Utilizing an Interim Futility Analysis of the OVAL study (VB-111-701/GOG 3018) for Potential Reduction of Risk: A Phase III, Double Blind, Randomized Controlled Trial of Ofranergene obadenovec (VB-111) and Weekly Paclitaxel in Patients with Platinum Resistant Ovarian Cancer

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Abstract

Objective: Report the results from a preplanned interim analysis of a phase III, double blind, randomized controlled study of ofranergene obadenovec (VB-111), a targeted anti-cancer gene therapy, in combination with paclitaxel in patients with platinum resistant ovarian cancer (PROC).

Methods: The OVAL (NCT03398655) study is an on-going study where patients are randomly assigned in a 1:1 ratio to weekly paclitaxel 80 mg/m^2 with VB-111 or placebo. The protocol specifies a pre-planned unblinded futility interim analysis of CA-125 response per GCIG criteria in the first 60 evaluable patients. The futility rule determined for this analysis was that the response rate of VB-111 must be greater than the response rate of placebo by at least 10% in order to continue the study. Coincident with the interim analysis, the blinded CA-125 response rate was estimated as a proportion of the first 60 evaluable patients with per CA-125 response per GCIG criteria. Post-treatment fever is provided as a possible surrogate marker of VB-111 therapy activity.

Results: The median age of the evaluable patients was 62 years (range 41–82); 97% had high-grade serous cancer; 58% had been treated with 3 or more previous lines of therapy, 70% received prior anti-angiogenic treatment, 43% received prior PARP inhibitors. CA-125 response in the VB-111 and weekly paclitaxel treated arm met the pre-specified interim criterion of an absolute advantage of 10% or higher compared to the control. Blinded results show a 53% CA-125 response rate (32/60) with 15% complete response (n=9). Assuming balanced randomization and an absolute advantage of 10% or higher to the VB-111 arm, it may be deducted that the response in the VB-111 treatment arm is 58% or higher. Among patients with post-treatment fever, the CA-125 response rate was 69%.

Conclusions: At the time of the interim analysis, response rate findings are comparable to the responses seen in a similar patient population in the phase I/II study. The independent data and safety monitoring committee (iDSMC) recommended continuing the OVAL trial as planned. No new safety signals were identified.

Introduction

Ovarian cancer is one of the leading causes of gynecologic cancer death affecting approximately 300,000 women per year globally [1]. The current standard of care for newly diagnosed advanced epithelial ovarian cancer (EOC) includes cytoreductive surgery in combination with platinum and taxane-based chemotherapy. Fortunately, the chemosensitivity of EOC at time of presentation is high for the majority of women. While a fraction of women will never recur (15%), most women will recur within 3 years of diagnosis. While many therapies exist to prolong OS, responses decrease with each line of therapy. Once a tumor is classified as resistant to platinum (defined as recurrence within 6 months of therapy), the standard of care regimen of non-platinum chemotherapy and bevacizumab has reasonable response rates. After this, only monotherapy chemotherapy remains with dismal expected benefit. This is an area of high unmet need where VB-111 may have activity.

Ofranergene obadenovec (VB-111)

Ofranergene obadenovec, also known as VB-111, is a viral-based cancer therapy with a dual mechanism of action: antiangiogenesis/vascular disruption and induction of intra-tumoral immune response. VB-111 has three main components (Figure 1): a vector, a tissue and condition-specific promoter, and a functional transgene which encodes the therapeutic protein [2-4]. The vector is a non-replicating adenovirus type 5, which serves as the vehicle for distributing the promoter and transgene throughout the body. The promoter, PPE-1-3X, a proprietary modified murine pre-endothelin 1 promoter, is genetically modified to induce expression of the transgene only in angiogenetic blood vessels. The transgene is a Fas-TNFR1 chimeric pro-apoptotic protein, which is expressed on the surface of cells in which the promoter is activated. In this transgene, the extracellular portion of the TNFR1 cell-death receptor is genetically linked to the intracellular domain of its family-member Fas receptor. The Fas receptor is a highly potent inducer of apoptosis, but its ligand is normally not present in the tumor microenvironment. TNF alpha is abundant in the tumor microenvironment, and when it binds to the extracellular portion, leads to receptor activation and targeted apoptosis of angiogenic endothelial cells that nourish the tumor. The anti-angiogenic

effect of VB-111 is anticipated to trigger tumor starvation and destruction of tumor cells. The subsequent release of cellular debris and tumor neo-antigens that are ingested by antigen presenting cells, further stimulates the anti-tumor immune response.

The efficacy and safety of VB-111 in combination with standard of care weekly paclitaxel were assessed in a phase I/II study (NCT01711970), which was a prospective, open label, dose escalation study in patients with recurrent platinum-resistant ovarian cancer (PROC). Results showed that VB-111 was well tolerated and most commonly associated with mild flu-like symptoms, which is characteristic of a viral vector. Median overall survival (OS) with the therapeutic dose was 16.6 months compared to 5.8 months in the sub-therapeutic dose ($p = 0.028$). The therapeutic dose group showed a CA-125 (GCIG) response rate of 58%, with mean duration of response of 10 months. A trend for improved OS was seen in patients with a CA-125 decrease of at least 50% (808 days vs. 351 days $p=0.067$). Post-treatment tumor specimens demonstrated infiltration of cytotoxic CD8 T-cells in regions of apoptotic cancer cells, which supports the VB-111 immunologic mechanism of action and its ability to make tumors more immunogenic [5]. Following these encouraging results, the OVAL study (NCT03398655) was initiated.

In an effort to preserve patient resources, and reduce the chance of exposing patients to an ineffective therapy, this phase III study included an interim futility analysis based on the GCIG defined CA-125 response rate. It was pre-specified in the protocol that if at the time of the interim analysis, the difference in CA-125 change by GCIG criteria was not at least 10% different in the combination arm than the paclitaxel alone arm, in an effort to appropriately allocate resources, the trial would be discontinued. We believe CA-125 response is an indicator of clinical benefit, providing some preliminary evidence for activity of the experimental therapy. Here we report the results from a pre-planned interim analysis of the OVAL study.

Methods

Study Design

The OVAL study is an international, randomized, double-blind, placebo-controlled, phase III study investigating the efficacy and safety of VB-111. The study is conducted in compliance with local and national regulations in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board (IRB) at each site and conducted in accordance with the Good Clinical Practice (GCP) requirements. All patients provided written informed consent and were made fully aware that they could withdraw from the study at any time without any consequences to future care.

Study Population and Eligibility Criteria

The OVAL study enrolls women with recurrent PROC, including primary peritoneal and fallopian tube cancers. Key eligibility criteria include progression within 180 days from the last platinum-based therapy, measurable disease by RECIST 1.1, and Eastern Cooperative Oncology Group (ECOG) performance score of 0-1. Patients with primary platinum refractory disease are excluded. Up to five previous lines of anti-cancer therapy are permitted; however, patients with more than two prior anti-cancer regimens following the diagnosis of platinum resistant disease are excluded. Patients with a *BRCA* mutation may enroll after disease progression on a PARP inhibitor, or if they are intolerant of, or ineligible for PARP inhibitors. Key exclusion criteria include non-epithelial tumors, low-grade serous tumors, clear cell tumors, mucinous tumors, prior radiotherapy to the pelvis or whole abdomen, history of abdominal fistula or gastrointestinal (GI) perforation, significant vascular disease, proliferative and/or vascular retinopathy, known brain metastases, and inadequate clinical laboratory tests.

Treatment Regimens

The experimental regimen includes intravenous VB-111 ($1x10^{13}$ VPs) every 8 weeks in combination with standard of care weekly paclitaxel ($80mg/m^2$). In a 56-day cycle, VB-111/placebo is infused on

day 1 of every cycle (Q8W) and paclitaxel is infused weekly on days 1, 8, 15, 22, etc. of every cycle. The reference regimen adds placebo every 8 weeks to weekly paclitaxel (Figure 2).

Patients receive treatment until unacceptable treatment-related toxicities or withdrawal of consent. Even in the setting of disease progression (PD) per RECIST 1.1, study therapy may be continued per physician's discretion until progression is confirmed by follow up imaging.

The treatment regimens are randomly assigned in a 1:1 ratio in a stratified block design. Randomization is stratified by the number of prior treatment lines, prior antiangiogenic therapy, and the platinum free interval (PFI).

Clinical Assessments

Tumor assessments by computer tomography (CT) scans are performed at baseline and subsequently every 12 weeks until disease progression, death, or withdrawal of consent. CA-125 testing is performed every 4 weeks. Adverse events, vital signs, physical exams, and lab work are accessed for safety and tolerability during the treatment period and until 7 days after discontinuing study treatment. Adverse events are graded by Common Terminology Criteria for Adverse Events (CTCAE Version 5.0).

Study Objectives

The primary efficacy endpoint is overall survival (OS). Since part of VB-111's mechanism of action includes induction of an anti-tumor immune response, a delay in its effect on OS is expected, as seen with other cancer immunotherapies [6]. The secondary endpoints are progression free survival (PFS), objective response rate (ORR) by RECIST 1.1, and CA-125 response by GCIG criteria. RECIST response is evaluated both locally and by a blinded independent central reading center to assure standardized assessment. CA-125 testing is processed at a central laboratory. A GCIG CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be classified as CA-

125 responders only if they have a pretreatment sample that is at least twice the upper limit of normal, measured within 2 weeks prior to starting treatment.

Exploratory analyses include the quality of life (QoL) questionnaires FACT-O and EORTC QLQ-C30, as well as assessments of tumor samples for histopathology, immune-therapeutic activity, viral transgene expression, genetic analysis, and assessments of serum samples for analysis of antibodies and biomarkers.

Statistical Analysis Plan

A pre-planned interim futility analysis was conducted by the iDSMC after 60 patients had a minimum of 60 days follow-up and were evaluable for CA-125 response (per GCIG criteria). Analysis examined whether there was at least 10% improvement in CA-125 response in favor of the VB-111 treatment arm. This interim analysis was designed as a bridge between the relatively small uncontrolled phase I/II study and the large pivotal randomized controlled trial that followed. This was done to confirm that the CA-125 response following treatment with VB-111 and paclitaxel that was seen in phase I/ II was repeated in a blinded, controlled setting before proceeding to the full scale enrolment of 400 patients. A second interim analysis for safety assessing OS (from randomization) is anticipated after 100 patients have been followed for at least 3 months.

We report a blinded review CA-125 response rate for the first interim analysis cohort. The CA-125 response rate is the binomial proportion of the 60 evaluable patients who met the GCIG CA-125 response criteria. The CA-125 response rate among patients who experienced a fever after treatment with VB-111 is also presented. Post-treatment fever may be an indicator of response to VB-111 therapy.

The study is designed to have 92% power, using a 5% level two-sided test, to detect a 35% reduction in the hazard of death 100 days after enrollment among patients treated in VB-111. At maturity, sample size of 400 patients will be enrolled.

Results

Patient characteristics

Seventy-four patients with platinum-resistant ovarian cancer were enrolled in the study at the time of interim analysis and had received up to 8 doses of VB-111/placebo. Sixty of these patients (81%) were evaluable for a CA-125 response according to GCIG criteria and these patients were included in the interim analysis.

Baseline characteristics are shown in Table 1. High grade serous was the most common histology (n=72, 97%). The most common cancer stage at diagnosis was IIIC (n=44, 60%) followed by stage VI (n=18, 24%). Patients had been treated with a median number of 3 prior therapies. 58% had been treated with 3 or more previous lines of therapy, 70% received prior anti-angiogenic treatment, 43% received prior PARP inhibitors. All the patients progressed after a PFI of less than 180 days and 49% had a PFI of 0-90 days. 15% (n=11) were known to carry a BRCA mutation. Median age at enrollment was 62 years (range 41–82) and 88% of the patients were Caucasian.

CA-125 Response

The results met the pre-defined futility rule of an absolute percentage advantage of 10% or higher in CA-125 GCIG response in the VB-111 treated arm compared to the control arm. The DSMC recommended that the trial will continue.

The blinded results of the combined population show a CA-125 response in 32 of 60 patients (53.3%), including 9 patients (15%) with complete response (Table 2). The iDMC recommended continuing the OVL trial without modification. Detailed results from DSMC review have not been disclosed. In patients with post-treatment fever, the blinded CA-125 response rate was 69%.

Given the 53% cumulative CA-125 response rate in all 60 patients in both arms, and assuming balanced randomization and an absolute advantage of 10% or higher to the VB-111 arm, it may be deducted that the CA-125 response rate in the VB-111 treatment arm is 58% or higher.

Discussion

The OVAL study is an on-going phase III, pivotal, double-blind, randomized controlled trial assessing the safety and efficacy of VB-111 in combination with standard of care paclitaxel in PROC with a primary efficacy endpoint of OS. The aim of the interim analysis was to reduce potential risks to additional patients based on futility. The first interim analysis in the OVAL study follows the encouraging results of an uncontrolled open label phase I/II study in a similar patient population in which treatment of VB-111 with weekly paclitaxel was well tolerated and associated with a CA-125 response rate of 58% and median OS of 16.6 months.

The OVAL interim analysis was reassuring, suggesting that the CA-125 response in patients treated with VB-111 met the pre-specified criterion of an absolute percentage advantage of 10% or higher compared to the control arm.

This conclusion is based on the CA-125 response rate of 69% in women who developed a post-treatment fever, the most common adverse event and reliable indicator of VB-111 treatment. This is 16% higher than the cumulative CA-125 response rate of 53% in all 60 patients including in this phase III study. Moreover, these results are higher than the 58% CA-125 response noted in the phase I/II trial of VB-111 and paclitaxel in a similar patient population. The unblinded results of the interim analysis were only available to the DSMC; therefore, our ability to compare the two arms is limited. Post-treatment fever, which indicates immune activation, appears to be a reliable indicator VB-111 therapy and was seen in 48% of patients treated with VB-111 in the phase I/II study. In contrast, fever with paclitaxel treatment usually only occurs in the setting of a hypersensitivity reaction that occurs within the first 10 minutes.

In addition to similar responses as seen in the phase I/II study, the results of this interim analysis are favorable when considering the AURELIA study results. The AURELIA trial was a phase III open-label randomized study comparing bevacizumab, an anti-angiogenic agent, plus chemotherapy to

chemotherapy alone in platinum-resistant ovarian cancer patients. In the AURELIA study, 31.8% of the patients receiving bevacizumab and chemotherapy had a GCIG CA-125 response. The CA-125 response rates reported for VB-111 and paclitaxel in the phase I/II and interim analysis from OVAL are at least 53% [7]. VB-111 appears to be a promising therapeutic option for patients with platinum-resistant ovarian cancer, a subset of patients with few approved therapeutic options.

VB-111 has been administered to over 300 patients and has been found to be safe and well-tolerated. Given its mechanism of action specifically targeting proliferating endothelial cells within the angiogenic tumor, the surrounding tissue is spared from cell death. This leads to less tissue damage and common side effects associated with many chemotherapeutic agents. While frequent flu-like symptoms are often reported on dosing days as expected by the viral nature of the product, they are tolerable and effectively controlled with anti-pyretic medications.

Conclusions

In summary, this pre-planned interim analysis concludes that the initial GCIG CA-125 response rates for women participating on the OVAL study are reassuring. Using post-treatment fever as an indicator of VB-111 therapy, the response rates in this group of patient is higher than anticipated. The study suggests that the CA-125 response in the VB-111 treated arm met the pre-specified interim criterion of an absolute percentage advantage of 10% or higher compared to the control arm. A CA-125 GCIG response rate of 58% or higher in evaluable patients in the VB-111 treatment arm suggests that the favorable results of the phase I/II study have been successfully repeated in this randomized controlled blinded setting. VB-111 appears to be a promising novel agent in patients with platinum-resistant ovarian cancer, a disease with limited treatment options. Following these encouraging results, recruitment to the pivotal phase III study will continue as planned.

Conflict of Interest Statement **36 months prior to publication

Author Contributions

R. Arend, B. Monk, T. Herzog, K. Moore, R. Shapira-Frommer, J. Ledermann, K. Tewari, A. Secord, T. Minei, L. Freedman, A. Miller, S. Shmueli, M. Lavi, and R. Penson contributed to patient enrollment, study oversight, data interpretation, and manuscript editing. All authors discussed the results, commented on the manuscript versions, and provided critical feedback throughout all aspects of the research.

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Legends

F1: *Dual Mechanism of Action of VB-111*. Three main components of VB-111: (i) a vector, (ii) a tissue- and condition-specific promoter (DNA regulatory sequence) and (iii) a functional transgene which encodes the therapeutic protein. The dual mechanism of action of VB-111 promotes anti-angiogenesis/vascular disruption and induces tumor directed intra-tumor immune response.

F2: *OVAL Study Design*. Patients are randomized on a 1:1 ratio to receive either intravenous VB-111 ($1x10^{13}$ VPs) every 8 weeks in combination with standard of care weekly paclitaxel (80mg/m^2) or placebo every 8 weeks with weekly paclitaxel.

T1: *Patient Baseline Characteristics*

T2: *CA-125 (GCIG) Response (ITT Population)*