A Phase 1b Study of Toca 511, a Retroviral Replicating Vector, Followed by Toca FC in Patients With Advanced Cancer

CT067

Jaime Merchan,[1] Jordi Rodon,[2] Gerald Falchook,[3] Shree Venkat,[1] Derek Ostertag,[4] Dalissa Tejera,[1] Thian Kheoh,[4] Douglas J Jolly,[4] Harry E Gruber,[4] Jolene S Shorr[4]

[1]University of Miami; [2]Investigational Cancer Therapeutics Department, MD Anderson Cancer Center; [3]Sarah Cannon Research Institute at HealthONE; [4]Tocagen Inc.

BACKGROUND

Toca 511 (vocimagene amiretrorepvec) is an investigational, conditionally lytic, retroviral replicating vector (RRV). RRVs selectively infect cancer cells due to the presence of defects in innate and adaptive immune responses that support virus replication, and the RRVs' requirement for cell division for virus integration into the genome.

Following injection, Toca 511 spreads through tumors, stably delivering an optimized cytosine deaminase (CD) gene that converts the orally administered, antifungal prodrug, Toca FC (investigational, extended-release flucytosine [5-FC]) into fluorouracil (5-FU; Figure 1). 5-FU has a very short half-life, with direct cell killing localized to the cancer microenvironment.

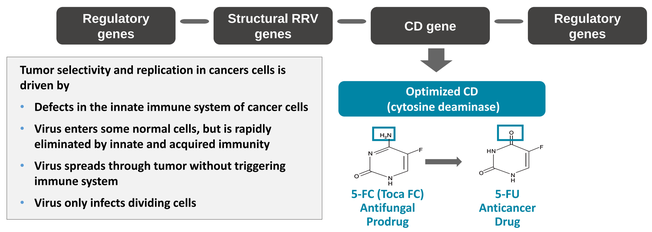

Figure 1. Mechanics of cancer gene therapy using a retroviral replicating vector (Toca 511).

Based on preclinical data, 5-FU kills infected dividing cancer cells and diffuses and kills surrounding cancer cells, myeloid derived suppressor cells (MDSCs), and tumor associated macrophages. Thus, treatment with Toca 511 & Toca FC activates the immune system against cancer with direct tumor cell killing by 5-FU, which promotes local inflammation, and by killing immunosuppressive myeloid cells in the tumor microenvironment. Together, these events promote T-cell infiltration into the tumor microenvironment and prime an antitumor immune response (Figure 2).[1,2]

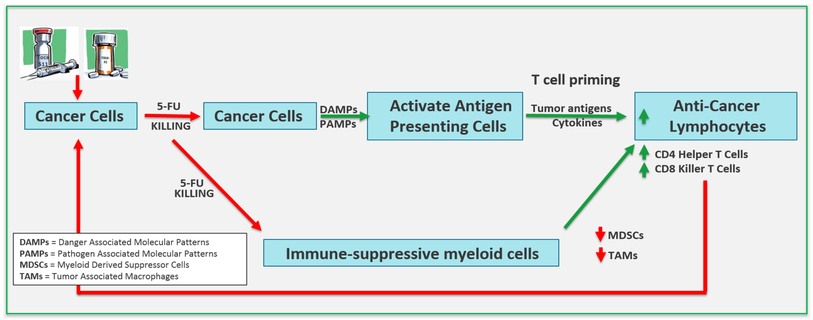

Figure 2. Proposed mechanism of action of Toca 511 & Toca FC based on preclinical data.[1-3]

Clinical Studies in Recurrent High Grade Glioma

Toca 511 & Toca FC treatment has been evaluated in three Phase 1, ascending dose studies in 127 patients with recurrent high grade glioma (HGG), each evaluating a different method of delivery of Toca 511. Data from a study in which Toca 511 was injected into resection cavity walls following resection show (1) 6 durable complete responses, with a median follow-up > 35.7 months[4]; (2) responses occurred in both IDH1 mutated and wildtype tumors (although there may be an enrichment of responses in IDH1 mutated tumors)[5]; and (3) prolonged survival relative to historic benchmarks.[4] A randomized Phase 3 trial of Toca 511 & Toca FC (Toca 5; NCT02414165)* in patients with recurrent HGG currently is underway.

In a study in which Toca 511 was injected intravenously (IV) to patients with recurrent HGG for 1, 3, or 5 consecutive days, CD protein was expressed in tumors that were subsequently resected.[6] The highest level of CD protein expression was observed following 3 days of IV injection.

Preclinical Models of Metastatic Colorectal Cancer

Extending development beyond HGG, we first showed the RRV-GFP (green fluorescent protein) can reach, productively infect, and spread in tumor in a mouse colorectal liver metastasis model, while no off-target infection was observed (Figure 3).[3]

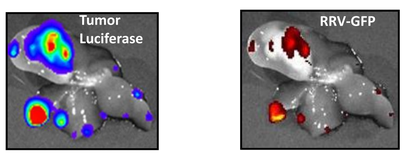

Figure 3. Images of same liver in colorectal cancer metastases model after IV delivery. CT26 (colon carcinoma) luciferase injected intrasplenically on Day 0, seeds liver; RRV- GFP injected IV on Day 3. RRV-GFP = retroviral replicating vector expressing green fluorescent protein

From Yagiz et al. Molecular Therapy: Oncolytics. 2018.

Based on encouraging preclinical data, as well as clinical data showing expression of CD protein within HGG tumors following IV delivery of Toca 511, a Phase 1b, open-label, multicenter study – Toca 6 (NCT02576665) – was initiated in patients with advanced solid tumors using IV administration of Toca 511. To maximize biological effects and the potential for clinical benefit, Toca 511 is injected both IV and intratumorally in this study, as preclinical data show that viral distribution within a tumor may be different following IV or intratumoral vector delivery.[7]

STUDY OBJECTIVES

- Primary
  - To evaluate changes in immune activity following treatment with Toca 511 & Toca FC in patients with solid tumors
- Secondary
  - Safety and tolerability
  - Vector deposition in tumor specimens following IV Toca 511
  - Clinical activity of Toca 511 & Toca FC, alone or in combination with standard of care therapies

METHODS

Study Population

Up to 30 patients with advanced malignancies will be enrolled into the study. Patients are qualified based on molecular characteristics and tumor type (Table 1).

Table 1. Tumor Molecular Characteristics and Type

Qualifying Molecular Characteristic of Tumor	Tumor Type
Presence of molecular characteristics that may increase cancer cell susceptibility to viral infection or sensitivity to 5-FU	Colorectal cancer Pancreatic cancer Triple negative breast cancer Non-small cell lung cancer Head and neck cancer Ovarian cancer Lymphoma Sarcoma Bladder cancer Melanoma
IDH1 mutated solid tumors (other than glioma)	Any

IDH1 = isocitrate dehydrogenase 1

Key Entry Criteria

Inclusion	Exclusion
18 to 75 years of age	Active infection requiring antibiotic, antifungal, or antiviral therapy within 2 weeks
Advanced malignancy that has progressed or recurred following standard therapy for advanced disease	Chemotherapy within 2 weeks; nitrosoureas within 6 weeks
No curative options available	Investigational treatment within 2 weeks; immunotherapy or antibody therapy within 28 days
Tumors accessible to biopsy and/or resection	Condition that would prevent patient from swallowing Toca FC tablets or absorbing flucytosine
Tumor amenable to injection of Toca 511	
Estimated life expectancy ≥ 6 months	
ECOG performance status 0 or 1	
Measurable disease by RECIST version 1.1	

Study Schema

*Infiltrating T-cell subpopulations, B cells, monocytes.
†Effector, memory, Treg, myeloid lineage cells.

RESULTS

Enrollment into the study is ongoing. As of the cut-off date for analysis (27 March 2018), 7 patients were enrolled into the study across 3 study sites

- University of Miami
- MD Anderson Cancer Center
- Sarah Cannon Research Institute

Analyses include vector deposition in tumor tissue, viral clearance from plasma, and adverse events; immune activity and response data are not yet available for this study. Demographic and baseline characteristics data are summarized in Table 2.

Table 2. Demographic and Baseline Characteristics

Characteristic	n = 7
Age, median (min, max)	55 (42, 66)
Female, n	4
Race, n	
White	5
Black	1
Asian	1
ECOG performance status, n	
0	1
1	6
Primary tumor type (histology), n	
Colorectal (adenocarcinoma)	5
Pancreas (adenocarcinoma)	1
Sarcoma (hemangiopericytoma)	1
Stage at diagnosis	
II	1
III	1
IV	4
Unavailable	1

Dosing and Patient Disposition

All patients completed 3 days of IV dosing with Toca 511. Intratumoral administration of Toca 511 was added as a part of an amendment to the protocol after the first 3 patients had been enrolled. For all 4 patients enrolled following the protocol amendment, Toca 511 also was injected into liver metastases.

As of the cut-off date for analysis, 5 patients had been treated with Toca FC (range 1 to 7 cycles); 6 patients discontinued treatment and 2 patients died due to disease progression (an additional patient died after the cut-off date). With sponsor consultation, the protocol permits initiation of concomitant anticancer therapy for clinical disease progression after Cycle 2 of Toca FC. Panitumumab was initiated in 2 patients with colorectal cancer (KRAS wt); 1 patient stabilized and remained on concomitant treatment for ~9 months before discontinuing treatment for clinical progression and going on to other therapy (this patient was alive as of the cut-off date, ~16 months after initiation of Toca 511, but died ~2 weeks later). The second patient, who was poorly compliant with Toca FC, progressed within a month of starting dual therapy.

Vector Deposition in Metastatic Tumor Tissue Following IV Administration of Toca 511

PCR of viral genomic RNA and DNA extracted from frozen tumor tissue was performed to assess viral delivery following IV administration of Toca 511. Immunofluorescence staining using antibodies directed against viral transgene (CD) expression was used to assess vector deposition in tumor FFPE samples. As of the cut-off date, analyses were completed for 5 of 7 patients, including 4 with liver metastasis from colorectal cancer and 1 with retroperitoneal lymph node metastasis from pancreas cancer.

IV administration of Toca 511 was associated with expression of viral protein in metastatic tumor tissue in 5 of 5 patients analyzed, including liver metastases from 4 of 4 patients with colorectal cancer (Figure 4).

Patient ID	Primary Tumor	Location of Metastasis
114-1001	Colorectal	Liver
114-1003	Pancreas	Retroperitoneal lymph node
114-1004	Colorectal	Liver
114-1006	Colorectal	Liver
018-1007	Colorectal	Liver

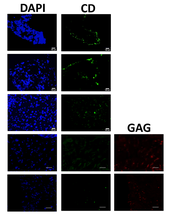

Figure 4. FFPE sections from patient biopsies obtained 11 to 25 days following IV delivery of Toca 511 were stained for nuclei (DAPI; blue), cytosine deaminase (CD; green), and viral protein (GAG; red).

Viral Clearance

Viral clearance is determined by measurement of viral RNA in plasma by qRT-PCR at multiple time points following initiation of IV Toca 511. In all 7 patients, peak viral levels were observed at the first measurement 1 to 2 weeks following the start of IV dosing, and levels had decreased near or below the limit of quantification by 2 to 4 weeks later.

Treatment-Emergent Adverse Events

Toca 511 & Toca FC was generally well tolerated. Treatment-related adverse events were reported for 4 of 7 patients (Table 3). Although not considered related to treatment, adverse events leading to discontinuation of Toca FC were reported for 1 patient (hypovolemia [grade 2], GGT increase [grade 2], and hyponatremia [serious; grade 4]). Non-treatment-related grade 5 embolism also was reported for this patient. Transient, treatment-related pyrexia, with an onset within 1 to 2 days after IV or intratumoral Toca 511 administration, was reported for 2 patients.

Table 3. Treatment-Related Adverse Events

System Organ Class Preferred Term	Number of Patients With Events (n = 7)			
	Grade 1	Grade 2	Grade 3	Grade 4
Any treatment-related event	1	2	1	0
Gastrointestinal disorders				
Abdominal pain	0	1	0	0
Colitis	0	0	1	0
Diarrhea	1	0	0	0
Frequent bowel movements	1	0	0	0
Nausea	1	2	0	0
Vomiting	0	2	0	0
General disorders and administration site conditions				
Chills	1	0	0	0
Fatigue	1	0	0	0
Influenza like illness	1	0	0	0
Pyrexia	1	1	0	0
Any treatment-related SAE	0	0	1	0
Colitis	0	0	1	0

CONCLUSIONS

Based on limited experience to date in this ongoing study of patients with advanced solid tumors,

- IV administration of Toca 511 was associated with expression of viral protein in metastatic sites of disease in 5 of 5 patients, including liver metastases from 4 of 4 patients with colorectal cancer.
- Virus was cleared from plasma within 6 weeks following IV administration.
- IV administration of Toca 511 is feasible, and was not associated with infusion-related reactions.
- Toca 511 & Toca FC treatment has been generally well tolerated, with treatment-related adverse events limited to predominantly grade 1 and 2 gastrointestinal toxicities (consistent with the safety profile of 5-FC) in 3 patients, and transient, grade 1 or 2 fever following administration to Toca 511 in 2 patients.

Future analyses will provide information on changes in immune activity following treatment with Toca 511 & Toca FC in patients with metastatic colorectal cancer and other solid tumors. Data from this study will inform future development of Toca 511 & Toca FC alone or in combination with other therapies.

REFERENCES

1. Mitchell LA, Lopez Espinoza FL, Mendoza D, et al. Neuro Oncol. 2017; 19:930-939.
2. Hiraoka, Inagaki A, Kato Y, et al. Neuro Oncol. 2017; 19:918-929.
3. Yagiz K, Rodriguez-Aguirre ME, Lopez Espinoza, F et al. Molecular Therapy: Oncolytics. 2018; 8:14-26.
4. Cloughesy TF, Landolfi J, Vogelbaum MA, et al. Society for Neuro-Oncology 22nd Annual Meeting, San Francisco, California, 2017.
5. Cloughesy TF, Ostertag D, Landolfi JC, et al. J Clin Oncol. 2017; 35 (suppl; abstr e13504).
6. Walbert T, Bota D, Vogelbaum MA, et al. Society for Neuro-Oncology 22nd Annual Meeting, San Francisco, California, 2017.
7. Huang TT, Parab S, Burnett R, et al. Human Gene Ther. 2015; 26:82-93.
8. Mitchell LA, Yagiz K, Munday A, et al. Society for Immunotherapy of Cancer 32nd Annual Meeting, National Harbor, Maryland, 2017.

*Toca 5 is supported by a grant from the Food and Drug Administration Office of Orphan Products Development.

Thanks to all the patients, their families and caregivers who have supported this work.