PARP Inhibitors for Ovarian Cancer

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Disclosure

- I have nothing to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation.
Objectives

- Review the treatment guidelines for ovarian cancer
- Discuss the role of PARP inhibitors in ovarian cancer
- Understand basic pharmacology of FDA-approved PARP inhibitors
- Review pertinent literature evaluating PARP inhibitors in ovarian cancer

PARP: poly(ADP-ribose) polymerases
Ovarian Cancer
Ovarian Cancer

Statistics for 2017
- 22,440 new ovarian cancer diagnoses
- 14,080 deaths
- 5\textsuperscript{th} leading cause of cancer deaths among women

Incidence increases with age
- Median age of diagnosis: 63 years old

Risk Factors

- **Increased**
  - Early menarche, nulliparity, late age first pregnancy, late menopause
  - Fertility drugs
  - Post-menopausal hormone therapy
  - Pelvic inflammatory disease
  - Family history
  - Hereditary
    - BRCA1 and BRCA2 genotypes

- **Decreased**
  - Multiple pregnancies
  - First birth ≤25 years
  - Prolonged oral contraceptives
  - Tubal ligation
  - Prophylactic oophorectomy and/or salpingectomy
Prognosis

- Lifetime risk: 1 in 75
- Median overall survival 15-23 months
- Factors:
  - Stage of disease
  - Residual disease
  - Histology
  - CA-125
  - Obesity and dose-intensity

<table>
<thead>
<tr>
<th>Stage of Disease</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>90%</td>
</tr>
<tr>
<td>II</td>
<td>70%</td>
</tr>
<tr>
<td>III</td>
<td>39%</td>
</tr>
<tr>
<td>IV</td>
<td>17%</td>
</tr>
</tbody>
</table>

Pathology

- **Histological sub-types**
  - Epithelial ovarian cancer (>90%)
    - Serous (70%)
    - Endometrioid (10%)
    - Clear-cell (10%)
    - Mucinous (3%)

Staging

- **Stage I**
  - Confined to ovaries or Fallopian tube(s)

- **Stage II**
  - One or both ovaries or Fallopian tubes with pelvic extension or primary peritoneal cancer

- **Stage III**
  - Stage II with cytologically or histologically confirmed spread to peritoneum outside of the pelvis and/or metastasis to the retroperitoneal lymph nodes

- **Stage IV**
  - Distant metastases excluding peritoneal metastases

Image adapted from: <http://ovarian.org/about-ovarian-cancer/what-is-ovarian-cancer/types-and-stages>
Guidelines for Treatment
Primary Treatment

- Stage IA-IB: Fertility-sparing surgical intervention
- Stage IA – III: Surgical Intervention
- Bulky Stage III, IV or poor surgical candidate: Neo-adjuvant chemotherapy ± interval debulking

Genetic Risk Evaluation

NCCN. Ovarian Cancer. Version 2.2017
Primary Chemotherapy

Stage IA or IB
- Observation or IV chemotherapy

Stage IC
- IV chemotherapy

Stage II, III, IV
- IP or IV chemotherapy and completion of surgery

Symptom management and best supportive care

Secondary adjuvant therapy

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Persistent or Recurrent Disease

- Progression, stable or persistent disease on primary chemotherapy
- Complete remission and relapse < 6 months OR stage II, III, IV partial response
- Complete remission and relapse ≥ 6 months after completing prior chemotherapy

Clinical trial ± best supportive care ± recurrence therapy

Biochemical relapse

Clinical trial or delay until clinical or recurrence therapy ± best supportive care

Radiographic and/or clinical relapse

Secondary cytoreductive surgery

Clinical trial or recurrence therapy ± best supportive care

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### Recurrence Therapies

#### PRINCIPLES OF SYSTEMIC THERAPY (5 of 8)

Acceptable Recurrence Therapies for Epithelial (including LCOH) Fallopian Tube/Primary Peritoneal Cancer

<table>
<thead>
<tr>
<th>Cytotoxic Therapy (In alphabetical order)*</th>
<th>Targeted Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platinum-Sensitive Disease</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Single Agents</strong></td>
</tr>
<tr>
<td>Carboplatin&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Bevacizumab&lt;sup&gt;1,8,19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carboplatin/docetaxel&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>Olaparib&lt;sup&gt;20,21&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carboplatin/gemcitabine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Rucaparib&lt;sup&gt;6,24&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carboplatin/gemcitabine/bevacizumab&lt;sup&gt;k,l,m,4&lt;/sup&gt;</td>
<td><strong>(platinum-resistant disease)</strong></td>
</tr>
<tr>
<td>Carboplatin/liposomal doxorubicin&lt;sup&gt;5&lt;/sup&gt; (category 1)</td>
<td><strong>Platinum-Resistant Disease</strong></td>
</tr>
<tr>
<td>Carboplatin/paclitaxel, albumin bound (for patients with confirmed taxane hypersensitivity)</td>
<td>Docetaxel&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carboplatin/paclitaxel (category 1)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Etoposide, oral&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carboplatin/paclitaxel (weekly)</td>
<td>Gemcitabine&lt;sup&gt;11,12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cisplatin&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Liposomal doxorubicin&lt;sup&gt;11,12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cisplatin/gemcitabine&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Liposomal doxorubicin/bevacizumab&lt;sup&gt;k,l,13&lt;/sup&gt;</td>
</tr>
<tr>
<td>Additional options for mucinous carcinoma only: 5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Paclitaxel (weekly)&lt;sup&gt;14,15&lt;/sup&gt; ± pazopanib&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td>Capecitabine + oxaliplatin</td>
<td>Paclitaxel (weekly)/bevacizumab&lt;sup&gt;k,l,13&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*NOTE: For LCOH, all regimens are category 2A unless indicated.*
PARP Inhibitors: Place in Therapy

- **Maintenance Therapy: Category 2A**
  - Niraparib
    - Partial or complete response
    - Platinum–sensitive disease

- **Recurrent Disease: Category 2A**
  - Preferred
    - Olaparib
    - Rucaparib
    - For platinum-resistant disease
  - Potentially active
    - Rucaparib
    - For platinum-sensitive disease
PARP Basics
What is PARP?

PARP: Poly(ADP-ribose) polymerases

- Family of 18 proteins
- PARP1 and PARP2
  - Enzymes activated by DNA damage
  - Facilitate DNA repair in pathways involving single-strand breaks (SSBs) and base excision repair (BER)

PARP Inhibitors: Mechanism

- Inhibition of PARP
  - Prevents repair of persistent SSBs
  - Leads to degradation into double strand breaks (DSBs)
- BRCA mutated cells
  - Leads to homologous recombination (HR) deficiency
- Rationale for PARP inhibitors
  - Prevent repair that occurs after cytotoxic chemotherapy
  - Synthetic lethality in cells with underlying HR defects
  - PARP inhibition with BRCA mutation results in genomic instability and cell death

Fig. 1. A) Proper DNA repair mechanism with functional PARP protein and DNA repair proteins. B) Attempted DNA repair of SSB in the presence of PARP inhibitor resulting in DSB formation. BRCA-proficient cells have the ability to repair the DSB and restart the cell cycle. BRCA-deficient cells are unable to repair the accumulating DSBs and this results in cell death.
Pharmacology
<table>
<thead>
<tr>
<th>Indication</th>
<th>Olaparib</th>
<th>Rucaparib</th>
<th>Niraparib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer, advanced: Monotherapy of deleterious germline <strong>BRCA-mutated</strong> advanced ovarian cancer in patients who have been treated with <strong>3 or more prior lines of chemotherapy</strong></td>
<td>Ovarian cancer, advanced: Monotherapy of deleterious germline and/or somatic <strong>BRCA mutation</strong> associated advanced ovarian cancer in patients who have been treated with <strong>2 or more prior lines of chemotherapy</strong></td>
<td>Ovarian, fallopian tube, or primary peritoneal cancer: <strong>Maintenance</strong> treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who are <strong>in a complete or partial response</strong> to platinum-based chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>
# Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Rucaparib</th>
<th>Niraparib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage Forms</strong></td>
<td>Capsules: 50 mg</td>
<td>Tablets: 200 mg, 250 mg, 300 mg</td>
<td>Capsule: 100 mg</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>400 mg (8 capsules) twice daily</td>
<td>600 mg (2 tablets) twice daily</td>
<td>300 mg (3 capsules) daily</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Whole, with or without food</td>
<td>Whole, with or without food</td>
<td>Whole, with or without food</td>
</tr>
<tr>
<td><strong>Dose Adjustments</strong></td>
<td>Renal Impairment, CYP3A4 Inhibitors</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>CYP3A4 (major), P-glycoprotein</td>
<td>CYP1A2 (minor), CYP2D6 (minor), CYP3A4 (minor), BCRP, P-glycoprotein</td>
<td>BCRP, P-glycoprotein</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>CMP/CBC with differential baseline and monthly</td>
<td>CMP/CBC with differential baseline and monthly</td>
<td>CMP baseline and monthly CBC with differential weekly for the first month, then monthly Monitor blood pressure and heart rate monthly during the first year and periodically</td>
</tr>
</tbody>
</table>

*CMP: Complete metabolic panel
CBC: Complete blood count*
**Adverse Reactions (ADRs)**

- Warning: Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML)

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Rucaparib</th>
<th>Niraparib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warnings</strong></td>
<td>Pneumonitis&lt;br&gt;Bone marrow suppression</td>
<td>Bone marrow suppression</td>
<td>Bone marrow suppression&lt;br&gt;Cardiovascular effects</td>
</tr>
<tr>
<td><strong>Common ADRs</strong></td>
<td>≥ 20%&lt;br&gt;Fatigue&lt;br&gt;Headache&lt;br&gt;<strong>Nausea/vomiting/diarrhea</strong>&lt;br&gt;<strong>Anorexia</strong>&lt;br&gt;Abdominal pain&lt;br&gt;Dysgeusia&lt;br&gt;Nasopharyngitis/pharyngitis/URI&lt;br&gt;Cough&lt;br&gt;Arthralgia/musculoskeletal pain&lt;br&gt;Myalgia&lt;br&gt;Back pain&lt;br&gt;Dermatitis/rash</td>
<td>≥ 20%&lt;br&gt;Fatigue&lt;br&gt;Nausea/vomiting&lt;br&gt;Constipation &gt; diarrhea&lt;br&gt;<strong>Abdominal pain</strong>&lt;br&gt;Dysgeusia&lt;br&gt;Anorexia&lt;br&gt;Dyspnea&lt;br&gt;Photosensitivity</td>
<td>≥ 20%&lt;br&gt;Hypertension&lt;br&gt;Fatigue&lt;br&gt;Headache&lt;br&gt;Insomnia&lt;br&gt;Nausea/vomiting&lt;br&gt;Diarrhea/constipation&lt;br&gt;Anorexia&lt;br&gt;Abdominal pain/distention&lt;br&gt;Mucositis/stomatitis&lt;br&gt;Nasopharyngitis&lt;br&gt;Dyspnea&lt;br&gt;Rash</td>
</tr>
</tbody>
</table>

Olaparib (Lynparza™)[package insert]. Wilmington, DE. AstraZeneca Pharmaceuticals LP; 2017.
Cancer Anorexia–Cachexia Syndrome

- Persistently elevated basal metabolic rate without appropriate compensation
  - Anorexia
  - Loss of adipose tissue
  - Loss of muscle mass

- Contributing factors
  - Digestive factors
  - Tumor factors
  - Metabolic changes
  - Humoral factors

NCCN. Palliative Care. Version 2.2017
Cancer Anorexia–Cachexia Syndrome

- Treatment
  - Underlying causes
  - Caloric supplementation and hydration
  - Pharmacologic intervention

**Confirmed efficacy**
- Prednisone 10-20 mg BID
- Megestrol acetate 400-800 mg/day

**Conflicting results**
- Metoclopramide
- Methylphenidate
- Dronabinol
- Medical marijuana

**Investigational**
- Anamorelin (ghrelin agonist)
- Thalidomide
- Omega-3 fatty acids
- Anabolic steroids
Chemotherapy Induced Diarrhea

- Due to direct toxicity to epithelial cells
  - Inflammation and prostaglandin release
- Contributing factors
  - Chemotherapeutic agent
  - Underlying malignancy
  - Infectious disease
  - Radiation
  - Dietary changes
  - Supportive care drugs

### Uncomplicated
- Grade 1 or 2
- <4-6 stools/day
- No complicating factors

### Complicated
- Grade ≥ 3 diarrhea
- Moderate to severe cramping
- ≥ Grade 2 nausea/vomiting
- Decreased performance status
- Fever, sepsis, neutropenia
- Bleeding or dehydration

---

Chemotherapy Induced Diarrhea

- **Treatment**
  - **Uncomplicated**
    - Conservative management
    - Continue treatment
  - **Complicated**
    - Aggressive management
    - Hold treatment
    - Resume at reduced dose

- **Uncomplicated**
  - Dietary modifications
  - Loperamide
    - Treat as complicated after 24-48 hours
  - Second-line agents

- **Complicated**
  - Admission
  - Octreotide
  - IV hydration/electrolyte replacement
  - IV antibiotics as needed

Nausea and Vomiting

- Nausea: inclination to vomit
  - Loss of gastric tone with reverse peristalsis
  - Concurrent tachycardia and hypersalivation
- Retching: labored movement of abdominal and thoracic muscles
  - Spasmodic abortive respiratory movements
- Vomiting: ejection or expulsion of gastric contents
  - Contraction of diaphragm and abdominal muscles, with opening of lower esophageal sphincter
Nausea and Vomiting

Guidelines

- American Society of Clinical Oncology (ASCO)
- National Comprehensive Cancer Network (NCCN)
- Multinational Association of Supportive Care in Cancer (MASCC)

- Serotonin Antagonist
- Promethazine
- Prochlorperazine
- Lorazepam
- Metoclopramide
- H2 blocker or PPI
- Olanzapine

NCCN. Antiemesis. Version 2.2017
Cancer Related Fatigue

Definition
- Distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness
- Not proportional to recent activity
- Interferes with usual functioning

Treatment
- Management of concurrent symptoms and contributing factors
- Non-pharmacologic
- Pharmacologic
Cancer Related Fatigue

**Non-pharmacologic**
- Physical activity (category 1)
- Massage therapy (category 1)
- Psychosocial interventions
- Nutrition consultation
- Sleep management

**Pharmacologic**
- Psychostimulants
- Sleep aids
- Pain management
Laboratory Abnormalities

- Decrease in blood counts
  - Hemoglobin
  - Lymphocytes
  - Neutrophils
  - Platelets

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Rucaparib</th>
<th>Niraparib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase</td>
<td>• Serum creatinine</td>
<td>• Serum creatinine</td>
<td>• Liver function tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liver function tests</td>
<td>• Cholesterol</td>
</tr>
</tbody>
</table>

Olaparib (Lynparza™) [package insert]. Wilmington, DE. Astra Zeneca Pharmaceuticals LP; 2017.
Olaparib: Dose Adjustments for ADRs

If dose reduction below 200 mg per day is required, discontinue olaparib

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>400 mg twice daily</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>200 mg twice daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>100 mg twice daily</td>
</tr>
</tbody>
</table>
Rucaparib: Dose Adjustments for ADRs

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>600 mg twice daily</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>400 mg twice daily</td>
</tr>
<tr>
<td>Third dose reduction</td>
<td>300 mg twice daily</td>
</tr>
</tbody>
</table>
Niraparib: Dose Adjustments for ADRs

Non-Hematologic ADRs

- For non-hematologic CTCAE ≥ grade 3 treatment-related ADRs
  - Withhold for maximum of 28 days or until resolution
  - Resume at reduced dose
- Discontinue niraparib
  - Dose reductions below 100 mg per day is required
  - CTCAE ≥ grade 3 treatment-related ADRs lasting > 28 days while on niraparib 100 mg daily

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>300 mg daily</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>200 mg daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>100 mg daily</td>
</tr>
</tbody>
</table>

Niraparib: Dose Adjustments
Hematologic ADRs

- Monitor CBC weekly for the first month, monthly for the next 11 months, and periodically after this time
- If ADR occurs withhold niraparib for maximum 28 days monitoring CBC weekly

<table>
<thead>
<tr>
<th>Dose Modifications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count &lt;100,000/μL</td>
<td>First occurrence</td>
</tr>
<tr>
<td></td>
<td>• If platelet count 75,000/μL–100,000/μL resume at same dose or reduced dose</td>
</tr>
<tr>
<td></td>
<td>• If platelet count &lt;75,000/μL resume at reduced dose</td>
</tr>
<tr>
<td>Neutrophil &lt; 1,000/μL or Hemoglobin &lt;8 g/dL</td>
<td>• Resume at reduced dose when:</td>
</tr>
<tr>
<td></td>
<td>• Neutrophils ≥ 1,500/μL</td>
</tr>
<tr>
<td></td>
<td>• Hemoglobin ≥ 9 g/dL</td>
</tr>
<tr>
<td>Requiring transfusion</td>
<td>• Platelets &lt; 10,000/μL</td>
</tr>
<tr>
<td></td>
<td>• Resume at reduced dose</td>
</tr>
</tbody>
</table>

Clinical Evidence
Olaparib

- Domchek et al.
  - Single-arm
  - Patient population
    - Germline BRCA-mutated advanced cancers
    - Previously received 3 lines of chemotherapy
  - Intervention
    - Olaparib 400 mg twice daily monotherapy
Olaparib

Safety

Grade ≥ 3 occurred in 52% of patients
Discontinuation in 5% of patients

<table>
<thead>
<tr>
<th>ORR (95% CI)</th>
<th>34% (26 – 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2%</td>
</tr>
<tr>
<td>PR</td>
<td>32%</td>
</tr>
<tr>
<td>Median DOR (95% CI)</td>
<td>7.9 months (5.6 – 9.6)</td>
</tr>
</tbody>
</table>

ORR: overall response rates
CR: complete remission
PR: partial remission
DOR: duration of response
Rucaparib

ARIEL 2

- Multi-center, single-arm, open-label
- Patient population
  - Advanced BRCA-mutant ovarian cancer
  - Progression after 2 or more prior lines of chemotherapy
- Intervention
  - Rucaparib 600 mg twice daily

Rucaparib

<table>
<thead>
<tr>
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<th>N=106</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>54% (44 – 64)</td>
</tr>
<tr>
<td>CR</td>
<td>9%</td>
</tr>
<tr>
<td>PR</td>
<td>45%</td>
</tr>
<tr>
<td>Median DOR (95% CI)</td>
<td>9.2 months (6.4 – 12.9)</td>
</tr>
</tbody>
</table>

- Safety
  - Any grade in 100% of patients
  - Dose reductions in 39% patients
  - Discontinuation in 9% patients
Niraparib

NOVA

- Double-blind, placebo-controlled

Patient population

- Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Following CR or PR to platinum-based therapy

Intervention

- Niraparib 300 mg daily vs placebo

### Niraparib

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>gBRCAmut (n= 203)</td>
<td>74%</td>
<td>0.26 (0.17 – 0.41)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>non-gBRCAmut (n= 350)</td>
<td>55%</td>
<td>0.45 (0.34 – 0.61)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

- **Adverse events**
  - Any grade in 100% of patients
  - Discontinuation in 14.7% patients
Ongoing Clinical Trials

- 70+ ongoing
  - Monotherapy
  - Combination
    - Chemotherapy
    - Anti-angiogenics
  - Alternate cancer types

- Investigational
  - Veliparib
  - Fluzoparib
  - Talazoparib

Conclusion

- Viable treatment option in recurrence and maintenance setting
- Ongoing research for broadening the spectrum of PARP inhibitor utilization
- Agent choice
  - Indication
  - Organ function, Performance status
  - Pill burden
  - Tolerance
PARP Inhibitors for Ovarian Cancer

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