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Macrogenics' safety scare could be contagious

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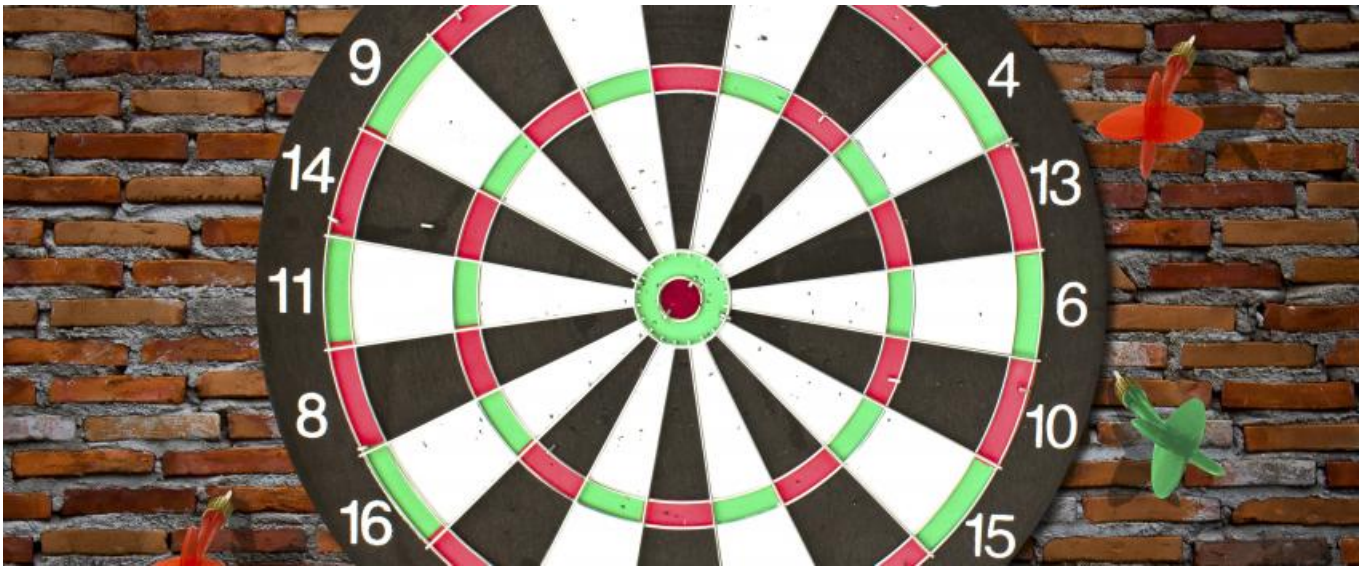

It could be hard for Macrogenics to shake off new safety concerns, whether it is the DART bispecific construct or its protein target that is to blame.

The sellside did its best to reassure the markets that the clinical hold on Macrogenics' MGD009 had nothing to with either the project's target, B7-H3, or the company's bispecific technology. But one of these seems likely to be at fault for the liver toxicity observed – and either way it would be bad news for the group.

Macrogenics has several other bispecifics in its pipeline that, like MGD009, aim to recruit T cells to tumours, so if something about this construct is to blame it would be a big blow. But the company also has two other projects that hit B7-H3, including its second-most advanced candidate, enoblituzumab.

For its part, Macrogenics blamed the liver enzyme elevations on cytokine release syndrome due to increased T-cell activity, which can also be a side effect of CAR-T therapy. In addition, the company pointed out that the liver signals seen with MGD009 were resolved quickly after the affected patients were given Actemra.

The group hopes that by January it will resume the two halted phase I trials of MGD009: a monotherapy study, where the liver issues were seen, and a study in combination with MGD012, a PD-1-targeting agent.

Bispecific burnout…

However, the US FDA might not agree with Macrogenics' benign interpretation of the adverse events, and a longer delay could drag down the company along with others in the bispecific arena too, perhaps.

One of the most popular strategies in bispecifics is to use these antibodies to bring T cells into the vicinity of tumours so they can destroy the cancerous cells. One "arm" of the antibody targets the CD3 receptor found on T cells, while the other hits an antigen present on cancer cells.

Amgen's Blincyto is one bispecific that works this way and is already approved, but the field has developed slowly. Bispecifics have also been hit with several safety setbacks recently, including a second clinical halt for Johnson & Johnson's CD3/CD123-targeting project JNJ-63709178 in August.

In that candidate's case the suspicion largely fell on CD123, which is also expressed on healthy tissue, as there have been toxicity concerns with other projects acting on this target.

However, Affimed's AFM11, which hits CD3 and CD19, was put on hold in October after a patient died and two more experienced life-threatening events. And last year J&J handed back another Macrogenics project, the CD19-targeting duvortuxizumab, at least partly over toxicity concerns (*Macrogenics and J&J fallout could spell*

double trouble, 1 September 2017).

Bispecific constructs can vary greatly – Macrogenics' molecules are DARTs, or dual-affinity re-targeting antibodies, which use a very simple format. Even if there is an issue here it is conceivable that other types of bispecifics might escape unscathed.

…Or B7-H3?

However, Evercore ISI's Umer Raffat believes that there is a more likely explanation for the issues seen with MGD009: its target, B7-H3. This protein, also known as CD276, is overexpressed on a variety of cancer cells, but Mr Raffat adds that there is some evidence suggesting that B7-H3 "has medium to high expression in various tissues, including the liver".

While this might represent a less serious setback to the bispecific field it would hit Macrogenics hard: as well as MGD009 and the aforementioned antibody enoblituzumab, the company also has an antibody-drug conjugate targeting B7-H3 in preclinical development, MGC018. Only a couple of other companies are looking at B7-H3, according to *EvaluatePharma*.

At risk? Assets in development targeting B7-H3		
Project	**Company**	**Approach**
Phase II		
Omburtamab	Y-Mabs Therapeutics	Anti-B7-H3 MAb-I-124 & I-131 conjugate
Enoblituzumab	Macrogenics	Anti-B7-H3 MAb
Phase I		
MGD009/orlotamab	Macrogenics	Anti-B7-H3 & CD3 bispecific MAb
Preclinical		
MGC018	Macrogenics	Anti-B7-H3 MAb-cytotoxic drug conjugate
DS-7300	Daiichi Sankyo	Anti-B7-H3 MAb-cytotoxic drug conjugate
HuB7-H3	Y-Mabs Therapeutics	Anti-B7-H3 MAb
Omburtomab-DTPA	Y-Mabs Therapeutics	Anti-B7-H3 MAb-Lu-177 conjugate
Source: EvaluatePharma.		

Macrogenics played down the readacross from the MGD009 setback to its other programmes, but its stock opened down 25% this morning. With analysts not yet ascribing any value to MGD009 this suggests that investors are jittery about the group's other B7-H3 assets, its bispecifics, or its broader antibody design platform.

With a huge readout ahead next quarter from the pivotal Sophia study of Macrogenics' lead candidate, the engineered Her2-targeting antibody margetuximab, it is perhaps understandable that the markets are nervous.