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Interview – Tocagen touts two-step cancer vaccine

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After plenty of setbacks over the years, the gene therapy space seems to be undergoing something of a renaissance. One player to try its luck in the field, California's Tocagen, is aiming its unusual two-step approach at oncology – initially brain cancer.

This is a disease without many options. The treatment has shown potential in many cancer types, Tocagen's chief executive, Harry Gruber, tells *EP Vantage*. "But we've started in brain cancer because we believe that if you're taking something into humans and you're not sure of the outcome you should start in the sickest patients possible."

In spite of this caution he is convinced that Tocagen's lead candidate, Toca 511 & Toca FC, is safe, and says that no serious adverse events have emerged in phase I trials so far – including auto-immunity, a concern with other immunotherapies.

On the brain

Tocagen is in the midst of a phase II/III trial of Toca 511 & Toca FC, called Toca 5, in recurrent brain cancer that should return results late next year and could be enough for approval because of the unmet need.

The signs from phase I are good, Mr Gruber says. "We saw approximately a doubling of survival across three different phase I studies. What's really exciting is that we're seeing 40% survival probability at two years."

However, the phase I studies used historical controls as a comparator – a risky strategy, particularly in a disease like glioblastoma that is highly heterogeneous. Although most patients only live for eight or nine months after diagnosis, a few survive for much longer.

The Toca 5 study will be the real test, as it compares Toca 511 & Toca FC with the investigator's choice of standard-of-care treatment such as Avastin.

Tocagen is also about to start enrolling patients in a phase Ib trial, Toca 6, in other metastatic cancers including breast, colorectal and lung.

One-two

Toca 511 is the gene therapy part of the treatment. The viral vector is injected into the tumour site after resection where it is taken up by dividing cells – which should mean that it is selective for cancer cells – and delivers the cytosine deaminase (CD) gene.

The agent spreads through the tumour and causes the infected cells to produce the CD enzyme. This is important for the next step: oral dosing of Toca FC or 5-fluorocytosine, a prodrug that is converted by the CD enzyme to fluorouracil (5-FU), a known chemotherapy drug.

The approach means that "we can achieve much higher levels of 5-FU in the tumour than you would otherwise safely achieve", according to the chief exec. "Systemic 5-FU doesn't work in the same models, where this localised 5-FU does work."

As well as killing the infected cancer cells, 5-FU also destroys immunosuppressive cells such as myeloid-derived suppressor cells, which act as a brake on the immune system. "We don't believe we're getting into every cancer cell, so it's critical to activate the immune system," says Mr Gruber.

The localised nature of the treatment should mean a lower risk of adverse events. "5-FU has an extremely short half-life so is destroyed very quickly – we measure very high levels in tumours but we can't detect any in the blood, so there are no systemic side effects."

The chief exec does not believe that Toca 511 is being taken up by healthy cells to a large degree. "Healthy cells carry innate immunity that can rapidly clear this virus. But it can grow in cancer cells, which are defective

in innate immunity.”

Tocagen still has work to do, but if its project shows efficacy in glioblastoma it could capture market share in a space where off-patent chemotherapy is still standard of care.

Other cancer vaccines are in development but Northwest Biotherapeutics' is on hold amid other questions over its technology; Agenus’s trials have had problems recruiting patients because a large amount of tumour tissue is required to create the therapy, according to Mr Gruber.

Success in brain cancer could also pave the way for other, more lucrative indications or maybe even combinations with checkpoint inhibitors. “Right now we feel it’s strong enough to be approved as a single agent, so we’re pushing hardest on that,” says Mr Gruber. “But there are a lot of physicians who’ve asked to do checkpoint combinations with us, so it’s on our radar screen.”

Study	Trial ID
Toca 5	NCT02414165
Toca 6	NCT02576665

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