Evaluate Vantage

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Asco – Bristol-Myers fails to stem the losses

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The loss of $4.3bn in market value yesterday shows how Asco went for Bristol-Myers Squibb this year – in the minds of investors at least. Despite laying out plans for its next wave of immuno-oncology assets at an event over the weekend, the company failed to quash concerns that it is falling even further behind Merck & Co.

Underwhelming two-year survival data from Opdivo plus Yervoy in a phase I lung cancer study probably did most damage; the stakes are incredibly high here ahead of a crucial pivotal read out early next year. Even Bristol's announcement that it would be fast-tracking its in-house IDO inhibitor into pivotal studies could not lift spirits.

Given that IDO is emerging as the next I-O mechanism to watch, this is perhaps surprising. Data released on the Incyte-partnered asset epacadostat showed intriguing response rates across a range of tumours, presenting ways forward for both Merck and Bristol-Myers here (*Asco – Solid progress for IDO inhibitors, June 6, 2017*).

The strong response rates seen in non-small cell lung cancer patients in the Keytruda-epacadostat study Echo-202 were likely interpreted as a further threat to Bristol-Myers' Opdivo-Yervoy combo strategy in this tumour type. The data are far too early to make an informed call on this; however, Bristol's announcement on BMS-986205 is telling of the potential seen in the IDO mechanism.

This in-house IDO inhibitor will be quickly pushed into several registrational studies, including in NSCLC, the company revealed in Chicago, while the collaboration with Incyte will also continue. Having already learnt a painful lesson in lung cancer, with the IDO combination Bristol is clearly making sure every base is covered.

Place at the front

While confirmation of the potential of any PD-1 + IDO combination in lung cancer is still a couple of years away, Bristol's bet on PD-1 + CTLA4 will read out sooner. The confirmatory Checkmate-227 study is due to yield data in the first half of next year – interim read outs could emerge sooner.

This trial will determine whether Opdivo plus Yervoy has a place in the first-line setting, a space where Merck won early approval for Keytruda in combination with chemotherapy last month (*Merck cements its lung cancer lead, May 11, 2017*).

Checkmate-012 is a phase I test of Bristol's combination strategy, although as a very small study (n=77) with no randomised control arm it has clear limitations.

Updated two-year survival data unveiled at Asco appear to show little incremental benefit to adding Yervoy to Opdivo in all comers at two years. When stratified for PD-L1 expression, those in the ≥1% do appear to show a benefit, however notably in the ≥50% group, at two years the Opdivo monotherapy group had a better rate of survival.

Searching for a signal in Checkmate-012			
	All patients	**≥1% PD-L1 expression**	**≥50% PD-L1 expression**
	(n=77 for combo/52 for mono)	(n=47 for combo/32 for mono)	(n=13 for combo/12 for mono)
1-year PFS rates (%)			
Opdivo + Yervoy	43%	53%	64%
Opdivo	21%	24%	38%
2-year PFS rates (%)			
Opdivo + Yervoy	29%	38%	54%
Opdivo	14%	20%	38%
1-year OS rates (%)			
Opdivo + Yervoy	76%	87%	100%
Opdivo	73%	69%	83%
2-year OS rates (%)			
Opdivo + Yervoy	49%	58%	62%
Opdivo	44%	47%	75%

In Keynote-021G, the data on which Keytruda won its early approval, only a progression free survival benefit was seen – overall survival data were confounded by patient crossover. And on PFS, the Opdivo plus Yervoy combination in Checkmate-012 also showed consistently better results than monotherapy.

For what the cross trial comparison is worth, the two strategies appear to show similar survival benefits at one year.

Keytruda vs Opdivo				
	Keynote-021G		**Checkmate-012**	
	Keytruda + chemo	chemo	Opdivo + Yervoy	Opdivo
One-year PFS	56%	34%	43%	21%
One-year OS	76%	69%	76%	73%

The signals from Checkmate-012 are mixed, but with so much a stake it is not surprising that investors are reading into the negatives. And while Checkmate-227 is a very different trial – patients are stratified into PD-L1 expressors (≥1%) and non-expressors (<1%) and it includes a chemotherapy doublet as well as the combination and Opdivo monotherapy arms – the additional toxicity of an anti-CTLA4 agent will be a relevant consideration.

Concerns that Bristol-Myers has conceded much ground in first-line lung are well founded, but there are wider issues here. At Asco, Merck left the impression it had more to say about near-market combinations, which will not satisfy Bristol-Myers investors looking for a quick return to form.

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