



Memorial Sloan-Kettering  
Cancer Center

# Update

IN GYNECOLOGIC ONCOLOGY

PROGRESS TOWARD INDIVIDUALIZED CANCER CARE

## PARP Inhibitors: *BRCA* Patients and Beyond

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The treatment of ovarian cancer has for quite some time been a “one size fits all” phenomenon. The arrival of the poly-ADP-ribose polymerase (PARP) inhibitors represents one of the first examples in the field of gynecologic oncology of branching out to specific therapies for specific subsets of patients. Several companies are currently developing PARP inhibitors, and studies with olaparib and MK4827 in ovarian cancer have been presented and/or published. The use of these agents in *BRCA1* and *BRCA2* mutation carriers relies on what has been coined “synthetic lethality” [1]. In *BRCA1* and *BRCA2* patients, the tumors have an underlying deficit in the homologous recombination (HR) pathway for DNA repair. The tumors rely on the PARP enzyme more heavily for DNA repair. By blocking the PARP pathway in these cells, DNA damage is magnified (Fig. 1), and cell death of tumor cells is achievable at doses that are not harmful to cells retaining *BRCA* function.

The initial phase I study of olaparib in *BRCA* mutation carriers was promising [2]. A cohort of ovarian cancer patients with *BRCA* mutations showed a favorable response rate of 28%. Olaparib was studied further in the *BRCA* population in an additional dose-finding study of 100 mg BID and 400 mg BID [3]. A 33% response rate was seen at the 400 mg BID dose, but only one third of that was seen at the 100 mg BID dose. This was interesting in light of the pharmacodynamic (PD) data from the phase I study, which showed that 90% inhibition of the PARP enzyme was reached at 100 mg BID. This did not seem to increase further with higher doses. However, it must be noted that the PD data was in peripheral blood mononuclear cells and not tumor tissue.

A third study of olaparib was recently reported in which *BRCA* mutation carriers were randomized to liposomal doxorubicin versus olaparib at 200 mg BID or 400 mg BID [4]. Interestingly, progression-free survival (PFS) times did not vary significantly between the groups, with a median PFS of 7.1 months for the liposomal doxorubicin group, 6.5 months for the 200 mg group, and 8.8 months for the 400 mg group. The side effect profile was different between the arms, with approximately twice as many grade 3+ toxicities seen with liposomal doxorubicin as with olaparib. The significant improvement in PFS for liposomal doxorubicin in this

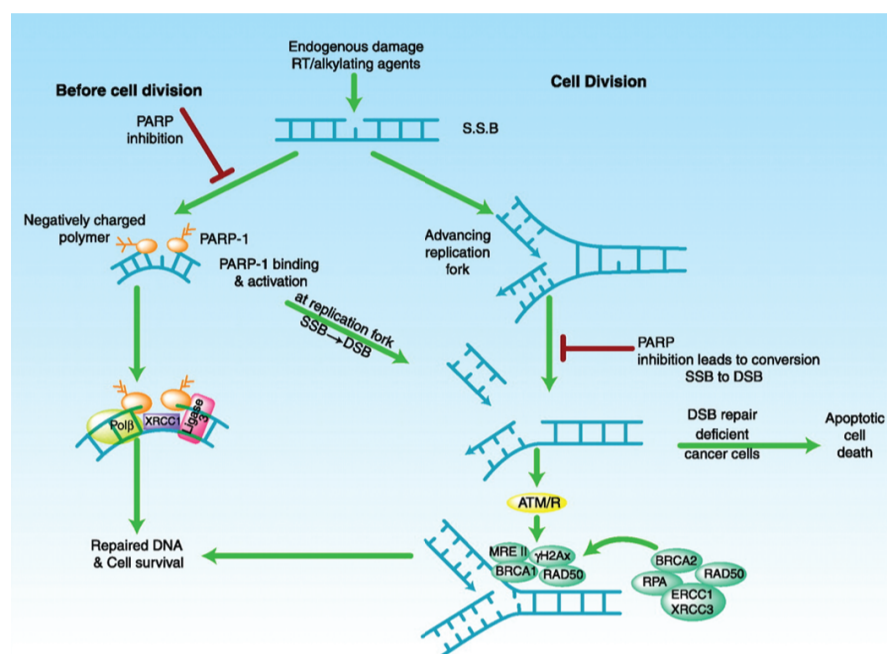


Fig. 1. The potential fate of a single-strand DNA break in the presence of PARP inhibition. Activation of PARP-1 by a DNA SSB in a nondividing cell will be repaired as shown on left-hand side of figure. PARP inhibition will prevent this repair; during replication, this SSB will become a DSB at the replication fork. In DSB repair-proficient cells, this can be repaired (right-hand side); in DSB repair-deficient cells, the DSB will persist and is a potent signal to apoptosis. Reprinted with permission from Plummer ER, Calvert H. Targeting Poly(ADP-Ribose) Polymerase: A Two-Armed Strategy for Cancer Therapy. *Clinical Cancer Research* 2007;13:6252-6256.

study over the historical data suggests that *BRCA* patients may not only be more sensitive to platinum agents but may be more sensitive to any chemotherapy that induces DNA damage.

A phase II study of MK4827 presented at the American Society of Clinical Oncology (ASCO) annual meeting in June 2010 showed responses not only in *BRCA* patients but also in serous ovarian cancer patients [5]. Patients with *BRCA1* or *BRCA2* loss or non-*BRCA*-related HR defects were enrolled. Responses were seen in both groups, with some prolonged partial responses of more than 44 weeks. We await the correlative studies, which will help distinguish which features may be necessary for a patient with sporadic serous ovarian cancer to be sensitive to PARP inhibitor monotherapy.

Current ongoing trials at MSKCC are evaluating the safety and benefit of adding PARP inhibitors to existing platinum-containing regimens. PARP inhibitors enhance the DNA damage potential of platinum agents but can also enhance hematologic toxicity. Ongoing phase I studies include 1) the Gynecologic Oncology Group (GOG) 9923 study adding velaparib to the adjuvant regimen of carboplatin, paclitaxel, and bevacizumab; 2) a phase I study adding velaparib to carboplatin and gemcitabine for platinum-sensitive recurrent ovarian cancer; and 3) a phase I study adding MK4827 to carboplatin for patients who have had no more

than 2 prior chemotherapeutic regimens. Additional studies are currently in development and include a study evaluating the addition of olaparib to adjuvant intravenous/intraperitoneal treatment for optimally debulked ovarian cancer patients. ■

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