1025P

Fully intravenous delivery regimen of oncolytic adenovirus coding for TNFa and IL-2 (TILT-123) in patients with advanced solid cancers

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Background

- TILT-123 (Ad5/3-E2F-d24-hTNFa-IRES-IL2) is an oncolytic virus (OV) with serotype Ad3 knob facilitating intravenous delivery, and carrying transgenes for TNFa and IL-2.
- TILT-123 was developed to induce strong inflammatory responses in solid tumors.
- Use of OV therapy has been limited due to intratumoral dosing, and due to hepatic uptake of vectors.
- Safety and efficacy of completely intravenous TILT-123 regimen was studied in extension cohort of TUNIMO (NCT04695327).

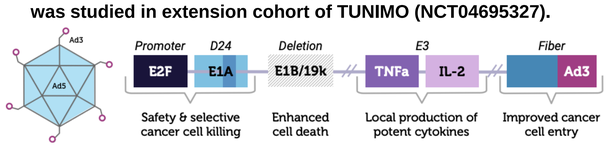


Figure 1. Genetic structure of TILT-123.

Regimen & Demographics

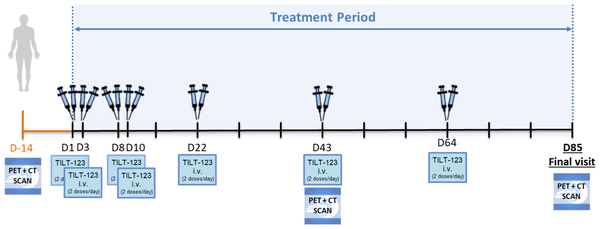


Figure 2. Treatment regimen of completely intravenous TILT-123.

- To facilitate hepatic bypass and tumor transduction, TILT-123 was given as two doses: the first dose is aimed to inhibit hepatic Kupffer cell function for enhanced tumor transduction by the second dose.
- TILT-123 was administered with a double daily dose, 10^{12} viral particles (VP) 3 hours apart.
- The double dose was given on days 1, 3, 8, 10, 22, 43, and 64.
- 6 patients with advanced solid tumors were enrolled, 3 rectal carcinoma, 1 gastric adenocarcinoma, 1 PDAC and 1 liposarcoma.
- Treatment efficacy was assessed with PET + CT scan at baseline, day 43 and day 85.
- Samples for correlative research were collected in the forms of tumor biopsies, serum and PBMC samples.

Patient	Age	ECOG	Tumor type	Mutational status	Stage	Previous systemic treatment lines, n	Previous immunotherapy
20114	63	1	Liposarcoma	-	IV	2	No
20220	66	1	Rectal carcinoma	NRAS/KRAS/ BRAFwt	IV	4	No
20115	49	0	Gastric adenocarcinoma	-	IV	3	No
20221	63	0	Rectal carcinoma	-	IV	6	No
20116	59	1	Pancreatic ductal adenocarcinoma	-	IV	4	No
20222	72	1	Rectal carcinoma	NRAS/KRAS/ BRAFwt	IV	6	No

Table 1. Patient demographics enrolled to the intravenous regimen.

Safety & Efficacy

✓ No grade 4-5 AEs reported

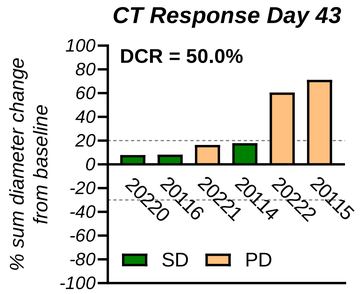
✓ Most common grade 1-3 AEs included flu-like symptoms: chills (100% of patients), fever (67%) and fatigue (50%)

✓ No significant liver enzyme elevation observed after therapy

Adverse Event	Total (% of patients)	Grade 1	Grade 2	Grade 3
Chills	14 (100)	11	3	-
Fever	9 (67)	4	4	1
Fatigue	4 (50)	3	1	
Lymphocyte count decreased	4 (33)	-	2	2
Alanine aminotransferase increased	2 (33)	2	-	-
Aspartate aminotransferase increased	2 (33)	2	-	-
Alkaline phosphatase increased	1 (17)	1	-	-
Blood bilirubin increased	1 (17)	1	-	-
Diarrhea	1 (17)	1	-	-
Flu-like symptoms	1 (17)	1	-	-
Headache	1 (17)	1	-	-
Rhinitis	1 (17)	1	-	-
Subfebrile body temperature	1 (17)	1	-	-
Syncope	1 (17)	-	-	1

Table 2. Adverse events related to TILT-123 as judged by the trial site investigator. Data updated 24th August 2024.

✓ Disease control by RECIST 1.1 in 50.0% of patients



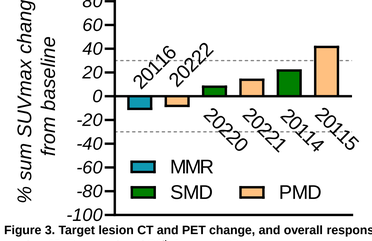
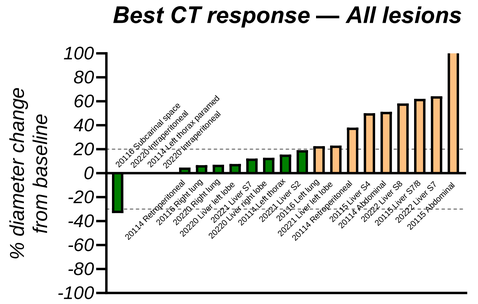


Figure 3. Target lesion CT and PET change, and overall response on day 43. Data updated 24th August 2024.

✓ Lesion control observed in 78,9% lesions with PET and 57,1% lesions with CT.

✓ Comparable to previously reported i.v. + i.t. regimen: PET 71,0% and CT 56,3% (S.A. Pakola CCR 2024)



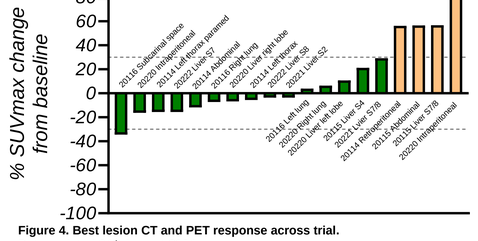


Figure 4. Best lesion CT and PET response across trial. Data updated 24th August 2024.

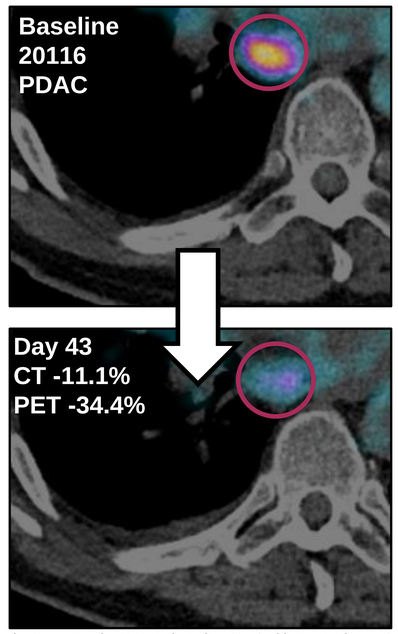


Figure 5. Example response in patient 20116 with metastatic PDAC.

Correlative Research

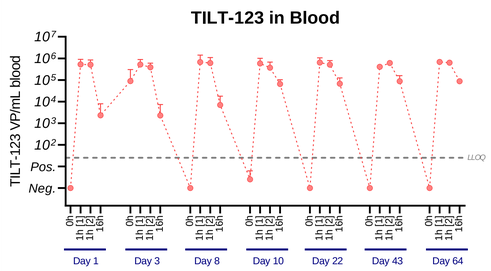


Figure 6. TILT-123 in blood by qPCR. Mean of all patients +/- SD.

✓ Blood qPCR positivity 16h post-treatment seen in 87.5% of samples

✓ Tumor transduction seen with viral hexon IHC

✓ Increases in intratumoral activated CD8+ T cells and NK cells observed

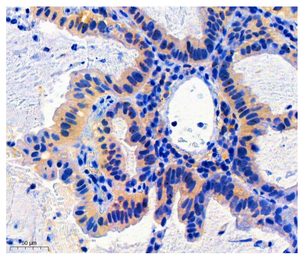


Figure 7. Intratumoral virus hexon IHC showing successful i.v. delivery in patient 20116

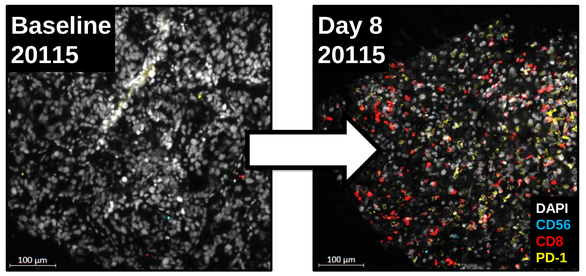


Figure 8. Multiplex IF of patient 20115 showing marked immune infiltrate post TILT-123.

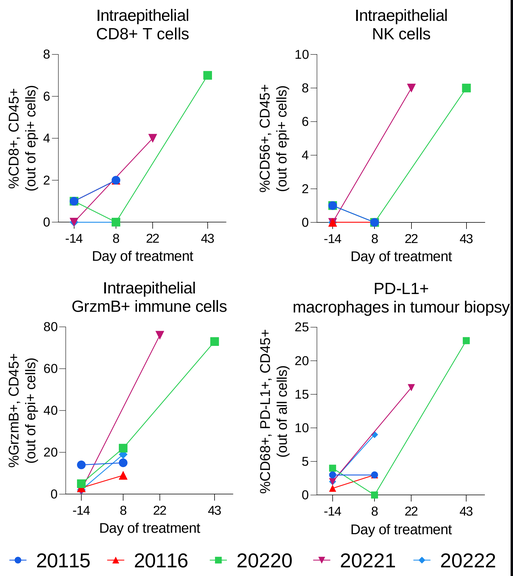


Figure 9. Quantified mIF of tumor biopsies.

Conclusions

✓ Completely intravenous delivery regimen of TILT-123 is safe

✓ DCR of 50.0% with RECIST 1.1 and PET criteria on day 43

✓ Tumor transduction with congruent increases in immune cell infiltrates seen

➢ Future studies of TILT-123 intravenous regimen with combinatory therapies are planned

The presenting author has no COI declare.

We thank the patients and staff at HUS & Docrates Cancer Centers.

Interested in collaborating?

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