

# Addressing Current Questions and Emerging Considerations with the Use of PARP Inhibitors in the Management of Ovarian Cancer

## CME Information

### TARGET AUDIENCE

This activity is intended for gynecologic oncologists, medical oncologists, gynecologists and other healthcare providers involved in the treatment of gynecologic cancers.

### OVERVIEW OF ACTIVITY

The American Cancer Society estimates that in 2019, 22,530 new cases of ovarian cancer (OC) will be diagnosed in the United States and 13,980 deaths from the disease will occur. For this reason, significant financial and intellectual 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. Perhaps the largest recent advance in OC has been the introduction of PARP inhibitors into the therapeutic milieu. However, the paradigm shift brought forth by the availability of PARP inhibitors has significant ramifications for practicing clinicians who must now confront a variety of practical issues, and uncertainties with regard to the safe and efficacious use of these agents persist.

This CME program developed from the proceedings of a satellite symposium held during the Society of Gynecologic Oncology's 2019 Annual Meeting on Women's Cancer features video slide presentations given by leading researchers with an expertise in gynecologic cancers on the emerging considerations that drive clinical decision-making about the use of PARP inhibitors in the management of OC. By providing information on the latest research developments and their potential application to routine practice, this activity is designed to assist medical oncologists, gynecologic oncologists and other healthcare providers with the formulation of up-to-date clinical management strategies.

### LEARNING OBJECTIVES

- Recognize the recent FDA approval of olaparib as maintenance therapy after first-line platinum-based chemotherapy for patients with advanced OC and a deleterious or suspected deleterious BRCA germline or somatic mutation, and consider how the availability of this strategy affects current therapeutic algorithms.
- Assess available clinical trial data with and FDA indications for the various PARP inhibitors when used as maintenance

therapy for recurrent, platinum-sensitive OC, and develop strategies to identify patients for whom this approach might be appropriate.

- Identify patients with multiregimen-refractory OC who may be appropriate candidates for a PARP inhibitor, and safely integrate these agents into nonresearch therapy.
- Recognize the toxicities associated with PARP inhibitors commonly used in the care of patients with OC, and offer supportive management strategies to minimize and/or ameliorate these side effects.
- Develop an understanding of the mechanisms of action of, available data with and possible clinical roles of other investigational PARP inhibitors in preparation for their potential introduction into clinical practice.
- Recall the biologic rationale for and ongoing research efforts evaluating the role of PARP inhibitors in combination with chemotherapy, targeted therapy or immunotherapy, and refer appropriate patients for clinical trial participation.

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1 Medical Knowledge MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Please note, this program has been specifically designed for the following ABIM specialty: **medical oncology**.

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### HOW TO USE THIS CME ACTIVITY

This CME activity consists of a video component. To receive credit, the participant should review the CME information, watch the video, complete the Post-test with a score of 80% or better and fill out the Educational Assessment and Credit Form located at [ResearchToPractice.com/GynOnc19/PARP/Video/CME](https://www.researchtopractice.com/GynOnc19/PARP/Video/CME).

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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:

#### **Robert L Coleman, MD**

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**Advisory Committee and Contracted Research:** AbbVie Inc, Array BioPharma Inc, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, GamaMabs Pharma, Genentech, Genmab, ImmunoGen Inc, Janssen Biotech Inc, Merck, Novartis, Tesaro; **Data and Safety Monitoring Board/Committee:** AstraZeneca Pharmaceuticals LP.

#### **Professor Jonathan A Ledermann**

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**Advisory Committee:** Artios Pharma, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Cristal Therapeutics, Merck Sharp & Dohme Corp, Pfizer Inc, Roche Laboratories Inc, Seattle

Genetics; **Contracted Research:** AstraZeneca Pharmaceuticals LP, Merck Sharp & Dohme Corp; **Data and Safety Monitoring Board/Committee:** Regeneron Pharmaceuticals Inc; **Speakers Bureau:** AstraZeneca Pharmaceuticals LP, Clovis Oncology.

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Staff, Medical Oncology-Gynecology and Drug Development Program  
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No relevant conflicts of interest to disclose.

#### **Kathleen Moore, MD**

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Associate Professor, Section of Gynecologic Oncology  
Director, Gynecologic Oncology Fellowship  
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**Advisory Committee:** Aravive Inc, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Genentech, ImmunoGen Inc, Janssen Biotech Inc, Merck, OncoMed Pharmaceuticals Inc, Pfizer Inc, Roche Laboratories Inc, Samumed, Tesaro, VBL Therapeutics; **Contracted Research:** Clovis Oncology, Genentech, Merck, PTC Therapeutics, Roche Laboratories Inc.

**MODERATOR** — **Dr Love** is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Ariad Pharmaceuticals Inc, Array BioPharma Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biondine Inc, biTheranostics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech, Genmab, Genomic Health Inc, Gilead Sciences Inc, Guardant Health, Halozyme Inc, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Kite Pharma Inc, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seattle Genetics, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, Teva Oncology, Tokai Pharmaceuticals Inc and Tolero Pharmaceuticals.

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**Hardware/Software Requirements:**

A high-speed Internet connection  
A monitor set to 1280 x 1024 pixels or more  
Internet Explorer 11 or later, Firefox 56 or later, Chrome 61 or later, Safari 11 or later, Opera 48 or later  
Adobe Flash Player 27 plug-in or later  
Adobe Acrobat Reader  
(Optional) Sound card and speakers for audio

**Last review date:** June 2019

**Expiration date:** June 2020

## Select Publications

### Kathleen Moore, MD

- Burger RA et al. **Incorporation of bevacizumab in the primary treatment of ovarian cancer.** *N Engl J Med* 2011;365(26):2473-83.
- Gonzalez-Martin A et al. **A randomized, double-blind phase 3 trial of niraparib maintenance treatment in patients with HRD+ advanced ovarian cancer after response to front-line platinum-based chemotherapy.** *Proc ASCO* 2016;Abstract TPS5606.
- Hodgson D et al. **Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes.** *Br J Cancer* 2018;119(11):1401-9.
- Konstantinopoulos PA et al. **Homologous recombination deficiency: Exploiting the fundamental vulnerability of ovarian cancer.** *Cancer Discov* 2015;5(11):1137-54.
- Ledermann JA et al; ESMO Guidelines Working Group. **Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.** *Ann Oncol* 2018;24(Suppl 6):vi24–32.
- Litton J et al. **EMBRACA: A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline BRCA mutation.** San Antonio Breast Cancer Symposium 2017;Abstract GS6-07.
- Norquist B et al. **Mutations in homologous recombination genes and outcomes in ovarian carcinoma patients in GOG 218: An NRG Oncology/Gynecologic Oncology Group study.** *Clin Cancer Res* 2018;24(4):777-83.
- Vergote I et al. **Current perspectives on recommendations for BRCA genetic testing in ovarian cancer patients.** *Eur J Cancer* 2016;69:127-34.

### Professor Jonathan A Ledermann

- Coleman RL et al. **Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2017;390(10106):1949-61.
- Friedlander M et al. **Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy.** *Br J Cancer* 2018;119(9):1075-85.
- Kaufman B et al. **Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation.** *J Clin Oncol* 2015;33(3):244-50.
- Ledermann J et al. **Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial.** *Lancet Oncol* 2014;15(8):852-61.
- Ledermann J et al. **Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.** *N Engl J Med* 2012;366(15):1382-92.
- Mirza MR et al. **Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer.** *N Engl J Med* 2016;375(22):2154-64.
- Moore KN et al. **QUADRA: A phase 2, open-label, single-arm study to evaluate niraparib in patients (pts) with relapsed ovarian cancer (ROC) who have received  $\geq 3$  prior chemotherapy regimens.** *Proc ASCO* 2018;Abstract 5514.
- Oza AM et al. **Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2.** *Gynecol Oncol* 2017;147(2):267-75.
- Pujade-Lauraine E et al. **Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, phase 3 trial.** *Lancet Oncol* 2017;18(9):1274-84.

### Robert L Coleman, MD

- Barton DL et al. **Wisconsin Ginseng (*Panax quinquefolius*) to improve cancer-related fatigue: A randomized, double-blind trial, N07C2.** *J Natl Cancer Inst* 2013;105(16):1230-8.
- Berek JS et al. **Safety and dose modification for patients receiving niraparib.** *Ann Oncol* 2018;29(8):1784-92.
- Coleman RL et al. **Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2017;390(10106):1949-61.

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- Farrés J et al. **PARP-2 sustains erythropoiesis in mice by limiting replicative stress in erythroid progenitors.** *Cell Death Differ* 2015;22(7):1144-57.
- Friedlander M et al. **Practical guidance on the use of olaparib capsules as maintenance therapy for women with BRCA mutations and platinum-sensitive recurrent ovarian cancer.** *Asia Pac J Clin Oncol* 2016;12(4):323-31.
- Jones P et al. **Discovery of 2-[4-[(3S)-piperidin-3-yl]phenyl]-2H-indazole-7-carboxamide (MK-4827): A novel oral poly(ADP-ribose)polymerase (PARP) inhibitor efficacious in BRCA-1 and -2 mutant tumors.** *J Med Chem* 2009;52(22):7170-85.
- Kassan M et al. **Enhanced NF- $\kappa$ B activity impairs vascular function through PARP-1-, SP-1-, and COX-2-dependent mechanisms in type 2 diabetes.** *Diabetes* 2013;62(6):2078-87.
- Ledermann J et al. **Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial.** *Lancet Oncol* 2014;15(8):852-61.
- Mirza MR et al. **Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer.** *N Engl J Med* 2016;375(22):2154-64.
- Moore KN et al. **The poly (ADP ribose) polymerase inhibitor niraparib: Management of toxicities.** *Gynecol Oncol* 2018;149(1):214-20.
- Moore KN, Monk BJ. **Patient counseling and management of symptoms during olaparib therapy for recurrent ovarian cancer.** *Oncologist* 2016;21(8):954-63.
- Perrotta I et al. **iNOS induction and PARP-1 activation in human atherosclerotic lesions: An immunohistochemical and ultra-structural approach.** *Cardiovasc Pathol* 2011;20(4):195-203.
- Pujade-Lauraine E et al. **Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, phase 3 trial.** *Lancet Oncol* 2017;18(9):1274-84.
- Sandhu SK et al. **The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: A phase 1 dose-escalation trial.** *Lancet Oncol* 2013;14(9):882-92.
- Swisher EM et al. **Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): An international, multicentre, open-label, phase 2 trial.** *Lancet Oncol* 2017;18(1):75-87.
- Stephanie Lheureux, MD, PhD**
- De Bono J et al. **Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline BRCA1/2 mutations and selected sporadic cancers.** *Cancer Discov* 2017;7(6):620-29.
- Donawho CK et al. **ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models.** *Clin Cancer Res* 2007;13(9):2728-37.
- Konstantinopoulos P et al. **TOPACIO/Keynote-162 (NCT02657889): A phase 1/2 study of niraparib + pembrolizumab in patients (pts) with advanced triple-negative breast cancer or recurrent ovarian cancer (ROC)—Results from ROC cohort.** *Proc ASCO* 2018;Abstract 106.
- Leo E et al. **A head-to-head comparison of the properties of five clinical PARP inhibitors identifies new insights that can explain both the observed clinical efficacy and safety profiles.** *Proc AACR* 2018;Abstract LB-273.
- Lin KK et al. **BRCA reversion mutations in circulating tumor DNA predict primary and acquired resistance to the PARP inhibitor rucaparib in high-grade ovarian carcinoma.** *Cancer Discov* 2019;9(2):210-19.
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- Shen Y et al. **BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency.** *Clin Cancer Res* 2013;19(18):5003-15.
- Stewart RA et al. **Development of PARP and immune-checkpoint inhibitor combinations.** *Cancer Res* 2018;78(24):6717-25.

## Select Publications

Walsh CS. **Two decades beyond BRCA1/2: Homologous recombination, hereditary cancer risk and a target for ovarian cancer therapy.** *Gynecol Oncol* 2015;137(2):343-50.

Wielgos ME et al. **Variable off-target effects of clinically advanced PARP inhibitors.** *Proc AACR* 2018;Abstract 335.