Treatment of Recurrent High Grade Glioma Patients with the Retroviral Replicating Vector Toca 511 & Toca FC Resulted in Durable Responses and Survival Lasting 3 Years or Longer: Immune Mechanism and Molecular Analyses of Tumors

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Executive VP R&D
Tocagen Inc.

ASGCT Chicago - May 17 2018
Outline

- Phase 1 data from patients with recurrent high grade glioma
- Preclinical mechanism of action
- Clinical immune measurements & correlation with responses
- Molecular analyses of tumors and blood
- Phase 3 trial in recurrent high grade glioma (rHGG) enrolling
Toca 511 (vocimagene amiretrorepvec)

Retroviral replicating vector (RRV): encodes prodrug activator enzyme, selectively infects and spreads in tumor tissue, high local levels of 5-FU, cell lysis & anti-tumor immune activation, after prodrug administration

Tumor selectivity and replication in cancers cells is driven by:

- Defects in the innate immune system of cancer cells
- Virus may abortively infect 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

5-FU has a very short half-life with direct cell killing localized to cancer microenvironment
Toca 511 selectively infects and spreads in tumors in multiple animal models

Intracranial Tu2449 brain tumor model
Intratumoral RRV injection

Liver CT 26-luc metastases model;
Tail vein, IV RRV administration

Images of same liver in colorectal cancer metastases model
after IV delivery.

RRV-GFP = retroviral replicating vector expressing green fluorescent protein
High local levels of 5-FU after prodrug administration

**Reversed 5-FU from blood to tumor**

- Toca 511 & 5-FC generates 100 fold IC 50 level of 5-FU in the tumor
- Toca 511 and 5-FC does not generate clinically relevant 5-FU in the blood
- 5-FU produced in tumor microenvironment has a very short half-life in blood

<table>
<thead>
<tr>
<th>Setting</th>
<th>Treatment</th>
<th>5-FU (µg/g)</th>
<th>Plasma 5-FU (µg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat F98 glioma¹</td>
<td>Toca 511 &amp; 5-FC</td>
<td>69</td>
<td>0.4</td>
</tr>
<tr>
<td>Human CRC²</td>
<td>IV 5-FU</td>
<td>0.1-2.8</td>
<td>52</td>
</tr>
</tbody>
</table>

¹ Data on file
Typical Clinical Course of High Grade Glioma (HGG)

Development in HGG: A Deadly and Aggressive Disease

- Newly diagnosed GBM
  - Surgery, radiation, Temodar SOC
  - Brain tumor by MRI
  - Hedgehog pathway inhibitors
  - New clinical trials
  - Median survival: 8 months

- Recurrent GBM or AA (rHGG)
  - Bevacizumab, lomustine, carmustine wafer
  - NCCN guidelines recommend consideration of clinical trials
  - Hospice
  - ~ 8 months median survival

HGG includes glioblastoma (GBM) and anaplastic astrocytoma (AA)

Limited treatment options
No evidence of clonal expansion or preferential integration near genes linked to cancer initiation
Three phase 1 ascending dose trials* evaluating delivery approaches in recurrent high grade glioma (rHGG) (n=127)

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

NCT01470794 (n = 56)

**Intratumoral**
Direct injection into tumor

NCT01156584 (n = 54)

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

NCT01985256 (n = 17)

*All three trials finished enrollment
### Adverse Events Related to Toca 511 and Toca FC

*Data Pooled Across Three Phase 1 Studies, treatment appears to be well tolerated*

#### Low incidence of Grade 3/4 treatment-related AEs

<table>
<thead>
<tr>
<th>Treatment-Related AEs</th>
<th>Toca 511 &amp; Toca FC n = 127</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
</tr>
<tr>
<td>Any treatment-related event</td>
<td>n (%)</td>
</tr>
<tr>
<td>Treatment-related event ≥5% patients</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>38 (29.9)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>18 (14.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (11.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (7.1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (5.5)</td>
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#### Low incidence of treatment-related SAEs

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<tr>
<td>Any treatment-related event</td>
<td>n (%)</td>
</tr>
<tr>
<td>Treatment-related event ≥1% patients</td>
<td></td>
</tr>
<tr>
<td>Vasogenic cerebral oedema¹</td>
<td>2 (1.6)</td>
</tr>
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¹ Both SAEs were Grade 3; no Grade 4 SAE

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<th>AE leading to death</th>
<th>Toca 511 &amp; Toca FC n = 127</th>
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<tr>
<td>Any AE leading to death</td>
<td>n (%)</td>
</tr>
<tr>
<td>Brain herniation</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Intracranial tumor hemorrhage</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1 (&lt;1)</td>
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Data cutoff 04Jan2018; excludes data from continuation study.
PCR analyses of tissues from a patient autopsy confirms tumor selectivity in humans
Overall survival comparable in both surgical and non-surgical settings

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<th>Resection Tg 511-11-01 (n = 23)*</th>
<th>Intratumoral Tg 511-08-01 (n = 24)†</th>
<th>Intravenous Tg 511-13-01 (n = 17)</th>
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</thead>
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<tr>
<td>mOS, months</td>
<td>14.4 (11.3, 28.1)</td>
<td>13.8 (7.1, 22.2)</td>
<td>13.6 (5.8, 19.7)</td>
</tr>
</tbody>
</table>

*Patients at 1\textsuperscript{st}/2\textsuperscript{nd} recurrence with no prior Avastin, tumor ≤ 5 cm, in high-dose cohorts.
†Patients receiving Toca 511 via biopsy needle.

Preliminary, unaudited data – cutoff Dec 2017 for Tg511-11-01, May 2016 for Tg511-08-01, Apr 2017 for Tg511-13-01
Three phase 1 ascending dose trials evaluating delivery approaches in recurrent high grade glioma (rHGG) (n=127)

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<th>Method</th>
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*All three trials finished enrollment
Phase 1 Resection Study: Best response and 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)

- mOS Toca 511 & Toca FC = 14.4 months
- Responses occurred gradually over time ~ 6-19 months, consistent with immunologic response
- All Responders alive 38.0+ to 57.5+ months, so far
- CRs received no additional brain cancer treatment after entering trial
- Each CR occurred in a different clinical site and all are confirmed
- Median duration of response is 37.4+ months

Data as of 20Dec2017

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Complete Response in a Patient with Progressive GBM, IDH1 wt

Toca FC cycles (1 week per 6 weeks)

PR and CR by independent Radiology Review, Macdonald criteria.
Preclinical Mechanism of Action
Toca 511 and 5-FC alter immune profile in the tumor microenvironment true in intracranial, subcutaneous, and liver metastases models

Systemic immune cells spared effects of 5-FU

Immune-suppressive myeloid cells (MDSCs, TAMs, Monocytes)

T cells (CD4, CD8)

T-regs not significantly impacted

Tumor Burden

Placebo Control Baseline

Day 0  Day 3  Day 6  Day 9  Day 14
Clinical Immune Measurements & Correlation with Clinical Responses
Upper barplot shows the total number of high confidence mutations called by MUSE from exome sequencing data of patient tumors before treatment with Toca 511 and Toca FC; OS in months is shown in the lower barplot.
Longitudinal Patient Cytokine Measurements in Patient Sera

• **Goals**
  – Demonstrate immune signaling in responders vs non-responders
  – Find shorter-term blood marker of response than survival
    • to facilitate drug development and allow shorter/smaller trials

• **Methods**
  – Serum from 25 patients sent for multiplex ELISA
    • Up to 6 samples from different time points for each patient (6 responders, 19 SD or PD)
    • Total of 87 serum samples were assessed
    • Each serum sample had 40 different inflammatory cytokines measured
Cytokines putatively associated with patient outcomes Identified by multivariate analysis

**Survival**

- **E-Selectin Maximum:**
  - Above Median
  - Below Median
  - Crude p-value = 0.34
  - Adjusted p-value = 0.45

- **MIP1 Beta Maximum:**
  - Above Median
  - Below Median
  - Crude p-value = 0.16
  - Adjusted p-value = 0.013

(Wald test p-values +/- age and gender adjustment displayed)
Survival-associated cytokine principal components (scores) Identified by multivariate analysis

Component #8 Maximum: Above Median vs Below Median
- Crude p-value = 0.069
- Adjusted p-value = 0.042

Component #12 Minimum: Above Median vs Below Median
- Crude p-value = 0.037
- Adjusted p-value = 0.024

(p-values from Wald test, adjustment for Age and Gender)
Clonality and Tumor-Infiltrating T Lymphocytes Fraction in the Tumor- Pretreatment

- Responders have significantly higher Tumor-Infiltrating T Lymphocytes (TITL) fractions than non-responders
- Responders also have a trend towards higher TITL clonality than non-responders (not significant)

Wilcoxon Rank Sum Test

p = 0.351

p = 0.023
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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

Walbert et al. Society of Neuro-Oncology Conference, 2017
Toca 5 Pivotal Phase 3 Trial Ongoing

Primary Endpoint: Overall Survival
Secondary Endpoints Include Durable Response Rate

Eligibility

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

Surgery and Randomization
N=380

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

Toca 511*

Toca FC**

Chemotherapy**
(lomustine or temozolomide) or bevacizumab

1:1

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

ClinicalTrials.gov Identifier: NCT02414165

Biomarker monitoring includes blood (lymphocytes, immune activation markers, cytokines) and tumor (TILS and immune-suppressive myeloid cells)
Conclusions

- Phase 1 trials showed overall survival comparable in both surgical and non-surgical settings
  - Treatment was well tolerated – limited Grade ≥ 3 drug-related toxicities in three phase 1 studies (127 patients)
  - No evidence of clonal expansion in vector-infected cells in tumors or blood
  - IV Study: Vector deposition in tumor (same observation in liver metastases with solid tumors)
  - Resection Study: Strong linkage between durable response (> 6 months) and survival
  - Immunological correlates to responses observed in tumor and blood
  - Tumor selectivity seen in animals is maintained in human patient
- Toca 511 & 5-FC activates durable T-cell mediated immune responses pre-clinically
  - CD4 and CD8 T cell dependent, with local myeloid cell depletion
- Tumor selectivity seen in animals is maintained in human patient
- Phase 3 trial in rHGG enrolling – plan to complete enrollment by end-2018
- Planning to expand in newly dx HGG and initiate new studies in other solid tumors
Thanks to all the patients, their families and caregivers who have supported this work and to the Clinical Investigators for the Phase 1 trials.

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