Roche takes it to the tumour

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Roche targets bispecifics to get ahead in oncology.

Forget cytokines. Forget adoptive cell therapy. To push forward the frontiers of immuno-oncology, Roche is reaching for the bispecifics.

These dual-targeted antibodies should be able to generate responses in patients and tumour types that fail to respond to existing immunotherapies, Roche believes; Dan Chen, head of cancer immunotherapy at the Swiss company, describes this as taking a "sledgehammer" to the problem. Roche has five bispecifics in the clinic and should unveil data on a couple of them later this year, he tells *EP Vantage.*

Two of Roche's bispecifics are being tested in haematological cancers, and it is these that should generate results next, he says. Mr Chen was speaking to *EP Vantage* at Asco earlier this month; when asked more recently to elaborate, Roche declined to be any more precise.

Given Roche's existing cancer drug portfolio, and the investment it has made here, the results are keenly awaited. Both of the group's blood cancer bispecifics hit CD20, an antigen expressed on all B cells and also targeted by Roche's hugely successful monoclonal antibodies Rituxan and Gazyva. In fact both RG6026 and RG7828 are being tested in combination with Gazyva as part of their phase I programmes.

RG7828, now generically known as mosunetuzumab, looks to be the biggest bispecific bet placed so far by Roche. The asset is in a very large phase I/II study in B cell lymphoma and chronic lymphocytic leukaemia, alone and in combination with Tecentriq; this trial got under way in 2015.

Roche's bispecific bets (clinical-stage assets)			
Project	Mechanism	Indications	Trial ID
ERY974	Anti-glypican 3 & CD3	Various solid tumours	NCT02748837
RG6026	Anti-CD20 & CD3	Relapsed/Refractory NHL	NCT03075696
RG7386	Anti-FAP & DR5	FAP+ solid tumours/sarcomas	NCT02558140
RG7802 (RO6958688)	Anti-CEA & CD3	CEA+ tumours	NCT02324257; NCT02650713
RG7828 (mosunetuzumab)	Anti-CD20 & CD3	Relapsed/Refractory NHL; CLL	NCT02500407; NCT03075696

Mr Chen describes bispecifics as a crucial part of the company's attempt to stimulate "direct immunity" in patients who fail to respond to currently available immunotherapies. These patients typically have cancers that Roche has termed immune-excluded or desert, in which the T-cell response is either ineffective or completely absent.

Until researchers can work out how to unlock the potential of immunotherapy for these patients a simpler approach is required, he says. "While we're waiting to find those keys we've taken a sledgehammer to the door. So instead of relying on endogenous immunity and the cancer immunity cycle to drive activity – which is really complicated and we don't know all the answers yet – we've decided to bypass that."

Roche's bispecific efforts mostly use a CD3 backbone to recruit T-cells to the tumour. Roche has already generated some evidence that by recruiting T cells to the site of the tumour bispecifics can be effective in hard-to-treat patients, Mr Chen said. A phase I trial of RG7802 in CEA-positive colon cancer, presented last year, showed encouraging response rates in "a very immunologically difficult" tumour.

"We have multiple assets in the clinic and are by far the leaders in the field," he says.

Elsewhere?

Of course, when it comes to the immuno-oncology arms race, bispecific antibodies represent only one novel mechanism among many others being pursued.

Interestingly, Mr Chen is fairly dismissive of cytokines, one of the most closely watched immuno-oncology fields, and insists that Roche's lack of presence in the CAR-T space was a "deliberate decision".

"We believe that cytokines will be important, we just don't believe that they will be the key that unlocks the door" to non-immunogenic tumours, he says. "If you can unlock those, then you can add your cytokine."

And while Mr Chen points out that Roche does have a cell therapy collaboration with Kite in NHL, he insists that bispecifics can produce activity as good as or better than CAR-T, with the advantage of being "off the shelf".

He also says that by homing in on malignancies more effectively bispecifics could well prove more effective than CAR-T in solid tumours. Still, until Roche and the CAR-T players start generating data in solid tumours, this will remain conjecture.

Place the faith

With three bispecifics being tested in solid tumours, this evidence should begin to emerge soon. Studies of RG7802 are under way while ERY974, an asset discovered by Chugai, and RG7386 have been in the clinic since 2015. The former targets glypican 3, which is expressed in most liver cancers and is also found in lung and gastric tumours, while the latter is in a phase I expansion study selecting for patients with FAP-positive cancers.

Roche is not alone in pursuing bispecifics. Amgen is probably its biggest competitor here, and the US biotech can claim to have the first commercially successful bispecific in Blincyto, which is on the market for certain B-cell precursor acute lymphoblastic leukaemias.

Indeed Amgen might quibble with Mr Chen's claim to be the most advanced here – it lists seven experimental bispecific projects in its pipeline, though only two are in solid tumours. Notably, an anti-CEA project, AMG 211, looks to have been fairly recently abandoned (*Behold the son of Blincyto*, September 2, 2016).

But much remains to be proven in this space. And, while Roche's cancer pipeline extends well beyond bispecifics, the company is placing a great deal of faith here. After falling behind the likes of Merck & Co and Bristol-Myers Squibb in the checkpoint inhibitor race, the world's biggest cancer company will be keen to take the lead somewhere in the hugely competitive immuno-oncology field.

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