



# Are there clinical factors that can predict prolonged survival of patients receiving olaparib as maintenance therapy for *BRCA*-mutated ovarian cancer?

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Ovarian cancer is highly prevalent and the second most deadly gynecological cancer (1). It is estimated that globally in the year 2018 there were 295,414 new cases and 184,799 deaths because of this disease. Epithelial ovarian carcinomas account for 85% to 90% of all malignant ovarian cancers, and more than half of those are the histotype serous carcinoma (2). Furthermore, the median age of women diagnosed with this disease is about 60–65 years old (3). Typically, the initial stages of ovarian cancer are asymptomatic, and thus early detection is difficult and only occurs for about 20% of newly diagnosed patients (4). Nevertheless, when detected at an early stage, 94% of patients can live more than 5 years after initial diagnosis (5).

Treatment options for patients with ovarian cancer depend upon the type and stage of the disease, as well as special circumstances that could impact therapeutic efficacy. Localized treatment usually includes debulking surgery or more rarely radiotherapy. For systemic treatment, chemotherapy, hormone therapy, or an ovarian cancer targeted approach is employed.

The genetic makeup of ovarian cancer has been exploited to design and explain the mechanistic basis for effective precision treatments. *BRCA1* and *BRCA2* are tumor suppressors that participate in repair of DNA damage, such as double strand breaks, through homologous recombination. Germline and somatic mutations in one or both of the genes are present in greater than 25% of high-grade serous carcinomas (6). Since homologous recombination can

repair double strand DNA breaks caused by such drugs as platinum, the favorable response of ovarian cancer patients bearing *BRCA1* or *BRCA2* mutation, and thus deficiency in this repair process, to this treatment is predictable. Other proteins and pathways can also repair damage caused by platinum. For example, Poly(ADP-ribose) polymerase 1 (PARP1) plays numerous roles that impact repair of DNA damage, functioning in single-strand break repair, nucleotide excision repair, double-strand break repair, the stabilization of replication forks, and modulating chromatin structure, as well as in homologous recombination repair (7). A genetically engineered mouse model was used to demonstrate that *BRCA1*-deficiency sensitizes mammary tumors to the PARP1 inhibitor olaparib, alone as well as in combination with platinum drugs (8). Based on the synthetic lethal effects caused by blocking alternative pathways that impact DNA repair, platinum-based chemotherapy is used in combination with PARP inhibitors to treat ovarian cancer patients with inherent deficiencies in homologous recombination due to *BRCA1* and *BRCA2* mutation (9).

Labidi-Galy *et al.* (10) reported the results of a multi-center retrospective, 115 patient cohort study to assess the benefit of using the PARP1, PARP2, and PARP3 inhibitor olaparib as maintenance therapy for patients with epithelial ovarian cancer bearing germline or somatic mutation in *BRCA1* or *BRCA2*. Of the patients examined, 95% had germline mutations (including one patient with a *BRCA1* and *BRCA2* mutation), and only 6 had somatic mutations,

all in *BRCA1*. Data from the single patient with the double *BRCA1/BRCA2* mutation were evaluated separately. The study demonstrates three factors that predict prolonged response and survival to olaparib when used as maintenance therapy. Patients with a platinum-free interval longer than 12 months, radiological indication of a partial or complete response, and normalization of marker CA-125 levels before olaparib treatment provided expectation of the best response. Interestingly, these investigators noted that a subset of the relapsing cohort had limited benefit from olaparib treatment alone. They cited studies reporting that *BRCA* mutated epithelial ovarian cancers had high quantities of infiltrating lymphocytes (11,12), as well as express PD-1 and PD-L1 (13). They speculate that this subset of patients might benefit by the combination of PARP inhibitor and anti-PD-1/PD-L1 treatment, which is backed up by pre-clinical mouse studies focused on anti-PD-1 (14). They cite two ongoing clinical trials, and there are others testing the efficacy of combined PARP inhibitor and anti-PD-1/PD-L1 immune checkpoint blocking treatments (NCT02484404, NCT02571725, NCT02657889, NCT02734004).

There is clearly increased interest in tailoring cancer treatment to individuals based on the genetic makeup of tumors and status of disease, using a precision medicine approach. The study by Labidi-Galy and co-workers (10) is an example of this strategy and provides information to aid in determining the subset of ovarian cancer patients who would benefit most from olaparib maintenance treatment. Future studies could focus on stratifying patients for predicted treatment response, based on exact *BRCA1/BRCA2* mutation, or degree of homologous recombination deficiency. It would also be important to evaluate different PARP inhibitors, such as olaparib (AZD2281 #A10111), rucaparib (AG014699 #A10045) and niraparib (MK4827 #A11026), for efficacy in this treatment scenario.

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