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Bristol waits for the other PD-1 shoe to drop

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Bristol-Myers Squibb has already been hammered twice this year on disappointments over Opdivo's potential in lung cancer, the latest setback seeing its market cap lose $10bn over the Esmo weekend. Now it faces the prospect of being squeezed in the second-line setting, where Roche's Tecentriq is likely to be approved next week.

Tecentriq is backed by unexpectedly strong data from the Oak trial. Even though Opdivo still retains the advantage of being eligible to treat all-comers second line, the monumental failure of its Checkmate-026 trial suggests that in the long run a gap is opening up that Bristol will struggle to close.

The sellside is fast cottoning on. In a note from Bernstein today Tim Anderson writes that it might no longer be correct to assume that Opdivo will outsell Merck & Co's Keytruda in the long term – even though this is precisely what consensus, and Bernstein itself, still models.

The assault has come quickly and from a several sides. While this year consensus, as compiled by *EvaluatePharma*, still sees Opdivo outselling Keytruda by $4.7bn versus $1.3bn, the Merck agent beats Opdivo hands down in the number of studies initiated, which Jefferies reckons could result in almost twice as many approved indications versus Opdivo.

Much of this is based on an in-depth analysis of ongoing clinical trials by The Cancer Letter, the upshot of which is that there are now 20 anti-PD-1/PD-L1 agents in the clinic, in a combined 803 trials seeking to enrol 166,736 patients. Moreover, Keytruda is being tested in 337 trials, versus just 222 for Opdivo.

A similar analysis by *EP Vantage* last year looked at the burgeoning number of immuno-oncology combination studies ongoing, and the conclusion that this area has become hugely competitive – and perhaps that pharma has staked too much cash on the same horse – is unavoidable.

Pincer movement

Against this pressure Opdivo now looks to be attacked in a pincer movement from Tecentriq in relapsed patients and Keytruda first line – Opdivo's potential in first-line NSCLC has evaporated as the Esmo presentation showed Checkmate-026 to be even worse than expected, with no benefit for Opdivo even in >50% PD-L1 expressers.

The Roche agent has a US FDA action date of October 19 and, given the strength of the Oak data, approval looks certain (*Esmo – Roche shows its heart of Oak, October 9, 2016*). Keytruda, meanwhile, has a US PDUFA date of December 24, based on the Keynote-024 readout in first-line, PD-L1-high, NSCLC patients.

A major evolving theme is whether all PD-1-targeting MAbs might not be the same after all. This is one explanation for the discrepancy between Keynote-024 and Checkmate-026 data in high PD-L1 expressers, though trial design, patient characteristics, PD-L1 assay and luck will have played their part, too.

With Tecentriq the argument is different, because it has a distinct mechanism, blocking the ligand PD-L1, not PD-1. Mechanistically the difference could be significant since, for instance, PD-1 binds to the ligands PD-L1 and PD-L2, while PD-L1 can bind either PD-1 or B7.1 on the T-cell.

Practical differences and similarities between these mechanisms will be closely watched as the next anti-PD-L1 agents – AstraZeneca's durvalumab and Pfizer's avelumab – near the market. It is abundantly clear that Roche has a great asset on its hands, with Oak showing an unexpectedly strong effect in non-squamous and high PD-L1-expressing patients.

For now Bristol's main strength is Opdivo's all-comers label in second-line NSCLC, and Yervoy plus Opdivo leads the combination race, though other combos are coming up strongly, and Yervoy's toxicity remains a major stumbling block.

Consensus sellside forecasts compiled by *EvaluatePharma* before the Esmo data saw Opdivo selling over $13bn in 2022 – double the expected total for Keytruda. The underdog, Tecentriq, stands at some $5.5bn in the same year.

However, a buyside survey by Evercore ISI in the aftermath of Esmo showed mean peak expected Opdivo sales of just $8bn. No doubt the sellside will soon catch up.

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