Evaluate Vantage

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Bristol scores early

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The first of several perioperative Opdivo trials is said to read out positively, reminding the markets of such settings' importance.

Checkpoint blockade has yet to establish itself in perioperative cancer settings, but Bristol Myers Squibb has invested heavily here with Opdivo. Investors yesterday rewarded the group handsomely for what it said was the first time a checkpoint MAb had beaten chemo as neoadjuvant treatment for lung cancer.

Despite Bristol revealing no actual data from the trial in question, Checkmate-816, its stock closed up 5%, equivalent to an amazing $6bn valuation increase. With *EvaluatePharma* sellside consensus seeing Opdivo sales falling this year more victories in adjuvant and neoadjuvant settings are needed, and competition is not far behind.

The setting of NSCLC is important too. It is in first-line use here that Bristol famously lost an apparent upper hand to Merck & Co's Keytruda, and it has not been able to catch up since. Keytruda is now the go-to drug in unresectable NSCLC, but perioperative use threatens to shake things up.

If, for instance, an anti-PD-(L)1 drug were to establish itself in the neoadjuvant or adjuvant setting that could eliminate the scope for subsequent checkpoint blockade. This is analogous to the bet Astrazeneca is making in postoperative but pre-metastatic stage III NSCLC, where Imfinzi is approved thanks to the Pacific trial.

Checkmate-816 was not the first neoadjuvant NSCLC study to read out, but it was the first with a proper control.

Results of selected uncontrolled neoadjuvant NSCLC trials					
Study	**Treatment**	**Setting**	**n**	**pCR**	**MPR**
NCT02259621	Opdivo monotherapy	Stage I-IIIa	22	15%	45%
Nadim	Opdivo + chemo	Stage IIIa	46	71%	85%
Neostar	Opdivo, vs Opdivo + Yervoy	Stage I-IIIa	44	9% vs 29%	17% vs 33%
LCMC3	Tecentriq monotherapy	Stage Ib-IIIb	101	5%	20%
NCT02716038	Tecentriq + chemo	Stage Ib-IIIa	18	21%	50%
ChiCTR-OIC-17013726	Tyvyt monotherapy	Stage Ib-IIIa	40	16%	41%
Source: Asco & J Thorac Dis 2020 Apr; 12(4): 1615–1620. Note: responses to neoadjuvant treatment are measured by counting viable cancer cells in subsequently resected tumor tissue; if those cells comprise <10% of the tumour, the outcome is a major pathological response (MPR); having no viable tumour cells is a pathological complete response (pCR).					

In Checkmate-816 Opdivo was given with chemo as neoadjuvant treatment, meaning before surgery. The result, in terms of pathological complete response at time of surgery, and disease-free survival at up to six years, was compared versus chemo alone.

Yesterday Bristol said the first co-primary endpoint had been hit, without giving numbers. It said nothing about the second, which will clearly take considerably more time to generate data, or about a third cohort, testing Opdivo plus Yervoy, which had been scrapped two years ago.

So does this justify the investor enthusiasm? Evercore ISI’s Umer Raffat pointed out that the disease-free survival endpoint was the more important, but speculated that approval on pCR alone was possible.

Moreover, it is not entirely clear how big an opportunity NSCLC presents for drug therapy before or at the time of surgery, and neoadjuvant chemo is by no means standard practice.

NSCLC (neo)adjuvant studies of anti-PD-(L)1 MAbs				
Study	**Setting**	**Enrolment**	**Primary**	**Data**
Opdivo (Bristol Myers Squibb)				
Checkmate-816	Neoadjuvant (stage Ib-IIIa)	358	pCR & DFS	Toplined Oct 7, 2020
Checkmate-77T	Neoadj-adj (stage II-IIIb)	452	DFS	Ends Dec 2023
Anvil*	Adjuvant (stage Ib-IIIa)	903	DFS & OS	2022
Imfinzi (Astrazeneca)				
Aegean	Neoadjuvant (stage IIa-IIIb)	800	MPR & DFS	H2 2020
BR31*	Adjuvant (stage Ib-IIIa)	1,360	DFS in PD-L1+ve & all-comers	2020/21
Tecentriq (Roche)				
Impower-030	Neoadjuvant (stage II-IIIb)	302	pCR & DFS	2020/21
Impower-010	Adjuvant (stage Ib-IIIa)	1,127	DFS in PD-L1+ve & all-comers	H2 2020
Keytruda (Merck & Co)				
Keynote-671	Neoadjuvant (stage II-IIIa)	786	DFS & OS	Ends Jan 2024
Keynote-091/Pearls	Adjuvant (stage Ib-IIIa)	1,177	DFS	Ends Aug 2021
*Notes: *investigator-sponsored trial; pCR=pathological complete response; DFS=disease-free survival; MPR=major pathological response.*				

There are several competitor trials for perioperative NSCLC reading out soon, the imminent ones being Astrazeneca's Aegean, Merck's Keynote-091/Pearls and Roche's Impower-010. However, the last two are adjuvant studies, where the drug is given at the time of surgery; Merck and Roche's neoadjuvant studies read out later.

Overall (neo)adjuvant settings remain a wild card for immunotherapy and for Bristol alike. But the company has invested in them heavily, and is betting on them to turn Opdivo around; the drug sold almost $8bn last year, but 2020 revenue is projected to fall to $7.8bn, *EvaluatePharma* sellside consensus suggests.

Investors must hope that the Checkmate-816 result holds up on further scrutiny, and that it is a sign of further successes to come.

Upcoming phase III readouts for Opdivo in (neo)adjuvant settings				
Study	**Disease setting**	**Enrolment**	**Primary endpoint(s)**	**Primary completion**
Checkmate-274	Adjuvant bladder or upper urinary tract cancer	700	DFS vs placebo	Nov 2020
Checkmate-577	Adjuvant oesophageal or gastroesophageal junction cancer	760	DFS vs placebo	May 2021
Checkmate-7FL	Neoadjuvant ER+ve Her2-ve breast cancer	1,200	DFS & pCR of chemo combo vs chemo	Jun 2032
Source: clinicaltrials.gov.				

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