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Interview – Merck's Rigontec buy primes another immuno-oncology combo

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Immuno-oncology combinations have become a hot topic in the past couple of years, and there could soon be a new pairing on the cards after Merck & Co's takeout of the early-stage German company Rigontec. The start-up claims to harness the innate immune system with its RIG-I agonist RGT100 and, while Merck has not said whether it will combine the project with Keytruda or other IO assets, this seems a likely course of action.

"When you loosen the brakes of the immune system with the checkpoint inhibitors you rely on the immune system already being in play – and that is what we accomplish with our technology," Christian Schetter, Rigontec's chief executive, tells *EP Vantage*. With RGT100 appearing to be the only RIG-I-targeting project in clinical development for cancer, it is perhaps no wonder that Merck was keen to get involved (see table below).

The craze for combining different immuno-oncology approaches has reached fever pitch this year – at the last count there were no fewer than 765 studies involving combos of PD-1 or PD-L1 assets, with Keytruda the most popular (*Immuno-oncology combinations surge as sector seeks the fairy dust, June 1, 2017*).

However, when asked if it was planning a combo approach with RGT100, Merck was tightlipped, only saying it is "eager to build upon Rigontec's science".

RIG-I-targeting projects in development

Project	Company	Pharmacology class	Indication(s)
Phase II			
SB 9200	Spring Bank Pharmaceuticals	Retinoic-acid-inducible gene I (RIG-I) & nucleotide-binding oligomerization domain containing 2 (NOD2) activator	Hepatitis B; other viral indications
Phase I			
RGT100	Rigontec	RIG-I agonist	Solid tumours
Preclinical			
Immuno-Oncology Program	Kineta	RIG-I agonist	Colorectal cancer
RIG-I	Kineta	RIG-I agonist	General viral indications
ImOl200	Rigontec	RIG-I agonist	General cancer indications
ImOl201	Rigontec	RIG-I agonist	General cancer indications

Source: EvaluatePharma.

The acquisition, which involves a €115m ($138m) up-front fee and milestone payments of up to €349m, came just three years after Rigontec was founded and months after it took RGT100 into the clinic. A phase I/II trial in solid tumours is recruiting, with results due in 2019.

Merck must have seen something it liked in preclinical development. Mr Schetter believes that RGT100, which

at present is delivered via intra-tumoural injection, could make “cold” tumours immunogenic by targeting RIG-I, a receptor that plays a role in cell death after a viral infection.

Part of the project's mechanism seems similar to a therapeutic cancer vaccine, an approach that has so far not met with success. RGT100 comprises a short synthetic double-stranded RNA molecule designed to fool the body into thinking a virus is present and mounting an immune response, Mr Schetter explains.

Activating the RIG-I receptor has several effects, according to Mr Schetter: first, it triggers apoptosis in tumour cells, “which healthy cells can counter”, he says. Dying tumour cells release antigens that might provide targets to reactivate the immune system in the tumour microenvironment.

It also triggers a typical innate immune response, with the recruitment of natural killer and T cells, he says. Then “there’s this switch later on, after 10-14 days, to the adaptive immune system, where you see long-term anti-tumour immunity being developed”, he concludes.

Eye of the cytokine storm?

However, as with any novel technology, there remains a lot to prove. Evercore ISI analyst Umer Raffat highlighted possible safety concerns with such immune stimulation, including uncontrolled inflammation.

Mr Schetter concedes that the RIG-I receptor “is present on virtually all cells of the body”, but is confident that this will not lead to any serious side effects.

He believes that the nature of RIG-I, and the fact that RGT100 hits this receptor exclusively, means the therapy will avoid problems like cytokine release syndrome. “In evolution, [RIG-I] developed as a quick response against a virus, leading to a very narrow and specific immune response – then it has to be controlled again. It activates T cells to some extent, but not to the extent that you get this typical side effect of very strong T-cell activators.”

Although Mr Schetter says RGT100 has not yet shown any signs of toxicity, this is no doubt something that will be closely watched in clinical trials.

As for the competition, he says: “We have not seen any company with a technology for specifically and effectively activating RIG-I.”

Kineta’s project is a small molecule, which could have the advantage of oral dosing but might not work, according to Mr Schetter. “We believe that a small molecule won’t be specific enough to identify the RIG-I receptor. It’s just not contacting with the receptor in a way that activates it.”

Of course, there is still the chance that RGT100 will not succeed. But with Merck behind it, the RIG-I-targeting approach at least now has big pharma endorsement.

Study	**Trial ID**
Phase I/II trial in advanced or recurrent tumours	NCT03065023

EP Vantage’s immuno-oncology combination report can be downloaded here.

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