

## Hot Topic: PARP Inhibitors and BRCA-Associated Breast Cancer Update

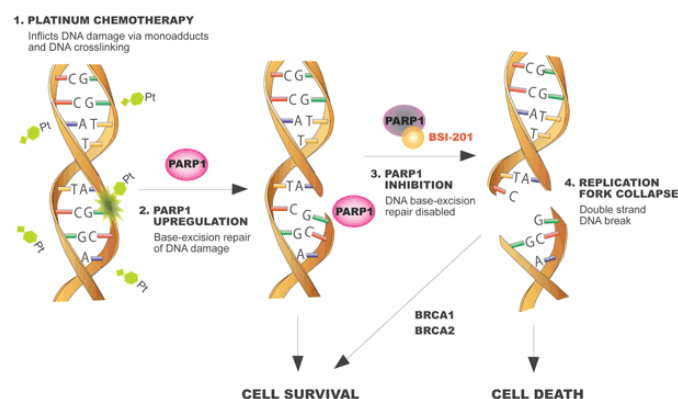
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Exciting clinical advancements in the treatment of BRCA-associated breast cancer were presented at the 2009 Annual Meeting of the American Society of Clinical Oncology (ASCO) this summer. Preliminary effectiveness of poly (ADP-ribose) polymerase-1 (PARP1) inhibitor was demonstrated in two independent clinical trials in this patient population.

PARP is a critical enzyme involved in detecting and binding to DNA damage and is intimately involved in its repair. During the course of a normal cell's lifespan, the cell is exposed to a wide variety of stressors that can lead to DNA damage. For the most part, when normal cells acquire DNA damage, they attempt to overcome and repair this damage (via mechanisms like BRCA or PARP assisted repair). In BRCA-mutant (or deficient) cells, they are more reliant on PARP assisted repair of DNA damage. In the laboratory setting, when PARP assisted repair is chemically inhibited in BRCA mutant cells, this double knockout of repair mechanisms leads to exceptional lethality. As such, the PARP inhibitors appear to have selected advantage in killing cancerous BRCA mutant cells over normal ones.

The so-called "triple-negative" (ER-, PR-, HER2 normal) breast cancers, account for ~15% of all breast cancers, and are associated with a more aggressive natural history compared to hormone receptor positive disease. These "triple negative" cancers appear to share many features with BRCA-related breast cancers (primarily due to dysfunctional BRCA1 activity). It should be noted, however, that not all "triple negative" breast cancers have abnormal BRCA activity, and conversely, that not all BRCA-associated breast cancers are "triple negative".

In the first study to be discussed, Tutt and colleagues<sup>(1)</sup> presented a non-randomized, single arm, open label, "proof of concept" phase II study. The goal was to evaluate the safety, tolerability and efficacy of the oral PARP inhibitor olaparib in heavily pretreated patients with BRCA-associated, metastatic breast cancer. Two sequential cohorts of 27 patients each (average age early 40's) were enrolled to receive continuous twice-daily oral therapy at one of two different dose levels. Fifty to sixty-four percent of patients had "triple negative" disease, 56-67% had



BRCA1 mutation alone, 33-41% BRCA2 alone, and 0-4% had both BRCA(1+2). Both groups had received an average of 3 prior therapies for breast cancer prior to enrollment on this study. Overall, the drug was well tolerated. Clinical response (tumor shrinkage) was seen at both drug dose levels but more so in the higher (400 mg twice daily) group, whereby ~40% patients had documented disease response (this in the 4<sup>th</sup> line treatment setting, on average). To put this into context, typical response rates in the 1<sup>st</sup> line chemotherapy treatment setting for advanced breast cancer are in the order of 50-75%, with a significant decreased likelihood of response and clinical benefit with each subsequent line of palliative chemotherapy thereafter.

In the second pivotal study, O'Shaughnessy and colleagues<sup>(2)</sup> reported the preliminary results of their phase II, open-labeled study of a PARP1 inhibitor (BSI-201), in combination with gemcitabine / carboplatin (GC) chemotherapy, in patients with advanced "triple-negative" breast cancer. Most of the patients were in their early 50s and had also received prior chemotherapy for breast cancer (56-64% in the neo-adjuvant setting, 22-33% in the 1<sup>st</sup> line metastatic setting and 10-13% had received 2 or more lines of therapy). Of the 123 patients enrolled to the study, half were randomized to receive the GC chemotherapy alone, and the other half to receive GC plus BSI-201. The addition of BSI-201 to GC chemotherapy appeared to be well tolerated and did not show signs of significant excess toxicity (side effects) above GC alone. Compared to the GC treated group, those that received BSI-201 had more tumor shrinkage (7% vs. 20% radiologic response rate, respectively) and more importantly had a 65% statistically significant improvement in

survival (median survival: 5.7 months vs. 9.2 months, respectively). For those patients who had disease progression in the GC treatment arm, crossover to receive BSI-201 was allowed (with 40% choosing to crossover).

Although interesting in their own right, taken together, these two small, preliminary, studies provide us with a glimpse of the potential future to come in the treatment of BRCA associated breast cancers. It is expected that these studies will help lead the charge for other, much larger, well designed phase III studies of this unique, targeted class of agents in both the advanced and ultimately in the early stage treatment setting, as well. The future is looking better and brighter all the time !

### References:

Tutt A, Robson M, Garber JE, et al. Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer. Program and abstracts of the 2009 Annual Meeting of the American Society of Clinical Oncology; May 29 - June 2, 2009; Orlando, Florida. Abstract CRA501.

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. Program and abstracts of the 2009 Annual Meeting of the American Society of Clinical Oncology; May 29-June 2, 2009; Orlando, Florida. Abstract 3.

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