Immunologic trends associated with patient outcomes in a phase 1 clinical trial of Toca 511 and Toca FC in recurrent high grade glioma

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Background and Introduction

Toca 511 (tococogene amiretrovec) is a cancer selective, retroviral replicating vector encoding a codon optimized, heat stabilized cytosine deaminase (CD) that converts Toca FC (extended-release S- fluorocytosine, S-FC) into the anticancer agent S-fluorouracil (S-FU). Preclinical evidence demonstrates that the Toca 511 & Toca FC regimen kills cancer cells and immunosuppressive myeloid cells in the tumor microenvironment, leading to durable antitumor immune responses that can be adoptively transferred to untreated animals.14

In an ascending dose trial (NCT01470794) in patients with recurrent high grade glioma (HGG). Toca 511 was injected into the resection cavity walls at the time of resection, and then multiple courses of oral Toca FC were administered. Multiyear durable and complete responses by independent radiology review have been reported.3,23

Methods & Objectives

Immunologic assessments of recurrent high grade glioma patient samples from a phase I clinical trial of Toca 511 & Toca FC included:

- Tumor microenvironment immune infiltrate quantification via deconvolution of RNA-seqencing using CIBERSORT
- T-cell receptor sequencing of blood and tumor DNA
- Peripheral serum cytokine quantification via digital multiplex ELISA
- Peripheral blood mononuclear cell immunophenotyping via flow cytometry

The objectives of this study were as follows:

- Demonstrate an immune-related mechanism of action for Toca 511 and Toca FC treatment in human patients
- Identify treatment-associated immune modulations that could serve to monitor patient response to treatment
- Define immunobiological markers that can potentially predict patient outcomes

Tumor Microenvironment (TME) Results

Immune infiltrates quantified using mRNA

Frequencies of 22 immune subsets were estimated in 110 high grade glioma tumor samples from 46 patients using CIBERSORT. Immune infiltrate signatures may predict patient survival

Objective response is associated with tumor immune infiltrates

- Complete Response in a Patient with Progressive GBM
- PR at 6 Months, CR at 48 Months

Immune infiltrate signatures may predict patient survival

- Kaplan Meier survival curves are displayed for patients stratified by RNA-based TIL signatures including (A) resting NK cells, (B) M0 macrophages, (C) activated CD4+ T-cells, and (D) a TME biomarker that incorporates all of these subsets. Censored marks indicate follow up time for a patient who was alive at last contact. Log rank p-values are shown, and hazard ratios with 95% confidence intervals were determined via Cox proportional hazard modeling and refer to the below median group.

T-cell receptor DNA sequencing

- Results from 16 patients suggest that responses exhibited significantly higher levels of tumor T-cell infiltrates.
- No associations were identified between patient response to therapy and T-cell receptor rearrangements or T-cell clonality.

Peripheral Blood Results

Cytokine modulations may reflect response to therapy

- T-cell activation in a complete responder
- T-cell proliferation in a complete responder

Cytokine signatures could indicate long term survival

- Human immune monitoring results support an immunologic mechanism of action for Toca 511 & Toca FC treatment. Preliminary analyses identified potential immunobiologic biomarkers that may reflect patient outcomes and should be explored further.
- Immune infiltrate signatures in the tumor microenvironment prior to Toca 511 & Toca FC treatment were associated with objective response and survival. Preliminary results suggest NK cells, M0 macrophages and activated CD4+ memory T-cell infiltrates may predict patient outcomes.
- Peripheral serum cytokine modulations during Toca 511 & Toca FC treatment were associated with objective response and survival. Preliminary results suggest that cytokine measurements may be useful to monitor patient responses, and could indicate long term survival.
- Post-treatment expansion of PD-1+ and Ki-67+ T-cell subsets associated with clinical benefit to Toca 511 and Toca FC therapy suggests potential immune activation.

Conclusions

- This clinical work helps support and clarify the immune-related mechanism of action for Toca 511 & Toca FC previously observed in non-clinical models.
- Potential immunobiologic biomarkers of patient outcomes will be evaluated in the ongoing randomized Phase 3 trial in patients with HGG (NCT021414165), Toca 5.