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Fully intravenous split-dose administration of oncolytic adenovirus TILT-123 in advanced solid tumors

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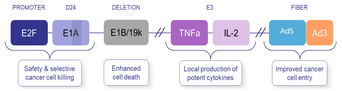
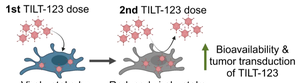
INTRODUCTION

- Oncolytic adenovirus TILT-123 (igrelimogene litadenorepvec), is armed immunostimulatory transgenes TNF and IL-2.
- Dual selectivity devices restricts viral replication to cancer cells and capsid chimerism optimizes intravenous (i.v.) delivery.

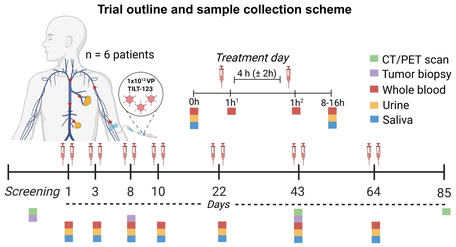


- Intratumoral (i.t.) delivery remains the most common administration method for oncolytic viruses, but limits clinical applicability.
- Patients were treated with two daily doses (split-dose) of i.v. TILT-123 to overcome Kupffer cell mediated clearance of virus in an extension cohort of TUNIMO (NCT04695327).



METHODS

Trial outline and sample collection scheme



1x10^{12} VP of TILT-123 were administered twice per treatment day (total 2x10^{12} VP).

Tumor Biopsy Analyses

- Immunohistochemistry for viral protein detection
- Multiplex immunofluorescence for immune cell analysis
- Quantitative PCR for detection of viral DNA
- Transcriptomic & proteomic analysis

Blood Analyses

- **Serum** - Proteomic analysis
- **Serum** - Neutralizing antibody analysis
- **Whole blood** - Quantitative PCR for detection of viral DNA

Table 1. Patient demographics and clinical characteristics

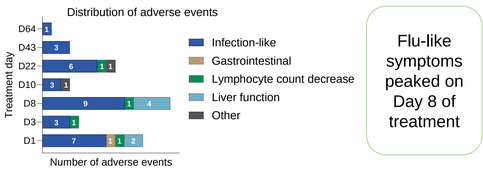
Patient ID	Age	Sex	ECOG status	Cancer type	Stage	No. of targeted lesions	No. of previous systemic treatments
20114	62	F	1	Liposarcoma	IV	5	2
20115	49	F	0	Gastric adenocarcinoma	IV	3	3
20116	59	M	1	Pancreatic ductal adenocarcinoma	IV	3	4
20220	66	M	1	Rectal carcinoma	IV	5	4
20221	63	M	0	Rectal carcinoma	IV	3	6
20222	71	M	1	Rectal carcinoma	IV	2	6

Six patients presenting with stage IV disease and having received median 4 lines of systemic therapy were treated.

RESULTS

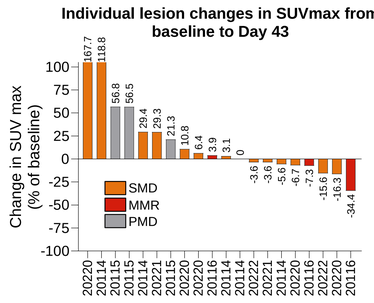
1. Fully i.v. TILT-123 is safe

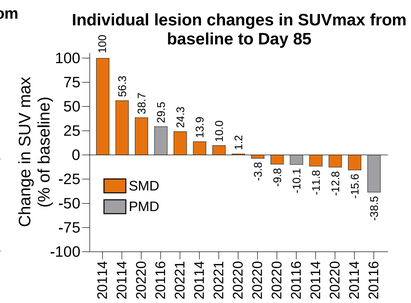
Summary of most frequently occuring adverse events (total)		
TILT-123 related adverse events, n (%)	**Any grade**	**Grade ≥ 3**
Chills	14 (32.6%)	
Fever	9 (20.9%)	1 (2.3%)
Fatigue	4 (9.3%)	
Lymphocyte decrease	4 (9.3%)	2 (4.7%)
Alanine aminotransferase increased	2 (4.7%)	
Aspartate aminotransferase increased	2 (4.7%)	

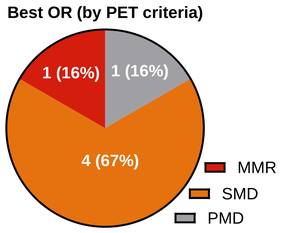


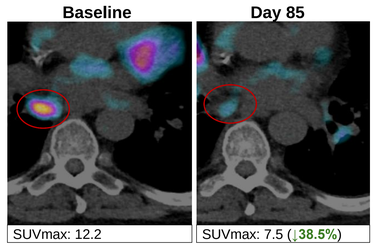
Flu-like symptoms peaked on Day 8 of treatment

2. Target lesion imaging demonstrated evidence of stable disease and a minor metabolic response

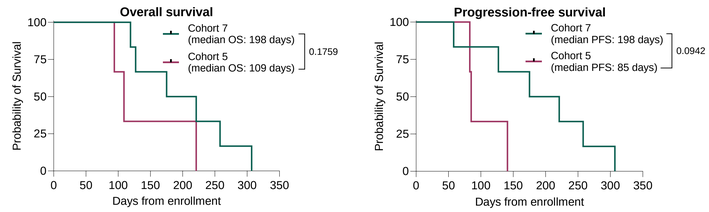




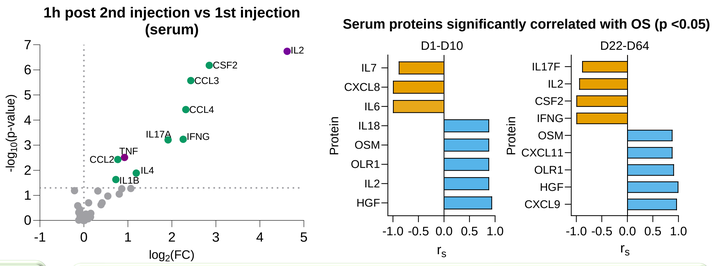




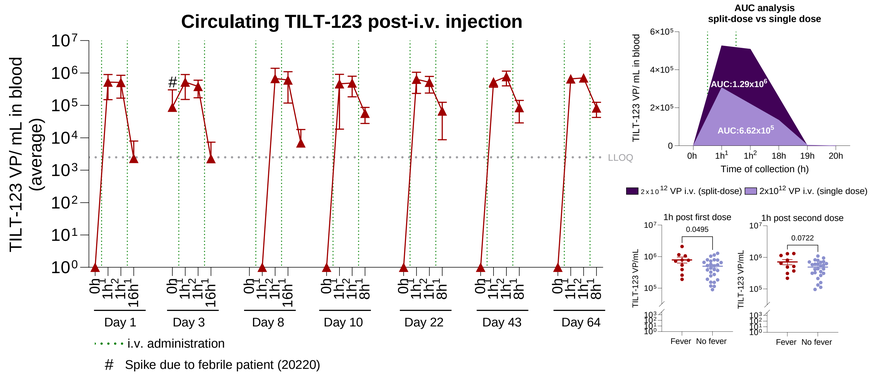
3. Fully i.v. administration delivers comparable OS and PFS as standard (i.v. + i.t.) treatment regimen



4. Repeated TILT-123 injection induces pro-inflammatory response; post-treatment serum proteins correlate with OS

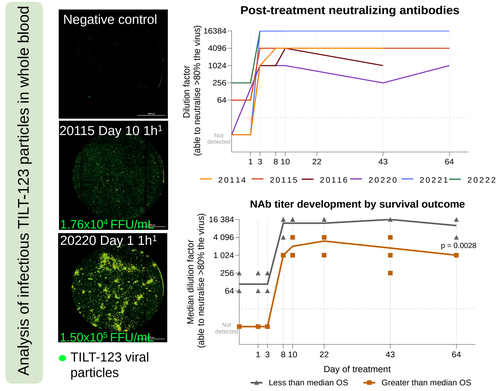


5. Circulating TILT-123 DNA levels are comparable to single-i.v. administration and are associated with fever

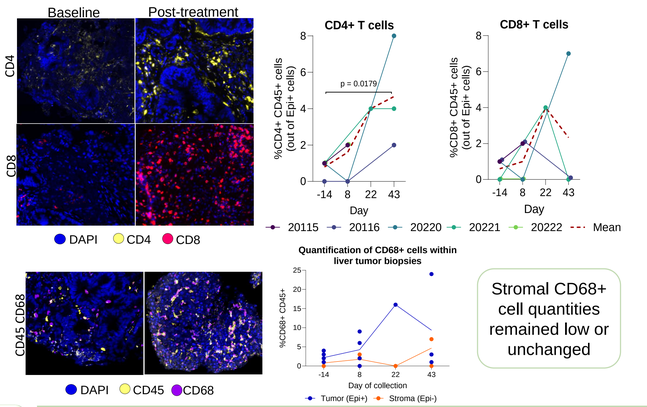


- 2 out of 8 samples were positive for hexon
- 2 out of 8 samples were positive for TILT-123 DNA by qPCR

6. TILT-123 evades immediate neutralization, but neutralizing antibodies might impact long-term benefit

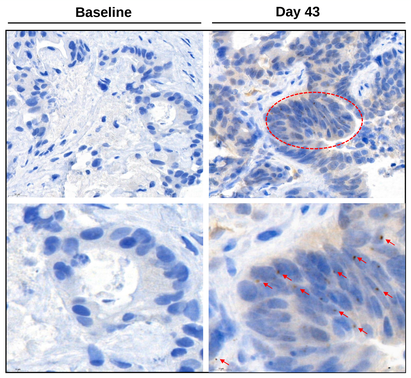


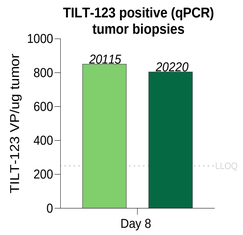
7. Fully i.v. TILT-123 induces immune cell influx within tumors



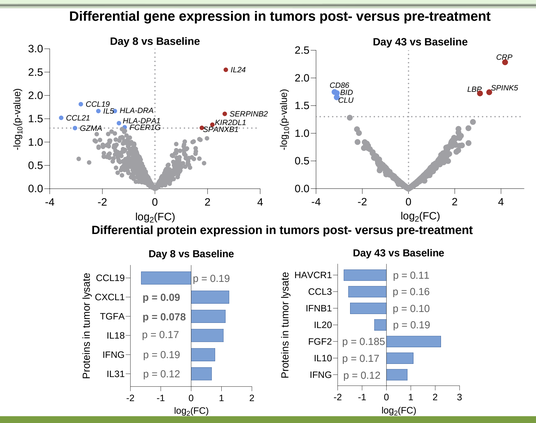
Stromal CD68+ cell quantities remained low or unchanged

8. TILT-123 is able to reach and infect tumors through the i.v. route





9. Transcriptomic & proteomic differences observed in post-treatment tumors



CONCLUSION

- ✓ A fully intravenous TILT-123 treatment regimen is safe and well-tolerated in patients with advanced and difficult to treat solid tumors.
- ✓ The split-dosing treatment regimen induces a pro-inflammatory response.
- ✓ Neutralizing antibodies may hinder virus delivery and reduce therapeutic benefit in the fully i.v. administration schedule.
- ✓ Signs of tumor transduction was noted in patient tumors through increases in intratumoral immune cells, presence of viral protein and DNA, as well as transcriptomic alterations.

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