#1032TiP

A phase I, first-in-human, study of TILT-123, a tumor-selective oncolytic adenovirus encoding TNFa and IL-2, in participants with advanced melanoma receiving adoptive T-cell therapy with tumor-infiltrating lymphocytes

I. M. Svane[1], J.M. Santos[2], V. Cervera-Carrascon[2], R. Havunen[2], S. Sorsa[2], E. Ellebaek[1], T. Monberg[1], M. Donia[1], A. Khammari, B[3]. Dréno[3], A. Hemminki[2]

(1) Department of Oncology, National Center for Cancer Immune Therapy (CCIT-DK), Copenhagen University Hospital, Herlev, Denmark,
(2) TILT Biotherapeutics Ltd, Helsinki, Finland, (4) Department of Dermatology, CIC, CRCINA Inserm, CHU Nantes, Nantes, France

Background

- Adoptive transfer of Tumor-infiltrating Lymphocytes (TIL) yields effective and long-term responses in melanoma
- Typical lymphodepleting and IL-2 postconditioning regimens used during therapy induce high toxicities. TILT-123 could be a safer alternative to conditioning.
- TILT-123, a novel oncolytic adenovirus designed to stimulate T-cells, is currently being tested in phase I clinical trials

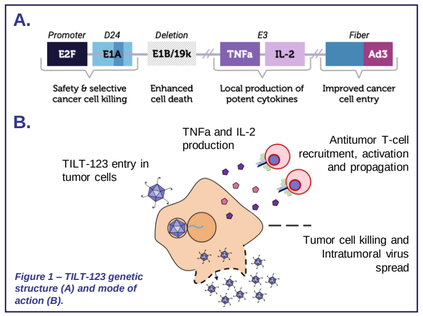
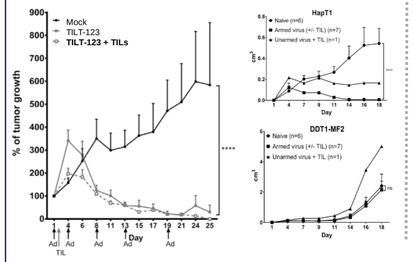


Figure 1 – TILT-123 genetic structure (A) and mode of action (B).

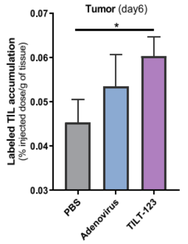
TILT-123 and TILs: Road towards bedside

A. TILT-123 enables 100% tumor regression in animals receiving TIL therapy and no conditioning regimens[1]



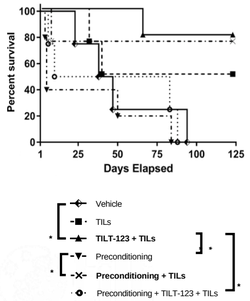
After cured animals were rechallenged with pancreatic HapT1 or leiomyosarcoma DDT1-MF2 cell lines

B. TIL trafficking increases in TILT-123-treated tumors[2]



TILs were radiolabeled with ^{111}In before infusion

C. Combination of TILs and TILT-123 enables long-term survival without lymphodepletion[3]



D. Adenovirus-delivered IL-2 induces the best TIL efficacy without IL-2 postconditioning[4]

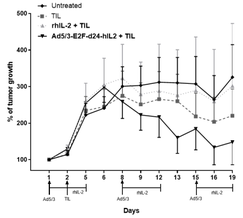


Figure 2. Summary of preclinical data (A-D). Animal Model: Syrian Hamster bearing HapT1 pancreatic tumors Virus Treatments: Intratumoral injections of Ad5/3-D24-E2F (B) or TIL-123 (A,B,C). TIL treatments: intratumoral (A,D) and intraperitoneal (B,C) injection of TILs. Pre- and postconditioning: Cy/Flu and recombinant human IL-2, respectively.

TILT-T215 Trial Design

- Phase I dose-escalation clinical trial with a classic 3+3 design;
- **Participants with refractory or recurrent stage III/IV melanoma,** that cannot be treated with curative intent;
- 1 TIL infusion at Herlev Hospital, Denmark or 2 TIL infusions at CHU Nantes, France hospital **without lymphodepletion or IL-2 postconditioning;**
- Patients will receive TILT-123 through intravenous and intratumoral administration routes;
- TILT-T215 is currently open for enrollment at Herlev Hospital, Denmark and at the CHU Nantes, France.

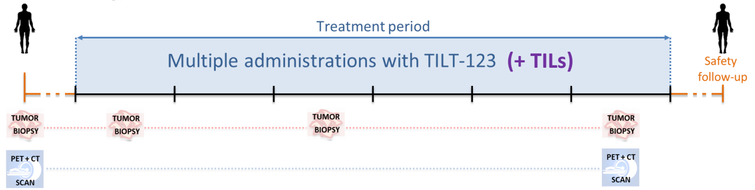


Figure 3 – TILT-T215 Clinical trial design.

Primary endpoint

- TILT-123 safety by day 36

Secondary endpoints

- TILs + TILT-123 safety by day 78
- Efficacy [CT/PET imaging (RECIST 1.1, iRECIST); PFS, OS)
- Mode of Action (immune response to TILT-123)
- Maximum Tolerated Dose
- Pharmacokinetics/Biosafety

Exploratory Endpoints

- Biological effects in injected and non-injected tumors

Results

1 Progress, Demographics and Safety

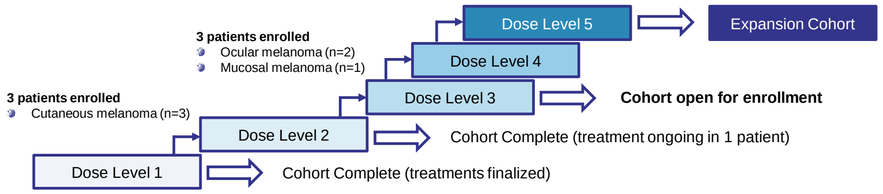


Figure 4 – Dose-escalation scheme and current progress of TILT-123. As of 20th of August of 2021.

Table 1 – Patient details

Dose Level 1		Dose Level 2	
Patient Code	Tumor histology	Patient Code	Tumor histology
10102	Cutaneous melanoma*	10105	Ocular melanoma*
10103	Cutaneous melanoma*	10106	Ocular melanoma*
10104	Cutaneous melanoma*	10201	Mucosal melanoma*

- All participants had progressive disease at the time of enrollment;

Table 2 – Demographics of Enrolled Patients. Data cut-off 20th of August 2021

Parameter	Total (n=6)
Sex	
Male	5
Female	1
Age at enrollment (years)	
Median	43.5 (33 - 68)
Prior Cancer Therapies	
Median	2.5 (2 - 4)
Immunotherapies	13*
Chemotherapy	3
Radiation	2
Surgery	9*

**Some patients underwent several surgical proceedures before enrolling in the trial. Patients underwent several several immunotherapies before enrollment in the trial.*

- Treatment-related AEs are in line with immunotherapies;
- Dose level 1 showed grade 1-2 AEs while dose level 2 showed grade 2-3 AEs;
- **No treatment-related AEs were classified as serious;**
- No grade 4-5 events were observed.

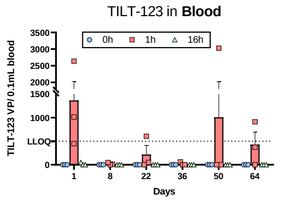
Table 3 – Treatment-related adverse events as judged by the investigators. Data cut-off 20th of August 2021

Preferred Term	Grade 1*	Grade 2*	Grade 3*
Anorexia		1	
Arthralgia	2		
Chills	1		
Dizziness	1		
Fatigue	1		
Fever	2	2	2
Flushing	2		
Headache	1		
Myalgia	2		
Nausea	1	2	
Pain	1		
Pain in liver from injection			1
Pain from injection	2		
Pain, left knee	1		
Vomiting	1		
Worsening of Headache		3	
Total	**18**	**8**	**3**

**Adverse events graded based on the Common Terminology Criteria for Adverse Events (CTCAE).*

2 TILT-123 Shedding and Biodistribution

A.



B.

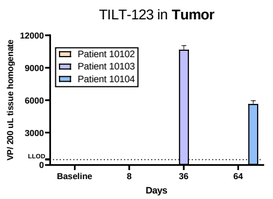


Figure 5 – Distribution of TILT-123 in blood (A) and in Injected tumors (B). Data from 3 patients in dose level 1 (each data point represents a patient).Data cut-off 20th of August 2021.

- TILT-123 was found in blood, 1 hour after injection at different treatment days;
- Virus was also found in one patient at 16h, however it was below the lower limit of quantitation;
- **No virus detected in saliva;**
- Virus was detected at 16h after virus injection in only one urine sample from the first visit in only one patient (below the lower limit of quantitation);
- TILT-123 was found from biopsies in **injected tumors** at day 36 (before TILT-123 injection on that day and before the TIL treatment) and day 64 (before TILT-123 injection on that day and after the TIL treatment).

Conclusions

- TILT-123 is considered safe at dose levels 1 and 2;
- Combination of TILT-123 and TILs is also deemed safe with the lowest doses of TILT-123;
- The virus appears to be highly immungenic prompting rapid clearance from the patient's body fluids at the lowest dose level;
- TILT-123 appears to be replicating in tumors from patients even at the lowest dose
- Further analyses will continue as the trial progresses

For more information contact:
Inge Marie Svane
Principal investigator on TILT-T215
Email: inge.marie.svane@regionh.dk

João Manuel Santos
Head of Cell Therapy at TILT Biotherapeutics
Email: joao.santos@tiltbio.com

We thank the patients and staff at:
Herlev Hospital
CHU de Nantes

Study sponsored by:
https://tiltbio.com/

References:

1. Havunen, R., et al., Mol Ther Oncolytics 2017, 4:77-86
2. Cervera-Carrascon, V., et al., Mol Ther Oncolytics., 2020. 17: p. 47-60.
3. Santos, J.M., et al., Mol ther 2018, 26:2243-2254.
4. Santos, J.M., et al., Int J Cancer 2017, 141:1458-1468.

Inge Marie Svane has the following declaration of interest: Financial interests: BMS, Invited Speaker, Personal; BMS, Advisory Board, Personal; MSD, Invited Speaker, Personal; MSD, Writing Engagement, Personal; Novartis, Advisory Board, Personal; Novartis, Invited Speaker, Personal; Pierre Fabre, Advisory Board, Personal; Pierre Fabre, Invited Speaker, Personal; Roche, Invited Speaker, Personal; IO Biotech, Stocks/Shares; Personal, Cofounder and Founder warrents; Adaptimmune, Research Grant, Institutional, No financial interest; Enara Bio, Research Grant, Institutional, No financial interest; Evaxion, Funding, Institutional, No financial interest; Lytix Biopharma, Research Grant, Institutional, No financial interest; TILT Biotherapeutics, Research Grant, Institutional, No financial interest; **Non-Financial Interests:** BMS, Principal Investigator; Lytix Biopharma, Principal Investigator; Novartis, Principal Investigator; Roche, Principal Investigator; TILT Biotherapeutics, Principal Investigator.