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Abstract LB179

Oncolytic virus TG6002 locates to tumors after intravenous infusion and induces tumor-specific expression of a functional pro-drug activating enzyme in patients with advanced gastrointestinal carcinomas

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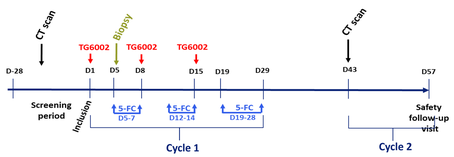
BACKGROUND

Oncolytic viruses (OV) are a promising immunotherapeutic modality in number of cancers. OV administration leads to profound changes in tumor immune contexture by inducing a shift towards a pro-immune tumor microenvironment and to immunogenic cancer cell death resulting in the onset of an adaptive anti tumor T-cell response. Effective use of OV in clinical setting is limited by the requirement of intra-tumoral administration. Hence, there is a great need to develop OV able to localize to tumor tissue following intravenous delivery. TG6002 is a vaccinia virus deleted for Thymidine Kinase/Ribonucleotide Reductase and encoding the FCU1 enzyme that converts the pro-drug 5-Fluorocytosine (5-FC) to its active metabolite 5-Fluorouracil (5-FU). Herein, we report preliminary results from a dose-escalation phase I study combining intravenous TG6002 and oral 5-FC in patients with advanced gastrointestinal (GI) carcinomas. Exploratory analyses were performed to document TG6002 pharmacokinetic (PK), biodistribution, and conversion of 5-FC to 5-FU.

METHODS

A total of 15 patients received TG6002 infusions on days 1, 8 and 15 at the dose of $3{\cdot}10^8$ pfu (n=3), $1{\cdot}10^9$ pfu (n=10) or $3{\cdot}10^9$ pfu (n=2) combined with 5-FC (4 times 50 mg/kg/day) from days 5 to 7, 12 to 14, and 19 to 28. Blood was sampled 30 min, 3h and 24h after TG6002 infusion on day 1 and 15 for plasma TG6002 PK and one hour after intake of 5-FC at screening (single dose of 50 mg/kg) and on days 5, 7, 14 and 28 for serum 5-FC and 5-FU measurements. A 28G metastasis biopsy was performed on day 5 along with synchronous blood sampling. Virus presence was assessed by qPCR and plaque assay, and 5-FC, 5-FU and F-BAL quantified using HPLC-MS. Urine, saliva and feces samples were collected on day 2 and 7 for viral shedding assessment. Neutralizing antibodies (NAb) titers were assessed using a plaque inhibition assay at baseline, days 28 and 43.

STUDY SCHEDULE



KEY INCLUSION CRITERIA

- Advanced GI carcinomas having failed and/or intolerant to standard therapeutic options
- At least one metastatic lesion amenable to biopsy
- Age ≥18 years
- ECOG performans status 0 or 1

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Among the 15 patients, 11 were male and 4 were female.
Median age was 62 years, range 46 - 70 years
Median weight was 73.0 kg, range 55.3 - 106.0 kg
Primary tumors were colorectal (n=9), pancreatic (n=2), oesophagus (n=1), gastric (n=1), ampulla of Vater (n=1), and cholangio (n=1) carcinomas.
All patients except one received at least 3 prior lines of anticancer therapy

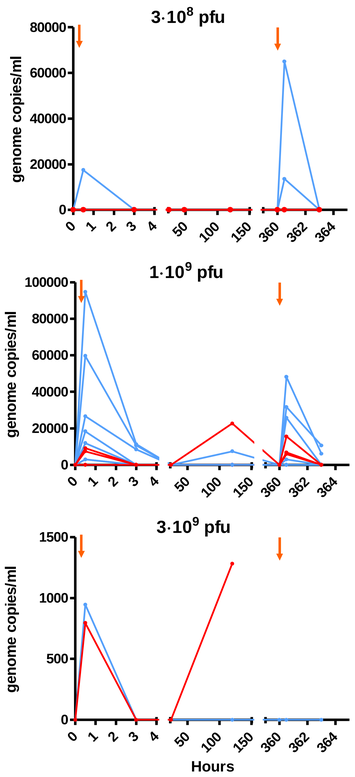
SAMPLES AND DATA POINT AVAILABILITY

X: Available data ; n/a: missing sample

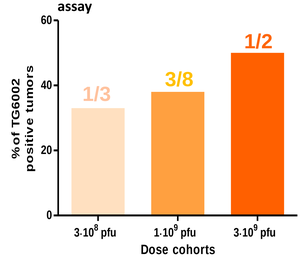
Patient #	Dose Level	PERIPHERAL BLOOD								D5 TUMOR ANALYSES	
		Virus detection				FCU1 activity					
		D1	D2	D5	D15	D5	D7	D14	D28	Virus detection	FCU1 activity
Patient 1	$3{\cdot}10^8$	x	x	x	x	x	x	x	x	x	x
Patient 2	$3{\cdot}10^8$	x	x	x	x	x	x	x	x	x	x
Patient 3	$3{\cdot}10^8$	x	x	x	x	x	x	x	x	x	x
Patient 4	$1{\cdot}10^9$	x	x	x	x	x	x	x	x	x	x
Patient 5	$1{\cdot}10^9$	x	x	x	x	x	x	x	x	x	x
Patient 6	$1{\cdot}10^9$	x	x	x	x	x	x	x	n/a	x	x
Patient 7	$1{\cdot}10^9$	x	x	x	x	n/a	x	x	n/a	x	n/a
Patient 8	$1{\cdot}10^9$	x	x	x	x	x	x	x	n/a	n/a	n/a
Patient 9	$1{\cdot}10^9$	x	x	x	n/a	x	x	n/a	n/a	n/a	n/a
Patient 10	$1{\cdot}10^9$	x	x	x	x	x	x	x	x	x	x
Patient 11	$1{\cdot}10^9$	x	x	x	x	x	n/a	x	n/a	x	x
Patient 12	$1{\cdot}10^9$	x	x	x	x	x	x	x	x	x	x
Patient 13	$1{\cdot}10^9$	x	x	x	x	x	x	x	n/a	x	x
Patient 14	$3{\cdot}10^9$	x	x	x	x	n/a	x	x	x	x	n/a
Patient 15	$3{\cdot}10^9$	x	x	x	n/a	x	n/a	n/a	n/a	x	x

DISTRIBUTION AND TUMOR LOCALIZATION OF TG6002

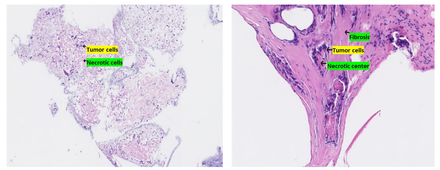
A. Plasma TG6002 copy number over time in the three dose cohorts. ➔ are time of TG6002 infusion. —●—patients for whom direct evidence of TG6002 was shown in tumor biopsy on day 5.



B. Fraction of tumor tissue positive for TG6002 by qPCR or plaque assay



C. Representative image of H&E staining on tumor biopsy used for qPCR and Plaque assay showing low abundance of viable tumor cells in this patient population



TG6002 was transiently detected in the plasma following administration and was not found in urine, saliva or feces, suggesting that plasma clearance was essentially driven by the entry of virus in cells.
In 3 patients we observed a rebound on day 5, in line with preclinical experience with TG6002 (Fig A).

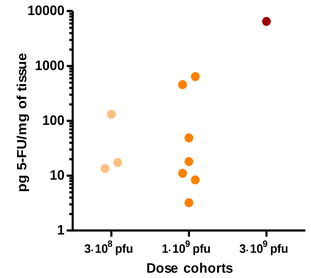
Depending on the dose-level cohort, 30% to 50% of patients showed direct evidence of the virus in the tumor by qPCR or plaque assay (Fig. B). Sensitivity of these analyses was limited by the scarcity and heterogeneity of tissue as demonstrated by histologic examination (Fig. C).

We detected 5-FU in tumor tissue in most of the evaluable patients across the 3 dose-level cohorts (Fig D) as well as 5-FU at peripheral levels (Fig. E).

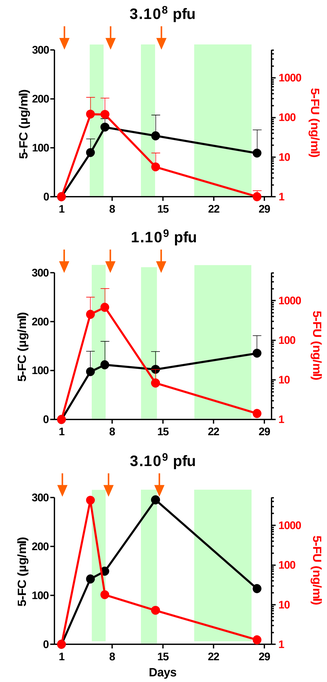
Plasma and tumor levels of 5-FU were correlated on day 5. Interestingly, patients with the highest levels of 5-FU in blood and tumor were patients for which there was direct evidence of TG6002 in the tumor (Fig F).

Neutralizing antibodies were detected in all patients 28 days and 43 days after administration of TG6002. None of the patients had detectable levels at baseline (Fig. G).

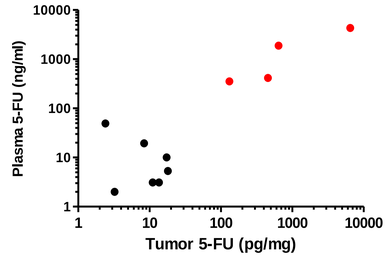
D. 5-FU quantification by HPLC-MS in lesion biopsy on day 5



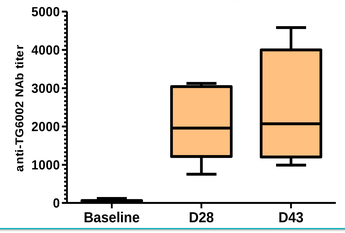
E. 5-FU ● and 5-FC ● quantification by HPLC-MS in longitudinal plasma samples in the $3{\cdot}10^8$,$1{\cdot}10^9$ and $3{\cdot}10^9$ pfu dose cohorts.
➔ times of infusion of TG6002
▮ times of 5-FC administration.



F. Correlation between plasma and tumor 5-FU on day 5.
● Patients with direct evidence of TG6002 in tumor



G. Titration of TG6002 neutralizing antibodies



CONCLUSIONS

- Our data demonstrate that TG6002 localizes to the tumor after IV administration, replicates in tumor cells and is able to express a functional payload
- Absence of widespread virus body distribution and association of FCU1 activity with high virus concentration in tumor tissue suggest a specificity of replication of TG6002 in tumor cells. Furthermore, none of the patient experienced sign of vaccinia induced disease.

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