Phase 2 Study of VB-111, an Anti-Cancer Gene Therapy, as Monotherapy Followed by Combination of VB-111 with Bevacizumab, in Patients with Recurrent Glioblastoma

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Trial is sponsored by VBL Therapeutics
VB-111 is a Novel, First-in-Class Anti-Cancer Gene Therapy

- First-in-class, novel, targeted anti-angiogenic gene-therapy agent with applicability for multiple solid tumor indications
  - Mechanism:
    - Broad anti-angiogenic activity - leads to tumor starvation
    - Effective in combination therapy
    - Suggested immune response
  - Efficacy signal demonstrated in 3 tumor-specific Phase 2 trials
  - Safe and Convenient:
    - Simple IV infusion, once every 2 months
    - Safe and well tolerated in over 170 cancer patients
  - Regulatory Incentives:
    - SPA
    - Fast Track
    - Approved Orphan Drug Status in GBM (US and Europe)
VB-111: Novel, Targeted Anti-Angiogenic Therapy

1. Viral vector is internalized into endothelial cells in angiogenic blood vessels.

2. PPE-1-3x promoter leads to expression of Fas-TNFR-1 receptor on the surface of angiogenic endothelial cells.

3. Cell apoptosis is induced when circulating TNF-α interacts with the Fas-TNFR-1 receptor.

4. Tumor Starvation

The tumor activates the VB-111 drug by secreting TNFα and thereby loses its ability to build new blood vessels, which are needed for its further growth.
**Primary Endpoint:** Overall Survival

**Secondary Endpoint:** PFS, response rate (RANO Criteria)

62 patients were enrolled in 4 medical centers: CTRC (TX), DFCI (MA), Duke (NC), TASMC (Israel).
Phase 2 Results: Safety

- VB-111 was safe and well tolerated in over 170 cancer patients.

- In 62 patients with rGBM -
  - Most frequent toxicity was self-limited fever, starting several hours post therapy and usually resolving by 24 hours and controlled with anti-pyretics
  - There were 22 AEs classified as grade ≥ 3, of which 7 were considered possibly related to VB-111 including asthenia, pyrexia, brain edema, depressed consciousness, pulmonary embolism - PE (in a patient with PE prior to study) and hypertension (only when combined with Avastin)
  - Safety results were reviewed repeatedly (x5) by the trial DSMB, as well as by FDA, without safety concerns
### Results: Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Continuous Exposure Cohort</th>
<th>Limited Exposure Cohort</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>60 (19-73)</td>
<td>57 (27-76)</td>
<td>0.63</td>
</tr>
<tr>
<td>KPS (median)</td>
<td>80 (60-100)</td>
<td>90 (60-100)</td>
<td>0.36</td>
</tr>
<tr>
<td># prior lines of therapy (mean)</td>
<td>1.8</td>
<td>1.4</td>
<td>0.08</td>
</tr>
<tr>
<td># of VB-111 doses (median)</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Time to 1&lt;sup&gt;st&lt;/sup&gt; progression on VB-111</td>
<td>2 months</td>
<td>2 months</td>
<td></td>
</tr>
<tr>
<td>Time to 2&lt;sup&gt;nd&lt;/sup&gt; progression on VB-111+Avastin™</td>
<td>4 months</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
Phase 2 Open-Label Multicenter Study of VB-111 in Patients with rGBM: Time to Progression & Overall Survival

Limited Exposure Cohort (n=22)

ORR 9% (2/22)
Median # of VB-111 doses = 1
Average # of VB-111 doses = 2.2
Phase 2 Open-Label Multicenter Study of VB-111 in Patients with rGBM: Time to Progression & Overall Survival

Continuous Exposure Cohort (n=24)

ORR 29% (7/24)
Median # of VB-111 doses = 4
Average # of VB-111 doses = 4.6
Partial Responses on Multiple Doses of VB-111

Patient 1

Description
- 50 year old white male (Pt 62-011)
- Diagnosed with GBM at November 2010
- Underwent surgery (1 partial resection) and received radiotherapy and chemotherapy (temodar)

Treatment timeline

- Recurrence
- Biopsy
- 3x10^12 VB-111
- Partial Response
- Compassionate 1x10^13
- Expired 360 days from initial dose (August 2012)

Patient 2

Description
- 52 year old white male (Pt 62-019)
- Diagnosed with GBM at January 2012
- Underwent surgery, received radiotherapy and chemotherapy (temodar)

Treatment timeline

- GBM Diagnosis
- V8-111 1x10^13
- V8-111 1x10^13
- V8-111 1x10^13
- V8-111 1x10^13
- V8-111 1x10^13
- V8-111 1x10^13
- V8-111 1x10^13
- V8-111 + Avastin™
- Recurrence
- Partial response
- PD

PD = progression of disease
Complete Response on Multi-Dose Treatment with VB-111

Description

- 69 year old white male (Pt 62-032) diagnosed with GBM
- Had a recurrence at July 2013, after getting triple therapy (resection, radiotherapy and temodar) at diagnosis
- Had a second, complete resection, but five months later had a 2nd recurrence
- At that point started receiving VB-111

Treatment timeline

First recurrence & 2nd Resection

2nd recurrence

Partial Response Nov14-Mar15

Complete Response Mar15- ongoing

Still actively receiving treatment with CR!
VB-111-122 Phase 2 rGBM Waterfall: RANO best response

Limited Exposure Cohort

Continuous Exposure Cohort
VB-111 in rGBM: Continuous Vs. Limited Exposure Overall Survival

Median OS: 15 Vs. 8 months
VB-111 Continuous Exposure (n=24) Vs. Limited Exposure (n=22)

\[ p=0.048 \]
### Baseline Characteristics in VB-111 Continuous Exposure Cohort Vs. Historical Control Avastin™ Arm in BELOB Study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VB-111 Continuous Exposure Cohort (n=24)</th>
<th>BELOB Avastin™ Arm (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median, range)</strong></td>
<td>60 (19-73)</td>
<td>58 (37-77)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male (%)</td>
<td>54</td>
<td>64</td>
</tr>
<tr>
<td><strong>Prior Lines of therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>87.5%</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>12.5%</td>
<td>0</td>
</tr>
<tr>
<td><strong>WHO performance status &gt; 0 (%)</strong></td>
<td>58</td>
<td>74</td>
</tr>
<tr>
<td><strong>Diameter of max enhancing tumor (mm)</strong></td>
<td>33 (11-62)</td>
<td>35 (12-88)</td>
</tr>
<tr>
<td><strong>Days since last radiotherapy</strong></td>
<td>338 (73-1707)</td>
<td>254 (101-2087)</td>
</tr>
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</table>
**VB-111 Continuous Exposure Cohort Vs. Historical Control Avastin™ Arm in BELOB Study**

Median OS: 15 vs. 8 months

VB-111 Continuous Exposure (n=24) Vs. Avastin™ Arm (BELOB) (n=50)

\[ p = 0.005 \]
Median OS: 15 Vs. 8 Vs. 8 months
VB-111 Continuous Exposure (n=24) Vs. Avastin™ Arm (BELOB) (n=50)  \( p=0.005 \)
VB-111 Continuous Exposure (n=24) Vs. Limited Exposure (n=22) \( p=0.048 \)
All patients: Fever Vs No Fever Post Dosing of VB-111
Overall Survival

Median OS: 16 Vs. 8.5 months
Fever (n=25) Vs. No Fever (n=21)

\[ p = 0.03 \]
Phase 1/2 Trial in rGBM: Summary and Conclusions

- **VB-111** is a first-in-class, novel, targeted anti-angiogenic gene-therapy agent:
  - With applicability for multiple solid tumor indications
  - Broad anti-angiogenic activity - leading to tumor starvation

- **VB-111** was found to be safe and well-tolerated in patients with recurrent GBM
  - Both as monotherapy and in combination with Avastin™

- **Advantage to VB-111 Continuous Exposure:**
  - Comparable baseline risk factors & time to progression when compared to treatment with Limited Exposure
  - Improved OS: **15 Vs. 8 months** (p=0.048)
  - Favorable OS Vs. BELOB Avastin™ monotherapy arm: **15 Vs. 8 months** (p=0.005)

- **Intriguing fever response - suggests an immuno-therapeutic effect**
VB-111 Phase 3 Pivotal Study in rGBM: Study Design

- Event-driven trial
- 40-60 sites
- FPI Achieved AUG2015
- CRO: PPD

Primary endpoint: Overall Survival

VB-111 $1 \times 10^{13}$ VPs Q2M + BEV 10mg/kg Q2W (n=126)

Until Significant Progression

N=252

Now Recruiting!