

# Profile of olaparib in the treatment of advanced ovarian cancer

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**Abstract:** Olaparib is a poly(ADP-ribose) polymerase inhibitor that received accelerated approval from the US Food and Drug Administration as monotherapy for patients with germline BRCA mutations and ovarian cancer treated with three or more prior lines of chemotherapy. This article summarizes the mechanism of poly(ADP-ribose) polymerase inhibition, therapeutic profile and uses of olaparib, and current and ongoing literature pertaining to olaparib in advanced ovarian cancer.

**Keywords:** olaparib, PARP, ovarian cancer

## Introduction

Olaparib (AZD-2281, trade name Lynparza) is a poly(ADP-ribose) polymerase (PARP) inhibitor approved by US Food and Drug Administration (FDA) as monotherapy for ovarian cancer patients with germline BRCA mutations who have been treated with three or more prior lines of chemotherapy. The FDA concurrently approved the BRCAAnalysis CDx™ (Myriad Genetics) as a companion diagnostic test. The BRCAAnalysis CDx™ tests for deleterious or suspected deleterious variants in BRCA 1/2 using whole blood specimens. PARP 1/2 enzymes repair single-stranded DNA breaks through base excision repair. Unrepaired single-stranded breaks are converted into double-stranded breaks when cells attempt replication or transcription. Double-stranded breaks are normally repaired with homologous recombination. However, up to 50% of high-grade serous ovarian cancers lack homologous recombination through a combination of germline mutations in BRCA 1/2; silencing via methylation of the, eg, BRCA promoter or Fanconi F; activation of pathway inhibitors; or other mechanisms.<sup>1</sup> This leaves cells dependent on nonhomologous end joining, an error-prone repair method that leads to genetic instability and cell death. BRCA 1/2 are homologous repair proteins; therefore, cells with BRCA 1/2 mutations are specifically targeted by PARP inhibition. PARP inhibitors also trap PARP1 and 2 enzymes on DNA, leading to complexing, which interferes with DNA replication and causes further cellular damage.<sup>2</sup> This article reviews the pharmacologic and safety profile of olaparib as well as the effects of BRCA mutations and platinum sensitivity on efficacy and the ongoing research in the use of olaparib for advanced ovarian cancer.

## Pharmacokinetics, dose response, and safety

Olaparib is a rapidly absorbed orally active agent with peak plasma levels attained at 1–3 hours after administration and a mean terminal half-life of 11.9 hours. Phase I pharmacokinetic and pharmacodynamic testing of olaparib in 60 patients with solid tumors, including 21 ovarian cancer patients, established a maximum tolerated dose

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of 400 mg taken twice daily continuously. Toxicities were generally mild and included fatigue and gastrointestinal symptoms, such as nausea, vomiting, taste alteration, and anorexia.<sup>3</sup> Table 1 demonstrates the frequency of adverse events encountered in clinical trials using olaparib. The most common laboratory abnormalities included increased mean corpuscular volume, decreased hemoglobin, increased creatinine, and decreased neutrophil count. There is a specific warning in the product insert regarding the development of myelodysplastic syndrome (MDS). Of 2,618 patients who had received olaparib at the time of the June 2014 FDA briefing, 21 (0.8%) had reported MDS and/or acute myeloid leukemia. Although the prior administration of platinum-based chemotherapy may predispose patients to the development of MDS/acute myeloid leukemia, this percentage is larger than what would be expected. Olaparib is metabolized via CYP3A, and metabolites are excreted in urine (44%) and feces (42%).<sup>4</sup>

The FDA-approved formulation of olaparib is a 50 mg capsule. The achievement of the recommended dose requires administration of eight capsules twice daily. A tablet formulation has also been developed that is available as 100 mg or 150 mg, with a recommended dose of 300 mg bid. While the tablet form has increased bioavailability compared to the capsule formation, the efficacy and tolerability of the 300 mg bid tablet dose is comparable to those of the 400 mg bid capsule formulation.<sup>5</sup> The recommended dosing regimen for olaparib is 400 mg twice daily. A prospective multicenter Phase II study of patients with recurrent ovarian cancer and germline BRCA 1/2 mutations and one or more prior lines of chemotherapy evaluated the objective response rate (ORR) in patients treated with continuous olaparib 400 mg twice daily (maximum tolerated dose) or 100 mg twice daily (dose of first clinical response). The ORR was 33% (eleven of 33 patients, 95% confidence interval [CI] 20–51) in the 400 mg group and 13% (three of 24 patients, 95% CI 4–31) in the 100 mg group. There was an unscheduled interim analysis and protocol amendment allowing patients in the 100 mg group to increase dose to 400 mg twice daily due to an observed increased frequency of early progression in the lower dose group. The median progression-free survival was 5.8 months (95% CI 2.8–10.6) in the 400 mg group versus 1.9 months (95% CI 1.8–3.6) in the 100 mg group.<sup>6</sup>

The effect of food on the rate and amount of absorption of olaparib was studied in an open-label randomized trial of 32 patients. Compared to fasting state, administration after a standard meal or high-fat meal increased exposure to olaparib by ~20%, which was not considered

**Table 1** Major study results and toxicities

Population (n)	Kaye et al <sup>14</sup>	Audeh et al <sup>6</sup>	Gelmon et al <sup>8</sup>	Kaufman et al <sup>10</sup>	Oza et al <sup>11</sup>	Ledermann et al <sup>9</sup>
	BRCA mutation, recurrent HGSOc, platinum sensitive (97)	BRCA mutation, recurrent HGSOc (57)	+/- BRCA, recurrent HGSOc, sensitive (65)	BRCA mutation, HGSOc, platinum resistant (193)	+/- BRCA, recurrent HGSOc, platinum sensitive (162)	+/- BRCA, recurrent HGSOc, platinum sensitive (265)
Olaparib dose	400 mg bid, 200 mg bid	400 mg bid, 100 mg bid	400 mg bid	400 mg bid	200 mg bid with chemo, 400 mg bid maintenance	400 mg bid maintenance
<b>Toxicities (%)</b>	<b>200 mg</b>	<b>100 mg</b>			<b>200 mg</b>	<b>400 mg</b>
Nausea	59	37	66	61.7	69	68.4
Vomiting	34	0	39	38.9	26	31.6
Diarrhea	19	13	23	29	42	22.8
Anorexia	NA	NA	30	18.7	26	18.4
Fatigue	41	38	70	60.1	64	48.5
Dysgeusia	NA	NA	21	20.2	25	14
Dyspepsia	NA	13	NA	19.7	26	16.2
Anemia	12	17	NA	32.1	26	16.9
Outcome	PFS 6.5 mo (200 mg), 8.8 mo (400 mg), and 7.1 mo (PLD)	ORR 33% in 400 mg bid and 13% in 100 mg bid groups	ORR 29% (41% in BRCA mutated, 24% WT)	PFS 7 mo, OS 16.6 mo, TRR 31.3%	PFS 12.2 mo in olaparib plus chemo group versus 9.6 mo in chemo-alone group	PFS 8.4 mo in olaparib group versus 4.8 mo in placebo group

**Abbreviations:** HGSOc, high-grade serous ovarian cancer; PFS, progression-free survival; mo, month; PLD, pegylated liposomal doxorubicin; ORR, objective response rate; OS, overall survival; TRR, tumor response rate; WT, wild type; NA, no data.

clinically significant. Feeding also increased the rate of absorption.<sup>7</sup>

## Efficacy in patients without BRCA mutations

Olaparib has also demonstrated efficacy in patients without BRCA mutations. Gelmon et al conducted a multicenter, nonrandomized Phase II study that included 63 women with advanced high-grade serous ovarian cancer. The patients were treated with olaparib 400 mg twice daily. The ORR was 41% (seven of 17, 95% CI 22–64) for patients with BRCA 1/2 mutations and 24% (eleven of 46, 95% CI 14–38) for patients without BRCA 1/2 mutations. In this study, patients with platinum-sensitive disease had ORR 50% in the BRCA 1/2 mutation negative cohort versus 60% in the cohort with mutation. This contrasted with the platinum-resistant population, where the ORR was 33% in patients with BRCA 1/2 mutation and 4% in the BRCA 1/2 mutation negative cohort.<sup>8</sup>

## Efficacy of olaparib in platinum-sensitive and platinum-resistant diseases

Maintenance therapy in platinum-sensitive patients improved progression-free survival in comparison to placebo in a randomized, double blind, Phase II trial by Ledermann et al. Two hundred and sixty-five patients with recurrent ovarian cancer who had at least two prior courses of platinum-based chemotherapy and an objective response to the most recent regimen were randomized to olaparib 400 mg twice daily or matching placebo until progression. The progression-free survival was 8.4 months with olaparib compared to 4.8 months with placebo (hazard ratio [HR] 0.35, 95% CI 0.25–0.49;  $P < 0.001$ ). The patient's quality of life, as measured by Functional Assessment of Cancer Therapy – Ovarian (FACT-O) and variables derived from the FACT-O, was not different between olaparib and placebo groups. Most patients reported a best treatment outcome index as “improved” or “no change” during treatment, supporting the conclusion that there was no negative impact on the patient's quality of life during treatment.<sup>9</sup>

Efficacy in platinum resistance was investigated in a multicenter Phase II trial by Kaufman et al. A study population of 298 patients with platinum-resistant cancers and a germline BRCA 1/2 mutation (including 193 patients with ovarian, primary peritoneal, or fallopian tube cancers) was administered olaparib 400 mg twice daily until disease progression. These patients had a mean of 4.3 prior regimens. The tumor response rate was 26.2% overall (95% CI 21.3–31.6), and

the response rate for ovarian cancer patients was 31.1% (95% CI 24.6–38.1). The median duration of response was 225 days, and the median progression-free survival was 7 months.<sup>10</sup>

## Olaparib in combination with chemotherapy

It has been proposed that olaparib could potentiate the effect of DNA-damaging chemotherapy. Oza et al conducted a randomized, open-label, Phase II study of 162 patients with recurrent, platinum-sensitive, high-grade serous ovarian cancers who had received up to three prior regimens of platinum-based chemotherapy. Patients received olaparib 200 mg twice daily plus paclitaxel 165 mg/m<sup>2</sup> and carboplatin AUC4 followed by olaparib 400 mg twice daily maintenance versus carboplatin and paclitaxel alone. Patients in the olaparib plus chemotherapy group had a longer progression-free survival (12.2 versus 9.6 months for chemotherapy alone, HR 0.51, 95% CI 0.34–0.77;  $P = 0.0012$ ). This benefit was more pronounced in patients with known BRCA mutation (HR 0.21, 95% CI 0.08–0.55;  $P = 0.0015$ ).<sup>11</sup>

The addition of antiangiogenic agents to olaparib has also been studied. An open-label comparison of olaparib 400 mg twice daily or olaparib 200 mg twice daily with cediranib 30 mg daily in patients with recurrent, high-grade, platinum-sensitive serous ovarian cancer or BRCA-related ovarian cancer evaluated 90 patients, stratified by BRCA status. Progression-free survival was 17.7 months in the group receiving cediranib versus 9 months in the olaparib-only group. (HR 0.42, 95% CI 0.23–0.76;  $P = 0.005$ ). However, toxicity was higher in the combination group than in the olaparib-alone group (27% versus 11% fatigue, 41% versus 0% hypertension, and 23% versus 0% diarrhea), and 75% of the combination group required dose reduction.<sup>12</sup> A small Phase I study investigated increasing doses of olaparib in combination with bevacizumab 10 mg/kg every 2 weeks. Adverse events were generally mild, and the most frequent events were fatigue and nausea. Significant adverse events (small bowel obstruction with perforation) were attributed to bevacizumab, rather than olaparib.<sup>13</sup>

## Efficacy in recurrent ovarian cancer compared to pegylated liposomal doxorubicin

An open-label, randomized trial of women with ovarian, primary peritoneal, or fallopian tube cancers that recurred or progressed within 12 months of the most recent platinum-based chemotherapy investigated olaparib at 200–400 mg

twice daily versus intravenous pegylated liposomal doxorubicin (PLD) 50 mg/m<sup>2</sup> every 28 days. The trial enrolled 97 patients and allowed crossover from PLD group to 400 mg olaparib group in the event of disease progression. In the 200 mg olaparib, 400 mg olaparib, and PLD groups, the median progression-free survival was 6.5 months (95% CI 5.5–10.1), 8.8 months (95% CI 5.4–9.2), and 7.1 months (95% CI 3.7–10.7 months), respectively. The ORRs were 25%, 31%, and 18%, respectively. There was no statistically significant difference between the olaparib or PLD groups in terms of either progression-free survival or ORR. Grade 3 to 4 treatment associated adverse events were more common in the PLD group. Improvement in the patient's quality of life as measured by FACT-O was significantly increased in the olaparib group versus the PLD group (odds ratio 7.23, 95% CI 1.09–143.3;  $P=0.039$ ).<sup>14</sup>

## Long-term safety and efficacy

Van der Noll et al collected data on the long-term safety and efficacy of olaparib in a Phase I cohort of 21 patients who had received olaparib in combination with carboplatin and/or paclitaxel. Patients continued olaparib monotherapy (400 mg bid) after the Phase I combination study if they had completed six or more cycles of combination therapy, had no evidence of disease progression, and had significant toxicity from the combination therapy. Bone marrow suppression, fatigue, pain, and nausea decreased over time after combination therapy was discontinued. Gastrointestinal toxicities, such as gastritis, esophagitis, and dyspepsia, increased in frequency with longer duration use of olaparib, but were reduced with proton pump inhibitors. Response to therapy was diurnal, with the median duration of treatment 52 weeks. The best overall response was 43% complete response, 22% partial response, 29% stable disease, 5% progressive disease, and 5% not evaluable.<sup>15</sup>

## Ongoing research

SOLO-1 and SOLO-2 are multicenter, double-blind studies of olaparib 300 mg bid versus placebo in patients with high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer. Both SOLO-1 and SOLO-2 have primary outcomes of progression-free survival by response evaluation criteria in solid tumors (RECIST) criteria in olaparib 300 mg twice daily monotherapy maintenance compared to placebo. The study population of SOLO-1 is BRCA-mutated high-risk advanced ovarian cancer patients who achieved complete or partial response with first-line platinum chemotherapy, whereas the population of SOLO-2 is BRCA-mutated relapsed ovarian cancer patients who achieved

complete or partial response with platinum chemotherapy. In SOLO-1, the patients will receive olaparib versus placebo for up to 2 years or until objective response by RECIST criteria and the treatment may continue beyond 2 years for those with stable disease or progression. Patients in SOLO-2 will receive olaparib versus placebo until progression by RECIST criteria or as long as they are benefiting from treatment and do not meet other criteria for discontinuation.<sup>16,17</sup>

The current FDA approval for olaparib is for patients who have received three or more prior lines of chemotherapy. A recent study by Marques et al investigated whether the administration of chemotherapy affected intratumoral PARP expression. Tissue samples were obtained from three cohorts, totaling 313 high-grade serous ovarian cancers. PARP1 expression was measured by immunohistochemistry and Western blot protein analysis. Samples from patients who had undergone chemotherapy had significantly lower protein expression than chemotherapy-naïve tumor samples. Of 15 samples from patients which had both pre- and postchemotherapy (carboplatin and paclitaxel), six had absent PARP1 expression and eight had reduced PARP1 levels postchemotherapy. The clinical significance of this change in PARP1 expression is unknown; however, the dynamic interaction of PARP1 and chemotherapy should be taken into consideration in future studies.<sup>18</sup> It is possible that the use of olaparib before exposure to multiple lines of chemotherapy would be a more effective use.

## Conclusion

Olaparib is a well-tolerated oral chemotherapeutic agent that has FDA approval for the treatment of ovarian cancer in patients with germline BRCA 1/2 mutations who have received three or more prior lines of chemotherapy. In the future, development of assays for function of homologous recombination may help to identify patients without a germline BRCA 1/2 mutation who would also benefit from treatment with olaparib. Further studies will also help delineate the optimal timing and setting of olaparib administration.

## Disclosure

The authors report no conflicts of interest in this work.

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