Evaluate Vantage

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Bristol's persistence pays off, but for now the relevance is limited

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Friday's US approval for Opdivo plus Yervoy in first-line non-small cell lung cancer is a reward of sorts for Bristol-Myers Squibb's determination to pursue this use against the odds. The supporting Checkmate-227 trial had been headed for failure, but was overhauled to look at a measure that was subsequently deemed insufficient, before a yet further analysis claimed a post-hoc win that led to a resubmission. But the approval looks fairly inconsequential, given that it applies only to patients whose tumours express PD-L1 at 1% or above; Merck & Co's Keytruda can already be used as monotherapy in precisely these patients, and a Keytruda/chemo combo is approved in all-comers, without any need for PD-L1 testing. And Bristol has been stymied in the EU, where a filing based on this and an earlier analysis was withdrawn after the regulator criticised Checkmate-227's "multiple protocol changes". Bristol's best chance of an all-comers first-line NSCLC label now is the Checkmate-9LA study of Opdivo plus Yervoy plus chemo, on the basis of which a US verdict is expected by August 6. Checkmate-9LA's upcoming Asco presentation is sure to generate interest.

The Checkmate-227 timeline	
Date	**Note**
Nov 2017 (initial design)	Part 1a: O+Y or O mono, vs chemo, in PD-L1+ve
	Part 1b: O+Y or O+chemo, vs chemo, in PD-L1-ve
	Part 2: O+chemo, vs chemo, in all comers
Feb 2018	Bristol claims PFS win in TMB-high patients in O+Y in part 1 combined
May 2018	EMA accepts filing in TMB-high patients
Jun 2018	US FDA accepts filing in TMB-high patients; Feb 2019 action date
Mid-2018	EMA requests OS analysis in TMB-low subjects – and this is almost equal to that in TMB-high cohort
Oct 2018	US FDA considers OS data in TMB-low subjects, and delays action date to May 2019
Jan 2019	Bristol pulls US filing (TMB-high)
Jul 2019	Part 2 fails
Sep 2019	Exploratory analysis of part 1a (PD-L1≥1%) in O+Y all is numerically positive for OS
2019	Part 1a analysis (OS for O+Y in PD-L1≥1%) added to EMA filing
Jan 2020	FDA accepts part 1-based filng; May 2020 action date
Jan 2020	Bristol pulls EMA filing (TMB-high & part 1a)
Apr 2020	Bristol files CM-9LA data in US (6 Aug action date) & EU
May 2020	US approval on CM-227 part 1a data (PD-L1≥1% only)