Current and Future Role of PARP Inhibitors in the Management of Ovarian Cancer

Conversations with Oncology Investigators Bridging the Gap between Research and Patient Care

Faculty Interviews
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Editor
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OVERVIEW OF ACTIVITY
The American Cancer Society estimates that 22,280 new cases of ovarian cancer (OC) will be diagnosed in the United States in 2016 and 14,240 individuals will die of the disease. Significant resources have been invested over the past few decades in attempts to better understand the natural history of the disease, identify genetic and other factors responsible for its proliferation and develop novel therapies with the potential to significantly improve outcomes for patients. One such avenue, investigating PARP inhibition as a mechanism to combat OC development and progression, ultimately led to the 2014 FDA approval of the PARP inhibitor olaparib. Given the significant number of clinical and research questions created by this recent introduction and the rapidly expanding database surrounding PARP inhibition in general, it is clear that additional educational resources are needed to keep practicing clinicians up to date and informed. To that end, this special RTP On Demand program uses one-on-one discussion with leading investigators in the field to assist practicing clinicians with the formulation of up-to-date management strategies.

LEARNING OBJECTIVES
• Use available guidelines and consensus statements to develop an evidence-based algorithm for conducting genetic screening for patients with OC.
• Understand the rationale for the investigation of PARP inhibition as monotherapy or in combination with other novel agents for patients with BRCA mutation-positive and BRCA wild-type advanced OC, and use this information to inform protocol and nonresearch treatment options for these individuals.
• Appreciate the recent approval of olaparib for patients with highly refractory advanced OC, and appropriately integrate this agent into the clinical management of such cases.
• Develop an understanding of the available efficacy data and toxicity profiles of investigational PARP inhibitors to effectively prioritize clinical trial opportunities for appropriate patients with OC.
• Educate patients about the side effects associated with approved and investigational PARP inhibitors, and provide preventive and emergent strategies to reduce or ameliorate these toxicities.

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FACULTY — The following faculty (and their spouses/partners) reported relevant conflicts of interest, which have been resolved through a conflict of interest resolution process:

- **Dr Matulonis** — Advisory Committee: AstraZeneca Pharmaceuticals LP, Genentech BioOncology, ImmunoGen Inc, Merck.
- **Dr Herzog** — Advisory Committee: Amgen Inc, AstraZeneca Pharmaceuticals LP, Caris Life Sciences, Pfizer Inc, Roche Laboratories Inc. **Dr Birrer** — Advisory Committee: Acceleron Pharma, AstraZeneca Pharmaceuticals LP, ImmunoGen Inc, Merrimack Pharmaceuticals Inc, OXiGENE Inc, Roche Laboratories Inc, Sanofi, Threshold Pharmaceuticals Inc.


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Case discussion: A 55-year-old woman with recurrent ovarian cancer (OC) is found to harbor a germline BRCA1 mutation and receives olaparib on a clinical trial.

Activity and ongoing investigation of cediranib in platinum-sensitive and platinum-resistant OC.

Antitumor activity of olaparib and management of associated side effects.

Importance of BRCA testing in OC.

Identification of factors predictive of benefit from PARP inhibition.

Role of PARP in DNA repair.

Background of the Phase III ENGOT-OV16/NOVA trial evaluating maintenance niraparib versus placebo for platinum-sensitive recurrent OC.

Results of Study 19: Olaparib maintenance therapy for platinum-sensitive relapsed OC.

Perspective on the failure of olaparib to receive FDA approval as maintenance recurrent OC.

Results of the ENGOT-OV16/NOVA trial: Niraparib significantly improves progression-free survival in platinum-sensitive recurrent OC irrespective of BRCA mutation or homologous recombination deficiency (HRD) status.

Somatic versus germline testing and identification of other genomic signatures that may predict benefit from PARP inhibition.

Second opinion: A 45-year-old woman with optimally debulked Stage IIIA serous OC with a germline BRCA2 mutation and no evidence of disease after adjuvant chemotherapy.

Clinical trials evaluating the use of PARP inhibitors alone and in combination in earlier-line settings.

KEYNOTE-162: A Phase I/II study of niraparib with the anti-PD-1 antibody pembrolizumab for patients with recurrent OC or triple-negative breast cancer.

Second opinion: Monitoring blood counts in patients receiving olaparib and the use of erythropoiesis-stimulating agents.

Second opinion: Therapeutic options for patients experiencing disease progression on olaparib.

Efficacy and side-effect profiles of the novel PARP inhibitors rucaparib, niraparib and veliparib.

Continuation or switching of PARP inhibitor therapy for patients experiencing disease progression.

Management of gastrointestinal toxicity in patients receiving olaparib.

Differences in form, strength and number of pills or capsules administered per day among approved and investigational PARP inhibitors.

Case discussion: A 54-year-old woman with recurrent, platinum-resistant OC who is found to harbor a BRCA1 germline mutation.

Perspective on the importance of up-front BRCA testing for patients with epithelial OC.

Benefits and limitations of genetic counseling and currently available genetic tests.

Clinical experience with gastrointestinal toxicity and anemia with PARP inhibitors in OC.

Risk of second cancers with olaparib.

Editor’s note: On December 19, 2016, the FDA granted accelerated approval to rucaparib for the treatment of advanced OC associated with deleterious BRCA mutations (germline and/or somatic) in patients who have received 2 or more chemotherapies.
Visit www.ResearchToPractice.com/RTPODOvarian116/Video to view video highlights of the interviews with (from left) Drs Matulonis, Herzog and Birrer by Dr Love and earn up to 1 additional AMA PRA Category 1 Credit™.

Topics covered include:
- Genetic assessment for women with OC
- Biologic rationale for the use of PARP inhibitors
- Niraparib maintenance therapy for platinum-sensitive, recurrent OC
- Efficacy and side-effect profiles of the various PARP inhibitors
- Management of PARP inhibitor-associated side effects
- Therapeutic options for patients experiencing disease progression on olaparib
SELECT PUBLICATIONS

A phase 2, open-label, single-arm study to evaluate the safety and efficacy of niraparib in patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received three or four previous chemotherapy regimens. NCT02354586

A phase 2, open-label study of rucaparib in patients with platinum-sensitive, relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (ARIEL2). NCT01891344

A phase III, open label, randomised, controlled, multi-centre study to assess the efficacy and safety of olaparib monotherapy versus physician’s choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying germline BRCA1/2 mutations. NCT02282020

A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO Stage III-IV) ovarian cancer following first line platinum based chemotherapy. NCT01844986

Banerjee S et al. Management of nausea and vomiting during treatment with the capsule (CAP) and tablet (TAB) formulations of the PARP inhibitor olaparib. Proc ECCO 2015; Abstract 2759.


Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: Clearing up the misunderstandings. Mol Oncol 2011;5(4):387-93.


Kristeleit RS et al. Clinical activity of the poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib in patients (pts) with high-grade ovarian carcinoma (HGOC) and a BRCA mutation (BRCAmut): Analysis of pooled data from Study 10 (parts 1, 2a, and 3) and ARIEL2 (parts 1 and 2). Proc ESMO 2016; Abstract 8560.


Mackay HJ et al. OV21/PETROC: A randomized Gynecologic Cancer Intergroup (CGIG) phase II study of intraperitoneal (IP) versus intravenous (IV) chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer (EOC). Proc ASCO 2016; Abstract LBA5503.


Phase 3 study of rucaparib as switch maintenance after platinum in relapsed high grade serous and endometrioid ovarian cancer (ARIEL3). NCT01968213

Randomized, double-blind, phase III trial olaparib vs placebo patients with advanced FIGO Stage IIIIB-IV high grade serous or endometrioid ovarian, fallopian tube, or peritoneal cancer treated standard-first-line treatment. NCT02477644

Sandro P et al. The MITO8 phase 3 international multicenter randomized study testing the effect on survival of prolonging platinum-free interval (PFI) in patients with ovarian cancer (OC) recurring between 6 and 12 months after previous platinum-based chemotherapy: A collaboration of MITO, MANGO, AGO, BGOG, ENGOT, and GCIG. Proc ASCO 2016; Abstract 5505.
QUESTIONS (PLEASE CIRCLE ANSWER):

1. Olaparib monotherapy is FDA approved for patients with deleterious germline BRCA mutation-positive advanced OC previously treated with 3 or more lines of chemotherapy.
   a. True
   b. False

2. For which of the following patients with platinum-sensitive, recurrent OC did the use of niraparib maintenance therapy provide a significant progression-free survival benefit in comparison to placebo on the Phase III ENGOT-OV16/NOVA trial?
   a. Patients with germline BRCA mutation
   b. Patients with no germline BRCA mutation but with HRD positivity
   c. Patients with no germline BRCA mutation
   d. All of the above
   e. Both a and b
   f. Both b and c

3. For how long did patients on the Phase III ENGOT-OV16/NOVA trial receive niraparib maintenance therapy?
   a. One year
   b. Two years
   c. Indefinitely (until either disease progression or toxicity)

4. The most common cytopenia observed with niraparib on the Phase III ENGOT-OV16/NOVA trial was __________.
   a. Anemia
   b. Neutropenia
   c. Thrombocytopenia
   d. All of the above

5. The Phase III PAOLA-1 trial is evaluating olaparib in combination with __________ as first-line therapy for advanced OC.
   a. Anti-PD-1/PD-L1 inhibition
   b. Bevacizumab
   c. Cediranib

6. Side effects of olaparib therapy include __________.
   a. Anemia
   b. Nausea
   c. Fatigue
   d. Vomiting
   e. All of the above

7. The Phase III SOLO1 trial is evaluating olaparib monotherapy maintenance for patients with __________ advanced OC after first-line platinum-based chemotherapy.
   a. BRCA wild-type
   b. Germline BRCA mutation-positive
   c. Both a and b

8. Rucaparib is a novel PARP inhibitor with demonstrated single-agent activity in the treatment of patients with BRCA mutation-positive advanced OC.
   a. True
   b. False

9. The Phase I/II KEYNOTE-162 trial is evaluating niraparib in combination with __________ for patients with recurrent OC or triple-negative breast cancer.
   a. Atezolizumab
   b. Nivolumab
   c. Pembrolizumab
   d. All of the above

10. It is recommended that __________ undergo BRCA testing.
    a. All patients with epithelial OC
    b. Patients with an Ashkenazi Jewish background
    c. Patients with a strong family history of breast cancer or OC at a young age
RTP On Demand: Current and Future Role of PARP Inhibitors in the Management of Ovarian Cancer

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<td>Appropriate use of BRCA testing for guidance in treatment selection for patients with OC</td>
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<td>FDA approval of olaparib monotherapy and current integration into clinical practice</td>
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<td>Investigation of PARP inhibitors as front-line therapy for BRCA mutation-positive OC</td>
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<td>KEYNOTE-162: A Phase I/II study of niraparib with the anti-PD-1 antibody pembrolizumab for patients with recurrent OC or triple-negative breast cancer</td>
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Practice Setting:
- [ ] Academic center/medical school
- [ ] Community cancer center/hospital
- [ ] Group practice
- [ ] Solo practice
- [ ] Government (eg, VA)
- [ ] Other (please specify): .................................................................

Approximately how many new patients with ovarian cancer do you see per year? ........................................... patients

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- Use available guidelines and consensus statements to develop an evidence-based algorithm for conducting genetic screening for patients with OC. ........................................... 4 3 2 1 N/M N/A
- Understand the rationale for the investigation of PARP inhibition as monotherapy or in combination with other novel agents for patients with BRCA mutation-positive and BRCA wild-type advanced OC, and use this information to inform protocol and nonresearch treatment options for these individuals. ............................................... 4 3 2 1 N/M N/A
- Appreciate the recent approval of olaparib for patients with highly refractory advanced OC, and appropriately integrate this agent into the clinical management of such cases. .......................................................... 4 3 2 1 N/M N/A
As a result of this activity, I will be able to:

- Develop an understanding of the available efficacy data and toxicity profiles of investigational PARP inhibitors to effectively prioritize clinical trial opportunities for appropriate patients with OC.
- Educate patients about the side effects associated with approved and investigational PARP inhibitors, and provide preventive and emergent strategies to reduce or ameliorate these toxicities.

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<td>Ursula A Matulonis, MD</td>
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