PARP Inhibition in Four Common Cancers: Biology, Clinical Research Database and Therapeutic Strategy

Audio Program

CME Information

TARGET AUDIENCE

This activity is intended for medical oncologists, hematologists, surgeons, radiation oncologists and other healthcare professionals involved in basic, translational and clinical cancer research or treatment.

OVERVIEW OF ACTIVITY

Over the past 2 decades, the oncology community has witnessed a significant transformation in the way clinicians think about and approach the diagnosis and treatment of a variety of solid tumors. A multitude of specific diseases are now classified by the presence or absence of various genomic alterations or biomarker expression profiles and are managed differently based on this information. Given that one cancer may share a number of biologic similarities with another and that abnormalities found in one disease may be present in others, it is not surprising that an attempt is under way to apply knowledge and therapeutic understanding across multiple diseases. This rational approach to clinical research has yielded a growing body of evidence that a single "targeted" therapy can provide demonstrable benefit for patients with the same identified genetic abnormality regardless of the primary cancer type. One of the most compelling and recent examples of this phenomenon has been the documentation of efficacy and the subsequent FDA approval of PARP inhibitors for both breast and ovarian cancer. Researchers are also attempting to document the therapeutic potential of these agents in pancreatic and prostate cancer.

These proceedings from a satellite symposium held during the 2019 AACR Annual Meeting feature discussions with leading investigators about the role of PARP inhibition as a therapeutic strategy for patients with ovarian, breast, prostate and pancreatic cancer. By providing information on important developments, this activity will assist medical oncologists and other healthcare professionals in addressing existing management uncertainties and determining the clinical role of PARP inhibition in these diseases.

LEARNING OBJECTIVES

 Appraise available guideline recommendations and investigator perspectives regarding genetic testing in ovarian, breast and prostate cancer, and use the results of these assessments to guide long-term treatment planning.

- Describe the rationale for testing patients with prostate cancer or pancreatic adenocarcinoma for mutations in DNA repair genes, and assess the possible clinical role of PARP inhibitors in the care of these patients.
- Evaluate available research data and investigator perspectives on the role of FDA-approved PARP inhibitors for patients with ovarian cancer, and safely integrate these agents into routine clinical care.
- Evaluate the FDA approvals of olaparib and talazoparib for patients with metastatic breast cancer and a germline BRCA mutation, and discern how these agents can be appropriately and safely integrated into routine clinical practice.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.25 AMA PRA Category 1 CreditTM. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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 1.25 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**.

Personal information and data sharing: Research To Practice aggregates deidentified user data for program-use analysis, program development, activity planning and site improvement. We may provide aggregate and deidentified data to third parties, including commercial supporters. We do not share

or sell personally identifiable information to any unaffiliated third parties or commercial supporters. Please see our privacy policy at **ResearchToPractice.com/Privacy-Policy** for more information.

HOW TO USE THIS CME ACTIVITY

This CME activity consists of an audio component. To receive credit, the participant should review the CME information, listen to the MP3s, complete the Post-test with a score of 80% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/AACR19/PARP/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:

Emmanuel S Antonarakis. MD

Associate Professor of Oncology and Urology Johns Hopkins University The Sidney Kimmel Comprehensive Cancer Center Baltimore, Maryland

Advisory Committee and Consulting Agreements: Amgen Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Dendreon Pharmaceuticals Inc, ESSA Pharma Inc, Janssen Biotech Inc, Medivation Inc, a Pfizer Company, Merck, Sanofi Genzyme; Contracted Research: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Dendreon Pharmaceuticals Inc, Genentech, Janssen Biotech Inc, Johnson & Johnson Pharmaceuticals, Merck, Novartis, Sanofi Genzyme, Tokai Pharmaceuticals Inc; Other Remunerated Activities: Co-inventor of a biomarker licensed to QIAGEN.

Kathleen Moore, MD

Jim and Christy Everest Endowed Chair in Cancer Research Associate Director, Clinical Research Director, Oklahoma TSET Phase I Program Stephenson Cancer Center Associate Professor, Section of Gynecologic Oncology Director, Gynecologic Oncology Fellowship Department of Obstetrics and Gynecology University of Oklahoma Health Sciences Center Oklahoma City, Oklahoma

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.

Michael J Pishvaian, MD, PhD

Phase I Program Director Medical Director of the CRMO Associate Professor Lombardi Comprehensive Cancer Center Washington, DC

Consulting Agreements: AstraZeneca Pharmaceuticals LP, Caris Life Sciences, Celgene Corporation, Merrimack Pharmaceuticals Inc, Perthera Inc, RenovoRx; Contracted Research: ARMO Biosciences, Bavarian Nordic, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Calithera Biosciences, Celgene Corporation, Celldex Therapeutics, Curegenix Inc, FibroGen, Genentech, Gilead Sciences Inc, GlaxoSmithKline, Halozyme Inc, Incyte Corporation, Karyopharm Therapeutics, Lilly, MedImmune Inc, Merck, Novartis, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Regeneron Pharmaceuticals Inc, Tesaro; Ownership Interest: Perthera Inc; Paid Travel: AstraZeneca Pharmaceuticals LP, Caris Life Sciences, Perthera Inc, Sirtex Medical Ltd; Speakers Bureau: Sirtex Medical Ltd.

Melinda Telli, MD

Associate Professor of Medicine Stanford University School of Medicine Leader, Breast Oncology Clinical Research Group Stanford Cancer Institute Stanford, California

Advisory Committee: Aduro Biotech, Celgene Corporation, Genentech, Immunomedics Inc, Merck; Consulting Agreement: Pfizer Inc; Contracted Research: Biothera Pharmaceuticals Inc, Calithera Biosciences, EMD Serono Inc, Genentech, OncoSec Medical, Pfizer Inc, PharmaMar, Tesaro; Data and Safety Monitoring Board: G1 Therapeutics.

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, Biodesix Inc, bioTheranostics 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

RESEARCH TO PRACTICE CME PLANNING COMMITTEE MEMBERS, STAFF AND REVIEWERS — Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

This educational activity contains discussion of published and/ or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor. This activity is supported by an educational grant from AstraZeneca Pharmaceuticals LP.

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

Neil Love, MD

LaFargue CJ et al. Exploring and comparing adverse events between PARP inhibitors. Lancet Oncol 2019;20(1):e15-8.

Kathleen Moore, MD

Berek JS et al. Safety and dose modification for patients receiving niraparib. Ann Oncol 2018;29(8):1784-92.

Burger RA et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011;365(26):2473-83.

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.

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 DR et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. *Br J Cancer* 2018;119(11):1401-9.

Kondrashova O et al. **Methylation of all BRCA1 copies predicts response to the PARP inhibitor rucaparib in ovarian carcinoma.** *Nat Commun* 2018;9(1):3970.

Konstantinopoulos PA et al. Homologous recombination deficiency: Exploiting the fundamental vulnerability of ovarian cancer. *Cancer Discov* 2015;5(11):1137-54.

Ledermann J et al. **Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.** *N Engl J Med* 2012;366(15):1382-92.

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.

Moore KN et al. Maintenance olaparib following platinum-based chemotherapy in newly diagnosed patients (pts) with advanced ovarian cancer (OC) and a BRCA1/2 mutation (BRCAm): Phase III SOLO1 trial. *Proc ESMO* 2018; Abstract LBA7_PR.

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 ≥3 prior chemotherapy regimens. *Proc ASCO* 2018; Abstract 5514.

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.

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.

Vergote I et al. Current perspectives on recommendations for BRCA genetic testing in ovarian cancer patients. *Eur J Cancer* 2016;69:127-34.

Melinda Telli, MD

Chen JH et al. Magnetic resonance imaging in predicting pathological response of triple negative breast cancer following neoadjuvant chemotherapy. *J Clin Oncol* 2007;25(35):5667-9.

Litton JK et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med* 2018;379(8):753-63.

McLornan DP et al. Applying synthetic lethality for the selective targeting of cancer. N Engl J Med 2014;371(18):1725-35.

Robson ME et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol* 2019;[Epub ahead of print].

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

Roy R et al. **BRCA1** and **BRCA2**: Different roles in a common pathway of genome protection. Nat Rev Cancer 2011;12(1):68-78.

Telli ML et al. Homologous recombination deficiency and host anti-tumor immunity in triple-negative breast cancer. *Breast Cancer Res Treat* 2018;171(1):21-31.

Select Publications

Telli ML et al. Homologous recombination deficiency (HRD) status predicts response to standard neoadjuvant chemotherapy in patients with triple-negative or BRCA1/2 mutation-associated breast cancer. *Breast Cancer Res Treat* 2018;168(3):625-30.

Vinayak S et al. Durability of clinical benefit with niraparib + pembrolizumab in patients with advanced triple-negative breast cancer beyond *BRCA*: (TOPACIO/Keynote-162). San Antonio Breast Cancer Symposium 2018; Abstract PD5-02.

Michael Pishvaian, MD, PhD

Aguirre AJ et al. Real-time genomic characterization of advanced pancreatic cancer to enable precision medicine. *Cancer Discov* 2018;8(9):1096-111.

Bailey P et al. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* 2016;531(7592):47-52.

Bang YJ et al. Randomized, double-blind phase II trial with prospective classification by ATM protein level to evaluate the efficacy and tolerability of olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer. *J Clin Oncol* 2015;33(33):3858-65.

Biankin AV et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* 2012;491(7424):399-405.

Bouwman P, Jonkers J. Molecular pathways: How can BRCA-mutated tumors become resistant to PARP inhibitors? *Clin Cancer Res* 2014;20(3):540-7.

Collisson EA et al. **Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy.** *Nat Med* 2011;17(4):500-3.

Golan T et al. **Phase II study of olaparib for BRCAness phenotype in pancreatic cancer.** Gastrointestinal Cancers Symposium 2018; **Abstract 297**.

Helleday T et al. **DNA repair pathways as targets for cancer therapy.** *Nat Rev Cancer* 2008;8(3):193-204.

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.

Lal S et al. **WEE1** inhibition in pancreatic cancer cells is dependent on DNA repair status in a context dependent manner. *Sci Rep* 2016;6:33323.

Lord CJ, Ashworth A. BRCAness revisited. *Nature* 2016;16(2):110-20.

Lowery MA et al. **Phase II trial of veliparib in patients with previously treated BRCA-mutated pancreas ductal adenocarcinoma.** *Eur J Cancer* 2018;89:19-26.

Lowery MA et al. An emerging entity: Pancreatic adenocarcinoma associated with a known BRCA mutation: Clinical descriptors, treatment implications, and future directions. *Oncologist* 2011;16(10):1397-402.

Mateo J et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373(18):1697-708.

Min A et al. **AZD6738**, a novel oral inhibitor of ATR, induces synthetic lethality with ATM deficiency in gastric cancer cells. *Mol Cancer Ther* 2017;16(4):566-77.

Nickoloff JA et al. Drugging the cancers addicted to DNA repair. J Natl Cancer Inst 2017;109(11):djx059.

O'Carrigan B et al. Phase I trial of a first-in-class ATR inhibitor VX-970 as monotherapy (mono) or in combination (combo) with carboplatin (CP) incorporating pharmacodynamics (PD) studies. *Proc ASCO* 2016; Abstract 2504.

O'Reilly EM et al. Phase 1 trial evaluating cisplatin, gemcitabine, and veliparib in 2 patient cohorts: Germline BRCA mutation carriers and wild-type BRCA pancreatic ductal adenocarcinoma. *Cancer* 2018;124(7):1374-82.

Peng G, Lin SY. Exploiting the homologous recombination DNA repair network for targeted cancer therapy. *World J Clin Oncol* 2011;2(2):73-9.

Pishvaian MJ et al. Molecular profiling of patients with pancreatic cancer: Initial results from the Know Your Tumor initiative. *Clin Cancer Res* 2018;24(20):5018-27.

Pishvaian MJ et al. **BRCA2** secondary mutation-mediated resistance to platinum and PARP inhibitor-based therapy in pancreatic cancer. *Br J Cancer* 2017;116(8):1021-6.

Rowe BP, Glazer PM. Emergence of rationally designed therapeutic strategies for breast cancer targeting DNA repair mechanisms. *Breast Cancer Res* 2010;12(2):203.

Select Publications

Strickland KC et al. Association and prognostic significance of BRCA1/2-mutation status with neoantigen load, number of tumor-infiltrating lymphocytes and expression of PD-1/PD-L1 in high grade serous ovarian cancer. *Oncotarget* 2016;7(12):13587-98.

Thijssen R et al. **Dual TORK/DNA-PK inhibition blocks critical signaling pathways in chronic lymphocytic leukemia.** *Blood* 2016;128(4):574-83.

Toledo LI et al. A cell-based screen identifies ATR inhibitors with synthetic lethal properties for cancer-associated mutations. *Nat Struct Mol Biol* 2011;18(6):721-7.

Waddell N et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature 2015;518(7540):495-501.

Wang Z et al. Comutations in DNA damage response pathways serve as potential biomarkers for immune checkpoint blockade. *Cancer Res* 2018;78(22):6486-96.

Witkiewicz AK et al. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. *Nat Commun* 2015;6:3744.

Emmanuel S Antonarakis, MD

Abida W et al. Preliminary results from TRITON2: A phase 2 study of rucaparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations. *Proc ESMO* 2018; Abstract 793PD.

Carney B et al. Target engagement imaging of PARP inhibitors in small-cell lung cancer. Nat Commun 2018;9(1):176.

Chowdhury S et al. Genomic profiling of circulating tumour DNA (ctDNA) and tumour tissue for the evaluation of rucaparib in metastatic castration-resistant prostate cancer (mCRPC). *Proc ESMO* 2018; Abstract 795PD.

Clarke N et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: A randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2018;19(7):975-86.

Fong PC et al. **Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers.** *N Engl J Med* 2009;361(2):123-34.

Fraser M et al. Genomic hallmarks of localized, non-indolent prostate cancer. Nature 2017;541(7637):359-64.

Isaacsson Velho P et al. Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. *Prostate* 2018;78(5):401-7.

Karzai F et al. Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations. *J Immunother Cancer* 2018;6(1):141.

Mateo J et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373(18):1697-708.

Marshall CH et al. Differential response to olaparib treatment among men with metastatic castration-resistant prostate cancer harboring BRCA1 or BRCA2 versus ATM mutations. *Eur Urol* 2019;[Epub ahead of print].

Pritchard CC et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016;375(5):443-53.

Robinson D et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161(5):1215-28.

Schweizer MT et al. Genomic characterization of ductal adenocarcinoma of the prostate. Proc ASCO 2018; Abstract 5030.

Smith MR et al. Phase II study of niraparib in patients with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD): Preliminary results of GALAHAD. Genitourinary Cancers Symposium 2019; Abstract 202.

Yu EY et al. Keynote-365 cohort a: Pembrolizumab (pembro) plus olaparib in docetaxel-pretreated patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC). Genitourinary Cancers Symposium 2019; Abstract 145.