Ovarian Cancer: New insights into biology and treatment

Ursula A. Matulonis, MD
**Ovarian Cancer 2017**

- **Incidence in U.S. women**
  - 22,440 new cases estimated in 2017
  - Remains the second most common gynecologic tumor in the U.S. (endometrial cancer is the most common)
  - ~1.4% lifetime risk of developing ovarian cancer

- **Mortality in U.S. women**
  - 14,080 estimated deaths in 2017
  - 5th most common cause of cancer death in women

- **5-year survival**
  - Very modestly improved over time
  - 36% (1975-1977); 38% (1987-1989); 43% (2002-2008)
Ovarian Cancer Risk Factors

- **Increased Risk**
  - Advanced age
  - Family history
  - Nulliparity
  - Estrogen replacement
  - Talc powder
  - Pelvic inflammatory disease
  - Living in industrialized Western countries
  - Being of Jewish descent

- **Decreased Risk**
  - Lactation
  - Oral contraceptives
  - Parity
  - Reproductive surgery (tubal ligation oophorectomy/hysterectomy)

Hereditary Ovarian Cancer

• Increasingly recognized that hereditary mutations may contribute to ovarian cancer risk
  • Most commonly associated genes: BRCA1 and BRCA2
    • BRCA1 associated with ~40% lifetime risk of ovarian cancer
    • BRCA2 associated with ~15% lifetime risk of ovarian cancer
  • ~10-15% of ovarian cancer may have BRCA1 or BRCA2 mutations
    • Up to 40% of patients with germline BRCA1/2 mutations may not have a suggestive family history
  • All women with a diagnosis of ovarian cancer are recommended to have genetic counseling regarding germline BRCA testing
Screening and Diagnosis

• **Why is ovarian cancer so deadly?**
  • No effective screening tests currently exist for ovarian cancer
  • Women often diagnosed with advanced-stage disease

• **Symptoms are usually non-specific**
  • Abdominal bloating, pain; other GI complaints
  • Shortness of breath
  • Urinary tract symptoms (frequency, urgency)

• **Work-up for suspected ovarian cancer**
  • Transvaginal ultrasound
  • CT scans are useful to evaluate upper abdomen, detect ascites/pleural effusions, and help ascertain appropriateness for upfront surgery
  • Cancer markers: CA125, CEA, CA19-9
  • Pathology: biopsy or surgical specimen needed for diagnosis
Can screening help us detect ovarian cancer sooner?

<table>
<thead>
<tr>
<th></th>
<th>PLCO (JAMA 2011)</th>
<th>UK Collaborative Trial of Ovarian Cancer screening (UKCTOCS) (Lancet 2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># of women entered</strong></td>
<td>78,216</td>
<td>202,638</td>
</tr>
<tr>
<td><strong>Patient population</strong></td>
<td>Ages 55 to 74</td>
<td>Ages 50 to 74</td>
</tr>
<tr>
<td><strong>Randomized Groups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Annual screening</td>
<td>(39,105)</td>
<td>1) ROCA (50,640) [divides pts into yearly follow-up, rpt CA125 in 3 mos or abnormal and repeat CA125/TVU needed]</td>
</tr>
<tr>
<td></td>
<td>Yearly CA125 for 6 years and TVU for 4 years</td>
<td>2) TVU (50,639) [divided pts into normal, unsatisfactory with rpt in 3 mos, and abnormal with rpt in 6 weeks]</td>
</tr>
<tr>
<td>2) No screening</td>
<td>(39,111)</td>
<td>3) No screening (101,359)</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Ovarian cancer stage distributions same for both groups</td>
<td>1) Lower stage cancers (I, II and IIIA) diagnosed more frequently in ROCA group compared to no screening</td>
<td></td>
</tr>
<tr>
<td>2) No reduction in mortality in the screened group</td>
<td>2) Ovarian cancer diagnosed in 0.6% in #2 and #3 and 0.7% in #1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Mortality was not reduced in any groups</td>
</tr>
</tbody>
</table>

TVU = transvaginal ultrasound  
ROCA = risk of ovarian cancer  
To date, **no effective screening** mechanism for ovarian cancer has been identified.
The fallopian tube is a site of origin for some “ovarian cancers”

- Many “ovarian cancers” may start in the fimbriae of the fallopian tube
  - Up to 50% of cancers in BRCA mutation carriers at prophylactic surgery originate in fallopian tube
  - Research has shown a potential evolution from precursor lesion to invasive carcinoma
- Trials now in progress to investigate whether removal of fallopian tubes can prevent “ovarian cancer” in high-risk women
  - Standard of care in U.S. remains oophorectomy/fallopian tube removal

Jones and Drapkin, Frontiers in Oncology, 2013
Classification of ovarian cancer is evolving to include molecular data
Classification of ovarian cancer is evolving to include molecular data

<table>
<thead>
<tr>
<th></th>
<th>High grade serous or endometrioid</th>
<th>Low grade endometrioid</th>
<th>Low grade serous</th>
<th>Clear Cell</th>
<th>Mucinous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic characteristics</td>
<td>Up to 50% with alterations in HR</td>
<td>PTEN, ARID1A, PIK3CA</td>
<td>KKRAS, B RAF</td>
<td>PIK3CA, ARID1A, PTEN</td>
<td>KRAS</td>
</tr>
<tr>
<td></td>
<td>Associated with TP53 and BRCA mutations</td>
<td>alterations May have MSI</td>
<td>mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>Increased plat-sensitivity PARP inhibitors with potential activity in HRD tumors</td>
<td>Potentially more responsive to hormonal therapy, although not established</td>
<td>Hormonal therapies Potentially MEK inhibitors</td>
<td>Often resistant to initial plat-based therapy Targeted or immuno-oncology agents being explored</td>
<td>Often chemotherapy-insensitive</td>
</tr>
</tbody>
</table>
Newly diagnosed ovarian cancer management: 2017

• **Basic principles**
  • Surgery by a gynecologic oncologist is associated with improved survival
  • Extent of cytoreduction (debulking) is classified by residual disease following surgery
    • Suboptimal: >1 cm of residual tumor
    • Optimal: ≤1 cm of residual tumor
    • NED (R0): No gross residual disease

• **Considerations in the approach to initial disease treatment**
  • Role of neoadjuvant chemotherapy
  • Dose-dense versus every 3 week treatment
  • Intraperitoneal chemotherapy
# Neoadjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Vergote et al, NEJM 2009</th>
<th>Kehoe et al, NEJM 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upfront surgery</td>
<td>Upfront chemotherapy (NACT)</td>
</tr>
<tr>
<td>Upfront surgery</td>
<td>Upfront chemotherapy (NACT)</td>
</tr>
<tr>
<td># of patients</td>
<td>336</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>257 (75.6%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>77 (22.9%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>12 months</td>
</tr>
<tr>
<td>Median OS</td>
<td>29 months</td>
</tr>
<tr>
<td>Death within 28 days post surgery</td>
<td>8 (2.5%)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>8 (2.5%)</td>
</tr>
</tbody>
</table>
## Dose-dense Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Arms</th>
<th>Median PFS, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JGOG 3016</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Carboplatin/paclitaxel every 21 days</td>
<td>17.5</td>
<td>62.2</td>
</tr>
<tr>
<td></td>
<td>Carboplatin every 21 days/paclitaxel weekly (dose dense)</td>
<td>28.2</td>
<td>100.5</td>
</tr>
<tr>
<td><strong>GOG 262</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Carboplatin/paclitaxel every 21 days +/- bevacizumab</td>
<td>14.0</td>
<td>39.0</td>
</tr>
<tr>
<td></td>
<td>Carboplatin every 21 days/paclitaxel weekly +/- bevacizumab</td>
<td>14.7</td>
<td>40.2</td>
</tr>
<tr>
<td><strong>GOG 262</strong>&lt;sup&gt;3&lt;/sup&gt; (no bevacizumab patients; 16% of total trial patients)</td>
<td>Carboplatin/paclitaxel every 21 days</td>
<td>10.3</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Carboplatin every 21 days/paclitaxel weekly</td>
<td>14.2</td>
<td>NR</td>
</tr>
</tbody>
</table>

<sup>1</sup>Katsumata et al., *Lancet* 2009; <sup>2</sup>Katsumata et al., *Lancet Oncol* 2013
Intraperitoneal Chemotherapy

- Chemotherapy delivered directly into the abdominal space
- Higher concentration of drug delivery to cells in the abdominal space
- Only effective if most of the disease burden has been surgically removed (i.e., optimally cytoreduced)
- Overall survival benefit initially demonstrated in 3 large studies
- NCI issued alert in 2006 stating that IP chemotherapy should be considered the preferred regimen for treatment
- GOG252 has raised question of optimal setting for IP chemotherapy use; lowered dose of cisplatin to 75 mg/m² has same PFS as IV chemotherapy¹.

¹SGO 2016
### Summary of Intraperitoneal Chemotherapy Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Arms</th>
<th>Median PFS, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SWOG 8501/GOG 104</strong></td>
<td>Cisplatin IV 100mg/m2 + IV Cyclophosphamide 600mg/m2</td>
<td>--</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Cisplatin IP 100mg/m2 + IV Cyclophosphamide 600mg/m2</td>
<td>--</td>
<td>49</td>
</tr>
<tr>
<td><strong>GOG 114</strong></td>
<td>IV Paclitaxel 135mg/m2 x 24 hrs (D1) + IV Cisplatin 75mg/m2 (D2)</td>
<td>22.2</td>
<td>52.2</td>
</tr>
<tr>
<td></td>
<td>IV Carboplatin AUC9 x 2 cycles → IV Paclitaxel 135mg/m2 x 24 hrs (D1) + IP Cisplatin 100mg/m2 (D2)</td>
<td>27.9</td>
<td>63.2</td>
</tr>
<tr>
<td><strong>GOG 172</strong></td>
<td>IV Paclitaxel 135mg/m2 x 24 hrs (D1) + IV Cisplatin 75mg/m2 (D2)</td>
<td>18.3</td>
<td>49.7</td>
</tr>
<tr>
<td></td>
<td>IV Paclitaxel 135mg/m2 x 24 hrs (D1) + IP Cisplatin 100mg/m2 (D2) + IP Paclitaxel 60mg/m2 (D8)</td>
<td>23.8</td>
<td>65.6</td>
</tr>
<tr>
<td><strong>GOG 252</strong></td>
<td>IV Paclitaxel 80mg/m2 (D1,8,15) + IV Carboplatin AUC6 (D1) + Bevacizumab 15mg/kg (D1 from Cycle 2 onwards)</td>
<td>26.8</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>IV Paclitaxel 80mg/m2 (D1,8,15) + IP Carboplatin AUC6 (D1) + Bevacizumab 15mg/kg (D1 from Cycle 2 onwards)</td>
<td>28.7</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>IV Paclitaxel 135mg/m2 x 3 hrs (D1) + IP Cisplatin 75mg/m2 (D2) + IP Paclitaxel 60mg/m2 (D8) + Bevacizumab 15mg/kg (D1 from Cycle 2 onwards)</td>
<td>27.8</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Chemotherapy for Newly-diagnosed Ovarian Cancer**

- Neoadjuvant chemotherapy can result in similar outcomes to upfront surgery and adjuvant chemotherapy
  - Defer to gynecologic oncology surgeon regarding when neoadjuvant chemotherapy is appropriate

- **Regimens that can be considered for upfront therapy**
  - Carboplatin and paclitaxel q3 weeks
  - Carboplatin q3 weeks and paclitaxel weekly (dose-dense)
  - Intraperitoneal chemotherapy – although exact benefit margin, best regimen, and appropriate population unclear

- **Note:** Addition of bevacizumab to carboplatin and paclitaxel results in PFS but no OS benefit, and is not approved by FDA for use in this setting
Recurrent Ovarian Cancer 2017

- The majority of patients with advanced stage ovarian cancer will recur
- Recurrences (in US) most often detected by rising CA125
  - Follow-up typically every 2-4 months for first 2 years, every 4-6 months for next 3 years following initial treatment
- Recurrences defined by time since initial platinum-based therapy
  - **Platinum-refractory**: failed to achieve at least a partial response to therapy
  - **Platinum-resistant**: recurrence within 6 months of last platinum-based therapy
  - **Platinum-sensitive**: recurrence more than 6 months after last platinum-based therapy
- Recent advances
  - Bevacizumab in conjunction with chemotherapy
  - PARP inhibitors
Current recommended therapies for recurrent ovarian cancer (NCCN Clinical Practice Guidelines Preferred Agents)

- **Platinum-sensitive disease**
  - Carboplatin
  - Carboplatin/docetaxel
  - Carboplatin/gemcitabine
  - Carboplatin/gemcitabine/bevacizumab (category 2B)
  - Carboplatin/liposomal doxorubicin (category 1)
  - Carboplatin/paclitaxel (category 1)
  - Carboplatin/paclitaxel (weekly)
  - Cisplatin
  - Cisplatin/gemcitabine
  - Targeted therapy
    - Bevacizumab
    - Olaparib

- **Platinum-resistant disease**
  - Docetaxel
  - Oral etoposide
  - Gemcitabine
  - Liposomal doxorubicin
  - Liposomal doxorubicin/bevacizumab
  - Paclitaxel (weekly)
  - Paclitaxel (weekly)/bevacizumab
  - Topotecan
  - Topotecan/bevacizumab
  - Targeted therapy
    - Bevacizumab
    - Olaparib

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®):
Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer, version 1.2016.
Deciding on the appropriate recurrence regimen

- Toxicities from prior therapies
- CA125 marker elevation only?
- Evidence of symptoms?
- Availability of clinical trials/suitability for clinical trials
- Patient convenience and choice
- Platinum-sensitivity
  - Platinum-based regimens not used in primary platinum-refractory cancers
  - Platinum-based doublets not clearly beneficial in platinum-resistant cancers
- Presence of somatic or germline BRCA1/2 mutation
  - Potential for incorporating PARP inhibitors
- Allergies to chemotherapy drugs (paclitaxel, platinum)
Use of Anti-angiogenics in Recurrent Ovarian Cancer

- Multiple anti-angiogenic agents have demonstrated single-agent activity in recurrent ovarian cancer in Phase 2 trials
  - Response rate 10-20%
  - Progression-free survival up to 4-5 months
- Combining anti-angiogenics with chemotherapy followed by maintenance therapy in newly diagnosed ovarian cancer with PFS benefit of 2-4 months, no OS benefit
  - Not approved in the U.S. for this indication
- Multiple trials have explored combining anti-angiogenics with chemotherapy in recurrent ovarian cancer
  - Platinum-sensitive: OCEANS, GOG213
  - Platinum-resistant: AURELIA
Bevacizumab + platinum-based chemotherapy improves PFS in platinum-sensitive recurrent ovarian cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen(s)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCEANS¹</td>
<td>(A) Carboplatin/gemcitabine (CG)</td>
<td>8.4 mos</td>
<td>35.2 mos</td>
</tr>
<tr>
<td>(plat-sens)</td>
<td>(B) CG/bevacizumab + bevacizumab maintenance</td>
<td>12.4 mos</td>
<td>33.3 mos</td>
</tr>
<tr>
<td>GOG-213²</td>
<td>(A) Carboplatin/paclitaxel (CP)</td>
<td>10.4 mos</td>
<td>37.3 mos</td>
</tr>
<tr>
<td>(plat-sens)</td>
<td>(B) CP/bevacizumab + bevacizumab maintenance</td>
<td>13.8 mos (p&lt;0.0001)</td>
<td>42.2 mos (p=0.056)</td>
</tr>
</tbody>
</table>

Bevacizumab approved by FDA in December 2016 in conjunction with carboplatin/paclitaxel or carboplatin/gemcitabine chemotherapy in recurrent platinum-sensitive ovarian cancer

Aghajanian et al., J Clin Oncol 2012; Coleman et al., SGO 2015
Bevacizumab + chemotherapy in recurrent platinum-resistant ovarian cancer: the AURELIA trial

Chemotherapy options:
- Paclitaxel 80 mg/m² on Days 1, 8, 15, 22 every 28 days
- Topotecan 4 mg/m² on Days 1, 8, 15 every 28 days or
- Topotecan 1.25 mg/m² on Days 1-5 every 21 days
- Pegylated liposomal doxorubicin (PLD) 40 mg/m² on Day 1 every 28 days

Pts with measurable OC that progressed < 6 mos from platinum-based chemotherapy; ≤ 2 prior therapies; no bowel involvement (N = 361)

Disease progression

Nonplatinum Chemotherapy + Bevacizumab

Stratified by chemotherapy, PFI (< 3 mos vs 3-6 mos), prior anti-angiogenesis

Pujade-Lauraine et al., J Clin Oncol 2014 and 2015
Bevacizumab + chemo improved PFS and QoL in platinum-resistant ovarian cancer

- Patient-reported (QOL) outcome benefit seen in patients with pre-existing abdominal symptoms

Bevacizumab approved by FDA in December 2014 in conjunction with chemotherapy in platinum-resistant ovarian cancer

Pujade-Lauraine et al., *J Clin Oncol* 2014
PARP inhibitors display synthetic lethality in the setting of homologous recombination loss

Silver and Iglehart, NEJM, 2009
PARP inhibitors are active agents in ovarian cancer and likely work via multiple mechanisms of action.

- Up to 50% of high-grade serous ovarian cancers with alterations in homologous recombination (HR) genes
- Clinical activity of PARP inhibitors in multiple settings in ovarian cancer
  - *BRCA* mutated (somatic or germline) relapsed disease
  - *BRCA* non-mutated relapsed disease
  - Maintenance therapy

Konstantinopoulos et al., *Cancer Discov* 2015
### PARP inhibitors have activity in relapsed BRCA-mutated ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Olaparib&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Rucaparib&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Niraparib&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Veliparib&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of pts</strong></td>
<td>137</td>
<td>106</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td><strong># of lines of prior therapy</strong></td>
<td>At least 3 prior lines</td>
<td>At least 2 prior lines (43% had 3 or more)</td>
<td>NA</td>
<td>1 prior: 32% 2 or 3: 68%</td>
</tr>
<tr>
<td><strong>Objective RECIST RR</strong></td>
<td>34%</td>
<td>54% (IRR&lt;sup&gt;5&lt;/sup&gt; 42%)</td>
<td>40%</td>
<td>26%</td>
</tr>
<tr>
<td><strong>RR based on platinum sensitivity</strong></td>
<td>NA for this population; other data available</td>
<td>Plat sens 66% Plat resist 25% Plat refract 0%</td>
<td>Plat sens 50% Plat resist 33% Plat refract 0%</td>
<td>Plat sens 35% Plat resist 20%</td>
</tr>
<tr>
<td><strong>Median Duration of response</strong></td>
<td>7.4 mos (IRR&lt;sup&gt;5&lt;/sup&gt; 6.7 months)</td>
<td>9.2 mos (IRR&lt;sup&gt;5&lt;/sup&gt; 6.7 months)</td>
<td>12.9 mos</td>
<td>8.18 mos (reported as median PFS)</td>
</tr>
</tbody>
</table>

- Olaparib approved by FDA in December 2014 for relapsed germline BRCA mutated ovarian cancer after 3 or more prior therapies.
- Rucaparib approved by FDA in December 2016 for relapsed germline or somatic BRCA mutated ovarian cancer after 2 or more prior therapies.

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<sup>1</sup> Olaparib FDA package insert; <sup>2</sup>Rucaparib FDA package insert; <sup>3</sup>Sandhu, Lancet Oncol 2013; <sup>4</sup>Coleman, Gyn Onc 2015; <sup>5</sup>IRR = independent radiology review
PARP inhibitors have equivalent activity in germline and somatic BRCA-mutated ovarian cancers

- ARIEL2 trial demonstrated similar response rate in tumors with germline and somatic BRCA mutations
- Data from additional trials of PARP inhibitors demonstrate similar efficacy of both niraparib and olaparib between somatic and germline BRCA-mutated tumors

<table>
<thead>
<tr>
<th>BRCA Mutation Type</th>
<th>Confirmed Objective Responses by RECIST</th>
<th>Objective Responses by Combined RECIST and CA-125</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA mutant (n=40)</td>
<td>32 (80%, 64-91)</td>
<td>34 (85%, 70-94)</td>
</tr>
<tr>
<td>Germline mutation (n=20)</td>
<td>17 (85%, 62-97)</td>
<td>17 (85%, 62-97)</td>
</tr>
<tr>
<td>Somatic mutation (n=19)</td>
<td>14 (74%, 49-91)</td>
<td>16 (84%, 60-97)</td>
</tr>
<tr>
<td>Indeterminate (n=1)</td>
<td>1 (100%, 3-100)</td>
<td>1 (100%, 3-100)</td>
</tr>
<tr>
<td>BRCA1 mutation (n=29)</td>
<td>23 (79%, 60-92)</td>
<td>25 (86%, 68-96)</td>
</tr>
<tr>
<td>BRCA2 mutation (n=11)</td>
<td>9 (82%, 48-98)</td>
<td>9 (82%, 48-98)</td>
</tr>
<tr>
<td>PFI &gt;6 to &lt;12 months (n=22)</td>
<td>20 (87%, 66-97)</td>
<td>20 (87%, 66-97)</td>
</tr>
<tr>
<td>PFI ≥12 months (n=17)</td>
<td>12 (71%, 44-90)</td>
<td>14 (82%, 57-96)</td>
</tr>
<tr>
<td>BRCA wild-type and LOH high (n=82)</td>
<td>24 (20%, 9-40)</td>
<td>36 (44%, 33-55)</td>
</tr>
<tr>
<td>BRCA wild-type and LOH low (n=70)</td>
<td>7 (10%, 4-20)</td>
<td>14 (20%, 11-31)</td>
</tr>
<tr>
<td>BRCA wild-type and LOH not classified (n=12)</td>
<td>4 (33%, 10-65)</td>
<td>7 (58%, 28-85)</td>
</tr>
</tbody>
</table>

Data are n (%), 95% CI. Confidence intervals calculated using Clopper-Pearson method. CA-125 = cancer antigen 125, LOH = loss of heterozygosity. PFI = progression-free interval following completion of platinum-based chemotherapy. RECIST = Response Evaluation Criteria In Solid Tumors version 1.1.
What predicts likelihood of response to PARP inhibitors?

- Presence of a BRCA mutation (either germline or somatic)
- Platinum sensitivity
- Number of prior lines of treatment
- Presence of homologous recombination deficiency
  - Tests to look at markers of “genomic scarring” have some correlation with PARP inhibitor activity

Matulonis, Ann Oncol 2016
PARP inhibitors as “maintenance therapy”

- Ovarian cancer (newly diagnosed or recurrent) with high relapse rate
- Therapies with low toxicity profile that can delay recurrence and/or improve survival of greatest interest
- PARP inhibitors with overall favorable toxicity profile
  - Oral agents (taken once or twice daily)
  - Primary toxicities: Nausea, fatigue, myelosuppression (typically less than with chemotherapy)
- Study 19 was a randomized phase II study that showed benefit of maintenance therapy post platinum response\(^1\)
- Two Phase 3 studies of PARP inhibitor maintenance with evidence of PFS benefit
  - ENGOT-OV16/NOVA (niraparib)
  - SOLO2/ENGOT-OV21 (olaparib)

\(^1\)Study 19, NEJM 2012
**ENGOT-OV16/NOVA Trial**

**KEY INCLUSION CRITERIA**

- Histologically diagnosed ovarian cancer
  - Predominantly high-grade serous
- Completed at least two previous courses of platinum-containing therapy
- Platinum-sensitive to the penultimate platinum regimen, and remain in response to platinum

**KEY EXCLUSION CRITERIA**

- Invasive cancer other than ovarian cancer within 2 years
- Symptomatic uncontrolled brain metastasis
- Prior treatment with a known PARP inhibitor

ENGOT-OV16/NOVA Trial Schema

Platinum-Sensitive Recurrent High-Grade Serous Ovarian Cancer

Treatment with at least 4 Cycles of Platinum-based Therapy

Response to Platinum Treatment

gBRCAmut (N = 203)

Treat until Progression of Disease

Niraparib 300 mg once daily

Placebo

Non-gBRCAmut (N = 350)

Treat until Progression of Disease

Niraparib 300 mg once daily

Placebo

2:1 Randomization

2:1 Randomization

Primary Endpoint: PFS by central, blinded review: results for both gBRCA and non-gBRCA groups analyzed simultaneously

ENGOT-OV16/NOVA Primary Analysis demonstrates PFS improvement across all patients subsets

**Primary Efficacy Populations**

- **gBRCAmut**
  - Median PFS (months)
    - Niraparib: 21.0
    - Placebo: 5.5
  - HR = 0.27

- **Non-gBRCAmut HRDpos**
  - Median PFS (months)
    - Niraparib: 12.9
    - Placebo: 3.8
  - HR = 0.38

- **Non-gBRCAmut Overall**
  - Median PFS (months)
    - Niraparib: 9.3
    - Placebo: 3.9
  - HR = 0.45

Niraparib effect on PFS in patients without germline \textit{BRCA} mutations most notable in HRD-positive subset.

Exploratory Analyses

**HRD-positive**

- **sBRCA\text{mut}**
  - Niraparib: 20.9
  - Placebo: 11.0
  - HR = 0.27

- **BRCA\text{wt}**
  - Niraparib: 9.3
  - Placebo: 3.7
  - HR = 0.38

**HRD-negative**

- Niraparib: 6.9
- Placebo: 3.8
  - HR = 0.58

Niraparib approved by the FDA on March 27, 2017 as maintenance therapy in ANY woman with recurrent platinum-sensitive ovarian cancer following response to platinum-based chemotherapy.
SOLO2/ENGOT-OV21 Study Schema

Patients
- *BRCA1/2* mutation
- Platinum-sensitive relapsed ovarian cancer
- At least 2 prior lines of platinum therapy
- CR or PR to most recent platinum therapy

Placebo
- *n*=99

Olaparib
- 300 mg bid
- *n*=196

Primary endpoint
- Investigator-assessed PFS

Randomized 2:1
SOLO2/ENGOT-OV21 confirms olaparib maintenance significantly improves PFS in BRCA-mutated platinum-sensitive ovarian cancer

PFS by investigator assessment

Olaparib is approved by EMA in Europe for maintenance therapy in BRCA-mutated platinum-sensitive ovarian cancer following response to platinum-based chemotherapy; currently under priority review by US FDA
Summary: Ovarian Cancer 2017

• Remains a leading cause of cancer death in women in the U.S.
• No effective screening test has been identified
• Growing recognition of importance of molecular classifications of ovarian cancer
• Hereditary ovarian cancer increasingly recognized
  • All women with a diagnosis of ovarian cancer should have genetic counseling
• Upfront therapy for ovarian cancer continues to evolve
• Recent advances in recurrent ovarian cancer
  • Bevacizumab in combination with chemotherapy
    • Approved in platinum-sensitive and platinum-resistant recurrent setting
  • PARP inhibitors for recurrent ovarian cancer
    • Approved in women with relapsed BRCA-mutated ovarian cancer (rucaparib for 3rd line; olaparib for 4th line)
    • Approved as maintenance therapy in platinum-sensitive recurrence after response to platinum (niraparib approved; olaparib under review in BRCA-mutated cancers)