#2

Accession - Preclinical

Authors:

RC. Khanolkar[1], JA. Davies[1,2], AT. Baker[1,2], TA. Webb[1], S Shahreza[1], NK. Boparan[1], S. Hardy[1], HK. Uusi-Kerttula[2], LM. Williams[1], E Henderson[1], SL. Moore[1], JM. Pentier[1], BK. Jakobsen[1], AL. Parker[1,2], DK. Cole[1,2], AB. Gerry[1], D. Krige[1]

[1]Accession Therapeutics Limited, Building 7600C, The Quorum, Oxford Business Park North, Oxford, OX4 2JZ, UK.
[2]Division of Cancer and Genetics, School of Medicine, Cardiff University, Heath Park, Cardiff, CF14 4XN, UK.

Abstract:

TROCEPT - A tumor-targeted precision immunovirotherapy enabling avb6 integrin-positive tumor-localized expression of an immune checkpoint inhibitor following intravenous delivery

Oncolytic viruses encoding transgene payloads represent a tractable single-agent approach to targeted delivery of immunomodulatory therapies to tumours and have emerged as a promising modality in cancer therapy. TROCEPT is a next-generation genetically modified adenovirus type-5 rationally designed to overcome the limitations of existing IV delivered viruses to significantly increase tumour exposure. TROCEPT is uniquely de-targeted to avoid uptake by healthy cells, including the liver, by removal of normal cell tropisms, and is re-targeted to specifically infect and replicate in tumour cells that express αvβ6 integrin which is highly expressed in epithelial cancers. ATTR-01 is a first-in-class transgene modified variant of TROCEPT that, following infection of permissive tumour cells, expresses an anti-PD-L1 antibody payload. Intratumoral expression of the anti-PD-L1 checkpoint inhibitor locally, rather than via systemic delivery by IV infusion, may lead to higher local (tumour) concentrations of the drug and avoid exhaustion of systemic T cells, thereby increasing efficacy and reducing off tumour toxicity.

In vitro experiments demonstrate that viral replication, transgene expression and oncolytic cell death following infection with ATTR-01 is highly selective for αvβ6 integrin positive tumor cells compared to a panel of normal human primary cells. Intravenous delivery in *in vivo* human tumor xenograft mouse models demonstrate virus delivery, replication, and transgene expression in the tumor. Tumor regression and 100% survival was observed in all five tumour indications tested; ovarian, pancreatic, bladder, colorectal and lung tumors. In comparison to the parental Ad5 virus, the engineering of ATTR-01 led to more viral delivery to the tumour and less delivery and thereby toxicity to normal tissues including liver. A greater than 100-fold improved tumour-to-liver ratio was observed with ATTR-01 compared to parental Ad5. No liver enzyme or inflammatory cytokine changes were observed with ATTR-01 even at the top dose equivalent to $3x10^{14}$ viral particles.

This data validates the tumour selectivity and safety profile of ATTR-01. A phase 1 study, ATTEST, is evaluating safety and preliminary efficacy of intravenous delivery of ATTR-01 in patients with selected epithelial tumours expressing high levels of the target αvβ6 integrin, including non-small cell lung, urothelial, head and neck, pancreatic, endometrial and cholangiocarcinoma in multiple sites in UK.

Consent statement: All animal studies and human tissues had appropriate ethical approvals.