Evaluate Vantage

PD(L)anner - September 2022

BY JACOB PLIETH

Evaluate Vantage

Foreword

Since Evaluate Vantage's last PD(L)anner was published at the end of March the checkpoint inhibitor space has witnessed clinical readouts galore. But, while China approved the world's first anti-PD-1xCLTA-4 bispecific, in the west the stranglehold of the established players, led by Merck & Co's Keytruda, continues. True, in the approval of Bristol's Opdualag the US welcomed a brand new immuno-oncology mechanism, but as for follow-on PD-(L)1 inhibitors, all attempts to get to the market have so far landed on stony ground.

Failures to secure US regulatory green lights for Incyte/Macrogenics' retifanlimab and Agenus's balstilimab have been followed by a widely expected complete response letter for Innovent/Lilly's sintilimab. A separate CRL was handed to Coherus/Shanghai Junshi's toripalimab, Cstone/EQRX gave up – for now – trying to gain approval for sugemalimab, and Pdufa action deadlines were missed for Novartis/Beigene's tislelizumab and Akeso/Sino's penpulimab.

As before, this report focuses specifically on inhibitors of PD-(L)1, and considers novel immuno-oncology mechanisms only when these are part of a combination with anti-PD-(L)1.

Astrazeneca's anti-CTLA-4 MAb tremelimumab might become the next US immuno-oncology newcomer, while possibly the next new PD-(L)1 entrant to go before the FDA will be Checkpoint Therapeutics with cosibelimab; in the EU tislelizumab has recently been filed for four different settings.

Still, the past few months have been largely about clinical results, many of which were profiled at the Asco meeting. Here Tigit has loomed large, with the failure of Roche's attempts to combine Tecentriq with tiragolumab in the Skyscraper-01 and 02 studies having a major impact on others targeting this mechanism. Bristol finally gave up on bempegaldesleukin, while Keytruda failed several trials, most importantly perhaps in first-line liver cancer.

Commercially, Sanofi ceded control of Libtayo to its longstanding partner Regeneron, while Roche scored a clinical success for a subcutaneously delivered form of Tecentriq. SC delivery is now seen by many as a way to weather the expected loss of patent exclusivity on the first wave of anti-PD-(L)1s, and Roche might just have leapfrogged its rivals.

This report updates the major clinical, regulatory and commercial milestones, as well as outlining upcoming catalysts.

Advantage China

China, a country that already boasts more marketed anti-PD-(L)1 MAbs than the US, approved the world's first bispecific anti-PD-1xCTLA-4. The Akeso MAb, cadonilimab, got the green light for second-line cervical cancer in June, nine months after being submitted, based on uncontrolled data in a clinical trial that showed a 33% overall remission rate in around 100 subjects, and a 27% rate of severe treatment-related adverse events.

Akeso is separately awaiting US approval for penpulimab, a monospecific anti-PD-1 MAb, in 3rd-line nasopharyngeal carcinoma on the strength of a China-only study. However, this has likely missed its Pdufa date, believed to have fallen some time in the first half. There has been no public statement, but the likeliest reason for the delay seems the inability of the US FDA to make inspections owing to Covid travel restrictions – the same reason that has delayed Beigene's tislelizumab (table 1).

Cadonilimab's Chinese trade name is phonetically rendered as Kettany, and its phase 3 programme, entirely in China, includes trials for hepatocellular and gastric/gastroesophageal junction cancers, as well as a chemo combo, with or without Avastin, in front-line cervical cancer.

At this year's Asco meeting Akeso presented data from a first-line trial, in which cadonilimab plus chemo with or without Avastin yielded a 79% ORR at its optimal dose, including 75% ORR in those expressing PD-L1 at below 1%. Again, however, toxicity was high, with a 60% rate of grade 3 or higher treatment-related adverse events.

As this was an uncontrolled trial, for comparison Akeso could only cite the Keynote-826 study of Keytruda plus chemo with or without Avastin, which yielded a 66% ORR and backed the Merck & Co regimen's front-line US approval. Here ORR in PD-L1 <1% expressers was 50%, but overall rate of TRAEs was also high, at 68%.

Earlier in the year Shanghai Fosun's Henlius subsidiary secured China approval for serplulimab (HLX10), under the trade name Hansizhuang, for MSI-high solid tumours. The drug became the 13th monospecific anti-PD-(L)1 MAb approved in China, and faces regulatory decisions for two uses as a chemo combo, in front-line SCLC and squamous NSCLC.

Table 1. Pending regulatory decisions in China

Therapy	Indication	Supporting trial(s)
Hansizhuang (serplulimab/HLX10; Henlius (Fosun))		
Chemo combo	1st-line SCLC	NCT04063163 study
Chemo combo	1st-line sq NSCLC	NCT04033354 study
Cejemly (sugemalimab; Cstone)		
Monotherapy	Stage III NSCLC	Gemstone-301 study
Annik/penpulimab (Akeso)		
Monotherapy	3rd-line nasopharyngeal carcinoma	Unclear
Chemo combo	1st-line squamous NSCLC	Unclear
Baizean/tislelizumab (Beigene)		
Chemo combo	1st-line PD-L1 +ve gastric/GEJ adenocarcinoma	Rationale-305 study
Tyvyt/sintilimab (Innovent Biologics)		
Xelox combo	1st-line gastric cancer	Orient-16 study
Chemo combo	1st-line oesophageal squamous cell carcinoma	Orient-15 study
Chemo +/- IBI305 (biosimilar Avastin) combo	EGFR TKI-failed NSCLC	Orient-31 study
Monotherapy	2nd-line squamous NSCLC	Orient-3 study
Tuoyi/JS001/toripalimab (Shanghai Junshi Bioscience; lic to Astrazeneca for China, and to Coherus for US)		
Chemo combo	1st-line NSCLC	Choice-01 study
Chemo combo	1st-line oesophageal squamous cell carcinoma	Jupiter-06 study
Tecentriq (Chugai (Roche))		
Monotherapy	Adjuvant PD-L1 +ve (≥1%) stage II-IIIA NSCLC	Impower-010 study

Other PD-(L)1/CTLA-4 combos

Asco also featured data on Astrazeneca's rival anti-PD-1/CTLA-4 bispecific, MEDI5752, in renal cell carcinoma, with Astra highlighting activity in a cohort of front-line patients – a highly competitive space.

The discussant, Dr Brian Rini, of the Vanderbilt-Ingram Cancer Center, suggested that dual blockade of these checkpoints offered theoretical advantages of increased potency and durability, albeit with a toxicity price. However, Astra separately told *Evaluate Vantage* that MEDI5752 only binds CTLA-4 in the presence of PD-1, and that preclinically this gave it a better safety profile than hitting these targets using separate MAbs.

Astra is separately seeking US approval for Imfinzi plus tremelimumab in two indications (see table 2).

Also still pursuing the separate MAbs approach is Agenus, which at June's Esmo-GI conference presented late-breaking data for its balstilimab (anti-PD-1) plus botensilimab (CTLA-4) combo in 41 microsatellite-stable colorectal cancer patients. Opdivo (also as a Yervoy combo) and Keytruda are available in MSI-high/MMRd colorectal cancer, but for microsatellite-stable patients options are limited, Agenus argues, citing single-digit response rates in third-line subjects with other anti-PD-(L)1s and combinations.

Against this background the 24% ORR Agenus's combo yielded at Esmo-GI, in patients who had failed a median of four prior therapies, looked impressive. Still, balstilimab and botensilimab are both novel agents (the former having failed to secure an accelerated nod in cervical cancer), and there is no way to tell from the uncontrolled study how much efficacy can be attributed to each part of the combo. As such Agenus plans to start a global randomised phase 2 study in this setting later this year.

Clinical trials

Since March there have been numerous other clinical trial updates, and another that also featured at Esmo-GI was a late-breaker from Beigene and Novartis on tislelizumab in first-line oesophageal squamous cell carcinoma. In the Rationale-306 trial a tislelizumab/chemo combo yielded median overall survival of 17.2 months, versus 10.6 months for chemo alone, reducing risk of death by 34% ($p<0.0001$).

Tislelizumab is approved in China as Baizean for nine indications, recently receiving green lights for second-line oesophageal squamous cell carcinoma and first-line nasopharyngeal cancer, and being filed for front-line, PD-L1-positive gastric/gastroesophageal adenocarcinoma.

In the US it is awaiting approval in second-line oesophageal squamous cell carcinoma, based on the global Rationale-302 trial, and had a July 12 Pdufa date. However, no decision was made at that time, with Beigene stating that the agency had been unable to make necessary inspections in China owing to the Covid pandemic. As such the approval decision was deferred, Beigene said, and while tislelizumab remains under review no new Pdufa date has been specified.

The US oesophageal space is somewhat complicated, with Opdivo already available in the setting Beigene/Novartis are pursuing, and Keytruda having a label in PD-L1 ≥10% expressers. In May Opdivo additionally secured a front-line label, either as monotherapy or as part of a Yervoy combo, based on the Checkmate-648 study, presented at Asco 2021.

Chemo combos including Opdivo or Keytruda are also available first line, and Opdivo in the adjuvant setting, though not specifically for the squamous cell histology.

Other US approvals since Vantage's last PD(L)anner report include Keytruda for second-line MSI-high/mismatch repair-deficient endometrial carcinoma, directly challenging GSK's Jemperli, which carries accelerated approval in this setting. Jemperli's own green light here will ultimately depend on the outcome of Ruby, a confirmatory phase 3 trial due to read out around the end of 2022.

Jemperli also ended up being one of the stars of the Asco conference, but ironically GSK had little to do with this. Instead, the buzz was generated by an academic-sponsored trial in rectal cancer, and while many doctors and the generalist press were extremely excited GSK's response has so far been virtual radio silence.

Table 2. US status of anti-PD-1/PD-L1 MAbs in oesophageal cancer

Approval status	Therapy	Setting	Supporting trial(s)
Opdivo (Bristol-Myers Squibb/Ono)			
Approved May 2022	Yervoy or chemo combo	1st-line oesophageal squamous cell carcinoma	Checkmate-648 study
Approved May 2021	Monotherapy	Adjuvant oesophageal/GEJ cancer	Checkmate-577 study
Approved Apr 2021	Chemo combo	1st-line gastric/GEJ/oesophageal adenocarcinoma	Checkmate-649 study
Approved Jun 2020	Monotherapy	2nd-line oesophageal squamous cell cancer	Attraction-3 study
Keytruda (Merck & Co)			
Approved May 2021	Herceptin+chemo combo	1st-line Her2 +ve gastric/GEJ adenocarcinoma	Keynote-811 study (AA)
Approved Mar 2021	Chemo combo	1st-line oesophageal/GEJ carcinoma	Keynote-590 study
Approved Jul 2019	Monotherapy	2nd-line PD-L1 +ve (≥10%) oesophageal squamous cell carcinoma	Keynote-180 & 181 studies
Tislelizumab (Beigene/Novartis)			
Filed (missed 12 Jul 2022 Pdufa date)	Monotherapy	2nd-line oesophageal squamous cell cancer	Rationale-302 study

New mechanisms

Bristol heralded a new immuno-oncology mechanism with the approval in March of Opdualag, a combination of Opdivo and the anti-Lag3 MAb relatlimab, for front-line melanoma. In relatlimab Bristol appears to have found a less toxic drug than Yervoy to complement Opdivo, and an analysis by *Evaluate Vantage* has pinpointed nine additional studies in over 4,000 patients that should give a clue as to whether relatlimab might augment Opdivo or replace Yervoy in the established drugs' approved uses, and maybe in new indications, beyond metastatic melanoma.

Of course, publicly Bristol is not about to give up on Yervoy. But analysts at Mizuho, for instance, already see Opdualag replacing Opdivo monotherapy in first-line melanoma, and capturing a significant chunk of the Opdivo/Yervoy combo's share here. This view is driven by Opdualag's preferable safety profile to the existing combo, though the analysts stress that head-to-head comparison of long-term survival data will be needed for Opdualag to be considered in preference to Opdivo plus Yervoy in this setting.

Perhaps the next really big readout for relatlimab is a front-line NSCLC trial combining the drug with Opdivo with or without chemo, and comparing these regimens against Opdivo alone. This will measure progression-free survival as a co-primary endpoint, but it is not clear whether in itself it could back a regulatory filing.

One difficulty is that this study does not appear to use an appropriate comparator drug. Opdivo monotherapy is not approved for front-line NSCLC, though it is available as a Yervoy combo in ≥1% PD-L1 expressers, or as a Yervoy plus chemo combo in all-comers.

Meanwhile, Relativity-098, which might yield data in 2025, is a phase 3 study designed to extend Opdualag's use into adjuvant melanoma, where Opdivo and Yervoy are both approved as monotherapies, but where competition exists in the form of Merck & Co's Keytruda.

Also not to be underestimated is a solid tumour trial with a primary completion date of September this year, the biggest Bristol-sponsored relatlimab study, according to clinicaltrials.gov. This enrolled patients with a variety of solid tumours, and interestingly tests relatlimab monotherapy as well as an Opdivo combo.

Formally this is a phase 1/2 study primarily testing overall responses and adverse events, but it could provide Bristol with vital insight into which additional cancers to focus on. Notably, this began in 2013 seeking to enrol just 168 subjects, but today has an enrolment target of 1,499.

Relativity-047, the trial that backed Opdualag's metastatic melanoma approval, showed a 19% rate of serious treatment-related adverse events, versus 59% in Opdivo/Yervoy's pivotal Checkmate-067 study. The potential for this kind of safety advantage alone explains Bristol's investment into a programme whose phase 2 and 3 studies comprise over 5,000 patients. Next up is the EU, where Opdualag has already secured a positive CHMP opinion.

Table 3. Selected Bristol-sponsored relatlimab studies

Trial	Condition	Design	Enrolment	Approved therapy?		
				Opdivo	Yervoy	Opdivo+ Yervoy
NCT01968109	Solid tumours	Relatlimab +/- Opdivo	1,499	NA	NA	NA
Relativity-098*	Adjuvant stage III-IV melanoma	Opdivo + relatlimab vs Opdivo	1,050	Y	Y	N
Relativity-047	1st-line melanoma**	Opdivo + relatlimab vs Opdivo	714	Y	Y	Y
NCT04623775	1st-line NSCLC	Opdivo + relatlimab +/- chemo vs Opdivo	520	N	N	Y
Relativity-073	2nd-line hepatocellular carcinoma	Opdivo + relatlimab vs Opdivo	250	N^	N	Y
NCT03662659	Gastric/GEJ cancers	Opdivo + relatlimab + chemo vs Opdivo + chemo	274	Y	N	N^^
NCT02061761	R/r B-cell malignancies	Relatlimab +/- Opdivo	107	N	N	N
Relativity-069	Classical Hodgkin & non-Hodgkin lymphoma	Opdivo + relatlimab (uncontrolled)	68	Y~	N	N
Relativity-059	Solid tumours (China study)	Opdivo + relatlimab (uncontrolled)	12	NA	NA	NA
Checkmate-358	Various tumours, incl neoadjuvant	Opdivo +/- relatlimab, Yervoy or Darzalex	584	NA	NA	NA

*Notes: *phase 3 study; **approved Opdualag indication; ^approval in this indication was withdrawn; ^^approved for oesophageal squamous cell carcinoma; ~approved in 3rd-line classical Hodgkin lymphoma. Source: product labels & clinicaltrials.gov.*

Tigit blow-up

Perhaps the biggest clinical development over the past few months was the implosion of a separate I-O mechanism, Tigit blockade, courtesy of Roche's tiragolumab in first-line NSCLC. While it is still premature to say with certainty that this failure, in the Skyscraper-01 trial, was the death knell for Tigit blockade, it was surely not a good sign.

In Skyscraper-01, in PD-L1-high front-line NSCLC patients, tiragolumab plus Tecentriq failed to beat Tecentriq in terms of progression-free survival, although there was a numerical benefit. Analysis of overall survival, the co-primary endpoint, is immature.

This was the second pivotal trial in the Skyscraper programme to fail, after the Skyscraper-02 SCLC study, with eight more yet to read out. The Skyscraper-02 failure was easily dismissed given the intractable nature of SCLC, though the smaller Cityscape study in hindsight suggested that all was not well in NSCLC either.

Cityscape did show tiragolumab adding efficacy in terms of remissions and PFS over Tecentriq, but only in high PD-L1 expressers. The effect was flattered by Tecentriq monotherapy underperforming versus the Impower-110 trial, however, and there was no link between efficacy and Tigit expression. Ultimately, these facts cast doubt over what Tigit blockade was bringing to the party.

When in January 2020 Roche quietly put tiragolumab into the first of 10 Skyscraper studies investors assumed that it must have had convincing data in house. However, beyond the subsequent Cityscape results, with the drawbacks outlined above, little else has emerged to back the enthusiasm for a programme that currently has an enrolment target of 8,365 patients.

True, the lack of statistical significance despite a numerical improvement suggests that Skyscraper-01 might have been underpowered, and the lack of a PFS benefit need not translate into a fail on overall survival. Some analysts are also now asking whether a vanishingly small amount of statistical powering had been assigned to PFS – something that arguably was supported by a Skyscraper-02 late-breaker at Asco (see table 4).

The Roche setback coincided with an already shrinking biotech market, and hit a number of Tigit players hard, including Arcus, Compugen and Iteos. Iteos is now trading not far off cash, while Arcus has a Gilead-partnered asset, domvanalimab, whose Arc-7 study remains hidden behind an increasingly suspicious-looking cloud of secrecy. Gilead had handed across $750m to Arcus last November, after Glaxo paid $625m for Iteos's EOS-448; later Novartis paid $300m for an option over Beigene's ociperlimab. Among in-house assets Merck & Co has vibostolimab in the pivotal Keyvibe programme, some of whose studies mirror the design of the Skyscraper trials, and which is seeking to enrol 5,331 patients in total.

Given the history of disastrous deals under Gilead's belt, that company's chief executive, Daniel O'Day, might be sitting nervously. Arc-7, in first-line NSCLC, has a broadly similar design to Skyscraper-01 and Keyvibe-003, and all investors know so far is that a third interim analysis has taken place, and that the dataset appears to be improving.

Some might be frustrated at this dribbling out of information, and at the fact that Arcus has not held a publicly accessible investor webcast since last November. That coincided with Gilead licensing in domvanalimab, and seemingly imposing tight control over data disclosure.

Arc-7 tests domvanalimab on top of Arcus's anti-PD-1 zimberelimab in first-line NSCLC with ≥50% PD-L1 expression. At its first interim analysis last June ORR was said to be "encouraging", while at the second look, which triggered Gilead's opt-in, the combo was "differentiated" versus zimberelimab monotherapy, which importantly was described as having "activity similar to other marketed anti-PD-1 antibodies in the setting".

Then in a third analysis ORR for the Tigit/PD-1 doublet increased and separated further from zimberelimab, Gilead said. Response duration was measured for the first time, and this too showed improvement over zimberelimab, which was still showing activity consistent with marketed anti-PD-1s.

The last point is key to setting expectations. Merck's Keytruda as monotherapy in first-line NSCLC has shown ORR of 40-45% in ≥50% PD-L1 expressers in the Keynote-042 and 024 trials. Thus, for the domvanalimab combo to be differentiated and increasingly separating from PD-1 therapy the ORR should be well above 50%, and perhaps around 60%.

Crumbs of comfort

At this year's Asco investors in Tigit companies were thrown some crumbs of comfort, when researchers presented the findings of Skyscraper-02, Roche's failed SCLC trial. The Asco late-breaker laid bare the unmitigated disaster of Skyscraper-02, where adding tiragolumab to Tecentriq actually worsened progression-free survival numerically.

However, a key disclosure about Skyskraper-02's statistical analysis plan raised hopes that Skyscraper-01, the failed NSCLC study, might not be dead and buried just yet. A central question about the latter trial is what its numerical PFS miss looks like, and how Roche has divided up statistical powering; the standard of statistical significance at p=0.05 is typically split for multiple analyses across multiple endpoints.

Optimistic investors hope that Skyscraper-01's PFS result has yielded a p value well below 0.05, but that this nevertheless missed statistical significance, which had been set at a much more aggressive level. Even more important is how much statistical power remains to show an OS benefit at a subsequent interim analysis.

Hence the relevance of one Skyscraper-02 slide, posted at the Asco late-breaker by Memorial Sloan Kettering's Dr Charles Rudin, which revealed that almost the entirety of the alpha at p=0.05 was assigned to OS, meaning that a very tough p value of 0.001 needed to be cleared to declare a statistical win on PFS.

No one is suggesting that Skyscraper-01 has an identical statistical design, and clearly there is no salvaging anything from tiragolumab's SCLC study, which was a flop on all counts. But it is nevertheless possible that Roche has apportioned most of the alpha in Skyscraper-01 to OS. Evercore ISI's Umer Raffat wrote: "These tidbits raise our confidence that there is a real chance Roche can hit on a subsequent OS analysis of Skyscaper-01 in NSCLC; next interim [due] possibly later in the year."

As for SCLC, Merck started Keyvibe-008, a broadly similar front-line SCLC trial with its Tigit MAb vibostolimab plus Keytruda, at precisely the same time that Skyscraper-02 was toplined as a flop. However, speaking to *Evaluate Vantage* Eric Rubin, Merck's senior vice-president of early-stage oncology, said: "Roche's failure isn't going to detract from our interest in [vibostolimab]."

Of more importance will be Merck's work in NSCLC, where the Keyvibe-003 vibostolimab plus Keytruda trial is ongoing. Mr Rubin drew a distinction between Skyscraper-01 and Keyvibe-003, saying that Roche's Tecentriq comparator arm restricted enrolment to patients expressing PD-L1 at 50% or above, in line with Tecentriq's monotherapy label.

Because Keytruda is approved in PD-L1 ≥1% expressers, and comprises the comparator in Keyvibe-003, Merck can test its Tigit combo in the broader population. "It may be easier to detect a combination effect in lower biomarker positives rather than at the higher level, where the PD-1s are pretty effective by themselves," said Mr Rubin.

A third player, Beigene, is studying its Tigit ociperlimab plus tislelizumab versus Keytruda in the PD-L1 ≥50% population in the Advantig-302 trial.

Table 4. Roche and Merck square up in Tigit

Setting	Roche trials with tiragolumab...		...Merck & Co trials with vibostolimab	
1st-line SCLC	Skyscraper-02*	Tigit + Tecentriq + chemo, vs Tecentriq + chemo	Keyvibe-008	Tigit + Keytruda + chemo, vs Tecentriq + chemo
1st-line NSCLC	Skyscraper-01 (PD-L1≥50%)**	Tigit + Tecentriq, vs Tecentriq	Keyvibe-003 (PD-L1≥1%)	Tigit + Keytruda, vs Keytruda
Stage III NSCLC	Skyscraper-03^	Tigit + Tecentriq, vs Imfinzi	Keyvibe-006	Tigit + Keytruda + CRT, vs Imfinzi + CRT
1st-line NSCLC chemo combo	Skyscraper-06^^	Tigit + Tecentriq + chemo, vs Keytruda + chemo	Keyvibe-007	Tigit + Keytruda + chemo, vs Keytruda + chemo
*Notes: CRT=chemoradiotherapy; *failed for OS & PFS; **failed at interim for PFS; ^after, but not progressed on, CRT; ^^non-squamous. Source: company filings.*				

Clinical failures

Other recent failures included two from Opdivo, first in the Checkmate-901 trial in front-line urothelial bladder cancer in May. This Yervoy combination study was initially to have ended a year earlier, but was delayed after being upsized – rarely a positive sign – from 990 to 1,290 subjects.

Then in July the Checkmate-914 trial in adjuvant renal cell carcinoma, another Yervoy combo, failed to meet its primary endpoint of disease-free survival. This came just a week after Roche quietly slipped out news that Immotion-010, its own study in the same setting, was a dud – strengthening the position of Merck & Co's Keytruda, which secured US approval here last November based on a disease free survival (DFS) benefit seen in Keynote-564.

The remaining phase 3 player in adjuvant kidney cancer is Astrazeneca: the Rampart study of Imfinzi with or without tremelimumab has DFS and overall survival co-primary endpoints, and is due to end in mid-2024. However, Rampart is investigator sponsored, and was not listed in the clinical trials appendix Astra released with its 2022 second-quarter report.

Table 5. Pivotal trials of anti-PD-(L)1 drugs in adjuvant renal cell carcinoma

Study	Drug(s)	Primary endpoint(s)	Result
Keynote-564	Keytruda vs placebo	DFS	Hazard ratio for DFS 0.68, p=0.001; US approval 18 Nov 2021
Immotion-010	Tecentriq vs placebo	DFS	Failed
Checkmate-914	Opdivo +/- Yervoy vs placebo	DFS	Failed
Rampart	Imfinzi +/- tremelimumab vs placebo	DFS & OS	Primary completion Jul 2024
Source: company information & clinicaltrials.gov.			

Perhaps even more momentous for Bristol was the discontinuation of the Nektar-derived bempegaldesleukin, after its failures in the Pivot-09 and 10 Opdivo-combination trials. These had tested the combo in first-line renal and urothelial cancers respectively, and represent the end, at long last, of Bristol's hope to improve on Opdivo's efficacy with IL-2 stimulation, four years after the group struck its $1.85bn deal with Nektar.

Table 6. Failed studies of anti-PD-(L)1 antibodies across various cancer types

	Keytruda	Opdivo	Tecentriq	Imfinzi	Bavencio
	Merck & Co	Bristol-Myers Squibb	Roche	Astrazeneca	Merck KGaA/ Pfizer
Colorectal			Imblaze-370 (3L)*		
Melanoma	Keynote-252 (1L)**		Imspire-170 (1L)*		
Gastric	Keynote-061 (2L) Keynote-062 (1L)^				Javelin Gastric 300 (3L) Javelin Gastric 100 (1L)
Urothelial	Keynote-361 (1L)	Pivot-10 (1L)*** Checkmate-901^^	Imvigor-211 (2L) Imvigor-010 (adjuvant)	Danube (1L)^^	
Glioblastoma		Checkmate-143 (2L) Checkmate-498 (1L) Checkmate-548 (1L & 1L MGMT-met)			
NSCLC		Checkmate-026 (1L) Checkmate-227 pt 2 (1L)	Impower-131 (1L)^ Impower-132 (1L)^ Skyscraper-01 (1L)^^^	Arctic (3L) Mystic (1L)^^ Neptune (1L)^^	Javelin Lung 200 (2L) Javelin Lung 100 (1L)
SCLC	Keynote-604 (1L)	Checkmate-331 (2L) Checkmate-451 (1L)^^	Skyscraper-02 (1L)^^^		
Head & neck	Keynote-040 (2L) Keynote-412 (maintenance)	Checkmate-714 (1L)# Checkmate-615 (1L)^^		Eagle (2L)^^ Kestrel (1L)^^	Javelin Head & Neck 100 (1L)
Ovarian			Imagyn-050 (1L/ neoadj)##		Javelin Ovarian 100 (1L)
Hepatocellular	Keynote-240 (2L) Leap-002 (1L)###	Checkmate-459 (1L)			
TNBC	Keynote-119 (2L)		NeoTRIPaPDL1 (neoadj) Impassion-131 (1L) Ipatunity-170 (1L)~		
Multiple myeloma	Keynote-183 (3L) Keynote-185 (1L)				
Prostate	Keynote-921 (2L) Keylynk-010 (3L)~~				
Cervical				Calla (1L)	
Renal		Pivot-09 (1L)*** Checkmate-914 (adjuvant)^^	Immotion-010 (adjuvant)		

**Cotellic combo; **epacadostat combo; ***bempegaldesleukin combo; ^data inconclusive; ^^CTLA-4 combo; ^^^tiragolumab combo; #Opdivo vs Opdivo + Yervoy; ##Avastin combo; ###Lenvima combo; ~ipatasertib combo; ~~Lynparza combo. 1L=1st line; 2L=2nd line; 3L=3rd line.*

Another setting in which Keytruda has been able to consolidate its status as an approved first-line therapy is cervical cancer. Regulatory concerns had earlier already derailed attempts by Agenus, Regeneron/Sanofi and Iovance to gain second-line labels (see previous PD(L)anners). The latest cervical cancer setback concerned Astrazeneca's first-line Calla trial, combining Imfinzi with chemoradiation, which failed to show a progression-free survival benefit against chemoradiation alone.

Sanofi/Regeneron had pulled a US filing for Libtayo in second-line use, after Agenus did the same for balstilimab. The latter was down to the unviability of uncontrolled data backing an approval once Keytruda secured a formal first and second-line label, while the former was probably a result of 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 benefit in all-comers in the Empower-Cervical-1 trial was driven by ≥1% PD-L1 expressers, but researchers had obtained PD-L1 data from less than half of enrolees.

The next keenly awaited dataset in cervical cancer concerns Roche's combo of Tecentriq plus the anti-Tigit Mab tiragolumab in Skyscraper-04.

Table 7. Selected cervical cancer trials

Company	Trial	Setting	Design	Primary endpoint	Note
Merck & Co	Keynote-826	1st-line	Keytruda + chemo +/- Avastin, vs chemo +/- Avastin	Positive for OS in all-comers & PD-L1+ves	Backed full US approval 1st-line (PD-L1+ves) & 2nd-line
Seagen	InnovaTV-204	2nd-line	Tivdak (uncontrolled)	24% ORR	Backed accelerated US approval
Agenus	NCT03495882	2nd-line	Balstilimab (uncontrolled)	14% ORR	US filing withdrawn 2 mths before Pdufa date
Regeneron/ Sanofi	Empower-Cervical-1	2nd-line	Libtayo vs chemo	Positive for OS in all-comers	US filing withdrawn 2 days before Pdufa date
Iovance	NCT03108495	2nd-line	Lifileucel +/- Keytruda (uncontrolled)	44% ORR (57% for combo)	Filing delayed, pending FDA discussions
Astrazeneca	Calla	1st-line	Imfinzi + CRT vs CRT	Failed for PFS	–
Roche	Skyscraper-04	2nd-line	Tecentriq + tiragolumab, vs Tecentriq	ORR	Data due 2022
Pfizer/Merck KGaA	Intr@pid Cervical 017	2nd-line	Bintrafusp alfa (uncontrolled)	ORR	Ended Apr 2022
	Intr@pid Cervical 046	1st-line	Bintrafusp alfa + Avastin or various chemos (uncontrolled)	Safety	Ended May 2022
Source: company presentations & clinicaltrials.gov.					

That said, Keytruda has not had it all its own way, and Merck's attempt to combine it with Lynparza got off to a rocky start with the Keylynk-010 trial being halted for futility. Keylynk-010 had tested Keytruda plus Lynparza in castrate-resistant prostate cancer patients who had already failed chemotherapy and either Zytiga or Xtandi, pitting the combo against Xtandi or Zytiga in the two respective populations. A data-monitoring board recommended scrapping it after seeing no benefit in either of its co-primary endpoints, radiographic progression-free and overall survival.

The study was the first of several in the Keylynk programme to yield a result, and next up are three trials that will add Lynparza as maintenance therapy while patients are still in response to front-line Keytruda plus chemo, in cancers where Keytruda plus chemo is already approved: ovarian cancer (Keylynk-001), squamous NSCLC (Keylynk-008) and triple-negative breast cancer (Keylynk-009).

Table 8. Merck's solely funded Lynparza programme

Trial	Setting	Active	Control	Primary	Data due	Cost ($m)
Keylynk-010	3rd-line castrate-resistant prostate cancer	Keytruda + Lynparza	Zytiga or Xtandi	OS & rPFS	Failed	123
Keylynk-001	1st-line (maintenance) Brca W/T ovarian cancer	Lynparza (after 1st-line Keytruda + chemo)	Placebo	PFS	Imminent**	247
Keylynk-008	1st-line (maintenance) squamous NSCLC	Keytruda + Lynparza (after 1st-line Keytruda + chemo)	Keytruda + chemo	OS & PFS	Dec 2022**	138
Keylynk-009	1st-line (maintenance) triple-negative breast cancer	Keytruda + Lynparza (after 1st-line Keytruda + chemo)	Keytruda + chemo	OS & PFS	Dec 2022**	214
Keylynk-012	1st-line (maintenance) stage III NSCLC	Keytruda + Lynparza (after 1st-line Keytruda + CRT)	Imfinzi or Keytruda	OS & PFS	Apr 2023**	159
Keylynk-007*	≥2nd-line HRRm/HRD+ve cancers	Keytruda + Lynparza	None	ORR	Jun 2024	51
Keylynk-006	1st-line (maintenance) non-squamous NSCLC	Keytruda + Lynparza (after 1st-line Keytruda + chemo)	Keytruda + chemo	OS & PFS	Aug 2024	188
Keylynk-013	1st-line (maintenance) SCLC	Keytruda + Lynparza (after 1st-line Keytruda + CRT)	Placebo	OS & PFS	Oct 2027	120

*Source: Evaluate Pharma Omnium. *Phase 2; all others are phase 3. **Company/analyst expectation; all others per clinicaltrials.gov.*

Later Keytruda failed a second-line prostate cancer setting, Keynote-921, where a chemo combo was in August said not to have met its dual primary endpoints of OS and radiographic PFS versus chemo alone. The Merck drug also failed Keynote-412, a phase 3 head and neck cancer study in which it was given with chemoradiation, and then as maintenance. Head and neck is a cancer in which most of the leading anti-PD-(L)1s have failed, though Opdivo and Keytruda are approved in some settings.

Finally, Merck's quest to advance Keytruda from the second to the first line in liver cancer hit a second obstacle, after the Leap-002 trial, testing the drug in combination with Eisai's Lenvima, failed to show an OS or PFS benefit against Lenvima alone. Merck had earlier filed Keytruda plus Lenvima for accelerated approval in first-line liver cancer, based on the uncontrolled Keynote-524 study, but was handed a complete response letter.

Soon after the Leap-002 setback Beigene toplined its first-line liver cancer study of tislelizumab, Rationale-301, which it claimed was positive. However, the hit on its primary endpoint, overall survival, was only on the basis of non-inferiority to Nexavar, so it is hard to declare the study a success in the real world. Data from Rationale-301, a global study, are to be presented in full at the Esmo conference, but ultimately whether its outcome is sufficient will be down to regulators. Other developments in first-line liver cancer saw Shanghai Henlius Biotech scrap a Chinese phase 3 study of HLX10, citing the unsuitability of using a Nexavar control now that Tecentriq plus Avastin was available there.

In second-line liver cancer Keytruda's Keynote-240 study failed in 2019, calling into question the drug's accelerated US approval. However, subsequently the Keynote-394 trial, in second-line Asian patients, read out positively at Asco-GI in January. In its second-quarter presentation Merck revealed that it had submitted a second-line US filing, presumably comprising the Keynote-394 dataset, seeking formal approval.

Table 9. Selected phase 3 studies of anti-PD-(L)1 projects in first-line liver cancer

Project	Company	Design	Study	Result
Opdivo	Bristol Myers Squibb	Vs Nexavar	Checkmate-459	Fail
Tecentriq	Roche	Avastin combo vs Nexavar	Imbrave-150	Success; US approval
Tecentriq	Roche/Exelixis	Cabometyx combo vs Nexavar	Cosmic-312	Fail
Tyvyt	Innovent	Bevasda (Avastin biosimilar) combo vs Nexavar	Orient-32	Success; China approval
Imfinzi	Astrazeneca	+/- tremelimumab vs Nexavar	Himalaya	Success
Camrelizumab	Jiangsu Hengrui	Apatinib combo vs Nexavar	NCT03764293	Success (data at Esmo 2022)
Keytruda	Merck & Co/Eisai	Lenvima combo vs Lenvima	Leap-002	Fail (data at Esmo 2022)
Tislelizumab	Beigene	Vs Nexavar	Rationale-301	Non-inferior on OS (data at Esmo 2022)
Toripalimab	Shanghai Junshi	Lenvima combo vs Lenvima	NCT04523493	Ends Aug 2023
Opdivo	Bristol Myers Squibb	Yervoy combo vs Nexavar or Lenvima	Checkmate-9DW	Ends May 2024 (delay from Sep 2023)
HLX10	Shanghai Henlius/Fosun	HLX04 (Avastin biosimilar) combo vs Nexavar	NCT04465734	Terminated*

*Note: *used Nexavar as control, deemed unsuitable since Tecentriq + Avastin was approved in China in Oct 2020. Source: clinicaltrials.gov.*

So far the only other anti-PD-(L)1 challenger to Tecentriq's front-line liver cancer label has been Astrazeneca, whose positive Himalaya study of Imfinzi plus tremelimumab was accepted by the FDA in April, implying a fourth-quarter Pdufa date. This, or a first-line NSCLC filing based on the Poseidon trial, could become the first approved use for tremelimumab, making this the second anti-CTLA-4 MAb to reach the US market, after Yervoy. A separate US filing of Imfinzi plus chemo, based on the Topaz-1 trial in front-line biliary tract cancer, has a third-quarter action date.

Imfinzi, which after a relatively slow start is picking up momentum in terms of clinical successes, had another in the neoadjuvant NSCLC setting. This was courtesy of the Aegean trial, hailed as positive for one of its co-primary endpoints, pathologic complete response. However, it will be important for the study also to hit on event-free survival; the recent approval of Bristol's rival Opdivo plus chemo in neoadjuvant NSCLC was based on both endpoints. For now, Astra is not giving detailed data, but investors will want to see how Imfinzi stacks up against Opdivo.

Notably, the studies enrolled slightly different patient populations. Astra says it will await event-free survival (EFS) results before presenting the full data, so Asco 2023 is a potential venue. Next up in neoadjuvant NSCLC will be Roche's Impower-030 trial of Tecentriq – this has EFS as primary and pCR as a secondary endpoint, according to clinicaltrials.gov. Neoadjuvant disease is a smaller opportunity than adjuvant NSCLC, where Tecentriq currently has the edge.

Table 10. Selected anti-PD-(L)1 MAb studies in perioperative NSCLC

	Neoadjuvant NSCLC	Adjuvant NSCLC
Opdivo	Checkmate-816	Checkmate-77T
	FDA approved in stage IB-IIIA all-comers, 4 Mar 2022; EFS 31.6mth vs 20.8mth, pCR 24% vs 2.2% for Opdivo + chemo vs chemo alone respectively	Stage II-IIIB; 2023-24 readout
Imfinzi	Aegean	Mermaid-1
	Stage II-III; hit on pCR Jun 2022; continuing to EFS assessment	Stage II-III; 2024 readout
Tecentriq	Impower-030*	Impower-010
	Stage II, IIIA & "select IIIB"; 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)
	Stage II, IIIA & resectable IIIB; 2024 readout	At interim, positive on DFS in stage IB-IIIA all-comers but not in ≥50% PD-L1 expressers
**Also has an adjuvant stage. Source: clinicaltrials.gov & company expectations of timing.*		

Going subcutaneous

On the commercial front, Merck is increasingly having to field questions about how it plans to negotiate Keytruda's US patent expiry, perhaps in 2028, given that this has been one of pharma's most successful drug franchises ever. One plan is to develop a subcutaneous version of Keytruda. Most advanced here is a phase 3 front-line NSCLC trial due to end early next year that on its second-quarter call Merck said was designed to support filing.

Investors will note that Merck is not alone: Pfizer, for one, is working on sasanlimab, a SC anti-PD-1, though as a novel project this could have a tougher regulatory path than a reformulated Keytruda.

And shortly afterwards Roche appeared to jump ahead of Merck and Pfizer, saying it would take to the regulators newly generated data from the Imscin-001 study of a SC form of Tecentriq in post-chemo NSCLC. Imscin-001's phase 1 results showed the SC form to have similar serum trough concentration to IV, and the phase 3 part has now shown pharmacokinetic exposure of SC to be non-inferior to IV.

Roche's new formulation uses Halozyme's Enhanze technology, which also lies behind its SC forms of Rituxan and Herceptin, and which is also the secret sauce in Bristol Myers Squibb's SC nivolumab. As far as more convenient options go, SC has clearly overtaken oral delivery; Gilead's oral PD-L1 inhibitor GS-4224 has been discontinued, while clinicaltrials.gov shows no active studies of Curis's small-molecule anti-PD-L1/Vista, CA-170. Last November Alphamab hailed envafolimab as the world's first SC anti-PD-L1 MAb when this was approved in China for MSI-high or dMMR solid tumours.

Table 11. Selected trials of subcutaneous PD-(L)1 inhibitors

Study	Design	Primary completion
SC form of Tecentriq (Roche)		
BP40657	SC vs IV in 2L NSCLC	Apr 2022
Imscin-001*	SC vs IV in 2L NSCLC	Has data backing pharmacokinetics of SC vs IV
SC form of Keytruda (Merck & Co)		
3475-A86	SC vs IV chemo combo in 1L NSCLC	Feb 2023
SC form of Opdivo (Bristol Myers Squibb)		
Checkmate-67T	SC vs IV in renal cell carcinoma	Dec 2023
Checkmate-6GE	SC vs IV in melanoma	Dec 2023
Envafolimab (KN-035; Tracon/Alphamab/3D Medicines)		
KN035-BTC	Biliary tract cancer	Jan 2024 (last year delayed from 2021)
Sasanlimab (Pfizer)		
Crest	Non-muscle invasive bladder cancer	Jun 2024
SC form of Imfinzi (Astrazeneca)		
Scope-D1**	NSCLC & SCLC	Jan 2024
*Note: *phase "1b/3"; **phase 1/2; all others are phase 3. Source: clinicaltrials.gov.*		

In June Sanofi ceded control of Libtayo to its partner Regeneron in what looked like an acceptance that the French group missed the boat in PD-(L)1 inhibition.

For $900m up front, plus a $100m milestone and an 11% royalty – terms Wells Fargo analysts reckon amount to a $2.7bn deal value – rights passed from Sanofi to Regeneron. The two companies had collaborated on Libtayo's development since 2015, and on the discovery of other antibodies for many years before that. But the discovery deal expired in 2017 without being extended, and Sanofi sold off its $13bn equity stake in Regeneron two years ago, so the latest deal seemed a logical extension of those moves. Sanofi is known to be keen on new business development, and perhaps Regeneron offered it a sum it could not turn down. Regeneron investors thought their company was overpaying, however, and some on the sellside agreed. Wells Fargo analysts wrote in a note to clients that they did not like the deal, saying Libtayo was still a "show-me story", and that Regeneron would now be less attractive as a buyout target.

At least Libtayo is approved in the US, even if it is in a niche use. Many other newcomers' attempts have been set back, with Agenus's withdrawn balstilimab filing coming alongside CRLs for Incyte/Macrogenics' retifanlimab, Lilly/Innovent's sintilimab (see the previous PD(L)anner), and most recently a CRL for Coherus/Shanghai Junshi's toripalimab. If there was good news in toripalimab's US regulatory rejection it was that absence of clinical data relevant to a US population was not the reason behind it. Rather, the CRL cited a manufacturing issue that the companies claim is readily addressable; the filing has been resubmitted, and now has an action date of December 23.

Table 12. Late-stage anti-PD-(L)1 projects yet to be approved in the US

Project	Company	Targeted indication	Supporting study	US regulatory outcome
Retifanlimab	Incyte/ Macrogenics	Chemo-refractory squamous carcinoma of the anal canal	Pod1um-202 (US & Eur)	CRL 23 Jul 2021
Balstilimab	Agenus	2nd-line cervical cancer	NCT03104699	Filing pulled 22 Oct 2021
Sintilimab	Lilly/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; resubmitted, with new 23 Dec 2022 Pdufa date
Penpulimab	Akeso/Sino	3rd-line nasopharyngeal carcinoma	NCT03866967 (China only)	Missed H1 2022 Pdufa date with no outcome*
Tislelizumab	Novartis/ Beigene	2nd-line oesophageal squamous cell carcinoma	Rationale-302 (global)	Missed 12 Jul 2022 Pdufa date with no outcome**
Sugemalimab	Cstone/EQRX	1st-line NSCLC	Gemstone-302 (China only)	EQRX "continuing to engage in discussions with the FDA", but now targeting ex-US
Cosibelimab	Checkpoint (Fortress)	Cutaneous squamous cell carcinoma	NCT03212404	Topline reg-enabling ph1 data Jan 2022
Envafolimab	Tracon/ Alphamab/3D Medicines	1st-line biliary tract cancer (gemcitabine combo)	KN035-BTC	Ph3 trial ends Jan 2024 (delayed from Dec 2021)
Sasanlimab	Pfizer	Non-muscle-invasive bladder cancer (BCG combo)	Crest	Ph3 trial ends Jun 2024
Zimberelimab	Arcus (via Wuxi/Gloriabio)	1st-line PD-L1+ve NSCLC (+/- domvanalimab)	Arc-10	Ph3 trial ends Dec 2025
Cetrelimab	Johnson & Johnson	Muscle-invasive bladder cancer (TAR-200 combo)	Sunrise-2	Ph3 trial ends Dec 2026

*Note: *no formal announcement; **reason given was Covid-related travel restrictions. Source: Evaluate Vantage.*

Notably, not only did the FDA defer a regulatory decision on Novartis/Beigene's tislelizumab (and likely Akeso's penpulimab), Novartis scrapped plans to get the former drug approved in a separate indication, second-line NSCLC. Thus, over a year after ditching its own anti-PD-1 MAb spartalizumab in favour of tislelizumab, the Swiss firm still cannot get the latter across the US regulatory finish line.

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."

Until recently the plan in NSCLC 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.

Table 13. Selected indications for tislelizumab (trademarked Baizean in China)

Study	Setting	Regulatory status		
		EU	US	China
Rationale-301	1st-line hepatocellular carcinoma	–	Filing planned 2023	–
Rationale-302	2nd-line oesophageal sq cell carcinoma	Filing accepted Apr 2022	12 Jul 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 Dec 2019
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.

In Japan the past few months have been quiet on the regulatory front, with the only new approvals being Opdivo's Yervoy or chemo combo for the Checkmate-648 indication, and Keytruda for second-line TMB-high tumours. Merck & Co's second-quarter slide deck revealed three new Japan filings, in cervical and adjuvant renal cancers, and (neo)adjuvant TNBC.

Table 14. Pending regulatory decisions in Japan

Therapy	Indication	Supporting trial(s)
Imfinzi (Astrazeneca)		
Chemo +/- tremelimumab combo	1st-line NSCLC filing acceptance disclosed 10 Feb 2022	Poseidon study
Tecentriq (Chugai (Roche))		
Monotherapy	Adjuvant PD-L1 +ve (≥1%) NSCLC	Impower-010 study
Keytruda (Merck & Co/Taiho)		
Monotherapy	Adjuvant renal cell carcinoma	Keynote-564 study
Chemo +/- Avastin combo	1st-line PD-L1 +ve (≥1%) cervical cancer	Keynote-826 study
Chemo + monotherapy	Neoadjuvant + adjuvant triple-negative breast cancer	Keynote-522 study
Opdivo (Bristol-Myers Squibb/Ono)		
Monotherapy	Cancer of unknown primary	NivoCUP study
Monotherapy	Adjuvant high-risk urothelial carcinoma	Checkmate-274 study
Monotherapy	Adjuvant oesophageal/GEJ cancer	Checkmate-577 study
Chemo (or Yervoy?) combo	1st-line gastric cancer	Checkmate-649 + Attraction-4 studies

Evaluate

a norstella company

Evaluate provides trusted commercial intelligence for the pharmaceutical industry. We help our clients to refine and transform their understanding of the past, present and future of the global pharmaceutical market to drive better decisions. When you partner with Evaluate, our constantly expanding solutions and our transparent methodologies and datasets are instantly at your disposal, along with personalised, expert support.

Evaluate gives you the time and confidence to turn understanding into insight, and insight into action.

Evaluate Pharma offers a global view of the pharmaceutical market's past, present and future performance with best-in-class consensus forecasts to 2028, unique broker forecasts, and the application of proprietary methodologies to support highly robust, detailed and accurate analysis.

Evaluate Omnium provides a complete, dynamic view of development risk and commercial return across all phases of the clinical lifecycle – including early-phase and privately-developed drugs not covered by analysts' forecasts. With product-specific data including Predicted Peak Sales, Probability of Technical and Regulatory Success (PTRS), R&D Costs, Net Present Value, Time-to-Peak and more, Evaluate Omnium makes it easier than ever to quantify and compare risk and return across the full pipeline landscape.

Evaluate Epi is curated by epidemiology experts and delivers comprehensive, global epidemiological data in granular detail, on a highly interrogatable platform. Customers have access to impartial data for 15 therapeutic areas, and over 230 indications and 9,500 sub-populations across 27 core markets (up to 49 for some countries).

Evaluate Medtech provides a transparent and trusted source of market intelligence and consensus forecasting for the global medical device and diagnostic landscape, using the same proprietary methodologies as Evaluate Pharma. Customers can quickly understand how the market views products and portfolios – and where their opportunities, risks and priorities lie.

Evaluate Consulting & Analytics are specialists in solving unique and complex biopharma pipeline, portfolio and commercialisation challenges with best-in-class datasets, powerful analytical capabilities, and deep therapy and commercialisation expertise.

Evaluate Vantage provides award-winning, thought-provoking news and insights on current and future developments in the pharma, biotech and medtech industries, and is the only news service underpinned by Evaluate's commercial intelligence and data.

Subscribe to Evaluate Vantage Daily News

www.evaluate.com | **@Evaluate** **@EvaluateVantage**

Evaluate Headquarters
Evaluate Ltd.
3 More London
London SE1 2RE
United Kingdom
T +44 (0)20 7377 0800

Evaluate Americas
EvaluatePharma USA Inc.
60 State Street, Suite 1910
Boston, MA 02109
USA
T +1 617 573 9450

Evaluate Asia Pacific
Evaluate Japan KK
Holland Hills Mori Tower 2F
5-11-2 Toranomon, Minato-ku
Tokyo 105-0001, Japan
T +81 (0)70 4131 0112