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
- Upregulated in many cancers, AXL overexpression linked to metastasis, poor survival, and drug resistance
- Unusually strong binding affinity between GAS6 and AXL of ~ 30 pM makes development of inhibitors to the pathway challenging

Figure from Clinical Science Apr 01, 2012, 122 (8) 361-368
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
- Preclinical in vitro
  - AXL inhibition decreases invasion/migration
- Preclinical in vivo
  - 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
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

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

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

**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)

**Single Ascending Dose**
- 1 mg/kg
- 2.5 mg/kg
- 5 mg/kg
- 10 mg/kg

**Repeat Dose**
- 5 mg/kg weekly x 4 weeks

*Escalations after independent Data Monitoring Committee review of:
1) Safety, and
2) Target suppression via serum biomarker
PK/PD Model Using Biomarker Data from Healthy Volunteers Guides Dose Selection for Studies in Cancer Patients

Healthy Volunteer Data

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

Simulations assume 3x higher GAS6 in pts
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

Goals for expansion:
1) Safe & tolerated
2) AVB serum biomarker targets met

Expansion Cohort
Pac: n = 18
PLD: n = 18

AVB500 (AVB; AVB-S6-500): 10 mg/kg q14 days
Pegylated liposomal doxorubicin (PLD): 40 mg/m² d1; 28-day cycle
Paclitaxel (Pac): 80 mg/m² day 1, day 8, day 15; 28-day cycle
## Distribution of Baseline Characteristics and Prognostic Factors

<table>
<thead>
<tr>
<th>(Efficacy Population)</th>
<th>Pac arm (n=6)</th>
<th>PLD arm (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong>&lt;br&gt;median (min, max)</td>
<td>63.5 (55, 82)</td>
<td>66 (53, 81)</td>
</tr>
<tr>
<td><strong>Prior lines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>3 (50)</td>
</tr>
<tr>
<td>2</td>
<td>5 (83)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>3</td>
<td>1 (17)</td>
<td>1 (17)</td>
</tr>
<tr>
<td><strong>Platinum Free Interval</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3mo</td>
<td>4 (67)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>&lt; 3mo</td>
<td>2 (33)</td>
<td>2 (33)</td>
</tr>
<tr>
<td><strong>ECOG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (83)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>1</td>
<td>1 (17)</td>
<td>2 (33)</td>
</tr>
</tbody>
</table>
First Cycle Safety Data for the First Patients in Each Cohort

<table>
<thead>
<tr>
<th>Number of Subjects With (Safety Population)</th>
<th>AVB+Pac (n=6)</th>
<th>AVB+PLD (n=7)</th>
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<tbody>
<tr>
<td>AE</td>
<td>6 (100)</td>
<td>5 (71.4)</td>
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<tr>
<td>SAE</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Dose Limiting Toxicity</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Related AE with G&gt;3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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                                                                                                                      | 2 (33.3)                                | 2 (28.6)                                  |
| Nausea                                                                                                                            | 3 (42.9)                                | 2 (28.6)                                  |
| Vomiting                                                                                                                          | 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

<table>
<thead>
<tr>
<th></th>
<th>Response Rate</th>
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</thead>
<tbody>
<tr>
<td>AVB+PLD</td>
<td>33%</td>
</tr>
<tr>
<td>AVB+Pac</td>
<td>50%</td>
</tr>
<tr>
<td>Overall</td>
<td>42%</td>
</tr>
<tr>
<td>Clinical Benefit</td>
<td>58%</td>
</tr>
</tbody>
</table>

Percent Change in Sum of Target Tumor from Baseline to Best Response

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

Green = AVB + Pac
Blue = AVB + PLD
**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)
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

**Platinum-resistant EOC**
- ≤ 3 prior regimens
- Normal GI function

**Chemo selection by Physician**

**Cohort 1: AVB+Pac**

**Cohort 2: AVB+PLD**

**Cohort 3: Pac**

**Cohort 4: PLD**

**Chemotherapy Options**
- Paclitaxel 80 mg/m² d1, d8, d15; 28d cycle
- PLD 40 mg/m² d1; 28d cycle

**ClinicalTrials.gov Identifier: NCT03639246**