Intravenous Delivery of Toca 511 in Patients With High Grade Glioma Results in Quantifiable Expression of Cytosine Deaminase in Tumor Tissue

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Disclosures

• Advisory Board: AbbVie, Tocagen
Toca 511 (vocimagene amiretrorepvec) Retroviral Replicating Vector That Carries a Prodrug Activator Enzyme

Tumor selectivity and replication in cancers cells is driven by

- Defects in the innate immune system of cancer cells
- Virus enters some normal cells, but is rapidly eliminated by innate and acquired immunity
- Virus spreads through tumor without triggering immune system
- Virus only infects dividing cells

Optimized CD (cytosine deaminase)

5-FC (Toca FC) Antifungal Prodrug

5-FU has a very short half-life with direct cell killing localized to cancer microenvironment

RRV = retroviral replicating vector

Toca 511 & Toca FC: Toca 511 Spreads Then Converts Toca FC to 5-FU for Tumor Killing and Immune Activation

Novel 5-FU delivery kills tumor cells and activates immune system against cancer

Proposed MOA: Tumor killing and anti-cancer immune activation

Brain and tumor samples from Tocagen clinical trial patients

CD = cytosine deaminase (yeast)
Toca FC = extended release 5-FC
Toca 511 & 5-FC – A Cancer-Selective Immunotherapeutic

- Toca 511 infects and spreads selectively in the tumor
- Toca 511 encodes for the enzyme, cytosine deaminase, which converts the prodrug, 5-FC, into 5-FU in the tumor microenvironment
  - 5-FU kills tumor cells directly, which promotes local inflammation, and
  - 5-FU kills immunosuppressive myeloid cells in the tumor microenvironment

Together, these events promote T cell infiltration into the tumor microenvironment and prime an anti-tumor immune response

Toca 511 & Toca FC – Clinical Development in Primary and Metastatic Brain Tumors

<table>
<thead>
<tr>
<th>Indication</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent high grade glioma (rHGG)</td>
<td>Toca 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced solid tumors (including brain metastases)</td>
<td>Toca 6</td>
<td></td>
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<tr>
<td>Newly diagnosed high grade glioma</td>
<td>Toca 7</td>
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Phase 1 Ascending Dose Trials in rHGG Explored Different Delivery Techniques for Toca 511

**Resection**
Injection into cavity wall after removal of tumor

- NCT01470794

**Intratumoral**
Direct injection into tumor

- NCT01156584

**Intravenous**
Injection IV prior to resection and into cavity wall at resection

- NCT01985256
Study Overview

Design
- Open label, ascending dose
  - Toca 511 – $4.8 \times 10^8$ to $4.8 \times 10^{10}$
  - Toca FC – 135 to 300 mg/kg/day x 7 days, q 4-6 weeks

Objectives
- Vector deposition in tumor
- MTD; safety and tolerability
- Overall survival, objective response

Study Population (n = 17)
- Recurrent HGG
- Planned resection ≥ 80%
- 18-80 years old
- KPS ≥ 70

Analysis of cytosine deaminase expression in tumor
# Baseline Characteristics & Neuro-Oncology History

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 17</th>
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<tbody>
<tr>
<td>Age, median (range)</td>
<td>52.0 years (28-77)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>KPS, n (%)</td>
<td></td>
</tr>
<tr>
<td>70-80</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>90</td>
<td>11 (64.7)</td>
</tr>
<tr>
<td>100</td>
<td>3 (17.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History</th>
<th>n = 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since initial diagnosis, median (range)</td>
<td>16.8 (6-70)</td>
</tr>
<tr>
<td>Initial tumor histology, n (%)</td>
<td></td>
</tr>
<tr>
<td>GBM</td>
<td>14 (82.4)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Gross-total resection of initial tumor, n (%)</td>
<td>10 (58.8)</td>
</tr>
<tr>
<td>Number of recurrences (including on-study), n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>2</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>6 (35.3)</td>
</tr>
</tbody>
</table>
Tissue Processing for Analysis of Toca 511

IHC analysis performed on resected tumor tissue after IV delivery of Toca 511 to determine if T cell infiltrates altered viral entry and/or spread

- Portions of resected tissue representing various regions of tumor were formalin fixed and paraffin embedded (FFPE)

- Adjacent portions of tumor were frozen for PCR analysis of cytosine deaminase expression

Diagram:
- Resected tumor tissue (n = 17)
  - Cytosine deaminase expression (n = 11)
  - No cytosine deaminase expression (n = 6)
- 1 FFPE section from "cytosine deaminase high" expression region (n = 11)
- 1 FFPE section from "cytosine deaminase low" expression region (n = 11)

IHC
IV Administration of Toca 511 Results in Expression of Cytosine Deaminase Protein in Tumor

- **DAPI**: Nuclear stain
- **Cytosine Deaminase**: Target protein encoded by Toca 511
- **gag**: 1 of 3 major proteins encoded by the retroviral genome
- **Merge**: gag protein localizes with cytosine deaminase expression after IV delivery of Toca 511
IV Injection of Toca 511 on 3 Consecutive Days Trends With Higher Expression of Cytosine Deaminase Protein in Tumors
T Cell Infiltration in Tumor Does Not Limit Cytosine Deaminase Expression After IV Delivery of Toca 511

Data points of a given color represent samples from the same patient
- 1 “cytosine deaminase high” and 1 “cytosine deaminase low” sample analyzed/patient

Cytosine deaminase – target protein encoded by Toca 511
CD3 – pan T cell marker

Data suggest immunologically “hot” tumors with high T cell infiltrate will not limit Toca 511 entry and spread

R^2=0.20

X axis log transformed
Increased Regulatory T Cell Infiltration is Not Associated With Increased Cytosine Deaminase Expression

Data points of a given color represent samples from the same patient

- 1 “cytosine deaminase high” and 1 “cytosine deaminase low” sample analyzed/patient

Cytosine deaminase – target protein encoded by Toca 511

Foxp3 – transcription factor identifying regulatory T cells

Data suggest Toca 511 does not rely on regulatory T cell-mediated immune suppressive microenvironment for entry and spread

Y axis log transformed
Median Overall Survival

Median OS = 13.6 months (95% CI 5.8, 19.7)

Patients censored at last date of contact.

Data cut-off 17 April 2017.
Best Overall Response – Independent Radiologic Review

• Best response* – stable disease in 3 of 17 patients (17.6%)

• Radiologic responses with delayed onset in 2 of 17 patients following clinical progression
  • Anaplastic astrocytoma (IDH1 wt) at 3rd recurrence – PR
    • Noted on routine follow-up MRI, 9 months after discontinuing Toca FC (no other anticancer therapy)
  • GBM (IDH1 mt) at 1st recurrence – CR
    • Onset 13 months after initiating Toca FC
    • Toca FC ongoing (no other anticancer therapy)
    • Remains in response (16+ months) as of last assessment

Durable Complete Radiologic Response in GBM (IDH1 mt) Patient Treated With Toca 511 & Toca FC
### Treatment-Related Adverse Events

#### Related to Toca 511

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Any treatment-related event</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>Treatment-related event in ≥ 2 patients</td>
<td></td>
</tr>
<tr>
<td>Vasogenic cerebral edema</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Malaise</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Any treatment-related SAE</td>
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#### Related to Toca FC

<table>
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<tbody>
<tr>
<td>Any treatment-related event</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>Treatment-related event in ≥ 2 patients</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Any treatment-related SAE</td>
<td>0</td>
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</table>

*No treatment-related deaths.*

MTD not defined
- DLT at $1.5 \times 10^{10}$ TU Toca 511
  - Vasogenic cerebral edema (Grade 3)
- No additional DLTs observed
Conclusions

• Following IV delivery of Toca 511, cytosine deaminase protein is detectable and quantifiable in resected HGG tumor tissue

• Toca 511 can infect and spread in “hot” and “cold” tumors, with activity independent of high levels of immunosuppressive T cells in the tumor microenvironment

• mOS of 13.6 months is consistent with other Toca 511 & Toca FC ascending dose studies
  • 14.4 months for resection followed by Toca 511 injection
  • 13.8 months for delivery of Toca 511 via stereotactic biopsy needle

• Late onset (> 12 months) radiologic responses in 2 patients (1 GBM, IDH1 mt; 1 anaplastic astrocytoma, IDH1 wt), consistent with immunologic response

• Toca 511 & Toca FC appeared to be well tolerated – few Grade ≥ 3 treatment-related adverse events

• Results support evaluation of Toca 511 & Toca FC in other solid tumors, including metastatic brain tumors (Toca 6)
Thanks to all the patients and their families and caregivers who have supported this work.

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