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Bristol swings for the fences and strikes out

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Since the first anti-PD-1 agents secured approvals the first-line lung cancer indication has represented the biggest prize on offer. Today Bristol-Myers Squibb paid the price for overreaching with Opdivo and trying to knock Merck & Co's Keytruda, which had a slight time advantage, out of the park.

The failure of Bristol's Checkmate-026 trial is a huge blow for the group, whose stock crashed 17% this morning – losing $20bn of market cap – while Merck climbed 7%. Bristol now awaits results of a Yervoy combo study in this setting, after what looks like immuno-oncology's biggest upset so far.

It is very easy to say in hindsight, but the problem with Checkmate-026, an open-label trial testing Opdivo in 535 first-line NSCLC patients, was its design. Bristol had moved aggressively, recruiting relatively low PD-L1-expressing patients, and the first analysis concerned 5% or higher expressers, with the primary endpoint set at progression-free in preference to overall survival.

Perhaps it was just bad luck, or maybe Bristol had feared falling behind Keytruda. The Merck drug's first-line NSCLC trial, Keynote-024, rendered a positive topline result in June, hitting both co-primary endpoints of PFS and OS – but in patients expressing PD-L1 at 50% or above.

Until today the battle was playing out exactly as the sellside had expected. Keytruda was to be first to yield positive first-line NSCLC data in a narrow patient population, before Opdivo regained the upper hand with a benefit in lower PD-L1 expressers.

Indeed, on its second-quarter conference call just a week ago, Bristol was still boasting how Checkmate-026 could allow it to broaden the patient population further: if >5% expressers yielded positive data the company could look at the effect in those with PD-L1 at >1%, representing 70% of first-line patients.

Moreover, a positive PFS benefit could be backed up by OS data, a secondary endpoint. "And we can still file without a positive OS result," said Bristol's chief scientific officer, Francis Cuss.

Now, with Bristol today saying Checkmate-026 was a bust, failing to show a PFS benefit in the 5% or greater PD-L1-expressing population, the rulebook has been torn up.

Early worries

Still, there had been worries among some analysts about an initial reliance on PFS. On Bristol's fourth-quarter call Citi's Andrew Baum specifically raised the issue of so-called "pseudoprogression" – a known problem with some previous immuno-oncology trials that had obscured a potential benefit by making it seem like active patients were progressing as fast as the control group.

But realistically Bristol probably had little choice but to go with PFS. Waiting for an OS benefit to mature would have been unrealistic in a first-line study with the breadth of Checkpoint-026.

As it is Bristol might now try to cut the patient population down, looking at only the 50% or higher expressers, but since this had not been specified in the design of Checkmate-026 it would be exploratory, and would hold little water as regards regulatory filings.

Most likely Opdivo will for now be restricted to second-line use, an approved indication, with first-line reserved for Keytruda in its biomarker subgroup. Checkmate-227, a complex first-line NSCLC trial involving several combinations as well as Opdivo monotherapy, is under way but does not read out until 2018.

Anti-PD-1/PD-L1 MAb approvals in major Western markets				
Approval date	**Region**	**Therapy**	**Indication**	**Notes**
Tecentriq (Roche)				
18 May 2016	US	Monotherapy	2nd-line urothelial carcinoma	IMvigor 210 study
Opdivo (Bristol-Myers Squibb/Ono)				
17 May 2016	US	Monotherapy	3rd-line classical Hodgkin lymphoma	CheckMate-205 & 039 studies
11 May 2016	EU	Yervoy combo	1st-line melanoma regardless of Braf status	Checkmate-067 & 069 studies
6 Apr 2016	EU	Monotherapy	2nd-line renal cell carcinoma	Checkmate-025 study
6 Apr 2016	EU	Monotherapy	2nd-line non-squamous NSCLC	Checkmate-057 study
23 Jan 2016	US	Yervoy combo	1st-line Braf-positive melanoma	Checkmate-067 study
23 Jan 2016	US	Monotherapy	1st-line Braf-positive melanoma	Complete response letter on 27 Nov 2015
24 Nov 2015	US	Monotherapy	2nd-line renal cell carcinoma	First anti-PD1 to show OS benefit in renal cancer
24 Nov 2015	US	Monotherapy	1st-line Braf-W/T melanoma	Checkmate-066 study
9 Oct 2015	US	Monotherapy	2nd-line non-squamous NSCLC	Checkmate-057 study
1 Oct 2015	US	Yervoy combo	1st-line Braf-W/T melanoma	1st I-O combo in cancer; Checkmate-069
20 Jul 2015	EU	Monotherapy	2nd-line squamous NSCLC	–
19 Jun 2015	EU	Monotherapy	1st & 2nd-line melanoma regardless of Braf status	Checkmate-066 & 037 studies
4 Mar 2015	US	Monotherapy	2nd-line squamous NSCLC	Checkmate-017 study
22 Dec 2014	US	Monotherapy	2nd-line melanoma	First US approval; Checkmate-037 study
Keytruda (Merck & Co)				
2 Aug 2016	EU	Monotherapy	2nd-line PD-L1-positive NSCLC	Keynote-010
18 Dec 2015	US	Monotherapy	1st-line melanoma regardless of Braf status	Keynote-006 study
2 Oct 2015	US	Monotherapy	2nd-line PD-L1-positive NSCLC	Keynote-001 study
22 Jul 2015	EU	Monotherapy	1st & 2nd-line melanoma regardless of Braf status	Keynote-001, 002 & 006 studies
4 Sep 2014	US	Monotherapy	2nd-line melanoma	First anti-PD-1 agent to get US approval; Keynote-001 study

As well as Merck making strong gains, AstraZeneca and Roche shares spiked today, up 6% and 2% initially, though the UK group quickly faded (*Therapy focus – First-line lung cancer is an Opdivo vs Keytruda showdown, June 10, 2016*).

Until now *EvaluatePharma's* consensus of sellside forecasts saw Bristol generating 60% of 2022 Opdivo sales in NSCLC, across all lines of therapy. Evercore ISI's Mark Schoenebaum put the size of the first-line NSCLC market at over $12bn, and neatly summed up the Checkmate-026 failure, calling it "possibly the biggest clinical surprise of my career".

The consensus-based NPV of Opdivo in all forecast uses amounted to a staggering $71bn, or 57% of Bristol's market cap; little wonder that the selloff was so extreme today.

In terms of market cap gains and losses there have been other immuno-oncology rollercoaster moments, including Opdivo snatching Keytruda's early lead away from it, and Bristol reporting underwhelming and somewhat confusing biomarker data in a second-line NSCLC trial at last year's Asco meeting; in hindsight perhaps this was the canary in the coalmine.

While much more work still needs to be done to elucidate the importance of various biomarkers, the Checkmate-026 disappointment has triggered a massive shift in sentiment.

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