Evaluate Vantage

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Therapy focus – Immunotherapy closes in on triple-negative tumours

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Immunotherapy is on the horizon for another tough tumour type, triple-negative breast cancer. Celgene admitted as much last week by saying it would not push a promising Abraxane-containing chemotherapy regimen into pivotal trials in this tumour type, in favour of focusing on combinations with novel immuno-oncology agents.

Several studies are already under way, most notably a large first-line phase III trial of Abraxane plus Roche's anti-PD-L1 antibody Tecentriq. Early data are encouraging, and hopes are high that meaningful survival benefits will emerge in the next couple of years. Despite this, however, of the anti-PD-1/PD-L1 owners only the Swiss breast cancer giant and Merck & Co have made significant commitments to triple-negative disease (see tables below).

This means that if the trials below read out positively, these two companies could be first to the market in this cancer, where treatment for metastatic disease still relies on chemotherapy. No targeted agent is approved in the US in triple-negative tumours; patients typically live for 20 months after diagnosis.

This poor prognosis is down to triple negative's aggressive nature and its heterogeneity, on both pathological and molecular levels. While the breast tumours lack any of the targets for existing agents – oestrogen or progesterone receptors or Her2 – several genetic subtypes have been identified, and patients can respond very differently to treatment.

However, of the breast cancers it is considered highly immunogenic, which makes it a logical target for immunotherapy. The tumours frequently overexpress PD-L1, are highly mutagenic and associated with a high level of tumour-infiltrating lymphocytes, the presence of which are required for checkpoint inhibition to be effective.

Triple negative-focused I-O studies					
Trial name	**Enrolment**	**Details**	**Primary sponsor**	**Primary completion**	**Trial ID**
Phase III					
Keynote-119	600	Keytruda vs chemo	Merck & Co	May 2017	NCT02555657
Keynote-355	858	Keytruda + chemo vs placebo + chemo; first line	Merck & Co	Dec 2019	NCT02819518
IMpassion130	900	Tecentriq + Abraxane vs placebo vs Abraxane; first line	Roche	Apr 2020	NCT02425891
Phase II					
GeparNuevo	174	Durvalumab + chemo; first line	German Breast Group	Mar 2018	NCT02685059
Keynote-086	245	Keytruda monotherapy	Merck & Co	Apr 2018	NCT02447003
-	100	MCS-110 + chemo; first-line advanced with high TAMs	Novartis	Mar 2019	NCT02435680
TONIC	84	Opdivo; after radio/chemo induction therapy	Netherlands Cancer Institute	Aug 2019	NCT02499367
Phase I					
Keynote-173	100	Keytruda + chemo; neoadjuvant	Merck & Co	Nov 2017	NCT02622074

Early monotherapy trials of checkpoint inhibitors in heavily pretreated triple-negative patients established a case for further study, of which Merck's Keynote-012 was one of the first. At the San Antonio Breast Cancer Symposium (SABCS) last week an update on the triple-negative cohort from this large phase Ib trial was presented – a median progression-free survival (PFS) of 1.9 months and median overall survival of 11.3 months has been reached.

Merck started Keynote-086 to explore monotherapy further, using a higher dose. Results from this single-arm, open-label study will not be known until mid-2018, but next year data could emerge from the phase III Keynote-119 study, which pits the same dose of Keytruda against various chemo agents, again in heavily pretreated patients.

The drug has a relatively benign tolerability profile compared with chemotherapy, so presumably the bar to approval is pretty low in this very advanced setting. Merck would not need to see much of a separation in survival curves to send it to regulators next year.

First-line prize

The big target is of course first-line treatment of metastatic disease, and here there is a need to combine these checkpoint inhibitors with standard-of-care chemotherapy.

Merck is testing three different chemotherapies with Keytruda in its two-part, pivotal Keynote-355 trial, while Roche is explicitly using Abraxane with Tecentriq in Impassion130.

Tnacity, the study that prompted Celgene to proclaim the end of its work on chemo-only regimens in triple negative was also presented at SABCS, and this perhaps sets a bar for checkpoint-chemo combinations to beat. The phase II trial tested Abraxane combined with various other chemotherapies first line; carboplatin emerged as the most potent partner, and the two drugs generated PFS of 7.4 months.

Clearly, the hope is that immunotherapy will generate an even stronger response. PFS in this setting with chemotherapy is around six months. Bernstein analysts recently quoted Dr. Harold Burstein, an associate professor at Harvard Medical School, as saying that an extension to nine or 10 months should be enough to secure approval in this front-line setting.

Phase III results are unlikely to emerge for a few years, although an earlier test of the combination could come from a phase II study with AstraZeneca's durvalumab, an anti-PD-L1 antibody like Tecentriq. This is in a first-line combination study with Abraxane being undertaken by the German Breast Group; results are due in 2018.

A question to be answered further down the line is whether chemotherapy, which comes with a high side-effect burden, can eventually be removed from this first-line setting.

Looking elsewhere

Beyond Merck and Roche, however, the big immuno-oncology players have shown more reluctance in pushing forward in triple-negative disease.

Astrazeneca is running two phase Ib studies with durvalumab and the anti-CTLA4 MAb tremelimumab, exploring a wide range of advanced malignancies, including triple negative. The company is also collaborating with Incyte on a combination of the US company's epacadostat, an IDO inhibitor, with durvalumab. Incyte has struck a similar R&D pact with Merck over Keytruda; the agents are in two large phase I/II studies, Echo-203 and Echo-202, again in broad tumour types.

Novartis, meanwhile, is only testing its anti-MCSF antibody MCS-110 explicitly in triple-negative disease. Its anti-PD1 antibody PDR001 is being tested as a monotherapy in combination with MCS-110 in broad, early-stage studies.

Bristol-Myers' work seems to extend to a large study of Opdivo with or without Yervoy in six tumour types, and a couple of collaborator-sponsored trials. This is a surprising lack of interest considering the company's commitment to immuno-oncology.

The table below details the studies of various immunotherapy agents that include a triple-negative cohort, rather than specifically enrolling these patients. Many are early stage – however, given the success of Merck's Keynote-012, a phase I study that in the end recruited around 300 patients and generated groundbreaking data in several tumour types, the relevance of this type work should not be underestimated.

Of course there is also much work going on outside the immuno-oncology space in triple-negative disease. The Parp inhibitors for example are being widely explored, while triple-negative tumours that overexpress the androgen receptor are being targeted with antagonists like Xtandi. Antibody-drug conjugates are also showing early promise.

Data from all these trials will be closely watched in the coming years for signs of desperately needed progress in a tumour type that has so far proved tragically intractable.

Immunotherapy studies in advanced malignancies, which include a triple negative cohort					
Projects	**Sponsor (collaborator)**	**Enrolment**	**Primary completion**	**Phase**	**Trial ID**
Epacadostat + durvalumab	Incyte (Astrazeneca)	185	Mar 2017	Phase I/II	NCT02318277 (Echo-203)
Epacadostat + Keytruda	Incyte (Merck)	403	May 2017	Phase I/II	NCT02178722 (Echo-202)
Opdivo +/- Yervoy	Bristol-Myers Squibb	1,150	Aug 2017	Phase I/II	NCT01928394
Tremilimumab	Astrazeneca	66	Apr 2018	Phase II	NCT02527434
Durvalumab + tremilimumab	Astrazeneca	60	May 2018	Phase Ib	NCT02658214
TAK-659 + Opdivo	Takeda	120	Jul 2018	Phase I	NCT02834247
PDR001	Novartis	288	Aug 2018	Phase I/II	NCT02404441
Imprime PGG + Keytruda	Biothera (Merck)	95	Sep 2018	Phase II*	NCT02981303
PLX3397 + Keytruda	Plexxikon (Merck)	400	May 2019	Phase I/II	NCT02452424
MCS110 + PDR001	Novartis	95	Jun 2019	Phase I/II	NCT02807844
Tremelimumab + durvalumab	Ludwig Institute for Cancer Research (Astrazeneca)	102	Aug 2022	Phase I/II*	NCT02643303
**Not yet recruiting, according to clinicaltrials.gov*					

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