Durable Responses Observed in IDH1 Wildtype and Mutant Recurrent High Grade Glioma with Toca 511 & Toca FC Treatment

Cloughesy TF1, Landolfi J2, Vogelbaum MA3, Ostertag D4, Elder JB5, Bloomfield S2, Carter B6, Chen CC6, Kalkanis SN7, Kesari S8, Lai A1, Lee IY7, Liau LM1, Mikkelsen T7,9, Nghiemphu PL1, Piccioni D6, Accomando W4, Diago O4, Hogan D4, Jolly DJ4, Wood K4, Yang L4, Gruber HE4, Das A4, Walbert T7

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
The key Ph1 resection study update*

- Two patients with partial response (PR) changed to complete response (CR) status
  - One at 30 months
  - One at 48 months
- The delayed response is indicative of immunologic activity
- All 5 responders are in complete response and alive
- Median duration of durable response has not been reached with a median follow-up of 35.7 months
- A positive association between durable response and overall survival

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

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

STEP 1 - Toca 511 & CD

STEP 2 - Toca FC

Tumor

Brain and tumor samples from Tocagen clinical trial patients

CD = cytosine deaminase (yeast)
Toca FC = extended release 5-FC

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Toca 511 & 5-FC activates durable T cell mediated immune response against tumor

Syngeneic glioma in immune competent mice: 5-FU killing plus immune activation

Tumor re-challenge and adoptive transfer studies: T cell mediated immune response

Hiraoka et al. Neuro-Oncology, 2017; Mitchell et al. Neuro-Oncology, 2017
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

Cancer Cells → 5-FU KILLING → Cancer Cells

Cancer Cells → 5-FU KILLING

DAMPs = Danger Associated Molecular Patterns
PAMPs = Pathogen Associated Molecular Patterns
MDSCs = Myeloid Derived Suppressor Cells
TAMs = Tumor Associated Macrophages

Immune-suppressive myeloid cells

Activate Antigen Presenting Cells

T cell priming

Tumor antigens Cytokines

Anti-Cancer Lymphocytes

CD4 Helper T Cells
CD8 Killer T Cells

MDSCs
TAMs
Ph1 ascending dose trial of safety and tolerability of Toca 511 & Toca FC in rHGG
Toca 511 administered into the resection cavity wall

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

**Surgery**

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

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

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

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

\(^1\)includes gliosarcoma

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

Data cutoff date August 15\(^{th}\), 2017
### Response Category

<table>
<thead>
<tr>
<th>Response Category</th>
<th>All Patients N=53</th>
<th>Higher Doses and Ph3 Entry Criteria Subset N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Durable response rate (CR or PR ≥24 weeks)</strong></td>
<td>6 (11.3); All CR⁴</td>
<td>5 (21.7); All CR⁵</td>
</tr>
<tr>
<td><strong>Median duration of durable response</strong></td>
<td>Not reached (median follow-up: 35.1mos)</td>
<td>Not reached (median follow-up: 35.7mos)</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>10 (18.9)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>37 (69.8)</td>
<td>13 (56.6)</td>
</tr>
<tr>
<td><strong>Clinical Benefit Rate (CR, PR, and SD at 8 weeks)</strong></td>
<td>16 (30.2)</td>
<td>10 (43.5)</td>
</tr>
</tbody>
</table>

1Includes MRI by independent radiology review and clinical data
2Of 56 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 IDH wildtype and 2 IDH mutant patients
5Two patients converted from PR to CR status since last data cutoff

**Compares favorably with lomustine**:  
- Overall response - 4.3%
- Duration of response - 2.8-9.6 months

*Wick, JCO 2010

Data cutoff date August 15th, 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

- Clinical benefit rate (CR + SD) is 43.5% (10/23)
- All responders are CR, are alive and remain in response
- Median duration of response has not been reached after a median follow up of 35.7 months
- Initial responses occurred after ~ 6-19 months, consistent with immunologic response
- mOS is 14.4 months. 2 and 3 year survival is 34.8% and 26.1% respectively
- Data suggests an association between response and survival

Adapted from Cloughesy et al. AACR-NCI-EORTC Conference, 2017.
Complete response in a patient with progressive GBM, IDH1 wt PR at 19 months, CR at 30 months*, alive > 33 months

*Independent Radiology Review, Macdonald criteria

Toca FC cycle is every 6 weeks
Toca 511 associated with a very low % of treatment-related AEs, across all Grades

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>
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<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
</tr>
<tr>
<td></td>
<td>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>

No deaths considered related to Toca 511

Absence of vector insertion site clonality supports safety

Data cutoff 17 Apr 2017; excludes data from continuation study
## Treatment-Related Adverse Events

**Toca FC**

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Events</th>
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</table>
| **Patients with any treatment-related event** | **Toca FC**
| | **n = 122** |
| | **Grade 1/2** | **Grade ≥ 3** |
| | **n (%)** | **n (%)** |
| Fatigue | 27 (22.1) | 0 |
| Diarrhea | 16 (13.1) | 1 (0.8) |
| Nausea | 12 (9.8) | 0 |
| Decreased appetite | 6 (4.9) | 0 |
| Vomiting | 4 (3.3) | 0 |
| Rash | 3 (2.5) | 0 |

**Patient with any treatment-related serious adverse event**

| Adverse Events Leading to Discontinuation | **Toca FC**
|-----------------------------------------| **n = 122** |
| | **Grade 1/2** | **Grade ≥ 3** |
| | **n (%)** | **n (%)** |
| 1 (0.8) | 2 (1.6) |

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 35.7 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.

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