Extended Benefits in Patients With Recurrent High-Grade Glioma That Continuously Receive Toca FC After Toca 511 Treatment

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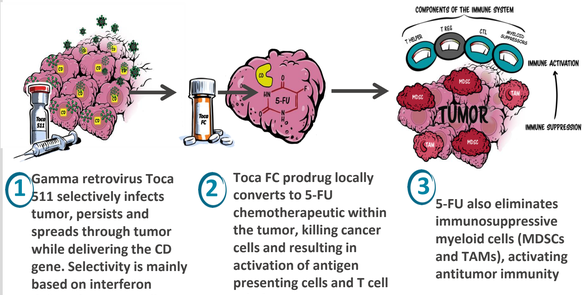
BACKGROUND

Toca 511 and Toca FC: Mechanism

- Toca 511 (vocimagene amiretrorepvec) is an investigational nonlytic, retroviral replicating vector (RRV) constructed with a codon-optimized yeast cytosine deaminase (CD) gene.
- Toca 511 infects cancer cells, and stably delivers CD gene whose protein product converts courses of the prodrug Toca FC (5-fluorocytosine) into 5-fluorouracil (5-FU).

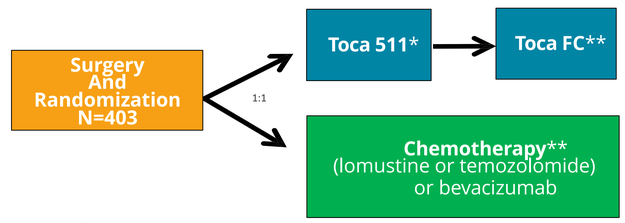


1. Gamma retrovirus Toca 511 selectively infects tumor, persists and spreads through tumor while delivering the CD gene. Selectivity is mainly based on interferon defects in cancer cells.
2. Toca FC prodrug locally converts to 5-FU chemotherapeutic within the tumor, killing cancer cells and resulting in activation of antigen presenting cells and T cell priming
3. 5-FU also eliminates immunosuppressive myeloid cells (MDSCs and TAMs), activating antitumor immunity

- Five clinical phase 1 studies and a clinical phase 2/3 study tested Toca 511 in combination with Toca FC in patients undergoing planned resection for recurrent High Grade Glioma (rHGG), glioblastoma (rGBM) or anaplastic astrocytoma (rAA).
- The last trial was completed in 2019. While the Phase 2/3 study did not meet the primary objective:
- Long term disease control with continued treatment with Toca 5FC via compassionate use:
  - Seven patients total
  - 3 men, 4 women
  - Five with rGBM
  - Two with rAA
- The compassionate use program is conducted under expanded access INDs for individual patients.
- Subjects who have received Toca 511 in a prior study and, in the opinion of the PI, were benefitting from treatment with Toca FC were eligible for enrollment.

Phase 2/3 Trial Design, Setting, and Participants (Toca 511-15-01)

- Randomized, open-label trial in 58 centers comparing post-tumor resection treatment with Toca 511 followed by Toca FC vs a defined single choice of approved (SOC) therapies conducted from November 30, 2015, to December 20, 2019
- One of the largest trials in rHGG (403 patients enrolled) using viral mediated therapy
- Patients received tumor resection for first or second rGBM or rAA
- Experimental arm:
  - Toca 511: Up to 4 mL (1.3×10^9 TU)
  - Toca FC: 220 mg/kg/day
- Control arm: Investigator choice single agent bevacizumab, lomustine, or temozolomide



ClinicalTrials.gov Identifier:
NCT02414165

* Administered at time of surgery
** Begins 6 weeks post-surgery

Phase 2/3 Trial Results (Toca 511-15-01) (1)

- Among patients who underwent tumor resection for first or second rGBM or rAA, administration of Toca 511 and Toca FC, compared with SOC, did not improve overall survival or other efficacy end points
- The rates of adverse events were similar in the Toca 511/FC group and the SOC control group

Compassionate Use Program, Patient History

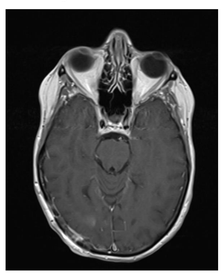
PI-Site of Patient	Gender	Current age	Date of Initial Diagnosis	Date of Recurrence	Toca 511 injection date	Toca FC dose starting date (220mg/kg/day)	Total FC Treatment duration (mo)	Type of tumor (when started Toca 5 study)	CR or PR SD or PD	Pathology
Cloughesy-UCLA	F	50	2015-11	2016-11	2016-08-12	2017-01-13	52	rAA to the right frontal lobe	SD	Unmethylated MGMT
Martinez - Jefferson Health	M	41	2012-11	2016-01	2017-01-17	2017-04-18; 2020-12-29	44 (with a 4 mo gap)	rGBM left anterior temporal lobe	SD	IDH1 mutant with methylated MGMT
Singer – Hackensack University	F	61	2017-10	2018-05	2018-06-11	2018-07-31	39	rGBM, right partial	SD	Methylated MGMT, EGFR amplification, duplication exons 18-26, EGFRvIII wt
Damek - Univ. Colorado	F	52	2017-07	2018-04	2018-05-10	2018-06-18	35	Progression of GBM	SD	Methylated MGMT, IDH wt, EGFRvIII wt
Walbert – Henry Ford	F	38	2018-04	2018-10	2018-11	2018-12-18	29	GBM	SD	GBM, IDH wt, MIB 50%; mMGMT; EGFR viii negative, 1p/19 LOH: Negative for allelic loss
Walbert – Henry Ford	M	33	2013-02		2013-10	2013-12-03	89	AA, WHO 3, Toca 11	CR	1p/19q intact; 1DH1-R132H(+); Ki-67/MIB-1 up to 10%.
Piccioni – UCSD	M	Deceased at 76	2014-01	2014-10	2014-10; 2019-04	2014-11 - 2019-02; 2019-05 - 2020-05	63	Patient started with Toca 11 study, GBM and then Toca 5 study	1st injection-CR; 2nd injection-PR	NGS: BTG1 E50Dfs*30; TBM low 4.2mut/Mb

Compassionate Use Program, Patient Case Studies

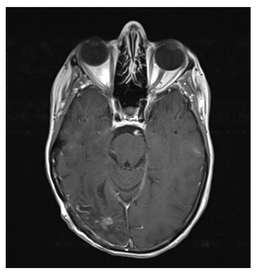
SINGER - Hackensack

A 57-year-old woman presented with confusion, and a right parieto-occipital tumor was resected in 11/2017, revealing GBM, MGMT methylated, IDH wild-type.
She was treated with radiation (60 Gy) and concurrent temozolomide, complicated by pancytopenia, limiting adjuvant temozolomide. She was treated with pembrolizumab for 2 cycles, followed by progressive enhancement, resected in 6/2018 on treatment arm of protocol Toca511-15, with pathology confirming recurrent tumor.
She initiated Toca FC per protocol, without enhancement on baseline MRI. She has completed 28 cycles to date, well tolerated. Scans initially showed increased enhancement which subsided with time.

Baseline t1 axial post
Pre cycle 1 5FC



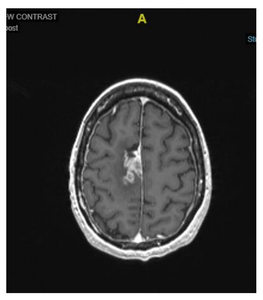
Pre cycle 24 T1 axial post



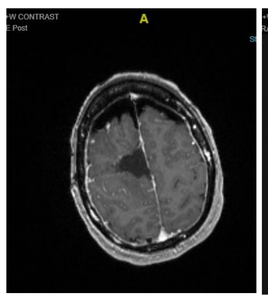
CLOUGHESY - UCLA

A 49-year-old woman was initially diagnosed with anaplastic astrocytoma, WHO III, unmethylated MGMT in 11/2015. The patient received DC Vax therapy followed by proton radiation from 3/21/2016 to 5/5/2016. In addition to 3 doses of DC Vax, she received 3 treatments with experimental Gamma Delta treatment, all in 2016. After her MRI showed disease progression, the patient underwent repeat surgery as part of the phase 2/3 randomized protocol Toca 511-15-01 on 12/8/2016. The patient was randomized onto the TOCA-511 arm and had a gross total resection. She initiated Toca FC per protocol. The patient has started Cycle 33 on 7/19/2021.

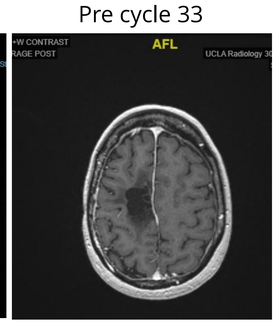
02 Dec 2016
Pre-Surgery



08 Dec 2016
Pre cycle 1 5FC



19 Jul 2021
Pre cycle 33



Conclusions

- Duration of extended treatment with Toca FC ranges 29 months - 7 years and 5 months (average 49.2 months)
- Six patients who are still on active treatment with Toca FC have either stable disease or complete response
- Toca FC is well tolerated in these patients, typical side effects include diarrhea
- Some patients with rGBM or rAA appear to benefit from extended TocaFC treatment after Toca 511
- Further analysis is needed to explore factors that might predict prolonged responses in select patients

Acknowledgement

Acknowledgment:
Toca 511 and Toca FC are now under development by Denovo Biopharma LLC. Denovo continuously provides the Toca FC drug supply for patients in the compassionate use programs.

Bibliography

- (1) Cloughesy TF, et al. Durable complete responses in some recurrent high-grade glioma patients treated with Toca 511 + Toca FC. Neuro Oncol. 2018;20(10):1383–1392
- (2) Cloughesy TF, et al. Effect of Vocimagene Amiretrorepvec in Combination With Flucytosine vs Standard of Care on Survival Following Tumor Resection in Patients With Recurrent High-Grade Glioma. A Randomized Clinical Trial. JAMA Oncol. 2020;6(12):1939-1946