

Therapy focus - Curis thinks small to hit big immuno-oncology target



[Amy Brown](#)

Curis looks set to put the third TIM-3 asset into the clinic next year, joining Novartis and Tesaro as companies with clinical projects addressing this novel immuno-oncology target.

Like PD-1, Tim-3 is a checkpoint found on T cells, and in the past few years blocking it has attracted attention for the potential to harness the immune system to attack tumours. Curis is unique in pursuing a small-molecule approach, but given that the rest of the industry pipeline comprises antibodies it has more to prove than most (see table below).

The antibody approach makes sense because Tim-3 is a large transmembrane protein whose activity, presumably, a small molecule would struggle to inhibit sufficiently.

Tim-3 – or T-cell immunoglobulin and mucin domain-3 – plays a similar role to PD-1 in terms of dampening the immune response. The T-cell response controlled by Tim-3 and its ligand, galectin-9, is thought to be involved in numerous diseases, autoimmune as well as cancer.

In cancer Tim-3 and PD-1 pathways are thought to interact, and as such most drug development efforts are taking a dual-targeting approach, either via one bispecific molecule or using two distinct compounds. It is hoped that, by blocking both Tim-3 and PD-1, T-cell function can be restored even more effectively than through PD-1 inhibition alone.

In the clinic

Novartis is probably the most advanced in testing this in the clinic. It started a 250-patient phase I/II trial late last year in advanced malignancies, testing MGB453 on its own or in combination with PDR001, its anti-PD-1 antibody. The Swiss pharma giant has remained characteristically tight-lipped about the project, however; MGB453 does not even appear in its pipeline on its website.

Tesaro is taking much the same approach, testing its anti-Tim-3 antibody TSR-022 in a large, open-label, dose-escalation and cohort-expansion phase I study – seeking 402 patients – in various advanced solid tumours. The agent will also be tested alone and in combination with an anti-PD-1 antibody, and started earlier this year.

The anti-Tim oncology pipeline

Project	Pharma class	Company (partner)	Trial ID	Primary completion
<i>In early clinical testing...</i>				
MGB453	Anti-Tim-3 MAb	Novartis	NCT02608268	Jun 2018
TSR-022	Anti-Tim-3 MAb	Tesaro (AnaptysBio)	NCT02817633	Dec 2019
<i>Preclinical and earlier...</i>				
CA-327 (AUPM-327)	PD-L1 & Tim-3 antagonist	Curis (Aurigene)	-	-
Anti-Tim3 Research Project	Anti-Tim-3 MAb	Lilly	-	-
STI-600	Anti-Tim-3 MAb	Sorrento Therapeutics	-	-
ENUM005	Anti-Tim-3 MAb	Enumeral Biomedical	-	-
Anti-Tim Research Program	Anti-Tim-3 MAb	Roche	-	-
Sym016	Anti-PD-L1, Lag-3 & Tim-3 MAb	Symphogen (under Shire collaboration?)	-	-
Anti-PD-1/Tim-3 Antibody	Anti-Tim-3 & PD-1 MAb	Tesaro (AnaptysBio)	-	-
<i>Source: EvaluatePharma.</i>				

With the small molecule now called CA-327 (AUPM-327) Curis will also be targeting both PD-1 and Tim-3. The compound was licensed from Aurigene, the drug discovery arm of India's Dr Reddy's Laboratories, under a collaboration that has also yielded CA-170, a small molecule that the groups say hits PD-L1 and Vista ([Curis's turn with the immuno-oncology buzzword, January 22, 2015](#)).

An IND for CA-327 should be filed next year, Curis says.

The company presented a [poster with some preclinical data](#) on both molecules at AACR this year. CA-170 showed activity in melanoma and colon carcinoma tumour lines, while CA-327 showed anti-tumour activity in colon and lung, with the company claiming oral bioavailability for both.

However, there are good reasons why Curis is the only company brave enough to push a small-molecule approach to these targets into the clinic. Should they work the advantages are obvious, but the biological barriers to hitting such large and complex targets with a chemistry-based approach are also readily apparent.

Still, Ali Fattaey, chief executive of Curis, argues that is not the size of the checkpoint protein, it is identifying and targeting the right contact sites required for the function of the checkpoint protein.

"The years of chemistry and optimization conducted by Aurigene has now clearly demonstrated that these surface proteins are amenable to small-molecule targeting strategies," he told *EP Vantage* in an email. "Our preclinical results in cell-culture assays and in *in vivo* animal model settings clearly demonstrate that our small-molecule drug candidates are behaving very similar to antibodies that target the same immune checkpoints."

CA-170 went into a 150-patient phase I trial in May this year, and data will be keenly awaited to prove whether this approach has any utility. Curis's \$390m market cap, and notable lack of big pharma interest, suggests that few are holding out hope.

It is not inconceivable, however, that results will start trickling out later next year on the antibody approaches - the Novartis and Tesaro studies likely contain many arms. While the small-molecule avenue might turn into a dead end, other roads could still lead to Tim-3 success.

Project	Mechanism	Trial ID
CA-170	PD-L1/Vista dual antagonist	NCT02812875

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