Progress in Drug Development for Rare Epithelial Ovarian Cancers: The NRG Oncology Experience and Beyond

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Framework

• Scope of discussion: Rare EOC
  • Clear Cell Carcinoma
  • Low-Grade Serous Carcinoma
  • Mucinous Carcinoma

• All rare ovarian cancers are not created equal
• GOG established Rare Tumor Committee in 2005
• No rare EOC trials existed prior to that time
• Essentially no prospective data for rare subtypes
Challenges and Barriers

• Small number of cases
• Long accrual times
• Few interested investigators
• Less attention by scientific community
• Funding priority has been low
• Low priority for Pharma
• Fewer patient advocates
• Lack of standard bioinformatics methods and trial designs
### Clinical Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Clear Cell</th>
<th>Low-Grade Serous</th>
<th>Mucinous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>5%</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Stage Distribution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stages I/II</td>
<td>67%</td>
<td>10%</td>
<td>61%</td>
</tr>
<tr>
<td>Stages III/IV</td>
<td>33%</td>
<td>90%</td>
<td>39%</td>
</tr>
<tr>
<td>Biology</td>
<td>Aggressive</td>
<td>Indolent</td>
<td>Aggressive</td>
</tr>
<tr>
<td>Relative Chemoresistance</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Outcomes in Early Stage</td>
<td>Similar to HGSC HR = .87</td>
<td>Unknown but thought to be excellent</td>
<td>Similar to HGSC HR = .87</td>
</tr>
<tr>
<td></td>
<td>Median OS = 21 mo Worse than HGSC HR = 2.2</td>
<td>Median OS = 101 mo Better than HGSC HR = ?</td>
<td>Median OS = 15 mo Worse than HGSC HR = 2.7</td>
</tr>
</tbody>
</table>
Mucinous Carcinoma: Key Pathways & Potential Targets

- Angiogenesis pathway

- HER-2/neu amplification (20%)

- MAPK (KRAS mutation, 40-50%)
mEOC/GOG 241: A Randomized Phase III Trial of Capecitabine/Oxaliplatin vs. Paclitaxel/Carboplatin +/- Bevacizumab in Patients with Previously Untreated Mucinous Ovarian Cancer

Stage II-IV or Recurrent Stage I Mucinous Carcinoma of Ovary (N = 332)

Carboplatin AUC 5/6
Paclitaxel 175 mg/m²
X 6 cycles

Bevacizumab 15 mg/kg
Q. 3 wk. X 6

Oxaliplatin 130 mg/m²
Capecitabine 850 mg/m² bd
X 6 cycles

Bevacizumab 15 mg/kg
Q. 3 wk. X 6

No Bevacizumab

No Bevacizumab
- Target accrual = 330
- Closed early for slow accrual: Only 50 pts accrued (34 UK, 16 US)
- 40/50 cases available for central pathology review: Only 18 (45%) were diagnosed as primary mucinous ovarian cancer
- Neither of experimental regimens (Oxal/Cape vs. Pac/Carbo or Bev versus no Bev) clearly improved OS or PFS
Mucinous Carcinoma: Future Directions

- Advanced stage mucinous carcinoma is rarer than originally thought
- Path for progress: Smaller phase II trials or basket trials
- Prospective central pathology review is essential
- Potential trials:
  - Targeting KRAS mutations
  - Targeting HER-2/neu amplification
  - Immunotherapy: Pts whose tumors have high CD8+ tumor-infiltrating lymphocytes have improved survival
  - PI3K/mTOR + MEK inhibitors show synergistic anti-tumor effects preclinically
  - Oxaliplatin + dasatinib reduces cancer cell viability and promotes apoptosis in human mEOC cell lines
Clear Cell Carcinoma: Key Pathways & Potential Targets

- ARID1A mutation 50%
- PI3K/AKT/mTOR pathway 30-40%
- Angiogenesis pathway
- PD-1 and PD-L1
  - HNF-1β upregulation 100%
  - IL6-HIF-1α pathway upregulation 50%
  - MET amplification 20-30%
  - HER-2 amplification 14%
  - PPM1D amplification 10%
  - Microsatellite instability (MSI) 7-18%
## Clear Cell Carcinoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Setting</th>
<th>No. Pts</th>
<th>Agent(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>JGOG3017</td>
<td>III</td>
<td>First-line</td>
<td>667</td>
<td>Irinotecan/Cisplatin vs Paclitaxel/Carboplatin</td>
<td>2-yr OS = 85.5% vs 87.4% (NS)</td>
</tr>
<tr>
<td>GOG 268</td>
<td>II</td>
<td>First-line</td>
<td>90</td>
<td>Paclitaxel/Carboplatin + Temsirolimus → Temsirolimus maintenance</td>
<td>54% with PFS &gt; 12 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No better than historical controls</td>
</tr>
<tr>
<td>GOG 254</td>
<td>II</td>
<td>Recurrent</td>
<td>35</td>
<td>Sunitinib</td>
<td>ORR = 6.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median PFS = 2.7 mo</td>
</tr>
<tr>
<td>NRG-GY-001</td>
<td>II</td>
<td>Recurrent</td>
<td>13</td>
<td>Cabozantinib</td>
<td>ORR = 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median PFS = 3.6 mo</td>
</tr>
<tr>
<td>Princess Margaret Cancer Centre Trial</td>
<td>II</td>
<td>Recurrent</td>
<td>40</td>
<td>ENMD-2076</td>
<td>ORR = 5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median PFS = 3.7 mo</td>
</tr>
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<tbody>
<tr>
<td>GOG 283</td>
<td>II</td>
<td>Recurrent</td>
<td>35</td>
<td>Dasatinib</td>
<td>Pending analysis</td>
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<tr>
<td>NiCCC</td>
<td>Randomized II</td>
<td>Recurrent</td>
<td>--</td>
<td>Nintedanib vs SOC</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NRG-GY-014</td>
<td>II (basket)</td>
<td>Recurrent</td>
<td>--</td>
<td>Tazemetostat</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>NRG-GY-016</td>
<td>II</td>
<td>Recurrent</td>
<td>--</td>
<td>Pembrolizumab + Epacadostat</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>ATARI/NCRI</td>
<td>II</td>
<td>Recurrent</td>
<td>--</td>
<td>AZD6738 +/- Olaparib</td>
<td>Not yet recruiting</td>
</tr>
</tbody>
</table>
Clear Cell Carcinoma: Future Directions

• Continue to conduct phase II or basket trials

• Targets of most interest:
  – PD-1 or PD-L1
  – ARID1A mutation
  – PI3K/AKT/mTOR pathway
  – Angiogenesis pathway
Low-Grade Serous Carcinoma: Key Pathways & Potential Targets

• MAP Kinase pathway
  – KRAS 20-40%
  – BRAF 5-10%
  – NRAS 15%
• Estrogen Receptor
• Angiogenesis pathway
• IGFR-1
Phase II study of selumetinib (MEKi) in 52 women with recurrent LGSC

- **ORR = 15%**
- **Clinical benefit rate = 80%**
- **No correlation of outcome with KRAS/BRAF mutations**
Randomized Phase III Trial

NCT01849874
MILO Trial

Recurrent LGSC

Physician’s Choice:
Paclitaxel
Liposomal Doxorubicin
Topotecan

MEK162
NCT02101788
GOG-0281

Randomized Phase III Trial

Physician’s Choice:
- Weekly Paclitaxel
- Liposomal Doxorubicin
- Topotecan
- Letrozole
- Tamoxifen

Trametinib

Recurrent LGSC
Randomized Phase II Trial

NCT01936363
Phase I Study of Selumetinib + Olaparib in Women with KRAS Mutant Tumors (SOLAR)
A Phase II Trial of Ribociclib + Letrozole in Women with Recurrent Low-Grade Serous Carcinoma

- **Recurrent Low-Grade Serous Carcinoma**

- Letrozole 2.5 mg daily + Ribociclib 600 mg x 21d then 7d off

- **Sponsor:** Novartis
- **GOG Foundation Trial**
- **Target:** 50 pts
- **Estimated to activate Q3 2018**
Pilot Study of Neoadjuvant Fulvestrant + CDK 4/6 Inhibitor in Low-Grade Serous Ovarian Cancer

- **Sponsor:** AZ
- **Target:** 15 pts
- **Estimated to activate Q4 2018**
NRG-GY-019:
Randomized Phase III Trial of Paclitaxel/Carboplatin Followed by Maintenance Letrozole versus Letrozole Monotherapy in Stage II-IV Low-Grade Serous Carcinoma

- Sponsor: NCI (NRG Oncology)
- International phase III trial
- Primary Objective: PFS
- Target: 450 pts
- Estimated to activate Q2 2019
Low-Grade Serous Carcinoma: Future Directions

• Continue to study genomics of low-grade serous carcinoma
• Await findings from MEKi trials
• Conduct combination targeted aged trials
  – MEKi + PARPi
  – MEKi + Letrozole
  – MEKi + PI3Ki
  – MEKi + IGF-1R inhibitor
  – MEKi + Metformin
  – MEKi + BRAFi
• Activate trials focused on hormonal therapy