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Merck’s first-line lung cancer delay puts more pressure on Bristol

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Merck & Co’s decision to promote overall survival to a co-primary endpoint in Keytruda’s confirmatory first-line lung cancer study, Keynote-189, will delay its readout by 18 months – or roughly a year after Bristol-Myers Squibb’s competing Checkmate-227 yields results.

Perhaps the most important effect of the delay is that it pushes out the risk, however remote, that Keytruda’s US accelerated approval in this vital setting could be rescinded; little wonder that Bernstein called this a “strategic move that makes commercial sense”. It also puts the pressure on Bristol, especially as the Checkmate-227 readout could influence the way Merck analyses Keynote-189.

One increasingly important subgroup analysis concerns tumour mutational burden (TMB), and recent trials, such as Checkmate-032 in second-line SCLC, suggest that this is an important biomarker of response.

However, despite significant pressure from the sellside, Bristol yesterday refused to say whether it had amended the statistical analysis plan of Checkmate-227 to include a specific look at TMB; in contrast, Merck today confirmed that a prospective TMB subgroup analysis would not be carried out in Keynote-189.

Key readouts

The two rival trials, along with Roche’s imminent data in the Impower-150 study, represent some of the most important upcoming readouts in immuno-oncology.

Of course, first-line NSCLC has belonged to Merck since May, when Keytruda plus chemo gained accelerated US approval on the basis of the Keynote-021G trial. Today the company celebrated the first quarter of Keytruda sales above $1bn; some 55% of this was accounted for by NSCLC, and Merck said a third of NSCLC patients were now being started off on Keytruda.

It is also highly unlikely that an accelerated immuno-oncology approval would be rescinded, though the theoretical risk exists. Rather, the three companies are racing to show a survival benefit to influence whether and how their drugs are prescribed by doctors.

With Merck’s change, all three trials – Keynote-189, Checkmate-227 and Impower-150 – now comprise OS and PFS co-primary endpoints. Merck today said its trial had been amended to assign more power to OS; Keynote-021G has already given it confidence in PFS, it stated.

It is not clear whether PFS could be reported before OS – Merck said there were opportunities for interim analyses, and that it would announce PFS once the data turned positive, but that it wanted to “preserve the integrity of the study”. Impower-150 looks like it might yield PFS data imminently; meanwhile, Bristol yesterday said it would decide how to announce the Checkmate-227 result once it saw the data.

Perhaps it is Bristol that is under the most pressure, given the perceived lead that Opdivo lost when its Checkmate-026 first-line NSCLC trial bombed – in part owing to an aggressive design. Merck points out that it will be important to compare across studies the effect of Keytruda with chemo against Opdivo plus Yervoy, given the toxicity that Yervoy is known to add.

Another issue is crossover, something that can hit OS after a positive PFS result by virtue of progressing control arm patients being switched to immuno-oncology. Merck points out that Keynote-021G is continuing to show an OS advantage despite crossover, though in that study only 60-70% of control patients crossed to Keytruda on progression.

That said, Merck accepts that in the real world most patients will be treated with immuno-oncology. “Realistically [Keynote-189] is early Keytruda versus late Keytruda,” it said on today’s call. “That’s the thing we really want to understand, because that’s practice-changing.”

Selected 1st-line NSCLC readouts				
Study	**Treatment arms**	**Comparison**	**Data readout**	**Trial ID**
Impower-150	Tecentriq + chemo + Avastin	Chemo + Avastin	PFS imminent; OS might be 3-6 mths later	NCT02366143
Checkmate-227	PDL1+: Opdivo +/-Yervoy; PDL1-: Opdivo +Yervoy	Chemo	H1 2018 (interim data might be disclosed)	NCT02477826
Keynote-189	Keytruda + chemo	Chemo	Feb 2019 (interim analyses possible)	NCT02578680

Beyond pointing out Yervoy's toxicity Merck would not comment on whether it was looking for Bristol's Checkmate-227 to answer any questions about Keynote-189.

The importance of patients' TMB can be gauged by the fact that the first analyst questions in both Bristol's and Merck's third-quarter calls this week were about this. However, Evercore ISI's Umer Raffat doubts whether Checkmate-227 could at this late stage be modified to include TMB subgroup data cuts.

The issue is lack of powering; in a previous Opdivo trial 58% of patients were evaluable for TMB status, but only 30% of these – depending on the definition – were TMB high, a proportion that would be whittled down further by being split between Checkmate-227's three arms. How TMB is analysed – whole exome sequencing or via Foundation Medicine's cancer-related gene panel, for instance – has also not been decided.

Yet Bristol's silence on TMB is intriguing. It might be that some analysis of this biomarker does end up being done, or simply that Bristol is keeping its options open.

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