

# Olaparib for *BRCA*-mutated advanced ovarian cancer

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**E**pithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and the fifth most common cause of cancer-related mortality. Treatment options, particularly for tumors with mutations in the breast cancer susceptibility genes, *BRCA1* and *BRCA2*, are currently limited, and significant research has focused on the development of novel therapies.

Inhibitors of poly(ADP)ribose polymerase (PARP), which specifically target *BRCA*-mutant cancer cells by exploiting the defective DNA repair pathways inherent in these tumors, have proven particularly promising, though clinical development has not been without challenges. Development of olaparib was halted in 2011 following disappointing clinical trial results, but the manufacturer resurrected the drug following retrospective analyses in patients with *BRCA1/2* mutations.

In mid-2014, the US Food and Drug Administration's (FDA) Oncologic Drugs Advisory Committee (ODAC) voted against accelerated approval of olaparib as maintenance therapy, but submission of an amended New Drug Application at the FDA's request, led to approval in December 2014 of this first-in-class PARP inhibitor for the treatment of patients with advanced ovarian cancer associated with defective *BRCA* genes and who have been treated with 3 or more previous lines of chemotherapy.

Between February 21, 2010 and July 31, 2012, 193 heavily pretreated patients aged 18 years or older, with platinum-resistant, *BRCA*-mutant disease, were enrolled in an ovarian cancer cohort of a single-arm, open-label, multicenter, nonrandomized phase 2 clinical trial that included 178 patients with ovarian cancer, 4 with fallopian tube cancer, and 11 with primary peritoneal cancer. Data on a subgroup of 137 patients who received 3 or more lines of previous chemotherapy was submitted to the FDA for accelerated approval.

Eligible patients were required to have  $\geq 1$  measurable or evaluable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 2, life expectancy of  $\leq 16$  weeks, and platinum-resistant epithelial ovarian cancer (relapse within 6 months of platinum therapy). Patients who had received previous PARP-inhibitor therapy; had previous malignancy that was active

## What's new, what's important

Treatment options for epithelial ovarian cancer, especially in tumors with *BRCA1* and *BRCA2* mutations, are limited. Olaparib, a poly(ADP)ribose polymerase inhibitor that targets *BRCA*-mutant cancer cells, has been approved by the US Food and Drug Administration for the treatment of patients with advanced ovarian cancer associated with defective *BRCA* genes and who have been treated with 3 or more previous lines of chemotherapy. The recommended dose is 400 mg (8 x 50 mg capsules) twice-daily. Dose interruption or adjustment should be considered to manage adverse events, with a recommended dosage reduction to 200 mg twice-daily, then to 100 mg twice-daily if necessary. Olaparib is metabolized predominantly by CYP3A4, so there should not be concomitant use of strong and moderate CYP3A4 inhibitors in patients receiving the therapy, and the dosage should be reduced if the use of these drugs can't be avoided.

The label carries warnings and precautions relating to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), pneumonitis, and embryo-fetal toxicity. MDS or AML occurred in 2% of patients in clinical trials and was fatal in most of the cases. To guard against that, complete blood counts should be done at baseline and monitored monthly, and olaparib treatment should be started only after a patient has recovered from hematologic toxicity caused by previous therapy. Pneumonitis occurred in  $<1\%$  of patients and treatment should be stopped and the possibility of pneumonitis should be considered in patients with respiratory symptoms. The FDA also approved a companion diagnostic called to detect defective *BRCA* genes in patients with ovarian cancer to determine eligibility for olaparib therapy. However, as encouraging as these advances are, there remain concerns about the cost-effectiveness of the therapy.

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or had been treated within 5 years of study (except second suspected *BRCA*-related malignancy, treated in situ cervical carcinoma, stage I endometrial cancer, or nonmelanoma skin cancer); had received systemic chemotherapy or radiotherapy within 2 weeks of study; had received potent cytochrome P450 3A4 (CYP3A4) inhibitors; had persistent

## Mechanism of action

### PARP inhibitors exploit synthetic lethality in *BRCA*-mutant ovarian cancer

Olaparib is a first-in-class, small-molecule inhibitor of the poly(ADP-ribose) polymerase 1 (PARP-1) enzyme. PARP-1 plays an important role in the base excision repair pathway that repairs single-strand breaks (SSBs) in DNA, a common form of DNA damage. PARP inhibitors have several documented mechanisms of action: they inhibit PARP-1 enzymatic function, thus preventing SSB repair and leading to the generation of double-strand breaks (DSBs); and they trap PARP enzymes on DNA (normally PARP-1 is released from DNA once the repair process begins), thus blocking DNA replication.

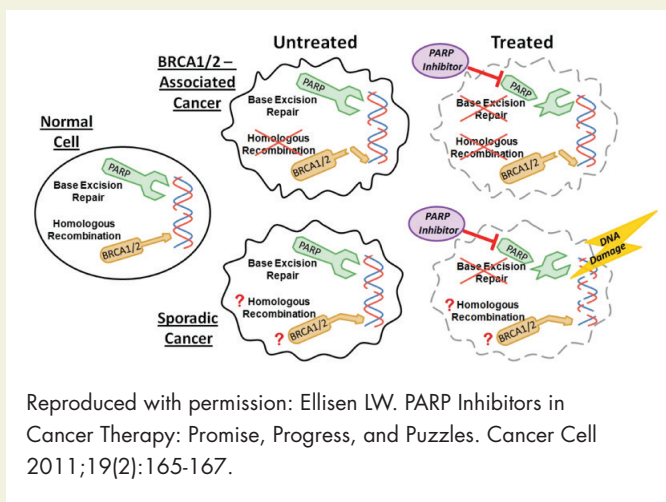
Both of these molecular mechanisms can be fatal to the cell, but DSBs can still be repaired by the homologous recombination (HR) pathway, thus PARP inhibition by itself is insufficient to drive cancer cell death. However, tumors that have a defect in the HR DNA repair pathway, and therefore cannot repair DSBs, have been shown to be exquisitely sensitive to PARP inhibitor therapy. Since neither SSBs nor the resultant DSBs can be repaired the combination is fatal to the cell, a phenomenon described as synthetic lethality.

It's thought that up to half of high-grade serous ovarian cancers could be deficient in HR repair because of inherited and

acquired mutations, most commonly in the breast cancer susceptibility (*BRCA1* and *BRCA2*) genes. It is estimated that 10-15% of ovarian cancers are associated with hereditary *BRCA1/2*

mutations. In normal cells the *BRCA* proteins are tumor suppressors, functioning in the HR pathway to repair DSBs without introducing any errors into the DNA sequence. In some cancers, the *BRCA1/2* genes are mutated, leading to the production of defective *BRCA* proteins and a breakdown of the HR pathway. The cell is forced to use error-prone pathways to repair DSBs, which leads to the genomic instability that is a hallmark feature of cancer cells.

Other inherited or acquired mutations or epigenetic alterations that lead to defects in the HR pathway may also be synthetically lethal with PARP inhibition, a quality that has been dubbed *BRCAness*. Furthermore, in sporadic cancers that are not driven by *BRCA* mutations or any other *BRCA*-like alterations in the DNA repair pathways, PARP inhibitors could display synthetic lethality with DNA-damaging chemotherapeutic drugs. Although PARP inhibitors are an area of intensive research, with numerous ongoing clinical trials, the current FDA approval status for the PARP inhibitor olaparib is only for patients with *BRCA*-mutant tumors.



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therapy-related toxicities; had major surgery <2 weeks prior to study; had symptomatic, uncontrolled brain metastases; or had other medical conditions indicative of poor medical risk, were excluded from the study.

All of the patients received continuous treatment with 400 mg twice-daily oral olaparib until disease progression. Tumor assessments were performed at baseline and at the end of every 2 cycles, up to and including withdrawal visit. The primary endpoint was tumor response rate according to RECIST, with confirmation of response at least 28 days apart. Secondary endpoints included objective response rate (ORR), progression-free survival (PFS), and duration of response (DoR). Safety and tolerability were assessed by adverse events (AEs) and changes in laboratory parameters. The median age of patients enrolled in the study was 58 years, 94% were white, 93% had an ECOG-PS of 0 or 1, 77% had a germline *BRCA1* mutation and 23% a *BRCA2* mutation, while 1 patient had a mutation in both.

Data submitted to the FDA and outlined in the prescribing information reported that the ORR was 34%, including 2% complete response (CR) and 32% partial response (PR), and the median DoR was 7.9 months. Among the 193 patients in the pivotal clinical trial, the tumor response rate was 31.1%, with a median duration of response of 225 days. The response rate among *BRCA1* mutant carriers was 29.7% and among *BRCA2* mutant carriers, 36.3%. In 40.4% of patients, stable disease persisted for 8 weeks and longer. The median PFS was 7 months, with 54.6% patients progression-free at 6 months, and median overall survival (OS) was 16.6 months, with 64.4% of patients alive at 12 months.

The safety of 400 mg olaparib administered twice-daily as monotherapy has been evaluated in 300 patients (including those in the pivotal trial) with germline *BRCA*-mutated advanced ovarian cancer, 223 of whom received 3 or more previous lines of chemotherapy. The most common AEs (experienced by ≥20% of patients) were fatigue

(66%), nausea (64%), vomiting (43%), abdominal pain/discomfort (43%), and anemia (34%). Serious AEs included myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and lung inflammation. Dosage reductions (to 200 mg or 100 mg twice-daily) or interruptions were permitted in response to toxicity and this occurred in 4% and 40% of patients, respectively, with discontinuation in 7% of patients. AEs led to death in 4% of patients.

According to the prescribing information, the recommended dose of olaparib is 400 mg (8 x 50 mg capsules) twice-daily. Dose interruption or adjustment should be considered to manage AEs, with a recommended dosage reduction to 200 mg twice-daily, then to 100 mg twice-daily if necessary. Olaparib is metabolized predominantly by CYP3A4, thus concomitant use of strong and moderate CYP3A4 inhibitors with olaparib is recommended against, and dosage reduction is suggested when use of these drugs can't be avoided.

The prescribing information details warnings and precautions relating to MDS and AML, pneumonitis, and embryo-fetal toxicity. MDS or AML occurred in 2% of patients in clinical trials and was fatal in most of the cases; to guard against this eventuality complete blood counts should be monitored at baseline and monthly thereafter

and olaparib treatment should not be started until patients have recovered from hematologic toxicity caused by previous therapy. Pneumonitis occurred in <1% of patients and treatment should be stopped and investigation into the possibility of pneumonitis should be carried out in patients presenting with new or worsening respiratory symptoms. Patients should also be advised that olaparib can cause fetal harm in pregnant women.

Olaparib is marketed as Lynparza by AstraZeneca. In conjunction with its approval, the FDA also approved a companion diagnostic called BRCAAnalysis CDx (Myriad Genetics) to detect defective *BRCA* genes in patients with ovarian cancer to determine eligibility for olaparib therapy. The test can be used to detect *BRCA* mutations in blood samples taken from patients with ovarian cancer.

### References

1. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline *BRCA1/2* mutation. *J Clin Oncol*. 2015;33:244-250.
2. Lynparza (olaparib) capsules, for oral use. Prescribing information, AstraZeneca Pharmaceuticals LP, December 2014. [http://www.azpicentral.com/Lynparza/pi\\_lynparza.pdf#page=1](http://www.azpicentral.com/Lynparza/pi_lynparza.pdf#page=1). Accessed May 1, 2015.
3. FDA approves Lynparza to treat advanced ovarian cancer. FDA News Release. December 19, 2014. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427554.htm>. Accessed May 1, 2015.