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Seattle benefits from Merck's long shot

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Merck's move on a target that has attracted little attention – Liv-1 – means future data readouts are now eagerly awaited.

While the biopharma world was trying to figure out how Gilead got to $21bn for Immunomedics yesterday, Merck & Co and Seattle Genetics unleashed the next question for the sector: what had the pharma giant seen in the smaller developer's Liv-1 targeting antibody-drug conjugate, ladiratuzumab vedotin?

Limited data released over the past few years have underwhelmed – clinical trials started back in 2013 – and understandably the ADC has been largely ignored by the financial community. Yet Merck plans to pump $1.6bn into Seattle to corner the project, and is potentially on the hook for much more, with progress-dependent milestones of up to $2.6bn on the table.

True, these terms are a fraction of what Gilead is handing over for Trodelvy, Immunomedics' sole asset and another ADC (*Gilead's cancer ambitions stretch to $21bn, September 14, 2020*).

A look at deals that have been struck over these conjugates over the past few years confirms that they are now considered prized assets – and Merck can certainly afford it.

Paying up: ADC deals have been getting more expensive					
Deal Date	**Company**	**Product (target)**	**Product Source**	**Upfront payment ($m)**	**Total deal value ($m)**
Mar 2019	Astrazeneca	Enhertu (Her2)	Daiichi Sankyo	1,350	6,900
Jul 2020	Astrazeneca	DS-1062 (Trop2)	Daiichi Sankyo	1,000	6,000
Sep 2020	Merck & Co	Ladiratuzumab vedotin (Liv-1)	Seattle Genetics	600	3,200
Aug 2017	Jazz Pharmaceuticals	IMGN779 (CD33)*	Immunogen	75	175
Apr 2019	Everest Medicines**	Trodelvy (Trop2)	Immunomedics	65	775
Oct 2018	Innate Pharma	Lumoxiti (CD22)	Astrazeneca	50	75
Feb 2016	Takeda	XMT-1522 (Her2)*	Mersana Therapeutics	40	455
Dec 2012	Celgene	CC-99712 (BCMA)	Sutro Biopharma	22	46
**Project abandoned. **China and other Asian markets. Source: EvaluatePharma.*					

The potential to combine the asset with Keytruda appears to be the main draw here, specifically in triple negative breast cancer, although Merck might also have seen signals of promise in other tumour types.

Seattle has reported data two from two studies of ladiratuzumab vedotin: a single-agent TNBC trial back in 2017, and a ongoing phase I/II trial in combination with Keytruda in first-line, metastatic disease. The latter, which had interim data at SABCS last December, showed a 35% overall response rate among 66 patients, regardless of PD-L1 status, although the majority were partial responses.

At the time, this result did not stand out – chemotherapy generally achieves an ORR of 31-45%, according to Leerink analysts, while Tecentriq achieved a 53% response rate in PD-L1 ≥1% patients, in combination with Abraxane, a result that won that Roche drug approval.

Still, the track record of checkpoint inhibitors in this cancer type can only be described as mixed, with both Roche and Merck notching up wins and losses. The assumption must be therefore that Merck has seen later cuts of various Seattle data that do warrant pushing on, particularly in patients with low PD-L1 expression.

On a call yesterday Seattle executives also spoke of working on a once-weekly dosing regimen that should optimise the safety and efficacy of a PD-(L)1 combination, although they declined to say when further data might be released, or when pivotal trials might commence.

Leerink analysts wrote today that early data combining Seattle's vedotin payloads with Keytruda have yielded very promising signals. They believe that the first real test of this approach will come with readout of a phase III trial of another Seattle ADC, Adectris. This is being trialled in combination with Opdivo in the Hodgkin's lymphoma trial Checkmate-812, which should yield data next year.

Further confirmation

Most metastatic breast cancers express Liv-1; however, other tumours types such as ovarian and prostate also express the marker, to lesser extents, and Merck has presumably also been party to data from a separate, ongoing solid tumour study. This only got under way late in 2019, however; Seattle executives yesterday promised "optimised data" in several tumour types in the future.

The terms of the deal see both partners sharing profits and costs equally, and there is a suggestion that second-generation Liv-1 targeting ADCs are on the horizon.

And for $125m up front Merck also bought itself another revenue in terms of rights to commercialise Tukysa, a Her2 targeting kinase inhibitor, in Asia, the Middle East and other global locations.

But Merck's move was very much about Liv-1, a target that does not seem to feature in any other company's

pipeline, according to a search of *EvaluatePharma*'s database. While this makes ladiratuzumab vedotin a unique opportunity, it also raises the question of why others have not managed to get anything into the clinic – with such high expression in breast cancer, it would seem to be an attractive target to pursue.

Much more data are needed to explain Merck's move here. In the meantime, perhaps this deal will also see others finally take Liv-1 more seriously.