DEVELOPMENT OF ONCOLYTIC ADENOVIRUS AD53-E2F-D24-HTNFα-IRESHIL2 (TILT-123) FOR THE TREATMENT OF SOLID TUMOURS – FROM PRECLINICAL TESTING TO PHASE I CLINICAL TRIALS

1James Clubb*, 2Victor Cervera-Carrasco, 3Katiina Peltola, 4Tuomo Alanko, 4Riitta Korpiasari, 3Marjut Jaakkola, 3Iurma Sormunen, 3Juha Kononen, 3Joao Manuel Santos, 3Santeri A Pakola, 2Else Jirovec, Tatiana Kudling, 2Lyna Haybout, 2Dafne CA Quixabeira, 2Claudia Kistler, 2Riikka Havunen, 2Susi Sorsa, 1Akseli Hemminki. TILT Biotechtherapeutics, Helsinki, Finland; 2Cancer Gene Therapy Group, Translational Immunology Research Program, University of Helsinki, Helsinki, Finland; 3Comprehensive Cancer Centre, Helsinki, Finland; 4Docrates Cancer Center, Helsinki, Finland; 5University of Helsinki, Helsinki, Finland

Abstract

Here, we cover the development timeline leading up to multiple Phase I clinical trials with an oncolytic adenovirus coding the cytokines TNFα, Interleukin-2 (IL-2). The construction of Ad53/E2F-D24-hTNFα-IRESHIL2 (TILT-123) began over a decade ago following observations in humans enrolled in an individualized treatment program (Advanced Therapy Access Program). The findings were taken into the lab and preceded a series of in vivo cytokine screens in mice, which identified transgenes optimal for recruiting T cells and improving the efficacy of adoptive cell therapy. TILT-123 has been evaluated in several preclinical studies with encouraging efficacy and mechanistic insight. For example, we have reported complete responders when combining TILT-123 with immune checkpoint blockade or adoptive cell therapy in mouse and Syrian hamster models of melanoma and pancreatic cancer. Further, we observed induction of a tertiary lymphoid structure signature in a mouse model of immune checkpoint inhibitor refractory head and neck squamous cell carcinoma. Here will also discuss the ongoing trials, with focus on TILT-123 monotherapy (NCT04695327). Patients enrolled in five cohorts tolerated the treatments well and no dose-limiting toxicities have been reported. Several patients have shown benefit from the treatment in CT or PET imaging, allowing them to be subsequently enrolled into an extension protocol featuring prolonged treatment with TILT-123. Additionally, multiple biological samples collected throughout the trial are being analysed to investigate the mechanism of action of the therapy, to validate the preclinical established observations regarding the interaction between the virus, the tumour, and the immune system.

Methods In the Advanced Therapy Access Program (ATAP), over 290 patients were treated in an individualized patient-by-patient basis. Different oncolytic adenoviruses were used to treat various types of solid tumours. Treatments are described elsewhere. Preclinical studies detailing cytokine screens and evaluating TILT-123 in murine and Syrian hamster models are described elsewhere. Patients enrolled in NCT04695327 include five cohorts comprising 15 patients with various solid tumour indications. Patients received multiple rounds of intravenous or intratumoural injection of TILT-123. Biological samples including tumour biopsies were collected at different time points for multi-omic analysis. Clinical responses were assessed by PET or RECIST 1.1.

Conclusions The oncolytic adenovirus TILT-123 was constructed using an evidence based design approach and has now entered Phase I clinical trials in Europe and US. Monotherapy treatment demonstrates parallels with preclinical studies in terms of immune cell stimulation.

Acknowledgements We wish to thank all the animals, patients, family members and staff that were involved in the studies described here.

REFERENCES


Ethics Approval This study was approved by the Finnish National Committee on Medical Research Ethics (TUKIJA); approval number HUS/1804/2020.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0711