Evaluate Vantage

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Immuno-oncology approval conflict in the firing line

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Opdivo's additional US approval for second-line liver cancer highlights what could be a growing disparity between the FDA and its European counterpart. Bristol-Myers Squibb had earlier quietly dropped its EU application for the same use after the CHMP had told it that Opdivo could not have been approved on the data presented.

The issue likely centres on the validity of remission rates – an extremely important surrogate endpoint in immuno-oncology – when separate ongoing trials are shortly to yield survival data. Two other anti-PD-(L)1 approvals on Friday also highlighted the point.

These others concerned Merck & Co's Keytruda, rubber-stamped by the FDA for PD-L1-positive third-line gastric cancer, based on responses seen in the phase II Keynote-059 trial, and Roche's Tecentriq, given the EU green light for second-line NSCLC after showing an overall survival benefit in the phase III Oak study.

The Roche approval came roughly a year after Tecentriq got the second-line NSCLC nod from the US FDA, and it is noteworthy that the Swiss group felt the need to file on hard survival data seen in Oak rather than pursuing an accelerated strategy using one of the NSCLC trials that had earlier shown a benefit in remission rates.

Tecentriq approvals in major Western markets

Region	Therapy	Indication	Notes
US & EU	Monotherapy	2nd-line NSCLC	Oak study
US & EU	Monotherapy	1st-line urothelial carcinoma (chemo ineligible)	Imvigor-210 study

Showing a benefit on disease remission has become an important surrogate endpoint in immuno-oncology because the striking improvements often seen have deemed it unethical to wait for a survival benefit to emerge before allowing approval. Moreover, progression-free and overall survival advantages have proved tricky to demonstrate because of pseudoprogression and study crossover.

Such considerations have apparently cut little ice with the EU regulator, which two weeks ago revealed that Bristol had pulled its Opdivo filing in liver cancer.

While relying on remission rates is not spelled out as the stumbling block, this is a likely reason. The study on which Bristol was relying, Checkmate-040, which yielded durable remissions in around 20% of patients, was deemed to be insufficient to support approval.

It should be noted that Checkmate-459, a phase III study with a Nexavar control arm, is ongoing and due to read out in a year's time. If the EU application is now destined to languish until Checkmate-459 yields survival data, the same problem has not troubled the US FDA, which on Friday approved Opdivo for liver cancer based on Checkmate-040.

Opdivo approvals in major Western markets			
Region	**Therapy**	**Indication**	**Notes**
US	Monotherapy	2nd-line liver cancer	Checkmate-040 study
US	Monotherapy	2nd-line MSI-H or mismatch repair-deficient colorectal cancer	Checkmate-142 study
US & EU	Monotherapy	2nd-line squamous head & neck cancer	Checkmate-141 study
US	Monotherapy	2nd-line urothelial carcinoma	Checkmate-275 study
US & EU	Monotherapy	3rd-line classical Hodgkin lymphoma	Checkmate-205 study
EU	Yervoy combo	1st-line melanoma regardless of Braf status	Checkmate-067 & 069 studies
US & EU	Monotherapy	2nd-line renal cell carcinoma	Checkmate-025 study
US & EU	Monotherapy	2nd-line squamous & non-squamous NSCLC	Checkmate-017 & 057 studies
US	Yervoy combo	1st-line Braf-positive melanoma	Checkmate-067 study
US & EU	Monotherapy	1st-line melanoma	Checkmate-066 & 037 studies

Meanwhile, Merck's Keytruda US approval, for third-line gastric or gastro-oesophageal junction cancer, was also based purely on a remission benefit – 11-16% seen in the Keynote-059 trial, as reported at Asco this year. This is the first US gastric cancer approval for an anti-PD-(L)1 therapy, so perhaps relying on a surrogate endpoint is less controversial here.

Interestingly, the FDA approval relates specifically to patients whose tumours express PD-L1 – some 55% of the Keynote-059 population. The issue of PD-L1 expression gained fresh importance in Checkmate-214, a renal cancer study of Opdivo presented at Esmo (*Spotlight – Medical disclosure farrago hits Esmo 2017, September 15, 2017*).

Keytruda approvals in major Western markets			
Region	**Therapy**	**Indication**	**Notes**
US	Monotherapy	3nd-line PD-L1-positive gastric cancer	Keynote-059 study
EU	Monotherapy	2nd-line or chemo-ineligible urothelial carcinoma	Keynote-045 & 052 studies
US	Monotherapy	2nd-line MSI-H or mismatch repair-deficient tumours	Keynote-016, 164 & 158 studies
US	Monotherapy	1st-line urothelial carcinoma (chemo ineligible)	Keynote-045 & 052 studies
US	Chemo combo	1st-line Alk & EGFR -ve NSCLC	Keynote-021 study (cohort G)
EU	Monotherapy	3rd-line classical Hodgkin lymphoma	Keynote-087 & 013 studies
US	Monotherapy	4th-line classical Hodgkin lymphoma	Keynote-087 study
EU	Monotherapy	1st-line PD-L1-positive (>50%), Alk & EGFR -ve, NSCLC	Keynote-024 study
US	Monotherapy	2nd-line head & neck cancer regardless of PD-L1 status	Keynote-012 study
US & EU	Monotherapy	1st & 2nd-line melanoma regardless of Braf status	Keynote-001, 002 & 006 studies

In an immuno-oncology approval bonanza Opdivo was also approved on Friday for gastric cancer in Japan – based on the survival benefit shown in the Attraction-2 trial run by Bristol's partner Ono specifically in Japanese patients.

A final note about regulatory reliance on surrogate endpoints is that such approvals have to be confirmed later with a survival benefit. However, as the failure of Roche's Tecentriq in the Imvigor-211 confirmatory study in bladder cancer shows, it would take a brave regulator indeed to revoke approval at a time when cancer patients are demanding PD-(L)1 therapy.

There has been no indication that the US FDA is about to revoke bladder cancer approvals of either Tecentriq or Imfinzi, Bavencio or Opdivo – all greenlit on the strength of remission rates in uncontrolled studies.

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