A PHASE III CLINICAL TRIAL OF BEVACIZUMAB WITH IV VERSUS IP CHEMOTHERAPY IN OVARIAN, FALLOPIAN TUBE AND PRIMARY PERITONEAL CARCINOMA NCI-SUPPLIED AGENT(S): BEVACIZUMAB (NSC #704865, IND #7921)

NCT01167712 a GOG/NRG Trial (GOG 252)

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Verbal Disclosure

• This clinical trial was supported by Genentech for bevacizumab and drug distribution
• Dr. Walker has not personally received funding for this trial
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GOG 252: IP chemo and dose dense Paclitaxel showed improved OS, both have toxicities; which is best?

<table>
<thead>
<tr>
<th>Key questions for GOG 252</th>
<th>Indications and contemporary results</th>
<th>Implications for GOG 252 schema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should we use dose dense Paclitaxel?</td>
<td>• JGOG 3016 showed improved OS, but not replicated in the US</td>
<td>Arm 1: Dose dense Paclitaxel</td>
</tr>
</tbody>
</table>
| Should we use IP chemotherapy? | • GOG 172 showed survival advantage, but was toxic, with only 42% receiving 6 cycles; additional studies were done to address the toxicity: -GOG9916/17 Substituted IP carbo for cisplatin -GOG9921 Reduced IP cisplatin dose | Arm 2: IP Chemo substitute  
Arm 3: IP chemo, reduced cisplatin dose |
| Should we use Bevacizumab? | • GOG 218 showed improved PFS with Bev, and feasibly safe with IP Chemo | All: Include Bevacizumab |
GOG 252: Schema

Eligibility
- Stage II-III Epithelial Carcinoma: Ovary, Fallopian Tube, Peritoneal
- Resected to optimal: less than or equal to 1 cm visible tumor by surgeon report
- Exploratory: suboptimal (7%) and Stage IV (5%)

Phase A: Cycles 1-6*
- Arm 1
  - Paclitaxel
    - 80 mg/m² IV over 1 hour days 1, 8, and 15
  - Carboplatin
    - AUC 6 IV on day 1
  - Bevacizumab
    - 15 mg/kg IV on day 1 beginning on cycle 2

- Arm 2
  - Paclitaxel
    - 80 mg/m² IV over 1 hour days 1, 8, and 15
  - Carboplatin
    - AUC 6 IV on day 1
  - Bevacizumab
    - 15 mg/kg IV on day 1 beginning on cycle 2

- Arm 3
  - Paclitaxel
    - 135 mg/m² IV over 3 hours day 1
  - Cisplatin
    - 75 mg/m² IP on day 2
  - Paclitaxel
    - 60 mg/m² IP on day 8
  - Bevacizumab
    - 15 mg/kg IV on day 1 beginning on cycle 2

Phase B: Cycles 7-22*
- Bevacizumab
  - 15 mg/kg IV on day 1 for cycles 7-22
Differences in Dosing in GOG 252 Arm 3 IP Cisplatin compared to GOG 172

- Dose reduction cisplatin (100 down to 75 mg/m²)
- Infusion time reduction 135 mg/m² paclitaxel (3 hr instead of 24h)
- All outpatient therapy
- Bevacizumab 15 mg/m² for all arms on cycles 2-22
- Comparison arm dose dense paclitaxel with carbo IV AUC 6- GOG 262 (JGOG)
- Second experimental Arm IP carbo and dose dense paclitaxel
GOG 252 accrual and demographics

• 1560 participants from July 2009-Nov 2011
• Median age - 58 years
• White 90%; Black 3%; Hispanic 3%
• Stage III - 84%
• Stage II - 10%
• Grade 3 Serous – 72%
• No visible residual disease per surgeon – 57%
• Exploratory aim: suboptimal (7%) and Stage IV (5%)
## GOG 252 assigned treatment completion

<table>
<thead>
<tr>
<th>Arm</th>
<th>At least 6 cycles of Platinum</th>
<th>At least 6 cycles of taxane</th>
<th># Bev Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1: IV Carbo</td>
<td>90%</td>
<td>87%</td>
<td>20</td>
</tr>
<tr>
<td>Arm 2: IP Carb</td>
<td>90%</td>
<td>88%</td>
<td>19</td>
</tr>
<tr>
<td>Arm 3: IP Cisp</td>
<td>84%</td>
<td>87%</td>
<td>17</td>
</tr>
</tbody>
</table>

Cross-over to the IV only therapy occurred in 16% randomized to IP carbo arm and 28% randomized to IP cis arm.

Twice as many patients stopped protocol directed bevacizumab prior to completion of Cycle 6 on the arm 3 IP cisplatin (30% vs 15%).
## GOG 252 Toxicity

<table>
<thead>
<tr>
<th>Event</th>
<th>IV Carbo</th>
<th>IP Carbo</th>
<th>IP Cisp</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G2</td>
<td>&gt;G3 G2</td>
<td>&gt;G3 G2</td>
</tr>
<tr>
<td>Feb/neut</td>
<td>2.5%</td>
<td>2.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Neut</td>
<td>71%</td>
<td>68%</td>
<td>64%</td>
</tr>
<tr>
<td>Platelets</td>
<td>17.6%</td>
<td>15.1%</td>
<td>6.1%</td>
</tr>
<tr>
<td>HTN</td>
<td>11.9%</td>
<td>13.8%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Thromb</td>
<td>6.3%</td>
<td>8.4%</td>
<td>9.0%</td>
</tr>
<tr>
<td>N/V</td>
<td>5.1%</td>
<td>4.7%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Fistula</td>
<td>5.3%</td>
<td>3.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Urine Prot</td>
<td>2.7%</td>
<td>3.1%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Sens Neur</td>
<td><strong>24.1</strong></td>
<td><strong>5.7%</strong></td>
<td><strong>22.6</strong></td>
</tr>
</tbody>
</table>
Progression Free Survival Optimal Stage II-III (10% stage II)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>Median PFS</th>
<th>HR [95% CI]</th>
<th>Logrank</th>
<th>Logrank</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Carbo</td>
<td>461</td>
<td>303</td>
<td>26.8 months</td>
<td>Reference arm</td>
<td>P-value</td>
<td>Chi square</td>
</tr>
<tr>
<td>IP Carbo</td>
<td>464</td>
<td>300</td>
<td>28.7 months</td>
<td>0.947 [0.808-1.11]</td>
<td>0.416</td>
<td>0.661</td>
</tr>
<tr>
<td>IP Cisp</td>
<td>456</td>
<td>307</td>
<td>27.8 months</td>
<td>1.01 [0.858-1.18]</td>
<td>0.727</td>
<td>0.122</td>
</tr>
</tbody>
</table>

- Estimated hazard ratios, and logrank tests are adjusted for stage of disease and size of residual disease micro vs < 1cm
- CT required every 6 months for surveillance (not required in GOG 114/172)
Progression Free Survival Optimal Stage II-III

Stage II or III Optimally Debulked Progression-Free Survival by Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Crb(IV)+T+Bev</td>
<td>303</td>
<td>461</td>
<td>26.8</td>
</tr>
<tr>
<td>2: Crb(IP)+T+Bev</td>
<td>300</td>
<td>464</td>
<td>28.7</td>
</tr>
<tr>
<td>3: Cis(IP)+T+Bev</td>
<td>307</td>
<td>456</td>
<td>27.8</td>
</tr>
</tbody>
</table>
Progression-Free Survival by Treatment Group
Stage III with No Gross Residual Disease

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Crb(IV)+T+Bev</td>
<td>144</td>
<td>239</td>
<td>31.3</td>
</tr>
<tr>
<td>2: Crb(IP)+T+Bev</td>
<td>145</td>
<td>238</td>
<td>31.8</td>
</tr>
<tr>
<td>3: Cis(IP)+T+Bev</td>
<td>138</td>
<td>239</td>
<td>33.8</td>
</tr>
</tbody>
</table>

Months on Study

Proportion Surviving Progression-Free

0.0 0.2 0.4 0.6 0.8 1.0
Proportion Surviving Progression-Free
## Across Study Comparisons for PFS

<table>
<thead>
<tr>
<th>Arm Study</th>
<th>PFS Median in mos No visible dx Stage 3</th>
<th>PFS median mos 1 cm or less visible dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 114 &amp; 172 IV cisplatin</td>
<td>33.4</td>
<td></td>
</tr>
<tr>
<td>GOG 172 IV cisplatin</td>
<td>43.2</td>
<td>18.3</td>
</tr>
<tr>
<td>GOG 252 IV carbo</td>
<td>31.3</td>
<td>26.8 (10% stage II)</td>
</tr>
<tr>
<td>GOG 114 &amp; 172 IP cisplatin</td>
<td>43.2</td>
<td></td>
</tr>
<tr>
<td>GOG 172 IP cisplatin</td>
<td><strong>60.4</strong></td>
<td>23.8</td>
</tr>
<tr>
<td>GOG 252 IP carboplatin</td>
<td>31.8</td>
<td>28.7 (10% Stage II)</td>
</tr>
<tr>
<td>GOG 252 IP cisplatin</td>
<td>33.8</td>
<td>27.8 (10% Stage II)</td>
</tr>
</tbody>
</table>
Discussion

• Survival for optimal and no residual disease participants will not be available for a few years.
• Dose reductions of paclitaxel and cisplatin as well as cross-over may have compromised efficacy.
• Dose dense paclitaxel may have improved efficacy to allow us to abandon IP chemo- must we wait- combine both?
• Bevacizumab interactions could have clouded analysis
Conclusions

- All arms have excessive toxicity
- Neurotoxicity is similarly high in all arms
- Reserve changes in treatment recommendations until survival data available for no residual disease high grade serous Stage III participants.
- IP Cisplatin increases bevacizumab associated HTN
GOG 172 Schema

Ovarian cancer
Optimal (<1cm)
Stage III
Stratify:
Gross residual
Planned 2\textsuperscript{nd} look

Randomize

Paclitaxel 135 mg/m\textsuperscript{2}/24h
Cisplatin 75 mg/m\textsuperscript{2}
q 21 days x 6

Paclitaxel 135 mg/m\textsuperscript{2}/24h
Cisplatin 100 mg/m\textsuperscript{2} IP D2
Paclitaxel 60 mg/m\textsuperscript{2} IP D8
q 21 days x 6

GOG 172: Ovarian (Optimal III)

CDDP (IP) Paclitaxel (IP + IV) (n = 206)
CDDP (IV) Paclitaxel (IV) (n = 210)

Residual disease and Survival: GOG 172, 114

Landrum et al. Gyn Onc 2013

PFS

OS

P = <0.001
43 months

P = <0.001
110 months
RESIDUAL DISEASE AND SURVIVAL: GOG 172, 114

Significantly Longer PFS and OS for NGR and IP

P = <0.001
43 months

P = <0.001
110 months
Histology and Survival: GOG 172,114

PFS

| serous adenocarcinoma | endometrioid adenocarcinoma | mixed epithelial carcinoma | clear-cell carcinoma | other |

P = 0.001

OS

| serous adenocarcinoma | endometrioid adenocarcinoma | mixed epithelial carcinoma | clear-cell carcinoma | other |

P = < 0.001
Histology and Survival: GOG 172,114

PFS

P = 0.001

OS

P = < 0.001