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Updated data of biodistribution and activity of oncolytic virus TG6002 after intravenous administration in patients with advanced gastrointestinal carcinomas

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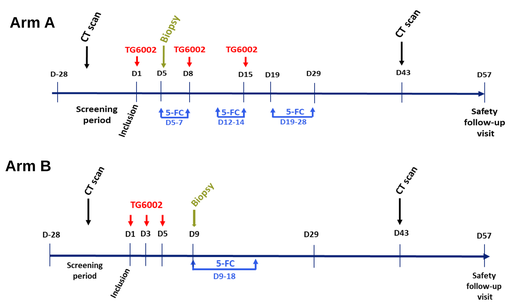
BACKGROUND

In a report on 15 patients included in TG6002.02 dose-escalation trial (ESMO 2021, Abstract #3550, Poster 486P), we showed that TG6002, an oncolytic vaccinia virus deleted in 2 viral genes to selectively replicate in tumor cells and encoding FCU1, an enzyme converting 5-FC into 5-FU, was biodistributed and replicated in tumor tissue after IV administration and expressed a functional payload. Herein, we supplement the data with 22 additional patients treated with higher doses of TG6002 and/or a more intensive schedule of administration.

METHODS

A total of 37 patients received TG6002 infusions either 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=8) combined with oral 5-FC on days 5-7, 12-14, and 19-28 (Arm A), or TG6002 infusions on days 1, 3 and 5 at the dose of $1{\cdot}10^9$ pfu (n=9) or $3{\cdot}10^9$ pfu (n=7) combined with 5-FC on days 9-18 (Arm B). Blood was sampled 30 min, 1h, 3h and 24h after the first and the third TG6002 infusion for monitoring of plasma TG6002 and on days 5, 7, 14 and 28 for serum 5-FC and 5-FU measurements. A tumor biopsy was performed on day 5 (Arm A) or day 9 (Arm B) along with concomitant blood sampling for virus detection by qPCR and plaque assay, and 5-FC and 5-FU quantification.

STUDY SCHEDULE



KEY INCLUSION CRITERIA

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

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Among the 37 patients, 20 were male and 17 were female.

- Median age was 62 years, range 32 - 78 years
- Median weight was 65 kg, range 38,6 – 105,6 kg
- Primary tumors were colorectal (n=20), pancreatic (n=10), oesophagus (n=2), ampulla of Vater (n=2), gastric (n=1), cholangio (n=1) carcinomas, and pseudomyxoma peritoneum (n=1).

All except 6 patients received at least 3 prior lines of anticancer therapy, including at least one fluoropyrimidine-based chemotherapy.

EFFICACY/SAFETY DATA

- None of these heavily pre-treated patients had a response (partial or complete) according to RECIST v1.1 and 7 patients had stable disease at Week 6.
- In terms of safety, the TG6002/5-FC combination was well tolerated
- The maximum tolerated dose was not reached in any of the 2 arms.
- Most common adverse events related to trial treatment were grade 1-2 of intensity and consisted of pyrexia (76% of patients), chills (46%), nausea (35%), hypertension (32%), diarrhea (24%), fatique (24%), hypotension (24%), tachycardia (19%), lymphopenia (19%), asthenia (16%), vomiting (14%), AST increased (14%), headache (11%) and rash pustular (11%), with no notable differences between arm A and arm B schedules.

AKNOWLEDGMENTS

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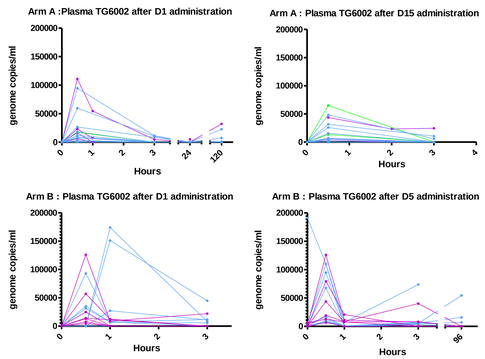
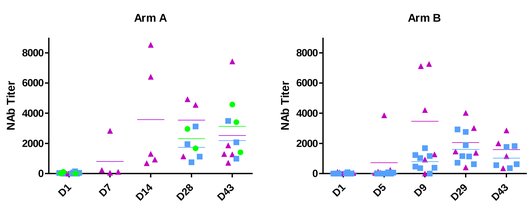
DISTRIBUTION AND TUMOR LOCALIZATION OF TG6002

A. Plasma TG6002 copy number over time after administration on D1 and D15 (Arm A, n=21)) and on D1 and D5 (Arm B, n=16). (Green: 3.10^8 pfu, Blue: 1.10^9 pfu, Purple: 3.10^9 pfu)



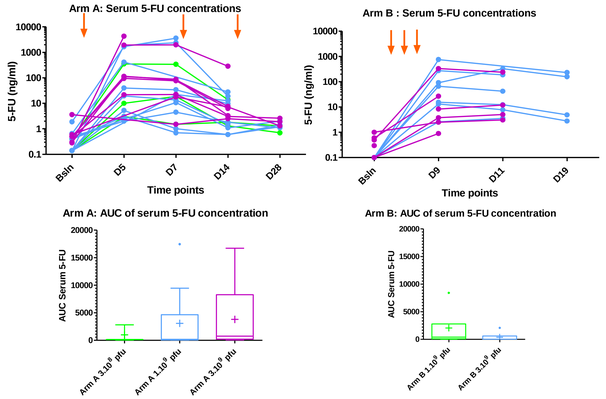
TG6002 was detected transiently after administration in both arms. TG6002 measurement by qPCR was associated with high variability across patients. No significant difference was seen on kinetics after the different injections. Furthermore, in some instances, **a rebound in circulating virus was detected 96 to 120 hours after administration**. This timing corresponds to viral replication time.

B. Onset of neutralizing antibodies in arm A (left) and arm B (right). (Green: 3.10^8 pfu, Blue: 1.10^9 pfu, Purple: 3.10^9 pfu)



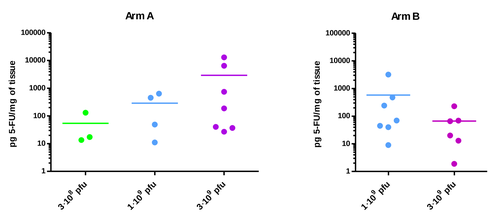
Administration of TG6002 induced the onset of neutralizing antibodies (NAb) in the second week following initiation of treatment. NAb titer was defined as serum titer inhibiting 50% of infectious activity *in vitro* on Vero cells. No difference in NAb onset was visible across doses of TG6002 or arms.

C. Upper panel : Serum 5-FU concentration over time (TG6002 administration : orange arrow). Lower panel: Tuckey boxplot for Area under the curve for serum 5-FU in each arm(Green: 3.10^8 pfu, Blue: 1.10^9 pfu, Purple: 3.10^9 pfu)



5-FU concentration in serum reflects active conversion of 5-FC into 5-FU by the FCU1 enzyme. A pre-study challenge with 5-FC demonstrated that conversion to 5-FU did not occur spontaneously. **Serum 5-FU in the arm B showed a tendency towards higher persistence over time hower higher exeposure was achieved with the Arm A schedule.**

D. Tumor titers of 5-FU by dose cohort 4 days after the first infusion of TG6002 (arm A) (n=21) or after 3 infusions in arm B (D1, D3, D5) (n=13) (Green: 3.10^8 pfu, Blue: 1.10^9 pfu, Purple: 3.10^9 pfu)



All patients with available tumor tissue biopsy had detectable 5-FU in the tumor. In the arm A, a dose effect was observed with patients receiving a higher dose of TG6002 also presenting higher titer of 5-FU in the tumor. This dose effect was not observed in the arm B, where the higher dose of TG6002 yielded lower tumor 5-FU. This observation was comforted by the detection of virus in the tumor (see panel E).

E. Detection of TG6002 using different techniques in tumor samples collected 4 days after the first infusion of TG6002 (arm A, n=21) or after 3 infusions on D1, D3 and D5 in arm B (n=13)

Presence of the virus in tumor samples was assessed using qPCR, RT-PCR or plaque titration assay.

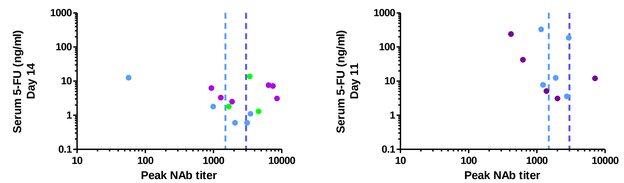
In the arm A, frequency of positive findings was dose dependent with higher dose being associated with higher frequency of direct evidence of tumor TG6002. In the arm B, on the contrary, no direct detection of the TG6002 occurred in the higher dose group.

		Positive	Negative	% positive
Arm A	$3{\cdot}10^8$	1	2	33%
	$1{\cdot}10^9$	5	5	50%
	$3{\cdot}10^9$	5	1	83%
Arm B	$1{\cdot}10^9$	5	2	71%
	$3{\cdot}10^9$	0	6	0%

F. Absence of correlation between Peak neutralizing antibodies and tumor localization of TG6002 across all patients

		Positive	Negative	% positive
NAb	Low (titers ≤ 1500)	8	7	50%
	Medium (titers >1500; ≤3000)	3	4	43%
	High (titers > 3000)	5	5	53%

G. Absence of correlation between Peak neutralizing antibodies and serum 5-FU on day 14 (arm A) or Day 11 (arm B) (Green: 3.10^8 pfu, Blue: 1.10^9 pfu, Purple: 3.10^9 pfu; dotted vertical bar delimitates low/Medium/high antibody titers)



NAbs are often hypothesized as a limiting mechanism for biological activity of oncolytic viruses. Here we showed that peak level of NAbs was not correlated to virus localization in the tumor, or transgene activity on day 14 (arm A) or day 11 (arm B) despite titer of Nab reaching a plateau. However, we cannot exclude an impact on a longer time scale.

CONCLUSIONS

- These updated data confirmed that TG6002 localizes to the tumor after IV administration, replicates in tumor cells and is able to express a functional payload.
- The two schedules of TG6002/5-FC administration offer different profiles of activity: weekly administrations in arm A led to dose-dependent expression of the payload in tumor tissue to relatively higher levels than the more intensive arm B schedule. On the other hand, the arm B schedule warranted longer lasting effect with transgene activity being detected in blood 14 days after treatment.
- However, administration of high dose of virus with an intensive schedule seemed to trigger limiting mechanisms on the activity that require special consideration.
- The limiting effect observed by high doses in intensive schedules is unlikely related to neutralizing antibodies titer. The kinetic on this effect (within 4 days) suggests a cellular innate immunity mediated mechanism as previously shown (Samson A et al, Cancer Immunol Res. 2022;10(6):745-756). The precise nature of these mechanisms and their impact on tumor activity will be investigated.