Evaluate Vantage

PD(L)anner - February 2023

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Foreword

PD(L)1 drugs are great, but what can be added to them to make them even better? Combinations have again taken centre stage. Recent months have seen only the second anti-CTLA-4 MAb approved in the US – Astrazeneca's Imjudo, which got the nod a remarkable 11 and a half years after the first, Bristol Myers Squibb's Yervoy. Padcev could soon be approved as part of a Keytruda combo, while Opdualag continues to make inroads into new markets.

A fourth combo partner, Tigit blockade, just about remains in play, and offers investors three clinical catalysts as 2023 gets under way. Arcus and Gilead hope to make more of domvanalimab, and Merck & Co is set to present the first controlled data with vibostolimab, both expected at Asco. Crucially, some analysts are pinning their hopes on an overall survival benefit in tiragolumab's Skyscraper-01 trial, though Roche has strongly hinted against expecting anything material before August.

The latest PD(L)anner analyses all the major clinical, regulatory and commercial milestones in this space since last September, focusing specifically on inhibitors of PD-(L)1, and considering novel immuno-oncology mechanisms only when these are part of a combination with anti-PD-(L)1.

A recurring theme concerns the difficulties China-based developers are having in getting anything approved in the US; one group has stopped trying entirely, a second has seen a key deal canned, and three projects are held up amid inspection delays at the FDA.

However, Fosun is far from giving up, recently launching a bold clinical study head to head against Tecentriq. And China was also the source of one of the most extraordinary biotech deals of recent times, featuring the micro cap Summit, a $500m up-front fee and the former chief executive of Pharmacyclics.

Clinical trials of new and established PD-(L)1 assets continue reading out thick and fast across numerous tumour types, with recent months seeing many successes and a few failures. These, combined with regulatory developments, have turned at least two cancers – NSCLC and gastric/oesophageal – into complex minefields for prescribers. Both involve options many and varied, with choices of monotherapies and chemo or IO-IO combos, and dividing disease by histology, PD-L1 expression and Her2 status.

The rest of 2023 promises much more, and by the time the year is out there could be a new anti-PD-1 drug on the US market, plus two newcomers in the EU. The theme of patent expiries will not go away either – Keytruda could sell $34bn in 2028, ostensibly the last year of its patent exclusivity. The latest PD(L)anner tells you what Merck and others are doing to hang on to their monopolies, and future editions should reveal whether these efforts are proving successful.

Regulatory

The period since Evaluate Vantage's last PD-(L)1 report in September 2022 saw various drugs make inroads with additional approvals in new cancer types. But perhaps the most notable was the approval of Astrazeneca's Imjudo, only the second anti-CTLA-4 MAb to make it to the US market, after Bristol's Yervoy.

In short succession Astra's Imjudo plus Imfinzi combo got the US nod in first-line liver cancer, on the basis of **the Himalaya study**, and in first-line NSCLC (Poseidon). The latter use also includes chemotherapy, and it was notable that the FDA did not give a label to Imfinzi plus chemo without Imjudo, a **doublet that in Poseidon read out positively for progression-free but not overall survival**.

Remarkably, 11 and a half years separated the US approvals of Yervoy and Imjudo (separately Kettany, Akeso's anti-PD-1xCTLA-4 bispecific, was approved in China in mid-2022). Imjudo's Himalaya and Poseidon uses were also approved in Japan, and were filed for approval in the EU, receiving positive CHMP opinions in December.

Table 1. Recent US regulatory developments

Therapy	Indication	Regulatory status	Supporting trial(s)
Cosibelimab (Fortress Biotech)			
Monotherapy	Cutaneous squamous cell carcinoma	BLA filed 4 Jan 2023	NCT03212404
Libtayo (Sanofi/Regeneron)			
Chemo combo	1st-line Alk, EGFR & Ros1 -ve NSCLC	Approved 8 Nov 2022	Empower-Lung-3
Imfinzi (Astrazeneca)			
Chemo + Imjudo combo	1st-line Alk & EGFR -ve NSCLC	Approved 10 Nov 2022	Poseidon
Imjudo combo	1st-line liver cancer	Approved 24 Oct 2022	Himalaya
Chemo combo	1st-line biliary tract cancer	Approved 5 Sep 2022	Topaz-1
Tecentriq (Roche)			
Monotherapy	Alveolar soft part sarcoma	Approved 9 Dec 2022	NCI ML39345
Monotherapy	1st-line urothelial carcinoma (chemo ineligible; PD-L1 ≥5% if eligible for non-cisplatin)	Approval withdrawn 28 Nov 2022	Imvigor-210 (AA; had been restricted 19 Jun 2018)
Keytruda (Merck & Co)			
Padcev combo	1st-line urothelial cancer not eligible for cisplatin chemo	Awaiting approval (21 Apr 2023 Pdufa date)	Keynote-869/EV-103
Monotherapy	Adjuvant stage IB-IIIA NSCLC	Approved 26 Jan 2023	Keynote-091 (Pearls)
Monotherapy	1st-line Merkel cell carcinoma	Awaiting conversion to full approval	Keynote-017 supports AA
Monotherapy	2nd-line liver cancer	Awaiting conversion to full approval	Keynote-224 supports AA

Note: AA=accelerated approval.

Other US approvals included Roche's Tecentriq for alveolar soft part sarcoma, a use backed by an NCI study that the Swiss group had not even revealed was being pursued, and Merck & Co's Keytruda for adjuvant NSCLC. Importantly, the Keytruda label, specifically in stage IB-IIIA all-comers, is broader than Tecentriq's corresponding approved use in **stage II-IIIA disease that is PD-L1 positive at ≥1%**.

Regeneron's Libtayo as a chemo combo got the US nod in front-line NSCLC on the basis of the Empower-Lung-3 trial that, like the study supporting the drug's monotherapy use in ≥50% PD-L1 expressing NSCLC, controversially included very few US sites. This, plus the Imjudo approval, means that the **first-line NSCLC space in the US has become very complex for prescribers**.

Table 2. A complex US landscape in 1st-line NSCLC

Therapy	Indication	Supporting trial(s)
Libtayo (Sanofi/Regeneron)		
Chemo combo	1st-line Alk, EGFR & Ros1 -ve NSCLC	Empower-Lung-3
Monotherapy	1st-line PD-L1 +ve (≥50%), Alk, Ros1 & EGFR -ve, NSCLC	Empower-Lung-1
Imfinzi (Astrazeneca)		
Chemo + Imjudo combo	1st-line Alk & EGFR -ve NSCLC	Poseidon
Monotherapy	1st-line (not progressed on chemo/radio) stage III NSCLC	Pacific
Tecentriq (Roche)		
Monotherapy	Adjuvant PD-L1 +ve (≥1%) stage II-IIIA NSCLC	Impower-010
Abraxane combo	1st-line non-squamous, EGFR & Alk w/t NSCLC	Impower-130
Avastin combo	1st-line Alk & EGFR -ve non-squam NSCLC	Impower-150
Opdivo (Bristol-Myers Squibb/Ono)		
Yervoy+chemo combo	1st-line Alk & EGFR -ve NSCLC	Checkmate-9LA
Yervoy combo	1st-line PD-L1 +ve (≥1%), Alk & EGFR -ve NSCLC	Checkmate-227 part 1a
Keytruda (Merck & Co)		
Monotherapy	1st-line (not candidates for chemo/radio) PD-L1 +ve (≥1%), Alk & EGFR -ve, NSCLC (incl stage III)	Keynote-042
Chemo combo	1st-line squam NSCLC	Keynote-407
Chemo combo	1st-line Alk & EGFR -ve non-squam NSCLC	Keynote-021 (G) (AA -> full after Keynote-189)
Monotherapy	1st-line PD-L1 +ve (≥50%) NSCLC	Keynote-024

After Bristol's Lag-3/Opdivo combo Opdualag was approved in March 2022, another new combo could soon get the FDA's blessing: Seagen/Astellas's Padcev, already available as monotherapy, was filed as a Keytruda combo for first-line urothelial bladder cancer ineligible for cisplatin chemo on the basis of the Keynote-869 trial. The FDA's action date is April 21.

Opdualag itself got EU approval – albeit with a narrower label than that granted by the FDA, with the EU regulator restricting it to melanoma patients expressing PD-L1 at <1%, where the combo's effect versus Opdivo monotherapy was most pronounced.

Table 3. Relativity-047 study in 1st-line melanoma

	Opdualag mPFS	Opdivo mPFS	PFS HR	OS HR
All-comers (backs US approval)	10.1mth	4.6mth	0.76	0.80 (0.64, 1.01)
PD-L1 <1% (backs EU approval)	6.7mth	3.0mth	0.68	0.78 (0.59, 1.04)

The EU, as well as Japan, also approved Libtayo for second-line cervical cancer, the use whose **filing had been pulled in the US** after Keytruda secured a full first-line label. This became Libtayo's first approval in Japan, where separately Merck disclosed a Keytruda filing for B-cell lymphoma – a use not thought to have been studied with the PD-1 MAb to a meaningful extent.

Two other first-time western PD-L1 approvals have been requested, with Fortress filing cosibelimab in the US for cutaneous squamous cell carcinoma, and Cstone/EQRX filing a sugemalimab chemo combo for first-line NSCLC in the EU.

Table 4. Recent regulatory developments in Europe

Therapy	Indication	Regulatory status	Supporting trials(s)
Sugemalimab (EQRX/Cstone)			
Chemo combo	1st-line sq & non-sq NSCLC	Filed in UK on 19 Dec 2022	Gemstone-302 study
Tislelizumab (Beigene/Novartis)			
Chemo combo	1st-line squam NSCLC	Awaiting EU approval	Rationale-307
Chemo combo	1st-line non-squamous NSCLC	Awaiting EU approval	Rationale-304
Monotherapy	2nd-line NSCLC	Awaiting EU approval	Rationale-303
Monotherapy	2nd-line oesophageal squamous cell carcinoma	Awaiting EU approval	Rationale-302
Libtayo (Sanofi-Regeneron)			
Chemo combo	1st-line NSCLC	Awaiting EU approval	Empower-Lung-3
Monotherapy	2nd-line cervical cancer	EU approved 22 Nov 2022	Empower-Cervical-1
Imfinzi (Astrazeneca)			
Imjudo combo	1st-line liver cancer	Positive CHMP opinion 19 Dec 2022	Himalaya
Chemo + Imjudo combo	1st-line NSCLC	Positive CHMP opinion 19 Dec 2022	Poseidon
Chemo combo	1st-line biliary tract cancer	EU approved 21 Dec 2022	Topaz-1
Opdivo (Bristol-Myers Squibb/Ono)			
Chemo combo	Neoadjuvant NSCLC	Awaiting EU approval	Checkmate-816
Opdualag (relatlimab combo)	1st-line PD-L1 -ve (<1%) melanoma	EU approved 16 Sep 2022	Relativity-047
Keytruda (Merck & Co)			
Monotherapy	Adjuvant stage IB-IIIA NSCLC	Awaiting EU approval	Keynote-091 (Pearls)

Table 5. Recent regulatory developments in Japan

Therapy	Indication	Regulatory status	Supporting trial(s)
Libtayo (Regeneron)			
Monotherapy	2nd-line cervical cancer	Approved 23 Dec 2022	Empower-Cervical-1
Imfinzi (Astrazeneca)			
Imjudo combo	1st-line liver cancer	Approved 28 Dec 2022	Himalaya
Chemo combo	1st-line biliary tract cancer	Approved 28 Dec 2022	Topaz-1
Chemo + Imjudo combo	1st-line NSCLC	Approved 28 Dec 2022	Poseidon
Tecentriq (Chugai (Roche))			
Monotherapy	Adjuvant PD-L1 +ve (≥1%) NSCLC	Awaiting approval	Impower-010
Keytruda (Merck & Co/Taiho)			
?	B-cell lymphoma	Awaiting approval	?
Monotherapy	Adjuvant stage IIB/C melanoma	Approved 27 Sep 2022	Keynote-716
Monotherapy	Adjuvant renal cell carcinoma	Approved 27 Sep 2022	Keynote-564
Chemo +/- Avastin combo	1st-line PD-L1 +ve (≥1%) cervical cancer	Approved 27 Sep 2022	Keynote-826
Chemo+monotherapy	Neoadjuvant + adjuvant triple-negative breast cancer	Approved 27 Sep 2022	Keynote-522
Opdivo (Bristol-Myers Squibb/Ono)			
Monotherapy	Cancer of unknown primary	Awaiting approval	NivoCUP
Monotherapy	Adjuvant high-risk urothelial carcinoma	Awaiting approval	Checkmate-274
Monotherapy	Adjuvant oesophageal/GEJ cancer	Awaiting approval	Checkmate-577
Chemo (or Yervoy?) combo	1st-line gastric cancer	Awaiting approval	Checkmate-649 + Attraction-4

In the US three delayed projects continue to await verdicts: Coherus/Shanghai Junshi's toripalimab, Akeso/Sino's penpulimab and Novartis/Beigene's tislelizumab. The first had received a complete response letter, and Pdufa dates for all three have been missed likely because of Covid-related travel restrictions preventing the FDA from inspecting China manufacturing sites.

Novartis investors might be wondering if tislelizumab will ever get US approval. In October the group cancelled plans for an FDA filing in nasopharyngeal cancer, which had emerged as an important indication after a delay in tislelizumab's lead use, second-line oesophageal squamous cell carcinoma.

Additionally the Swiss company formally abandoned NSCLC as a US tislelizumab use. Given the FDA's stance on China-only data, it is notable that first-line NSCLC studies – on which an EU filing was based – were carried out in Beigene's home country. A key risk now is that Novartis's US plans in small-cell lung cancer might also be affected; this indication, where tislelizumab is to be filed next year, is supported by the Chinese Rationale-312 study.

There was an even bigger disappointment for EQRX, which abandoned plans to get sugemalimab approved for any major US indication, and formally tore up its founding strategy to “radically lower” US drug prices.

EQRX’s original idea – that by using China-generated data, a me-too PD-(L)1 inhibitor could be approved in the US for a major use like NSCLC at a reduced price – was already on life support. That was the result of a **US adcom, which in February slammed Lilly/Innovent’s sintilimab**, saying this drug’s NSCLC trial, conducted in China, was not generalisable to a US population.

There had been hopes that the issues, which resulted in a highly predictable complete response letter, were specific to sintilimab, but it was not to be. In September EQRX prioritised ex-US filings while insisting that it was engaging the FDA in discussions over sugemalimab. In November those US plans were formally abandoned.

Sugemalimab’s first US use was to have been front-line NSCLC, as part of a chemo combo based on the Gemstone-302 study. While that trial was technically a success, crucially it had been conducted solely in China, and compared the combo against chemo alone rather than against a US standard-of-care anti-PD-(L)1 drug.

EQRX has instead now filed sugemalimab in the UK for NSCLC. In the US its hopes turn to extranodal NK/T-cell lymphoma – an important but smaller use than NSCLC. It seems likely that an indication that is not, like NSCLC, a major US use would not be subject to the same regulatory problems regarding China-generated data, but neither will it offer a similar scope for pricing disruption.

As far as PD-(L)1 blockade is concerned, the sugemalimab situation will be watched by other latecomers to the US market, though it is notable that most now target relatively niche indications.

One exception is Shanghai Henlius/Fosun’s serplulimab, which is being targeted at the major use of first-line SCLC. In November the drug, which is now available for this use in China, started a phase 3 US study head to head against Tecentriq designed to serve as a bridge to an FDA approval. 100 pairs of patients are to be recruited, and the primary endpoint – on which serplulimab presumably needs to show non-inferiority – is overall survival.

Table 6. How Chinese anti-PD-(L)1 projects are faring in the US

Project	Company	Targeted indication	Supporting study	US regulatory outcome
Sintilimab	Innovent	1st-line non-squam NSCLC (Alimta combo)	Orient-11 (China only)	CRL on 24 Mar 2022, data not generalisable to US population
Toripalimab	Coherus/ Shanghai Junshi	1st-line chemo combo & 3rd-line monoRx nasopharyngeal carcinoma	Polaris-02 (China only) Jupiter-02 (Asia only)	CRL on 2 May 2022, quality process change required; new Pdufa date 23 Dec 2022 missed
Penpulimab	Akeso/Sino	3rd-line nasopharyngeal carcinoma	NCT03866967 (China only)	H1 2022 Pdufa date missed; no further info
Tislelizumab	Novartis/Beigene	2nd-line oesophageal squamous cell carcinoma	Rationale-302 (global)	12 Jul 2022 Pdufa date deferred owing to Covid travel restrictions; US filing plans in nasopharyngeal cancer & NSCLC abandoned
Sugemalimab	Cstone/EQRX	1st-line NSCLC (chemo combo)	Gemstone-302 (China only)	US filing plan abandoned; FDA discussions continue re pathway for extranodal NK/T-cell lymphoma
Envafolimab	Tracon/ Alphamab/3D Medicines	1st-line biliary tract cancer (gemcitabine combo)	KN035-BTC (China only)	None; ph3 trial ends Jan 2024 (delayed from Dec 2021)
Serplulimab	Shanghai Henlius/Fosun	1st-line SCLC	Ph3 (US) vs Tecentriq ends Jun 2024	"Based on positive feedback" from FDA

Continuing with disappointments, Tecentriq's use in bladder cancer had already been curtailed, and Roche saw the US indication **pulled entirely in late November**. The issue here had been that Roche's Imvigor-211 trial had failed to show an OS benefit and thus confirm an accelerated approval. This had already caused Roche to withdraw Tecentriq's second-line urothelial carcinoma use, in March 2021, and the first-line label was narrowed.

The narrowed front-line indication was highly confusing, and in any case the availability of a drug first line but not second line looked like an anomaly, though **at the time Roche stressed that Tecentriq retained its first-line label**. Now the ambiguity has been swept away after Roche said final readout from Imvigor-130, the last potentially confirmatory trial that had **already raised serious doubts**, drew a blank.

Table 7. Recent regulatory developments in China

Therapy	Indication	Regulatory status	Supporting trial(s)
Hansizhuang (serplulimab/HLX10; Henlius (Fosun))			
Chemo combo	1st-line SCLC	Approved 17 Jan 2023	Astrum-005
Abraxane combo	1st-line sq NSCLC	Approved 1 Nov 2022	Astrum-004
Cejemly (sugemalimab; Cstone anti-PD-L1 human IgG4)			
Monotherapy	R/r extranodal NK/T-cell lymphoma	Awaiting approval	Gemstone-201
Monotherapy	Stage III NSCLC	Approved 6 Jun 2022	Gemstone-301
Annik/penpulimab (Akeso)			
Monotherapy	3rd-line nasopharyngeal carcinoma	Awaiting approval	
Chemo combo	1st-line squamous NSCLC	Approved 15 Jan 2023	AK105-302
Baizean/tislelizumab (Beigene)			
Monotherapy	1st-line liver cancer	Awaiting approval	Rationale-301
Chemo combo	1st-line oesophageal squamous cell carcinoma	Awaiting approval	Rationale-306
Chemo combo	1st-line PD-L1 +ve gastric/GEJ adenocarcinoma	Awaiting approval	Rationale-305
Ailituo/AiRuiKa/camrelizumab (Jiangsu Hengrui)			
Chemo combo	1st-line nasopharyngeal carcinoma	Approved May 2022	Jupiter-02
Chemo combo	1st-line oesophageal squamous cell carcinoma	Approved	
Chemo combo	1st-line squam NSCLC	Approved	CameL-sq
Tyvyt/sintilimab (Innovent Biologics)			
Chemo +/- IBI305 (biosimilar Avastin) combo	EGFR TKI-failed NSCLC	Awaiting approval	Orient-31
Monotherapy	2nd-line squamous NSCLC	Awaiting approval	Orient-3
Xelox combo	1st-line gastric/GEJ adenocarcinoma	Approved 27 Jun 2022	Orient-16
Chemo combo	1st-line oesophageal squamous cell carcinoma	Approved 20 Jun 2022	Orient-15
Tuoyi/JS001/toripalimab (Shanghai Junshi Bioscience; lic to Astrazeneca for China)			
Chemo combo	1st-line NSCLC	Approved 20 Sep 2022	Choice-01
Chemo combo	1st-line oesophageal squamous cell carcinoma	Approved 16 May 2022	Jupiter-06
Tecentriq (Chugai (Roche))			
Monotherapy	Adjuvant PD-L1 +ve (≥1%) stage II-IIIA NSCLC	Awaiting approval	Impower-010
Keytruda (Merck & Co/Taiho)			
Chemo+monotherapy	Neoadjuvant + adjuvant triple-negative breast cancer	Approved 2022	Keynote-522
Monotherapy	2nd-line liver cancer	Approved 2022	Keynote-394 (Asia trial)

Business Development

Fallout from the above mentioned US non-approvability of drugs backed by China data saw Lilly formally **can its sintilimab deal with Innovent** in October.

But there was good news for deal bankers by way of a huge transaction involving ivonescimab/AK112, a little-known anti-PD-1xVEGF bispecific MAb being developed by Akeso. The tie-up concerned a micro-cap biotech, Summit Therapeutics, being used as a vehicle to **license rights from Akeso to develop the asset in the US, Canada, Europe and Japan**.

The up-front fee was $500m, an incredible amount given that Summit was worth a mere $150m before the announcement. The deal is worth up to $5bn in biodollars, and is initially being funded by a loan from Summit's co-chief executives, Bob Duggan and Maky Zanganeh; the former owns 81% of Summit, and a subsequent $500m rights issue will start to pay them back.

Mr Duggan made billions selling Pharmacyclics to Abbvie and is presumably betting that he can repeat the trick here. Ivonescimab still has much to prove. Akeso contends that adding anti-VEGF to PD-1 inhibition can boost potency, with tolerability improvements to boot; data at Asco this year in various NSCLC populations found a reduced risk of haemorrhage – a big VEGF toxicity – even in those with squamous histology.

Efficacy also looked respectable, although ivonescimab was dosed on top of chemotherapy. Akeso already has the project in **a large China-focused clinical programme**, while Summit plans to start NSCLC trials next year.

Clinical Updates

Recent months have seen PD-(L)1 data galore, with many successful trials and a few failures.

For example, Opdivo read out **positively for PFS (58% reduction in risk of progression)** in Checkmate-76K, a trial in adjuvant stage IIB/C melanoma. The 12-month relapse-free rate was 89%, versus 79% for placebo. The Bristol drug is already approved for adjuvant melanoma with lymph node involvement, meaning stage III or higher (Checkmate-238), so the new trial win represents a potentially broader use.

In December 2021 Keytruda was approved for adjuvant stage IIB/C melanoma (Keynote-716), on data that appeared worse than Checkmate-76K – 35% reduction in risk of progression, and **12-month relapse-free survival of 90.5% versus 83.1%**.

But arguably the most notable readout, and one that is crucial to this year's catalysts, concerns Tigit blockade, a mechanism many had once thought to have been key to the next big immuno-oncology combo. Here Arcus/Gilead's domvanalimab finally yielded numerical data in December from its Arc-7 study in first-line NSCLC, in which it was combined with the in-house anti-PD-1 project zimberelimab.

The best that can be said of the readout, however, was that it was numerically positive. On the debit side, the Tigit/PD-1 combination underperformed Roche's corresponding combo in the ostensibly positive Cityscape trial. And Arc-7's control arm, the Arcus/Gilead anti-PD-1 project zimberelimab, strongly underperformed Keytruda – almost exactly mirroring Roche's experience in Cityscape, which preceded the blow-up of the phase 3 Skyscraper-01 trial.

Because of the Skyscaper-01 failure Tigit expectations had already been reset. But there had still been hope for Arc-7, given that Gilead saw enough to exercise a $750m opt-in with Arcus, and that its fourth analysis, in November, was said to show "continued clinically meaningful differentiation across all efficacy measures".

Arc-7 compared domvanalimab plus zimberelimab against zimberelimab alone in first-line NSCLC with ≥50% PD-L1 expression. It is the comparator arm, and Arcus's disclosures about it, that raise the biggest questions.

Last May the company had said: "The clinical activity of zimberelimab alone was in line with established anti-PD-1 therapies in this patient population." In fact, median PFS with zimberelimab came in at just 5.4 months, and overall remission rate at 27%. Cross-trial comparisons for Keytruda in first-line NSCLC patients expressing PD-L1 at ≥50% reveal 7-10 months' mPFS and ORR of 39-45% in the Keynote-042 and 024 studies.

Table 8. Selected data in ≥50% PD-L1 expressing 1st-line NSCLC

Company	Arcus/Gilead		Roche		Merck & Co	
Trial	Arc-7		Cityscape*		Keynote-042*	Keynote-024
PD-(L)1 +/- Tigit	Zimberelimab + domvanalimab	Zimberelimab	Tecentriq + tiragolumab	Tecentriq	Keytruda	Keytruda
ORR	41%	27%	69%	24%	39%	45%
mPFS	12.0mth	5.4mth	16.6mth	4.1mth	6.9mth	10.3mth
	HR=0.55		HR=0.29			

Note: *study enrolled patients with PD-L1 expression down to 1%, but data above relate only to the ≥50% subgroup.

Source: product labels, Asco & Esmo.

Speaking to *Evaluate Vantage* Arc-7's presenting author, Dr Melissa Johnson of The Sarah Cannon Cancer Center, accepted that zimberelimab monotherapy came in at the low end of expectations, but said the result of Keynote-024 was an outlier that had not been repeated since. Evercore ISI analysts pointed out that the first-line NSCLC landscape was not the same as when Merck's trials were run.

The domvanalimab/zimberelimab combo in Arc-7 beat the zimberelimab numbers handsomely, even yielding a 0.55 hazard ratio for the PFS measure. "This gives us confidence that the addition of a Tigit inhibitor is doing something important to the tumour microenvironment that allows more durable antitumour response in a way that is well tolerated," said Dr Johnson.

However, the absolute benefit of Arcus/Gilead's combo looks uncompetitive: a 41% ORR and 12 months' mPFS. On a cross-trial basis these numbers barely beat Keytruda monotherapy, and come up well short of Roche's Cityscape trial.

Dr Johnson said no formal statistical analysis was done for the Arc-7 data; it will be noted that for PFS the confidence interval's upper bound of 1.0 implies a wide margin of error, but this is not unexpected from a relatively small study that had just 44 patients in each cohort.

Another red flag for Arc-7: a third cohort, a triplet of domvanalimab, zimberelimab and the A2a/b adenosine receptor antagonist etrumadenant, numerically performed even worse than the doublet. Dr Johnson insisted that the triplet was showing "equivalent" data to the doublet.

It was Cityscape that yielded large PFS and ORR benefits for tiragolumab plus Tecentriq, but against a Tecentriq arm that came up well short of Keytruda, and short of what Tecentriq itself scored in Roche's Impower-110 study.

On the basis of Cityscape Roche began a pivotal Tigit programme across various cancers, the first two of which, SCLC and NSCLC (so far only for PFS), have drawn a blank. If Roche erred in using Cityscape as the basis to start pivotal trials, Gilead does not even have the luxury of making a go/no go decision: the domvanalimab/zimberelimab combo is already in the phase 3 Arc-10 study in first-line, ≥50% PD-L1 expressing NSCLC.

It is in Arc-10 that Gilead might confront its biggest problem, as the comparator arm that domvanalimab and zimberelimab will be trying to beat in this phase 3 trial is Keytruda.

Merck itself has also started a large pivotal programme of its own Tigit MAb, vibostolimab, albeit in NSCLC patients expressing PD-L1 as low as 1%, in line with Keytruda's monotherapy label. There is some hope that it might be easier for Merck to detect a combination effect in lower PD-L1 expressers. Evercore says that if vibostolimab now gives a similar benefit to domvanalimab, but on top of Keytruda, the Merck combo could be tough to beat.

An Asco press release accompanying the Arc-7 abstract sought to differentiate domvanalimab's efficacy from the "mixed signals from prior studies looking at Tigit" by pointing to the project's Fc-silent design, which avoids depleting peripheral immune cells. However, Arc-7 data look just as mixed as earlier trials, and perhaps the most important finding from the trial is that zimberelimab is a rather poor PD-1 agent.

The scene is now set for further Tigit catalysts this year. Domvanalimab itself will yield a more mature data cut from Arc-7 at Asco, and Merck & Co will later present the first pivotal data for vibostolimab, an asset about which little has been disclosed. Vibostolimab is in a phase 2/3 programme called Keyvibe, whose scale rivals that of Roche's Skyscraper trials.

What little early results have emerged so far about the Merck asset have not generated great expectations. The 2020 Esmo meeting showed data from the uncontrolled phase 1 Keyvibe-001 trial. Here a Keytruda combo yielded a 29% ORR in PD-(L)1 treatment-naive NSCLC – an underwhelming result given the 27% ORR in front-line disease cited on Keytruda's label. In PD-(L)1 pretreated patients the ORR was a disappointing 5% for the combo, or 7% for vibostolimab monotherapy.

The next trial to read out will be Keyvibe-002, in the first half, possibly at Asco. This trial tests vibostolimab plus Keytruda, with or without chemo, against chemo, in NSCLC patients who have already progressed after immunotherapy and chemo; given the Keyvibe-001 data this seems unlikely to succeed, though the data might be used to handicap the chances of vibostolimab/Keytruda's more important trial, Keyvibe-003 in first-line NSCLC, which has a December completion date.

And it is the first look at overall survival from the Skyscraper-01 study of Roche's tiragolumab that has investors' immediate attention. Skyscraper-01 failed for PFS, but so far no actual numbers from it have been revealed, so it is impossible to gauge the failure numerically or statistically. First data from Skyscraper-01's OS endpoint are possible in February, though Roche has played down the chances of a positive hit at this interim stage.

On February 2 Roche's chief executive, Severin Schwan, told analysts: "We still expect interim readout in February, but the most likely scenario is that the study will continue to final readout in the second half. If Skyscraper-01 is negative we will communicate that immediately, but if the study continues to final readout we are not going to make a specific announcement."

He also confirmed, as had largely been assumed, that most of the statistical powering in Skyscraper-01 was assigned to final OS readout. Evercore ISI's Umer Raffat had long suggested that this was likely, and thus surmised that a hit on OS was still possible.

Analysts generally believe that until OS data from Skyskraper-01 are revealed interest in Gilead/Arcus's first-line NSCLC Arc-7 study will remain muted. First OS data from Arc-7 will likely come towards the end of the year.

Like with Skyscraper-01 Evercore's Mr Raffat takes a contrarian view of Arc-7, for instance citing the possibility of extra as-yet unconfirmed remissions being reported later. He also plays down the value of comparing Arc-7 to the ultimately confounding result of Roche's Cityscape trial, which he stresses was based on a subgroup analysis.

Table 9. A battle of three Tigits

Study	Skyscraper-01	Keyvibe-002	Arc-7
Company	Roche	Merck & Co	Gilead/Arcus
Setting	1st-line NSCLC (≥50% PD-L1)	Post-PD-(L)1/chemo NSCLC	1st-line NSCLC (≥50% PD-L1)
Design	Tiragolumab + Tecentriq, vs Tecentriq	Vibostolimab + Keytruda +/- chemo, vs chemo	Domvanalimab + zimberelimab, vs zimberelimab
What do we know?	Failed for PFS (no data)	Keyvibe-001 underwhelmed	Positive for PFS but clinically disappointing
What's expected?	First OS data	First data (PFS & OS?)	More mature PFS data
When?	Q1 2023	Asco	Asco
	(then final analysis in Q3 2023)		(then first OS data later in 2023)
Why is it important?	Could reignite interest in Tigit if most alpha was allocated to OS, leading to a positive result	First controlled data for vibostolimab, could help handicap Keyvibe-003 in 1st-line NSCLC	Improved dataset could suggest better activity if combined with a better PD-(L)1 drug

Source: company disclosures.

Elsewhere, GSK had something to celebrate at last when Jemperli plus chemo beat chemo alone on PFS in the phase 3 Ruby trial in endometrial cancer; OS was immature at interim, but was said to show "a favourable trend". Ruby is the confirmatory study for Jemperli's accelerated US approval, in second-line mismatch repair-deficient (dMMR) disease, and GSK said the PFS benefit was seen in dMMR/microsatellite-unstable (MSI-high) patients as well as in those with mismatch repair proficient/microsatellite stable disease.

Nevertheless, while this will probably suffice to confirm the dMMR approval, anything broader is unlikely, as GSK said Ruby showed only a "clinically relevant" (not statistically significant) benefit in MMR-proficient/microsatellite-stable tumours. And as of March 2022 Keytruda carries full approval in second-line dMMR/MSI-high endometrial carcinoma.

Tecentriq plus Avastin gave Roche investors a pleasant surprise when the combo apparently succeeded in the Imbrave-050 trial in adjuvant liver cancer. This outcome was especially unexpected given Tecentriq's decidedly mixed track record in perioperative cancers. In Imbrave-050 the combo was said to have beaten active surveillance alone on its primary endpoint of relapse-free survival.

The precise contribution of Avastin to this result is unknown, but the success comes after the same combo was approved three years ago for first-line inoperable liver cancer on the basis of Imbrave-150. Tecentriq's other perioperative success was in adjuvant NSCLC, where the drug is approved in ≥1% PD-L1 expressers on the basis of Impower-010, and an Abraxane combo read out positively in the perioperative triple-negative breast cancer (TNBC) trial Impassion-031, albeit on pathological complete response, likely not an approvable endpoint.

Apart from that Tecentriq monotherapy and combos have failed several pivotal perioperative trials, including Imvigor-010, Imagyn-050, Impassion-050 and Immotion-010; the next big readout, from Impassion-030 in adjuvant TNBC, is expected soon. Specifically in adjuvant liver cancer this year could also see data from three other anti-PD-(L)1 drugs: Shanghai Junshi's toripalimab, Astrazeneca's Imfinzi and Innovent's sintilimab.

Table 10. Phase 3 studies in adjuvant hepatocellular carcinoma

Drug	Trial	Setting	Primary endpoint & status
Tecentriq (Roche)	Imbrave-050	+ Avastin, vs active surveillance	RFS, toplined positive Jan 2023
Toripalimab (Shanghai Junshi)	Jupiter-04*	MonoRx, vs placebo	RFS, ends Apr 2023
Imfinzi (Astrazeneca)	Emerald-2	+/- Avastin, vs placebo	RFS, ends May 2023
Sintilimab (Innovent)	Dadali*	+ Avastin, vs active surveillance	RFS, ends Dec 2023
Camrelizumab (Jiangsu Hengrui)	SHR-1210-III-325*	+ apatinib, vs active surveillance	RFS, ends Jul 2024
Opdivo (Bristol/Ono)	Checkmate-9DX	MonoRx, vs placebo	RFS, ends Dec 2024
Tislelizumab (Beigene)	NCT05564338	+/- sitravatinib, vs placebo	RFS, ends Sep 2026
Keytruda (Merck & Co)	Keynote-937	MonoRx, vs placebo	RFS & OS, ends Oct 2027

Notes: RFS=relapse-free survival; *China study. Source: clinicaltrials.gov.

Less positive news came for Astrazeneca in December, when the phase 3 Pearl study of Imfinzi failed to hit statistical significance for OS versus platinum chemo as a monotherapy for first-line NSCLC expressing PD-L1 at ≥25%. There was no benefit either in the intent-to-treat population or in a subgroup of patients at low risk of early mortality. The trial was conducted primarily in Asia.

While EQRX suffered its existential crisis over sugemalimab in the west (above), the Cstone-derived molecule continued to score clinically. One success was in Gemstone-304, in which it read out positively for OS and PFS as part of a chemo combo for first-line oesophageal squamous cell carcinoma. This is a setting where Opdivo, combined with Yervoy or chemo, has US approval on the basis of Checkmate-648. Cstone said it would file in China "in the near future".

And in November sugemalimab read out positively for PFS in Gemstone-303, a registrational chemo combo trial in front-line gastric/gastroesophageal junction adenocarcinoma expressing PD-L1 at ≥5%.

The study seems to be analogous to Bristol's Checkmate-649, which backs Opdivo plus chemo's all-comers approval. It is somewhat similar also to Merck's Keynote-590 (Keytruda + chemo) and Keynote-811 (Keytruda plus Herceptin plus chemo for Her2-positive patients).

These settings are relevant given that Keytruda itself read out positively in November for overall and progression-free survival in Keynote-859, a chemo combo study in first-line Her2-negative gastric/GEJ adenocarcinoma. That result was said to be irrespective of patients' PD-L1 expression.

The full data will be of interest especially in the context of Keytruda's approval in third-line PD-L1 ≥1% gastric/GEJ adenocarcinoma, an indication that was withdrawn after a 2021 US adcom looking into "dangling" accelerated approvals (see the **September 2021 PD(L)anner**). The use was withdrawn because Keytruda had failed the second-line Keynote-061 trial, and yielded inconclusive data in the front-line Keynote-062 study.

At the time Keynote-859 had been cited as a potentially relevant trial, as were Keynote-811 in Her2-positive patients and Keynote-585 (neoadjuvant/adjuvant setting). But these three were all combination studies, while the relevant setting was monotherapy, and so the indication was pulled.

The matter has since become somewhat academic: Keynote-811 read out positively and backed Keytruda's separate accelerated US approval as a Herceptin plus chemo combo. And Opdivo plus chemo is fully approved first-line – irrespective of Her2 status even though the supporting Checkmate-649 trial excluded Her2-positives; and Opdivo monotherapy can be used in oesophageal/GEC cancer in the adjuvant setting.

Also in this complicated mix is Beigene/Novartis's tislelizumab, which at Asco-GI 2023 yielded full data from the first interim analysis of Rationale-305 in Her2-negative gastric/GEJ adenocarcinoma – like sugemalimab in PD-L1 ≥5% expressers. Rationale-305, 74% of whose patients were enrolled at Asian hospitals, is the basis for approval in China, where a tislelizumab filing was accepted last June. A US filing backed by it is planned for this year.

This study had enrolled patients irrespective of PD-L1 expression, but so far, in accordance with its design, only the ≥5% PD-L1 expressing patients have been analysed. Thanks to this sequential analysis Beigene was able to say the 0.0056 p value for the OS benefit in PD-L1-positive patients was statistically significant. OS in the all-comers set, to be presented at a later congress, will be tested at final analysis, which Beigene told *Evaluate Vantage* would happen later this year.

Table 11. Selected studies in gastric/oesophageal/GEJ cancer

Trial	Therapy	Indication	Outcome	Comment
Opdivo (Bristol-Myers Squibb/Ono)				
Attraction-3	Monotherapy	2nd-line oesophageal squamous cell carcinoma	Backed US approval 10 Jun 2020	
Checkmate-649	Chemo combo	1st-line gastric/GEJ/oesophageal adenocarcinoma	Backed US approval 16 Apr 2021	Trial excluded Her2 +ves (cf KN-811 below)
Checkmate-577	Monotherapy	Adjuvant oesophageal/GEJ cancer	Backed US approval 20 May 2021	
Checkmate-648	Yervoy or chemo combo	1st-line oesophageal squamous cell carcinoma	Backed US approval 27 May 2022	Data at Asco 2021
Keytruda (Merck & Co)				
Keynote-059	Monotherapy	3nd-line PD-L1 +ve (≥1%) gastric/GEJ adenocarcinoma	Had backed US AA 22 Sep 2017	AA withdrawn 1 Jul 2021 after adcom vote against
Keynote-061	Monotherapy	2nd-line PD-L1 +ve (≥1%) gastric/GEJ adenocarcinoma	Failed	
Keynote-062	Monotherapy	1st-line PD-L1 +ve (≥1%) gastric/GEJ adenocarcinoma	Inconclusive	
Keynote-180 & 181	Monotherapy	2nd-line PD-L1 +ve (≥10%) oesophageal squamous cell carcinoma	Backed US approval 30 Jul 2019	EU filing pulled 31 Jan 2020
Keynote-590	Chemo combo	1st-line oesophageal/GEJ carcinoma	Backed US approval 22 Mar 2021	
Keynote-811	Herceptin+chemo combo	1st-line Her2 +ve gastric/GEJ adenocarcinoma	Backed US AA 5 May 2021	
Keynote-859	Chemo combo	1st-line Her2 -ve gastric/GEJ adenocarcinoma	Toplined +ve for OS & PFS	Press released 22 Nov 2022
Tislelizumab (Beigene/Novartis)				
Rationale-305	Chemo combo	1st-line Her2 -ve gastric/GEJ adenocarcinoma	Stat sig for OS in PD-L1 +ve (≥5%)	Data at Asco-GI 2023
Rationale-306	Chemo combo	1st-line oesophageal squamous cell carcinoma	Stat sig for OS	Data at Esmo-GI 2022
Sugemalimab (Cstone/EQRX)				
Gemstone-303	Chemo combo	1st-line PD-L1 +ve (≥5%) gastric/GEJ adenocarcinoma	Stat sig for PFS, numerically +ve for OS	Press released 11 Nov 2022
Gemstone-304	Chemo combo	1st-line oesophageal squamous cell carcinoma	Stat sig for OS & PFS	Press released 3 Jan 2023

Keytruda had a separate success in first-line biliary tract cancer, a space where currently Astrazeneca's Imfinzi is the only anti-PD-(L)1 drug approved, after January's Asco-GI conference saw Roche's Tecentriq underwhelm.

Merck said Keytruda succeeded in Keynote-966, a study analogous to Astra's registrational Topaz-1 trial, combining Keytruda with chemo and showing an effect on its primary endpoint, overall survival, that Merck called "statistically significant and clinically meaningful". The bar is low, as Imfinzi plus chemo added just over a month of median OS to chemo alone, cutting risk of death by 20%.

Meanwhile, Roche's approach, in the Imbrave-151 trial, was different, investigating Tecentriq with or without Avastin, and not having a chemo control arm. Adding Avastin to Tecentriq cut risk of progression by 24%, and risk of death by 26%, but neither effect hit statistical significance. Since this trial was uncontrolled the absolute benefit is of interest: six-month OS was 92% for the combo and 81% for Tecentriq alone, while in Topaz-1 it was around 75%.

Table 12. Anti-PD-(L)1 drugs in 1st-line biliary tract cancer

Study	Design	mOS	mPFS
Topaz-1^	Imfinzi + chemo, vs chemo	12.8mth vs 11.5mth (HR=0.80)	7.2mth vs 5.7mth (HR=0.75)
Imbrave-151*	Tecentriq + Avastin, vs Tecentriq	NR vs 11.4mth (HR=0.74)	8.3mth vs 7.9mth (HR=0.76)
Keynote-966	Keytruda + chemo, vs chemo	"Stat sig & clinically meaningful"	Not reported

Notes: NR=not reached; ^approved use; *ph2 study, other two are ph3.

Source: prescribing info, Asco-GI & company presentation.

But Keytruda failed as part of an Xtandi combo in the Keynote-991 study in hormone-sensitive prostate cancer. There had been some hope for this trial given that the combo had shown activity in castration-resistant disease, in the Keynote-199 and 365 studies. A separate Merck plan in prostate cancer is to combine Keytruda with Lynparza, but **that plan is off to an inauspicious start**.

For Merck a much bigger issue than the occasional failure of Keytruda in the clinic is what to do once the drug's US patents start to expire, an event Merck has confirmed it expects to happen in 2028. A Keytruda subcutaneous formulation might extend market exclusivity, and this is why the development of SC forms of PD-(L)1 drugs is an emerging theme to watch for 2023.

With $34bn of forecast 2028 Keytruda sales at stake, little wonder that analysts see the imminent readout of a lung cancer study called 3475-A86, as a hugely important catalyst that could form the basis for a US filing. Still, Roche looks set to get there first: the Swiss company's SC Tecentriq could be approved as soon as September.

This is more important for maintaining Roche's own market for Tecentriq, whose exclusivity could end in 2032, according to *Evaluate Pharma*, than to mounting a threat against Keytruda. But Roche does provide Merck with a sort of regulatory blueprint, having based its filing on the Imscin-001 trial, which was toplined positive last August.

In December Imscin-001 data were quietly presented at the Esmo-IO meeting, and just as quietly Roche filed the SC form with the FDA. The filing has just been accepted under standard review, and the agency has set a September 15 action date, Roche told *Evaluate Vantage*.

A key detail: though Imscin-001 concerned second-line, post-chemo NSCLC, the data it generated are expected to support the registration of the SC formulation "across all approved indications of IV Tecentriq", according to Roche's statement. If this plan succeeds the same will apply also to Merck, whose phase 3 3475-A86 trial compares IV Keytruda plus chemo against SC Keytruda plus chemo in patients with front-line NSCLC.

The Merck trial's co-primary measures concern bioavailability, in terms of area under curve and trough concentrations, while adverse events, PFS and OS feature as secondary endpoints. The co-primaries are broadly similar to those in Roche's trial, and the aim is to show SC to be non-inferior to IV dosing, just as Roche did in Imscin-001.

However, Merck has not spelled out the margin SC Keytruda needs to hit to demonstrate non-inferiority. In Imscin-001 the primary endpoints were both met, exceeding a non-inferiority floor defined as a lower bound of the 90% confidence interval of at least 0.80. PFS curves were virtually identical for IV and SC Tecentriq, and so was the occurrence of adverse events.

Mizuho analysts reckon 2028 loss of exclusivity on IV Keytruda could erode over 75% of the drug's sales within five years, but say successful launch of a SC form could limit the damage to just 30%. They base this claim on J&J's multiple myeloma drug Darzalex, whose SC form captured over 80% of the IV's market share within five years of launch.

For Roche less than a third of this sales number is at stake, but similar post-exclusivity dynamics probably apply. It is also important to remember that all the big PD-(L)1 players are pursuing SC formulations, and trials of Bristol Myers Squibb's Opdivo and Astrazeneca's Imfinzi are due to end late this year and early in 2024 respectively.

Another key player is Pfizer, which is developing sasanlimab as its SC contender, but a crucial difference here is that this is a new molecular entity, so a separate pivotal trial will be needed for every indication.

Table 13. 2023 catalysts for subcutaneous PD-(L)1 drugs

Drug	Company	2028e sales ($m)	US patent expiry	Status of SC formulation
Tecentriq	Roche	7,019	Jun-32	Filed in US, Pdufa date 15 Sep 2023
Keytruda	Merck & Co	33,636	Dec-28	Study 3475-A86 reads out imminently
Opdivo	Bristol/ Ono	15,262	Dec-28	Checkmate-67T trial ends Dec 2023

Source: Evaluate Pharma.

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