A PHASE I CLINICAL TRIAL OF REGULATED INTERLEUKIN-12 IMMUNOGENE THERAPY FOR RECURRENT GLIOBLASTOMA

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Francois Lebel, Ziopharm Oncology
Disclosure

- Consultant for Stemgen, Merck, Alcyone Biosciences, NanoTX (not relevant to topic)
- Consultant for Tocagen, DNAtrix, Ziopharm (relevant)
Biological properties of IL-12: “Master Regulator”

Activated APC

IL-12 → IFN-γ

IL-12

IL-12

IFN-γ

IFN-γ

CD8⁺ Tc

Expression of IP-10 and MIG

Antiangiogenic effect

Reprogramming myeloid-derived suppressor cells

NK

Cytotoxic effect

Repertoire of IgG

CD4⁺ Th0

CD4⁺ Th1

Th1-type cytokines

Cancer cells

Adenovirus Serotype 5 NR

Witold Lasek et al, 2014
Control using the RheoSwitch Therapeutic System® (RTS®)

Intratumoral injection of Ad-RTS-hIL-12

Veledimex taken by mouth

IL-12 production calls in cellular immune response

Cellular immune response shows durability beyond initial IL-12 signaling
ATI001-102: Phase 1 Study of IL-12 Gene Therapy in Recurrent or Progressive Glioblastoma/Grade III Malignant Glioma

Group 1

Cohort 1: 20mg V + Ad $2 \times 10^{11}$ vp
Cohort 2: 40mg V + Ad $2 \times 10^{11}$ vp
Cohort 3: 30mg V + Ad $2 \times 10^{11}$ vp
Expansion Cohort: 20mg V + Ad $2 \times 10^{11}$ vp

Clinicaltrials.gov: NCT02026271
# ATI001-102: Patient Characteristics

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Ad-RTS-hIL-12 (2 x 10^{11} vp)</th>
<th>Total (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg (n=15)</td>
<td>30 mg (n=4)</td>
</tr>
<tr>
<td>Age in years: Mean (Min, Max)</td>
<td>46 (26, 68)</td>
<td>60 (43, 75)</td>
</tr>
<tr>
<td>Gender Male : Female</td>
<td>10 : 5</td>
<td>2 : 2</td>
</tr>
<tr>
<td>Recurrence (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>2nd</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>3rd or more</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Prior Lines of Treatment (mean)</td>
<td>2.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Grade at Study Entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HGG Grade III Glioblastoma</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>KPS at Screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 90</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>≥ 70 and &lt; 90</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Total steroid use in mg Day 0: Median (Min, Max)</td>
<td>4 (0, 10)</td>
<td>7 (0, 14)</td>
</tr>
<tr>
<td>Total steroid use in mg Days 1-3: Median (Min, Max)</td>
<td>18 (0, 44)</td>
<td>36 (0, 44)</td>
</tr>
<tr>
<td>Total steroid use in mg Days 0-14: Median (Min, Max)</td>
<td>48 (0, 140)</td>
<td>106 (0, 136)</td>
</tr>
<tr>
<td>Veledimex dosing compliance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean days of V dosing</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>% Veledimex Dosing Compliance</td>
<td>84%</td>
<td>63%</td>
</tr>
<tr>
<td>Serum cytokines (Day 3-7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak IL-12 levels</td>
<td>24±7</td>
<td>56±36</td>
</tr>
<tr>
<td>Peak IFN-γ levels</td>
<td>57±27</td>
<td>57±47</td>
</tr>
</tbody>
</table>
Veledimex Crosses the Blood Brain Barrier with a Corresponding Serum Cytokine Response

**Increase**
- dose of oral ligand

**Controls**
- transcription

**Proportional output and effects**

**Veledimex Peak Plasma PK**
- Cmax

**Veledimex Tumor Level**
- At Craniotomy

Crosses the blood-brain-barrier (BBB)

**Serum**

- IL-12
- IFNγ

20 mg 30 mg 40 mg
ATI001-102: 20 mg mOS Maintained

**February 2017**

<table>
<thead>
<tr>
<th>Median OS (m)</th>
<th>6- mos</th>
<th>9- mos</th>
<th>12- mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5</td>
<td>80</td>
<td>68</td>
<td>57</td>
</tr>
</tbody>
</table>

**June 2017**

<table>
<thead>
<tr>
<th>Median OS (m)</th>
<th>6- mos</th>
<th>9- mos</th>
<th>12- mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5</td>
<td>72</td>
<td>63</td>
<td>53</td>
</tr>
</tbody>
</table>
Dexamethasone Impact on Survival in the 20 mg Cohort

<table>
<thead>
<tr>
<th>Dexamethasone Use (Days 0-14)</th>
<th>Alive</th>
<th>Deceased</th>
<th>mOS</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10 mg</td>
<td>4</td>
<td>0</td>
<td>Not reached</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>11-100 mg</td>
<td>2</td>
<td>5</td>
<td>12.5</td>
<td>3.3</td>
<td>Not reached</td>
</tr>
<tr>
<td>≥100 mg</td>
<td>0</td>
<td>4</td>
<td>8.0</td>
<td>1.8</td>
<td>12.7</td>
</tr>
</tbody>
</table>

Survival probability vs. Time in Months from Dosing

- ≤10 mg
- >10 and ≤100 mg
- >100 mg
Peripheral Blood CD8+/FOXP3 Ratio at 14-28 days after Vector Injection Suggests Correlation with Survival

Centrally processed samples, N=11

Change in % of cytotoxic T cell to T reg ratio from baseline

Alive
deceased

Centrally processed samples, N=11
Subject 037 - MRI Showing Progression (PD) but biopsy shows Pseudo-progression (PSP)

Baseline | Week 2 | Week 4 | Week 24
---|---|---|---
Occipital Lobe | ![MRI Occipital Lobe Baseline](image) | ![MRI Occipital Lobe Week 2](image) | ![MRI Occipital Lobe Week 4](image) | ![MRI Occipital Lobe Week 24](image)
Parietal Lobe | ![MRI Parietal Lobe Baseline](image) | ![MRI Parietal Lobe Week 2](image) | ![MRI Parietal Lobe Week 4](image) | ![MRI Parietal Lobe Week 24](image)
Interim Conclusion on Phase 1 Study for Recurrent GBM

Action

• Tight transcriptional control of the RTS® gene switch by veledimex regulates IL-12 protein expression and downstream IFN-g in a dose-related manner

• There is a strong correlation between veledimex dose, BBB penetration, IL-12 and IFN-g production

Safety

• Related AEs were tolerable, predictable, and rapidly reversible upon discontinuing veledimex

• Severity and frequency of CRS correlated with veledimex dose, serum IL-12 and IFN-g levels, and was always reversible upon holding veledimex

• Neurologic adverse events were relatively mild and transient. There were no drug-related deaths.

Efficacy

• Survival at 20 mg of veledimex is maintained at 12.5 months with a mean follow-up time of 9.2 months and continues to compare favorably to historical controls

• Survival appears to correlate with cellular immune modulation with documented PsP rather than PD in 3/3 biopsied patients

• Steroid use during first 15 days suggests a marked deleterious effect on survival, presumably because of interference with immune activation