Evaluate Vantage

January 25, 2021

The year immuno-oncology could break into perioperative settings

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Keytruda could soon be approved in periadjuvant breast cancer, but adjuvant lung cancer, a bigger setting, is 2021's big showdown.

The leading anti-PD-(L)1 drugs have yet to break meaningfully into adjuvant and neoadjuvant cancer treatment, but analysts increasingly say these uses could add billions of dollars to peak sales. And 2021 is the year in which a breakthrough could come at last.

On the regulatory front March will see the US FDA decide on the approvability of Merck & Co's Keytruda in perioperative breast cancer. But the big 2021 showdown is between Merck and Roche, whose trial readouts could open up an even bigger potential market, namely adjuvant lung cancer.

The studies in question are Keynote-091 and Impower-010. Both have similar designs, though the former is blinded while the latter is open label; with the Roche trial's timing slipping by about a year both could read out this year.

The big ticket

In a sense the current potential presented by perioperative use of anti-PD-(L)1s mirrors that in metastatic cancers some years ago: back in 2014 melanoma was an initial indication for Keytruda and Bristol Myers Squibb's Opdivo, but NSCLC was the ticket to mega-blockbuster sales.

Opdivo and Keytruda are already approved for adjuvant treatment of melanoma, but so far this is the only perioperative use that features on the label of any checkpoint antibody. Just last week Opdivo was filed for adjuvant stomach cancer on the basis of the Checkmate-577 trial, but this too is a relatively niche use.

Triple-negative breast cancer (TBNC) promises to be the next big battleground, and so far Merck seems to have outplayed Roche. The Swiss firm's win here so far has been limited to neoadjuvant use – where a drug is given before surgery to debulk the tumour – in the Impassion-031 trial.

Merck, however, scored a major victory in Keynote-522, a study that included a neoadjuvant as well as an adjuvant element; the latter, where a drug is given after surgery but before progression to mop up remaining cancer cells, is seen as a much bigger opportunity than the former.

This sleight of hand in study design could give Keytruda first-mover advantage in perioperative TNBC; a US filing has March 29 set as its action date, but before that an adcom has been set for February 9. Merck has

confirmed that it is seeking approval for neoadjuvant Keytruda plus chemo followed by Keytruda monotherapy in the adjuvant setting.

Whether the adcom recommends – and the FDA agrees with – such a broad label is the big question for investors. But Bernstein analysts reckon that Keynote-522 is one element backing $7.2bn of "pan-adjuvant" sales for Keytruda by 2028 across all cancers, which itself makes up a big chunk of overall Keytruda sales rising from $14bn to $25bn in 2025.

Lung

Of course by far the biggest contributor will be NSCLC. Interestingly, it was not Merck but Bristol that scored the first victory here, when the Checkmate-816 study of neoadjuvant Opdivo read out positively for pathologic complete response last October.

However, again adjuvant is a much bigger possible market than neoadjuvant, and it is not clear whether pCR is an approvable endpoint in NSCLC (the second co-primary, event-free survival, is some way off). Perhaps the biggest relevance of a filing here is that it would reveal the FDA's stance on relevant endpoints.

In the adjuvant NSCLC setting Opdivo trails Keytruda and Tecentriq by a couple of years, as does a fourth immuno-oncology player, Astrazeneca, whose Mermaid-1 study has a 2024 completion date.

Cautious investors will point to the failures of Tecentriq in Imvigor-010 and Imagyn-050, trials in bladder and ovarian cancers respectively that both had adjuvant elements. However, NSCLC, like melanoma, is thought to be relatively immunogenic, so there is cause for optimism for those looking to the next big growth area for PD-(L)1 blockade.

Selected anti-PD-(L)1 MAb studies in perioperative NSCLC settings

	Neoadjuvant NSCLC	Adjuvant NSCLC
Tecentriq	Impower-030*	Impower-010
	2021 readout	Readout delayed from 2020 to 2021
Keytruda	Keynote-671	Keynote-091 (Pearls)
	2024 readout	2021 readout
Opdivo	Checkmate-816	Checkmate-77T
	7 Oct 2020: positive for pCR	2023-24 readout
Imfinzi	Aegean	Mermaid-1
	2022 readout	2024 readout

*Source: clinicaltrials.gov & analyst expectations of timing. *Also has an adjuvant stage.*