

## Breast Cancer In Focus

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### PARP Inhibition in Breast Cancer

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#### **H&O** What is PARP and what happens during PARP inhibition?

**JG** DNA repair in the cell is a multi-faceted process. This process requires several different ways in which the cell can repair various types of errors in the DNA. Poly (adenosine diphosphate-ribose) polymerase (PARP) is an enzyme that is involved in a specific kind of DNA repair called base-excision repair, which is used when there is an error in a strand of the DNA. Cancers are caused by the cell's failure to accurately repair errors that occur in the DNA due to the accumulation of mutations in women who inherit a mutated copy of BRCA1 or BRCA2, the hereditary breast ovarian cancer susceptibility genes. Chemotherapy induces errors in the DNA—breaks that are so complicated that the cell cannot repair them adequately. The hope is that by blocking a repair system, the cancer cells will accumulate errors more rapidly, and basically will no longer be viable, leading to apoptosis.

It is known that BRCA1 and BRCA2 work, in part, in the double strand break repair pathway also called homologous recombination. In individuals with tumors who have already inherited 1 mutated copy of either BRCA1 or BRCA2, the gene stops functioning correctly and cannot repair errors in the cell, and thus depends strongly on the base-excision repair pathway. These defective DNA repair mechanisms can be selectively targeted by PARP inhibitors, which disable base-excision repair. Synthetic lethality is the term used for the mechanism to selectively kill tumor cells by inhibiting a DNA-repair enzyme.

#### **H&O** What is the role of PARP inhibitors in patients with sporadic versus hereditary cancers (with or without BRCA mutations)?

**JG** In individuals with the BRCA mutation, it has been shown in the laboratory and in early trials in patients that PARP inhibitors are an effective treatment for their tumors. However, in individuals who do not have an inherited mutation, the role of PARP inhibitors has not yet been substantiated. At the 2009 annual meeting of the American Society of Clinical Oncology (ASCO), the findings of a phase II study of olaparib (AZD2281, Astra-Zeneca), a novel orally active PARP inhibitor, in patients with BRCA1/2 mutated tumors were reported. The study analyzed olaparib (400 mg and subsequently 100 mg) in patients with advanced refractory breast cancer. Dr. Tutt and colleagues found that olaparib at 400 mg twice daily is well tolerated and highly active. The toxicity that was seen in BRCA1/BRCA2 carriers was similar to the previously reported toxicity in noncarriers.

Another recently published early study (phase I), led by Dr. Fong, evaluated olaparib in patients who had BRCA1 or BRCA2 mutations. The researchers reported an acceptable toxicity profile and objective antitumor activity only in mutation carriers, all of whom had ovarian, breast, or prostate cancer.

It is possible that some women develop breast cancer that is very much like the cancers that women with BRCA1/2 mutations develop, and there is good reason to believe that these tumors might be sensitive to PARP inhibitors as well. In other women, it is possible that

PARP inhibitors really potentiate the effects of chemotherapy because they make it harder for the cell to repair the mistakes that chemotherapy causes, possibly making chemotherapy more powerful even in women with no BRCA1/2 mutations.

### **H&O** Is there any evidence that PARP inhibitors benefit other types of cancer?

**JG** We have early evidence that PARP inhibitors have been effective in individuals with BRCA1/2 mutations and certainly very effective in ovarian cancer in the early trials. Dr. Audeh and colleagues presented results of a study of olaparib therapy in BRCA1/BRCA2 carriers with advanced chemotherapy-refractory ovarian cancer at this year's ASCO meeting. They found that olaparib was well tolerated and showed high activity in this population, with even greater activity seen at higher doses. The previously mentioned study led by Dr. Fong, although early-stage, also demonstrated olaparib's antitumor activity in BRCA1/2 mutation carriers with ovarian and prostate cancers. Researchers are now looking at other tumors known to occur excessively in people with these mutations, like pancreatic cancer.

### **H&O** Is there evidence supporting the use of PARP inhibitors in combination with chemo/radiotherapy?

**JG** I am not aware of any data of PARP inhibitors combined with radiation therapy in breast cancer patients. However, there are some ongoing early trials of an agent called ABT-888 (Enzo) in combination with radiotherapy and temozolomide in patients with glioblastoma multiforme.

Some data have been presented on combinations of chemotherapy and PARP inhibitors. At the last ASCO meeting, Dr. Joyce O'Shaughnessy presented the results of a phase II study of BSI-201 (BiPar Sciences) administered in women with metastatic triple-negative breast cancer. In the study, intravenous BSI-201 was added to a standard chemotherapy regimen of gemcitabine and carboplatin and compared to the standard chemotherapy regimen alone. The findings showed that in patients receiving the combination therapy, clinical benefit nearly tripled. Overall response rate, median survival, and progression-free survival were also higher in the combination group compared to the standard chemotherapy group. Hence, there is some evidence that PARP inhibitors may be efficacious in combination, and hopefully future combination studies will be able to corroborate this finding.

### **H&O** Is there any concern of resistance to PARP inhibitors?

**JG** Just as with other targeted therapies, cells can develop resistance in individuals being treated with single-agent PARP inhibitors, as observed in mouse models of BRCA1-associated tumorigenesis by Dr. Jos Jonkers. Part of the resistance may occur because of the typical pump mechanisms. There has been some interesting research showing that in some animals and some people receiving PARP inhibitors, resistance happens because the cell repairs the mutation in BRCA1 or BRCA2 that made the cells vulnerable in the first place. Once it has repaired that defect even in one copy, that is enough to make the cells resistant to the PARP inhibitor.

### **H&O** Will PARP inhibitors have a role in chemoprevention?

**JG** This research has so far only been performed in mice. We are hopeful that, particularly for oral versions of PARP inhibitors that seem to have less toxicity than chemotherapy drugs, we will have an opportunity to try these for prevention; however, we have to prove how safe they are in individuals with cancer before we are able to move to the prevention setting where we give these drugs to healthy people. Although using PARP inhibitors as chemopreventative agents is something that is certainly being considered, we are still many years away from being able to do this.

### **H&O** What is the focus of future research in PARP inhibitors?

**JG** There are a large number of trials that are in development or are still in early phase, almost all in combination with either single agents in mutation carriers or in combinations with chemotherapy in broader populations. The phase III study of BSI-201 in women with metastatic triple-negative breast cancer, commenced in July, will evaluate the safety and efficacy of BSI-201 in combination with gemcitabine and carboplatin as first-, second-, and third-line therapy. BSI-201 will be investigated in a phase II ovarian cancer study with the same chemotherapy combination toward the end of this year. This agent will also be studied in patients with advanced, persistent, or recurrent uterine cancer. Other agents including AGO14699 (Pfizer), ABT888, and MK4827 (Merck) are also being investigated in early trials. Because of the promising results seen with PARP inhibitors at the recent ASCO meeting, many other pharmaceutical companies will be initiating studies with these agents as well.

## Suggested Readings

- Audeh MW, Penson RT, Friedlander M, et al. Phase II trial of the oral PARP inhibitor olaparib (AZD2281) in BRCA-deficient advanced ovarian cancer. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27(15s):Abstr 5500.
- O'Shaughnessy J, Osborne C, Pippen J, et al. Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): Results of a randomized phase II trial. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27(18s):Abstr 3.
- Tutt A, Robson M, Garber JE, et al. Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27(18s):Abstr CRA501.
- Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med*. 2009;361:123-134.
- Bouwman P, Jonkers J. Mouse models for BRCA1 associated tumorigenesis: from fundamental insights to preclinical utility. *Cell Cycle*. 2008;1;7:2647-2653.