Evaluate Vantage

February 04, 2016

Takeda joins the battle against Kadcyla

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Drug development tends to build on previous successes, and when a decent target is discovered it makes sense to throw increasingly efficacious technologies at it. One such target is Her2, whose targeting by Roche via the antibody Herceptin heralded the birth of personalised medicine.

Industry has not stopped at antibodies, as evidenced by the variety of Her2-directed antibody-drug conjugates in development, and by Takeda's willingness to part with $60m yesterday for non-US rights to a preclinical asset (see table below). The trick now is to bypass Roche's stranglehold on this space.

This is because the Swiss firm sells not only Herceptin but also Perjeta, a follow-on anti-Her2 MAb, and Kadcyla, an anti-Her2 antibody-drug conjugate (ADC) of its own, based on technology it licensed from Immunogen. Kadcyla sold $769m in breast cancer last year, though the vast majority of its 51% growth came not in the US but in Europe.

One strategy for developers of follow-on ADCs against Her2 is to look at indications outside breast cancer. Takeda, in yesterday's deal with the private firm Mersana Therapeutics, cites applicability also in gastric and lung cancers, as well as data presented at last year's AACR meeting suggesting activity of Mersana's XMT-1522 even in patients expressing low levels of Her2.

This fits in with the pharmacological notion behind ADCs; while a MAb merely binds its antigen and triggers cell-mediated cytotoxicity, an ADC goes further, using its antibody component as a targeting moiety, and employing the attached cytotoxic payload to cause destruction of the cancer cell thus targeted.

Her2-directed antibody-drug conjugates			
Project	**Company**	**Pharmacology**	**Status**
Kadcyla (ado-trastuzumab emtansine)	Roche/Immunogen	Anti-HER2 MAb-DM1 maytansinoid conjugate	Marketed
MM-302	Ligand/Merrimack	Anti-HER2 MAb-doxorubicin conjugate	Phase III
Pb-212-TCMC-Trastuzumab	Roche/Areva	Anti-HER2 MAb-lead 212 conjugate	Phase I
DS-8201	Daiichi Sankyo	Anti-HER2 MAb-drug conjugate	Phase I
ARX788	Ambrx	Anti-HER2 MAb-cytotoxic drug conjugate	Phase I
SYD985	Synthon	Anti-HER2 MAb-duocarmycin conjugate	Phase I
HER2-Negative Breast Cancer Research Project	Amgen/Immunogen	Anti-HER2 MAb-maytansinoid conjugate	Preclinical
Trastuzumab-PM050489 ADC	Grupo Zeltia	Anti-HER2 MAb-microtubule assembly inhibitor conjugate	Preclinical
ALT-P7	3SBio	Anti-HER2 MAb-drug conjugate	Preclinical
PRS-343	Pieris Pharmaceuticals	Anti-HER2 & CD137 MAb-drug conjugate	Preclinical
ANG4043	AngioChem	Anti-HER2 MAb-peptide conjugate	Preclinical
Anti-HER2 Paclitaxel Prodrug	Immune Pharmaceuticals	Anti-HER2 MAb-paclitaxel conjugate	Preclinical
HER2 & CD20 Antagonist Research Project	Esperance Pharmaceuticals	Anti-HER2 & CD20 MAb-drug conjugate	Preclinical
Anti-HER2 Paclitaxel NanomAbs	Immune Pharmaceuticals/STC Biologics	Anti-HER2 MAb-paclitaxel conjugate	Preclinical
XMT-1522	Mersana/Takeda	Anti-HER2 Mab-auristatin conjugate	Preclinical
BT2111	biOasis Technologies	Anti-HER2 MAb-p97 conjugate	Preclinical
ALT-P7	Alteogen	Anti-HER2 MAb-drug conjugate	Preclinical
HER2-Negative Breast Cancer Research Project	Oxford BioTherapeutics	Anti-HER2 MAb- maytansinoid conjugate	Preclinical
IGN001	Immungene/Caliber	Anti-HER2 MAb-IFN conjugate	Preclinical
Source: EvaluatePharma.			

There are, of course, strategies that take this notion further, such as therapeutic cancer vaccines targeting Her2 – *EvaluatePharma* lists 16 in clinical trials – and bispecific antibodies, while a group at London's King's College is working on a CAR-T therapy that targets Her dimers in head and neck cancer.

Takeda is betting not only on Mersana's lead asset, but also on its Fleximer technology, and handing across $40m up front for something still in preclinical trials, plus $20m once the first IND is cleared, shows either extreme confidence or extreme desperation.

Difficulties

Immunogen, one of the founding fathers of the ADC concept, knows better than most the importance of getting the technology right: the group's fluctuating share price testifies to the difficulties with designing an ADC that is both sufficiently potent and has a sufficiently stable linker between antibody and payload to allow efficacious tumour targeting.

Speaking to *EP Vantage* at last month's JP Morgan healthcare conference, Immunogen's chief executive, Dan

Junius, said the starting point was a target expressed on a cancer cell, with “less expression in healthy tissue”.

Then there is getting the linker and the payload right: “Some [cancers] may not be sensitive to the mechanism of action we have with the payload we worked with historically ... so we’ve now developed a second payload. This is significantly more potent than what is already a highly potent agent, meaning it can be used in cancers that don’t express the target in sufficient quantities.”

Mersana’s technology is still some way off being validated, but Takeda is not the first company to have made a bet on it; the private group closed a $35m series B round a year ago, counts Pfizer as an investor, and in 2010 struck a lucrative Fleximer-focused deal with Teva.

While work on ADCs has gone on for well over a decade Kadcyla was only the third to reach the market, after Pfizer’s Mylotarg – pulled in 2010 over safety concerns – and Seattle Genetics’ Adcetris. Takeda has a separate alliance with Immunogen, as well as rights to Seattle’s Adcetris that today yielded a $20m milestone.

For now the tie-up with Mersana does not even give Takeda rights in North America, so the Japanese group’s faith both in this technology and in ADCs in general must be considerable.

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