Long-term follow-up data from 126 patients with recurrent high grade glioma from three Phase 1 trials of Toca 511 and Toca FC: Update and justification for a Phase 2/3 trial

Douglas J. Jolly¹, Manish K. Aghi², Michael A. Vogelbaum³, Steven N. Kalkanis⁴, Daniela Bota⁵, Bob Carter⁶, Clark C. Chen⁶, J Bradley Elder⁷, Johnathan Engh⁸, Samuel Goldlust⁹, George J. Kaptaṇ³⁰, Santosh Kesari¹⁰, Joseph Landolfi¹¹, Linda Liau¹², Tom Mikkelsen⁴,¹³, David Piccioni⁶, Jana Portnow¹⁴, Samuel Singer⁹, Tobias Walbert⁴, Harry Gruber¹, Carlos Ibañez¹, Leah Mitchell¹, Derek Ostertag¹, Jolene S. Shorr¹, Liqiang Yang¹, Asha Das¹, Timothy F. Cloughesy¹².

¹Tocagen Inc.; 2University of California, San Francisco; 3Cleveland Clinic Foundation; 4Henry Ford Hospital; 5University of California, Irvine; 6University of California, San Diego; 7Ohio State University; 8University of Pittsburgh Medical Center; 9John Theurer Cancer Center; 10John Wayne Cancer Institute at Saint John’s Health Center; 11JFK Medical Center; 12University of California, Los Angeles; 13Ontario Brain Institute; 14City of Hope
Disclosures

• Douglas J. Jolly is an employee and shareholder of Tocagen
Toca 511 (vocimagene amiretrorepvec)

- Toca 511 is a RRV encoding yeast-derived cytosine deaminase (CD)
  - Temperature-stabilized, codon optimized yeast CD, called yCD2
- Based on gamma replicating retrovirus with an amphotropic envelope
  - Enables infection of human cells
  - Highly selective for infection of tumor cells
  - Spreads without tumor cell lysis
- Used in combination with prodrug Toca FC: extended-release 5-FC
  - Local high levels of 5-FU
  - Leads to sustained anti-tumor immune responses in animals by novel MOA
  - Clinical data is consistent with this MOA

Toca 511 Vector Construct
Toca 511 & 5-FC activated a durable anti-cancer immune response in tumor models
Evaluation of immune modulation during 5-FC

Monitoring immune cell population changes as tumor shrinks

Syngeneic Tu2449 glioma subcutaneous mouse model starting with Toca 511 2% pre-transduced
Immune activation after 5-FC (14d) in glioma model

Reduced Myeloid Derived Suppressor Cells (MDSC)

Increased CD4 “helper” cells

Increased CD8 “effector” cells
5-FU produced in tumor microenvironment kills tumor cells and immune-suppressive myeloid cells leading to immune activation and long-term durable responses.
High Grade Glioma (HGG): Deadly and aggressive

Glioblastoma (GBM) and anaplastic astrocytoma (AA)

- Few treatment options: High unmet need
  - Break through, Fast track and orphan drug designations
- Newly diagnosed GBM: surgery, radiation, Temodar
  - ~16 months median survival
- Recurrent HGG: Avastin, lomustine, Gliadel
  - NCCN guidelines recommend consideration of clinical trials
  - ~8 months median survival

Common symptoms:
- seizures
- headaches
- neuro defects
Three Phase 1 Studies Using Different Toca 511 Delivery Methods in Recurrent HGG

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

**Intratumoral**
Direct injection into tumor

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

n = 56  
n = 53  
n = 17
Overall Survival Comparable in Both Surgical and Non-Surgical Settings

<table>
<thead>
<tr>
<th></th>
<th>Resection (n = 24)*</th>
<th>Intratumoral (n = 24)†</th>
<th>Intravenous (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, months (95% CI)</td>
<td>14.3 (11.1, 28.1)</td>
<td>13.8 (7.1, 22.2)</td>
<td>13.6 (5.8, 20.6)</td>
</tr>
<tr>
<td>OS 6 (%)</td>
<td>100</td>
<td>86.1</td>
<td>76.5</td>
</tr>
<tr>
<td>OS 9 (%)</td>
<td>87.5</td>
<td>62.2</td>
<td>64.7</td>
</tr>
<tr>
<td>OS 12 (%)</td>
<td>62.5</td>
<td>57.4</td>
<td>57.5</td>
</tr>
</tbody>
</table>

*Patients at 1st/2nd recurrence with no prior Avastin, tumor ≤ 5 cm, in high-dose cohorts.

†Patients receiving Toca 511 via biopsy needle.

Preliminary data – cutoff October 2016; †31 May 2016
Resection Study: Long-Term Survival in Higher Dose Cohort

All Responses are Durable & Associated with Long Term Survival

Adapted from M.Aghi et al, SNO, Nov. 18, 2016.
All Responses Are in the Higher Dose Cohorts

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Higher Doses &amp; P2/3 Entry Criteria Subset</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=24 n (%)</td>
<td>N=43 n (%)</td>
</tr>
<tr>
<td>Overall response</td>
<td>5 (20.8) 3CR + 2PR</td>
<td>5 (11.6)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (20.8)</td>
<td>7 (16.3)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>14 (58.3)</td>
<td>31 (72.1)</td>
</tr>
<tr>
<td>Clinical Benefit Rate (CR, PR, and SD at 8 wks)</td>
<td>10 (41.7)</td>
<td>12 (27.9)</td>
</tr>
</tbody>
</table>

1 Includes MRI by independent radiology review and clinical data
2 Higher doses (cohorts 4-7a) and meet P 2/3 entry criteria of 1st and 2nd recurrence, no prior Avastin in rHGG, tumor not > 5cm
Data cutoff date September 1st 2016

% of activated CD8 T cells increases over time in “responder” patients from resection study

From ‘cohort 7’ for which blood cells were available for FACS.
Non-responders= 7 Progressive Disease; “Responders “= 1 Complete Response, 5 Stable Disease
All patients clear quantifiable Toca 511 signal

Toca 511 quantitation by qPCR (DNA) or qRT-PCR (RNA) from the blood or plasma of subjects treated with Toca 511 in three Phase I clinical trials

- Transient Toca 511 viral signal found in the blood or plasma of some subjects
- Quantitative Toca 511 viral RNA and DNA signal is cleared by all subjects within first few of Toca FC cycles

Adapted from T.Cloughesy, SNO, Nov. 18, 2016.
Toca 511 integration profiles support its clinical safety and are cell type specific

No evidence for subclonal expansion linked to Toca 511 integration.

The number of total integration events for each sample are color coded by the proportion of sites represented once (grey) and sites represented multiple times (black).

Genes that harbor Toca 511 integration sites encode proteins linked to the site from which samples were taken.

Adapted from D. Hogan, SNO, Nov. 18, 2016.
Conclusions

• Toca 511 & 5-FC leads to elevated 5-FU levels locally in tumor
• These 5-FU levels activate durable T-cell mediated immune responses pre-clinically
• Three Phase 1 studies of Toca 511 & Toca FC (126 patients) with rHGG indicate:
  – Treatment was well tolerated – limited Grade ≥ 3 drug-related toxicities
  – Any Toca 511 in the blood is rapidly cleared
  – Prolonged survival relative to historical benchmarks
  – No evidence of clonal expansion in blood or tumor
Conclusions Continued

• In a subset (n=24) that mirrors Phase 2/3 study population
  – All responses (3 CRs and 2 PRs) are ongoing (median duration of 26.7 months)
  – Responses in tumors without elevated neo-Ag load
  – IDH1 mutants appear to be over-represented but also responses (CR) in non-mutated tumors
  – Objective response rate of 21%, clinical benefit rate of 42%
  – Responses start 6-19 months after Toca 511, consistent with an immunologic mechanism
  – Initial clinical T cell analyses show correlation of response and activated CD8 T cell levels

Findings support ongoing Phase 2/3 randomized study in patients with rHGG
Potential Registrational Phase 2/3 Study

Toca 5 Trial - Primary Endpoint: Overall Survival
Phase 2, N=170, 1:1 randomization (Full enrollment reached in February 2017)

Stratify by IDH1 mutation status
KPS (70-80 vs. 90-100) and region

Surgery And Randomization

Toca 511* — Toca FC**

Chemotherapy** (lomustine or temozolomide) or bevacizumab

Eligibility
• GBM or AA
• First and 2nd recurrence
• Tumor ≤ 5cm

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

ADVOCACY FROM CANCER CENTERS
Thank you to all of the patients and families who have supported our work.

Financial support also provided by: