Evaluate Vantage

April 13, 2018

AACR preview – an existential crisis for Opdivo

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As the biopharma world's attention turns this weekend to Chicago and what promises to be the most important AACR meeting in recent memory you can't blame Bristol-Myers Squibb investors for feeling uneasy.

They have had to contend with Opdivo falling behind Merck & Co's Keytruda, and on Monday AACR will see Bristol desperately attempt to defend its claim that Opdivo is still relevant in first-line lung cancer, especially after Keytruda's recent success in the Keynote-042 trial. Here are six key questions that the markets will want answered at the meeting.

1. How big is Checkmate-227's PFS benefit in TMB-high subjects?

Bristol famously tore up its analysis design just before reading out the Checkmate-227 study and claiming a progression-free survival benefit in patients with high tumour mutation burden (TMB) given Opdivo plus Yervoy.

The numerical benefit has not been disclosed, but should be on Monday – setting up a head-to-head battle against Merck, which should reveal the overall survival and PFS numbers from its Keynote-189 all-comers trial of Keytruda plus chemo. If the Bristol combo strongly outperforms Keytruda plus chemo Merck might of course carry out its own TMB analysis – something it has not yet done.

2. How many TMB-high patients in Checkmate-227 were PD-L1-low?

Smart investors will look to Bristol to provide data on each of the individual treatment arms in parts 1a and 1b of Checkmate-227, though the company will not confirm whether this will be done; in the study reboot these parts were combined, although Opdivo monotherapy patients are still not considered in primary endpoints, and all Bristol will say is that it "will work with authors to publish additional analyses from Checkmate-227 in due course".

A particularly pertinent data point will be patients' PD-L1 status. If it is found that this correlated with TMB it would throw Bristol's data into further doubt, as PD-L1-high subjects can already receive Keytruda monotherapy. Indeed, it is patients with low PD-L1 expression but high TMB that likely represent the only realistic shred of hope for Opdivo plus Yervoy.

3. How much toxicity did Yervoy add?

Yervoy is a notoriously toxic drug, and without a strong efficacy benefit in Checkmate-227 it might be impossible for it to establish a role in first-line NSCLC, given the availability of Keytruda monotherapy for PD-L1 expressers and Keytruda plus chemo in all-comers.

4. To what extent does all this still matter given Keynote-042?

This week's unexpected topline OS hit for Keytruda in the Keynote-042 trial moved the goalposts further still, and means that the Merck drug's monotherapy use might be extended from >50% PD-L1 expressers to the >1% group, representing some 70% of first-line NSCLC patients. This gives Opdivo – and Roche's Tecentriq – an even smaller slice of the market to play for.

5. How consistent are Keynote-189's PFS and OS benefits across PD-L1 status?

Just as eagerly awaited as Checkmate-227 are numerical data from Keynote-189, also due at Monday's "Immunotherapy combinations" AACR session. Investors' primary focus will be on the hazard ratios for PFS and OS, which they will compare directly across whatever PFS data Bristol reports in TMB-high Checkmate-227 subjects.

However, the importance of Keynote-189 patients' PD-L1 status should not be ignored. If, for instance, all-comer survival is found to be driven by PD-L1 expressers this would undermine the relevance of the overall result, and could open up a gap for Bristol and Roche in patients with low or no PD-L1 expression.

6. How consistent is Impower-150's benefit across PD-L1 status?

For the same reason investors will focus on cuts by PD-L1 status in Roche's Impower-150 trial of Tecentriq combined with Avastin and chemo. This has already yielded numerical survival numbers, and Monday's AACR session will focus on PD-L1 expression subgroups.

AACR 1st-line NSCLC preview: things we know so far

Study	Histology	Treatment	Result	Reference
Keynote-024	Sq & non-sq	Keytruda monotherapy, vs chemo	Basis of accelerated approval for monotherapy in >50% PD-L1 expressers	-
Keynote-021G	Non-sq	Keytruda + chemo, vs chemo	Basis of accelerated approval for chemo combo in all-comers	-
Keynote-042	Sq & non-sq	Keytruda monotherapy, vs chemo	OS met in >1% PD-L1 expressers (no numbers revealed yet)	*Merck tightens grip on first-line lung cancer*
Keynote-189*	Non-sq	Keytruda + chemo, vs chemo	PFS & OS met in all-comers (no numbers revealed yet)**	*Surprise! Keytruda scores early lung cancer win*
Impower-150 (arm B)	Non-sq	Tecentriq + Avastin + chemo, vs Avastin + chemo	PFS 8.3mth vs 6.8mth (HR=0.62); OS 19.2mth vs 14.4mth (HR=0.78)	*All to play for in first-line lung cancer, Roche insists*
Impower-150 (arm A)	Non-sq	Tecentriq + chemo, vs Avastin + chemo	PFS and OS fail at interim, but data insufficiently mature for full analysis	-
Impower-131	Sq	Tecentriq + chemo, vs chemo	PFS met (no numbers revealed yet)	*Tecentriq's chance to seize a poorly served lung cancer type*
Checkmate-026	Sq & non-sq	Opdivo vs chemo	Failed PFS & OS	*Bristol swings for the fences and strikes out*
Checkmate-227 (part 1a)	Sq & non-sq	Opdivo +/- Yervoy, vs chemo (PD-L1>1%)	OS to look at Opdivo + Yervoy subgroup***	-
Checkmate-227 (part 1b)	Sq & non-sq	Opdivo + Yervoy, vs Opdivo + chemo (PD-L1<1%)	No longer considered in primary endpoints	-
Checkmate-227 (1 combined)	Sq & non-sq	Opdivo + Yervoy, vs chemo (excludes Opdivo monotherapy)	PFS met in TMB-high (>10mt/MB) group (no numbers revealed yet)**	*Bristol-Myers turns alchemist to get lung cancer win*
Checkmate-227 (part 2)	Sq & non-sq	Opdivo + chemo (all comers)	Due in 2019	-
Mystic	Sq & non-sq	Imfinzi + tremelimumab, vs chemo	Failed first PFS analysis	*Mystic falls at the first hurdle*
Pacific	Sq & non-sq	Imfinzi vs placebo	Basis of approval for stage III, non-metastatic disease	*Astra makes waves in first-line lung cancer*

*Source: Company reports. Notes: *confirmatory trial for US, and basis of EU chemo combo filing; **numbers & hazard ratios due at AACR; ***PFS in TMB-high, and OS in PD-L1-high, both for Opdivo + Yervoy, are new co-primary endpoints.*

If the Keynote-042 data are numerically strong – this will not be disclosed until after AACR – Keytruda will become even more dominant.

And if this leads to Keytruda's monotherapy approval being extended to >1% PD-L1 expressers that will leave only about 30% of the first-line market to be fought over by Keytruda plus chemo, Tecentriq/Avastin/chemo –

likely to be favoured by doctors already used to prescribing Avastin first line – and Opdivo plus Yervoy.

True, some patients will not want or will not tolerate chemotherapy, but it is arguable whether replacing the toxicity of chemo with that of Yervoy is worth it. Indeed, it is hard not to see the tough battle that lies ahead for Bristol – even if it can persuade investors and doctors that TMB is relevant, and that its rewriting of Checkmate-227's design holds water statistically.

A separate consideration is patients' tumour histology. Many of the Merck and Bristol studies enrolled squamous as well as non-squamous subjects, but Roche recently scored a hit in Impower-131 with Tecentriq plus Abraxane and chemo specifically in squamous patients; depending on the extent of the purported PFS benefit this could give the Swiss firm the upper hand in this intractable NSCLC histology.

Still, while Roche has yet to reveal its first-line NSCLC filing strategy, it is Bristol that has the most to prove. An especially prominent red flag is the group's astonishing choice of Checkmate-227's new co-primary endpoints: PFS in TMB-high subjects across most of the combined 1a and 1b groups, but OS only in Opdivo plus Yervoy subjects with high PD-L1 expression in group 1a.

Was this done because high TMB is known not to correlate with an OS benefit? AACR will not provide an answer, but this does not mean that investors should stop asking the question, and they should also remain highly sceptical over any other gaps in Checkmate-227 data.

This story has been corrected to reflect the redesign of Checkmate-227.

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