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Perioperative use proves elusive for Tecentriq

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Adjuvant and neoadjuvant settings are an important target for Roche's Tecentriq, but how likely is the drug to become broadly applicable?

While immuno-oncology is making inroads into ever more cancer types, settings where the drugs are given during or just after surgery remain an untapped opportunity. Judging by recent comments, however, this is a space on which Roche is making a sizeable bet, and analysts are naturally monitoring the opportunity closely.

Indeed, those at Nomura have already called results of Roche's Impower-010 trial, testing adjuvant Tecentriq versus best supportive care in NSCLC, as immuno-oncology's primary point of the coming year. But, while cautious forecasts exist, until Roche records a major win its chances of broad success will remain nebulous.

And, so far anyway, success has proved elusive. Just last month Roche revealed that Imvigor-010, testing adjuvant Tecentriq in high-risk muscle-invasive urothelial cancer, had failed to extend disease-free survival versus observation; the company had earlier called this a $1bn opportunity.

Continued confidence

At Roche's fourth-quarter results presentation the group worked hard to stay positive, and expressed continued confidence in future Tecentriq (neo)adjuvant trials, of which at least 10, including Impower-010, should read out by 2025.

True, urothelial is one cancer where immunotherapies have struggled to generate unequivocally positive data, so each tumour type should be judged on its merits.

But an earlier failure, in neoadjuvant triple-negative breast cancer, could see Tecentriq diverging from Merck & Co's Keytruda: the small NeoTRIPaPDL1 trial read out negatively in December. And earlier a separate neoadjuvant TNBC study with imminent readout, Impassion-031, had its enrolment increased, which is rarely a positive sign.

Meanwhile, Keytruda has scored a positive hit in Keynote-522, a TNBC trial that could open what Evercore ISI's Umer Raffat reckons could be a $2bn neoadjuvant and adjuvant market. Merck has yet to disclose its TNBC filing strategy.

For now, only Keytruda and Bristol-Myers Squibb's Opdivo boast adjuvant use on their labels – both in melanoma – and while the latter now seriously lags the I-O race Bristol is itself also making a sizeable bet on (neo)adjuvant settings.

For instance, the Checkmate-816 trial of neoadjuvant Opdivo plus Yervoy and chemo in NSCLC should yield pathological complete response data this year. And Checkmate-274, testing adjuvant Opdivo in muscle-invasive urothelial cancer, should read out later in 2020, and will be closely watched given Imvigor-010's failure.

Of course, not only is each tumour type different, each competing study has a slightly different design, including different cuts of patients by PD-L1 status at baseline, for instance. And, while Imvigor-010 used observation only as control, Checkmate-274 gives subjects placebo, a subtle but important difference.

Roche's Impower-010, which should read out by the end of 2020, has as its primary endpoint disease-free survival, but will look at subpopulations; subjects with stage II-IIIA NSCLC will be assessed by cuts of PD-L1 expression and across the board, and there will also be an all-comers, intent-to-treat analysis.

Finally, it is not clear whether the FDA will always insist on hard survival data for perioperative approvals, or whether a measure like pathological complete response could suffice, at least initially. Investors should know a lot more once Merck reveals what it will do with the Keynote-522 data, and once Impower-010 reads out.

Selected (neo)adjuvant studies of Tecentriq					
Trial	**Enrolment**	**Cancer setting**	**Design**	**Primary**	**Status**
NeoTRIPaPDL1	278	Neoadjuvant TNBC	Chemo combo	DFS vs chemo	Failed Dec 2019
Imvigor-010	800	Adjuvant muscle-invasive urothelial	Monotherapy	DFS vs observation	Failed Jan 2020
LCM3	180	Neo & adjuvant NSCLC	Monotherapy	pCR	Ends Feb 2020
Imagyn-050	1,300	1st-line ovarian (has neoadjuvant element)	Avastin + chemo combo	PFS & OS, in all-comers & in PD-L1+ve, vs Avastin + chemo	Ends Apr 2020
Impassion-031	324	Neoadjuvant TNBC	Abraxane combo	pCR in all-comers & in PD-L1+ve vs Abraxane	Ends Sep 2020*
Impower-010	1,127	Adjuvant NSCLC	Monotherapy	DFS vs best supportive care in PD-L1+ve & all-comers	Ends Nov 2020 (fully enrolled)
Atomic	700	Adjuvant MSI-H colorectal	Chemo combo	DFS vs chemo	Ends Dec 2020
Impassion-050	453	Neoadjuvant Her2+ breast	Herceptin + Prejeta + chemo combo	pCR in PD-L1+ve vs vs Herceptin + Prejeta + chemo	Ends Apr 2021 (FPI Q4 2018)
Impassion-030	2,300	Adjuvant TNBC	Chemo combo	Invasive DFS vs chemo	Ends Jan 2022 (FPI Q3 2018)
Immotion-010	664	Adjuvant renal cell	Monotherapy	DFS vs observation	Ends May 2022 (fully enrolled)
Imbrave-050	662	Adjuvant hepatocellular	Avastin combo	DFS vs observation	Ends Mar 2023 (FPI Q4 2019)
Imvoke-010	400	Adjuvant aquam H&N	Monotherapy	DFS & OS vs placebo	Ends Aug 2023 (FPI Q1 2018)
GeparDouze	1,520	Neoadjuvant TNBC	Monotherapy	pCR & DFS vs chemo	Ends Dec 2023
Impower-030	302	Neoadjuvant NSCLC	Chemo combo	pCR & DFS vs chemo	Ends Mar 2025 (FPI Q2 2018)

*Note: TNBC=triple-negative breast cancer; DFS=disease-free survival; pCR=pathological complete response; FPI=first patient in. *Completed enrolment of 120 additional subjects, per IDMC recommendation, in Q3 2019.*

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