Evaluate Vantage

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Bristol makes investors squirm a little more

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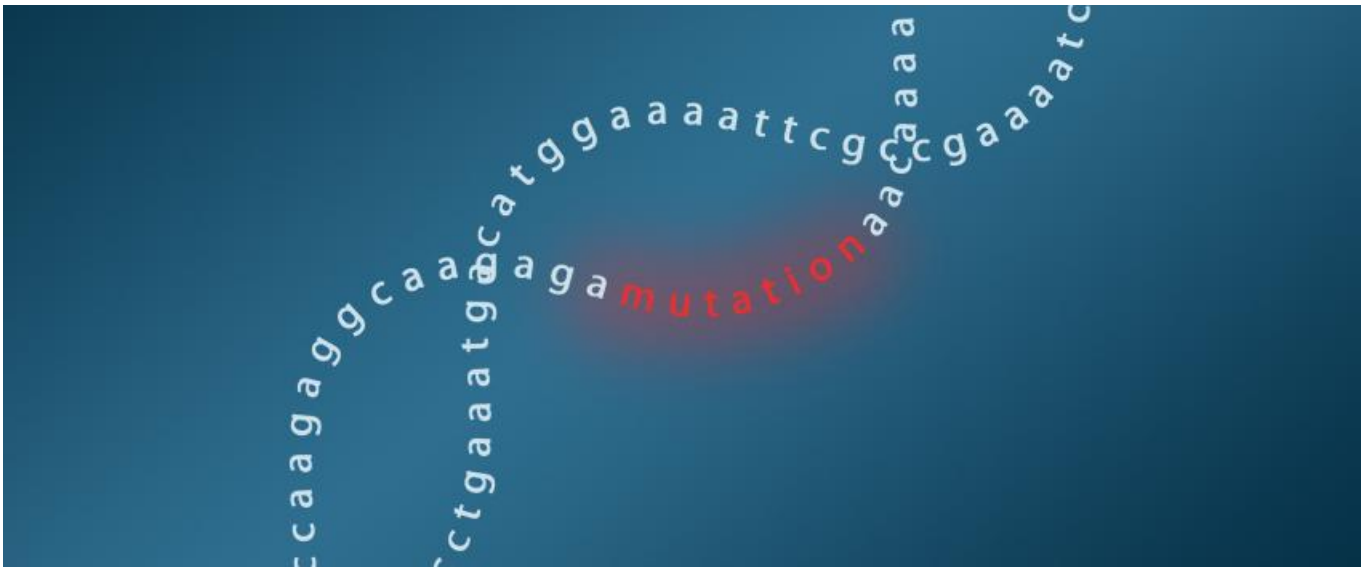

The latest setback to Bristol-Myers Squibb's first-line lung cancer plan sees it pull its US filing for Opdivo plus Yervoy.

Bristol-Myers Squibb bulls who still cling to the hope that tumour mutation burden might provide Opdivo and Yervoy a way into first-line treatment of lung cancer have had an uncomfortable few months. Today the company made them squirm some more, revealing that it was pulling its US filing in this setting.

This decision, it said, was driven by a US FDA request for data from part 1a of the Checkmate-227 trial that are not yet available. Investors following the sorry saga of this study might shrug and wonder what difference yet another delay makes, but one read of the situation is the regulator has lost any confidence it might have had in tumour mutation burden (TMB) as a predictive biomarker.

To understand why this might be the case it is necessary to go back a year to Bristol's first unveiling of Checkmate-227, a study originally designed in three parts – 1a and 1b, cutting patients by PD-L1 expression, and part 2, looking at Opdivo without Yervoy in all-comers.

This design was torn up at the eleventh hour to look at parts 1a and 1b combined but cut by TMB, a move that yielded Bristol its purported win on progression-free survival for Opdivo plus Yervoy versus chemo (*Bristol-Myers turns alchemist to get lung cancer win, February 5, 2018*).

A favourable interim overall survival for TMB-high patients in part 1 was presented at the AACR meeting, and a US filing followed. But things unravelled last October, when an EU regulatory request for overall survival in TMB-low subjects revealed a virtually identical hazard ratio to that in TMB-highs.

Furthermore, the added data had to be submitted to the FDA, which deemed this a major amendment and delayed its approval decision by three months to May 20, 2019. With today's pulling of the whole file the chances of and timeline for approval in first-line NSCLC become open questions.

Why 1a?

If you are still following the convoluted development of Checkmate-227 you might wonder what the relevance of part 1a is, and why the FDA has suddenly expressed an interest in it. After all, parts 1a and 1b were combined for the PFS analysis, while standalone analysis of part 1b was effectively ditched.

The relevance is that one of Checkmate-227's co-primary endpoints is final overall survival in part 1a – meaning in PD-L1-high subjects. A pessimistic view therefore is that the FDA, seeing the preliminary TMB-based overall survival analyses, has determined that there is no value in TMB, and that it is switching attention

back to PD-L1, although this cannot be confirmed.

As an aside, Bristol today delayed slightly the timing for further Checkmate-227 readouts, as well as that for Checkmate-9LA, another trial it has been touting as a way into first-line NSCLC, possibly also by way of a TMB analysis. Investors, therefore, have a few more months of agonising ahead of them.

Bristol stock initially fell 3% in today's pre-market, but recovered to open flat after the company's conference call to present full-year 2018 financials and discuss the NSCLC filing setback. The group insisted that it believed in TMB as a marker of response, but accepted that its understanding was in its early days.

Perhaps the latest delay will give the market more time to ponder the question why any lung cancer doctor would order a TMB test when Merck & Co's Keytruda plus chemo can already be used first-line in the absence of any biomarker testing.

Bristol's unravelling 1st-line NSCLC plan					
Trial	**Active treatment**	**Population**	**Readout**	**Previous timing**	**New timing**
Checkmate-227 part 1	Opdivo + Yervoy	TMB high/low	PFS, interim OS	Reported	
Checkmate-227 part 1a	Opdivo + Yervoy	PD-L1-positive	Final OS	2018/19	H1 2019
Checkmate-227 part 2	Opdivo + chemo	All-comers	OS	Early 2019	Mid-2019
Checkmate-9LA	Opdivo + Yervoy +/- chemo	All-comers (cut by TMB?)	OS	H2 2019	2020