Evaluate Vantage

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Three imminent second chances in first-line lung cancer

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Last summer's shock failure of Bristol-Myers Squibb's Opdivo in the Checkmate-026 study brought into play several competing trials of checkpoint inhibitors in first-line lung cancer. Three of these could shortly yield data.

These all involve combinations, and Merck & Co's Keytruda will not relinquish the upper hand in monotherapy, gained at the expense of Opdivo, just yet. However, with a data-rich 2017 barely under way, investors in Astrazeneca, Roche and Bristol already have vital binary events to look forward to.

The spotlight will initially fall on Astrazeneca's durvalumab and Roche's Tecentriq, whose respective Mystic and Impower-150 trials have primary completion dates in January 2017. Actual data reporting could occur later, of course.

Latecomer

Mystic could give Astrazeneca, a latecomer in immuno-oncology, a chance to catch up. The trial combines durvalumab with Astra's answer to Yervoy – the anti-CTLA4 MAb tremelimumab.

It measures progression-free and overall survival as primary endpoints, but only the former is expected to read out imminently. Mystic is important not only owing to its first-line setting, but also because it will indicate how tremelimumab squares up to Yervoy; relatively little clinical data have so far been revealed for tremelimumab, especially on safety.

However, the lack of guidance for Mystic given at Astra's pipeline update last month disappointed analysts. For instance, it is still unclear what statistical plan Astra will use, and how and in which order it will analyse PD-L1 expression cut-offs.

It is also not clear whether PFS might be good enough for approval, or whether OS will need to be shown – this of course goes for all players, not just Astra. In checkpoint inhibitor trials PFS has tended to be a poor proxy for the OS gold standard.

Selected 1st-line NSCLC studies

Study	Treatment	Population	Primary endpoint	Primary completion	Note	Trial ID
Mystic	Durvalumab +/- tremelimumab	1,092 pts	PFS & OS	Jan 2017 (OS 2018)	Statistical analysis plan unclear	NCT02453282
Impower-150	Tecentriq + chemo + Avastin	1,200 non-squamous pts	PFS	Jan 2017	OS is secondary endpoint	NCT02366143
Checkmate-568	Opdivo + Yervoy	590 pts	ORR	Jan 2017	Single-arm study. Enrolment expanded from 170 pts	NCT02659059

After the failure of Checkmate-026 Bristol itself quickly pivoted to Opdivo plus Yervoy combinations in the Checkmate-012 and 568 trials, hinting at generating a data package that could be filed. Checkmate-568 should read out shortly.

However, both of these are uncontrolled studies, and Bristol would be relying on accelerated approval based on a primary endpoint of remission rate – a risky strategy given the first-line availability of Keytruda, albeit in high

PD-L1 expressers (>50%) only.

A measure of Bristol's keenness to make up lost ground is its expansion of Checkmate-568 from 170 to 340 and recently to 590 patients. At Bristol's third-quarter conference call Francis Cuss, its chief scientific officer, said the group was continuing to look at potential for an earlier submission, but cautioned that this depended on data and the FDA.

The group's first controlled trial in first-line NSCLC is Checkmate-227, whose Opdivo plus Yervoy arm has been boosted by 200 patients, but this does not read out until 2018.

In Checkmate-012 adding Yervoy to Opdivo more than doubled objective response rate to 43% in high PD-L1 expressers, Bristol said last month, though it is the effect in PD-L1-low patients that will be key.

Empowering Roche

The last of the trio of near-term readouts is the Impower-150 trial of Roche's Tecentriq. This takes a slightly different approach, combining the anti-PD-L1 MAb not with another immuno-oncology agent but with chemotherapy and Avastin.

Study design again raises questions about the efficacy measure – PFS is its primary endpoint, while OS is a key secondary measure. Moreover, Impower-150 follows Roche's earlier strategy of splitting histologies, and it recruited only non-squamous patients.

The combination is itself controversial, since while some claim that chemo can make a tumour immunogenic and thus apt for checkpoint therapy, others argue that its purpose is fundamentally to be immunosuppressive. Merck and Bristol are also looking at chemo combos, in Keynote-189 and as part of Checkmate-227 respectively.

Either way, the focus of all the big players now is to capture the 70% of first-line NSCLC patients – those expressing PD-L1 at <50% – that are not served by Keytruda monotherapy, and the best way to do this is via combination.

Bernstein analysts have already stressed the need for Merck to get a phase III programme under way quickly for Keytruda plus Yervoy, in case this mechanistic approach becomes dominant. Upcoming data will point the way forward, but when it comes to the competitive threat Merck could find that it only has a short amount of time to play with.

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