Evaluate Vantage

November 27, 2018

Testing times for Opdivo – and for the US regulator

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A Yervoy combo of the Bristol-Myers Squibb drug has flunked Checkmate-451, a confirmatory study for treating small-cell lung cancer, and that means decision time for the US FDA.

Bristol-Myers Squibb's latest lung cancer setback, the failure of Opdivo in first-line treatment of patients with small-cell histology, will turn up the heat on the US FDA. The regulator will now need to decide whether the drug's third-line use, granted in August under accelerated approval, should stand.

Those banking on the FDA to continue allowing anti-PD-(L)1 drugs to remain on the market despite numerous failures of so-called confirmatory trials should watch carefully how this situation plays out. The agency might so far have embraced immuno-oncology come what may, but this is now the second time that Opdivo has failed to improved overall survival in SCLC.

Nevertheless, so far its accelerated approval, based on remission rates in the uncontrolled Checkmate-032 study, continues to stand. This trial had tested Opdivo alone or combined with Yervoy in various tumour types, but the SCLC cohort concerned third-line Opdivo monotherapy, and it was this use that resulted in accelerated US approval being granted.

Things started to go wrong last month when the second-line Checkmate-331 trial failed. This was the first of two studies that could have converted Opdivo's accelerated approval in SCLC into a formal label, but it failed to demonstrate an overall survival benefit for Opdivo versus chemo.

The other shoe dropped yesterday, in the front-line setting, with the failure of Checkmate-451. This recently upsized trial tested Opdivo either alone or in combination with Yervoy, given as maintenance while patients were still responding to first-line platinum chemo, but its combination arm failed to beat placebo in terms of overall survival, Bristol said.

Lacking teeth?

A response from the FDA is now awaited. So far the agency has lacked teeth when it comes to checkpoint blockers failing confirmatory studies, such as Roche's Tecentriq and others in urothelial carcinoma, and Merck & Co's Keytruda in gastric cancer (*Will the real FDA please stand up, May 23, 2018*).

Bristol can of course argue that the settings of Checkmate-331 and 451 are not analogous to the approved

third-line use, where there are virtually no other options for patients.

But Evercore ISI's Umer Raffat, for one, thinks Checkmate-451 puts Opdivo's SCLC indication in jeopardy. In a note yesterday he criticised Bristol for looking at the maintenance setting, saying it was unclear what thought process the group had used in deciding not to run a clear, first-line SCLC trial.

A favourable regulatory stance towards immuno-oncology is key to calming investor fears in what has become a volatile market for biotech stocks. Other examples of the FDA's leniency include approving Opdivo plus Yervoy in renal cancer, where the EMA refused to issue a green light because it said the respective benefits of the two agents could not be deduced from the Checkmate-214 trial.

And the US regulator has allowed Astrazeneca's Imfinzi to be marketed to all-comers in stage III NSCLC even though the Pacific trial showed a numerically deleterious effect in PD-L1-negatives, something that resulted in the drug's EU label being restricted to PD-L1 expressers.

Selected trials in small-cell lung cancer

Company	Regimen	Study	Design	Results	Trial ID
Roche	Tecentriq + chemo	Impower-133 (n=403)	First-line	mOS 12.3mth vs 10.3mth	NCT02763579
Bristol-Myers Squibb	Opdivo +/- Yervoy	Checkmate-451 (n=1,327)	First-line maintenance	Failed	NCT02538666
Merck & Co	Keytruda + chemo	Keynote-604 (n=453)	First-line	Mid-2019	NCT03066778
Astrazeneca	Imfinzi + chemo +/- treme	Caspian (n=984)	First-line	H2 2019	NCT03043872

Source: clinicaltrials.gov & company statements.

Meanwhile, SCLC remains an extremely tough lung cancer to treat. But a breakthrough was made this year when first-line Tecentriq plus chemo beat chemo alone in the Impower-133 study.

Though numerically the benefit was small – just 2.0 and 0.9 months of median overall and progression-free survival benefit respectively – this was hit with high statistical significance. Tecentriq thus looks approvable in front-line SCLC, a setting that next year will see two further phase III trials read out: Merck & Co's Keynote-604, and Astrazeneca's Caspian.

Like Checkmate-451 Caspian has been upsized, from 795 to a planned 984 subjects. Astra investors could find this disturbing, perhaps surmising that Caspian was deemed to lack statistical powering.

Certainly, the precedent of Checkmate-451 and other upsized trials does not bode well for Astra, but for now the immediate risk is to Opdivo and to the reputation of the FDA.