Ofranergene Obadenovec (VB-111) in Platinum-Resistant Ovarian Cancer: Favorable Response Rates in a Phase I/II Study are Associated with an Immunotherapeutic Effect

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BACKGROUND

VB-111 is a Novel, First-in-class Anti-cancer Gene Therapy

- VB-111 (ovarian abedonevac) is a targeted anti-cancer viral gene therapy, based on a non-replicating non-integrating Adenovirus 5 vector that contains a transgene targeting angiogenic blood vessels.
- VB-111 has a dual mechanism of action:
  - Apoptosis of angiogenic endothelium and vascular disruption, leading to tumor starvation
  - Induction of an anti-tumor directed immune response
- Administered by IV infusion once every 8 weeks
- Well tolerated in over 300 cancer patients
- The safety and tolerability of combination of VB-111 and weekly paclitaxel was evaluated in a phase I/II study in patients with recurrent or progressive platinum-resistant ovarian cancer (AURELIA trial*).

Ovarian Cancer

- Ovarian cancer is the leading cause of death from gynecologic cancers; Disease is difficult to detect and often diagnosed only when advanced.
- Most patients ultimately develop platinum-resistant resistance.
- Anti-angiogenic therapy has been shown to be efficacious in ovarian cancer. Bevacizumab VB-111 has a dual mechanism of action: angiogenic blood vessels
- Well tolerated in over 300 cancer patients
- Safety and tolerability of combination of VB-111 and weekly paclitaxel
- The safety and tolerability of combination of VB-111 and weekly paclitaxel was evaluated in a phase I/II study in patients with recurrent or progressive platinum-resistant ovarian cancer (AURELIA trial*).

STUDY DESIGN

- Study NCCT01711790 was a prospective, open-label dose escalating phase I/II study assessing combination treatment of VB-111 QW and weekly paclitaxel.
- Population: Patients with recurrent platinum-resistant ovarian cancer
- Treatment: Patients with recurrent platinum-resistant ovarian cancer
- Treatment:
  - Phase 1: escalating doses of intravenous VB-111 and paclitaxel to identify dose limiting toxicities
  - Phase 2: therapeutic doses of VB-111 x10× Viral Particles and paclitaxel (80mg/m2) until disease progression.
- Assessments: Safety, OS, PFS, tumor response (CA-125 and RECIST 1.1) and histopathology.
- Study objectives:
  - Safety and tolerability of combination of VB-111 and weekly paclitaxel
  - Exploratory efficacy (RECIST 1.1 response, CA-125 response, PFS and OS) in an expanded cohort of the optimally tolerated dose.

RESULTS

Table 1 - Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sub-Therapeutic Dose (N=8)</th>
<th>Therapeutic Dose (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.3 (range: 55-77)</td>
<td>64.5 (range: 55-77)</td>
</tr>
<tr>
<td>Race: White</td>
<td>4 (100)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Prior Anti-Angiogenic treatment: Yes</td>
<td>3 (75.0)</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>IIIC</td>
<td>1 (25.0)</td>
<td>11 (64.7)</td>
</tr>
<tr>
<td>Platinum Free Interval</td>
<td>498 vs. 172.5 days</td>
<td>p=0.03</td>
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<td>Papillary serous</td>
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| Safety

- VB-111 was well tolerated other than fever and the anticipated side-effects of an anti-angiogenic.
- Toxicity on the combination was similar to the expected with anti-angiogemics and taxanes in this patient population.
- One toxicity causing treatment discontinuation was reported: an anaphylactic reaction confirmed a re-challenge to be related to placebo.
- 9 patients (43%) reported AEs grade >=3
- Most frequent AE included fatigue (53%), nausea (52%), fever (48%), anemia (38%), diarrhea (37%), headache (29%)
- Most common of VB-111 related AEs were transamidase fever flu like symptoms.

SUMMARY AND CONCLUSIONS

- Safety: VB-111 in combination with paclitaxel, was safe and well tolerated.
- Efficacy signal was seen in patients treated with the therapeutic dose despite unfavorable prognostic characteristics:
  - Safety: No adverse events (AE) in 59% of evaluable patients
  - Survival: significant increase in OS at therapeutic dos vs. sub-therapeutic dose 498 vs. 172.5 days, p=0.03
- Biomarkers: A trend for improved survival seen in patients with post treatment fever and in patients with a 50% decrease in CA-125
- Immunotherapeutic effect: post treatment tumor infiltrating CD8+ T-cells and anti-cancer protein concluded tumor transformation from immunologically "cold" to immunologically "hot", possibly contributing to the favorable clinical outcomes
- Encouraging results are the basis for further exploration in the randomized controlled, pivotal OVLH study, NCCT01711790 that is currently recruiting patients with platinum-resistant ovarian cancer.

GCIG CA-125 Response Rate of 58% Doubled Compared to AURELIA Historical Data

- 58.3% (7/12) of evaluable patients treated with the therapeutic dose had a GCIG CA-125 response (defined as a decrease CA-125 confirmed over 4 weeks), compared with 31.8% with bevacizumab and chemotherapy.
- Safety: No chemotherapy related adverse events occurred in the AURELIA trial.

Figure 17.7.1

Durable Disease Control: CA-125 Change

Figure 17.7.2

Durable Disease Control: Tumor Burden Change

Figure 17.7.3

Subgroup Analysis

ITT Population

Figure 17.7.4

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Percent change from baseline is calculated as \[(\text{visit value } - \text{baseline value}) / \text{baseline value}\] * 100.

Censored patients are those who did not die until cutoff date (3 MAY 2017).