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Phase 1b study of AVB-500 in combination with paclitaxel or pegylated liposomal doxorubicin platinum-resistant recurrent ovarian cancer

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HIGHLIGHTS

- The combination of AVB-500 plus chemotherapy was safe and tolerable with no DLTs identified.
- At the AVB-500 RP2D (15 mg/kg), AVB-500+PAC demonstrated better clinical activity than AVB-500+PLD.
- Patients with no prior bevacizumab had greater clinical response than those with prior bevacizumab and historical control.
- An exposure-response relationship was identified for AVB-500 trough levels >13.8 mg/L exhibiting greater clinical response.
- A pretreatment serum biomarker may identify patients who benefit from AVB-500 in combination with chemotherapy.

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ABSTRACT

Objective: GAS6 and AXL are expressed in high-grade serous ovarian cancer but not in normal ovarian tissue. AVB-500, a novel high affinity Fc-sAXL fusion protein, binds GAS6 preventing AXL signaling. This Phase 1b study (NCT03639246) evaluated safety, efficacy, and exploratory predictive markers of AVB-500 combined with paclitaxel (PAC) or pegylated liposomal doxorubicin (PLD) in patients with platinum-resistant ovarian cancer (PROC), and used a model informed drug development (MIDD) approach for identification of the recommended phase 2 dose (RP2D).

Methods: Eligible patients received AVB-500 at 10, 15, or 20 mg/kg IV q2wk combined with PAC (n = 23) or PLD (n = 30). Patients were treated until progression or unacceptable toxicity. All were followed for survival.

Results: No dose limiting toxicities were observed and serum GAS6 was completely suppressed across the three dose levels evaluated. AVB-500 + PAC yielded better clinical activity than AVB-500 + PLD with an ORR of 34.8% (8/23, 2 complete responses) and median DoR, PFS, and OS of 7.0, 3.1, and 10.3 months, respectively. Subgroup analyses showed AVB-500 + PAC patients who had no prior bevacizumab or whose AVB-500 trough levels were >13.8 mg/L exhibited the best clinical response. The ORR and median PFS and OS in patients with these characteristics were ≥50%, ≥7.5 months, and ≥19 months, respectively. Given AVB-500 nor the combination with chemotherapy was expected to cause DLTs, the RP2D of AVB-500 was 15 mg/kg identified using an MIDD approach.

Conclusion: AVB-500 was well-tolerated in combination with PAC or PLD and contributed to the clinical activity of PAC in PROC patients. Subgroup analyses identified a population of PROC patients who may benefit the most from AVB-500 treatment, which will be further assessed in an ongoing Phase 3 PROC trial.

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1. Introduction

Advanced/recurrent ovarian cancer remains a highly lethal disease despite improvement in overall survival over the last 30 years [1,2]. The treatment strategy for recurrent ovarian cancer depends largely on the platinum-free interval (PFI). One of the most difficult to treat are tumors that are platinum-resistant (PROC) with progression within 6 months after the last platinum-based therapy. While the introduction of targeted therapies, including PARP inhibitors and VEGF inhibitors, has improved overall outcomes for certain patients, the prognosis of patients with PROC remains poor.

In normal tissues, AXL promotes immune regulation and the clearance of apoptotic material [3,4]. In ovarian tissue, AXL is predominantly expressed in advanced ovarian cancer tumors and metastases but not in normal ovarian epithelium [5]. Activation of the AXL receptor tyrosine kinase by its sole ligand, growth arrest specific 6 (GAS6), leads to increased cellular adhesion, invasion, migration, pro-tumoral immune response, anti-apoptosis, proliferation, resistance, and survival in several cancers [6]. Furthermore, AXL and GAS6 expression are associated with poor prognosis, acquired and inherent resistance to treatment, and poor survival. The strong picomolar binding affinity between endogenous GAS6 and AXL (14–33 pM) [7,8], and the promiscuity of small molecule AXL inhibitors have historically presented a barrier to the development of specific and potent AXL inhibitors.

AVB-500 (formerly AVB-S6-500) is a recombinant fusion protein dimer containing a truncated and modified portion of the extracellular region of human AXL fused with a human immunoglobulin G1 (IgG1) heavy chain (Fc). AVB-500 acts as a decoy, trapping GAS6 with an ~200-fold higher affinity than wild-type AXL. This strong interaction significantly reduces the availability of free GAS6 for binding to endogenous AXL, thereby potentially inhibiting downstream signaling of many cancer-related physiological processes implicated in the epithelial-to-mesenchymal transition (EMT), migration, invasion, angiogenesis, and immune suppression and evasion [9]. Analysis of AXL and GAS6 germline knockout mice shows that the GAS6/AXL signaling cascade is not required for embryonic development or normal tissue function [10,11]. Consistent with these knockout data, preclinical toxicology studies of AVB-500 did not demonstrate a maximum tolerated dose.

Preclinical studies on AXL signaling in ovarian cancer models showed that AXL-specific therapy is sufficient to significantly reduce metastatic tumor progression in vivo using aggressive models of ovarian cancer [12]. AVB-500 in combination with doxorubicin or paclitaxel yielded significantly decreased tumor burden in PROC xenograft models [12,13]. The paclitaxel combination results were demonstrated in patient derived tumor xenograft models [13] and serve as preclinical rationale for the combinations evaluated in this Phase 1b study.

AVB-500 has been evaluated in healthy volunteers in a single-ascending dose and repeat-dose Phase 1 clinical study (NCT03401528). AVB-500 treatment was well-tolerated and resulted in an immediate maximal reduction in circulating serum GAS6. The duration of this GAS6 suppression was at least two weeks and dose-related. The pharmacokinetic (PK) profile of AVB-500 exhibited target mediated drug disposition (TMDD) and supported using a MIDD approach to further inform identification of the RP2D [14]. Based upon encouraging preclinical data and promising safety and PK/pharmacodynamic (PD) profile observed in the healthy human volunteer study, escalating doses of AVB-500, at an every two week schedule, was evaluated in combination with PAC or PLD in PROC patients according to a study design proposed by the National Cancer Institute (NCI) clinical trial design task force recommendations on design of Phase 1 combination trials (Recommendation 4C) [15].

2. Methods

2.1. Study design

This is a Phase 1b, open-label, multicenter, study to evaluate safety, tolerability, clinical activity and identification of the RP2D of AVB-500 in combination with pegylated liposomal doxorubicin (AVB-500 + PLD) or paclitaxel (AVB-500 + PAC) in patients with platinum-resistant ovarian cancer (PROC) (NCT03639246) (Fig. 1 and Fig. S1). Safety and tolerability were evaluated in the first six patients enrolled to each combination and followed for at least 28 days. Demonstration of tolerability by the Data Monitoring Committee (DMC) enabled expansion of each combination for further evaluation of PK, PD, and preliminary efficacy. Using an MIDD approach demonstrating that higher drug exposures correlated with improved clinical outcome, the study was amended to evaluate two additional dose levels of AVB-500 in combination with either PAC or PLD. The DMC assessed the safety data in at least 6 patients followed for at least 28 days prior to each dose escalation.

2.2. Participants

Key eligibility criteria included age ≥ 18 years; ovarian, fallopian tube, or primary peritoneal platinum-resistant cancer including adenocarcinoma not otherwise specified (NOS), grade 3 endometrioid adenocarcinoma, mixed epithelial carcinoma with at least an 80% high grade serous component, high-grade serous adenocarcinoma, and undifferentiated carcinoma; measurable disease as assessed by Response Evaluation Criteria in Advanced Solid Tumors (RECIST 1.1), Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function. All patients were required to provide tumor tissue from a newly obtained biopsy sample or an archived tumor sample. Patients were excluded if they received more than 3 prior treatment regimens, not including maintenance, hormonal, or other adjuvant therapy; received prior therapy with Pac in the recurrent setting (if physician-chosen chemotherapy in this study was Pac) or PLD (if physician-chosen chemotherapy in this study was PLD); if they were platinum refractory (defined as progression during or within 4 weeks after completion of first platinum regimen); or if they received an anticancer or hormonal therapy within 4 weeks of the first dose of study treatment.

2.3. Treatments

AVB-500 at doses of 10, 15, or 20 mg/kg was dosed intravenously (IV) once every 2 weeks (q2wk) in combination with either PAC (80 mg/m^2) IV on Days 1, 8, and 15 or PLD (40 mg/m^2) IV on Day 1 of a 28-day cycle. For those who had a complete or partial response after 6 cycles of chemotherapy and AVB-500, single agent AVB-500 at the same dose could be continued as maintenance. Treatment was continued until disease progression, unacceptable toxicity, or a physician or patient decision to discontinue therapy.

Written informed consent was provided by all patients before undergoing any study-specific procedures. The study protocol was reviewed and approved by an Institutional Review Board and were carried out in accordance with the International Conference on Harmonisation tripartite guideline E6(R2) for Good Clinical Practice.

2.4. Objectives and clinical assessments

The primary objective of this study was to evaluate the safety and tolerability of AVB-500 in combination with PLD or PAC in patients with PROC. Key secondary objectives included identification of the RP2D and PK/PD analyses. Preliminary efficacy was also evaluated.

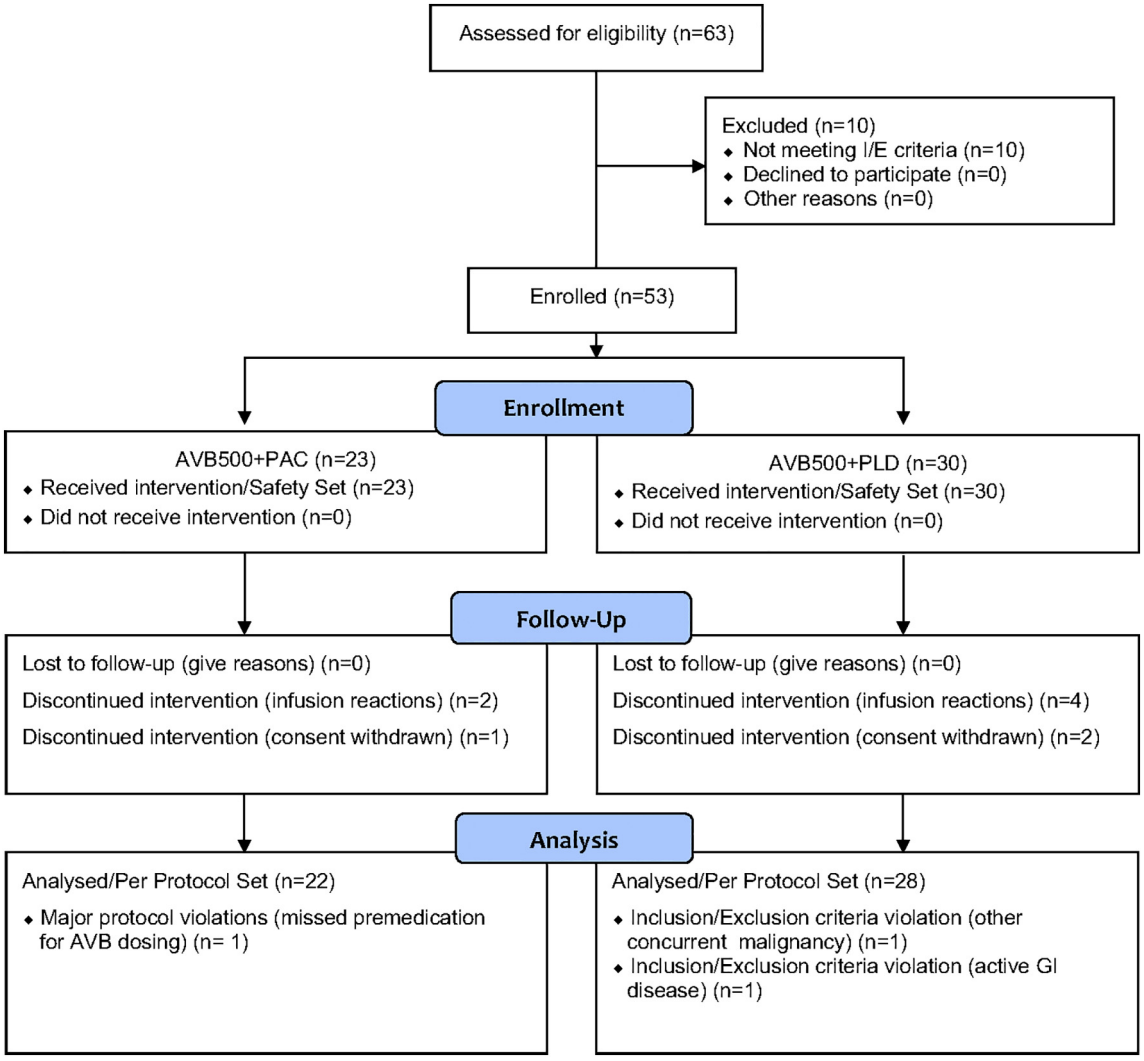

Fig. 1. CONSORT 2010 Flow Diagram of Patient Disposition.

Safety evaluations included AEs, 12-lead ECGs, physical examinations, vital signs, and clinical laboratory assessments. Adverse events were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) v5 collected each cycle and up to 30 days after the last dose of study drug. Tumor assessments were performed every odd numbered cycle after C1. Samples for AVB-500 concentration and serum AXL and GAS6 were obtained at baseline and prior to each AVB-500 dose.

2.5. Statistical analysis

The total number of patients required for the phase Ib portion of this study was dependent on the toxicity profile and correlation of PK/PD with efficacy. A sample size of approximately 60 patients in phase Ib was planned to assess the RP2D across the three AVB-500 dose levels. The Safety Set (SS, N = 53) included all enrolled participants who receive at least one dose of study drug. The Per Protocol Set (PPS, N = 51) included SS participants who met all inclusion and exclusion criteria. The objective response rate (ORR) was assessed per RECIST 1.1 criteria by the investigator and associated two-sided 95% confidence intervals (CI) by subgroup were calculated using the Clopper-Pearson method. The distributions of duration of response (DoR), progression-free survival (PFS), and overall survival (OS) were summarized using Kaplan-Meier estimation. The data cutoff date was March 9, 2021.

An unsupervised analysis was conducted to identify patient characteristics, including the first AVB-500 trough level, associated with PFS of ≥6 months.

Serum levels of AXL and GAS6 were obtained using a validated ELISA method (Altasciences, Everett WA). The optimal baseline serum soluble AXL/GAS6 ratio as a predictor of RECIST response was determined by ROC analysis using Youden's J statistic [16].

3. Results

3.1. Patients

Fifty-three patients were enrolled between December 2018 and April 2020. Forty patients were administered AVB-500 at 10 mg/kg (16/40 + PAC, 24/40 + PLD), 6 patients at 15 mg/kg (3/6 + PAC, 3/6 + PLD), and 7 patients at 20 mg/kg (4/7 + PAC, 3/7 + PLD). As of March 2021, 45 patients had discontinued study treatment due to progressive disease, 6 due to investigator decision, and 2 withdrew consent. Thirty-seven patients have died during the study, 15 in the AVB-500+PAC group and 22 in the AVB-500 + PLD group (Table S1).

Table S2 summarizes the baseline characteristics of the patients enrolled. Patients had a mean age of 64 (range, 37 to 82) years, and an ECOG performance status of 0 (57%) or 1 (43%). Of the 53 patients, 47 (89%) had HGSOC and 35 (66%) had received at least 2 prior lines of

chemotherapy. Forty-seven percent and 26% of patients received prior bevacizumab or a PARP inhibitor, respectively, prior to study entry. Most baseline characteristics were similar between the AVB-500 + PAC and AVB-500 + PLD groups, except more patients in the AVB-500 + PAC group had 2 to 3 prior lines of therapy and < 3 months PFI compared with the AVB-500 + PLD group (96% vs 43% and 44% vs 23%, respectively).

3.2. Safety

As summarized in Table 1, treatment-emergent adverse advents (TEAEs) for AVB-500 + chemotherapy were observed in 18/23 (78%) and 19/30 (63%) patients treated with AVB-500 + PAC and AVB-500 + PLD, respectively. Because AEs were similar regardless of dose level (Table S3), the overall safety profile is described in aggregate. TEAEs of any grade observed in 3 or more patients were fatigue, infusion-related reactions (IRR), anemia, nausea, and headache. IRRs are an AE of special interest identified for AVB-500 that were observed in 11/53 (21%) patients with all events grade 2 or less. Grade 3 or 4 TEAEs were observed in 4/23 (17%) AVB-500 + PAC and 2/30 (7%) AVB-500 + PLD treated patients. Two grade 4 TEAEs (pulmonary embolism and small bowel obstruction) and 4 grade 3 TEAEs (pulmonary embolism, enteritis, neutropenia, fatigue) were documented. Two patients in the 10 mg/kg AVB-500 + PAC dose level experienced grade 3 or 4 pulmonary embolisms and one patient in the 10 mg/kg AVB-500 + PAC dose level experienced a grade 4 small bowel obstruction, each assessed as related by the investigator. The grade 4 pulmonary embolism occurred in a patient with a history of venous thromboembolism and prior treatment with bevacizumab. Although assessed as "related", the patient with the small bowel obstruction had a history of ascites, as well as documented progression within 3 days of the small bowel obstruction, which suggests that the AE was likely due to the patient's underlying disease. The grade 4 pulmonary embolism and grade 3 enteritis (15 mg/kg AVB-500 + PLD) were both considered serious TEAEs. No patients experienced a grade 5 TEAE or discontinued therapy due to a TEAE, and no dose limiting toxicities were observed.

3.3. Efficacy

Efficacy was evaluated in the PPS population (N = 51, Table 2). The ORR observed with AVB-500 + PLD across all doses was 10.7% (95% CI: 2.3%, 28.2%) and a median DoR (mDoR), PFS (mPFS), and OS (mOS) of 4.2 (95% CI: 1.8, 8.8), 3.6 (95% CI: 1.8, 5.0), and 11.2 (95% CI: 6.5, 13.6) months, respectively. Across all doses, AVB-500 + PAC (vs. AVB-500 + PLD) yielded a greater ORR at 8/23 (34.8%; 95% CI: 16.4%, 57.3%), including 2 complete responses (CR), with 3 patients achieving complete resolution of their target lesions (Fig. 2A), and mDoR, mPFS, and mOS of 7.0 (95% CI: 2.3, 7.6), 3.1 (95% CI: 1.8, 5.5), and 10.3 (95% CI: 8.1, 19.0) months, respectively.

For both combinations, clinical activity was greater in patients treated at the 10 and 15 mg/kg AVB-500 dose levels compared to those administered the 20 mg/kg dose (Table 2). Three patients' responses were maintained for 4-8 months on AVB-500 (2 PAC patients, 1 PLD patient) (Fig. 3A, B). One treated at 15 mg/kg had a CR, and 2 patients treated at 10 mg/kg had partial responses (PR). For the 2 patients on maintenance AVB-500 alone, tumors progressed after missed scheduled AVB-500 administration because they could not come to clinic due to a COVID infection or because of requested treatment holiday from infusions. This included one patient who was maintained on AVB-500 alone for 7.5 cycles.

Table 1
Summary of Related Treatment Emergent Adverse Events Experienced by >3 Patients in the AVB-500 + PAC and AVB-500 + PLD Groups.

Preferred Term	AVB-500 + PAC N = 23 n (%)	AVB-500 + PLD N = 30 n (%)
Number of Subjects with at Least One Related TEAE	18 (78.3%)	19 (63.3%)
Related TEAE with Grade ≥ 3 (Severe)[a]	4 (17.4%)	2 (6.7%)
Serious Related TEAE	1 (4.3%)	1 (3.3%)
Death Related to TEAE	0 (0%)	0 (0%)
DLT	0 (0%)	0 (0%)
Discontinued Due to Related TEAE	0 (0%)	0 (0%)
Fatigue	7 (30.4%)	5 (16.7%)
Infusion-related Reaction	5 (21.7%)	6 (20.0%)
Anemia	5 (21.7%)	2 (6.7%)
Nausea	3 (13.0%)	4 (13.3%)
Headache	2 (8.7%)	2 (6.7%)

[a] No Grade 5 TEAEs reported. Abbreviations: N, number of patients in the Safety Set where percentages are based on N; DLT, dose limiting toxicities; TEAE, treatment emergent adverse event where related TEAEs are 'Possibly related', 'Probably related' or Definitely related' to treatment.

3.4. Pharmacodynamics and pharmacokinetics

All AVB-500 dose levels completely suppressed serum GAS6 to below the level of quantitation in 49/50 (98%; data not shown) patients on C1D15. In the remaining patient, GAS6 was suppressed to 10% of baseline levels on C1D15. Moreover, suppression was observed over all dosing intervals in 45/52 (87%) patients and endured to the end of treatment in 33/36 patients (92%).

3.5. Subgroup analyses

An exploratory exposure-response analysis conducted using the 10 mg/kg cohort, identified that a higher AVB-500 trough level at C1D15 was associated with longer PFS, defining a model-based minimally efficacious concentration (MEC) of AVB-500 of 13.8 mg/L. As shown in Fig. 3 and Table 3, a difference in clinical activity was seen in 2 key subgroups of patients treated with AVB-500 with PAC or PLD: 1) prior treatment with bevacizumab (Fig. 3A, B and Table 3A) and 2) C1D15 trough above or below the MEC (Fig. 3A, B and Table 3B). Given that the pharmacokinetic modeling yielded a RP2D for AVB-500 of 15 mg/kg, the subgroup analyses were restricted to the 10 and 15 mg/kg doses combined across the AVB-500 + PAC or + PLD combinations.

Among patients treated with AVB-500 + PAC, those whose trough levels were above the MEC had greater benefit than those below the MEC, with the above MEC subgroup showing an ORR of 5/10 (50%, 95% CI: 18.7%, 81.3%), including the 2 CRs and a mDoR, mPFS, and mOS of 7.4 (95% CI: 6.0, NE), 7.5 (95% CI: 1.8, 9.3), and 19 (95% CI: 8.1, NE) months, compared to the below MEC subgroup showing an ORR of 2/9 (22%, 95% CI: 2.8%, 60%), and a mDOR, mPFS, and mOS of 3.7 (95% CI: NE), 2.8 (95% CI: 1.7, 5.5), and 8.7 (95% CI: 2.3, NE) (Table 3B).

Across both PAC and PLD patients, those who had never received bevacizumab prior to study entry had an ORR of 9/24 (37%, 95% CI: 18.8%, 59.4%) including 2 CRs, compared to 1/20 (5%, 95% CI: 0.1%, 24.9%) and no CRs in patients previously treated with prior bevacizumab (Table 3A). Moreover, among patients with PFS > 6 months, 92% (11/12) had never received prior bevacizumab (Fig. 3A & B). Median PFS in the bevacizumab naïve was 7.3 months, versus 3.3 months in those previously treated with bevacizumab (Table 3A). Among the AVB-500 + PAC subset, those who had never received prior bevacizumab had a higher ORR of 6/9 (67%, 95% CI: 29.9%, 92.5%), including the 2 CRs, and a mPFS of 7.7 (95% CI: 1.7, 9.3) months, versus ORR of 1/10 (95%CI: 0.3%, 44.5%) and mPFS of 2.8 (95% CI: 1.8, 3.6) in the prior bevacizumab subset (Table 3A). No difference in clinical activity was observed by prior PARP inhibition (data not shown).

Patients with the historically poor prognostic indicators of advanced lines of chemotherapy, defined as two prior lines of chemotherapy [17], or PFI < 3 months [18] showed beneficial activity (Table S4). The ORR in patients treated with 2 to 3 prior lines of therapy was 8/29 (28%, 95% CI:

Table 2
Clinical Activity for All Patients by Treatment Arm and Dose, Per Protocol Set.

Parameter	AVB-500 + PAC				AVB-500 + PLD			
	10 mg/kg N = 16	15 mg/kg N = 3	20 mg/kg N = 4	Overall N = 23	10 mg/kg N = 23	15 mg/kg N = 2	20 mg/kg N = 3	Overall N = 28
CR	1	1	0	2	0	0	0	0
n (%)	6.3%	33.3%	0.0%	8.7%	0.0%	0.0%	0.0%	0.0%
PR	4	1	1	6	2	1	0	3
n (%)	25.0%	33.3%	25.0%	26.1%	8.7%	50.0%	0.0%	10.7%
SD	5	1	0	6	10	1	1	12
n (%)	31.3%	33.3%	0.0%	26.1%	43.5%	50.0%	33.3%	42.9%
PD	6	0	3	9	9	0	2	11
n (%)	37.5%	0.0%	75.0%	39.1%	39.1%	0.0%	66.7%	39.3%
NA	0	0	0	0	2	0	0	2
n (%)					8.7%			7.1%
ORR	5	2	1	8	2	1	0	3
n (%)	31.3%	66.7%	25.0%	34.8%	8.7%	50.0%	0.0%	10.7%
95% CI	11.0%, 58.7%	9.4%, 99.2%	0.6%, 80.6%	16.4%, 57.3%	1.1%, 28.0%	1.3%, 98.7%	0.0%, 70.8%	2.3%, 28.2%
(n) mDOR	(5) 7.0	(2) 10.2	(1) 2.3	(8) 7.0	(3) 4.2	(1)	(0)	(4) 4.2
(95% CI)	(3.7, 7.6)	NE	NE	(2.3, 7.6)	(1.8, 8.8)	NE	NE	(1.8, 8.8)
mOS	10.3	NE	NE	10.3	12.71	7.6	4.4	11.2
(95% CI)	(6.7,19.0)	NE	NE	(8.1,19.0)	(10.2, 15.6)	(6.0, 9.1)	(2.7, 8.3)	(6.5,13.6)
mPFS	3.0	13.6	1.8	3.1	3.6	3.8	1.8	3.6
(95% CI)	(1.8, 7.3)	(3.7,13.6)	(1.7, 4.1)	(1.8, 5.5)	(1.7, 5.6)	NE	(1.8, 3.0)	(1.8, 5.6)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR = Objective Response Rate (CR + PR); NA, disease response not available; NE, values not determined given the low number of subjects; mDOR, median duration of response in months; mPFS, median progression-free survival in months; mOS, median overall survival in months.
N: Number of subjects in the Per Protocol (PP) Set. Percentages are based on N.
ORR: assessed by the investigator per RECIST 1.1 criteria.
95% CI: Two-sided 95% confidence interval is calculated using Clopper-Pearson method.
mDOR, mOS, mPFS: median (95% CI), based on g-transformed 95% CI for Survival Function in SAS Lifetest procedure, where calculable.
mDOR: The duration of response is only for responders shown as (n): best confirmed response of CR or PR.

12.7%, 47.2%) including 2 CRs (Table S4 A). The ORR in patients with a PFI < 3 months was 2/13 (15%, 95% CI: 1.9%, 45.4%), including 2 CRs (Table S4 B).

The pretreatment serum soluble AXL/GAS6 ratio was evaluated as a predictor of RECIST response. The optimal AXL/GAS6 ratio dichotomy as determined by ROC analysis (AUC = 0.7833, p = 0.047) using Youden's J statistic was 0.773. Negative predictive value was 100%. Patients with ratios above 0.773 were significantly more likely to have achieved a RECIST response with a calculated sensitivity of 100% and a specificity of ~60%. The ORR in patients receiving AVB-500 + PAC whose baseline serum soluble AXL/GAS6 ratio was above 0.773 (N = 11) was 58% (17% CRs). There were no responders in the patients whose baseline ratio was at or below 0.773 (Fig. S2). A similar outcome was observed in patients administered AVB-500 + PLD (data not shown).

4. Discussion

Here, we report the results of a Phase 1b study of AVB-500 in combination with PAC or PLD for patients with PROC. Given the encouraging activity observed in combination with PAC across several critical subgroups, the Phase 3 trial of AVB-500 + PAC vs PAC alone in patients with PROC (NCT04729608) has been initiated. The safety profile demonstrated that both combinations were well-tolerated with no DLTs, no AE requiring dose discontinuation, and no grade 5 AEs or deaths. The lack of toxicity observed with AVB-500 dosed as a monotherapy in healthy human volunteers (NCT03401528) and comparisons to toxicity profiles observed with PAC and PLD suggest that toxicity observed with these combinations are likely due to the chemotherapy partner. This benign toxicity profile is unique for an oncology treatment but consistent with the gene knock-out data showing that GAS6 (target) is

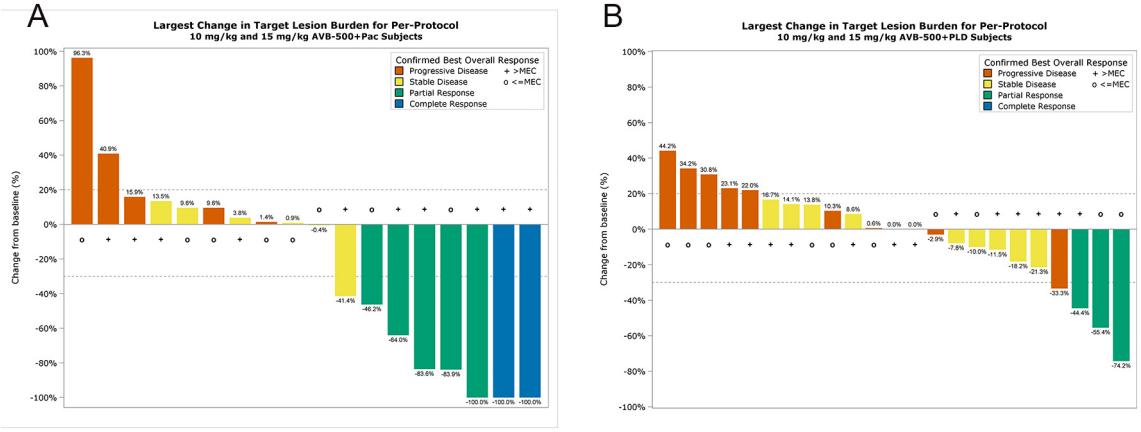

Fig. 2. Largest Change in Target Lesion Burden for PPS Patients Receiving (A) 10 or 15 mg/kg AVB-500 + PAC or (B) 10 or 15 mg/kg AVB-500 + PLD.
Minimal Efficacious Concentration (MEC) Threshold, AIC analysis identified 13.8 mg/L as the MEC. Aggregate confirmed best overall response for patients in the 10 and 15 mg/kg groups whose AVB-500 trough level were (+, >MEC) or lower (o, <MEC) than MEC shown.

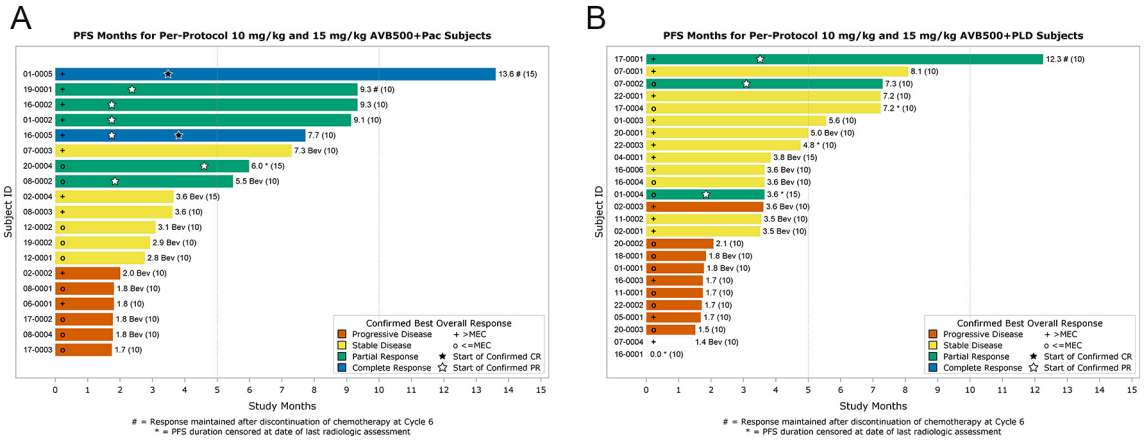

Fig. 3. Subgroup Analyses of Duration of Response and Treatment for PPS Patients Receiving 10 or 15 mg/kg AVB-500 (A) + PAC or (B) + PLD.
Confirmed best overall response for individual patients in the 10 and 15 mg/kg groups whose AVB-500 trough level were higher (+, >MEC) or lower (o, <MEC) than Minimal Efficacious Concentration (MEC) Threshold (13.8 mg/L) shown.

dispensable for normal tissue [8,9]. Fatigue and IRRs were identified as likely attributable to AVB-500, however all of the IRRs were grade ≤ 2 and adequately controlled with standard pre-medications.

Given the lack of DLTs observed across the 3 dose cohorts assessed in the study, identification of the RP2D was based upon pharmacokinetic and pharmacodynamic analyses using an MIDD approach. Complete suppression of GAS6 at C1D15 in patients treated at either 10 or 15 mg/kg and whose C1D15 AVB-500 trough was above the MEC suggested optimal PFS with little concomitant increase in efficacy expected with a higher dose. The AVB-500 trough levels were achieved at the 15 mg/kg dose level and were associated with 100% clinical benefit, albeit in a small number of participants.

This study's primary objective was to assess the safety and tolerability of AVB-500 in combination with either PAC or PLD and did not include single agent control arms. The preliminary clinical activity observed, even in this low number of patients, is encouraging. Patient subgroups with multiple poor prognostic factors including 3 prior lines of therapy [17] as well as short PFIs of <3 months [18] showed encouraging response to treatment. Although clinical activity was higher in the paclitaxel cohort regardless of dose, those with AVB-500 C1D15 trough levels greater than 13.8 mg/L tended to show better clinical activity.

Bevacizumab, a VEGF inhibitor, is administered in combination with chemotherapy in multiple treatment settings for patients with ovarian cancer. In this study, patients who had never received prior bevacizumab demonstrated better efficacy compared to patients who had been treated with prior bevacizumab. Prior treatment with bevacizumab has been associated with reduced clinical activity of subsequent cancer therapies in multiple treatment settings and with different mechanisms of actions [19–23]. Additionally, preclinical studies evaluating the effects of pre-administration of anti-VEGF antibodies on the pharmacokinetics and tissue distribution of other antibodies did demonstrate a reduced accumulation of trastuzumab in breast cancer tumor-bearing mice [24].

In summary, patients who received AVB-500 + PAC and who achieved the MEC or had not previously received bevacizumab achieved an ORR, mPFS, and mOS of >50%, >7.5 months, and at least 19 months, respectively. Conclusions drawn from small patient subgroups warrant caution; nonetheless, these data are compelling relative to the activity of monotherapy PAC in a less heavily treated patient population in which ORR was 30%, mPFS of 3–4 months, and mOS of 13 months [25]. Furthermore, meaningful clinical activity was observed in patients treated with 2 or 3 lines of therapy or PFIs of <3 months. These are traditionally poor prognostic markers in PROC, and the improved response in combination with AVB-500 is plausible given AXL's role in chemoresistance and metastasis.

Furthermore, in the 3 patients who reached a complete/partial response and were maintained on AVB-500 alone, tumor response was

Table 3A
Response in Patients Treated with 10 or 15 mg/kg AVB-500 + PAC or + PLD Based on Prior Treatment with Bevacizumab.

Prior BEV Per Protocol Set (PPS)	AVB-500 + PAC		AVB-500 + PLD		AVB-500 + PAC or + PLD	
	No Prior BEV N = 9 n (%)	Prior BEV N = 10 n (%)	No Prior BEV N = 15 n (%)	Prior BEV N = 10 n (%)	No Prior BEV N = 24 n (%)	Prior BEV N = 20 n (%)
CR	2 (22%)	0	0	0	2 (8%)	0 (0%)
PR	4 (44%)	1 (10%)	3 (20%)	0	7 (29%)	1 (5%)
SD	1 (11%)	5 (50%)	5 (33%)	6 (60%)	6 (25%)	11 (55%)
PD	2 (22%)	4 (40%)	6 (40%)	3 (30%)	8 (33%)	7 (35%)
ORR	6 (67%)	1 (10%)	3 (20%)	0 (0%)	9 (37%)	1 (5%)
(95% CI)	(29.9%, 92.5%)	(0.3%, 44.5%)	(4.3%, 48.1%)	(0.0%, 30.8%)	(18.8%, 59.4%)	(0.1%, 24.9%)
NA	0	0	1 (7%)	1 (10%)	1 (4%)	1 (5%)
(n) mDOR	(6) 7.4	(1) 3.7	(3) 6.5	(0)	(9) 7.4	(1) 3.7
(95% CI)	(6.0, NE)	NE	(4.2, NE)	NE	(4.2, 8.8)	NE
mOS	19.3	9.2	12.6	10.5	15.6	10.3
(95% CI)	(6.7, NE)	(2.3, 15.3)	(6.0, NE)	(1.4, 14.2)	(11.2, NE)	(6.5, 13.3)
mPFS	7.7*	2.8	5.6	3.6	7.3	3.3
(95% CI)	(1.7, 9.3)	(1.8, 3.6)	(1.7, 8.1)	(1.4, 3.6)	(1.8, 9.1)	(1.8, 3.6)

* Given the limited number of events, 7.7 has been reported as it is the value closest to the median.

Table 3B
Response in Patients Treated with 10 or 15 mg/kg AVB-500 + PAC or + PLD Based on the Minimal Efficacious Concentration.

MEC Threshold (PPS)	AVB-500 + PAC		AVB-500 + PLD		AVB-500 + PAC or + PLD	
	Above MEC N = 10	Below MEC N = 9	Above MEC N = 14	Below MEC N = 10	Above MEC N = 24	Below MEC N = 19
CR	2 (20%)	0	0	0	2 (8%)	0
PR	3 (30%)	2 (22%)	1 (7%)	2 (20%)	4 (17%)	4 (21%)
SD	3 (30%)	3 (33%)	9 (64%)	2 (20%)	12 (50%)	5 (26%)
PD	2 (20%)	4 (44%)	3 (21%)	6 (60%)	5 (21%)	10 (53%)
ORR	5 (50%)	2 (22%)	1 (7%)	2 (20%)	6 (25.0%)	4 (21%)
(95% CI)	(18.7%, 81.3%)	(2.8%, 60.0%)	(0.2%, 33.9%)	(2.5%, 55.6%)	(9.8%, 46.7%)	(6.1%, 45.6%)
NA	0	0	1 (7%)	0	1 (4%)	0
(n) mDOR	(5) 7.4	(2) 3.7	(1) 8.8	(2) 4.2	(6) 7.5	(4) 4.0
(95% CI)	(6.0, NE)	NE	NE	NE	(6.0, NE)	(3.7, NE)
mOS	19.0	8.7	11.2	12.6	13.6	10.3
(95% CI)	(8.1, NE)	(2.3, NE)	(5.5, 14.2)	(5.6, NE)	(10.2, 19.0)	(6.5, 15.3)
mPFS	7.5	2.8	3.7	2.0	4.4	2.1
(95% CI)	(1.8, 9.3)	(1.7, 5.5)	(1.7, 7.2)	(1.5, NE)	(3.5, 7.7)	(1.8, 3.6)

Abbreviations: BEV, bevacizumab; MEC, minimal efficacious concentration; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR = Objective Response Rate (CR + PR); NA, disease response not available; NE, values not determined given the low number of subjects; mDOR, median duration of response in months; mPFS, median progression-free survival in months; mOS, median overall survival in months.
ORR: Clopper-Pearson 95% CI.
mDOR, mOS, mPFS: median (95% CI), based on g-transformed 95% CI for Survival Function in SAS Lifetest procedure, where calculable.
mDOR: The duration of response is only for responders shown as (n): best confirmed response of CR or PR.
MEC Threshold: ROC analysis identified 13.8 mg/L (data not shown) as the MEC. Clinical activity for patients in the 10 and 15 mg/kg groups whose AVB-500 trough level were higher or lower than MEC shown.

maintained for 4 to 8 months. However, 2 of these patients progressed within a month after missing their scheduled AVB-500 dose suggesting that these tumors were acutely sensitive to GAS6 suppression. Additionally, this study demonstrated preliminary evidence that a pretreatment serum-based assay evaluating soluble AXL/GAS6 ratios identified all patients who had a response, indicating that serum soluble AXL/GAS6 may identify PROC patients who could benefit from chemotherapy plus AVB-500. Further biomarker development is ongoing.

In conclusion, AVB-500 + PAC is potentially a new treatment regimen for patients with PROC as the combination is tolerable and demonstrates encouraging anti-tumor activity. The Phase 3 trial of AVB-500 + PAC compared to PAC in patients with PROC will assess the PFS by RECIST 1.1 in PROC patients treated with up to 4 prior lines of therapy and will incorporate the 15 mg/kg AVB-500 dose identified in the RP2D. Further analyses on prior bevacizumab and serum soluble AXL/GAS6 also will be performed.

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