PARP Inhibitors: Current and Future Options for Breast and Ovarian Cancer

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Overview
This activity is designed to aid physicians in assessing the use of PARP inhibitors for ovarian cancer and for referrals for clinical trials for breast cancer, including patient-specific treatment regimens and monitoring for adverse events during therapy, and applying these data to their practices.

Target Audience
This activity is directed toward medical oncologists who manage and treat patients with breast and ovarian cancer. Surgical oncologists, radiation oncologists, pathologists, fellows, nurses, nurse practitioners, physician assistants, and other healthcare providers interested in the treatment of breast and ovarian cancer are also invited to participate.

Learning Objectives
After participating in this CME activity, learners should be better prepared to:
- List the role of the PARP enzymes in the cell
- Describe the rationale for PARP inhibition as an investigational treatment for tumors with BRCA mutations
- Describe the rationale for PARP inhibition in the treatment of tumors without BRCA mutations
- Identify PARP inhibitors that are in late-stage development for the treatment of ovarian and breast cancer

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The research and development of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors in the treatment of cancer is continuing to expand. This growth goes beyond just the treatment of tumors with germline mutations of *BRCA* genes.

There are 17 PARP proteins within the cell.[1] These proteins have numerous cellular functions, including DNA transcription and repair, cell metabolism, cell death/survival, and overall genomic stability.[1] Of the 17 PARP enzymes, PARP1 is the most plentiful and specifically increases in response to cellular stress such as DNA damage or "nicks," facilitating the repair of both single-stranded and double-stranded DNA breaks.[1] PARP also may support homologous recombinational repair (HRR) and nonhomologous end-joining (NHEJ), both of which are DNA double-stranded repair pathways.

Due to the multiple roles that PARP has in single-stranded and double-stranded DNA repair, pharmacologic agents that inhibit PARP (PARP inhibitors) are a focus for cancer treatment, including breast and ovarian cancer. The selective targeting of HRR-deficient tumors by PARP inhibitors relates to the concept known as synthetic lethality. This occurs when 2 non-lethal mutations lead to cell death only when they occur in combination.[2] PARP inhibitors have been shown to be toxic to HRR-deficient tumors, including those with hereditary *BRCA1* and *BRCA2* mutations.[3,4] However, there is no definite correlation among *BRCA* mutational status, platinum sensitivity, response to PARP inhibition, and clinical responses.[1] Furthermore, there are tumor characteristics other than mutations in *BRCA1* or *BRCA2* that are considered biomarkers for HRR deficiency and are categorized as "BRCAness."[5,6] Deficiencies in other cellular proteins that contribute to HRR, such as RAD51, RAD54, DSS1, RPA1, NBS1, ATR, ATM, CHK1, CHK2, FANCD2, FANCA, or FANCC, also lead to sensitivity to PARP inhibition. Deficiency in RAD52 does not lead to PARP inhibition responsiveness.[7] Many of the cellular proteins associated with an increased risk of ovarian or breast cancers (in addition to *BRCA1* and *BRCA2*) are analyzed on commercially available laboratory panels, including the myRisk, BreastNext, BROCA, and OncoGeneDx panels.[8] Ongoing research is aimed at identifying additional therapeutic roles for PARP inhibitors and biomarkers that predict favorable responses to PARP inhibitors in the treatment of cancer.

Olaparib is the PARP inhibitor approved by the US Food and Drug Administration (FDA) at the time of this article. It is an oral agent approved to treat advanced ovarian cancer in patients with *BRCA*-mutated tumors who have been previously treated with at least 3 lines of chemotherapy.[9] Olaparib is also being studied for triple-negative breast cancer. The **Table** lists PARP inhibitors in various stages of clinical development for the treatment of breast and ovarian cancer. Eight trials are currently studying PARP inhibitors that are in phase II (4 in breast cancer and 4 in ovarian cancer) and 6 trials in phase III (4 in breast cancer and 2 in ovarian cancer).[10]

Maurie Markman, MD, president of Medicine & Science, Cancer Treatment Centers of America, Philadelphia, shared his clinical insights into the research behind PARP inhibitors and their role in eradicating various types of tumors.

Moderator: *What is the role of PARP within the cell?*

Dr Markman: It would appear based on preclinical data that PARP is one of the critical enzymes responsible for DNA repair. It is well recognized that as part of the normal cell division process, errors occur. It's also part of the evolutionary process. Cells in all living organisms, certainly higher living organisms, have developed processes to repair damage when the cell is dividing. So, if there is something in the cell that doesn't come together properly, a break in DNA for example, that damage is repaired before the cell multiplies further. If that repair doesn't occur, the cell may die, which of course is the importance of the PARP inhibitors. So basically PARP is an important enzyme in the repair of DNA damage.

Moderator: *What is the rationale for PARP inhibition in BRCA-deficient tumors and preclinical evidence in this regard?*

Dr Markman: This is really a foundational question and a foundational observation. This goes back to more than a decade ago where preclinical models demonstrated that cells that have mutations in or lack of function in *BRCA* are very susceptible to PARP inhibitors, and cells that are wild-type in *BRCA* are not affected. The hypothesis here was that if a cell has normal *BRCA* function, which plays a role in DNA repair, then interfering with PARP would not have an effect on the ability of that cell to survive because there would be another mechanism for DNA repair. But in a cell that has the inability to perform *BRCA* repair, interfering with PARP could very effectively kill that cell. So, again, very importantly, the idea was that there are multiple pathways, 2 of which are very important pathways for DNA repair. It's not surprising that a living organism would come up with multiple ways to repair DNA damage for the survival of cells. So if you already have one genetic defect in *BRCA*, and then you interfere with another mechanism through a PARP inhibitor, you'd have a profound killing effect, whereas if *BRCA* were normal you wouldn't have an effect. So that was the preclinical data. They could demonstrate in cells that were wild-type *BRCA* that PARP inhibition did not have an effect, whereas if the cells were deficient in *BRCA* function, PARP inhibitors were very effective in killing those cells. This sums up the reason that in *BRCA* mutation-positive tumors, PARP inhibitors would be effective clinically.

Moderator: *Can you summarize completed clinical trials utilizing PARP inhibitors in ovarian cancer in patients with BRCA mutations?*

Dr Markman: There are a number of published studies, mostly in ovarian cancer, but also a smattering of other tumor types, that have demonstrated that in tumors that were *BRCA* mutation-positive, a single agent, olaparib, the only PARP inhibitor drug at the time, demonstrated response rates as high as into the upper 20% range and much less activity in so-called *BRCA* wild-type tumors. That now gets into the question of "BRCAness." This is a molecular abnormality that is *BRCA* mutation-positive, but it doesn't mean there can't be

TABLE. PARP Inhibitors in Clinical Trials for Breast and Ovarian Cancer[10,11]

Trial #	Trial Name	Tumor Type	Clinical Phase
NCT01623349	Phase I Study of the Oral PI3 Kinase Inhibitor BKM120 or BYL719 and the Oral PARP Inhibitor **Olaparib** in Patients With Recurrent Triple Negative Breast Cancer or High Grade Serous Ovarian Cancer	Ovarian cancer, breast cancer	I
NCT01749397	**Veliparib** and Floxuridine in Treating Patients With Metastatic Epithelial Ovarian, Primary Peritoneal Cavity, or Fallopian Tube Cancer	Stage IV fallopian tube cancer; stage IV ovarian cancer; stage IV primary peritoneal cancer	I
NCT00989651 (ASCO 2015, abstract 5507)	Carboplatin, Paclitaxel, Bevacizumab, and **Veliparib** in Treating Patients With Newly Diagnosed Stage II-IV Ovarian Epithelial, Fallopian Tube, or Primary Peritoneal Cancer	Malignant ovarian mixed epithelial tumor; ovarian Brenner tumor, ovarian cancer; ovarian clear cell cystadenocarcinoma; ovarian endometrioid adenocarcinoma; ovarian mucinous cystadenocarcinoma; ovarian serous cystadenocarcinoma; stage II, IIA, IIB, IIC, IIA, IIIB, IIIC, or IV ovarian cancer; stage IIA, IIB, IIIA, IIIB, IIIC, or IV fallopian tube cancer; stage IIIA, IIIB, IIIC, or IV primary peritoneal cancer; undifferentiated ovarian cancer	I
NCT01434316	**Veliparib** and Dinaciclib With or Without Carboplatin in Treating Patients With Advanced Solid Tumors	Advanced malignant neoplasm; *BRCA1* mutation carrier; *BRCA2* mutation carrier	I
NCT01366144	**Veliparib**, Paclitaxel, and Carboplatin in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery and Liver or Kidney Dysfunction	Adult solid neoplasm; bladder, breast, endometrial, esophageal, lung, malignant head and neck, ovarian, renal, pelvis, ureter, urothelial, or testicular cancer; lymphoma, melanoma	I
NCT01145430	**Veliparib** and Pegylated Liposomal Doxorubicin Hydrochloride in Treating Patients With Recurrent Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer or Metastatic Breast Cancer	Estrogen receptor-negative; *HER2/neu*-negative; male breast cancer; progesterone receptor-negative; recurrent breast, fallopian tube, ovarian, or primary peritoneal cancer; stage IV breast cancer; triple-negative breast cancer	I
NCT02227082	**Olaparib** and Radiotherapy in Inoperable Breast Cancer	Locally advanced malignant neoplasm; inflammatory breast cancer; triple-negative invasive breast cancer	I
NCT01989546	Pilot Trial of **BMN 673**, an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Deleterious BRCA Mutations	Advanced ovarian cancer; primary peritoneal cancer; advanced breast cancer; advanced solid tumors	I/II
NCT02396433	Combination of Carboplatin, Eribulin Mesylate, and **E7449** in BRCA-Related Cancers	Breast cancer	I/II
NCT01116648 (ASCO 2015, abstract 5559)	Cediranib Maleate and **Olaparib** in Treating Patients With Recurrent Ovarian, Fallopian Tube, or Peritoneal Cancer or Recurrent Triple-Negative Breast Cancer	Estrogen receptor-negative; HER2/neu-negative; ovarian endometrioid adenocarcinoma; ovarian serous cystadenocarcinoma; ovarian serous surface papillary adenocarcinoma; progesterone receptor-negative; recurrent breast, fallopian tube, ovarian, or primary peritoneal cancer; triple-negative breast cancer	I/II
NCT01618136	An Open-Label, Multicenter, Phase 1/2 Study of Poly(ADP-Ribose) Polymerase (PARP) Inhibitor **E7449** as Single Agent in Subjects With Advanced Solid Tumors or With B-cell Malignancies and in Combination With Temozolomide (TMZ) or With Carboplatin and Paclitaxel in Subjects With Advanced Solid Tumors	Malignant solid tumor; ovarian cancer; triple-negative breast cancer; advanced melanoma; B-cell malignancy, low-grade	I/II
NCT02354131 (ASCO 2015, abstract TPS5607–ENGOT-OV24-NSGO/ ANANOVA study)	**Niraparib** and/or Niraparib-Bevacizumab Combination Against Bevacizumab Alone in Platinum-Sensitive Ovarian Cancer	Ovarian cancer	I/II
NCT01472783	**Veliparib** Monotherapy for Relapsed Ovarian Cancer With BRCA Mutation	Recurrent, epithelial ovarian cancer	I/II
NCT01482715	A Study of Oral **Rucaparib** in Patients With a Solid Tumor (Phase I) or With gBRCA Mutation Ovarian Cancer (Phase II)	Ovarian, fallopian tube, or peritoneal cancer	I/II
NCT01351909	Cyclophosphamide With or Without **Veliparib** in Treating Patients With Locally Advanced or Metastatic Breast Cancer	Estrogen receptor-positive; *HER2/neu*-negative; male breast cancer; progesterone receptor-positive; recurrent breast cancer; stage IIIB, IIIC, or IV breast cancer	I/II

TABLE. PARP Inhibitors in Clinical Trials for Breast and Ovarian Cancer[10,11] *(Continued)*

Trial #	Trial Name	Tumor Type	Clinical Phase
NCT02401347	PARP Inhibitor **BMN-673** in Treating Patients With BRCA1 and BRCA2 Wild-Type, Metastatic or Recurrent, Triple-Negative or HER2-Negative Breast Cancer	Estrogen receptor-negative; *HER2/neu*-negative; male breast cancer; progesterone receptor-negative; metastatic breast cancer; stage IV breast cancer; triple-negative breast cancer	II
NCT02326844	BMN 673 (**Talazoparib**), an Oral PARP Inhibitor, in People With Deleterious BRCA1/2 Mutation-Associated Ovarian Cancer Who Have Had Prior PARP Inhibitor Treatment	Ovarian cancer	II
NCT02354586 (ASCO 2015, abstract TPS5609)	A Study of **Niraparib** in Patients With Ovarian Cancer Who Have Received at Least Three Previous Chemotherapy Regimens	Ovarian cancer	II
NCT01891344 (ASCO 2015, abstracts 5513, 5539, and 5508)	A Study of **Rucaparib** in Patients With Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (ARIEL2)	Ovarian cancer; epithelial ovarian cancer; fallopian tube cancer; peritoneal cancer	II
NCT02340611	A Study of Cediranib and **Olaparib** at the Time Ovarian Cancer Worsens on Olaparib	Ovarian cancer	II
NCT02034916 (ASCO 2015, abstract TPS1108)	A Phase 2, 2-Stage, 2-Cohort Study of **Talazoparib** (BMN 673), in Locally Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation (ABRAZO Study)	Breast neoplasms; *BRCA1* or *BRCA2* gene mutation	II
NCT02299999	Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Breast Cancer	Metastatic breast cancer	II
NCT01945775 (ASCO 2015, abstract TPS1107)	A Study Evaluating **Talazoparib** (BMN 673), a PARP Inhibitor, in Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation (EMBRACA Study)	Breast neoplasms; *BRCA1* or *BRCA2* gene mutation	III
NCT02000622	Assessment of the Efficacy and Safety of **Olaparib** Monotherapy Versus Physicians Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients With Germline BRCA1/2 Mutations	Metastatic breast cancer, *BRCA1* or *BRCA2* gene mutation	III
NCT01905592	A Phase III Trial of **Niraparib** Versus Physician's Choice in Her2 Negative, Germline BRCA Mutation-positive Breast Cancer Patients	Breast cancer; Human Epidermal Growth Factor 2-negative breast cancer, *BRCA1* or *BRCA2* gene mutation	III
NCT02163694 (ASCO 2015, abstract TPS1102)	A Phase 3 Randomized, Placebo-controlled Trial of Carboplatin and Paclitaxel With or Without **Veliparib** (ABT-888) in HER2-negative Metastatic or Locally Advanced Unresectable BRCA-associated Breast Cancer	Metastatic breast cancer	III
NCT01844986	**Olaparib** Maintenance Monotherapy in Patients With BRCA Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy.	Newly diagnosed; advanced ovarian cancer; FIGO stage III-IV; *BRCA* gene mutation; complete response; partial response; first-line platinum chemotherapy	III
NCT01968213 (ARIEL3 study)	A Study of **Rucaparib** as Switch Maintenance Following Platinum-Based Chemotherapy in Patients With Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer	Ovarian, fallopian tube, or peritoneal cancer	III

ASCO indicates American Society of Clinical Oncology.
PARP inhibitors in bold.

other molecular dysfunctional states that look like *BRCA*, known as BRCAness. But, clearly, if there's a mutation in *BRCA*, the cell will have the molecular profile that responds to PARP inhibition.

Moderator: *How about the use of PARP inhibitors in non-BRCA mutation carriers? Have any strategies with these compounds been assessed in this subset of patients?*

Dr Markman: The observation was made, again, probably 8 or 10 years ago, that if you know that a patient has a germline *BRCA* mutation, the tumor will have it as well. But the hypothesis was that even in the absence of a germline *BRCA* mutation, there were some ovarian cancers that actually might molecularly behave as if they have a mutation. So that's where the concept of BRCAness came from. In other words, if you'd look at the germline, you would define wild-

type. If you look at the tumor and you look at the molecular analysis, it looked similar to what one might see in a *BRCA* mutation-positive ovarian cancer. Then the next step was the trials that looked at that.

The trial that unquestionably changed the paradigm, regardless of what the FDA might say, is a landmark study published in *The New England Journal of Medicine* by Ledermann et al.[12] That trial changed the care of ovarian cancer that day and forever. It was a randomized phase II trial that looked at the use of single-agent olaparib versus placebo as maintenance therapy in patients who had attained a second response to platinum-based chemotherapy, or at least had stable disease on platinum-based therapy. And, at that point, they published in *The New England Journal of Medicine* in 2012. This study demonstrated very eloquently that if you stopped chemotherapy in that state—which was at that time perfectly reasonable—and gave placebo or olaparib, there was a spectacular, basically a 2-fold, improvement in progression-free survival in the patients who received olaparib compared with placebo, with benefit seen in both the documented *BRCA* mutation-positive patient population and less so, but still a significant benefit, in those patients with high-grade serous cancer. The eligibility criteria was high-grade serous, but as a part of the prospective part of the trial, they also collected data on *BRCA* status. They looked back at *BRCA* mutation-positive patients, and they looked at other populations, and showed a benefit in both patient populations, with the greatest benefit in those patients with *BRCA*-mutation positive tumors. So that's where we are with the evidence, but that's not where we are with the FDA approval.

Moderator: *What PARP inhibitors are in late-stage development for use in patients with breast cancer, and what clinical trial evidence is currently available?*

Dr Markman: There are some phase III studies looking specifically at PARP inhibitors in the *BRCA* mutation-positive patient population with breast cancer. Olaparib is still being studied for the treatment of breast cancer in patients with *BRCA* mutations. But there are a few other PARP inhibitors, too: talazoparib and niraparib, for example. (The **Table** lists selected trials for these agents, including those highlighted at the 2015 Annual Meeting of the American Society of Clinical Oncology.)

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