Evaluate Vantage

April 24, 2015

Celgene signals bigger immuno-oncology push into blood cancers

Amy Brown

Today's deal between AstraZeneca and Celgene shows that when companies are willing to yield full control of key assets, valuable transactions can be negotiated.

Astra will see its anti-PD-L1 antibody MEDI4736 explored in uses beyond its comfort zone without having to take on the full cost and risk of doing so, and gets to run a chunky $450m up-front fee through the books. Celgene meanwhile gets access to one of the most advanced assets in this class. The collaboration also shows that although it is still far from clear what role checkpoint inhibition might come to play in haematological cancers the biggest player in this space is willing to pay up to find out.

On a first-quarter conference call this morning AstraZeneca executives heavily hinted that further immuno-oncology (I-O) assets in its pipeline, both small molecules and biologicals, could be rolled into an expanded haematological collaboration later. So it seems likely that this deal could be only the first step in this partnership.

In the meantime the collaboration will focus on MEDI4736 in combination with Celgene's pipeline and other novel haematological agents, the companies said.

The up-front payment certainly looks generous, although no more than other I-O deals struck recently (*Astra deals add to ballooning up-front payments, April 24, 2015*). And it means that the US biotech will be working with an agent that could be on the market as soon as next year, rather than having to look for openings among earlier-stage or otherwise overlooked assets. Given the huge interest in immuno-oncology, these will be few and far between.

As well as committing the $450m up front Celgene will lead and fully fund research work until the end of 2016. Its UK partner will contribute 25% of R&D costs thereafter; Astra will also manufacturer the drug and book sales. Celgene will receive a royalty on haematological sales starting at 70%, decreasing to 50% over a period of four years.

This might seem like a big give away of future revenues, but at this moment Astra is highly motivated to forge these sorts of arrangements, having pledged to meet ambitious earnings guidance this year partly through "externalisation" (*AstraZeneca might need more than buzzwords to bridge the gap, February 6, 2015*). The up-front will be booked as externalisation revenue in the second quarter, or when the deal closes, finance chief Marc Dunoyer said today.

And should different assets be rolled into the collaboration, as seems likely, different terms can always be negotiated.

Mechanistic rationale

The entry of anti-PD-1 antibodies into haematological cancers was heralded at last year's ASH conference, when both Bristol-Myers Squibb and Merck & Co presented encouraging early-stage data with their respective candidates, Opdivo and Keytruda (*ASH – A way in for anti-PD-1 therapy in haematology, December 6, 2014*).

Strong response rates were reported in heavily pretreated classical Hodgkin's patients, although the scientists presenting the data highlighted the central role of 9p24.1 amplification, a genetic alteration that results in overexpression of PD-L1 and PD-L2 on cancer cells, in the finding. Because 9p24.1 amplification is frequent only in classical Hodgkin's and mediastinal large B-cell lymphoma, but few other haematological malignancies, the monotherapy potential of these checkpoint inhibitors in haematology would seem to be limited.

This viewpoint was supported by a negative Opdivo result in multiple myeloma. However, by pursuing combinations Celgene and AstraZeneca must feel that they can get around this limitation – the collaboration will initially focus on lymphoma and multiple myeloma, they said today.

For its part Astra has pursued little work in blood cancers with its I-O pipeline, although a phase Ib/II trial includes an arm testing a combination of its anti-Ox40 agent, MEDI-6469, with Celgene's Rituxan in patients

with diffuse large B-cell lymphoma. It also has a phase I/II trial ongoing with an anti-CD19 antibody, MEDI-551, in combination with immunomodulating agents in B-cell lymphomas. Such research might signal further paths to collaboration between the two groups.

The other players in the PD-1/PD-L1 space have also shown little enthusiasm for committing sizeable sums in blood cancers, as the table below shows, certainly in comparison with the efforts ongoing in solid tumours.

With novel combinations, and perhaps by bringing in other I-O targets, Celgene and Astra clearly see the potential to lead the way here.

Active blood cancer studies with anti-PD-1/PD-L1 antibodies		
AstraZeneca		
Phase Ib/II	NCT02205333	MEDI-6469 plus Rituxan in DLBCL
Phase I/II	NCT02271945	MEDI-551 plus immunomodulating therapies in aggressive B-cell lymphomas
Phase I	NCT02117219	MEDI4736 in myelodysplastic syndrome
Bristol-Myers Squibb		
Phase I	NCT01592370	Opdivo +/- ipilimumab or lirilumab in lymphoma and multiple myeloma
Phase Ib	NCT02011945	Sprycel plus Opdivo in CML
Phase II	NCT02038933	Nivolumab in relapsed or refractory DLBCL (CheckMate 139)
Phase II	NCT02038946	Nivolumab in relapsed or refractory Follicular Lymphoma (CheckMate 140)
Phase II	NCT02181738	Nivolumab in Hodgkin's lymphoma (Registrational) (CheckMate 205)
Phase II	NCT02397720	Nivolumab plus Vidaza in refractory/ relapsed AML
Merck & Co		
Phase I/II	NCT02332668	Keytruda in children with a PD-L1 positive lymphoma (Keynote-051)
Phase I	NCT01953692	Keytruda in various blood cancers (Keynote-013)
Phase I	NCT02036502	Keytruda plus Revlimid in multiple myeloma (Keynote-023)
Phase II	NCT02362997	Keytruda in relapsed/refractory classical Hodgkin lymphoma and DLBCL
Phase I/II	NCT02289222	Keytruda plus Pomylast in relapsed/refractory multiple myeloma
Roche		
Phase I	NCT02220842	MPDL3280A plus Gazyva in follicular and DLBCL
Curetech		
Phase II	NCT01096602	Pidilizumab plus dendritic cell/AML vaccine in AML

To contact the writer of this story email Amy Brown in London at AmyB@epvantage.com or follow @AmyEPVantage on Twitter