The Evolution of Poly(ADP-Ribose) Polymerase Inhibitors in the Treatment of Breast Cancer

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**H&O** Could you describe the indications for olaparib that have been added since it was first approved?

**SD** The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (Lynparza, AstraZeneca) received approval from the US Food and Drug Administration (FDA) in December 2014 for the treatment of women with *BRCA1* or *BRCA2* mutation–associated ovarian cancer who had received at least 3 prior lines of therapy. This indication met an urgent unmet medical need.

In December 2016, the FDA approved the PARP inhibitor rucaparib (Rubraca, Clovis Oncology) for patients with *BRCA1* or *BRCA2* mutation–associated advanced ovarian cancer previously treated with 2 or more chemotherapy regimens. Niraparib (Zejula, Tesaro) received approval in March 2017 as maintenance therapy in patients with platinum-sensitive ovarian cancer.

In August 2017, olaparib received additional approval for use as maintenance therapy in patients with relapsed ovarian cancer still sensitive to platinum-based chemotherapy. Most recently, in January of this year, olaparib received approval for the treatment of germ-line mutant *BRCA1*- and *BRCA2*-related metastatic breast cancer negative for human epidermal growth factor receptor 2 (HER2) and previously treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. This approval was based on the results of OlympiAD (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), which was the first clinical trial to demonstrate superiority of a PARP inhibitor over standard chemotherapy; olaparib was found to be superior. This is exciting because PARP inhibitors are oral agents that are taken twice a day, which makes administration very straightforward. Olaparib causes some nausea and fatigue, which generally decrease over time, but it does not cause hair loss.

**H&O** Might these agents be beneficial for other patients with breast cancer?

**SD** At least 10% of patients with triple-negative breast cancer have *BRCA1* or *BRCA2* mutations, so these patients are now eligible for treatment with a PARP inhibitor. It remains to be seen whether additional groups of patients might similarly respond to PARP inhibitors, such as those with mutations in other genes that repair DNA damage or with other subtypes of triple-negative breast cancer.

**H&O** Could you talk in more detail about the OlympiAD trial?

**SD** OlympiAD was a randomized phase 3 trial that compared olaparib with the physician’s choice of standard-of-care chemotherapy in patients—mostly women, but also a few men—with germline *BRCA1* or *BRCA2* mutation–associated metastatic breast cancer. Chemotherapy consisted of capecitabine, vinorelbine, or eribulin (Halaven, Eisai). The response rate was 60% in the olaparib arm vs 29% in the standard chemotherapy arm. Progression-free survival also was better with olaparib than with chemotherapy. Even more exciting, the health-related quality-of-
life scores were better in the olaparib group—patients felt better on olaparib than they did on chemotherapy.

Another interesting finding in OlympiAD is that the time to a treatment response was the same in the olaparib group as in the chemotherapy group. That is quite heartening because there is sometimes concern that oral medication might not work as quickly as intravenous medication, but in this case it did.

**H&O** Is it problematic that OlympiAD didn’t find a difference in overall survival between the 2 groups?

**SD** The initial report on OlympiAD, which appeared in the *New England Journal of Medicine*, was based on early data, so time will tell whether there is a difference in overall survival. In addition, the study was not powered to detect an overall survival benefit.

**H&O** What are some of the other important studies that have looked at the use of olaparib in breast cancer?

**SD** The ICEBERG 1 trial (Study to Assess the Efficacy and Safety of a PARP Inhibitor for the Treatment of BRCA-positive Advanced Breast Cancer), which Tutt and colleagues published in the *Lancet* in 2010, was a phase 2 trial looking at olaparib in *BRCA1* or *BRCA2* mutation–associated advanced breast cancer. Patients had received a median of 3 previous chemotherapy regimens. The overall response rate among the 27 patients who received the maximum tolerated dose of olaparib (400 mg twice daily) was 41% (95% CI, 25%-59%), which was a great finding.

A study from our group, authored by Kaufman and colleagues and published in the *Journal of Clinical Oncology* in 2015, was a phase 2 basket trial of patients with various types of recurrent cancer and a *BRCA1/2* mutation. The study included 62 women with metastatic breast cancer who had received at least 3 lines of chemotherapy. The median number of regimens was 4.6, so this was a very heavily pretreated group of patients. Although the response rate was only 13%, this was not a bad result. For comparison, in 2010 the FDA approved the use of eribulin in patients who had received more than 3 lines of therapy on the basis of a response rate of 13% in the EMBRACE trial (Eribulin Monotherapy Versus Treatment of Physician’s Choice in Patients with Metastatic Breast Cancer).

The MEDIOLA trial (A Phase I/II Study of MEDI4736 in Combination With Olaparib in Patients With Advanced Solid Tumors), which our group reported on most recently at the 2017 San Antonio Breast Cancer Symposium, is a phase 2 study that is examining the combination of olaparib and the programmed death ligand 1 (PD-L1) inhibitor durvalumab (Imfinzi, AstraZeneca) in patients with pretreated, germline *BRCA1/2* mutation–associated, HER2-negative metastatic breast cancer. We found a 12-week disease control rate of 80% and are waiting to see whether the combination might improve the duration of response.

Multiple trials are now in development or under way that are looking at olaparib in combination with immunotherapeutic or other agents. For example, one phase 2 study in patients with triple-negative breast cancer is comparing olaparib alone with 2 combinations: olaparib plus an inhibitor of ATR kinase and a Rad3-related protein kinase, and olaparib plus a WEE1 inhibitor (NCT03330847). The results are certainly anticipated.

**H&O** What other PARP inhibitors are being studied for use in breast cancer?

**SD** As I mentioned earlier, rucaparib has an FDA approval for ovarian cancer and there are limited data on its use in breast cancer, although studies are under way, including RUBY (A Study to Assess the Efficacy of Rucaparib in Metastatic Breast Cancer Patients With a BRCA-ness Genomic Signature; NCT02505048). Niraparib also is approved in ovarian cancer and is being studied for use in breast cancer in the phase 3 BRAVO trial (A Phase III Trial of Niraparib Versus Physician’s Choice in HER2 Negative, Germline BRCA Mutation-positive Breast Cancer Patients; NCT01905592).

Veliparib and talazoparib are not yet approved by the FDA for any indication but are being studied in breast cancer. Veliparib is the one PARP inhibitor that can be used in combination with chemotherapy, but its role right now is not clear. The phase 2 BROCADE 3 trial (Study Evaluating Efficacy And Tolerability Of Veliparib in Combination With Temozolomide or In
Combination With Carboplatin and Paclitaxel Versus Placebo in Subjects With BRCA1 and BRCA2 Mutation and Metastatic Breast Cancer), which was published by Han and colleagues in the Annals of Oncology earlier this year, found no improvement in progression-free survival when veliparib was added to chemotherapy in women with locally recurrent or metastatic triple-negative breast cancer and a germline BRCA1 or BRCA2 mutation. A phase 3 study that is studying veliparib in HER2-negative metastatic breast cancer associated with a BRCA1/2 mutation is awaiting results (NCT02163694).

In addition, Loibl and colleagues recently published the results of the BrighTNess trial (A Study Evaluating Safety and Efficacy of the Addition of ABT-888 Plus Carboplatin Versus the Addition of Carboplatin to Standard Chemotherapy Versus Standard Chemotherapy in Subjects With Early Stage Triple Negative Breast Cancer) in Lancet Oncology. They found that the addition of veliparib to chemotherapy as preoperative treatment in triple-negative breast cancer failed to improve the complete response rate compared with chemotherapy alone. So, what role of veliparib will be at the current time is not clear.

Talazoparib was studied in the phase 3 EMBRACA trial (A Study Evaluating Talazoparib, a PARP Inhibitor, in Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation), which Jennifer Litton presented at the 2017 San Antonio Breast Cancer Symposium. In this study, talazoparib improved the response rate and progression-free survival compared with standard-of-care chemotherapy in women with a BRCA1 or BRCA2 mutation in whom metastatic HER2-negative breast cancer had been diagnosed. The design of this study was very similar to that of OlympiAD.

**H&O** What other types of research are being conducted?

**SD** There is a great deal of interest in combining PARP inhibitors with either small-molecule inhibitors or immunotherapy. Preclinical data suggest that adding an ATR kinase inhibitor to a PARP inhibitor is much more effective than using a PARP inhibitor alone. These are the types of preclinical studies that are being translated now into human studies.

**H&O** Are patients without BRCA mutations potential candidates for PARP inhibition?

**SD** Right now, the best predictor of response to a PARP inhibitor is the presence of a BRCA1 or BRCA2 mutation. Might individuals with mutations in other genes, such as CHEK2, ATM, or PALB2, also respond to PARP inhibitors? That is yet not clear, but studies are ongoing or planned that are looking at that question.

Another significant area of interest is whether triple-negative breast cancers without a specific gene mutation might be sensitive to PARP inhibitors. We have very limited data suggesting that they are. We need a lot more information about which patients might respond, and whether an assay might predict this response.

**Disclosures**

Dr Domchek has received honoraria from AstraZeneca, Clovis Oncology, and Bristol-Myers Squibb.

**Suggested Readings**


