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Effect of split intravenous dosing of oncolytic adenovirus TILT-123 on normal tissue versus tumor macrophages and virus bioavailability in patients with advanced solid tumors

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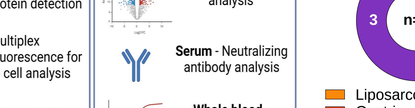
Background

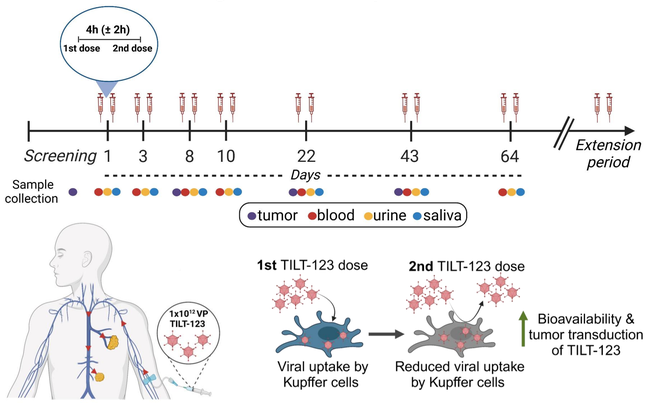
- TILT-123 (Ad5/3-E2F-D24-hTNFα-IRES-hIL2), is an oncolytic adenovirus armed with immunostimulatory cytokines TNFα and IL-2.
- TILT-123 capsid chimerism enables intravenous delivery and dual selectivity devices restrict viral replication to cancer cells**.**
- A split dose regimen was designed to overcome Kupffer cell mediated clearance of intravenous (i.v.) virus
- A fully i.v. treatment schedule of TILT-123 was studied in an extension cohort of TUNIMO (NCT04695327).

TILT-123 Igrelimogene litadenorepvec



Methods

Treatment regimen and sample collection scheme



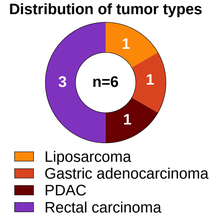
Tumor Biopsy Analyses

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

Blood Analyses

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

Distribution of tumor types



6 patients with advanced solid tumors (**stage IV**) having received 6 median lines of therapy were treated.

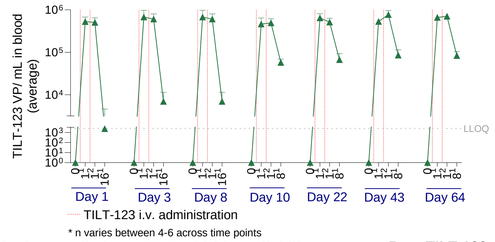
Safety & Bioavailability

Most frequent TILT-123 related adverse events

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%)	

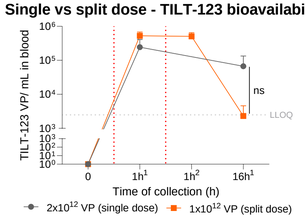
- ✓ Multiple intravenous TILT-123 injections were safe and well-tolerated.
- ✓ Shedding analysis of urine and saliva revealed no detectable viral DNA above quantification limits.

Circulating TILT-123 post i.v. injection

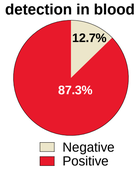


* n varies between 4-6 across time points

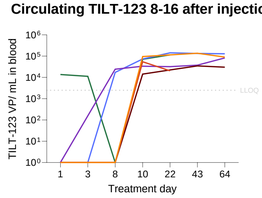
Single vs split dose - TILT-123 bioavailability



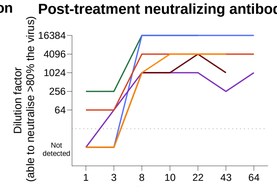
Post-TILT-123 detection in blood



Circulating TILT-123 8-16 after injection



Post-treatment neutralizing antibodies



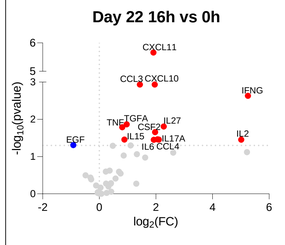
20114 — 20115 — 20116 — 20220 — 20221 — 20222

- ✓ Circulating TILT-123 remains detectable 8-16h post-administration despite presence of neutralizing antibodies.

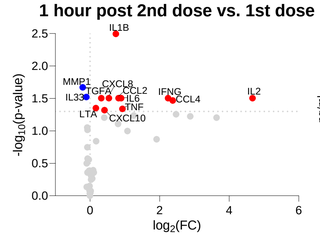
Immunogenicity & Tumor Transduction

Serum cytokine and chemokine changes post-TILT-123

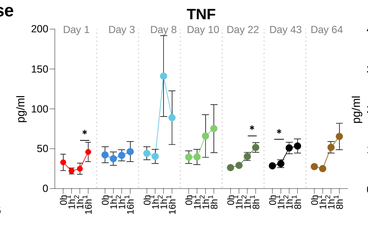
Day 22 16h vs 0h



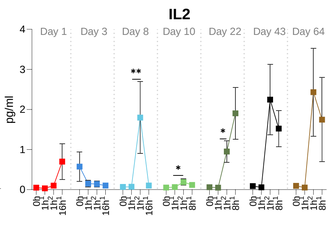
1 hour post 2nd dose vs. 1st dose



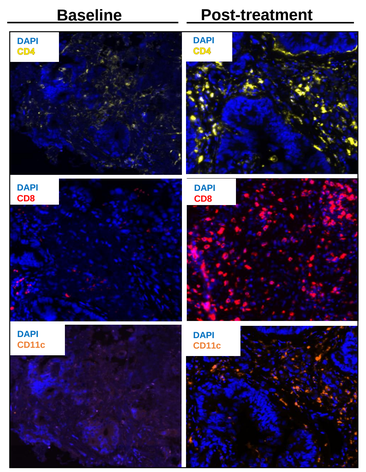
TNF

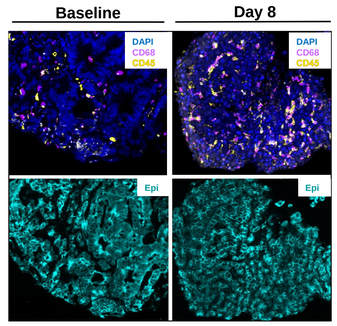


IL2

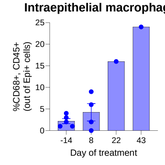


Immune cell infiltration of post-treatment biopsies

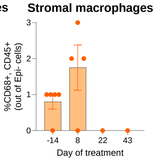




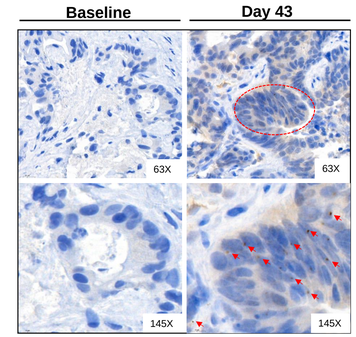
Intraepithelial macrophages



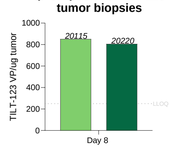
Stromal macrophages



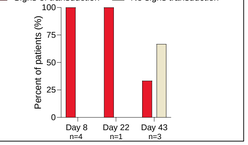
Viral protein and DNA detection in biopsies



qPCR positive TILT-123 tumor biopsies



Signs of tumor transduction



Conclusion

- ✓ A fully intravenous TILT-123 treatment regimen is safe and well-tolerated in patients with advanced and difficult to treat solid tumors.
- ✓ Intravenous TILT-123 injections result in systemic activation and tumor transduction.
- ✓ The split-dose regimen resulted in increased intraepithelial and decreased stromal macrophages, as predicted by pre-clinical work.
- ✓ Tumor transduction was observed in 75% of tumors treated with multiple rounds of i.v. TILT-123.

Acknowledgements & Contact

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The presenting author has no COI to declare.

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