Targeted Therapy in Ovarian Cancer
Rebecca C. Amend, MD
Division of Gyn Oncology

2015 US Female Cancer Statistics

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>New Cases</th>
<th>Deaths</th>
<th>Predicted Cases</th>
<th>Predicted Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>105,590</td>
<td>71,660</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>231,840</td>
<td>40,290</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital tract</td>
<td>98,280</td>
<td>30,440</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>47,200</td>
<td>23,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>24,120</td>
<td>19,850</td>
<td></td>
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</tr>
</tbody>
</table>

New Cancer Diagnoses and Estimated Deaths in the U.S.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Predicted Cases</th>
<th>Predicted Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>234,190</td>
<td>40,730</td>
</tr>
<tr>
<td>Uterine</td>
<td>54,870</td>
<td>10,170</td>
</tr>
<tr>
<td>Ovary</td>
<td>21,290</td>
<td>14,180</td>
</tr>
<tr>
<td>Cervical</td>
<td>12,900</td>
<td>4,100</td>
</tr>
<tr>
<td>Vulvar</td>
<td>5,350</td>
<td>1,080</td>
</tr>
</tbody>
</table>

Siegel R et al. CA Cancer J Clin 2015
**Histologic types of Epithelial Ovarian Cancer**

- High Grade Serous (70%) – resembling fallopian tube
- Endometrioid (10%) – resembling endometrium (associated with endometriosis)
- Clear Cell (10%) – glycogen rich cells resemble endometrial glands in pregnancy (associated with endometriosis)
- Mucinous (3%) – resembling endocervix
- Low Grade serous (<5%) – see above
- Transitional cell (<1%) – resembling bladder

**Ovarian Cancer Statistics and Standard of Care in 2015**

- 21,290 new cases and 14,180 deaths estimated in the US in 2015 – 75% diagnosed at late stage (stage III/IV)
- Most treated with surgical cytoreduction followed by adjuvant platinum-taxane based chemotherapy
- Most patients recur within 2 years and receive multiple rounds of chemotherapy
- 34% survive >10 years

**Ovarian Cancer - Progress in Outcome**

Modified from David Spriggs
**FDA approved drugs for Ovarian Cancer - Timeline**

- **1978** Cisplatin
- **1990** Altretamine
- **1991** Carboplatin
- **1992** Paclitaxel
- **1996** Topotecan
- **1999** Liposomal Doxorubicin (Accelerated)
- **2005** Liposomal Doxorubicin (Full)
- **2006** Gemcitabine
- **2014** Bevacizumab
- **2014** Olaparib (BRCA mutation carriers)

**New Chemotherapy Approaches in Advanced Ovarian Cancer**

- Intraperitoneal chemotherapy
- Neoadjuvant chemotherapy
- Dose dense taxanes
- Anti-angiogenic therapy
- PARP inhibitors

**Anti-angiogenic therapy**
VEGF Inhibition

Biologically-Targeted Drugs (Ovarian Cancer)

GOG 170 Series: Track Record

FDR Approval: November 2014

Bevacizumab

- FDA approved for use in combination with chemotherapy in the treatment of women with platinum-resistant, recurrent ovarian cancer
- Studied as primary therapy and consolidation with paclitaxel and carboplatin (GOG 218)
  - Not FDA approved
Angiogenesis as a target: Ovarian cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>VEGF Ligand</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 2181</td>
<td>II/II</td>
<td>Bevacizumab</td>
<td>0.72 (0.63-0.82)</td>
<td>0.89 (0.75-1.06)</td>
</tr>
<tr>
<td>ICON72</td>
<td>II/II</td>
<td>Bevacizumab</td>
<td>0.75 (0.67-0.85)</td>
<td>0.89 (0.75-1.06)</td>
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<tr>
<td>AURELIA5</td>
<td>II</td>
<td>Bevacizumab</td>
<td>0.48 (0.40-0.58)</td>
<td>0.84 (0.68-1.05)</td>
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<tr>
<td>GOG 2139</td>
<td>II</td>
<td>Bevacizumab</td>
<td>0.52 (0.43-0.63)</td>
<td>0.83 (0.66-1.04)</td>
</tr>
</tbody>
</table>

Frontline Anti-VEGF Therapy: GOG-0218

Previously unmet treatment of ovarian, primary peritoneal, or fallopian tube cancer

- Stage III optimal (macroscopic)
- Stage III suboptimal
- Stage IV

n=1873

Stratification variables:
- GOG performance status
- Stage/debulking status

Median Δ: 3.5 months

Frontline Anti-VEGF Therapy: GOG-0218

<table>
<thead>
<tr>
<th>No. of Blocks</th>
<th>CP low or placebo</th>
<th>Placebo</th>
<th>Paclitaxel</th>
<th>Carboplatin AUC 6</th>
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<tbody>
<tr>
<td>15</td>
<td>18</td>
<td>1,357</td>
<td>235</td>
<td>235</td>
</tr>
<tr>
<td>19</td>
<td>18</td>
<td>1,357</td>
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<td>235</td>
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</table>

Burger et al., NEJM 2011
Frontline ICON7: Similar findings for PFS

Parren et al., NEJM 2011

PARP inhibitors
Poly ADP-ribose polymerase inhibitor that blocks enzymes in repairing damaged DNA

Olaparib approved for women with advanced ovarian cancer with defective BRCA genes
Proportion Of Hereditary Ovarian Cancer

Ovarian Cancer

- 15%

Sporadic  Hereditary

Ovarian Cancer: GENETICS

- BRCA 1&2
  - Autosomal dominant inheritance
  - Tumor suppressor gene with loss of function when mutated
  - BRCA1 cancers median age 42
  - Lifetime ovarian cancer risk 39-54%
  - BRCA2 cancers - median age 52
  - Lifetime cancer risk 11-23%
  - Tend to have better outcomes than matched non-carrier controls

BRCA and PARP
Synthetic Lethality Concept

Can we combine an anti-angiogenic and Parp Inhibitor?

A Randomized Phase 2 Trial Comparing Efficacy of the Combination of the PARP-inhibitor Olaparib and the Anti-angiogenic Cediranib Against Olaparib Alone in Recurrent Platinum-sensitive Ovarian Cancer

Joyce F. Liu, William E. Barr, Michael Bitran, Jung-Mi Lee, Xiaohui Huang, Brenda Giometti, Crystal Norman, Asian Nicholas, Anne S. Jeffers, Lisa Coenegrachts, Carsten Wieden, Hong Lee, Eric Wiendl, Elisa Kaladi, David George, Lincoln A. Marcus

Mossadon Cancer Institute, Mossadon Cancer Hospital, National Cancer Institute, University of Michigan, University of Chicago, Colon Cancer Medical Center, Beth Israel Deaconess Medical Center, The Dana Farber Cancer Institute, and St. Jude Medical Center.

Presented at the 2014 ASCO Annual Meeting.
Primary Outcome: Cediranib/olaparib significantly increased PFS compared to olaparib alone

Presented By Joyce Liu at 2014 ASCO Annual Meeting

Cediranib/olaparib significantly increased PFS in patients without a BRCA mutation

Presented By Joyce Liu at 2014 ASCO Annual Meeting

Conclusions

- Combination of cediranib and olaparib was more active than olaparib alone
  - Improved PFS: median PFS 9.0 vs. 17.7 months (HR 0.42, p = 0.005)
  - Increased ORR: 49% vs. 62% (p = 0.002)
  - OS data not mature (18 total OS events)
- Activity observed in both BRCA mutation carriers and BRCA non-carrier/unknown patients
- Toxicity profile was acceptable
  - Most common toxicities were hypertension, diarrhea, fatigue
  - Generally manageable with symptom management and dose hold reductions
- Degree of activity supports additional clinical evaluation of cediranib/olaparib combination in ovarian cancer
Other targeted agents...

<table>
<thead>
<tr>
<th>Molecular Classification</th>
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<tbody>
<tr>
<td><strong>Type I</strong></td>
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<tr>
<td><strong>Histology</strong></td>
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<tr>
<td><strong>Mutations</strong></td>
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<tr>
<td><strong>Overexpression</strong></td>
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<tr>
<td><strong>Presentation</strong></td>
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</table>
(AGO-OVAR16) Study: Multikinase Inhibitor

• Background: Maintenance (Consolidation) therapy following successful primary treatment in ovarian cancer has been largely disappointing. This trial attempted to evaluate the utility of an oral multikinase inhibitor (pazopanib) for maintenance following primary therapy.
• Randomized double-blind, phase III trial of pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Results:
• 940 patient randomized (91% had Stage III/IV disease)
• Median PFS:
  • Pazopanib: 17.9 months
  • Placebo: 12.3 months (p=0.0021)
  • HR 0.766 (95% CI: 0.64 – 0.91)
• Higher mean exposure to placebo (11.7 months) than pazopanib (8.9)
• Similar OS between arms although only 189 events (20.1% of study) have occurred
• Adverse events:
  • Not surprisingly, pazopanib was associated with more AE

Conclusions:
• Pazopanib improved PFS in patients following primary therapy. OS data is immature.
How do we individualize treatment?

Ovarian cancers are molecularly heterogeneous

- 489 tumors: Genomic alterations observed in nearly every chromosome
- with the exception of TP53 mutations, any one genomic alteration is found in only a small fraction of patient tumors
  - One drug is unlikely to be effective for all patients
  - Drugs must be developed for specific molecular tumor types
  - Profiling of individual tumors using a broad profiling panel is necessary

Data provided by Dr. D. Levine [TCGA study: Nature 474, 609-615 (2011)]

Background on OVCA PMI Project at UAB

- Tumor Cancer Genome Atlas (TCGA) -> heterogeneity of high grade papillary serous ovarian cancer
- Chemo-refractory recurrent ovarian cancer (n=48) identified 67 "actionable" genomic alterations
  - predicted sensitivity or resistance to a FDA approved drug or standard therapy OR
    one that was either inclusion or exclusion criteria for a specific experimental therapy in an NCI registered clinical trial.
- Genotype-guided therapy: significantly improved lung cancer outcomes
Aim

- Capture patients that have a potential molecular target that may allow for the “off-label” use of targeted therapy against these “actionable” aberrations
  - This number will continue to grow within the 3 years
  - Phase 1 Trial Center also starting to grow
Recurrent Ovarian Cancer (~250/year)
Patient Consent
Next Generation Sequencing (NGS)

Electronic Medical Record (EMR)
1. FDA approved targeted agent
2. Clinical Trial

FDA approved targeted agent
Clinician drug of choice

Personalized Medicine Clinic Note
MTB Patient Example

Patient XX
Specific Pathways
KRAS or BRAF mutation status is a useful predictor of sensitivity to MEK inhibition in ovarian cancer

Clinical Trials

Futuristic trials are provided by Isis.

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Stage</th>
<th>Study Name</th>
<th>Study Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer</td>
<td>I</td>
<td>Study Name</td>
<td>Study Design</td>
<td>Duration</td>
</tr>
</tbody>
</table>

Published online: 3 November 2016
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Specific Pathways
Future

- US-based cohorts and networks
  - eMERGE consortium
  - Regeneron
  - ORIEN (The Oncology Research Information Exchange Network)
    - Now multi-institutional with 120,000 pts
    - Combines EMR with genomic data and pairs these patients up with treatment options

Questions?