Data + Perspectives

Clinical Investigators Explore the Emerging Role of PARP Inhibition in the Management of Breast Cancer

CME Information

TARGET AUDIENCE

This activity is intended for medical oncologists, breast surgeons, radiation oncologists and other healthcare professionals involved in the diagnosis and treatment of breast cancer (BC).

OVERVIEW OF ACTIVITY

BRCA1 and BRCA2 are not new entities, and it has been appreciated for some time that individuals harboring these abnormalities have increased susceptibility to developing BC as well as ovarian cancer and several other common tumor types. In fact, according to recent estimates, 55% to 65% of women who inherit a harmful BRCA1 mutation and approximately 45% of women who inherit a BRCA2 mutation will develop BC by age 70. Until recently, patients with BRCA1/2 mutations were largely cared for in the same manner as those without these genomic abnormalities. However, the promising findings observed with the use of PARP inhibitors as monotherapy or in combination with other agents led to the activation of a number of trials designed to definitively measure their efficacy and safety in large populations, which has most recently resulted in the first FDA approval for an agent in this class in BC. Owing to this approval and the host of ongoing clinical trials evaluating PARP inhibitors across a variety of settings, it is clear that oncologists in practice need to rapidly acquire knowledge regarding the efficacy and tolerability of this class of agents in order to effectively use them, both on and off protocol, in their clinics.

These video proceedings from a CME symposium held during the 2017 San Antonio Breast Cancer Symposium feature discussions with leading BC researchers regarding actual cases of patients who underwent treatment with a PARP inhibitor and related clinical research findings. By providing information on the latest research developments and their potential application to routine practice, this activity is designed to improve clinicians' knowledge of recent data related to this rapidly evolving area of BC treatment.

LEARNING OBJECTIVES

- Recall available guideline recommendations regarding the indications for BRCA mutation testing for patients diagnosed with BC, and use the results of this analysis to inform protocol and nonprotocol treatment decision-making.
- Understand the biologic rationale for the investigation of PARP inhibition as monotherapy or in combination with other systemic approaches for patients with BC, and use this insight to prioritize clinical trial opportunities for appropriate individuals eligible for participation.
- Recall efficacy data with the use of PARP inhibition in patients with metastatic BC harboring a BRCA1/2 mutation, and consider the diagnostic and therapeutic implications of these findings on clinical care.
- Educate patients regarding the side effects associated with the use of PARP inhibitors, and develop preventive and emergent strategies to reduce or ameliorate these toxicities.
- Describe mechanisms of acquired tumor resistance to PARP inhibitors, and identify investigational therapeutic opportunities to circumvent this process.

ACCREDITATION STATEMENT

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CREDIT DESIGNATION STATEMENT

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AMERICAN BOARD OF INTERNAL MEDICINE (ABIM) — MAINTENANCE OF CERTIFICATION (MOC)

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 Medical Knowledge MOC points 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/SanAntonioPARP17/CME**.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess conflicts of interest with faculty, planners and managers of CME activities. Conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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

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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

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Select Publications

Susan M Domchek, MD

Couch FJ et al. **Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer.** *J Clin Oncol* 2015;33(4):304-11.

Malone KE et al. **Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years.** *Cancer Res* 2006;66(16):8297-308.

Nilsson MP et al. **BRCAsearch: Written pre-test information and BRCA1/2 germline mutation testing in unselected patients with newly diagnosed breast cancer.** *Breast Cancer Res Treat* 2017;[Epub ahead of print].

Syrjäkoski K et al. **Population-based study of BRCA1 and BRCA2 mutations in 1035 unselected Finnish breast cancer patients.** *J Natl Cancer Inst* 2000;92(18):1529-31.

van den Broek AJ et al. **Impact of age at primary breast cancer on contralateral breast cancer risk in BRCA1/2 mutation carriers.** *J Clin Oncol* 2015;34(5):409-18.

Karen A Gelmon, MD

Han HS et al. **Efficacy and tolerability of veliparib (V; ABT-888) in combination with carboplatin (C) and paclitaxel (P) vs placebo (Plc)+C/P in patients (pts) with *BRCA1* or *BRCA2* mutations and metastatic breast cancer: A randomized, phase 2 study.** San Antonio Breast Cancer Symposium 2016;**Abstract S2-05**.

Mirza MR et al. **Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer.** *N Engl J Med* 2016;375(22):2154-64.

Pujade-Lauraine E et al; SOLO2/ENGOT-Ov21 investigators. **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.

Robson M et al. **Olaparib for metastatic breast cancer in patients with a germline BRCA mutation.** *N Engl J Med* 2017;377(6):523-33.

Mark Robson, MD

Farmer H et al. **Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy.** *Nature* 2005; 434(7035):917-21.

Gelmon KA et al. **Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: A phase 2, multicentre, open-label, non-randomised study.** *Lancet Oncol* 2011;12(9):852-61.

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

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.

Lord CJ, Ashworth A. **PARP inhibitors: Synthetic lethality in the clinic.** *Science* 2017;355(6330):1152-8.

Tutt A et al. **Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof-of-concept trial.** *Lancet* 2010;376(9737):235-44.

Hope S Rugo, MD

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):620-9.

Geyer CE et al. **Phase 3 study evaluating efficacy and safety of veliparib (V) plus carboplatin (Cb) or Cb in combination with standard neoadjuvant chemotherapy (NAC) in patients (pts) with early stage triple-negative breast cancer (TNBC).** *Proc ASCO* 2017;**Abstract 520**.

Hahnen E et al. **Germline mutation status, pathological complete response, and disease-free survival in triple-negative breast cancer: Secondary analysis of the GeparSixto randomized clinical trial.** *JAMA Oncol* 2017;3(10):1378-85.

Huang J et al. **The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a Brca1(-/-) murine model of ovarian cancer.** *Biochem and Biophy Res Comm* 2015;463(4):551-6.

Jiao S et al. **PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression.** *Clin Cancer Res* 2017;23(14):3711-20.

Select Publications

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.

Konstantinopoulos P et al. **Dose-finding combination study of niraparib and pembrolizumab in patients (pts) with metastatic triple-negative breast cancer (TNBC) or recurrent platinum-resistant epithelial ovarian cancer (OC) (TOPACIO/Keynote-162).** *Proc ESMO* 2017;**Abstract 1143PD**.

Lord CJ, Ashworth A. **PARP inhibitors: Synthetic lethality in the clinic.** *Science* 2017;355(6330):1152-8.

Luo X et al. **Poly(ADP-ribosyl)ation of FOXP3 protein mediated by PARP-1 protein regulates the function of regulatory T cells.** *J Biol Chem* 2015;290(48):28675-82.

Rugo HS et al; I-SPY 2 Investigators. **Adaptive randomization of veliparib-carboplatin treatment in breast cancer.** *N Engl J Med* 2016;375(1):23-34.

Wolf DM et al. **DNA repair deficiency biomarkers and MammaPrint high1/(ultra)high2 risk as predictors of veliparib/carboplatin response: Results from the neoadjuvant I-SPY 2 trial for high risk breast cancer.** San Antonio Breast Cancer Symposium 2016;**Abstract SN-06**.