Evaluate Vantage

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Bristol-Myers turns alchemist to get lung cancer win

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Bristol-Myers Squibb launched an audacious bid to regain lost ground in the valuable first-line lung cancer space today, declaring a win for Opdivo plus Yervoy in the Checkmate-227 study on one of the trial's co-primary endpoints and describing the result as a "breakthrough in cancer research".

However to achieve this result the company had to abandon its original statistical analysis plan and create a whole new cohort of patients stratified by tumour mutation burden (TMB). True, the new design was approved by the US FDA and TMB is becoming widely recognised as an important biomarker for immunotherapies. But with details thin on the ground and crucial overall survival data still unavailable, heralding Checkmate-227 as a game-changer feels premature.

Checkmate-227 details						
Trial	**Population**	**n**	**Active arm(s)**	**Comparator**	**Primary endpoint(s)**	**Next data**
Checkmate-227 part 1A	PD-L1 +ve	>1,200	Nivo + ipi	Soc chemo	OS in PD-L1 +ve, PFS in high TMB	Final data late 2018/early 2019
			Nivo		?	
Checkmate-227 part 1b	PD-L1 -ve	500	Nivo + ipi	Soc chemo	PFS in high TMB	
			Nivo + chemo		?	
Checkmate-227 part 2	All comers	750	Nivo + chemo	Soc chemo	OS	2019
Approximately 45% of the TMB-evaluable patients had tumours that expressed high (≥10 mut/mb) TMB in the study.						

Checkmate-227 was already a complicated study, effectively three trials in one, with patients stratified by PD-L1 status and testing Opdivo as a monotherapy and in combination with Bristol's anti-CTLA4 drug Yervoy.

According to Clinicaltrials.gov, OS and PFS were always co-primary endpoints, but presumably these were originally going to be run separately on each cohort – parts 1a and 1b, and part 2. Under the new design, the part 1 data are now all about the combination of Opdivo and Yervoy, with a new TMB-high cohort thrown into the mix.

An overall survival analysis will still be done on PD-L1-positive combination patients from part 1a. However, the co-primary endpoint of PFS has been switched to combination patients with high TMB, regardless of PD-L1 status – so patients from both part 1a and 1b. It was in this group that Bristol-Myers today declared a victory, describing the PFS reading as "highly statistically significant".

Executives said that the part 2 result – due next year – would help answer the question of what Yervoy adds to the combination. With rival Merck & Co already on the market with Keytruda plus chemo in first-line lung, Bristol really needs to prove that Yervoy brings something to the party.

"The data makes us confident that Yervoy is a big part of this," Tom Lynch, chief scientific officer, told investors. Yervoy is "clearly critical to the TMB high population".

Given the known toxicities of the anti-CTLA4s – and presumably the higher cost of two I-O agents versus I-O

plus chemo – this will remain an important question. Undeterred, Bristol-Myers made it clear that it intends to get these data to regulators as soon as possible.

Further questions

The role of Yervoy is far from the only outstanding question on Checkmate-227. Notably, the first question on Bristol's investor call this afternoon was why an OS analysis on the TMB high cohort was absent from the primary endpoint. This is a puzzling decision considering the lengths the company went to talking up this biomarker today.

Bristol-Myers claimed that this was to preserve "optionality" but, although there is much encouraging evidence about TMB as a predictive biomarker, hard data are relatively scarce. And, as Evercore ISI analyst Umer Raffat pointed out today, while high TMB status correlated with a PFS benefit in the earlier Checkmate-026 study and Roche's Oak lung cancer trial, no correlation was seen at the overall survival readouts.

An OS analysis will be done on the TMB cohort of Checkmate-227 – presumably as a secondary endpoint.

Other outstanding issues include the definition of "high" for TMB. Bristol-Myers chose 10 mutations per megabase as its cutoff, but executives admitted that this could shift with further research, and might not apply to other tumours.

These and other questions make this initial look at Checkmate-227 very hard to interpret. Investors are clearly scratching their heads – after opening 4% higher, Bristol shares were down 4% at the close. All pharma stocks fell on the day, amid a wider stock market rout.

Bristol will be desperate for a win after the big misstep with Checkmate-026 (*Bristol swings for the fences and strikes out, August 5, 2016*). Chief executive Giovanni Caforio can talk about making "bold and innovative changes" as the science evolves, but not everyone is convinced. Substantial changes to statistical plans or the addition of new data subsets – even when done prospectively and with the permission of regulators – should raise red flags.