Evaluate Vantage

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Dangling PD-1s emerge strong from three-day grilling

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A US advisory panel has largely endorsed three anti-PD-(L)1 drugs, with voting apparently driven by the availability of alternatives.

If the purpose of the US FDA and its acting commissioner, Janet Woodcock, in convening this week's three-day adcom was to show its new-found strictness then the meeting has – just about – given the agency ammunition to withdraw two anti-PD-(L)1 drug indications.

Overall, however, the adcom turned into a tedious exercise in rehashing information already provided in briefing documents, and even the most contentious use, Tecentriq in front-line bladder cancer, got a ringing endorsement from panellists. As for the four uses that had already been pulled voluntarily, perhaps their sponsors are now wondering whether they should have resisted.

Of course, few really know what discussions had taken place between the FDA and Merck & Co, Roche, Bristol Myers Squibb and Astrazeneca before the adcom. As such it can only be guessed how much pressure the agency had exerted to result in the withdrawals of Tecentriq and Imfinzi in second-line bladder cancer, and Opdivo and Keytruda in SCLC.

Either way, on balance the industry has emerged from the adcom stronger than it went in.

Summary results of 27-29 April adcom					
Drug	**AA cancer indication under review**	**Question**	**Pros**	**Cons (in addition to failing confirmatory trial)**	**Result**
Tecentriq	1L (PD-L1 ≥1%) triple-negative breast	Keep indication pending further trial data?	Alternative trials have different chemo backbone	OS not significant in Impassion-130 Possible OS detriment in Impassion-131	YES (7-2)
Keytruda	1L (chemo ineligible) urothelial bladder	Keep indication pending further trial data?	Lack of options for chemo-ineligible patients Keytruda has full 2nd-line approval	Bavencio maintenance approved with OS benefit	YES (5-3)
Tecentriq	1L urothelial bladder (chemo ineligible; PD-L1 ≥5% if eligible for non-cisplatin)	Keep indication pending Imvigor-130 final OS result?	Lack of options for chemo-ineligible patients	2nd-line use voluntarily withdrawn Also failed adjuvant study (Imvigor-010) Bavencio maintenance approved with OS benefit	YES (10-1)
Keytruda	3L (PD-L1 ≥1%) gastric/GEJ adenocarcinoma	Keep indication pending further trial data?	Alternative trials will not assess monotherapy	Low ORR shown in Keynote-059 Opdivo approved 1L with OS benefit	NO (6-2)
Keytruda	2L hepatocellular	Keep indication pending further trial data?	Potentially confirmatory Keynote-394 trial reads out soon	Low ORR shown in Keynote-224 Tecentriq + Avastin approved 1L with OS benefit	YES (8-0)
Opdivo	2L hepatocellular	Keep indication pending further trial data?	Numerical OS benefit in failed Checkmate-459 trial	Low ORR shown in Checkmate-040 Tecentriq + Avastin approved 1L with OS benefit Yervoy combo to retain 2L label, with higher ORR than monotherapy	NO (5-4)
Source: FDA adcom.					

Overall, the argument that seems to have played best with panel members was that certain indications should not be withdrawn because doing so would leave patients with no meaningful treatments – irrespective of the fact that the drug in question actually offered no clinically demonstrated benefit.

This seemed to sway the positive vote in favour of Tecentriq in chemo-ineligible urothelial bladder cancer, which a report by Evaluate Vantage had argued was perhaps the most complex issue of the three days. The recent approval of Bavencio maintenance was of little importance here, since that label does not help patients who are ineligible for chemotherapy.

A chemo-ineligible bladder cancer label was endorsed for Keytruda following similar logic, as well as the fact that the Merck & Co drug has a demonstrated overall survival benefit second line. In contrast, the second-line setting was one that Roche had already withdrawn for Tecentriq.

The panel’s backing for Tecentriq in triple-negative breast cancer was perhaps less contentious, given the statistical quirk that resulted in an OS advantage not being demonstrated in the Impassion-130 trial.

Thus it was not until yesterday that the adcom backed the withdrawal of two uses, Keytruda in late-line gastric and Opdivo in second-line liver cancer. Even so, the votes against were not unanimous, and clearly the FDA is not bound to follow any panel advice.

Both settings have recently seen new front-line entrants backed by OS data – Opdivo, and Tecentriq plus Avastin, respectively – meaning that patients have other options. And both had weak clinical backing anyway, in terms of remission rates demonstrated.

Pazdur steps in

There were interventions by Dr Richard Pazdur, director of the FDA’s Oncology Center of Excellence, who in arguing against these two uses might have helped swing the voting. This is ironic, as Dr Pazdur had earlier co-authored a “Perspective” piece in the NEJM that supported conditional approvals and argued for a measured stance.

Interestingly, however, a similar second-line, post-Nexavar liver cancer setting for Keytruda was endorsed, and by the adcom’s only unanimous vote, no less. Perhaps what also worked against Opdivo monotherapy was that, in any case, Opdivo plus Yervoy would remain available for second-line liver cancer.

It is now over to the FDA to decide how to act on the adcom’s recommendations, and on what further action to take.