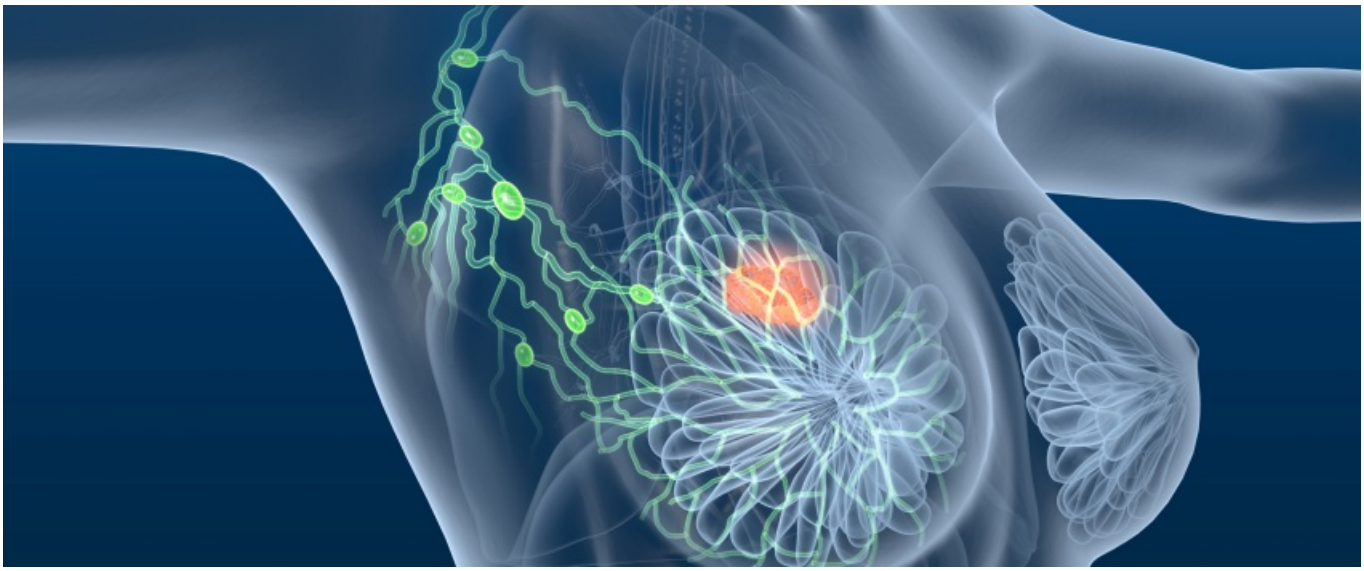
Evaluate Vantage

May 08, 2019

Astra and Daiichi lay out their plan for a better Herceptin

Jacob Plieth



The companies' DS-8201 succeeds in breast cancer patients who had failed Kadcyla, and will go before the regulators later this year.

There was a time, some years ago, when Roche's Kadcyla was seen by the sellside as the pharma industry's biggest upcoming launch. The bullish forecasts failed to materialise, but Kadcyla did spawn numerous other Her2-targeting projects seeking to become better versions of Herceptin.

Today one of these, Astrazeneca/Daiichi Sankyo's DS-8201, succeeded in a phase II breast cancer trial that will serve as the basis for a second-half regulatory filing. More lucrative uses might follow, and the result could vindicate the UK company's aggressive move to license DS-8201 from Daiichi.

That licensing deal had been roundly criticised both for its up-front element – $1.35bn seemed a huge amount for what was, ultimately, an early-stage project – and the fact that Astra raised equity to help finance it.

But the basis for the tie-up was phase I data that Astra called "unprecedented", amounting to a 60% remission rate in Her2-positive breast cancer subjects who had failed on an average of seven therapies. The UK company highlighted DS-8201 on last week's first-quarter financials call.

High-intensity conjugate

Like Kadcyla (trastuzumab emtansine) DS-8201 (trastuzumab deruxtecan) is an antibody-drug conjugate. What makes the Daiichi project unique, its makers argue, is a high-intensity payload and cell membrane permeability, which might enable it to target tumours that express Her2 at relatively low levels.

One line of thinking is that patients retain some degree of Her2 expression even after failing multiple anti-Her2 therapies, and the latest findings, from the Destiny-Breast01 study, suggest that DS-8201's characteristics translate into a real clinical benefit.

Enrolees had failed two Her2-targeting drugs, Herceptin and Kadcyla, yet a 5.4mg/kg DS-8201 dose showed strong clinical activity in terms of overall remission, the trial's primary efficacy measure, Astra said today.

Hard data are being held back for a scientific meeting. In addition to efficacy, safety will be closely scrutinised given the expression of Her2 on healthy as well as cancerous cells, the touted efficacy of DS-8201, and the off-tumour toxicity of some potent Her2-directed therapies like CAR-T.

Kadcyla was once thought by the sellside to be capable of bringing in 2020 sales of $4.5bn, but last year's revenue only just breached $1bn, and the current 2024 forecast is $1.4bn, *EvaluatePharma* computes.

The main problem is that in Her2-positive breast cancer Kadcyla failed to broaden its approved reach beyond Herceptin-relapsed subjects. In the front-line Marianne study Kadcyla-containing regimens were non-inferior but failed to beat Herceptin.

Analysts at present see DS-8201 selling $1.8bn in 2024, but this will not come from Destiny-Breast01's third-line use alone. For the drug to make its mark fully it must succeed in the second-line setting head-to-head against Kadcyla, and perhaps also in Her2-low subjects, a brand new use.

Selected trials of DS-8201 in breast cancer			
Study	**Setting**	**Detail**	**Trial ID**
DS8201-A-J101	~8th line, Her2-positive	59.5% ORR	NCT02564900
Destiny-Breast01	3rd-line, Her2-positive, post Herceptin & Kadcyla	Clinically meaningful ORR	NCT03248492
Destiny-Breast02	3rd-line, Her2-positive, phIII confirmatory trial	Data in 2020+	NCT03523585
Destiny-Breast03	2nd-line, Her2-positive, post Herceptin, vs Kadcyla	Data in 2020+	NCT03529110
Destiny-Breast04	Her2-low, vs physician's choice	Data in 2020+	NCT03734029

While there are now several Her2-targeting antibody-drug conjugates in development the evolving situation will also be of great interest to Macrogenics, which is developing a naked anti-Her2 MAb, margetuximab, that has an optimised Fc region.

Margetuximab scored a surprising success in the Sophia trial in subjects who had all failed Herceptin and Roche's Perjeta, and most of whom had also failed Kadcyla. The success was down to patients who carried the 158F allele, a genetic variant that promotes binding with Fc-optimised MAbs like margetuximab; full Sophia data are one of the big attractions of the upcoming Asco conference.

This subgroup-driven effect might not put margetuximab in direct competition with DS-8201, which Astra might now rely on, along with Tagrisso, to form the cornerstone of its oncology strategy. Given the travails of Imfinzi and tremelimumab in lung cancer the UK group needs all the breaks it can get.

Selected Her2-targeting industry projects		
Product	**Company**	**Pharmacology class**
Marketed		
Herceptin	Roche	Anti-Her2 MAb
Perjeta	Roche	Anti-Her2 MAb
Kadcyla	Roche/Immunogen	Anti-Her2 MAb-DM1 maytansinoid conjugate
Phase III		
DS-8201	Daiichi Sankyo/Astrazeneca	Anti-Her2 MAb-cytotoxic drug conjugate
Margetuximab	Macrogenics	Fc-optimised anti-Her2 MAb
BAT8001	Bio-Thera Solutions	Anti-Her2 MAb-maytansinoid conjugate
Phase II		
Tucatinib	Array/Seattle Genetics	Her2-selective TKI
TAS0728	Otsuka Holdings	Her2-selective TKI
Phase I		
RG6194	Roche	Anti-Her2 bispecific MAb
PRS-343	Pieris Pharmaceuticals	Anti-Her2 bispecific MAb
ARX788	Ambrx	Anti-Her2 MAb-cytotoxic drug conjugate
FS102	F-star	Anti-Her2 MAb
PF-06804103	Pfizer	Anti-Her2 MAb-cytotoxic drug conjugate
MEN1309	Oxford Biotherapeutics/Menarini	Anti-Her2 MAb-maytansinoid conjugate
Source: EvaluatePharma.		