A Phase 1b Study of Navicixizumab & Weekly Paclitaxel in Heavily Pre-Treated Platinum Resistant Ovarian, Primary Peritoneal or Fallopian Tube Cancer.

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Targeting Angiogenesis with Bevacizumab Is Standard of Care

- Phase III studies demonstrated efficacy for PFS in all settings and OS in PSROC
- AURELIA set the SOC in platinum resistant recurrent EOC (1-2 priors) with a HR of 0.48 (0.38-0.60) when bevacizumab was added to a chemotherapy backbone.

**GOG 218**
- 12.0 vs. 18.0 months
- HR 0.645 (0.551-0.756)

**GOG 213**
- 10.4 vs. 13.8 months
- HR 0.628 (0.534-0.739)

**AURELIA**
- 3.4 vs. 6.8 months
- HR 0.48 (0.38-0.60)

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- Unfortunately, in all settings, resistance to bevacizumab develops
- Despite up-regulation of angiogenesis being a near ubiquitous finding in EOC, there are, as of yet, no secondary means by which to target angiogenesis effectively
- Targeting NOTCH may represent a unique opportunity

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Role & Potential Therapeutic Benefit of Targeting Notch Signaling

Notch signaling has 5 ligands
- Delta-like (DLL) or Notch receptors 1, 2, 3, 4
- Jagged 1, 2
• In the normal ovary, Notch pathway inhibits ovarian angiogenesis and maintains the integrity of ovarian vasculature

• Ovarian cancer tissue has over-expression of DLL4, Notch1 and/or Notch3 and Jagged1

• This and other data suggest Notch signaling plays a key role in ovarian cancer angiogenesis and may be a therapeutic target
Efficacy Signal in a Phase 1 Monotherapy Anti-DLL4 Study

6/7 ovarian cancer patients had reductions in tumor volume

Demcizumab & Paclitaxel Activity in Heavily Pre-treated Platinum Resistant Ovarian Cancer

Overall response rate in the Phase 1b trial was 21% (95% CI: 6-45%)

- Demcizumab is an IgG2 monoclonal antibody targeting DLL4
- N= 19 (10 in expansion)
- 5 of 19 patients had prior bevacizumab:
  - 2 out of these 5 had PRs
  - 2 out these 5 had SD
- Safety: GI events were most common (89%), HTN 37% and pulm HTN 15%

- Overall combination was safe with a reasonable ORR in a heavily pre-treated population (bevacizumab pre-treated)

→ Can we do better with dual blockade of DLL4 and VEGF?

Coleman et al. Gynecol Oncol (2020) epub in press Feb 7, 2020
Navicixizumab: Anti-DLL4/VEGF Bispecific Antibody

• Dual inhibitor of both DLL4 and VEGF
• Proprietary bispecific antibody technology
  • Two distinct heavy chains recognizing DLL4 and VEGF respectively
  • Common light chain
  • Humanized IgG2

Dual Targeting of DLL4 and VEGF Pathways in Preclinical Human Tumor Xenograft Experiments

Simultaneous inhibition of DLL4 and VEGF with a bi-specific antibody produces anti-tumor effect superior to anti-DLL4 or anti-VEGF alone.
Phase 1A: Study of Navicixizumab in Patients with Previously Treated Solid Tumors – RECIST Data

- 4 patients (3 ovarian cancer, 1 uterine carcinosarcoma) had a partial response
- 17 patients had stable disease
- 19 patients had a reduction in the size of their target lesions including 7/11 patients with ovarian cancer

ORR among EOC was 25%
Phase 1A: Study of Navicixizumab in Patients with Previously Treated Solid Tumors – Response versus Duration

- Four patients remained on study for >300 days and 2 of these patients were on study for >500 days.
Phase 1A: Study of Navicixizumab in Patients with Previously Treated Solid Tumors – Safety Profile

• Treatment related adverse events (≥ 15% of patients) were:
  • Hypertension: 57.6%
  • Headache: 28.8%
  • Fatigue: 25.8%
  • Pulmonary hypertension: 18.2%

• Pulmonary hypertension was mostly asymptomatic at doses ≤ 5 mg/kg once every 3 weeks (6 - Grade 1, 1 - Grade 2) but was more severe at higher doses (4 - Grade 2, 1 - Grade 3)
Dose Escalation Phase

Tumor types for inclusion in dose escalation cohort:
Platinum-resistant Ovarian Cancer (PROC):
Previously treated with >2 prior therapies or prior bevacizumab

DLTs assessed on Days 0-28

Weekly Taxol + Navicixizumab Q2W

Weekly Taxol + 3 mg/kg Navi Q2W (N=3)
Weekly Taxol + 4 mg/kg Navi Q2W (N=2)

Expansion Cohort: Weekly Taxol + 3 mg/kg Q2W (N=39)

Outcome Measures

Primary: Incidence of DLT

Secondary:
• Response (RECIST)
• Response (CA-125)
• PFS
• Safety
• Immunogenicity

Trial location
• 7 US sites

Data-cut January 15, 2020
Phase 1B Study of Navicixizumab Plus Paclitaxel in PROC Patients: Demographics

<table>
<thead>
<tr>
<th>Navicixizumab Dose Level</th>
<th>3 mg/kg</th>
<th>4 mg/kg</th>
<th>Expansion 3 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3</td>
<td>2</td>
<td>39</td>
<td>44</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>66</td>
<td>73</td>
<td>60</td>
<td>63</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>2</td>
<td>2</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Primary Peritoneal Cancer</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fallopian Tube Cancer</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Platinum Resistant</td>
<td>3</td>
<td>2</td>
<td>38</td>
<td>43</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>0</td>
<td>1*</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Number (range) Prior Therapies</td>
<td>3 (3-4)</td>
<td>4.5 (4-5)</td>
<td>4 (2-12)</td>
<td>4 (2-12)</td>
</tr>
<tr>
<td>Prior Paclitaxel**</td>
<td>3</td>
<td>2</td>
<td>39</td>
<td>44/44 (100%)</td>
</tr>
<tr>
<td>Prior Bevacizumab</td>
<td>1</td>
<td>1</td>
<td>28</td>
<td>30/44 (68%)</td>
</tr>
<tr>
<td>Prior PARP Inhibitor</td>
<td>2</td>
<td>0</td>
<td>15</td>
<td>17/44 (39%)</td>
</tr>
</tbody>
</table>

* Protocol deviation.
** 1 patient received Abraxane*
### Phase 1B Study of Navicixizumab Plus Paclitaxel in PROC Patients: RECIST Response Data

<table>
<thead>
<tr>
<th></th>
<th>3 mg/kg</th>
<th>4 mg/kg</th>
<th>Expansion 3 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated/Ongoing/Evaluable</td>
<td>3/0/3</td>
<td>2/0/2</td>
<td>39/11/36</td>
<td>44/11/41</td>
</tr>
<tr>
<td>Complete Response</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (2.3%)*</td>
</tr>
<tr>
<td>Partial Response</td>
<td>2</td>
<td>2</td>
<td>14</td>
<td>18/44 (40.9%)*</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>1</td>
<td>-</td>
<td>14</td>
<td>15/44 (34%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>7/44 (16%)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>3/44 (77%)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>2</td>
<td>2</td>
<td>15</td>
<td>19/44 (43%)</td>
</tr>
<tr>
<td><strong>Clinical Benefit Rate</strong></td>
<td>3</td>
<td>2</td>
<td>29</td>
<td>34/44 (77%)</td>
</tr>
</tbody>
</table>

- 10 out of 30 (33%) bevacizumab-treated patients had a PR
- 9 out of 14 (64%) bevacizumab-naïve patients had a PR

* Unconfirmed response rates. The 56 day confirmed response rate was 16/44 (36%).
** CR+PR+SD
Phase 1B Study of Navicixizumab Plus Paclitaxel in PROC Patients: Best % Change in Target Lesion Size

Percentage of Maximal Reduction from Baseline in Sum of Longest Diameters

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Phase 1B Study of Navicixizumab Plus Paclitaxel in PROC Patients: Best % Change in Target Lesion Size – Bevacizumab Treated Patients

Percentage of Maximal Reduction from Baseline in Sum of Longest Diameters

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Phase 1B Study of Navicixizumab Plus Paclitaxel in PROC Patients: Best Percent Change in CA-125

Data-cut January 15, 2020
Phase 1B Study of Navicixizumab Plus Paclitaxel in PROC Patients: Duration of Response By Prior Bevacizumab Exposure

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab Naïve</td>
<td>14</td>
<td>8</td>
<td>7.6m</td>
<td>5.4m-NR</td>
</tr>
<tr>
<td>Bevacizumab Treated</td>
<td>30</td>
<td>21</td>
<td>5.4m</td>
<td>3.3-9.1</td>
</tr>
</tbody>
</table>

Data-cut January 15, 2020
Phase 1B Study of Navicixizumab Plus Paclitaxel in PROC Patients: Related Adverse Events ≥ 10% & > Grade 3 Adverse Events (n = 44)

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>30 (68.2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22 (50.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (27.3%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9 (20.5%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8 (18.2%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (18.2%)</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>8 (18.2%)</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>7 (15.9%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (13.6%)</td>
</tr>
<tr>
<td>BNP Increased</td>
<td>5 (11.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse event, n</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Large intestine perforation</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Small intestine hemorrhage</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>GFR decrease</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

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Anti-Drug Antibody (ADA) Data

• PK and ADA data available from 25 patients
• 4 out of 25 (18%) tested positive for ADAs
  o 1 ADA+ post-dosing → no observable impact on PK
  o 3 (12%) patients with observable impact of ADA on PK and associated infusion reaction
Phase 1B Study of Navicixizumab Plus Paclitaxel in PROC Patients: Conclusions

- Patients enrolled into the study were heavily pretreated:
  - Median of 4 prior therapies
  - 68% had received bevacizumab.
  - 39% PARP pretreated
- Efficacy data were encouraging
  - 43% response rate; 64% and 33% in bevacizumab naïve and pretreated patients, respectively
  - 75% had a GCIG CA-125 response; 100% and 60% in the bevacizumab naïve and pretreated patients, respectively
  - Median PFS = 7.2 months (95% CI: 3.9 – 8.9 months); median PFS = 7.6 & 5.4 months for bevacizumab naïve & pretreated patients
- Manageable Safety Profile
  - Related AEs > 15% were hypertension (68%), fatigue (50%), headache (27%), dyspnea (20%), diarrhea (18%), neutropenia (18%) and pulmonary hypertension (18%).
  - Hypertension was managed with a protocol defined standardized anti-hypertensive treatment algorithm.
- Navicixizumab + weekly paclitaxel has a solid signal, pre-clinical rationale and manageable safety profile that justify its movement into a randomized trial.
Thank you to all the patients, their families, investigators and their teams.