TOCA 511 & TOCA FC: EVALUATION OF DURABLE RESPONSE RATE IN THE POST-RESECTION SETTING AND ASSOCIATION WITH SURVIVAL IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMA


1University of California, Los Angeles, 2JFK Medical Center, 3Cleveland Clinic Foundation, 4Tocagen Inc., 5Ohio State University, 6University of California, San Diego, 7Henry Ford Hospital, 8John Wayne Cancer Institute, 9Ontario Brain Institute
Disclosure:

• I have been compensated for consultation with: Celgene, Tocagen, VBL, Puma, AbbVie, BMS, Merck, Genocea, Cortice, GW Pharma, Wellcome Trust, Cancer Panels

• I am Chairman for DSMB for VBI-1901

• I am on the Steering Committee for BBI-DSP7888

• I have stock option with: Notable Labs

• I am a board member and CMO for Global Coalition for Adaptive Research
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-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

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

(step 1) Toca 511 & CD
CD

(step 2) Toca FC
5-FU
CD

Brain and tumor samples from Tocagen clinical trial patients
Toca 511 & 5-FC
Activates a Durable Anti-Cancer Immune Response

Pre-Clinical Evidence of Durable Immune Activation

CONTROL

IMMUNE DEFICIENT

IMMUNE COMPETENT

Images modified for illustrative purposes

Multiple cycles of tumor-associated antigen (TAA) release during FC treatment cycles, coupled with simultaneous depletion of immune suppressive cells in the tumor microenvironment, leads to immune activation, effective TAA presentation, and lymphocytic infiltration, resulting in gradual killing and shrinkage of the tumor, sometimes completely, over a long period of time.

“Cured” Mice Reject Re-Challenge of Same Tumor in Flank

T Cells From “Cured” Mice Increase Survival in Adoptive Transfer Model

Toca 511 & Toca FC
A cancer-selective immunotherapeutic

Directly kills tumor cells and immune-suppressive myeloid cells leading to immune activation and long-term durable responses
Ph1 ascending dose trial of safety and tolerability of Toca 511 & Toca FC in rHGG
Toca 511 administered into the resection cavity wall

**Eligibility**
- Recurrent HGG
- Planned resection ≥ 80%
- 18-75 yrs old
- Single or contiguous tumor
- KPS ≥70
- Adequate lab values
- No prior bevacizumab for recurrence
- Tumor ≤ 5 cm

**Dose Escalation**
Objective: Safety, tolerability, and MTD

Toca 511 once
From $1.4 \times 10^7$ to $4.8 \times 10^9$ TU (half-log increases)

Cyclic Toca FC
From 135 to 220 mg/kg/day

Multi-center
Adaptive 3+3 design

Adapted from M.A. Vogelbaum, MD PhD, SNO, Nov. 21st, 2015
Basic demographics show predominantly GBM patients

<table>
<thead>
<tr>
<th>Population</th>
<th>All Patients N = 56</th>
<th>Higher Doses and Ph3 Entry Criteria Subset N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>56 (24-75)</td>
<td>54.8 (24-70)</td>
</tr>
<tr>
<td>Male</td>
<td>43 (77)</td>
<td>20 (87)</td>
</tr>
<tr>
<td>Karnofsky Performance Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-80</td>
<td>17 (30)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>90-100</td>
<td>39 (70)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Initial Tumor Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBM</td>
<td>46 (82)</td>
<td>19 (83)</td>
</tr>
<tr>
<td>Anaplastic Astrocytoma</td>
<td>6 (11)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Anaplastic Oligodendroglioma</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Other gliomas</td>
<td>3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Number of Recurrences Including Current</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28 (50)</td>
<td>19 (83)</td>
</tr>
<tr>
<td>2</td>
<td>13 (23)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>≥ 3 or greater</td>
<td>15 (27)</td>
<td>0</td>
</tr>
</tbody>
</table>

1Includes gliosarcoma
2Higher doses (cohorts 4-7a) and meet Ph3 entry criteria of 1\textsuperscript{st} and 2\textsuperscript{nd} recurrence, no prior Avastin in rAA or rGBM, tumor not > 5cm

Data cutoff date August 15\textsuperscript{th}, 2017
# All responders are now in complete response and alive

All responses are in higher dose cohort and durable

<table>
<thead>
<tr>
<th>Response Category¹</th>
<th>All Patients N=53²</th>
<th>Higher Doses and Ph3 Entry Criteria Subset³ N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Durable response rate (CR or PR ≥24 weeks)</td>
<td>6 (11.3); All CR⁴</td>
<td>5 (21.7); All CR⁵</td>
</tr>
<tr>
<td>Median duration of durable response</td>
<td>Not reached (median follow-up: 36.5mos)</td>
<td>Not reached (median follow-up: 37.4mos)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12 (22.6)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>35 (66.0)</td>
<td>13 (56.6)</td>
</tr>
<tr>
<td>Clinical Benefit Rate (CR, PR, and SD at 8 weeks)</td>
<td>16 (30.2)</td>
<td>10 (43.5)</td>
</tr>
</tbody>
</table>

Comparing favorably with [lomustine*]:

- Overall response - 4.3%
- Duration of response - 2.8-9.6 months

*Wick, JCO 2010

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¹Includes MRI by independent radiology review and clinical data
²56 safety evaluable patients, 53 patients who received Toca 511 & Toca FC are efficacy evaluable and of these 2 were not evaluable for response
³Higher doses (cohorts 4-7a) and meet Ph3 entry criteria of 1st and 2nd recurrence, no prior Avastin in rAA or rGBM, tumor not > 5cm
⁴Includes 4 IDH1 wildtype and 2 IDH1 mutant patients
⁵Two patients converted from PR to CR status since last data cutoff

Data cutoff date Dec. 20th, 2017
A positive association of durable response with overall survival
Best response & survival post progression

All Responses are Durable Complete Responses & Associated with Long Term Survival

Toca 511-11-01 Overall Survival and the Best Response
1st/2nd Recurrence, No prior bevacizumab, <=5cm, Higher Dose Cohorts (N=23)

- Responses occurred gradually over time ~ 6-19 months, consistent with immunologic response
- All Responders alive 38.0+ to 57.5+ months, so far
- All CRs confirmed
- CRs received no additional brain cancer treatment after entering trial
- Median duration of response is 37.4+ months

mOS Toca 511 & Toca FC* = 14.4 months

Data cutoff date Dec. 20th, 2017
Complete Response in a Patient with Progressive GBM, IDH1 wt


Alive and with ongoing complete response > 36 months
### Treatment-Related Adverse Events

Adverse events related to Toca 511 – pooled across three phase 1 studies

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Events</th>
<th>Toca 511 n = 127</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2 n (%)</td>
</tr>
<tr>
<td>Any treatment-related event</td>
<td>32 (25.2)</td>
</tr>
<tr>
<td>Treatment-related event in ≥ 3 patients</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (11.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>Convulsion</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Vasogenic cerebral edema</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Any treatment-related SAE</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

Data cutoff 17 Apr 2017; excludes data from continuation study

Absence of vector insertion site clonality supports safety

*No deaths considered related to Toca 511
Toca FC has very limited Grade ≥ 3 treatment-related toxicities

### Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Events</th>
<th>Toca FC (n = 122)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Patients with any treatment-related event</td>
<td>50 (41.0)</td>
</tr>
<tr>
<td>Treatment-related event in ≥ 3 patients</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>27 (22.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (13.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (9.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (4.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Patient with any treatment-related serious adverse event</td>
<td>0</td>
</tr>
<tr>
<td>Adverse Events Leading to Discontinuation</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

Data cutoff 17 Apr 2017; excludes data from continuation study

*No deaths considered related to Toca FC
Conclusions

• Toca 511 & 5-FC activates durable T-cell mediated immune responses pre-clinically
• Treatment was well tolerated – limited Grade ≥ 3 drug-related toxicities in three Ph1 studies (127 patients)
• Ph1 resection/injection study indicates:
  • Prolonged survival relative to historical benchmarks
  • In a subset (n=23) that mirrors Phase 3 study (Toca 5) population
    • 5 complete responses (3 rGBM with IDH1 wt, 2 rAA with IDH1 mt) are ongoing
    • Median duration of response has not been reached after a median follow-up of 37.4 months
    • Durable response rate may be a valuable endpoint for immunotherapeutics
    • A positive association between durable response and overall survival
• Clinical activity and MOA data supported Breakthrough Therapy and PRIME designations
• Findings support ongoing Phase 3 randomized study (Toca 5) in patients with rHGG
  • Currently enrolling patients with rAA or rGBM, at 1st or 2nd recurrence, no prior Avastin in rHGG, tumor not > 5cm
Thanks to all the patients, their families and caregivers who have supported this work.

Study sponsor: Tocagen

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