

## EMERGING RESULTS FROM THE USE OF AN ONCOLYTIC ADENOVIRUS ARMED WITH TNFA AND IL-2 (TILT-123) IN DIFFERENT PHASE I SOLID TUMOR CLINICAL TRIALS

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**Background** After the first Immune Checkpoint Inhibitor (ICI) was approved (ipilimumab, 2011 for cancer therapy, the list of indications routinely treated with ICIs keeps increasing. In this new era of cancer immunotherapy, the major drawback of the approach is the difficulty in delivering long term benefits to a larger portion of patients. Different forms of immunotherapy used in solid tumor cancer patients seem to work better in immunologically hot tumors. To that extent, TILT-123 (an Oncolytic Adenovirus armed with TNF $\alpha$  and IL-2) was designed to stimulate the immune system within the tumor to enable subsequent forms of immunotherapy. After discovery and preclinical testing, the therapy was taken into clinical trials in 2020. Two years after, four Phase I clinical trials are ongoing where TILT-123 is being tested to determine its safety as monotherapy (NCT04695327), together with adoptive cell therapy using tumor-infiltrating lymphocytes (NCT04217473), and ICIs (NCT05271318, NCT05222932).

**Methods** These phase I open-label, dose-escalation clinical trials, have the primary endpoint of establishing safety of the treatments in patients with injectable advanced refractory and recurrent solid tumors, that cannot be treated with curative intent. Safety is evaluated based on the occurrence of adverse events, impact on vital signs and safety laboratory tests. Additionally, secondary endpoints relative to the trials include efficacy of the approaches and mechanistic analyses based on biological samples, including studies on the presence and persistence of virus in different fluids and tissues, as well as, the proteomic and transcriptomic changes seen in tumors after therapy. Antitumor efficacy, according to RECIST 1.1/iRECIST/PET criteria, has been recorded in different patients.

**Results** Interim safety data emerging from patients treated with TILT-123 (n=18 patients), provided confidence to continue dose escalation as the investigational medicinal product did not cause dose limiting toxicities. The most frequent treatment related adverse events, as judged by investigators, were fever, nausea, chills and fatigue, typically low grade according to the CTCAE v5.0. Systemic antitumor efficacy according to RECIST 1.1/iRECIST/PET criteria has been seen in several patients. Biological sample analyses demonstrate the remodeling of the tumor microenvironment towards an antitumor status, when studying the T cell presence and the immune signature within the tumor.

**Conclusions** Preliminary data emerging from Phase I clinical trials using TILT-123, point to an adequately safe approach able to induce antitumor activity, both as monotherapy and in combination. Dose escalation continues in pursuit of a recommended dose to use in Phase II clinical trials.

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**Trial Registration** NCT04695327, NCT04217473, NCT05271318, and NCT05222932

**Ethics Approval** TILT-T115: This study was approved by the Finnish National Committee on Medical Research Ethics (TUKIJA); approval number HUS/1804/2020

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