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# PHASE 1B/2 STUDY OF AVB500 (HIGH AFFINITY INHIBITOR OF GAS6/AXL PATH) IN COMBINATION WITH PAC AND PLD IN PLATINUM RESISTANT RECURRENT OVARIAN CANCER (NCT03639246)

## Abstract 6602

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# DISCLOSURE SLIDE

All authors are either employees of Aravive, Inc. or paid consultants to Aravive, Inc.

# AXL Tyrosine Kinase Promotes Invasion, Metastasis, and Resistance

- AXL is a member of tyrosine kinases that include Tyro3, AXL, and Mer (TAMs)
- AXL is activated by a single ligand, growth arrest–specific 6 (GAS6); Mer and Tyro3 can be activated by GAS6 *and* Protein S [1]
- Upregulated in many cancers [2], AXL overexpression linked to metastasis [3,4,] poor survival [5-7], and drug resistance [8,9]
- Unusually strong binding affinity between GAS6 and AXL of ~ 30 pM makes development of inhibitors to the pathway challenging [1]

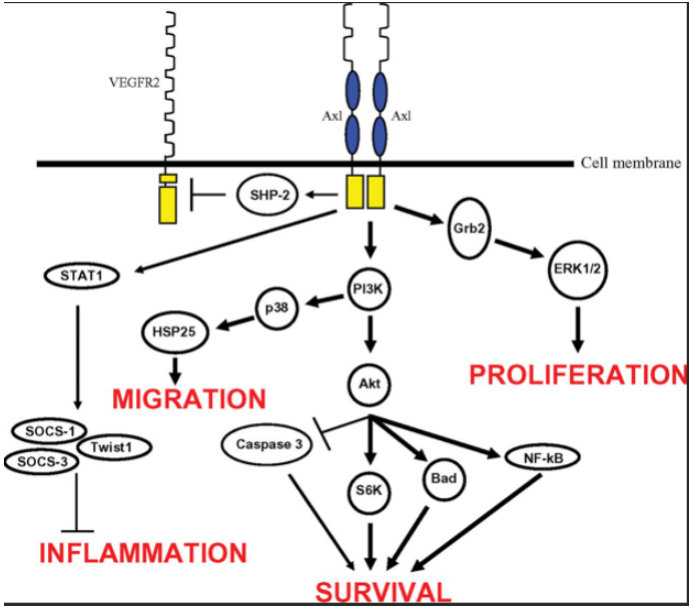
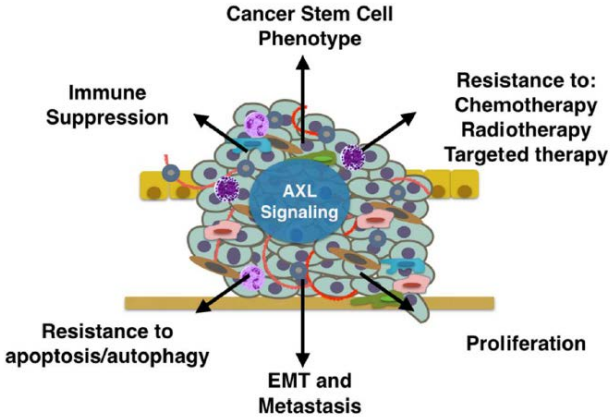



Figure from Clinical Science Apr 01, 2012, 122 (8) 361-368


*1 J Clin Invest. 2017;127(1):183–198.*
*2 Adv Cancer Res. 2008;100:35–83.*
*3 Oncogene. 2009;28(39):3442–3455*
*4 Cancer Res. 2010;70(19):7570–7579*
*5 Proc Natl Acad Sci U S A. 2006;103(15):5799–5804*
*6 Ann Diagn Pathol. 2013;17(5):425–429*
*7 Proc Natl Acad Sci U S A. 2010;107(3):1124–1129*
*8 Nat Genet. 2012;44(8):852–860*
*9 Cancer Res. 2013;73(1):331–340*

# GAS6/AXL Signaling Critical in Resistant Metastatic Ovarian Cancer

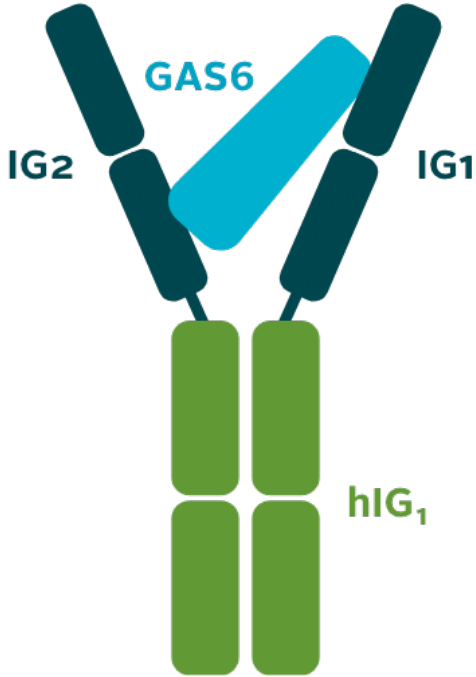
- AXL in 0% (0/10) of normal ovarian tissue
- AXL in 73% (219/297) ovarian tumor samples including low grade serous, endometroid and advanced stage tumors[1]
- Preclinical in vitro [1,2,3]
  - AXL inhibition decreases invasion/migration
- Preclinical in vivo [1,2,3]
  - AXL inhibition decreases tumor
  - AXL expression correlates with chemoresistance to carboplatin and paclitaxel
  - AXL inhibition improves sensitivity to platinum and taxane therapies




[1] Rankin et al, Cancer Res. Oct 1; 70 (19) 2010
[2] Divine et al, Oncotarget 7 (47) 2016; Quinn et al, Mol Cancer Ther November 26 2018; Kariolis et al, J Clin Invest. 2017
[3] Quinn et al. Mol Cancer Therapeutics 2019

# AVB500 Inhibits AXL Signaling by Neutralizing GAS6, Sole Ligand for AXL

- AXL-Fc protein engineered for very high affinity for GAS6
  - ~200 fold greater than native AXL
- Favorable safety and PK profile
  - GAS6 not needed by normal tissue
  - GLP preclinical studies demonstrate ≥ 30-fold safety margin (relative to max feasible dose in tox)
  - As biologic, does not compete for metabolism with chemotherapies; facilitates combination with other therapies
- Small molecules targeting AXL can have off target activities

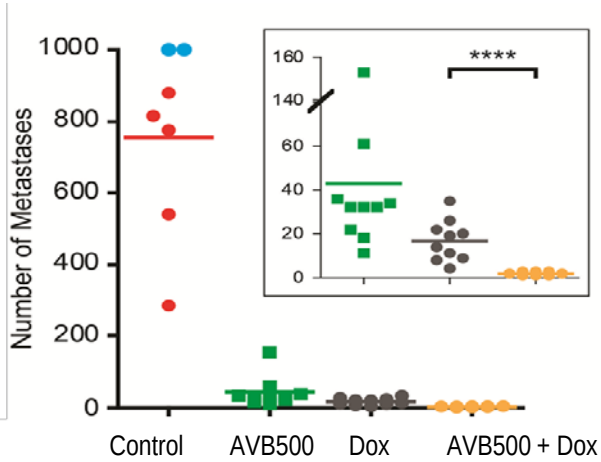


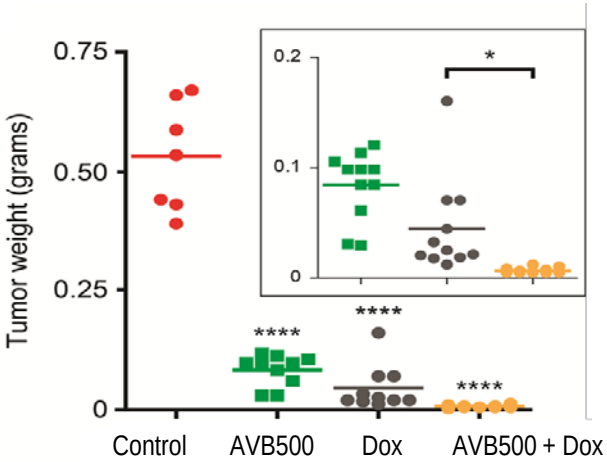



*J Clin Invest. 2017;127(1):183–198*

# AVB500 Demonstrated Activity in Multiple Preclinical Platinum-Resistant Ovarian Cancer Models

- **Single agent activity, synergistic with DNA damaging agent in multiple PROC models (OVCAR8 and SKOV3.IP) at 1mg/kg daily, a regimen that suppressed sGAS6 for 24h. Lower doses did not demonstrate same effect.**
- 20-30% cures seen and minimal detectable disease with all mice given combination

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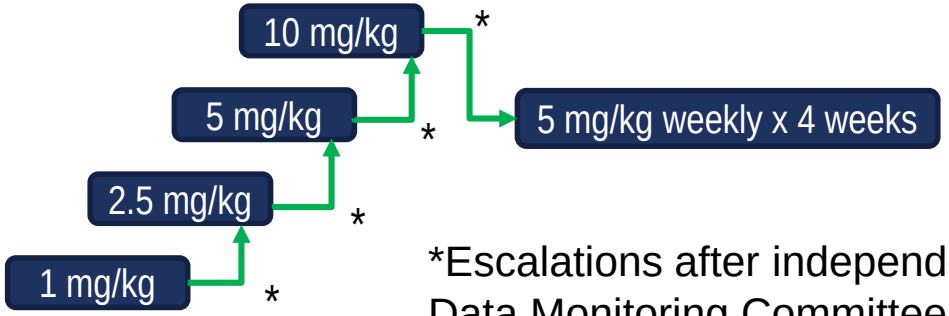
*J Clin Invest. 2017;127(1):183–198*

# Serum Biomarker-Guided Dose Escalation in First in Human Study Conducted in Healthy Volunteers

Single Ascending Dose | Repeat Dose




*Escalations after independent Data Monitoring Committee review of:
1) Safety, and
2) Target suppression via serum biomarker

RESULTS

- 42 Subjects enrolled
- No SAEs
- Well tolerated at all dose levels
- sGAS6 BLQ at all dose levels with higher doses providing longer suppression
- PK consistent with Target Mediated Drug Disposition (TMDD)

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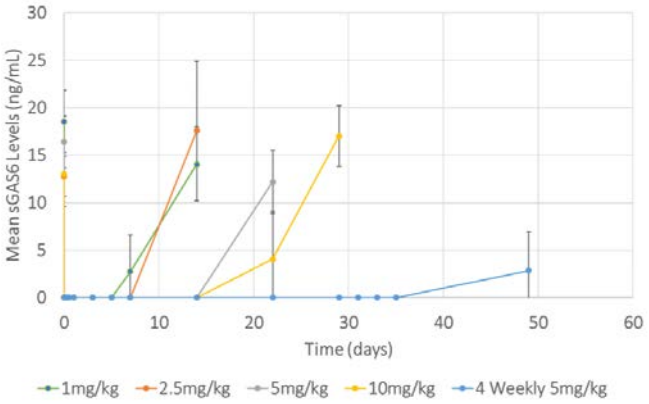
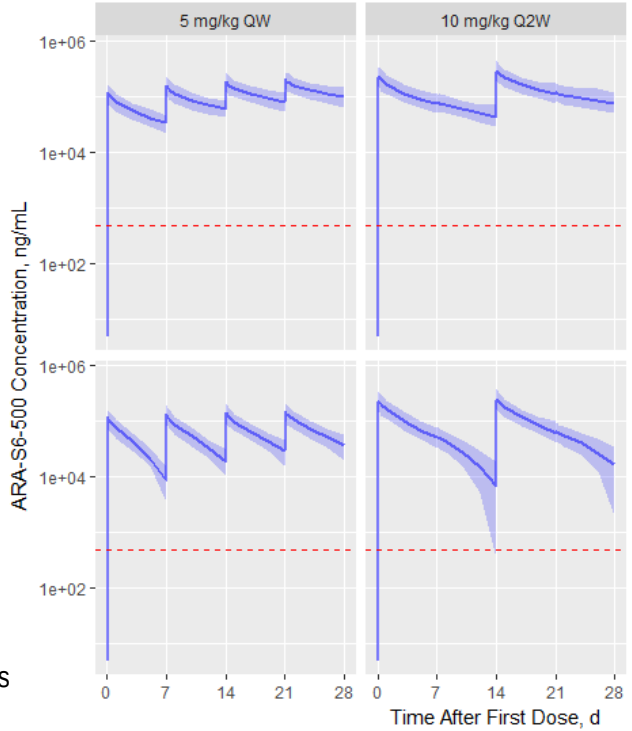
# PK/PD Model Using Biomarker Data from Healthy Volunteers Guides Dose Selection for Studies in Cancer Patients

## Healthy Volunteer Data




Simulations assume 3x higher GAS6 in pts

## Simulations in HV (top) & OC Pts (bottom)




Red dashed line shows 50% target engagement

Purple envelope represents 10-90% interval

Minimum targets based on modeling:

- 3720 ng/mL AVB trough
- BLQ (<2 ng/mL) sGAS6

HV= healthy volunteers
OC= ovarian cancer

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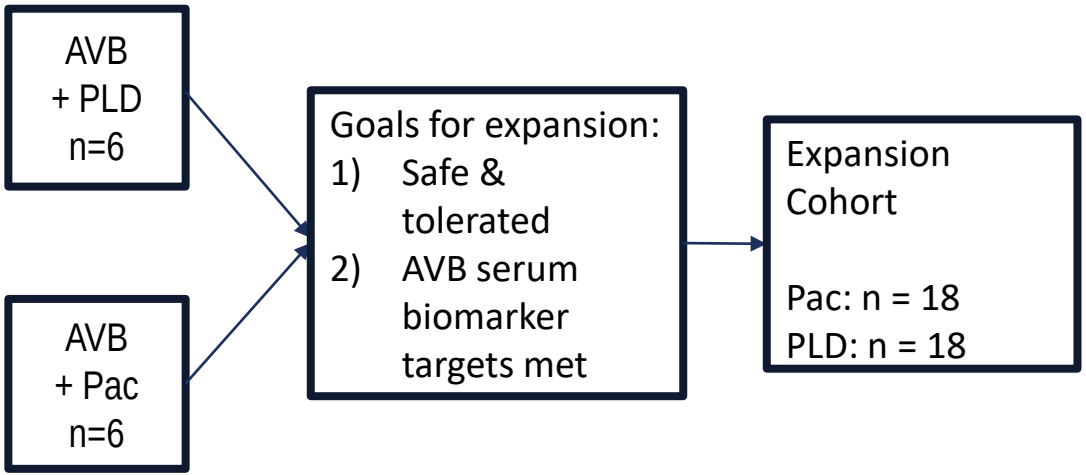
# AVB500-OC-002: A P1b Study of AVB-S6-500 in Combination with Single Agent Chemotherapy in Platinum-Resistant Ovarian Cancer

Key Eligibility Criteria

- 1-3 prior lines
- Measurable disease
- Platinum free interval ≤ 6mo after most recent platinum-containing regimen
- Adenocarcinoma NOS, high grade endometroid adenocarcinoma, mixed epithelial (≥ 80% high grade serous), high grade serous, or undifferentiated carcinoma
- ECOG performance status 0-1




AVB500 (AVB; AVB-S6-500): 10 mg/kg q14 days
Pegylated liposomal doxorubicin (PLD): 40 mg/m$^2$ d1; 28-day cycle
Paclitaxel (Pac): 80 mg/m$^2$ day 1, day 8, day 15; 28-day cycle

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NOS=not otherwise specified
ECOG = eastern cooperative oncology group

# Distribution of Baseline Characteristics and Prognostic Factors

| (Efficacy Population) | Pac arm (n=6) | PLD arm (n=6) |
|---|---|---|
| Age, years<br>median (min, max) | 63.5<br>(55, 82) | 66<br>(53, 81) |
| Prior lines | | |
| 1 | 0 | 3 (50) |
| 2 | 5 (83) | 2 (33) |
| 3 | 1 (17) | 1 (17) |
| Platinum Free Interval | | |
| > 3mo | 4 (67) | 4 (67) |
| < 3mo | 2 (33) | 2 (33) |
| ECOG | | |
| 0 | 5 (83) | 4 (67) |
| 1 | 1 (17) | 2 (33) |

# First Cycle Safety Data for the First Patients in Each Cohort

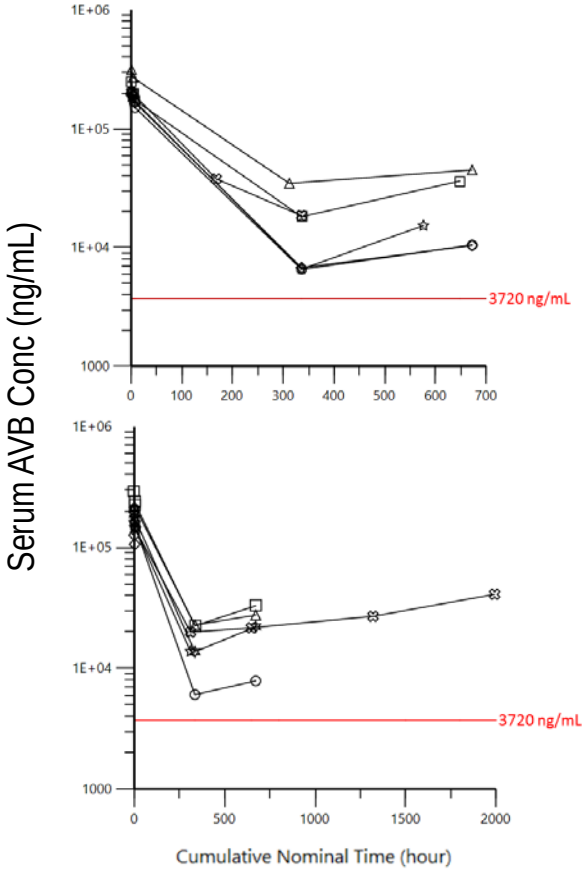
| Number of Subjects With (Safety Population) | AVB+Pac (n=6) | AVB+PLD (n=7) |
|---|---|---|
| AE | 6 (100) | 5 (71.4) |
| SAE | 0 | 0 |
| Dose Limiting Toxicity | 0 | 0 |
| Related AE with G>3 | 0 | 0 |

N=3 had Grade 2 infusion reactions with AVB infusion. A premedication regimen (anti-H2, anti-H1 ± steroid) now used for all pts in C1 per a subsequent protocol amendment. There have been no AVB-related infusion reactions in premedicated patients.

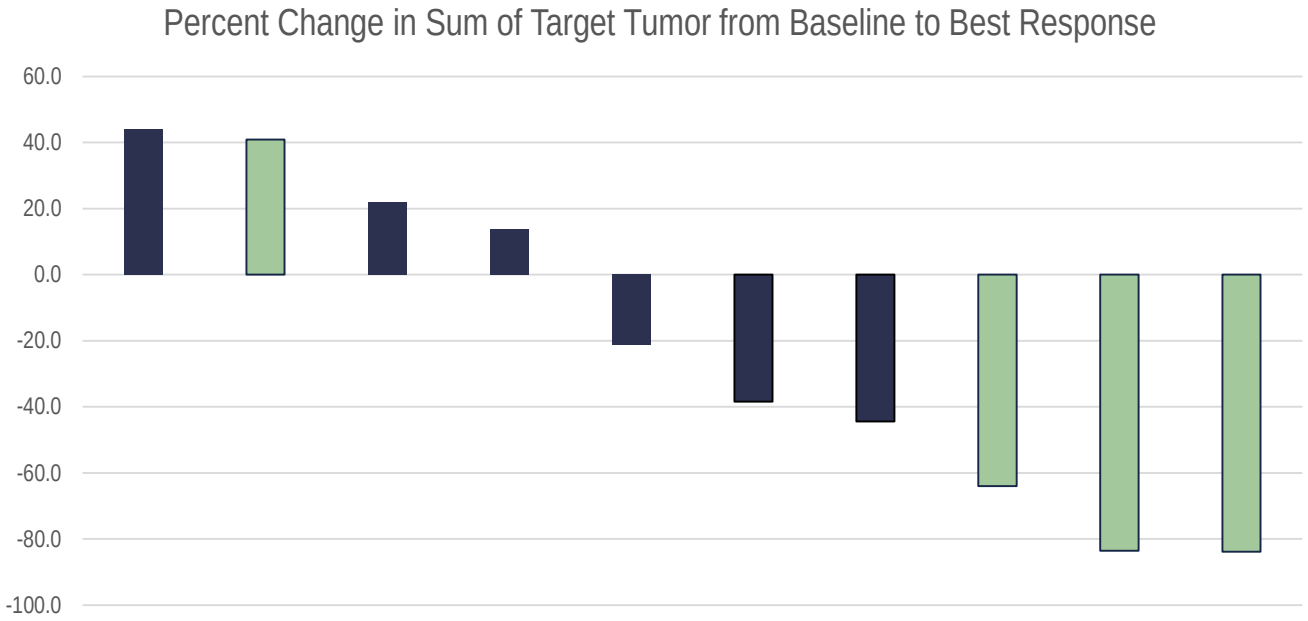
| Adverse Events (Preferred Term) Experienced During the First Cycle of Treatment by More Than 1 Patient in each Cohort (Safety Population) | | |
|---|---|---|
| | AVB+Pac (N=6) N (%) | AVB+PLD (N=7) N (%) |
| Constipation<br>Nausea<br>Vomiting | 2 (33.3) | 2 (28.6)<br>3 (42.9)<br>2 (28.6) |
| Fatigue | 3 (50.0) | 2 (28.6) |
| Headache | | 2 (28.6) |
| Infusion related reaction | | 2 (28.6) |

# First Cycle PK and PD Data for the First 6 Patients in Each Cohort

- GAS6 concentrations immediately decreased from baseline levels to BLQ in every patient, and remained BLQ throughout the two-week dosing period
- AVB500 concentrations did not decrease below 3720 ng/mL, the minimally acceptable trough exposure based on PK/PD modeling that incorporated animal and human data from the healthy volunteer clinical study



# Best Response Determined by Investigator-Assessed RECIST for First 12 Patients




| | Response Rate |
|---|---|
| **AVB+PLD** | 33% |
| **AVB+Pac** | 50% |
| **Overall** | 42% |
| **Clinical Benefit** | 58% |

Green = AVB + Pac
Blue = AVB + PLD

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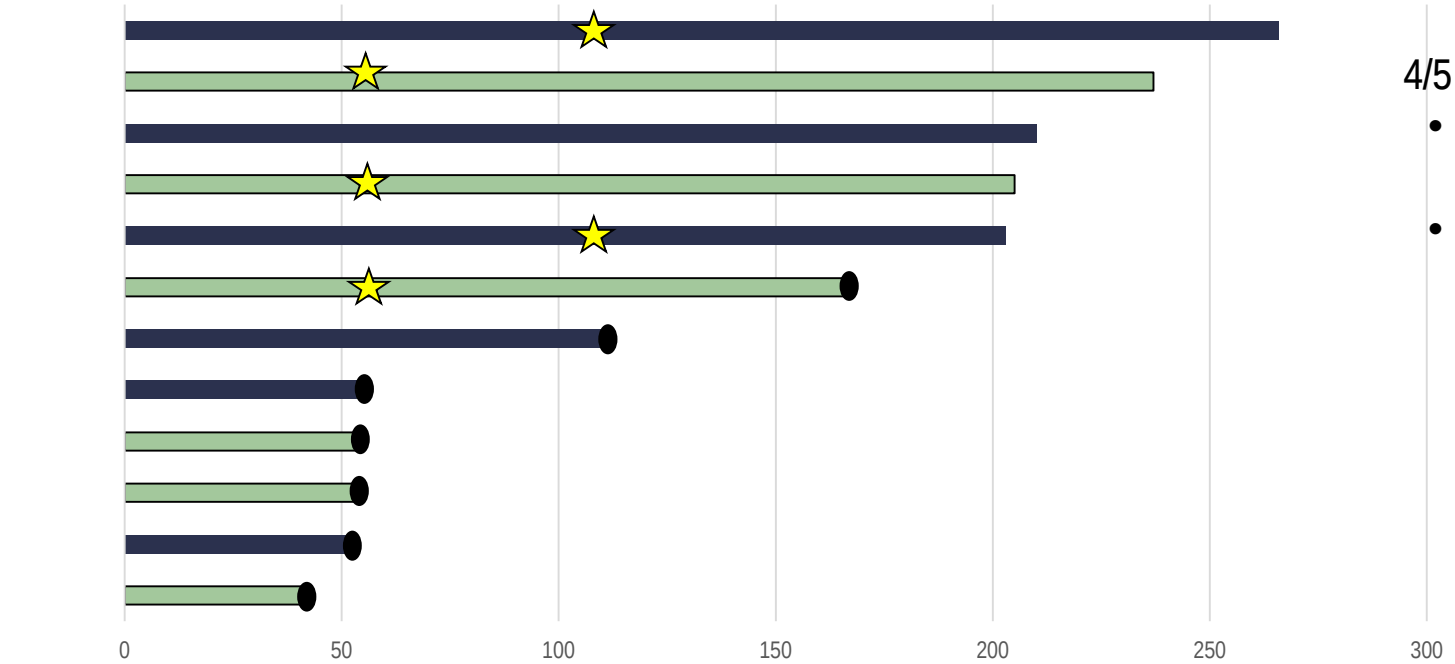
* 2 Progressive Disease patients (both in Pac arm) are not shown as CTs were not obtainable at time of progression

# Current Average Treatment Duration for Responders is 7 Months




4/5 PRs still ongoing

- 2 of the 4 continue to receive chemo + AVB
- 2 of the 4 are currently receiving AVB alone (no more chemotherapy)

AVB+Pac
AVB+PLD

★ = partial response (PR)

● = progressive disease (PD)

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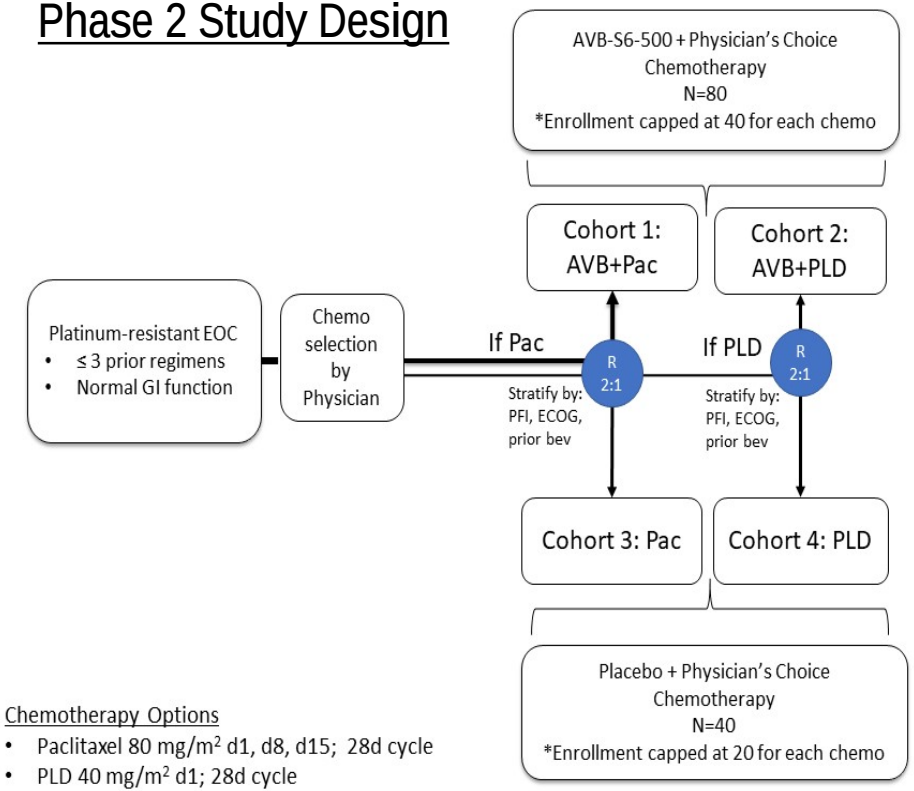
# Conclusions Based on Available Data from the First 12 Patients

- AVB500 effectively sequesters serum GAS6, the sole ligand for AXL, in platinum-resistant ovarian cancer patients
- AVB500 administration was not associated with any dose-limiting toxicities nor serious adverse events
  - Infusion reactions mitigated by premedication
- The efficacy data from these patients show early proof of concept with best overall response rate by Investigator-determined RECIST that is better than historical control

# Next Steps

- P1b study expanded to
  - Determine ORR data across larger population
  - Continuously update PK/PD model with additional data to identify optimal AVB500 dose
- Using Model-Informed Drug Development (MIDD) to guide selection of higher AVB doses for evaluation in P1b
  - Seeing preliminary data with lower response rate in subsequent patients with higher GAS6 and lower AVB500 troughs
  - Exposure response analysis indicates potential weak correlation with AVB500 trough levels and response
- Dose that is tolerated and has optimal PK/PD will be investigated in P2

## Phase 2 Study Design




Chemotherapy Options
- Paclitaxel 80 mg/m$^2$ d1, d8, d15; 28d cycle
- PLD 40 mg/m$^2$ d1; 28d cycle

ClinicalTrials.gov Identifier: NCT03639246