conterno	Ex-US	Chemo	OS
Sugemalimab	Cstone/ EQRX	1L NSCLC (chemo combo)	Yes	Positive data Jan 2022	Gemstone-302	China	Chemo	PFS
Envafolimab	Tracon/ Alphamab/ 3D	1L biliary tract cancer (gemcitabine combo)	No	Ph3 trial ended Dec 2021	NCT03478488	China	Chemo	OS
Zimberelimab	Arcus (via Wuxi/ Gloriabio)	1L PD-L1+ve NSCLC (+/- domvanalimab)	Yes	Ph3 trial ends Dec 2025	NCT04736173	Ex-US	Chemo	OS & PFS

Source: company statements.

But a huge question for companies seeking approval in a major indication is what to give patients in the comparator cohort when an entrenched incumbent like Keytruda is available, as in the case of front-line NSCLC.

The adcom said that when Orient-11 enrolled its first patient (not under a US IND) in August 2018 Keytruda plus chemo was already the standard of care, based on the Keynote-189 study. Had the FDA been consulted it would likely have recommended a head-to-head comparison showing sintilimab to be non-inferior to an approved anti-PD-(L)1/chemo regimen, the panellists said.

Companies with first-line NSCLC trials that do test OS but which use chemo comparators include Arcus with zimberelimab, and the Fortress subsidiary Checkpoint with cosibelimab. These might today be sitting nervously, but will point in their defence to the Empower-Lung-1 trial that backed US approval of Sanofi/Regeneron's Libtayo.

However, while Empower-Lung-1 did use a chemo comparator and was conducted ex-US it began in 2017, before Keytruda became a standard of care in NSCLC. Lilly/Innovent argued that a head-to-head trial for sintilimab would have required 2,000 patients to be enrolled and taken over seven years to run.

While pricing and competition were said to be outside the scope of the adcom, the panel meeting clearly had relevance beyond sintilimab. Other companies will have their work cut out persuading the FDA to be flexible in designing development paths but, with the agency apparently wanting to be flexible, early interaction holds the key.

Innovent said the adcom had helped it gain tremendous experience, and the same surely applies to its peer companies too. The next time point to watch is sintilimab's March 22 Pdufa date, and though the FDA is not obliged to follow the advice of an adcom the writing is on the wall.

CERVICAL CONTROVERSY

Recent weeks have also been notable for the ongoing controversy in cervical cancer, where last year Agenus's balstilimab foundered. The latest casualty here is Sanofi/Regeneron's Libtayo, whose second-line cervical cancer filing had a January 30 Pdufa date, but whose application the companies withdrew two days previously.

There is little similarity between the cases of balstilimab and Libtayo, however. Agenus's filing, on an accelerated basis, was backed by remission rates in an uncontrolled study, and this became an unviable strategy as soon as Merck & Co's Keytruda secured a formal green light in the first and second-line settings, backed by overall survival data.

But Libtayo's second-line filing was made on the basis of a controlled study, in which the drug did show an OS benefit versus chemo. The problem here appears to have concerned insufficient data on Libtayo's effect in patients who were not PD-L1-positive.

Notably the FDA had restricted Keytruda's label to ≥1% PD-L1 expressers, even though the Keynote-826 study had shown an effect in all-comers. Libtayo's Empower-Cervical-1 trial had also shown an effect in all-comers, but full data, published in February in the NEJM, showed this to be driven by ≥1% PD-L1 expressers.

Crucially, the Libtayo researchers had obtained PD-L1 data from less than half of Empower-Cervical-1's enrolees, likely creating too much uncertainty for the FDA to rule one way on the other. It seems that the agency wanted Sanofi/Regeneron to carry out post-marketing trials, possibly to confirm Libtayo's efficacy in a patient population stratified by PD-L1 expression, but the companies said they "were not able to align" on the post-marketing study requirement.

While this filing was pulled, Libtayo remains in play as a first-line NSCLC chemo combo in all-comers, backed by Empower-Lung-3, a study in which it showed a PFS benefit against chemo alone, and which did at least include some US hospitals in addition to East Europe and Asia sites. A US Pdufa date for this filing has been set for September 19, and this is one of several anti-PD-(L)1 filings pending in the US.

Regulatory developments and approval catalysts in the US

Therapy	Indication	Supporting trial(s)	Note
Sugemalimab (Cstone/EQRX)			
Chemo combo	1st-line NSCLC	Gemstone-302	Positive data; filing imminent?
Cosibelimab (Checkpoint (Fortress))			
Monotherapy	Cutaneous squamous cell carcinoma	NCT03212404	Positive data; filing imminent?
Penpulimab (Akeso/Sino)			
Monotherapy	3rd-line nasopharyngeal carcinoma	NCT03866967	Filed 24 May 2021 (Pdufa date unknown)
Opdivo (Bristol-Myers Squibb/Ono)			
Relatlimab combo	1st-line melanoma	Relativity-047	19 Mar 2022 Pdufa date
Yervoy or chemo combo	1st-line oesophageal squamous cell carcinoma	Checkmate-648	28 May 2022 Pdufa date
Sintilimab (Lilly/Innovent)			
Alimta combo	1st-line non-squam NSCLC	Orient-11	22 Mar 2022 Pdufa date (adcom voted 14-1 against)
Keytruda (Merck & Co)			
Monotherapy	2nd-line MSI-H/dMMR endometrial carcinoma	Keynote-158 (cohorts D & K)	28 Mar 2022 Pdufa date
Toripalimab (Coherus/Shanghai Junshi)			
Chemo combo & monoRx	1st-line chemo combo & 3rd-line monoRx nasopharyngeal carcinoma	Polaris-02 & Jupiter-02	Apr 2022 Pdufa date
Tislelizumab (Novartis/Beigene)			
Monotherapy	2nd-line oesophageal squamous cell carcinoma	Rationale-302	12 Jul 2022 Pdufa date
Libtayo (Sanofi/Regeneron)			
Chemo combo	1st-line NSCLC	Empower-Lung-3	19 Sep 2022 Pdufa date
Monotherapy	2nd-line cervical cancer	Empower-Cervical-1	Filing pulled 30 Jan 2022 (had 30 Jan 2022 Pdufa date)
Imfinzi (Astrazeneca)			
Chemo +/- tremelimumab combo	1st-line NSCLC	Poseidon	Filing acceptance disclosed 10 Feb 2022; Pdufa date not disclosed
Balstilimab (Agenus)			
Monotherapy	2nd-line cervical cancer	NCT03495882	Filing pulled 22 Oct 2021
Retifanlimab (Incyte/Macrogenics)			
Monotherapy	Chemo-refractory squamous carcinoma of the anal canal	Podium-202	CRL 23 Jul 2021

A separate US filing, for Opdivo plus chemo in neoadjuvant NSCLC based on the Checkmate-816 study, was accepted for review on February 28, with a Pdufa date of July 13. Less than a week later the FDA approved this new use, four months before the action date, strengthening Bristol's push into perioperative uses and allowing it to herald the first neoadjuvant immunotherapy for NSCLC – an important accolade as the company attempts to make up with perioperative Opdivo uses the ground it lost in some metastatic cancers.

Thus Opdivo has jumped ahead of Tecentriq, which was last October greenlit for adjuvant NSCLC in PD-L1-positive patients, and Merck & Co's Keytruda, whose Keynote-091 trial in a slightly broader adjuvant NSCLC population read out positively in January.

CHINA

In China the big development since Vantage's last report on this space was the first approval of Cstone's sugemalimab. This was in the first-line NSCLC setting as part of a chemo combo, based on the results of Gemstone-302, the same China-focused trial that will likely be used to support a US filing.

The approval means that the drug, now trademarked Cejemly, has become the 12th anti-PD-(L)1 antibody to gain China approval, according to Evaluate Vantage records. A separate Cejemly filing, for stage III NSCLC, had been accepted for review by the NMPA in September, on the basis of Gemstone-301, a trial that Cstone claimed had made Cejemly the first anti-PD-(L)1 drug with a benefit in stage III and IV NSCLC patients; this boast is contentious since Keytruda's NSCLC label covers both settings.

Shanghai Junshi's Tuoyi got an additional approval in front-line nasopharyngeal carcinoma on the basis of Jupiter-02, a trial partly backing its US filing, while Beigene's Baizean got the nod as monotherapy in second/third-line NSCLC – a use that might matter little given that as a chemo combo this drug already carries front-line labels in squamous and non-squamous NSCLC.

Recent regulatory submissions include Tuoyi in first-line NSCLC and Innovent's Tyvyt in three additional uses that were disclosed during the February 10 US adcom. The near-term focus will also fall on serplulimab, an anti-PD-1 MAb in development by Fosun's Henlius subsidiary, which is awaiting its first China approvals in MSI-high solid tumours and in front-line squamous NSCLC.

Upcoming approval catalysts in China

Therapy	Indication	Supporting trial(s)	Note
Serplulimab (Henlius (Fosun))			
Abraxane combo	1st-line squamous NSCLC	NCT04033354	Filed Sep 2021
Monotherapy	MSI-h solid tumours	NCT03941574	Filed Apr 2021
Cejemly/sugemalimab (Cstone)			
Monotherapy	Stage III NSCLC	Gemstone-301	Filing accepted Sep 2021
Annik/penpulimab (Akeso)			
Monotherapy	3rd-line nasopharyngeal carcinoma	?	Filing accepted 5 Aug 2021
Chemo combo	1st-line squamous NSCLC	?	Filing accepted Jul 2021
Baizean/tislelizumab (Beigene)			
Monotherapy	2nd-line oesophageal squamous cell carcinoma	Rationale-302	Filing accepted 7 Jul 2021
Tyvyt/sintilimab (Innovent Biologics)			
Xelox combo	1st-line gastric cancer	Orient-16	Filing disclosed 10 Feb 2022
Chemo combo	1st-line oesophageal squamous cell carcinoma	Orient-15	Filing disclosed 10 Feb 2022
Chemo +/- IBI305 (biosimilar Avastin) combo	EGFR TKI-failed NSCLC	Orient-31	Filing disclosed 10 Feb 2022
Monotherapy	2nd-line squamous NSCLC	Orient-3	Filing accepted 12 Jan 2021
Tuoyi/JS001/toripalimab (Shanghai Junshi Bioscience/Astrazeneca)			
Chemo combo	1st-line NSCLC	Choice-01	Filing accepted 10 Dec 2021
Chemo combo	1st-line oesophageal squamous cell carcinoma	Jupiter-06	Filing accepted 30 Jul 2021
Tecentriq (Chugai (Roche))			
Monotherapy	Adjuvant PD-L1 +ve (≥1%) stage II-IIIA NSCLC	Impower-010	Filing disclosed 20 Oct 2021

Investors will also be tracking the development of follow-on projects, which by the nature of clinical trial reporting in China can be hard to follow. Notably, five development-stage anti-PD-(L)1s are in pivotal trials, including the PD-L1-directed adebrelimab, Jiangsu Hengrui's follow-up to the marketed Ailituo (camrelizumab).

Also in phase 3 is Cstone's follow-up to Cejemly, the anti-PD-1 MAb coded CS1003; both are licensed to EQRX outside China. And Shanghai Junshi, which first launched Tuoyi in 2018 before licensing it in China to Astrazeneca and in the US to Coherus, has the follow-on compound JS003, though this appears not yet to have entered clinical trials.

Selected development-stage anti-PD-1/PD-L1 MAbs in China

Project	Company	Mechanism/type	Indication
Phase 3			
Pucotenlimab (HX008)	Taizhou Hanzhong	Anti-PD-1 (humanised IgG4)	Gastric cancer
TQB2450 (CBT-502)	Chiatiai Tianqing	Anti-PD-L1 (humanised IgG1)	Head & neck squamous cell carcinoma
Adebrelimab (SHR-1316)	Jiangsu Hengrui	Anti-PD-L1 (humanised IgG4)	SCLC & NSCLC (chemo combos)
Socazolimab (STI A1014/STI 1014/ZKAB001)	Sorrento/Lee's Pharmaceutical	Anti-PD-L1 (fully human)	1st-line SCLC (chemo combo)
CS1003	Cstone Pharmaceuticals	Anti-PD-1 (humanised IgG4)	1st-line hepatocellular carcinoma (Lenvima combo)
Phase 2			
KL-A167	Harbour Biomed/Kelun	Anti-PD-L1 (humansed)	Classical Hodgkin's lymphoma
Geptanolimab (CBT-501)	Genor Biopharma	Anti-PD-1 (humanised IgG4)	Peripheral T-cell lymphoma
Preclinical			
JS003	Shanghai Junshi	Anti-PD-L1 (humansed)	Solid tumours

CLINICAL SUCCESSES AND FAILURES

In terms of recently reported clinical data Astrazeneca stood out with its resurgent anti-CTLA-4 MAb tremelimumab, which most had written off. The Himalaya study, in first-line hepatocellular carcinoma, had been toplined positive last year, and the Asco-GI conference saw Astra claim an "unprecedented" level of overall survival versus Nexavar.

The findings are intended to challenge Roche's Tecentriq, which as part of an Avastin combo is the only other IO drug to carry a first-line label, but which on a cross-trial basis still has the upper hand. Keytruda has been hit with a complete response letter in this setting, leaving Merck & Co fighting it out for second-line use.

Himalaya and Merck's Keynote-394 trials had both been toplined as positive last year, but Asco-GI saw full data presented for the first time. Himalaya had been noted as a rare success for tremelimumab, and one that Astra attributes to use of the novel Stride regimen, comprising a single 300mg priming dose of treme together with Imfinzi, followed by Imfinzi alone.

"We are looking at whether this single [treme] priming dose could have application on other tumour types," Dave Fredrickson, Astrazeneca's head of oncology, told Evaluate Vantage.

Full data make Astra's claim of unprecedented survival hard to square, however. Tecentriq plus Avastin had been approved on the back of a 42% reduction in risk of death in the Imbrave-150 study, whereas the Astra combo managed only 22% in Himalaya, Asco-GI heard. Mr Fredrickson said what was truly unprecedented in Himalaya was three-year survival, which amounted to 31% for the combo versus 20% for Nexavar. Imbrave-150 has so far only shown data out to 18 months, so it has yet to be seen how Roche squares up against this claim.

The questions for Astra now are when it expects to file, and whether the company will submit Imfinzi monotherapy as well as the treme combo. Liver cancer would be only Imfinzi's third approved US use, after the withdrawal of its urothelial carcinoma label a year ago.

The group will not reveal whether it has filed, but said regulatory discussion began as soon as Himalaya was toplined last October. "The question with the FDA will indeed be whether [Imfinzi monotherapy] gets into the label," said Mr Fredrickson. "But our focus is going to be on the combination."

It was already known that the Imfinzi monotherapy cohort in Himalaya had performed worse than the combo, showing only non-inferiority versus Nexavar, and not superiority. Asco-GI revealed that at 16 or so months' follow-up median survival benefit was pretty close for the combo and monotherapy arms, but across the whole study risk of death was a less impressive 14% for Imfinzi alone.

Immuno-oncology in hepatocellular carcinoma

		ORR	mPFS	mOS
First line				
Imbrave-150 (Roche)*	Tecentriq + Avastin (vs Nexavar)	28% vs 12%	6.8mth vs 4.3mth (HR=0.59)	NE vs 13.2mth (HR=0.58)
Himalaya (Astrazeneca)**	Imfinzi + tremelimumab (vs Nexavar)	20% vs 5%	3.8mth vs 4.1mth (HR=?)	16.4mth vs 13.8mth (HR=0.78)
	Imfinzi (vs Nexavar)	17% vs 5%	3.7mth vs 4.1mth (HR=?)	16.6mth vs 13.8mth (HR=0.86)
Second line				
Checkmate-040 (Bristol Myers Squibb)^	Opdivo + Yervoy	33%	NA	NA
Keynote-224 (Merck & Co)^	Keytruda	17%	NA	NA
Keynote-394 (Merck & Co)^^	Keytruda vs placebo	14% vs 1%	2.6mth vs 2.3mth (HR=0.74)	14.6mth vs 13.0mth (HR=0.79)

Notes: *available under full approval; **possible registrational study; ^available under accelerated approval; ^^possible confirmatory study. Source: product labels & Asco-GI.

Other IO players have not fared well in first-line liver cancer: Bristol's Checkmate-459 trial of Opdivo monotherapy was a bust, while Merck/Eisai's Keytruda plus Lenvima combo got a US complete response letter because the uncontrolled Keynote-524 trial gave it insufficient backing.

Merck's next hope is Leap-002, a study of the same combo versus Lenvima alone that ends in July. In the meantime, at Asco-GI the company presented data from Keynote-394, a controlled study that might serve to formalise the second-line label that Keytruda was granted on an accelerated basis back in 2018.

Merck's big problem here is that Keynote-394 was conducted in Asia, and whether the US regulator will accept it is unclear. Asked about this the group told Vantage that the trial was only one of seven in Merck's global development programme in liver cancer, and would "add to the body of evidence", but confirmed that the data were being discussed with regulators as a potential confirmatory study in the US.

Moreover, the Keynote-394 data do not seem overwhelmingly strong. There was a 21% reduction in risk of death versus best supportive care, but the median survival advantage was only 1.6 months, and the response rate was below that of Opdivo plus Yervoy on a cross-trial basis. There were three Keytruda-related deaths, from gastrointestinal haemorrhage, autoimmune hepatitis and soft tissue infection, Merck said.

Front-line liver is one cancer type where Keytruda has failed to make its mark. Perhaps this is one reason why Astra expects it to serve as a springboard for the Imfinzi/treme combo into gastrointestinal cancers.

Also at Asco-GI Astra boasted of a win for Imfinzi plus chemo in bile duct cancer, courtesy of the Topaz-1 study in the first-line setting, though the overall survival benefit here might appear underwhelming. In the trial, toplined last October, Imfinzi plus chemo reduced risk of death by 20% versus chemo alone, but median overall survival was just 1.3 months longer than for chemo.

Dave Fredrickson, Astra's head of oncology, told Vantage that the medians belied a strong tail in the survival curves, adding: "At two years one in four patients are alive on the Imfinzi/chemo regimen versus one in 10 on chemo alone." As for biomarkers, he said patients' PD-L1 status did not seem to be an obvious reason for the late survival benefit.

Bile duct cancer patients have seen US approvals of Incyte's Pemazyre and Bridgebio's Truseltiq, both in FGFR2-mutant disease, and Agios's Tibsovo, but these have all been second line. Whether follow-on use of any of these might have affected the Topaz-1 data has yet to be analysed. Either way, Topaz-1 marks the first win for IO here, and 2023 should see data from front-line studies of Merck & Co's Keytruda (Keynote-966) and Roche's Tecentriq (Imbrave-151).

Summary of Topaz-1 data

		Imfinzi + chemo	Chemo
mOS (primary endpoint)		12.8mth	11.5mth
	Stats	HR=0.80 (p=0.021)	
mPFS (secondary endpoint)		7.2mth	5.7mth
	Stats	HR=0.75 (p=0.001)	
ORR (secondary endpoint)		26.7%	18.7%
Grade 3/4 AEs		75.7%	77.8%
Treatment-related deaths		2/341	1/344

Source: Astrazeneca & Asco-GI.

With perioperative uses still in focus for anti-PD-(L)1 drugs Keytruda in January scored a win in the adjuvant NSCLC trial Keynote-091. This came after Roche's US approval for Tecentriq in adjuvant NSCLC, and suggested that Keytruda might have an edge: while Tecentriq's Impower-010 trial supported approval only in PD-L1-expressing patients with stage II-IIIA disease, Keynote-091 appeared to be positive in all-comers at stages IB-IIIA.

Keynote-091 has disease-free survival versus chemo as primary efficacy measure, split between co-primary endpoints in all-comers and in PD-L1 ≥50% expressers, and an interim analysis concluded that the former is positive. DFS in PD-L1 ≥50% expressers "did not meet statistical significance per the pre-specified statistical plan", Merck said. However, this could be a quirk as the interim efficacy bar is likely high, and there might be a relatively low number of events at this point.

Potentially more important questions are how Keytruda performed in stage IB patients and in PD-L1 non-expressers, given that Tecentriq had no activity in the former and showed an illusory benefit in the latter. Next up in adjuvant NSCLC are readouts from Bristol Myers Squibb's Checkmate-77T and Astrazeneca's Mermaid-1 studies.

Still, Merck and Roche's successes were trumped by Bristol's lightning-quick approval for Opdivo plus chemo in neoadjuvant NSCLC, discussed above. In this setting the next anti-PD-(L)1 data catalysts will come from Roche's Impower-030 and Astrazeneca's Aegean trials, both of which have seen delays to their expected readouts.

Selected anti-PD-(L)1 MAb studies in perioperative NSCLC

	Neoadjuvant NSCLC	Adjuvant NSCLC
Tecentriq	Impower-030*	Impower-010
	Readout delayed from 2021 to 2022	FDA approved in PD-L1 +ve (≥1%) stage II-IIIA disease, 15 Oct 2021
Keytruda	Keynote-671	Keynote-091 (Pearls)
	2024 readout	At interim, positive in stage IB-IIIA all-comers but not in ≥50% PD-L1 expressers
Opdivo	Checkmate-816	Checkmate-77T
	FDA approved in stage IB-IIIA all-comers, 4 Mar 2022	Stage II-IIIB, 2023-24 readout
Imfinzi	Aegean	Mermaid-1
	Readout delayed from 2022 to 2023	Stage II-III, 2024 readout

Source: clinicaltrials.gov & company expectations of timing. *Also has an adjuvant stage.

Returning to the theme of metastatic lung cancer, Merck KGaA/Pfizer's Javelin Lung 100 trial of Bavencio in first-line NSCLC was declared a bust in February. However, it is a measure of the stranglehold that Keytruda has on this disease that this failure was revealed as a mere footnote in Pfizer's fourth-quarter earnings.

The miss came despite Pfizer and Merck KGaA's best efforts to maximise the trial's chances of success: Javelin had twice been enlarged, was refocused on PD-L1 expressers and had its primary endpoints overhauled. But protracted delays – readout had originally been slated for April 2019, before being put back four times – meant that Keytruda made hay while Javelin's results receded into near irrelevance.

On February 8 Pfizer said Bavencio had shown "clinical activity" but failed to beat chemo on the OS and PFS co-primary endpoints. In the changing NSCLC environment it is possible that control cohort patients went on to receive efficacious anti-PD-(L)1 therapy, including Keytruda, but it is increasingly looking as though Bavencio simply is not a particularly good drug. Its last US approval, in first-line bladder cancer maintenance, occurred in mid-2020.

Selected trials of anti-PD-(L)1 MAbs in 1st-line NSCLC

Product	Company	Study	Outcome
Monotherapies...			
Keytruda	Merck & Co	Keynote-042	Positive, US approved for PD-L1 ≥1%
Tecentriq	Roche	Impower-110	Positive, US approved for PD-L1 ≥50%
Libtayo	Sanofi/Regeneron	Empower-Lung 1	Positive, US approved for PD-L1 ≥50%
Tuoyi (toripalimab)	Shanghai Junshi/Coherus	Choice-01*	Positive for mPFS vs chemo in all-comers
Bavencio	Merck KGaA/Pfizer	Javelin Lung 100	Failed for mPFS & mOS vs chemo
Imfinzi	Astrazeneca	Pearl	Completion (OS in PD-L1 ≥25% is primary endpoint) Jun 2022**
...and combinations			
Keytruda + chemo	Merck & Co	Keynote-189 & 407	Approved in all-comers
Opdivo + Yervoy + chemo	Bristol Myers Squibb	Checkmate-9LA	Approved in all-comers
Imfinzi + tremelimumab + chemo	Astrazeneca	Poseidon	Positive for mPFS & mOS vs chemo in all-comers, but no apparent regulatory action
Tyvyt (sintilimab) + chemo	Lilly/Innovent	Orient-11*	Positive for mPFS vs chemo in all-comers; US adcom 10 Feb 2022
Libtayo + chemo	Sanofi/Regeneron	Empower-Lung 3	Positive for mPFS vs chemo in all-comers; US Pdufa date 19 Sep 2022
Sugemalimab + chemo	Cstone/EQRX	Gemstone-302	Positive for mPFS vs chemo in all-comers

Notes: *China study; **completion was originally Jul 2020, and PFS was a co-primary endpoint.

Source: clinicaltrials.gov & company statements.

EU

EU regulatory developments comprised Keytruda's approval for adjuvant renal cell carcinoma, and two filing submissions in front-line NSCLC: for Libtayo's chemo combo on the basis of Empower-Lung-3 and for Imfinzi's chemo or tremelimumab combo, backed by the Poseidon trial.

Meanwhile, in late February the CHMP issued three positive opinions for Bristol Myers Squibb's Opdivo that marked a tougher stance than that of the agency's US counterpart. Opdivo's EU approval in adjuvant high-risk urothelial carcinoma (Checkmate-274 trial) will be restricted to PD-L1-positive disease that is muscle-invasive; the drug's corresponding US label allows use in all-comers.

And the complicated study Checkmate-648, in first-line oesophageal squamous cell carcinoma, is set to yield separate EU approvals, for Opdivo combined with chemo and separately for use with Yervoy. However, while US and EU filings appear to have sought a broad label (the US Pdufa date here falls on May 28), the CHMP positive opinion backs use in ≥1% PD-L1 expressers only.

Upcoming regulatory approval catalysts in the EU

Therapy	Indication	Supporting trials(s)	Note
Libtayo (Sanofi-Regeneron)			
Chemo combo	1st-line NSCLC	Empower-Lung-3	Filing submission disclosed 19 Jan 2022
Imfinzi (Astrazeneca)			
Chemo +/- tremelimumab combo	1st-line NSCLC	Poseidon	Filing acceptance disclosed 10 Feb 2022
Tecentriq (Roche)			
Monotherapy	Adjuvant PD-L1 +ve (≥1%) stage II-IIIA NSCLC	Impower-010	Filing disclosed at Q3 2021 earnings
Opdivo (Bristol-Myers Squibb/Ono)			
Relatlimab combo	1st-line melanoma	Relativity-047	EMA validation 1 Oct 2021, started the review process
Monotherapy	Adjuvant PD-L1 +ve (≥1%) high-risk muscle-invasive urothelial carcinoma	Checkmate-274	+ve CHMP opinion 25 Feb 2022
Chemo combo	1st-line PD-L1 +ve (≥1%) oesophageal squamous cell carcinoma	Checkmate-648	+ve CHMP opinion 25 Feb 2022
Yervoy combo	1st-line PD-L1 +ve (≥1%) oesophageal squamous cell carcinoma	Checkmate-648	+ve CHMP opinion 25 Feb 2022

JAPAN

In Japan Keytruda secured two new approvals for use in combination with Eisai's Lenvima. December brought approval for second-line endometrial carcinoma on the basis of Keynote-775 – a notably broader label than granted by the US FDA, which back in 2019 limited use in this setting to disease that is not MSI-high or mismatch repair-deficient.

In its full-year earnings update Astrazeneca disclosed that Imfinzi plus chemo/tremelimumab had been filed and accepted for review by Japan authorities for the Poseidon-backed use of first-line NSCLC.

Upcoming regulatory approval catalysts in Japan

Therapy	Indication	Supporting trial(s)	Note
Imfinzi (Astrazeneca)			
Chemo +/- tremelimumab combo	1st-line NSCLC	Poseidon	Filing acceptance disclosed 10 Feb 2022
Tecentriq (Chugai (Roche))			
Monotherapy	Adjuvant PD-L1 +ve (≥1%) NSCLC	Impower-010	Filed 6 Jul 2021
Opdivo (Bristol-Myers Squibb/Ono)			
Monotherapy	Cancer of unknown primary	NivoCUP	Filed 14 Apr 2021
Monotherapy	Adjuvant high-risk urothelial carcinoma	Checkmate-274	Filed 31 Mar 2021
Monotherapy	Adjuvant oesophageal/GEJ cancer	Checkmate-577	Filed 18 Feb 2021
Chemo (or Yervoy?) combo	1st-line gastric cancer	Checkmate-649 + Attraction-4	Filed 10 Dec 2020

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