

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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HIGHLIGHTS

- VB-111 has a dual mechanism targeting tumor vasculature and inducing anti-tumor immune effects turning “cold” tumors “hot”.
- VB-111 with paclitaxel had a 58% CA-125 response rate that correlated with a survival benefit.
- VB-111 in combination with paclitaxel had a similar OS effect and better CA-125 response than in the AURELIA study.
- VB-111 was safe and well tolerated.

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ABSTRACT

Objective. Report final results of a phase I/II study of VB-111, a targeted anti-cancer gene therapy with a dual mechanism: anti angiogenic/vascular disruption and induction of an anti-tumor directed immune response, in combination with paclitaxel in patients with platinum-resistant ovarian cancer.

Methods. Study NCT01711970 was a prospective, open label, dose escalation study assessing combination treatment of VB-111 and weekly paclitaxel. In the Phase I part of the study, patients were treated with escalating doses of intravenous VB-111 and paclitaxel. In Phase 2, patients were treated with therapeutic doses of VB-111 and paclitaxel 80 mg/m². Assessments included safety, overall survival (OS), progression free survival (PFS), and tumor response (CA-125 and RECIST).

Results. 21 patients with recurrent platinum-resistant ovarian cancer were enrolled. 17/21 received the therapeutic dose. Patients had a median of 3 prior lines of therapy. Half of the subjects were platinum refractory, and half were previously treated with antiangiogenics. No DLTs were observed. VB-111 was well tolerated and associated with mild flu-like symptoms. In the therapeutic dose cohort, a 58% CA-125 GCIG response rate was seen in evaluable patients. The median OS was 16.6 months in patients treated with therapeutic dose compared to 5.8 months in sub-therapeutic dose ($p = 0.028$). Tumor specimens taken after treatment demonstrated tumor infiltrated with cytotoxic CD8 T-cells in regions of apoptotic cancer cells.

Conclusions. Treatment with VB-111 in combination with paclitaxel was safe and well tolerated. Favorable tumor responses and overall survival outcomes were associated with induction of an immunotherapeutic effect.

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1. Introduction

Ovarian cancer is the leading cause of gynecologic cancer death in the United States affecting approximately 22,000 women annually [1]. Risk factors associated with ovarian cancer include advanced age, nulliparity, obesity, and positive family history. The majority of ovarian cancers are diagnosed in advanced stages, largely as there are no reliable

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screening tests and the presenting symptoms (abdominal bloating, constipation, and weight loss) are nonspecific. Unfortunately, later diagnosis correlates with poor prognosis. The mainstay of management for advanced stages of ovarian cancer includes a combination of surgical resection consisting of hysterectomy with bilateral salpingo-oophorectomy, lymphadenectomy and indicated cytoreduction and chemotherapy. First line chemotherapy normally consists of 6 cycles of carboplatin and paclitaxel. Ovarian cancer is highly sensitive to chemotherapy with a 70–80% clinical response to first line platinum and taxane based therapy [2]. Unfortunately, most of the patients who achieve a complete remission with first line platinum-based chemotherapy will ultimately develop recurrent disease, and each subsequent line of therapy is characterized by shorter disease-free intervals. The median progression free survival (PFS) of patients with advanced ovarian cancer is about 18 months, and median survival is approximately 3 years. The worst outcomes are reported for patients with platinum-resistant disease defined as progression within 6 months of the last platinum-containing regimen. These patients have a 15%–20% potential for response to re-treatment and median survival of about 1 year [3].

About 15% of patients have a family history of ovarian cancer, most commonly due to germline mutations of *BRCA1* or *BRCA2*, which are implicated in the repair of double stranded DNA damage. Patients with germline *BRCA* mutations often have distinct characteristics such as increased chemosensitivity to platinum, and improved long-term outcomes [3,4]. In recent years, several advances were made in the treatment of recurrent ovarian cancer with the approval of bevacizumab and poly (ADP-ribose) polymerase (PARP) inhibitors for this indication. Inhibition of PARP can result in cancer cell death, especially in cells with defective DNA repairing mechanisms, such as in patients who hold a *BRCA* mutation. Recently, three PARP inhibitors—olaparib, niraparib and rucaparib—were approved by the FDA in the recurrent setting as maintenance therapy following platinum-based therapy [5–9]. The effect of PARP inhibitors is substantially more prominent in patients who carry a *BRCA* mutation [7].

In patients with platinum-resistant disease, the anti-angiogenic agent bevacizumab to chemotherapy has resulted in significantly improved PFS and response rate; median PFS was 3.4 months with chemotherapy alone versus 6.7 months with bevacizumab-containing therapy, and RECIST objective response rate (ORR) was 11.8% versus 27.3%. However, the addition of bevacizumab did not result in a significant

improvement of OS [10]. Given the limited response to additional therapies, there is an unmet need to make significant improvements in the outcomes of patients with recurrent platinum-resistant ovarian cancer following first line therapy.

Ofranergene obadenovec, also known as VB-111, is a viral-based cancer therapy that has a dual mechanism of action: anti-angiogenesis/vascular disruption and induction of tumor directed intra-tumor immune response, such as seen in viral immune-oncology (Fig. 1). VB-111 has three main components (Fig. 1) (i) a vector, (ii) a tissue- and condition-specific promoter (DNA regulatory sequence) and (iii) a functional transgene which encodes the therapeutic protein [11–13]. 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 angiogenic 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 part of the TNFR1 cell-death receptor is genetically linked to the intracellular domain of its family-member Fas receptor, which is a highly potent inducer of apoptosis but whose ligand is normally not present in the tumor microenvironment. Binding of TNF alpha, which is abundant the tumor microenvironment, to the extracellular portion leads to receptor activation and targeted apoptosis of angiogenic endothelial cells nourishing the tumor.

The immunologic mechanism-of-action of viral-mediated anti-cancer therapies takes advantage of the natural interplay of viruses with the immune system and the ability of viruses to ‘kick-start’ immune reactions [14]. In response to viral infection, cells within the tumor microenvironment express immune-stimulating cytokines attracting immune cells into the tumor. Furthermore, it is anticipated that the anti-angiogenic effect of VB-111 will trigger tumor starvation, destruction of tumor cells and subsequent release of cell debris and tumor neo-antigens that are ingested by antigen presenting cells, further stimulating the anti-tumor immune response. VB-111 specific expression in endothelial angiogenic cells focuses the immune reaction on tumor milieu and prevents systemic immune-mediated damage.

Here we report the results from the Phase I/II trial of VB-111 and paclitaxel for recurrent platinum-resistant ovarian cancer (NCT01711970).

VB-111: Novel, Dual Mechanism for Targeting Solid Tumors

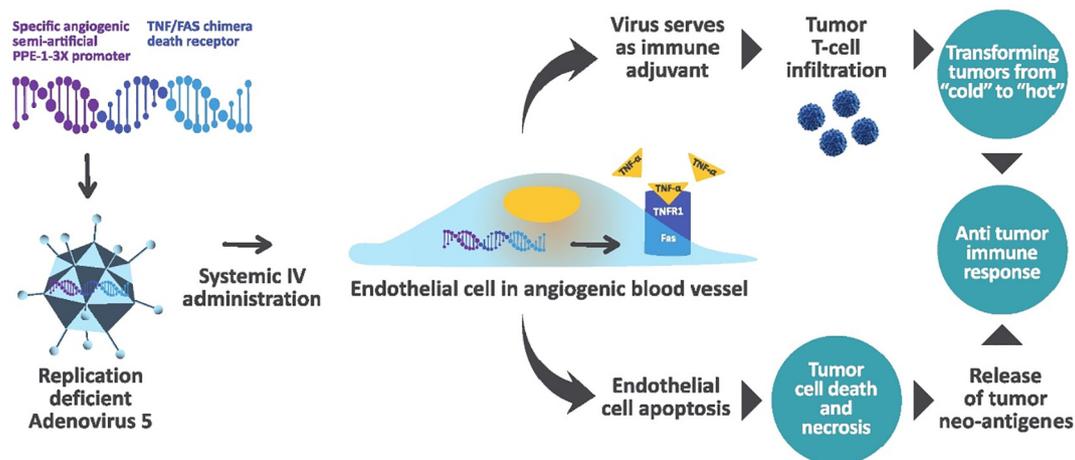


Fig. 1. Three main components of VB-111: (i) a vector, (ii) a tissue- and condition-specific promoter (DNA regulatory sequence) and (iii) a functional transgene which encodes the therapeutic protein. The dual mechanism of action of VB-111 promotes anti-angiogenesis/vascular disruption and induces tumor directed intra-tumor immune response.

Table 1
Patient baseline characteristics.

	Sub-therapeutic dose (N = 4)	Therapeutic dose (N = 17)	All doses (N = 21)
Age, mean (years)	66.3	64.5	64.9
Race: White, n (%)	4 (100)	17 (100)	21 (100)
Histology, n (%)			
Papillary serous	1 (25.0)	8 (47.1)	9 (42.9)
Clear cell	1 (25.0)	1 (5.9)	2 (9.5)
Adenocarcinoma	2 (50.0)	2 (11.8)	4 (19.0)
Carcinosarcoma	0	3 (17.6)	3 (14.3)
Other	0	3 (17.6)	3 (14.3)
Cancer stage at diagnosis, n (%)			
IA/B/C	1 (25.0)	2 (11.8)	3 (14.3)
IIIC	1 (25.0)	11 (64.7)	12 (57.1)
IV	2 (50.0)	4 (23.5)	6 (28.6)
Prior lines of therapy, mean [SD]	2.3 [96]	2.7 [92]	2.6 [92]
Prior anti-angiogenic treatment=Yes, n (%)	3 (75.0)	8 (47.1)	11 (52.4)
Platinum free interval, n (%)			
≥3 (platinum resistant)	3 (75.0)	8 (47.1)	11 (52.4)
<3 (platinum refractory)	1 (25.0)	9 (52.9)	10 (47.6)
ECOG performance status, n (%)			
00 - Fully active	2 (50.0)	8 (47.1)	10 (47.6)
01 - Restricted	2 (50.0)	9 (52.9)	11 (52.4)

2. Patients and methods

2.1. Study design and patient population

This was an open-label, multi-center, Phase I/II study investigating the safety and efficacy of VB-111 in patients with platinum-resistant ovarian cancer. The research objective was to determine if treatment with VB-111, added to weekly paclitaxel, had acceptable toxicity and if it was associated with increased response rates sufficient to warrant further evaluation in a controlled randomized trial. Key eligibility criteria included histologically confirmed epithelial ovarian, fallopian tube, primary peritoneal, gynecologic malignant mixed Müllerian tumors (MMMTs), carcinosarcomas or papillary serous Müllerian tumors. Patients had to have had prior platinum or platinum-based therapy and be platinum-resistant or refractory, defined as progressive disease by imaging or CA-125 within 6 months of completing or while receiving a platinum and taxane based chemotherapy regimen respectively. Patients were required to be ≥18 years old and have measurable or evaluable disease at baseline using RECIST or GCIG CA-125 criteria. An Eastern Cooperative Oncology Group (ECOG) performance of 0–1 was required.

The trial was conducted in compliance with local and national regulations and in accordance with the Declaration of Helsinki. The study

was approved by the Institutional Review Board (IRB) and conducted in accordance with Good Clinical Practice (GCP) requirements at each site. 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.

2.2. Treatment and assessments

In a 28-day cycle, VB-111 was infused on day 1 of every odd cycle (Q8W) and paclitaxel was infused weekly on days 1,8,15, and 22 of every cycle. In phase 1 of the study, patients were enrolled in a 3 + 3 design and received up to 3 escalating dose levels of intravenous VB-111 along with weekly paclitaxel in order to identify any dose limiting toxicities and determine the optimally tolerated combination dose. Once the optimal dose was defined, within subject dose escalation of VB-111 was allowed and the corresponding patients were considered part of the expansion cohort. In phase 2 of the study, the expansion cohort received therapeutic doses of VB-111 (1×10^{13} viral particles (VPs)) and 80 mg/m² paclitaxel. The design was a two-stage optimal design. After 10 patients were enrolled, an interim efficacy analysis was performed and if there were two or more responses, up to 19 additional participants were to be enrolled.

Tumor assessments by computer tomography (CT) were performed at baseline and then every 8 weeks until disease progression, death, or withdrawal. Overall survival and progression free survival were assessed, and tumor response was based on GCIG CA-125 criteria and RECIST 1.1 criteria. Adverse events were evaluated at every visit until 28 days after discontinuation of study treatment and were graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.0).

2.3. Endpoints

The primary endpoints were safety and tolerability of combination VB-111 and paclitaxel and efficacy in the expansion cohort of the optimally tolerated dose. Efficacy was determined by RECIST response, GCIG CA-125 response, defined as a 50% reduction in CA-125, and OS. Secondary endpoints included exploring predictive markers of toxicity and response.

2.4. Immunohistochemistry

Optional tumor biopsies were collected approximately 2 months after the initiation of VB-111 dosing. H&E and Immunohistochemistry (IHC) were performed for intratumoral CD8 and CD4 T cells.

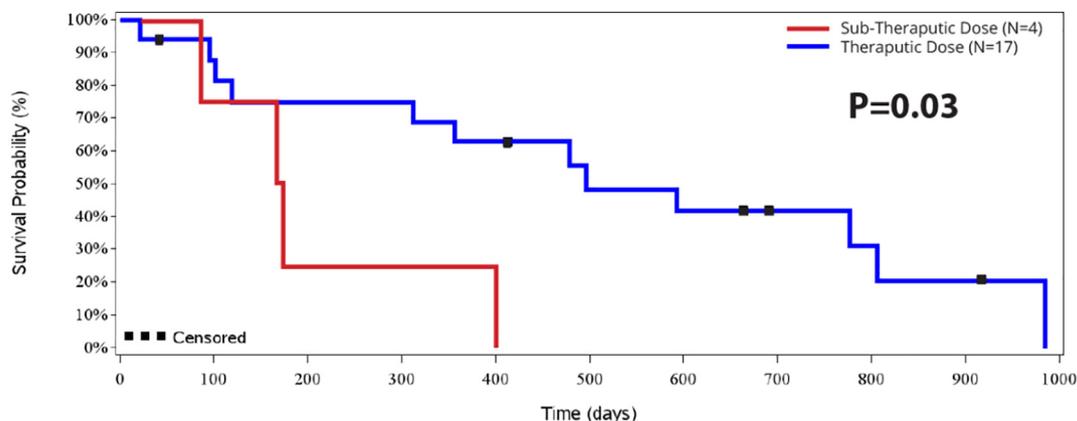
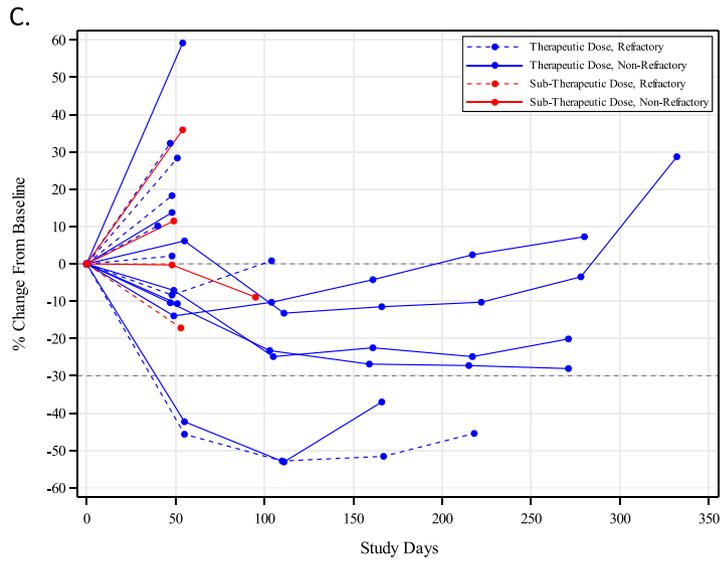
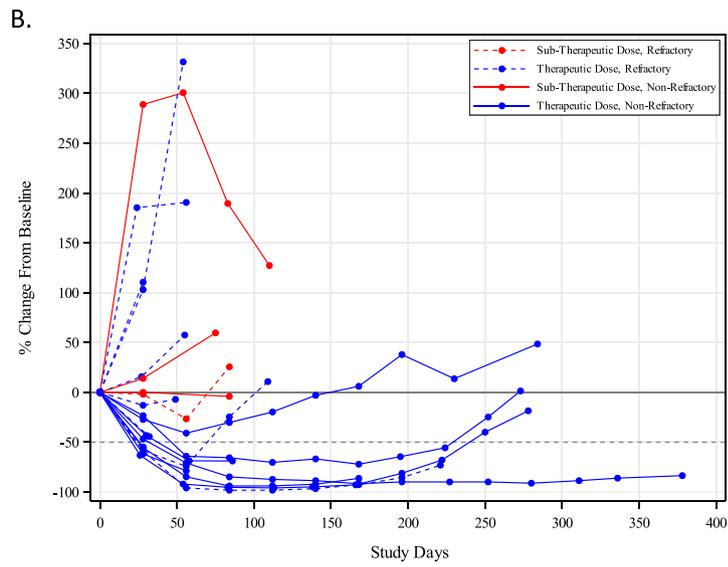
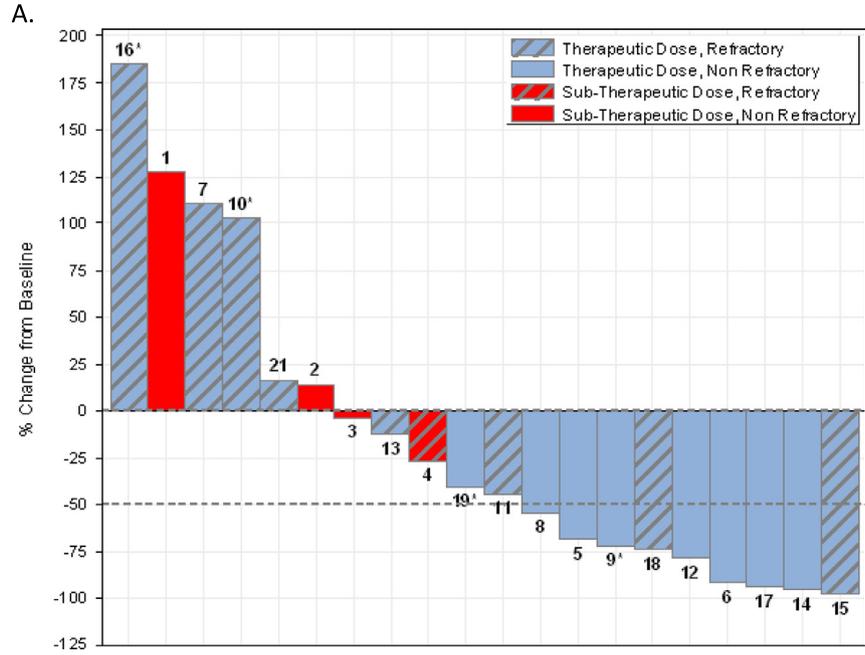


Fig. 2. Overall survival of patients who received therapeutic dose of VB-111 compared to those who received sub-therapeutic dose. Median OS was 498 days in the therapeutic dose vs. 172.5 days in the low dose.



2.5. Statistical analysis

Efficacy and safety analyses were assessed via the intention to treat (ITT) population of all enrolled subjects. Based on the study design, it was estimated that a maximum of 18 patients (6 per cohort) would be enrolled during dose escalation phase, and up to 29 patients in the optimal dose level expansion cohort. PFS and OS were calculated as the number of days from date of first study treatment until date of event. Subjects were right censored if the subjects had no events at the end of the study or if the subjects withdrew from the study early. Response rates were defined by RECIST 1.1 or GCIg CA125. The target response rate was defined as 30%, based on reported responses of combination chemo-antiangiogenic agents in patients with recurrent ovarian cancer, which typically fall in the 20–25% response range. Subgroup analyses were performed for efficacy endpoints, based on parameters of post-treatment fever events, platinum refractory status, prior antiangiogenic treatment and CA-125 responders vs. non-responders.

3. Results

3.1. Patients characteristics

Twenty-one patients with recurrent platinum-resistant ovarian cancer were enrolled in the study and received up to seven doses of VB-111. Four patients (19%) were treated at the sub-therapeutic dose and received 3×10^{12} VB-111 VPs with 40 to 80 mg/m² paclitaxel. Seventeen patients (80.9%) were treated at the therapeutic dose and received 1×10^{13} VB-111 VPs with 80 mg/m² paclitaxel. Patient baseline characteristics are listed in Table 1. Papillary serous carcinoma was the most common histology (n = 9, 42.9%); with other histologic subtypes including clear cell, adenocarcinoma, carcinosarcoma, and other (transitional/serous, mixed serous and clear-cell, and high grade serous with malignant mixed Müllerian tumor components). The most common cancer stage at diagnosis was IIIC (n = 12, 64.7%). Patients had been treated with a mean number of 2.6 prior therapies. Fifty-two percent received prior anti-angiogenic treatment and 48% were considered platinum refractory having a platinum free interval of <3 months. Median age at enrollment was 65 (41–79).

3.2. Safety

VB-111 with combination paclitaxel was well tolerated. One patient discontinued treatment due to an anaphylactic reaction that was determined after re-challenge to be related to paclitaxel. Serious adverse events were reported by 6 patients (29%), and 9 (43%) reported AEs grade ≥ 3 . The most frequent AEs included fatigue (52%), nausea (52%), fever (48%), anemia (38%), diarrhea (33%) and headache (29%). The most common VB-111 related AEs were transient mild-moderate fever/flu like symptoms, characteristic of infection with a viral vector. These events were generally grade 1–2 and responded to antipyretic treatment.

3.3. Antitumor effect

All 21 enrolled patients were included in the efficacy analysis. The median overall survival (OS) of patients who received the therapeutic dose was 498 days (16.6 months) compared to 172.5 days (5.8 months) for the patients who received the sub-therapeutic dose of VB-111 (p = 0.03) (Fig. 2).

Among the evaluable patients treated with the therapeutic dose, 58% (7/12) had a GCIg CA-125 response (Fig. 3A) confirmed over four weeks (Fig. 3B). Mean duration of response was 10 months (range 1.5–24.9).

Radiographic disease control was seen in 73% (11/15) of the patients; a partial response by RECIST criteria was confirmed in 13% and stable disease was confirmed in 60% (Fig. 3C).

Objective CA-125 response was associated with improved survival. Median OS was 808 vs. 351 days in patients with CA-125 decrease of 50% compared to those without 50% decrease in CA-125 (p = 0.067). Post treatment fever occurred in 29% and was also associated with a signal for improved survival: median OS was 808 days in patients with fever compared to 479 days in patients without fever (p = 0.27) (Fig. 4A and B).

3.4. Tumor immunogenicity

Biopsies were obtained from two patients approximately two months after the initiation of treatment with therapeutic doses of VB-111. One received one dose of VB-111, and the other was biopsied after receiving 2 doses. H&E and immunohistochemistry staining in the VB-111 treated patients showed regions of apoptotic tumor cells with increase tumor infiltrating CD8 lymphocytes with up to 38 cells per HPF, and increased number of CD4 lymphocytes (Fig. 5). Untreated controls showed minimal or no tumor T cell infiltration.

4. Discussion

In this study, patients with platinum-resistant ovarian cancer treated with VB-111 and weekly paclitaxel demonstrated durable anti-tumor effects. The favorable efficacy results were seen despite the poor prognostic features in this heavily pre-treated population in which 50% of patients had a platinum free interval of less than three months, and 50% previously received anti angiogenic medications.

Although tumor responses are not always correlated with improved survival outcomes, and there is often a mismatch between the two, the observed CA-125 tumor response rate of 58% seen with VB-111/paclitaxel treatment appears to be a meaningful predictive outcome, as it was durable with a PFS of 10 months, and appears to correlate with increased OS.

Of interest is the difference between the high CA-125 response rate and the modest RECIST response rate of 13%. This may be explained by VB-111's mechanism of action, that triggers blood vessel breakdown and induces an immunologic reaction which can increase edema in the tumor area that may be interpreted in the CT scans as pseudo-progression. The phenomenon of pseudo-progression is a controversial but well recognized event in patients treated with immune-based therapeutics whose disease met traditional RECIST disease progression criteria yet were later noted to have deep and durable responses [15].

This study's results provide further validation to an immunologic mechanism of action of VB-111. The increase in post treatment tumor infiltrating CD8 T-cells indicates tumor transformation from immunologically 'cold' to immunologically 'hot', possibly contributing to the favorable clinical outcomes. This is further supported by the correlation between increased survival and a post-treatment fever response, indicating immune activation.

In order to compare the treatment outcomes in this study with the current approved treatment options, the AURELIA trial was used as a control (NCT00976911) [10]. 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 epithelial ovarian cancer patients. The OS in the therapeutic dose of VB-111 was 498 days (16.6 months) compared to 16.7 months in the AURELIA study. In the AURELIA trial, 31.8% of the patients receiving bevacizumab and chemotherapy had a GCIg CA-125 response, while 58.3% of the patients at therapeutic doses of VB-111 had a GCIg CA-125

Fig. 3. A. Individual best CA-125% change from baseline by treatment and platinum refractory status. *Non evaluable for CA-125 response for GCIg criteria. B. Individual CA-125% change over time by treatment and platinum refractory status. C. Individual tumor burden % change over time as measured by RECIST criteria by treatment and platinum refractory status.

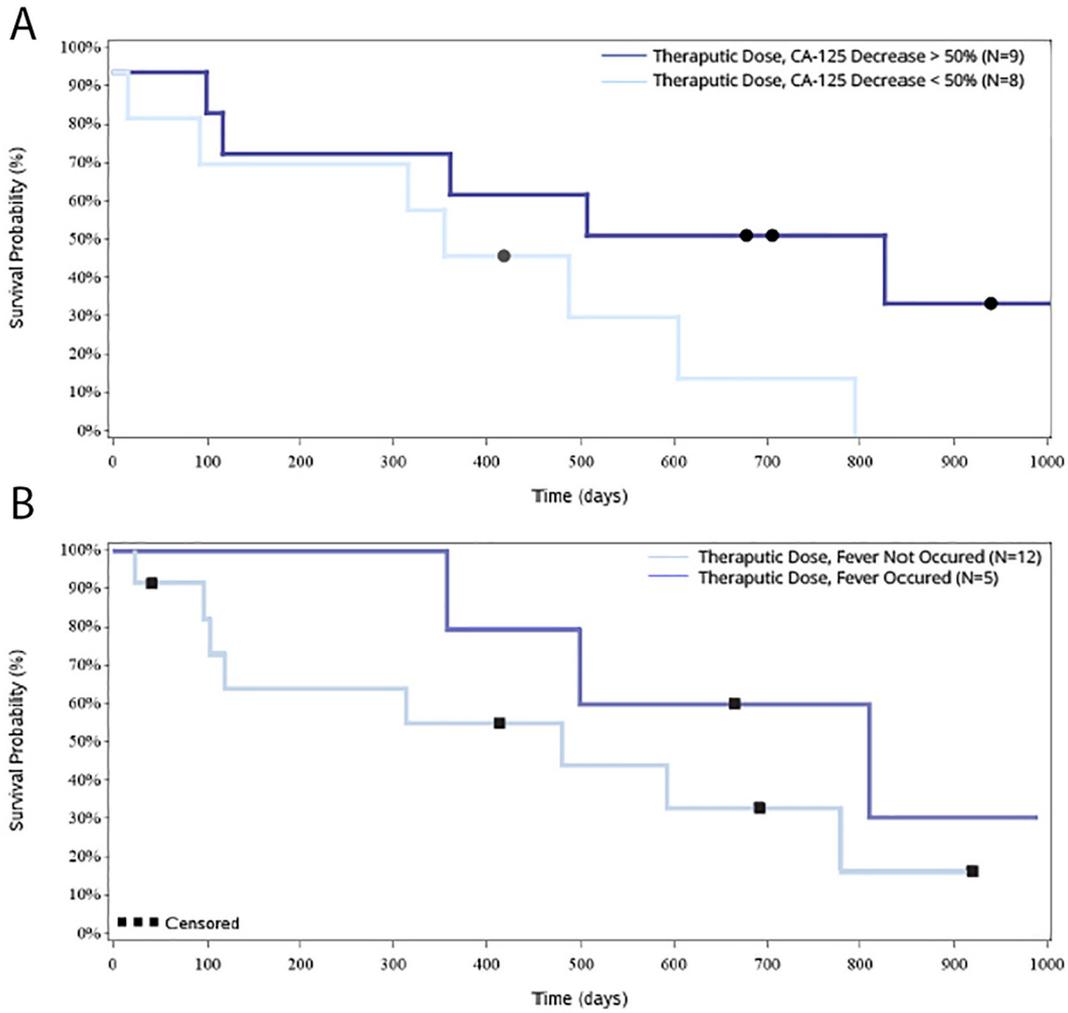


Fig. 4. A: Overall survival (OS) in patients with a CA-125 decrease of at least 50% compared to those without a 50% decrease in CA-125. Median OS was 808 in patients who were CA-125 responders vs. 351 days in non-responders ($p = 0.067$). B: Overall survival in patients receiving the therapeutic dose who experienced a post treatment fever compared to those with no fever. Post treatment fever was associated with: mOS of 808 days compared to 479 days in patients without fever ($p = 0.27$).

response. Comparison of these studies demonstrates that VB-111 has the potential to play a role in the platinum-resistant setting due to its similar effects on overall survival and slightly better anti-tumor effects. Also of note is that the favorable outcomes in our study were seen in a

population in which approximately 50% has progressed despite been previously treated with anti-angiogenic medications; this may be related to the fact that the anti-angiogenic effect of VB-111 is independent of the pro-angiogenic signaling pathways utilized by tumors, and

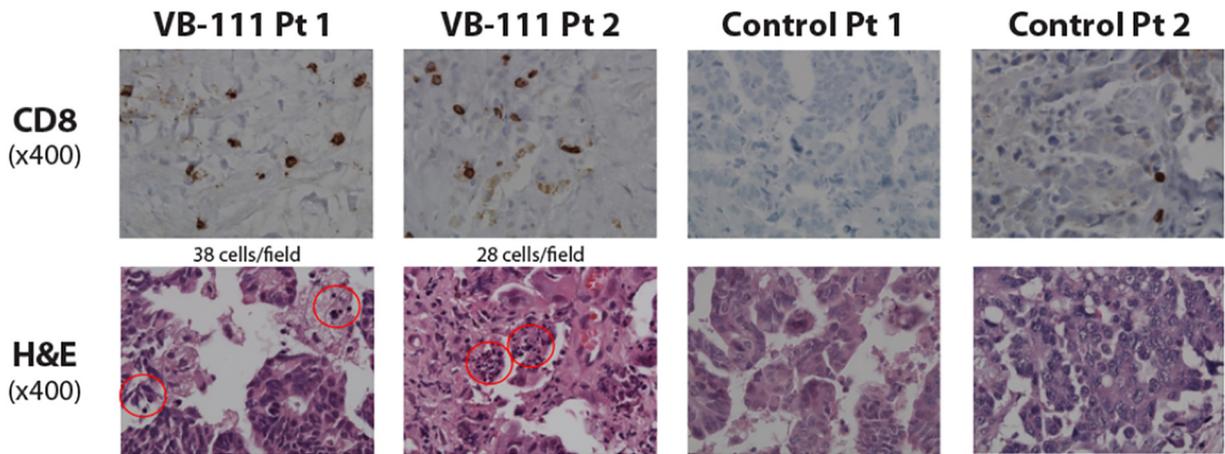


Fig. 5. H&E and immunohistochemistry staining show regions of apoptotic tumor cells (red circles) and increased tumor infiltrating CD8 lymphocytes in VB-111 treated patients. Specimens from untreated controls showed minimal or no tumor T cell infiltration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

therefore is not susceptible to many of the resistance mechanisms inherent to other anti-angiogenic approaches which target a certain ligand/receptor.

VB-111 was 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 which leads to less tissue damage and common side effects associated with many chemotherapeutic agents. The frequent flu-like symptoms reported on the dosing days were tolerable and effectively controlled with anti-pyretic medications.

Limitations of this study include the uncontrolled design and the small sample size. Therefore, the observed promising efficacy signals should be further evaluated in an adequately powered controlled study.

5. Conclusion

In summary, this study concludes that VB-111 is safe and well tolerated and shows promise in patients with recurrent platinum-resistant ovarian cancer, a disease with poor prognosis and limited treatment options. A 58% CA-125 GCIg response rate was seen in evaluable patients, including durable responses, and in patients with platinum refractory disease and post anti-angiogenic failure. The median OS was 16.6 months in patients treated with therapeutic dose compared to 5.8 months in sub-therapeutic dose ($p = 0.028$). Tumor specimens taken after treatment demonstrated tumor infiltrated with cytotoxic CD8 T-cells in regions of apoptotic cancer cells. The safety and efficacy of VB-111 and paclitaxel is being investigated in the OVAL study, a phase III randomized, controlled, double arm, double blind, multi-center study (NCT03398655) which is currently enrolling patients with platinum-resistant Ovarian Cancer.

Declaration of competing interest

HB, SB, SC, MF, and JW have no conflicts of interest to disclose. RA has financial activities with CLOVIS, TESARO, AstraZeneca and VBL Therapeutics. MB is on the Data Safety and Monitoring Board for VBL Therapeutics. YC and TRM report personal fees during the conduct of the study and have a patent Methods of Anti-Tumor Therapy pending. RP reported grants and personal fees from VBL during the conduct of the study. DH is CEO of VBL.

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Author contribution section

R. Penson, Y. Cohen, M. Birrer, and D. Harats contributed to the study idea, study design, and study implementation. S. Campos and S. Berlin

were site PIs and contributed to study implementation. R. Penson, T. Rachmilewitz, M. Birrer, and R. Arend conducted the analysis and interpretation of results. H. Beer, J. Wall, M. Foxall, and R. Arend wrote the manuscript. All authors discussed the results, commented on the manuscript versions, and provided critical feedback throughout all aspects of the research.

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