Oncolytic virus TG6002 safety and activity after intrahepatic artery administration in patients with liver-dominant metastatic colorectal cancer

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BACKGROUND

TG6002 is an engineered Copenhagen strain oncolytic vaccinia virus, deleted of thymidine kinase and ribonucleotide reductase to enhance tumor selective viral replication and expressing FCU1, an enzyme converting the non-cytotoxic prodrug 5-fluorocytosine (5-FC) into the chemotherapeutic compound 5-fluorouracil (5-FU).

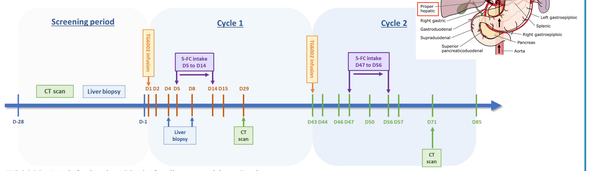
METHODS

A total of 15 patients received a TG6002 intrahepatic artery infusion (IHA) on Day 1 at the dose of $1{\cdot}10^6$ pfu (n=3), $1{\cdot}10^7$ pfu (n=3), $1{\cdot}10^8$ pfu (n=3) or $1{\cdot}10^9$ pfu (n=6), combined with oral 5-FC on Days 5-14. A second cycle of TG6002/5-FC treatment was to be administered in patients without progressive disease on day 43. Blood was sampled prior to, 30 min, 3h and 24h after each TG6002 infusion for TG6002 pharmacokinetics, on Day 8 (1h post 5-FC intake) for 5-FC and 5-FU measurements, and at various times up to day 43 for anti-vaccinia virus antibody and translational assays. A tumor biopsy was performed at screening and on Day 4 or 8 along with concomitant blood sampling for virus detection by qPCR and plaque assay, 5-FC and 5-FU quantification and translational assays.

KEY INCLUSION CRITERIA

- Unresectable liver-dominant metastatic colorectal cancer
- At least one liver metastasis amenable to biopsy
- Previous exposure to fluoropyrimidine
- Having failed oxaliplatin-, and irinotecan-based chemotherapy ± anti-VEGF and/or anti-EGFR monoclonal antibody and/or BRAF inhibitors and/or immunotherapy
- ECOG performance 0-1

TRIAL SCHEDULE



TG6002: IHA infusion in 100ml of saline over 30 ± 5 min
5-FC: 50 mg/kg QDS orally

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Among the 15 patients, 11 were male and 4 were female:

- Median age was 61 years, range 37 - 78
- ECOG PS was 0 (n=9) and 1 (n=6)
- Median weight was 81 kg, range 52 – 127.6
- Primary tumor location was colon (n=11) and rectum (n=4)
- Median time from diagnosis to Day 1 was 30 months, range 8.1 - 89.8
- Median number of prior lines of anticancer therapy (including adjuvant) was 4, range 1 - 5

SAFETY DATA

- A total of 34 TG6002-related adverse events were reported, of which 32 were grade 1-2 and 2 were grade 3.
- The maximum tolerated dose was not reached.
- A single dose-limiting toxicity was observed consisting of a myocardial infarction in a context of recent Covid-19 infection in one patient.

ACKNOWLEDGEMENTS

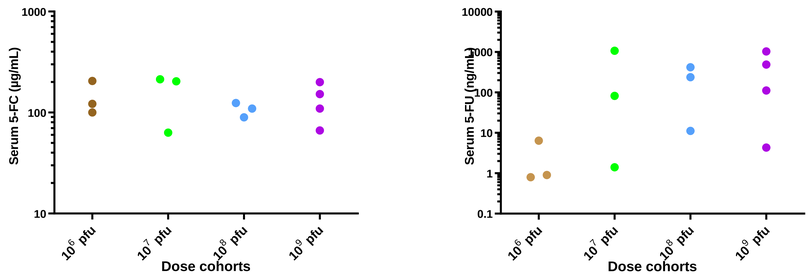
The authors wish to thank all patients, families, caregivers and all technical staff involved in the project.

REFERENCES

1. Tickotsky *et al.* (2017). McPAS-TCR: A manually-created catalogue of pathology-associated T cell receptor sequences. *Bioinformatics* **33**:2924-2929.

PHARMACOKINETICS/PHARMACODYNAMICS

At Day 8 after administration of TG6002, 5-FC and its active metabolite 5-FU were titrated in serum in patients from the four dose levels.

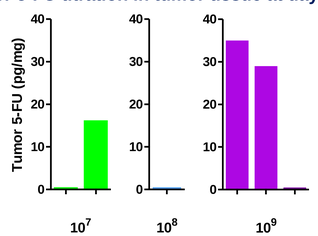


At Day 4 or Day 8 after TG6002 administration, tumor biopsies were taken and analyzed to obtain evidence of viral persistence in tumor tissue using one of the following methods: qPCR, RT-PCR against viral transcript, plaque titration or IHC staining. Patients were considered positive if one method returned positive evidence of viral presence.

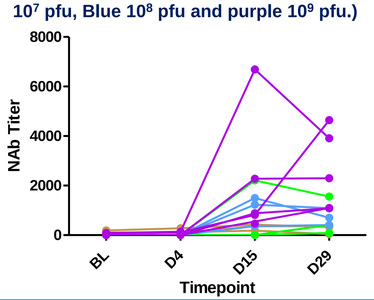
Dose group	Positive patients	Evaluable patients
10^6 pfu	2	3
10^7 pfu	1	3
10^8 pfu	3	3
10^9 pfu	2	4

5-FC to 5-FU conversion was detected in samples from all patients across the 4 dose cohorts. Serum 5-FU levels were significantly higher in patients receiving 10^7 pfu or more than in patients in the 10^6 pfu dose group. Overall 60% of patients included had evidence of viral presence in tumor on day 4 and 3 out of 6 evaluable patients had significant levels of 5-FU in their tumor tissue at day 8. TG6002 treatment was associated with onset of neutralizing antibodies from D15.

Tumor 5-FU titration in tumor tissue at day 4 or 8



Longitudinal titration of neutralizing antibodies in individual patients. (Brown 10^6 pfu, Green 10^7 pfu, Blue 10^8 pfu and purple 10^9 pfu.)



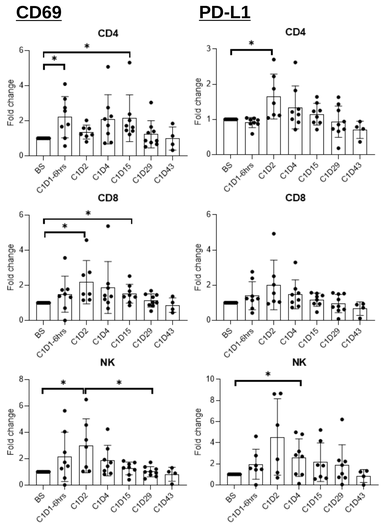
KEY FINDINGS

- IHA administration was feasible, well tolerated and resulted in tumor localization of TG6002.
- TG6002 administration led to the expression of a functional enzyme allowing 5-FC to 5-FU metabolization in the tumor.
- Detection of TG6002 in plasma and in tumor biopsies indicates viral replication in tumor.
- Translational analysis of blood samples shows evidence of T cell activation and immune checkpoint receptor expression and priming of an adaptive response against tumor-associated antigens.

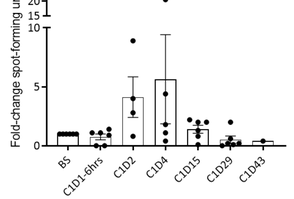
TRANSLATIONAL ANALYSES

Peripheral blood mononuclear cells (PBMCs) and plasma from patients in cohorts 1-3 (10^6, 10^7 & 10^8 pfu, where available) were analyzed for immune cell responses to TG6002 IHA infusion.

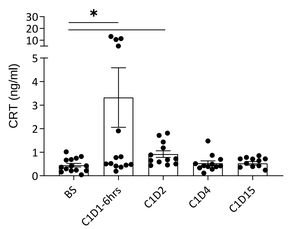
Immunophenotyping of PBMCs revealed changes in the expression of immune activation receptors and checkpoint molecules on immune cell subsets.



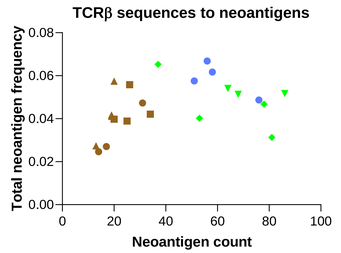
ELISpot detected functional T cell activation to carcinoembryonic antigen (CEA) peptides.



Release of calreticulin into plasma following TG6002 IHA infusion indicated immunogenic cell death.



TCRβ sequences to neoantigens



T cell receptor (TCR)β sequencing of patient PBMCs revealed an expansion in the number of TCRs specific for neoantigens in patients receiving higher titres of TG6002 (Brown 10^6 pfu, Green 10^7 pfu, Blue 10^8 pfu; each symbol represents samples from one patient). TCRs specific for human neoantigen sequences were identified using the McPAS-TCR database[1].