# Office Director Decisional Memo for Regulatory Action

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| **Date** | Electronic stamp date |
| **From** | Richard Pazdur, MD |
| **Subject** | Office Director Decisional Memo |
| **NDA #/Supplement#** | NDA 206162 |
| **Applicant** | AstraZeneca Pharmaceuticals LP |
| **Date of Submission** | February 3, 2014 |
| **PDUFA Goal Date** | January 3, 2015 |
| **Proprietary Name / Established (USAN) names** | Lynparza™/olaparib |
| **Dosage forms / Strength** | 50 mg capsules |
| **Proposed Indication(s)** | Lynparza™ (olaparib) is indicated as monotherapy in patients with deleterious or suspected deleterious germline *BRCA* mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. |
| **Recommended:** | Accelerated Approval |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| DD Review | Amna Ibrahim |
| RPM | Rajesh Venugopal |
| CDTL Review | Amy McKee |
| Medical Officer Review | Geoffrey Kim (efficacy)/ Gwynn Ison (safety) |
| Statistical Review | Hui Zhang |
| Pharmacology Toxicology Review | Tiffany Ricks / Haw-Jyh Chiu |
| CMC Review/OBP Review | Anne Marie Russell / Gaetan Ladouceur |
| Clinical Pharmacology Review | Elimika Pfuma |
| DDMAC | Marybeth Toscano |
| OSI | Lauren C Iacono-Connors |
| OSE/DMEPA | Davis Mathew |
| OSE/DRISK | Naomi Redd |
| QT-IRT | Dinko Rekic |
| DMPP | Morgan Walker |

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI= Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
Division of Medical Policy Programs (DMPP)

## 1. Introduction

On February 3, 2014, AstraZeneca submitted a New Drug Application (NDA) for olaparib as monotherapy for maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline *BRCA* (*gBRCA*) mutation as detected by an FDA-approved test who are in response (complete response or partial response) to platinum-based chemotherapy therapy based on a phase 2, randomized trial in patients. This application was discussed at the Oncologic Drugs Advisory Committee (ODAC) meeting in June 2014, and the committee determined that the trial did not demonstrate a favorable risk-benefit profile for olaparib in this indication by a vote of 11-2. The applicant submitted a major amendment to the NDA on July 24, 2014 with the new proposed indication of monotherapy in patients with advanced relapsed ovarian cancer with a germline *BRCA (gBRCA)* mutation (as detected by a FDA-approved test) who have had three or more prior lines chemotherapy treatment. The application was supported by a single-arm, Phase 2 trial in 137 patients with *gBRCA*-mutated (*gBRCA*m) platinum-resistant, recurrent, epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with chemotherapy. The trial demonstrated overall response rate of 34%.

## 2. Background

Olaparib is a new molecular entity. It is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair. Olaparib has been shown to inhibit growth of select tumor cell lines *in vitro* and decrease tumor growth in mouse xenograft models of human cancer both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with olaparib were noted in cell lines and mouse tumor models with deficiencies in BRCA. *In vitro* studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complex, resulting in disruption of cellular homeostasis and cell death.

According to the National Cancer Institute (NCI), a total of 21,980 and 14,270 women, respectively, were estimated to be diagnosed and die from ovarian cancer in 2014 (NCI 2014) in the United States.

More than 70% of patients present with advanced disease, and five-year survival rates are less than 30%. The primary treatment modality at initial diagnosis is debulking surgery followed by platinum- and taxane-based combination chemotherapy. Despite the high sensitivity of ovarian cancer to initial treatment with platinum- and taxane-based combination chemotherapy, which is the standard of care in the front-line setting, the majority of women (more than 80%) diagnosed with advanced-stage disease will have a recurrence of their cancer. After recurrence, the likelihood of cure is very low, but responses to therapy occur in the second-line setting and beyond. These responses tend to be of shorter duration with each subsequent line of therapy. Platinum remains the most active agent in the treatment of recurrent disease, but platinum resistance eventually occurs, and current treatment options have very limited efficacy in this setting. There are no agents approved for use specifically in the fourth-line setting for ovarian cancer setting in the U.S.

## 3. Chemistry, Manufacturing and Control

There are no issues that preclude approval from the CMC perspective.

CMC reviewers recommended an expiry for the olaparib drug product of 18 months under long-term conditions of 25ºC.

Stability data for olaparib 50mg capsules, showed appearance testing reports of thermal failure at [redacted] (b) (4) [redacted] (b) (4) for several batches. The appearance test results reported “capsules showed evidence of leakage”, “capsule shell has deformed” and “capsule shell has deformed and printing ink smudged suggesting leakage of capsule content” respectively. [redacted] (b) (4)

(b) (4) Therefore, the following language in the PI, carton and container states: (b) (4) (b) (4)

An overall acceptable recommendation was issued on November 21, 2014 for manufacturing and testing facilities.

## 4. Companion *In Vitro* Diagnostic Device

A Premarket Approval application (PMA) for the companion *in vitro* diagnostic assay was submitted by Myriad Genetics, Inc. to the Center for Devices and Radiological Health (CDRH) for use in selecting patients suitable for olaparib therapy. The proposed intended use statement for this test is following:

BRACAnalysis CDx™ is for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes using genomic DNA obtained from whole blood specimens collected in (b) (4) EDTA. Single nucleotide variants and small deletions are identified by PCR and Sanger sequencing. Large deletions and duplications in BRCA1 and BRCA2 are detected using multiplex quantitative PCR. Results of the test (b) (4) be used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with Lynparza™ (olaparib). This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories.

See the CDRH Summary of Safety and Effectiveness Data (SSED) and product labeling for more complete information on the BRACAnalysis CDx™.

## 5. Nonclinical Pharmacology/Toxicology

There are no nonclinical issues that would preclude approval of this application.

*Genetic-toxicology studies*
Olaparib was clastogenic in an *in vitro* chromosomal aberration assay in mammalian CHO cells and in an *in vivo* rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of olaparib and indicates potential for genotoxicity in humans. Olaparib was not mutagenic in a bacterial reverse mutation (Ames) test.

*Repeat-dose Toxicology Studies*
Repeat-dose toxicology studies were conducted in both rats and dogs. The major target organs were the bone marrow, spleen, thymus, liver, GI tract, kidney and prostate. No remarkable findings were noted at the end of recovery, and all animals survived to scheduled necropsy.

The Applicant reported toxicity primarily in hematopoietic organs, testes, liver, and nerves (in rats). Non-reversible testicular effects occurred in both rats and dogs at doses lower than the proposed human dose. Doses ≥ 1.2 mg/m$^2$ were lethal in the 29-day rat study and all doses tested in the rat chronic toxicology study. The end-of-treatment effects were not observed in the 29-day dog study or chronic dog and rat studies since all animals were terminated at the end of the recovery period.

*Genetic-toxicology studies*
A 5178Y/TK Mouse Lymphoma Mutagenesis assay indicating gene mutation/chromosomal damage and function loss was positive. Additionally, the *in vivo* rat micronucleus assay was strongly positive, indicating the potential for induction of chromosomal damage.

### Carcinogenicity

The Applicant did not conduct specific carcinogenicity studies because olaparib is intended for patients with advanced ovarian cancer (life-threatening malignancy).

### Reproductive toxicology

Results from embryonic fetal development studies confirmed the teratogenic potential of olaparib in rats at doses lower (with maternal systemic exposures approximately 11% of the human exposure at the recommended dose) than the proposed dose in humans. Olaparib caused embryo-fetal toxicities (with maternal systemic exposures approximately 0.3% of human exposure at the recommended dose), including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital) and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter and umbilical artery. The proposed label contains information that olaparib is expected to cause fetal harm when administered to pregnant women.

## 6. Clinical Pharmacology/Biopharmaceutics

There are no issues that would preclude approval of this NDA from a clinical pharmacology perspective.

The recommended dose of olaparib is 400 mg (eight 50 mg capsules) taken twice daily, for a total daily dose of 800 mg. Continue treatment until disease progression or unacceptable toxicity.

Single- and multiple-dose pharmacokinetic data are available from 13 phase 1 and 2 trials, including evaluation of food effect, mass balance, impact of renal impairment (preliminary data), and drug interaction potential for olaparib. The mean half-life 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. Following oral administration of olaparib via the capsule formulation, absorption is rapid with peak plasma concentrations typically achieved between 1 to 3 hours after dosing. On multiple dosing there is no marked accumulation (accumulation ratio of 1.4 – 1.5 for twice daily dosing), with steady state exposures achieved within 3 to 4 days. Limited data suggest that the systemic exposure (AUC) of olaparib increases less than proportionally with dose over the dose range of 100 to 400 mg, but the PK data were variable across trials. Olaparib had mean plasma protein binding of 89% (91% at 10, 100 and 1000 ng/mL and 82% at 10,000 ng/mL) in human plasma.

### Drug-drug interactions

Olaparib is primarily metabolized by CYP3A. Itraconazole (strong CYP3A inhibitor) increased the AUC of olaparib by 2.7-fold, and PBPK modeling predicted that fluconazole (moderate CYP3A inhibitor) would likely increase olaparib AUC by 2-fold. Therefore, a dose reduction to 150 mg BID is recommended for concomitant use of a strong CYP3A inhibitor, and a dose reduction to 200 mg BID is recommended for concomitant use of a moderate CYP3A inhibitor. Rifampin (strong CYP3A inducer) decreased the AUC of olaparib by 87%, and PBPK modeling predicted that efavirenz (moderate CYP3A inducer) would likely decrease olaparib AUC by half. Increasing the dose could be impractical given the number of capsules to be administered. Therefore, it is recommended that concomitant use of a strong or moderate CYP3A inducer be avoided. If a moderate CYP3A inducer must be co-administered, reduced efficacy may be a result.

### Pathway of elimination

Metabolism is an important elimination pathway for olaparib, but renal contribution cannot be ruled out. About 41.8% (6% unchanged) and 44.1% (15% unchanged) were found in feces and urine, respectively when a total of 85.8% of radioactivity was recovered.

### Evaluation of intrinsic factors potentially affecting elimination

Dedicated hepatic and renal impairment trials are currently ongoing. In the dedicated renal impairment trial, the AUC and Cmax of olaparib increased by 1.5- and 1. 2-fold, respectively, when olaparib was dosed in patients with mild renal impairment (CLcr = 50 - 80 mL/min; N=14) compared to those with normal renal function (CLcr > 80 mL/min; N=8). No dose adjustment to the starting dose is required in patients with CLcr of 50 to 80 mL/min, but patients should be monitored closely for toxicity. Data are not available in patients with CLcr < 50 mL/min, patients on dialysis, or patients with baseline serum bilirubin > 1.5 X ULN. Additionally, the clinical pharmacology review staff recommended two post-marketing requirements to submit the final reports from the pharmacokinetic trials in patients with normal and mild or moderate hepatic impairment and in patients with normal and impaired renal function.

### Demographic interactions/special populations

The population PK model submitted was not deemed adequate by the pharmacometrics reviewer and was not used to evaluate the effect of covariates on PK. In addition, the high variability in PK in part due to the inconsistency in the formulation introduced difficulty in assessing the effect of covariates on PK. Therefore, no conclusion can be drawn on the effect of age, body weight, gender and race on the PK of olaparib.

### Thorough QT study or other QT assessment

No QT signal was detected in clinical trials. The QT/IRT reviewer concluded that no large change (i.e., > 20 msec) in the QTc interval was detected at therapeutic drug exposures.

### Exposure-response relationships

Exploratory analyses were conducted to determine if there were exposure-response relationships for efficacy or safety with olaparib. There is high inter-patient variability of olaparib exposure at all dose levels, and there is no clear exposure-response relationship between olaparib exposure and tumor response or progression-free survival. There does appear to be an exposure-response relationship between olaparib exposure and the incidence of anemia.

## 7. Clinical Microbiology

Not applicable.

## 8. Clinical- Efficacy

This NDA was supported by an international, single-arm trial in patients with deleterious or suspected deleterious gBRCAm advanced cancers. The trial enrolled 137 patients with measurable, gBRCAm-associated ovarian cancer treated with three or more prior lines of chemotherapy.

Treatment continued until disease progression, unacceptable toxicity, and/or consent withdrawal. Of the 137 patients, 93% had ECOG performance status of 0 or 1. Deleterious or suspected deleterious gBRCAm status was verified retrospectively in 97% (59/61) of the patients for whom blood samples were available by the companion diagnostic BRACAnalysis CDxTM.

The trial results demonstrated an ORR of 34% (95% CI: 26, 42). The median response duration was 7.9 months (95% CI: 5.6, 9.6). See Table 1 below.

Table 1: Efficacy Results 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 (5.5[1], 9.6) |

[1] - The lower bound of the 95% CI differs from that calculated by the sponsor as the FDA analysis was performed with a newer version of JMP/SAS. The sponsor's calculation of 5.6 was included in the label.

These primary efficacy results are supported by a pooled analysis of patients with *gBRCA*m-associated ovarian cancer who have received three or more prior lines of chemotherapy culled from other trials. A total of 205 patients met the above criteria from Studies 42, 9, 12, 20, 24 and 2 in the AstraZeneca database. The overall results from this pool of patients are similar to the results from Study 42, as shown in the table below.

Table 2: Efficacy results from pooled population of patients with *gBRCA*m-associated ovarian cancer with measurable disease who have received three or more prior lines of chemotherapy

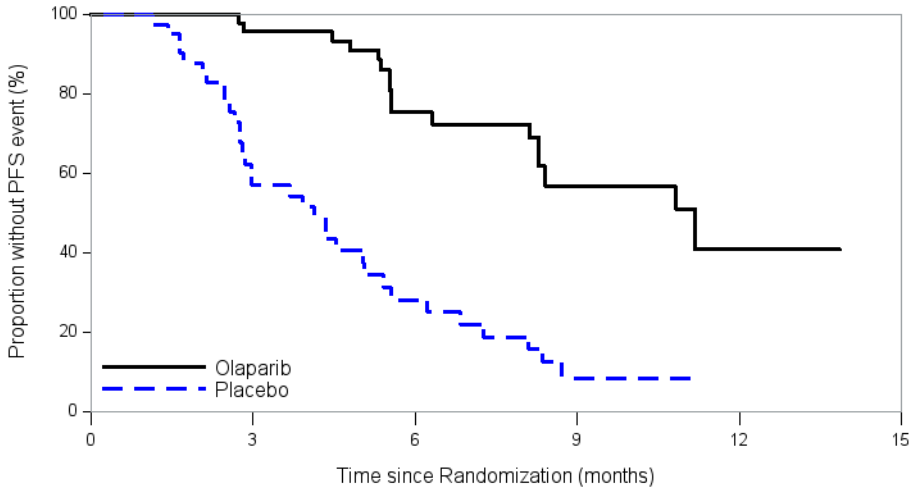
| Study Number | N | Responders | ORR % (95% CI) | Median DOR months (95% CI) |
|---|---|---|---|---|
| 42 | 137 | 43 | 34 (26, 42) | 7.9 (5.6, 9.6) |
| 9 | 26 | 8 | 31 (14, 52) | 8.1 (5.6, NC) |
| 12 | 16 | 3 | 19 (4, 46) | 6.4 (5.6, 7.3) |
| 20 | 12 | 3 | 25 (5, 57) | 3.7 (3.7, 9.1) |
| 24 | 11 | 2 | 18 (2, 52) | 5.5 (NC, NC) |
| 2 | 3 | 2 | 67 (9, 99) | NC (NC, NC) |
| Overall | 205 | 64 | 31 (25, 38) | 7.8 (5.6, 9.5) |

This application initially was submitted for an indication in the maintenance setting after response to platinum-based therapy. The trial supporting this indication, Study 19, was a randomized, double-blind, multicenter, placebo-controlled trial assessing progression-free survival in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer, in partial or complete response to their last platinum-containing regimen. Patients were randomized to receive olaparib or placebo while within eight weeks of confirming response to the last platinum-based regimen until progression, intolerable toxicity or patient withdrawal of consent. The results from the ITT population of 265 patients showed a hazard ratio of 0.35 (95% CI 0.25, 0.49) and median PFS of 8.4 months in the olaparib group and 4.8 months in the placebo group. In a pre-planned analysis, though without alpha adjustments, of the retrospectively identified *gBRCA*m subgroup, there were more striking results, as shown in the table and figure below.

Table 3: Progression-free Survival Analysis in the *gBRCA*m Population in Study 19

| | Olaparib (N=136) | Placebo (N=129) |
|---|---|---|
| Median PFS in months (95% CI) | 11.2 (8.4, NR) | 4.1 (2.8, 5.1) |
| Hazard Ratio (95% CI)[1] | 0.17 (0.09, 0.32) | |

Figure 1: Kaplan-Meier Plot of Progression-free Survival in the *gBRCA*m Population in Study 19




The key safety finding from this trial was MDS/AML at an incidence of 2.2% in the olaparib-treated arm. Otherwise, Grade 1-2 nausea and fatigue were the most common adverse reactions.

## 9. Safety

The most common adverse reactions (greater than or equal to 20%) in patients treated with olaparib were anemia, nausea, fatigue (including asthenia), vomiting, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, nasopharyngitis/pharyngitis/URI, cough, arthralgia/musculoskeletal pain, myalgia, back pain, dermatitis/rash and abdominal pain/discomfort. Myelodysplastic syndrome and/or acute myeloid leukemia occurred in 2% of the patients enrolled on this trial.

The clinical review discipline considered the safety profile of olaparib to be acceptable for the indicated population based on the overall adverse reaction profile for olaparib with a relatively high rate of overall adverse events but few Grade 3-4 adverse events. The risk of MDS/AML in two studies with *gBRCA*m ovarian cancer patients was approximately 2%. The general safety profile of olaparib appears acceptable for this advanced cancer population.

## 10. Advisory Committee Meeting

This application was discussed at ODAC. Key issues raised by FDA included loss of randomization for *gBRCA*m subgroup; estimation of the treatment effect of olaparib therapy; risks of olaparib therapy in the platinum-sensitive maintenance setting, including the risk of MDS/AML; and reproducibility of results in a larger trial with a pre-planned analysis for this *gBRCA*m subgroup. The following question was posed to the Committee:
*Do the safety and efficacy results from Study 19 in the gBRCAm population support an accelerated approval, or should marketing approval consideration be delayed until the results from SOLO-2 are available?*

There were eleven 'No' votes and two 'Yes' votes. Committee members cited the following to support negative votes: lack of an overall survival benefit for maintenance therapy; the unreliability of 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 the potential to hinder accrual to confirmatory study.

## 11. Pediatrics

Olaparib has been granted a full waiver for this indication.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Accelerated approval.

This application is supported by a single-arm trial (Study 42) demonstrating a 34% ORR with a median duration of response of 7.9 months in the heavily pre-treated population of *gBRCA*m, advanced ovarian cancer patients who had received at least three prior lines of chemotherapy. This result was supported by a similar finding in a pooled analysis of similarly heavily pre-treated patients, as well as the PFS results from Study 19 in the maintenance treatment setting.

Most adverse events were Grade 1-2 in severity. Grade 3-4 adverse events were rare, and many could not be distinguished from disease symptoms in Study 42, as the events are common in late-stage ovarian cancer, and there was no concurrent control arm. There were few discontinuations from adverse events. While the MDS/AML signal is concerning true rate of MDS/AML is unclear in a *gBRCA*-mutated patient population that has received prior chemotherapy, including platinum agents and alkylating agents. The inclusion of specific hematologic monitoring guidelines and early referral to a hematologist for bone marrow analysis in the event of prolonged hematologic toxicity may mitigate some of the risk.

While the Agency has most frequently used PFS and OS as endpoints in advanced ovarian cancer, the response rate demonstrated by olaparib is an improvement on response rates reported in the literature for this setting, and response rate is reasonably likely to predict a clinical benefit. AstraZeneca will conduct two additional clinical trials to confirm the clinical benefit for olaparib as a requirement of this accelerated approval. The risk-benefit profile was discussed in the reviews of Drs. Ibrahim, McKee and Kim. Furthermore, all review disciplines recommend approval of this application, and I concur with their recommendation.

- Recommendation for Post-marketing Risk Evaluation and Management Strategies

None.

- Recommendation for other Post-marketing Requirements and Commitments

See action letter.

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/s/

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TAMY E KIM
12/18/2014

RICHARD PAZDUR
12/19/2014