ATTEST: A phase 1 study of intravenous ATTR-01, a novel oncolytic adenovirus targeting αvβ6 integrin, expressing anti-PD-L1 antibody in epithelial tumors

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Introduction to TROCEPT Platform

Oncolytic viruses encoding transgenes represent a tractable single-agent approach to targeted delivery of immunomodulatory therapies to tumors and have emerged as a promising modality in cancer therapy (**Figure 1**).

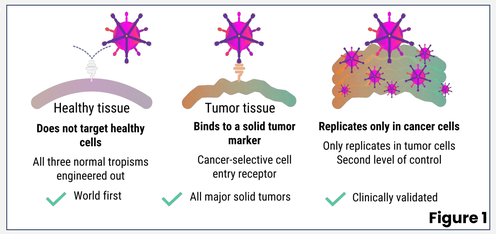


Figure 1

TROCEPT, a next-generation genetically modified adenovirus type-5, is rationally designed to overcome the limitations of existing IV delivered viruses and to increase tumor 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 tumor cells that express the cancer marker αvβ6 integrin (**Figure 2**).

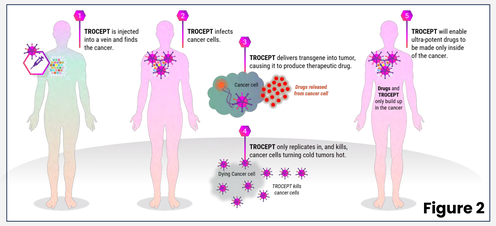


Figure 2

TROCEPT Pre-clinical Data

Administration of TROCEPT leads to tumor-specific transgene payload (luciferase) production which increases with time as TROCEPT replicates in the tumor, compared to unmodified Ad5 which leads to body-wide transgene payload production. This also confirms the removal of the native tropisms in TROCEPT and specificity for αvβ6 integrin (**Figure 3**).

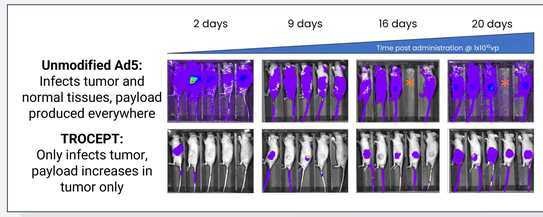


Figure 3

Luciferase transgene activity detected by IVIS in SKOV3 ovarian tumour xenografts in BALB/c nude mice after a single intravenous administration of $1x10^{10}$ vp/animal of unmodified Ad5 (top panel) or TROCEPT (bottom panel) expressing a luciferase transgene. n=5/group, the same mice are shown in the same order at each timepoint. * sacrificed due to tumor burden.

NSG mice engrafted with human tumors expressing αvβ6 integrin. Mice treated with vehicle demonstrated rapid tumor growth with 100% mortality. Intravenous injection of TROCEPT ($1x10^{11}$ vp) into mice with large established tumors led to tumor control (**Figure 4**).

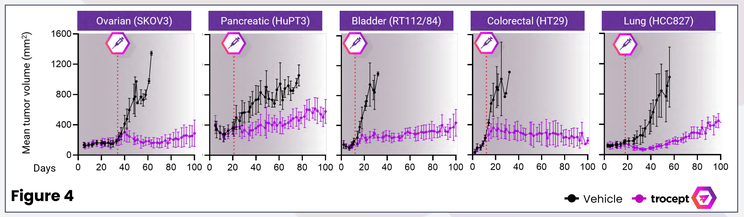


Figure 4

Introduction to ATTR-01

ATTR-01 is a first-in-class transgene modified variant of TROCEPT that, following infection of permissive tumor cells, expresses an anti-PD-L1 antibody.

Expression of the anti-PD-L1 checkpoint inhibitor in metastases (i.e locally), rather than via systemic delivery by IV infusion, may lead to higher local (tumor) concentrations of the drug and avoid exhaustion of systemic T cells, thereby increasing efficacy and reducing off tumor toxicity (**Figure 5).**

ATTEST is the first study of ATTR-01 in selected epithelial tumors with high frequency (≥ 75%) of αvβ6 expression.

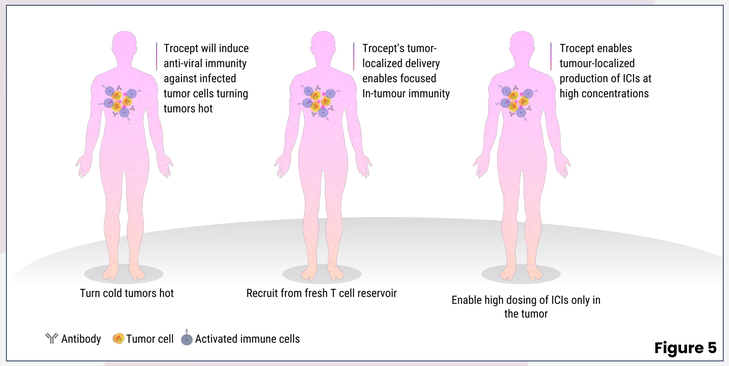


Figure 5

ATTEST Study Design

ATTEST is an open label, multi-centre, dose escalation study of ATTR-01 (**NCT06977737**).

Part 1 is a dose escalation, using a Keyboard design, up to a maximum dose of 1 x 10^{13} viral particles (n≤48 participants).

Up to two doses will be expanded in Part 2 to explore the optimal dose(s) (n≤24 participants).

Participants will be recruited having progressed after ≥ 1 line of standard of care therapy with six cancer types (non-small cell lung, urothelial, head and neck, pancreatic, endometrial, cholangiocarcinoma; **Figure 6**) that typically demonstrate a high frequency (≥ 75%) and high level of αvβ6 integrin expression.

Pharmacodynamic outcomes will be assessed using tumor tissues and blood.

Analysis of tumor tissues (biopsies at baseline, Day 15 and Day 36) will explore viral replication, transgene expression and immune/inflammatory responses.

Study objectives are described in **Table 1**.

Figure 6

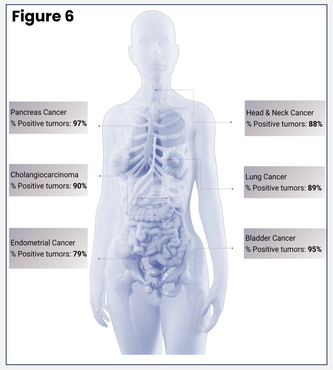


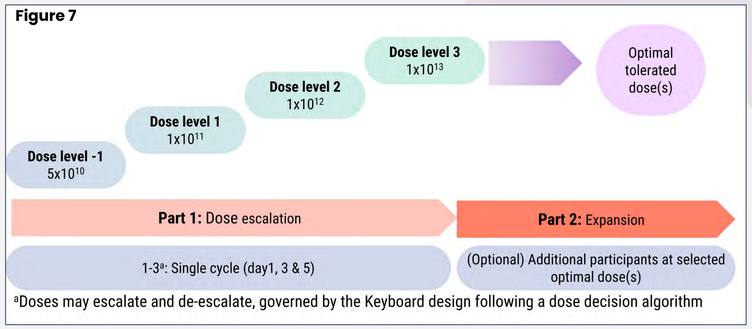
Table 1: Study Objectives

Co Primary
• Characterise the safety and tolerability of ATTR-01
• Recommended dose of ATTR-01
Secondary
• Preliminary anti-tumor activity of ATTR-01
• Immunogenicity and viral persistence

ATTEST Study Schema

The ATTEST study design is described in **Figure 7.**

Figure 7



[a]Doses may escalate and de-escalate, governed by the Keyboard design following a dose decision algorithm

ATTEST Study Read-outs

Clinical
- Safety and tolerability
- Definition of optimal dose
- Anti-tumor activity (secondary)

Translational
- Viral delivery, replication and transgene expression in tumor (platform POC)
- Pharmacodynamic read-outs
- Others (viral persistence, shedding etc)

Enrolment

- Up to 72 patients across 6 indications will be enrolled in Sub-protocol A.
- Enrolment into the first cohort is ongoing.
- 7 clinical sites are active with further investigator's sought:
  - **St James Hospital, UK** (Prof Adel Samson)
  - **Velindre Cancer Centre, UK** (Dr Magdelana Meissner)
  - **Churchill Hospital, UK** (Dr Eileen Parkes)
  - **Beatson Cancer Centre, UK** (Dr Pavlina Spiliopoulou)
  - **CIOCC, Spain** (Dr Emiliano Calvo)
  - **HM Nou Delfos, Spain** (Dr Tatiana Hernandez)
  - **FJD, Spain** (Dr Bernard Doger; Dr Victor Moreno)

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