Background

- While delivering cancer therapy breakthroughs, immunotherapy is not always able to provide benefit in most patients.
- In addition to tumor heterogeneity, patients with the tumor microenvironment is convoluted and infiltrating T-cells (or lack thereof) serve as a consistent target of suppression across different tumor types.
- Iglaziglumen is an oncogenic adenosine encoding for Ad5 helper virus neutralising >80% the virus.

Demographics and Safety

- Patients enrolled underwent several lines of therapy before enrolling into the trial (Table 1).
- WIND/SOGO performance status was mostly 1 (Table 1).
- Most common types of cancers in dose levels were Sarcoma, Melanoma, Ovarian and peritoneal cancer and head and neck (Table 1).
- The most frequent AEs observed were fever, chills and fatigue (Table 1).
- Dose-limiting toxicities were not observed (Table 2).

Trial Design

- TIL-TILT 115 (NCT04665327) is an open label phase 1 clinical trial using a standard 3+3 dose escalation scheme.
- Treatment is given to participants, who have advanced solid tumors, which are refractory to available therapies.
- TILT 123 was administered through intravenous (x1) and intratumoral/intravenous (at least x5) routes, throughout the trial.
- TILMND enrolled at 2 sites in Helsinki, Finland: Docrates Cancer Center and Helsinki University Hospital.

Anti-Tumor Activity

- The results have not ben fully monitored audited or verified by the quality assurance.
- Cytokine release, such as IL1B, TNFα, IL10, cytokine and cytokine like factor alpha, were designed for recruiting, propagating and stimulating T cells for re-infiltration of the tumor microenvironment.

Biodistribution

- T-cell inducing oncolytic virus (iglaziglumen lidatenopecv; TILT-123) shows safety, anti-tumor activity and induction of immune responses in advanced solid tumor patients (full report on TUNIMO).

Immunological activity

- This dose-escalation study indicates that TILT-123 is safe in humans.
- The safety profile observed is consistent with other virus based immunotherapies.
- Treatment with TILT-123 can enable anti-tumor responses as monotherapy, which can be seen in injected and non-injected lesions.
- TILT-123 can reach tumors and deliver efficacy despite neutralizing antibodies.
- Shedding of TILT-123 genotypes form analyzed urine samples was not detected.
- Administration of TILT-123 triggers a systemic inflammatory response and enriches the tumor microenvironment with T-cells.

Conclusions

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We thank the patient and their families, and all.

#1518

BIOATHERAPEUTICS
Emerging proteomic and safety analysis of blood from patients receiving TILT-123 (Ad5/3-E2F-d24-hTNFa-RES-hIL2) monotherapy in TUNIMO phase 1 clinical trial

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1. TILT-123 induces decrease in total lymphocytes indicative of sequestration into tumors and this correlates with response.
2. No clinically relevant decrease in neutrophils or total leukocytes.
3. Pro-inflammatory changes in the serum are seen after intravenous and intratumoral administration.
4. Repeated intratumoral dosing produces stronger serum proteomic changes – lymph node or tumor niche priming?

METHODS

• TILT-123 is currently evaluated in 4 clinical trials: TUNIMO (advanced solid cancers, monotherapy, NCT04695327), TUNINTIL (melanoma, with TIL therapy, NCT04217473), PROTA (ovarian cancer, with pembrolizumab, NCT05271318) and AVENTIL (anti-PD(L)1 resistant melanoma/SCCHN, with aveolumab, NCT0522932).

• TILT-123 administration induces predominantly lymphocyte decrease acutely in blood. (A)
• Lower lymphocyte count post TILT-123 treatment correlates with treatment efficacy when looking at first three i.t. administrations. (B)
• Lymphocyte count less than 0.75 x 10^9/L correlates with better response in all intratumoral administrations. (C and D)

COI & ACKNOWLEDGEMENTS & CONTACT

The presenting author has no COI to declare. TILT Biotherapeutics provided study material and reagents.

We like to thank the patients, families and hospital staff taking part in the TUNIMO study.

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Background

Recent clinical trials evaluating the potential of oncolytic virotherapy has revealed encouraging results, giving hope to patients with incurable advanced stage cancer.

Igrelimogene Ildenadorepvec (Ad5/3-E2F-ds4-TNF-IRE-IL-2; TILT-123), is an oncolytic adenovirus encoding for interleukin-2 and tumor necrosis factor alpha, designed for recruiting, propagating and stimulating T-cells and boosting the efficacy of existing T cell therapies such as immune checkpoint inhibitors and adoptive cell therapy.

After almost two decades of development, TILT-123 is now in multiple Phase I clinical trials around the world, for the treatment of different solid tumor indications. Promising clinical responses have been observed and analysis of samples proceeds with the hope of identifying biomarkers to improve patient stratification. However, additional ongoing preclinical characterisation has also revealed novel insights which may guide better exploitation of this promising therapy.

1 TILT-123 induces tertiary lymphoid structure formation

Preclinical study in mice demonstrates TILT-123 induces tertiary lymphoid structure formation and re-sensitisation of tumours to PD-L1 in a mouse model of PD-L1 refractory SCCC-N1.

Biopsies taken from patients tumours after treatment with TILT-123 shows localisation of virus E1a with induction of tertiary lymphoid structures.

2 TILT-123 induces immunogenic cell death in LUAD

Analysis of TILT-123 induced cell death pathways using single cell RNA-Seq and western blot

WT scRNA-Seq of TILT-123 infected LUAD cell line in vitro reveals distinct clusters

TILT-123 induces distinct cell death profiles

PARP cleavage induced by TILT-123 derived TNFα (sensitization)

TILT-123 derived IL-2 inhibits caspase 8 cleavage induced by TNFα

3 Effective elimination of metastatic lesions as monotherapy

TILT-T115 (TUMNO; NCT04985327) is an open label phase I clinical trial using a standard 3+3 dose- escalation scheme; Treatment is given to patients, who have advanced solid refractory to available therapies; TILT-123 was administered through intravenous and intratumoral routes, throughout the trial; TILT T115 is currently enrolling at 2 sites in Helsinki, Finland: Docrates Cancer Center and Helsinki University Hospital.

Anaplastic Thyroid Cancer

4 Complete response in combination with TILs in melanoma

TILT-T215 (TUNIT; NCT04217473) is an open label phase I clinical trial using TILT-123 in Melanoma patients receiving adoptive cell therapy with tumour infiltrating lymphocytes; Treatment is given to patients, who have advanced solid refractory to available therapies; TILT-123 was administered through intravenous and intratumoral routes, throughout the trial. TILT-T115 is currently enrolling at 2 sites in France and Herlev, Denmark.

Anaplastic Thyroid Cancer

Pathological complete response

Non injected nose lesion was later operated on and no cancer cells were found.

TILT-123 induces distinct cell death profiles

Neonptosis, Pymptosis, Apoptosis, Autophagy, Ferroptosis

Percent Expressed

Average Expression

Features

TILT-123 derived IL-2 inhibits caspase 8 cleavage induced by TNFα

Caspase 8

Bax

95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

Mucosal melanoma

Pre-treatment
d15
d30
TILT-123 treatment
d15
TILT-123 treatment
d30

2 Target lesions:

Nose Cavity
Neck Lymph node

PARTIAL RESPONSE

1 Target lesion:

Lower abdomen

4 Non-target lesions:

Bone lysis sternum
Mesenteric LN Solitary lung lower lobe
Bone lysis lumber

70 % reduction in injected target lesion as measured by CT value 166 days after first treatment.

100% reduction of non injected metastatic lesions as measured by CT value 166 days after first treatment.

Compassionate therapy program in Finland showcases potential of oncolytic adenosarvirus and reveals insights of guide preclinical development of TILT-123.

Preclinical development, beginning with a recombinant cytokine screen of FDA approved cytokines reveals IL-2 and TNFα as superior for enhancing adoptive cell therapy. These cytokines were later loaded into the Ad5/3-E2F-ds4-E2F backbone and TILT-123 was born. Preclinical studies later reveal complete responses in multiple tumor models.

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Immune cell profiling of advanced-stage solid tumors treated with an oncolytic adenovirus encoding for TNF-α and IL-2 (TILT-123)

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• Stimulating efficient anti-tumor response in poorly immune-infiltrated tumors is yet a challenge for currently approved immunotherapeutic drugs.
• Emerging immunotherapies, such as oncolytic viruses that have the potential to overcome tumor immunosuppression and stimulate immune cells’ response;
• TILT-123, a genetically modified oncolytic adenovirus expressing TNFa and IL-2 (AdS3-E2F-D24- hTNFa-IRES-hIL2), has shown potent efficacy in a series of pre-clinical studies as a monotherapy and as an enabler of clinically used immunotherapies such as checkpoint inhibitors and cell therapies.
• In the present work, TILT-123 is being tested in a phase I clinical trial as a monotherapy for the treatment of advanced-stage human solid tumors.

Treatment with TILT-123 oncolytic adenovirus changes the profile of immune cells circulating systemically and locally infiltrating injected and non-injected tumor sites. For an overview of TILT-123 virus development and trial safety profile and patient response, please check posters 711, 739, 749, and 1518.