Evaluate Vantage

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# Three days of reckoning for checkpoint blockers

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## Planning for this week's three-day adcom on US accelerated approvals for anti-PD-(L)1 drugs? Here's the background info you need.

The US advisory panel scrutinising selected accelerated approvals of Tecentriq, Keytruda and Opdivo kicks off tomorrow, but its most contentious session might take place on Wednesday, recently released briefing documents reveal.

It is on Wednesday that panellists are set to discuss Tecentriq and Keytruda's availability in urothelial bladder cancer – a highly complex and controversial area that has already seen two withdrawals and two label restrictions. With the FDA's reputation at stake the market will work hard to ascertain any shifts in the regulator's body language.

While the precise voting questions have not been set yet, in general the FDA seeks guidance on whether the six indications should stand. And the stated purpose of the adcom is to advise the US regulator on the next steps it should take, if any, for each drug based on the results of previous studies and the status of any ongoing or planned trials.

**Bladder complexity**

As a recent report by *Evaluate Vantage* describes, perhaps the most complex issue for panellists will be that of Tecentriq in first-line bladder cancer. The drug has already been voluntarily withdrawn in the second-line setting, as has Astrazeneca's Imfinzi, while Keytruda and Tecentriq had their first-line labels narrowed in 2018.

Briefing documents for Tecentriq and Keytruda alike in bladder cancer note the recent approval of Merck KGaA/Pfizer's Bavencio for this indication's maintenance setting. This new option for patients will not help Tecentriq or Keytruda's case, even before considering their failed confirmatory studies.

When the adcom kicks off tomorrow the discussion might be a bit less polarised. Tecentriq in triple-negative breast cancer did fail the confirmatory Impassion-131 trial, but it might have shown an overall survival benefit in PD-L1-positive patients in its original Impassion-130 trial were it not for a statistical quirk.

Though the briefing documents stress that the OS benefit in Impassion-130 "cannot be considered clinically meaningful", an addendum to the adcom reveals that Roche had met the FDA last December 1 to discuss running a new trial replicating Impassion-130, but that doing so would be problematic because it would deprive placebo recipients of what has become standard of care.

| What to expect at this week's adcom | | | |
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| **Drug** | **AA indication under review (briefing docs)** | **FDA guidance sought** | **Cited relevant studies yet to read out** |
| *Tue, April 27 (1pm-3:45pm ET)* | | | |
| Tecentriq | 1L (PD-L1 ≥1%) triple-negative breast cancer | Should indication be retained while additional trial(s) are conducted or completed? | Impassion-132 (NB: uses different chemo backbone; OS benefit in Impassion-130 not statistically tested) |
| *Wed, April 28 (9am-3pm ET)* | | | |
| Keytruda | 1L (chemo ineligible) urothelial bladder cancer | Should indication be retained while additional trial(s) are conducted or completed? | Leap-011 (1L, also has Lenvima combo arm), & Keynote-866 (neoadjuvant, muscle-invasive bladder cancer) & 905 (perioperative, muscle-invasive bladder cancer) |
| Tecentriq | 1L urothelial bladder cancer (chemo ineligible; PD-L1 ≥5% if eligible for non-cisplatin) | Should indication be retained pending final OS result from Imvigor-130? | Final OS readout from Imvigor-130 (expected Q4 2021) |
| *Thu, Apr 29 (9am-5:30pm ET)* | | | |
| Keytruda | 3L (PD-L1 ≥1%) gastric/GEJ adenocarcinoma | Further discussion regarding continued marketing is needed | Keynote-859 (checkpoint-naive), 811 (Her2-positive, Herceptin combo) & 585 (neoadj/adj) |
| Keytruda | 2L hepatocellular carcinoma | Should indication be maintained pending final results of one of the ongoing randomised trials? | Keynote-394 (Asian pts) & Leap-002 (1L, Lenvima combo) |
| Opdivo | 2L hepatocellular carcinoma | Should indication be maintained pending final results of one of the ongoing randomised trials? | Checkmate-9DX (adjuvant), 9DW (1L, Yervoy combo) & 74W (Yervoy + TACE combo) |
| *Source: FDA, clinicaltrials.gov & Evaluate Pharma.* | | | |

This highlights one of the problems the FDA might face if it tries to get even tougher with companies. In a recent "Perspective" piece in the NEJM Drs Julia Beaver and Richard Pazdur argued for a measured stance, claiming that conditional approvals left "dangling" because their clinical benefit has ultimately not been confirmed are the exception rather than the rule.

The authors claim that failure of a confirmatory study should not be viewed as a failure of the accelerated approval pathway, but rather as an "expected trade-off" in expediting drug development via a process that has allowed some oncology drugs to be made available much sooner than before, and brought meaningful survival advantages to patients.

On the other hand, the US drug cost watchdog Icer has called for some degree of action by the FDA to overhaul the accelerated approvals process so that a balance can be maintained between uncertainty, access, innovation and cost.

While praising some accelerated approval successes, Icer specifically calls out Sarepta's Exondys 51 as an example of the worrying direction in which this regulatory pathway has recently headed. No doubt these and many other issues will be aired extensively this week.

*Evaluate Vantage's report on the FDA's ongoing scrutiny of the status of some controversial drug approvals can be downloaded for free.*

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