Evaluate Vantage

September 02, 2021

# Tecentriq pullout dominates the latest PD-(L)1 moves

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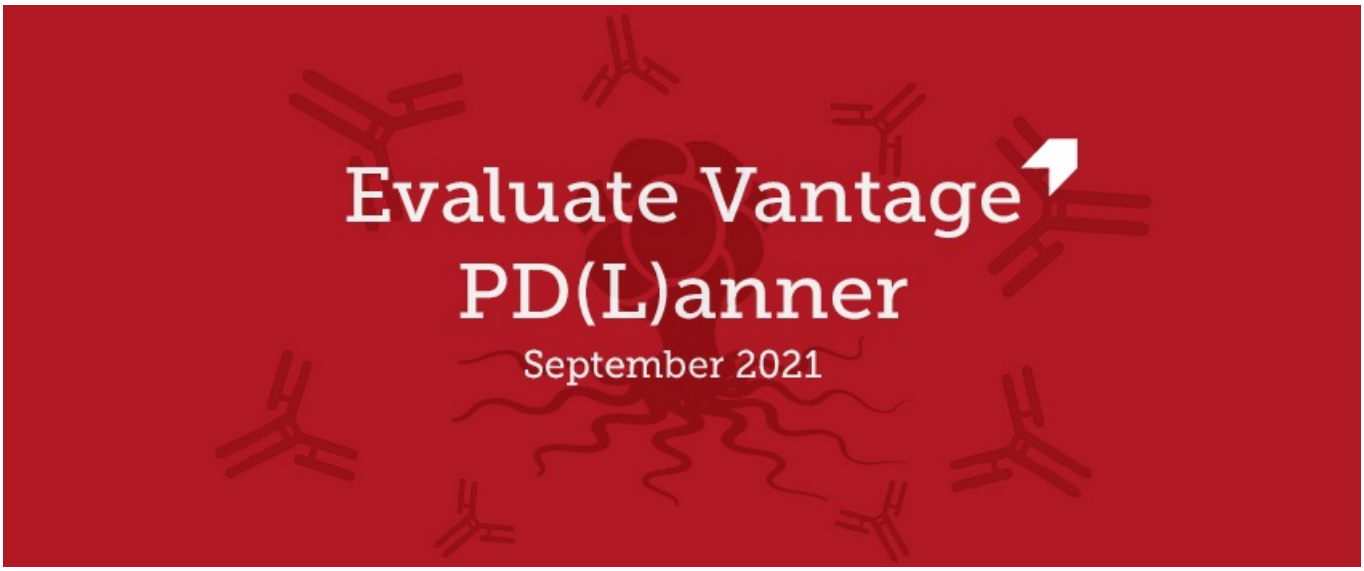


**July and August saw key regulatory and clinical developments for several anti-PD-(L)1 MAbs, with plenty more in store for oncology watchers.**

Welcome to the first in a series of periodic *Evaluate Vantage* updates on developments in the PD-(L)1 inhibitor space.

Perhaps the most significant move in July and August was last week's withdrawal by Roche of Tecentriq's first-line triple-negative breast cancer indication, a use backed by the Impassion-131 trial, but whose accelerated approval failed to be backed by Impassion-130.

The move means that four of six accelerated approvals of anti-PD-(L)1 drugs with failed confirmatory trials scrutinised at an April 27-29 US advisory panel meeting have now been pulled. The remaining two are Merck & Co's Keytruda in second-line liver cancer and in urothelial bladder cancer, an indication that had already been narrowed by the FDA.

The Roche development was surprising because the adcom appeared to have given Tecentriq a relatively strong endorsement, with panellists voting seven to two in favour of retaining the TNBC indication. Moreover, the failed Impassion-130 trial did not demonstrate an overall survival benefit largely owing to a statistical quirk.

Either way, an adcom seen at the time as endorsing most so-called "dangling" PD-(L)1 approvals – those with failed confirmatory studies – has actually resulted in numerous market withdrawals. Perhaps that had always been part of the FDA's thinking when the panel was convened.

Just four days later Keytruda had its front-line urothelial carcinoma label restricted further, specifying that it can only be used in this setting in patients ineligible for platinum chemo; previously it could have been used in those eligible for non-cisplatin chemo if their tumours expressed PD-L1 at ≥10%. On the plus side, this newly restricted use was granted full approval.

**Anti-PD-(L)1 drugs with accelerated US approvals and failed confirmatory trials**

| Drug (company) | Indication | Failed potentially confirmatory trial(s) | 27-29 Apr 2021 adcom vote | Regulatory outcome | Advanced potentially confirmatory trials remaining? |
|---|---|---|---|---|---|
| Keytruda (Merck & Co) | Urothelial bladder cancer (2L/1L) | Keynote-361 (1L) | Keep indication (5-3) | US label narrowed 3 Jul 2018 & 31 Aug 2021 | Keynote-676 (BCG combo in non-muscle invasive bladder cancer) |
| | Liver cancer (2L) | Keynote-240 (2L) | Keep indication (8-0) | None | Keynote-394 (2nd-line Asian patients) |
| | Gastric/GEJ adenocarcinoma (3L) | Keynote-061 (2L) & 062 (1L, inconclusive) | Withdraw (6-2) | Withdrawn 1 Jul 2021 | Keynote-585 (neoadjuvant/ adjuvant chemo combo) |
| | SCLC (3L) | Keynote-604 (1L) | (NA - already withdrawn) | Withdrawn 1 Mar 2021 | No |
| Tecentriq (Roche) | Urothelial bladder cancer (1L) | Imvigor-211 (2L) | Keep indication (10-1) | US label narrowed 3 Jul 2018; 2L use withdrawn 8 Mar 2021 | Imvigor-130 final readout |
| | TNBC (1L) | Impassion-131 (1L) | Keep indication (7-2) | Withdrawn 27 Aug 2021 | Impassion-132 (note OS benefit in Ipassion-130 not statistically tested) |
| Opdivo (BMS) | Liver cancer (2L) | Checkmate-459 (1L) | Withdraw (5-4) | Withdrawn 23 Jul 2021 | Checkmate-9DX (adjuvant) |
| | SCLC (3L) | Checkmate-331 (2L) & 451 (1L) | (NA - already withdrawn) | Withdrawn 29 Dec 2020 | No |
| Imfinzi (Astrazeneca) | Urothelial bladder cancer (2L) | Danube (1L, tremelimumab combo) | (NA - already withdrawn) | Withdrawn 22 Feb 2021 | Nile (tremelimumab combo) |

*Source: Company information*

In other regulatory developments Bristol Myers Squibb's Opdivo got its third US endorsement as adjuvant treatment – a setting that is vital if Opdivo is to regain lost ground on Keytruda.

On August 20 the FDA approved Opdivo for adjuvant high-risk urothelial carcinoma on the basis of the Checkmate-274 study, which at this year's Asco-GU meeting was reported as showing the drug improving disease-free survival to 21.0 months, versus 10.9 months for placebo recipients, amounting to a 30% reduction in disease recurrence at any point.

Interestingly, Opdivo's updated label makes no mention of muscle-invasive disease, the specific setting for the Checkmate-274 data. The approval is especially important since Roche's rival Tecentriq failed Imvigor-010, a separate trial as adjuvant therapy in high-risk, muscle-invasive urothelial carcinoma.

Two months earlier the US regulator had greenlit Opdivo for adjuvant treatment of oesophageal/gastroesophageal junction cancer on the basis of Checkmate-577. The Bristol drug's other approved perioperative use is for adjuvant melanoma, dating back to 2017.

Keytruda is of course also in the perioperative game, its own 2019 adjuvant melanoma label being supplemented in July with US approval for neoadjuvant and adjuvant triple-negative breast cancer.

This is backed by the controversially designed Keynote-522 trial, which is very similar to Tecentriq's Impassion-031 trial, which like Keynote-522 has yielded positive pCR data but – unlike the Merck study – has yet to show an effect on its much more important event-free survival endpoint.

## Recent approvals of anti-PD-1/PD-L1 MAbs

| Approval date | Region | Therapy | Indication | Supporting trial(s) |
|---|---|---|---|---|
| **Annik/penpulimab (Akeso)** | | | | |
| 5 Aug 2021 | China | Monotherapy | 3rd-line classical Hodgkin's lymphoma | Unclear |
| **Jemperli (Glaxosmithkline/Anaptysbio)** | | | | |
| 19 Aug 2021 | US | Monotherapy | 2nd-line dMMR solid tumours | Garnet study (AA) |
| **Imfinzi (Astrazeneca)** | | | | |
| 19 Jul 2021 | China | Chemo combo | 1st-line SCLC | Caspian study |
| **Tecentriq (Roche)** | | | | |
| 31 Jul 2020 | US | Cotellic+Zelboraf combo | 1st-line Braf +ve melanoma | Imspire-150 study |
| **Opdivo (Bristol-Myers Squibb/Ono)** | | | | |
| 25 Aug 2021 | Japan | Cabometyx combo | 1st-line renal cell carcinoma | Checkmate-9ER study |
| 20 Aug 2021 | US | Monotherapy | Adjuvant high-risk urothelial carcinoma | Checkmate-274 study |
| 30 Jul 2021 | EU | Monotherapy | Adjuvant oesophageal/GEJ cancer | Checkmate-577 study |
| **Keytruda (Merck & Co)** | | | | |
| 26 Aug 2021 | Japan | Monotherapy | 1st-line MSI-H or mismatch repair-deficient colorectal cancer | Keynote-177 study |
| 26 Aug 2021 | Japan | Chemo combo | 1st-line PD-L1 +ve (≥10%) triple-negative breast cancer | Keynote-355 study |
| 11 Aug 2021 | US | Lenvima combo | 1st-line renal cell carcinoma | Keynote-581/Clear study |
| 27 Jul 2021 | US | Chemo+monotherapy | Neoadjuvant + adjuvant triple-negative breast cancer | Keynote-522 study |
| 6 Jul 2021 | US | Monotherapy | Locally advanced cutaneous squamous cell carcinoma not eligible for surgery/RT | Keynote-629 study |

Other recent US approvals were rounded out by Keytruda's combo with Lenvima in front-line renal cell carcinoma, cementing Merck's lead in this fast-changing space, and a nod for Tecentriq plus Cotellic and Zelboraf in first-line Braf-positive melanoma.

Glaxosmithkline/Anaptysbio's Jemperli, meanwhile, had its initial second-line MMR-deficient endometrial cancer label expanded to comprise all second-line dMMR solid tumours, still on an accelerated basis and backed by the same Garnet trial. This drug's big threat is Keytruda, which has a March 28 2022 Pdufa date for a US regulatory decision in second-line MSI-high/dMMR endometrial carcinoma, backed by Keynote-258's cohorts D and K, to be presented in full at Esmo.

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