Evaluate Vantage

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Real threat to Opdivo’s small-cell chances will come from elsewhere

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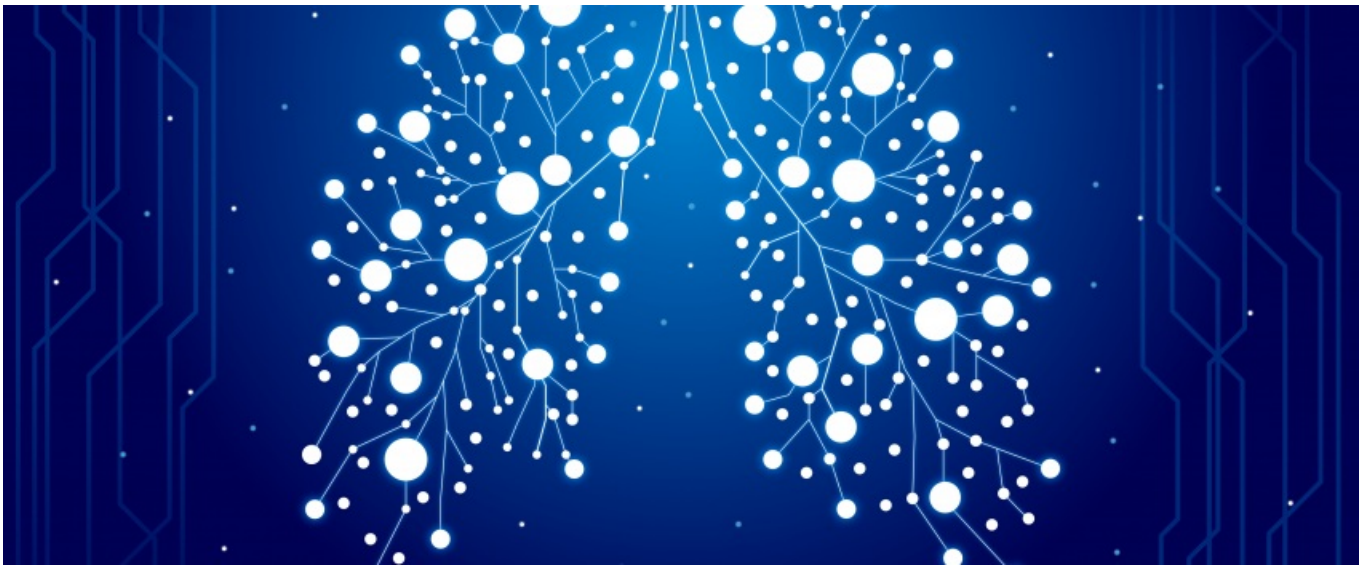

Bristol-Myers Squibb's Opdivo has flunked the Checkmate-331 study, but this is unlikely to lead to the revoking of US approval in this lung cancer setting.

Last week’s failure of Bristol-Myers Squibb’s confirmatory small-cell lung cancer trial, Checkmate-331, raises several questions. The most important relate to the threat of other immunotherapies in this highly intractable cancer, where Roche’s Tecentriq has already delivered the most important advance of the past 30 years.

What might initially seem like a pressing question looks almost certain to be answered in the negative: whether the US FDA should, based on the 331 failure, now revoke Opdivo’s accelerated approval in relapsed SCLC, secured just two months ago. After all, none of the previous three confirmatory trial failures concerning immunotherapies has resulted in approval revocation.

The most remarkable example of the FDA’s reluctance to change its mind came in urothelial bladder cancer, where five anti-PD-(L)1 drugs secured regulatory green lights during an accelerated approval frenzy. 17 months after the failure of Tecentriq’s confirmatory study in this setting none of these approvals has been revoked.

The only FDA action has been to urge doctors not to prescribe Tecentriq beyond the use specified in its label (*Will the real FDA please stand up, May 23, 2018*). Similarly, Merck & Co’s Keytruda retains accelerated approvals for gastric and head and neck cancers, despite last year’s failures of the confirmatory Keynote-061 and 040 trials in these respective settings.

No survival advantage

As such, Opdivo monotherapy is likely to retain third-line SCLC treatment on its label, backed by remission rates seen in Checkmate-032, despite Friday’s failure of Checkmate-331 (a second-line trial) to yield an overall survival advantage.

Interestingly, this was only the fourth SCLC study of a checkpoint MAb to read out, and the third in the relapsed setting, after Checkmate-032 and Keytruda’s positive Keynote-158 trial. These last two showed overall remission rates of 12% and 19% favouring the respective treatment arms.

One reason why Checkmate-331 might have failed is that it enrolled insufficient patients with high PD-L1 expression on their tumours; in Keynote-158 Keytruda’s efficacy was strongly driven by PD-L1-positive subjects. Checkmate-331 recruited all comers, but Bristol has not said what patients’ PD-L1 status was at

baseline.

In the successful Impower-133 trial of Roche's Tecentriq, from which positive data were reported last month, doctors were unable to provide data by PD-L1 status, saying tissue samples were largely of insufficient quality for analysis.

Selected SCLC trials of anti-PD-(L)1 MAbs				
Study	**Treatment line**	**Drug, company**	**Data**	**Trial ID**
Checkmate-032	3rd	Opdivo+/-Yervoy, BMS	ORR 12%	NCT03527251
Keynote-158	2nd	Keytruda, Merck & Co	ORR 19%	NCT02628067
Impower-133	1st	Tecentriq, Roche	mOS 12.3mth vs 10.3mth (p=0.0069)	NCT02763579
Checkmate-331	2nd	Opdivo, BMS	No OS benefit	NCT02481830
Checkmate-451	1st (maintenance)	Opdivo+/-Yervoy, BMS	OS, imminent	NCT02538666
Keynote-604	1st	Keytruda, Merck & Co	OS & PFS, Jan 2019	NCT03066778
Caspian	1st	Imfinzi, Astrazeneca	OS & PFS, Mar 2019	NCT03043872
Source: Clinicaltrials.gov & company filings.				

Impower-133 is highly relevant for another reason: it was carried out in front-line SCLC. While the benefit shown was fairly marginal, the result was hailed as the first study in over 30 years to show a clinically meaningful survival improvement over SCLC standard of care (*World Lung 2018 – Roche gives rivals a small-cell target to shoot for, September 25, 2018*).

The worry for Bristol is that, even if Opdivo is allowed to retain its third-line SCLC label, widespread exposure of first-line patients to Tecentriq might render the relapsed setting irrelevant for immunotherapies.

And the problems do not end there: Merck and Astrazeneca's own first-line trials will read out shortly, and so will Bristol's Checkmate-451. Crucially, however, Checkmate-451 is not a pure front-line trial but rather concerns the first-line maintenance setting.

This means that in an ideal scenario Bristol will be relying on doctors to give chemotherapy first, before adding Opdivo while the patient is still responding. Again, this expectation might no longer be realistic, since Impower-133 suggests that SCLC patients should get Tecentriq immediately on top of chemo before a maintenance treatment phase.

Any Bristol investors fretting about Opdivo's continued standing as an approved SCLC therapy should probably pay attention to the more obvious problems.