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Interview – Boehringer beats a brave route with oncolytic virus deal

Amy Brown

Despite having largely missed out on the immuno-oncology revolution so far, Boehringer Ingelheim appears happy to be making longer-term bets on the field. Last week it struck a typically early deal with a small start-up that has developed an oncolytic virus, a field that has yet to prove its potential.

ViraTherapeutics, however, reckons it has a way to enable systemic administration – the need for local injections into tumours has been held responsible for hobbling the effectiveness of oncolytic virus projects. Its lead candidate, VSV-GP, will move into the clinic in 2018, its chief executive and co-founder, Professor Dorothee von Laer, tells *EP Vantage*, and if the data are positive Boehringer has an option to take the whole company in-house.

The deal includes a €20m ($22m) up-front fee to fund the completion of preclinical work and a phase I trial; should the takeout option be triggered, Boehringer will pay another €190m for the whole company. ViraTherapeutics has raised €9.3m in two venture rounds to date, and the venture arm of the private German drugs giant has been on board since the beginning.

Rats and cattle

VSV-GP is based on the vesicular stomatitis virus, a disease of livestock and rodents against which humans do not have any latent immunity. This is important because it is thought that neutralising antibodies are present against vectors used in other oncolytic virus candidates, for example herpes simplex or reovirus, which the immune system recognises as foreign and destroys.

VSV-GP avoids this, however, and can therefore be delivered systemically. Once it is in the bloodstream it is not completely understood how it finds the tumour, Professor von Laer says, although the interferon response that helps inhibit virus replication, controlled by the innate immune system, is thought to be involved.

“At least one important factor is that advanced tumours are interferon-incompetent, so they are not protected by interferon against virus replication. So the virus does not replicate in all of the tissues, but does replicate in the tumour.”

Preclinical data have shown a very strong homing ability, with no off-target effects, even at high doses, she says.

But Boehringer is not the first pharma company to jump at this approach; in 2015 AstraZeneca licensed in an oncolytic virus programme from Omnis Pharmaceuticals (now part of Vyriad); this also involves a genetically engineered strain of vesicular stomatitis virus.

Limited potential

Inability to treat distant metastases has so far largely limited the potential of oncolytic viruses, and many now believe that their potential lies in combinations.

“There have been cases of the efficacy of a virus on its own but I don’t think anyone will use them in this way anyway, because it’s becoming clear that their effect can be boosted considerably by adding checkpoint inhibitors or whatever is available in the field,” Professor von Laer says.

Although testing VSV-GP will naturally start as a monotherapy, using the virus as a platform to load with other genes or in combination with other therapies is ultimately the goal of the Boehringer collaboration.

Completing the preclinical work will take about another year and a half. Phase I testing will take place in solid tumours; although Professor von Laer would not confirm which solid tumours, she said the company would not start in locally inaccessible ones.

Riding the wave

There is already evidence that a combination approach should yield results. Amgen's Imlygic (T-Vec), the only oncolytic virus to make it to market, recently generated encouraging data in a trial with Merck & Co's Keytruda – in melanoma the combination appeared to double the response rate, versus the checkpoint inhibitor alone. By driving the tumour into a more immunogenic state, it seems that these viruses boost the tumour's susceptibility to immunotherapy.

Interestingly this theory is also the basis for Boehringer's other step into the immuno-oncology arena, under its 2014 deal with Curevac (*CureVac emerges with €35m cancer vaccine endorsement, 18 September 2014*).

This bought rights to CV9202 – a transdermally administered, self-adjuvanting, naked mRNA vaccine coding for six antigens expressed in lung cancer. Boehringer describes it as its most advanced clinical immuno-oncology asset, although it is not clear whether its own clinical testing has started.

Advocates of cancer vaccines and oncolytic viruses have long believed that their utility would eventually be teased out; Curevac and ViraTherepeutics have built on years of setbacks and come up with what they believe are much improved assets. However, it will take years of clinical testing to determine whether this is indeed the case, and if Boehringer has found a way to ride the immuno-oncology wave.

To contact the writer of this story email Amy Brown in London at AmyB@epvantage.com or follow @AmyEPVantage on Twitter