Evaluate Vantage

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Tecentriq failure puts accelerated approval in a spin

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This morning's shock failure of Roche's Tecentriq to show a survival benefit in second-line urothelial bladder cancer gives the US FDA a headache: should the agency now revoke the drug's approval, granted on an accelerated basis a year ago?

Fresh doubts now surround the reliability of the accelerated approvals of three other agents, Opdivo, Imfinzi and Bavencio – the last granted just yesterday – given Tecentriq's flop. And this is not to mention the biggest irony: Merck & Co's Keytruda, the only anti-PD-1/PD-L1 asset to show a survival benefit in this cancer, is actually the one not to have received US approval (see table below).

It is possible that Merck simply did not view bladder cancer as a big enough indication to bother pursuing under early, accelerated approval. The Keynote-045 trial was stopped early after Keytruda improved overall survival by 2.9 months, reducing risk of death by 27% (p=0.0022), and Merck filed for full US approval, with an FDA action date set at June 14.

It is worth speculating whether the strength of the Keynote-045 result had spurred the US regulator to grant accelerated approvals – based solely on remission rates – to Keytruda's rivals. Yesterday's approval of Merck KGaA/Pfizer's Bavencio came a week after that of Astrazeneca's Imfinzi.

Head-scratcher

Now, with Tecentriq, the FDA faces a double head-scratcher. Not only is the Roche drug approved second-line, it also recently scored an accelerated green light in first-line bladder cancer patients ineligible for chemo – both on the basis of the Imvigor-210 study.

Early data showing striking tumour regressions in bladder cancer patients made Tecentriq the star of the 2014 Asco meeting, and approval came last year based on 15% overall remission rates, including 27% in high PD-L1 expressers (*Therapy focus – Immunotherapy crowds bladder cancer space, May 2, 2017*).

This has been thrown into doubt with Roche's revelation that Imvigor-211, the confirmatory trial for Tecentriq's bladder cancer approval, failed to extend survival.

Bernstein wrote that this was only the second time immuno-oncology did not boost survival in a post-chemo setting, after the not particularly relevant failure of Opdivo in the Checkmate-143 brain cancer study.

Little beyond guesswork is possible until full Imvigor-211 data are presented – Roche had hinted that Asco was a possibility, but September's Esmo meeting now looks a likelier venue. Overall survival can be a tough endpoint to hit if a study allows patient crossover, but it is not clear if this was the case in Imvigor-211.

However, Roche seems to have worked hard to avoid the trap Opdivo fell into in the Checkmate-026 first-line NSCLC trial. It had designed Imvigor-211 to look first at high PD-L1 expressers, then those with any level of expression, followed by all-comers.

Failure suggests that even that easiest first hurdle was missed. Roche said Imvigor-211 responses were similar to those in '210, hinting at outperformance of the chemo arm, though without crossover onto an immuno-oncology agent it is hard to see why control patients – who had mostly failed chemo – would respond after a second dose.

US approval status for anti-PD-1/PD-L1 MAbs in urothelial bladder cancer			
Relevant date	**Indication**	**Study data**	**Trial ID**
Tecentriq (Roche)			
18 May 2016	Accelerated approval for 2nd-line use	15% ORR in Imvigor-210 study	NCT02951767
17 Apr 2017	Accelerated approval for 1st-line (chemo ineligible) use	24% ORR in Imvigor-210 study	NCT02951767
10 May 2017	Failure to show OS benefit in 2nd-line use	Imvigor-211 study	NCT02302807
Opdivo (Bristol-Myers Squibb/Ono)			
2 Feb 2017	Accelerated approval for 2nd-line use	20% ORR in Checkmate-275 study	NCT02387996
Imfinzi (Astrazeneca)			
1 May 2017	Accelerated approval for 2nd-line use	17% ORR in Study 1108	NCT01693562
Bavencio (Pfizer/Merck KGaA)			
9 May 2017	Accelerated approval for 2nd-line use	13% ORR in Javelin Solid Tumor study	
27 Aug 2017	PDUFA date for maintenance treatment approval	16% ORR in Javelin Bladder 100 study	NCT02603432
Keytruda (Merck & Co)			
14 Jun 2017	PDUFA date for full 2nd-line approval	OS 10.3mth vs 7.4mth in Keynote-045 study	NCT02256436
14 Jun 2017	PDUFA date for 1st-line (chemo ineligible) use	24% ORR in Keynote-052 study	NCT02335424

The setback will spur further talk of the need to find biomarkers of response, and hasten the realisation that not all PD-1/PD-L1 inhibitors are created equal. Already Opdivo's NSCLC failure in Checkmate-026, set against Keytruda's success in Keynote-021, suggests that efficacy differences might not be entirely down to study design.

The Keynote-021 result is also relevant because today is the date by which the FDA is to issue a verdict regarding Merck's accelerated approval filing based on this trial (*Event – Merck's daring bid for lung cancer domination, April 28, 2017*). Extrapolating a survival benefit from remission data has been put on decidedly shaky ground.

Ultimately though, for Roche this is not the end of the world. Consensus sellside forecasts are that bladder cancer will make up just 16% of Tecentriq's 2022 sales of $4.9bn, *EvaluatePharma* calculates.

But after Bristol's Checkmate-026 calamity investors have been handed another reminder that with immuno-oncology it will not all be plain sailing. Now it's over to the FDA to decide how to deal with this mess.

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