

## **PARP Inhibitors (Dr. Eric Winer, June 2009)**

am headed back to Boston after this year's American Society of Clinical Oncology (ASCO) meeting in Orlando, and I want to share the results of two important studies that are likely to change breast cancer treatment in the years ahead. Both of these studies are preliminary, and neither will change treatment approaches for many months to come, but the findings of each were very promising.

### **PARP Inhibitors**

Both trials focused on the clinical use of the PARP inhibitors. PARP stands for Poly(ADP-Ribose)polymerase, which is an enzyme that is involved in the repair of DNA. DNA is, of course, the building block of the genetic code in each and every one of the cells in the human body. When DNA becomes damaged, our cells have a variety of ways of trying to repair it, allowing the cell to survive. Of importance, some chemotherapy drugs damage DNA and resistance to chemotherapy can develop if the cell is very efficient in repairing the damage. In addition, when women with BRCA1 or BRCA2 mutations develop breast cancer, those breast cancer cells have particular difficulty repairing DNA.

### **PARP Inhibition with Chemotherapy in Triple Negative Breast Cancer**

In one of the clinical trials, approximately 120 women with metastatic triple negative breast cancer were randomly assigned to receive either two chemotherapy drugs – carboplatin and gemcitabine – or those same two drugs in conjunction with the PARP inhibitor, BSI-201. The PARP inhibitor was administered intravenously four times every three weeks, but it did not appear to have significant side effects or make the side effects from the chemotherapy any more severe. The rationale behind the study design is that the chemotherapy would cause DNA damage in the triple negative breast cancer cells and that the PARP inhibitor would help prevent the cell from repairing the damage, leading to cell death. Although the study was quite small, it nevertheless demonstrated that the use of the PARP inhibitor increased the effectiveness of the chemotherapy, allowing women to have their cancer remain under control for a longer period of time. In addition, the women who received the PARP inhibitor actually had an improvement in survival of several months.

The next steps: The findings from the study described above must still be reviewed as preliminary. While they give us great hope that a new treatment may soon be available for women with triple negative breast cancer, the results need to be confirmed. The sponsor of the trial, BiPar Pharmaceuticals, is about to launch a larger study which will also randomize women to chemotherapy alone or chemotherapy plus BSI-201. In this study, however, any women whose cancer gets worse on chemotherapy alone will be able to receive the PARP inhibitor, and this “cross-over” should make the study very appealing to many women with triple negative metastatic breast cancer. The study is likely to open at many centers around the country this summer, and it is hoped that it will provide a definitive answer in the next year or so. At the moment, BSI-201 is not available outside of studies, but if the findings from the second study remain promising, it is very likely that the drug will be approved by the Food and Drug Administration.

## **PARP Inhibition in Women with Metastatic Breast Cancer and BRCA1/2 Mutations**

In a second study, another PARP inhibitor, Olaparib, was evaluated in 54 women with metastatic breast cancer who had a BRCA1 or BRCA2 mutation. Since BRCA1 and BRCA2 are involved in DNA repair, cells that do not contain BRCA1 or BRCA2 (which is the case in cancers that develop in women with mutations) are thought to be particularly sensitive to PARP inhibition since they rely on PARP to assist with DNA repair.

A total of 54 women with metastatic breast cancer and BRCA1 or 2 mutations were treated with Olaparib at one of two doses. Olaparib was administered as a single agent, meaning that there was no chemotherapy given during the course of the study and women did not receive other anti-cancer therapy. Approximately 40% of women who received the higher dose of Olaparib had significant shrinkage of their cancer, and shrinkage was seen both in women with BRCA1 mutations and in those with BRCA2 mutations. Although improvement was seen in some women who received the lower dose, there was the suggestion that the higher dose was more effective and this is the dose that will be used in subsequent studies. Because this was not a randomized trial (all of the women received Olaparib), it is not possible to determine if the treatment extended survival.

### **What's next?**

The results with Olaparib are also very encouraging. Additional studies will be needed to confirm these results. The study sponsor, AstraZeneca, is planning a large study in women with mutations. The exact design of this study is still under discussion, but even if some women do not initially receive Olaparib as part of the study, all women on the study will ultimately be able to be treated with the drug. It is hoped that the next study with Olaparib will lead to approval of the drug by the Food and Drug Administration.

At this time, it is not known if Olaparib will be useful in women with non-inherited triple negative breast cancer or other forms of the disease. To date, only limited studies have attempted to combine Olaparib with chemotherapy. It is hoped that research conducted in women with BRCA1 and BRCA2 mutations will ultimately be useful to a much larger group of women with breast cancer. That said, it is worth keeping in mind that as many as 9,000 women diagnosed with breast cancer each year in the United States have a BRCA1 or BRCA2 mutation, so even this rare problem affects a surprisingly large of individuals.

### **Summary**

The PARP inhibitors are a very exciting new class of drugs. While the results of studies are preliminary, and only 114 women were treated with PARP inhibitors in these studies, many of us are extraordinarily encouraged. These trials will immediately lead to additional trials, and it is hoped that these additional trials will result in FDA approval of one or both of these agents. If women with breast cancer have questions about PARP or the available trials, they should speak with their medical oncologist.