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CCR Perspectives in Drug Approval

Clinical Cancer Research

FDA Approval Summary: Olaparib Monotherapy in Patients with Deleterious Germline *BRCA*-Mutated Advanced Ovarian Cancer Treated with Three or More Lines of Chemotherapy

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Abstract

On December 19, 2014, the FDA approved olaparib capsules (Lynparza; AstraZeneca) for the treatment of patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.) was approved concurrently. An international multicenter, single-arm trial enrolled 137 patients with measurable g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy. Patients received olaparib at a dose of 400 mg by mouth twice daily until disease progression or unacceptable toxicity. The objective response rate (ORR) was 34% with median response duration of 7.9 months in this cohort. The most common adverse reactions (≥20%) in patients treated with olaparib were anemia, nausea, fatigue (including asthenia), vomiting, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, nasopharyngitis/pharyngitis/upper respiratory infection, cough, arthralgia/musculoskeletal pain, myalgia, back pain, dermatitis/rash, and abdominal pain/discomfort. Myelodysplatic syndrome and/or acute myeloid leukemia occurred in 2% of the patients enrolled on this trial. *Clin Cancer Res; 21(19); 4257–61. ©2015 AACR.*

Introduction

Therapy for relapsed ovarian cancer is dependent on the interval between the date of the final dose of initial therapy and date of relapse, with platinum-sensitive ovarian cancer being defined as relapse that occurs more than 6 months from the date of the last dose of platinum-based chemotherapy (1). Multiple options exist for relapsed ovarian cancer; however, data are limited on the response rates for therapy in the fourth-line setting regardless of platinum sensitivity. Several institutions have described their experience with third-line chemotherapy regimens, and the response rates ranged from 5% to 40% (2–5). There are no agents specifically approved in this disease setting.

The *BRCA* genes *BRCA*1 and *BRCA*2 encode proteins involved in the DNA damage repair pathway. Deleterious mutations of *BRCA*1 and *BRCA*2 are associated with an increased risk of the development of breast and ovarian cancers; however, not all mutations are considered to be deleterious (6, 7). The majority of deleterious mutations are protein-truncating mutations. Missense mutations and large rearrangements of DNA segments within the *BRCA* genes also result in loss of function. It is estimated that the incidence of deleterious germline *BRCA* mutation (g*BRCA*m)-associated ovarian cancer is approximately 10% to 15% of all cases of ovarian cancer, corresponding to an annual incidence of approximately 2,000 cases per year in the United States (8, 9).

Patients with g*BRCA*m-associated ovarian cancer are treated no differently than patients without a deleterious mutation, but the presence of a mutation appears to be positively correlated with increased survival and responsiveness to chemotherapy (10–12). Because of the increased susceptibility to chemotherapy, it is expected that the patient with g*BRCA*m-associated ovarian cancer will be exposed to multiple lines of chemotherapy, and cumulative toxicity is a key concern in heavily pretreated patients.

Chemistry

Olaparib is an inhibitor of the mammalian PARP enzyme. Its chemical name is 4-[(3-{[4-(cyclopropylcarbonyl)

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piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one. Olaparib is available in 50-mg capsules for oral administration.

Nonclinical Pharmacology and Toxicology

In vitro studies have shown that olaparib inhibits various isoforms of PARP, including PARP1, PARP2, and PARP3. Olaparib inhibits growth of selected tumor cell lines *in vitro* and decreases tumor growth in mouse xenograft models of human cancer. Increased cytotoxicity and antitumor activity following treatment with olaparib were noted *in vitro* and in mouse tumor models with cell lines deficient in *BRCA*. *In vitro* studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of the PARP–DNA complex, resulting in disruption of cellular homeostasis and cell death (13).

Repeat-dose toxicology studies evaluated the effects of daily doses of oral olaparib in rats and dogs for up to 26 weeks. The major target organ was the hematopoietic system, with reduced red cell mass and leukopenia reported in rats and dogs at $\geq$2% and 4%, respectively, of the human AUC at the recommended clinical dose. Gastrointestinal toxicities (discoloration, congestion, hemorrhage, and inflammation) were considered minimal in severity and noted in 4- and 26-week repeat-dose toxicity studies in dogs at $\geq$4% of the human AUC at the recommended clinical dose.

In embryo–fetal development studies, olaparib was embryotoxic and teratogenic when administered to pregnant rats during the period of organogenesis.

BRCA and PARP are key components of the DNA damage repair pathway. Specifically, both BRCA1 and BRCA2 proteins critically interact with Fanconi Anemia proteins in the homologous recombination pathway (14). Limited data exist regarding the increased risk for the development of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) in patients with germline BRCA mutations; however, because of the interactions among BRCA1, BRCA2, and Fanconi Anemia proteins, BRCA deficiency may increase the risk for the development of MDS/AML (15). The addition of further DNA damage induced by chemotherapy or other environmental factors, coupled with further impairment of a compensatory repair pathway by means of PARP inhibition, may prime patients with germline DNA repair deficiencies for the development of MDS/AML.

Clinical Pharmacology

Following oral administration of olaparib, absorption is rapid, with peak plasma concentrations typically achieved between 1 and 3 hours after dosing. Steady-state exposures are achieved within 3 to 4 days. The mean half-life of olaparib is 12 hours at the 400-mg dose with an accumulation ratio of 1.4 with twice daily dosing. A high-fat meal did not increase the exposure of olaparib significantly; therefore, olaparib can be dosed without regard to food intake.

The results from the oral mass balance trial suggest that metabolism is an important elimination pathway for olaparib, but the contribution of the renal route cannot be ruled out. At the level of 30 mL/min or higher, creatinine clearance (CLcr) had no influence on the exposure of olaparib. Data are not available in patients with CLcr less than 30 mL/min, patients on dialysis, or patients with baseline serum bilirubin > 1.5 $\times$ ULN.

The maximum tolerated dose of olaparib was identified as 400 mg twice daily based on safety assessments in a phase 1 study. In other trials with olaparib, an exposure–response relationship was identified for anemia in the dose range of 100 to 400 mg twice daily showing an increased risk of anemia with increase in olaparib steady-state concentrations.

Olaparib is primarily metabolized by CYP3A. A strong CYP3A inhibitor increased the AUC of olaparib by 2.7-fold, and PBPK modeling predicted that a moderate CYP3A inhibitor would likely increase olaparib AUC by 2-fold. Dose reductions to 150 mg twice daily are recommended for concomitant use of a strong CYP3A inhibitor and to 200 mg for concomitant use of a moderate CYP3A inhibitor. A strong CYP3A inducer decreased the AUC of olaparib by 87%, and PBPK modeling predicted that a moderate CYP3A inducer would likely decrease olaparib AUC by half. Concomitant use of a strong or moderate CYP3A inducer should be avoided. If a moderate CYP3A inducer must be coadministered, there is a potential for reduced efficacy.

Clinical Trials

FDA approval of olaparib was primarily based on an open-label, nonrandomized clinical trial in 298 patients with deleterious or suspected deleterious g*BRCA*m-associated cancer, including 193 patients with ovarian cancer (16). Patients were treated with olaparib capsules at a dose of 400 mg orally twice daily until disease progression or intolerance to therapy. Local test results for *BRCA* status were used to assess patient eligibility for the trial. Samples from a subset of enrolled patients from the intended population were retrospectively evaluated at one laboratory, Myriad Genetic Laboratories, Inc., using the BRACAnalysis CDx in a clinical bridging study.

Of the 193 patients in the ovarian cancer cohort, 137 patients had measurable disease at baseline and had received three or more prior lines of chemotherapy. The majority (94%) of these patients were white/Caucasian and had a baseline ECOG performance status of 0 or 1 (93%); the median age at enrollment was 58 years. The median number of prior chemotherapy regimens was five, and the maximum number of prior regimens was 14.

Efficacy results

The primary endpoint was investigator-assessed tumor response rate by RECIST v.1.1 in all treated patients. Secondary objectives included objective response rate (ORR) in patients with measurable disease only and duration of response (DOR). A blinded independent radiologic review was not performed. The ORR was 34% [95% confidence interval (CI), 26–42] with a median DOR of 7.9 months (Table 1).

Of the 137 patients, specimens from 61 patients were available for retrospective testing with the BRACAnalysis CDx in the

Table 1. Objective response and DOR in patients with g*BRCA*-mutated advanced ovarian cancer who received three or more prior lines of chemotherapy in Study 42

	***N* = 137**
Objective response rate (95% CI)	34% (26–42)
Complete response	2%
Partial response	32%
Median DOR in months (95% CI)	7.9 (5.6–9.6)

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bridging study for clinical validation of the device. The concordance between the local test results, as reported in the Case Report Form, and the results from the BRACAnalysis CDx were 96.7% (59/61; 95% CI, 88.7–99.6). Among the discordant results, one sample did not yield a callable result with the BRACAnalysis CDx, and another sample had different classification results between the local test and the BRACAnalysis CDx (deleterious vs. variant of unknown significance, respectively), although the specific variant that was detected by both tests matched. The ORR for the 59 patients with confirmed *gBRCA* mutations was 41% (95% CI, 28–54), with a median DOR of 8.0 months.

Safety results

The primary safety population included 223 patients from six studies, including patients with relapsed ovarian cancer with g*BRCA* mutation who had received three or more prior treatment regimens. The median exposure to olaparib in this population was 158 days. Dose interruptions were reported in 40% of these patients, and dose reductions were reported in 4%. Treatment discontinuations due to adverse drug reaction occurred in 7%. The most common adverse events leading to treatment discontinuation included nausea and vomiting, intestinal obstruction, anemia, and thrombocytopenia.

Eight patients (4%) had adverse reactions leading to death. The fatal adverse reactions included 2 patients with acute leukemia and 1 patient each with death attributed to chronic obstructive pulmonary disease, cerebrovascular accident, intestinal perforation, pulmonary embolism, sepsis, and suture rupture.

The most common (≥20%) grade 1–4 and grade 3–4 adverse reactions in patients receiving olaparib are shown in Table 2. Thirty-five percent of patients experienced one or more serious adverse events, and the most common of these events are shown in Table 3.

Myelodysplastic syndrome and acute leukemia are the most concerning adverse reactions associated with olaparib therapy. Six confirmed cases of MDS/AML occurred in the 298 patients (2%) enrolled in the single-arm study of olaparib monotherapy in patients with g*BRCA*m-associated ovarian cancer. In a randomized placebo controlled trial of olaparib maintenance monotherapy in platinum-sensitive ovarian cancer, MDS/AML occurred in 3 of the 136 patients treated with olaparib (2%) as compared with 1 of the 129 patients treated with placebo (0.8%). Among the 2,618 patients exposed to olaparib at the time of the FDA review, 22 cases of MDS/AML were reported (0.8%), with 17 cases resulting in death. The precise number of patients with *gBRCAm* status who have been exposed to olaparib is unknown, but the majority of cases occurred in patients with g*BRCA*m status ($n = 17$) and in patients who were currently being treated for ovarian cancer ($n = 18$). Of those patients with g*BRCA*m status, 6 patients with ovarian cancer had a prior history of breast cancer, and the 1 patient with breast cancer had a history of ovarian cancer. Further epidemiologic research is needed to understand the baseline risk of developing therapy-related MDS/AML in patients with *gBRCAm* status; however, given the mechanism of action and increased rates of MDS/AML seen in the randomized studies of olaparib, there exists a clear safety signal that olaparib may increase the risk of developing MDS/AML.

Table 2. Common adverse reactions in a pooled g*BRCA*m population

	Three or more lines of prior chemotherapy	
	Grade 1–4	Grade 3–4
Adverse reaction	***N* = 223 (%)**	***N* = 223 (%)**
Blood and lymphatic disorders		
Anemia	34	18
Gastrointestinal disorders		
Nausea	64	3
Abdominal pain/discomfort	43	8
Vomiting	43	4
Diarrhea	31	1
Dyspepsia	25	0
Decreased appetite	22	1
General disorders		
Fatigue/asthenia	66	8
Infections and infestations		
Nasopharyngitis/URI	26	0
Musculoskeletal and connective tissue disorders		
Myalgia	22	0
Arthralgia/musculoskeletal pain	21	0

Abbreviation: URI, upper respiratory infection.

Table 3. Serious adverse reactions in a pooled g*BRCA*m population

Serious adverse reaction	**Three or more lines of prior chemotherapy *N* = 223 (%)**
Patients with any serious adverse reaction	35
Blood and lymphatic system disorders	
Anemia	5
Neutropenia/febrile neutropenia/leukopenia	2
Gastrointestinal disorders	
Bowel obstruction	9
Abdominal pain	4
Nausea and vomiting	4
Infections and infestations	
Sepsis/infection	3

Discussion

Olaparib is the first new molecular entity approved for the treatment of ovarian cancer since 1996. The long gap between approvals demonstrates the challenge of developing novel therapeutics in ovarian cancer, as standard therapeutic regimens for the first-line and platinum-sensitive settings have high antitumor activity with benefits in overall survival, making it difficult to use an "add-on" trial design in which a new drug is added to an existing regimen. In more refractory ovarian cancer settings, randomized trials are possible, but a convincing demonstration of efficacy in a more resistant population has been elusive. Bevacizumab was recently approved as a supplemental Biologic License Application for use in combination with chemotherapy for the treatment of patients with platinum-resistant ovarian cancer based on the results of a randomized trial demonstrating an improvement in progression-free survival (PFS), which marked the first approval in this setting for over 15 years (17).

On June 25, 2014, New Drug Application 206162 was brought to the FDA's Oncologic Drug Advisory Committee (ODAC) to discuss olaparib for the maintenance treatment of g*BRCA*m-associated ovarian cancer based on the results of Study 19, a randomized placebo controlled trial assessing PFS in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer in partial or complete response to their last platinum-containing regimen (18). The efficacy results were based primarily on the prespecified subgroup analysis of 96 patients with deleterious germline *BRCA* mutations who were mostly retrospectively

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identified (19). The committee was asked whether the efficacy results, namely a 7-month improvement in median PFS and an HR of 0.17, along with the safety data in the g*BRCA*m population, demonstrated a favorable risk–benefit profile of olaparib maintenance monotherapy in g*BRCA*m-associated ovarian cancer.

After a robust discussion, the committee voted 11–2 that the results from Study 19 do not support an accelerated approval for the proposed indication. Primary reasons for voting against approval included a lack of OS benefit for maintenance therapy; uninterpretable results due to lack of multiplicity adjustment; unreliable results due to loss of randomization and small sample size; toxicity of therapy and risk of MDS/AML for patients not otherwise undergoing treatment; and a potential to hinder accrual to the confirmatory study.

Following the ODAC meeting and in further discussion with the FDA, the applicant submitted additional information in support of the use of olaparib monotherapy in a more refractory and narrowly defined population of patients with *gBRCA*m-associated ovarian cancer treated with three or more lines of chemotherapy. The applicant has addressed the concerns raised by the ODAC, as the approved indication is not in a maintenance setting, and patients typically would be treated with chemotherapy at this time. Enrollment for a potential confirmatory trial discussed at ODAC, SOLO-2, is complete.

This approval is not restricted to either the platinum-sensitive or platinum-resistant disease setting. Many patients with g*BRCA*m-associated ovarian cancer may still be responsive to platinum-based therapy even after three prior lines of chemotherapy; however, it is estimated that treatment with olaparib would have a better response rate and favorable safety profile as compared with available single-agent chemotherapeutic options. Patients in this disease setting will most likely have cumulative toxicity and would benefit from a drug with demonstrable antitumor activity and a relatively mild safety profile. The tolerability profile of olaparib in this heavily pretreated population was an important factor in determining the overall benefit–risk assessment of olaparib therapy. The applicant is conducting a randomized trial (SOLO-3) directly comparing the safety and efficacy of olaparib monotherapy versus chemotherapy in the third-line ovarian cancer setting that also could be a potential confirmatory trial.

Overall, olaparib monotherapy represents a new treatment modality for patients with advanced, heavily pretreated g*BRCA*m-associated ovarian cancer; however, the clinical benefit must be confirmed in a randomized clinical trial. In addition, the risks of the development of MDS/AML must be further characterized, and this led to a post-marketing requirement (PMR) for annual reporting to the FDA of all cases of MDS/AML from ongoing clinical trials and spontaneous safety reports. Other PMRs included the assessment of olaparib in patients with renal impairment and with hepatic impairment.

Further information regarding the review of the application can be found at the Drugs@FDA website (20). Information about the device application can be found online at the FDA PMA database website (21).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G. Kim, R. Venugopal
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Kim, G. Ison, A.E. McKee, H. Zhang, S. Tang, T. Gwise, R. Sridhara, H.-J. Chiu, T. Palmby, A.M. Russell, E. Pfuma, H. Li, L. Zhao, Q. Liu, A. Ibrahim, R. Pazdur
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References

1. Thigpen JT, Blessing JA, Ball H, Hummel SJ, Barrett RJ. Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. J Clin Oncol 1994;12:1748–53.
2. Bruchim I, Jarchowsky-Dolberg O, Fishman A. Advanced (>second) line chemotherapy in the treatment of patients with recurrent epithelial ovarian cancer. Eur J Obstet Gynecol Reprod Biol 2013;166:94–8.
3. Nishio S, Katsumata N, Matsumoto K, Tanabe H, Yonemori K, Kouno T, et al. Usefulness of third-line chemotherapy for women with recurrent ovarian, fallopian tube, and primary peritoneal cancer who receive platinum/taxane regimens as first-line therapy. J Cancer Res Clin Oncol 2009;135:551–7.
4. Tangjitgamol S, See HT, Manusirivithaya S, Levenback CF, Gershenson DM, Kavanagh JJ. Third-line chemotherapy in platinum- and paclitaxel-resistant ovarian, fallopian tube, and primary peritoneal carcinoma patients. Int J Gynecol Cancer 2004;14:804–14.
5. Villa A, Parazzini F, Scarfone G, Guarnerio P, Bolis G. Survival and determinants of response to third-line chemotherapy in sensitive recurrent ovarian cancer patients. Br J Cancer 1999;79:373–4.
6. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994;266:66–71.
7. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature 1995;378:789–92.
8. Pal T, Permuth-Wey J, Betts JA, Krischer JP, Fiorica J, Arango H, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer 2005;104:2807–16.
9. Zhang S, Royer R, Li S, McLaughlin JR, Rosen B, Risch HA, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol 2011;121:353–7.
10. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, Lubin F, Friedman E, Sadetzki S. Effect of BRCA1/2 mutations on long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. J Clin Oncol 2008;26:20–5.
11. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from

Published OnlineFirst July 17, 2015; DOI: 10.1158/1078-0432.CCR-15-0887

the Australian Ovarian Cancer Study Group. J Clin Oncol 2012;30:2654–63.
12. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA 2012;307:382–90.
13. Murai J, Huang SY, Das BB, Renaud A, Zhang Y, Doroshow JH, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res 2012;72:5588–99.
14. D'Andrea AD, Grompe M. The Fanconi anaemia/BRCA pathway. Nat Rev Cancer 2003;3:23–34.
15. Friedenson B. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer 2007;7:152.
16. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015;33:244–50.
17. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32:1302–8.
18. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366:1382–92.
19. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 2014;15:852–61.
20. Drugs@FDA [database on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration [cited 2015 Jan 15]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
21. Premarket Approval (PMA) [database on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration [cited 2015 Jan 15]. BRACAnalysis CDx; unique ID: P140020; [about 1 p.]. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=952. Files updated weekly.

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