CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206162Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 7, 2014
From	Amy E. McKee, M.D.
Subject	Cross-Discipline Team Leader Review
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:	Approval

Table of Contents

Table of Tables

Table of Figures

1. Introduction

On February 3, 2014, Astra Zeneca 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 a meeting of the Oncologic Drugs Advisory Committee in June 2014, at which 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%.

The following issues arose and were addressed during review of this product:

<u>Clinical/Statistical</u>

The primary issue with the initial application was whether the loss of randomization secondary to the post-hoc analysis of Study 19 in the maintenance setting for the *gBRCA*m subpopulation would be acceptable to support approval. It was determined that Study 19 would not be sufficient for an accelerated approval in this indication. The primary issue with Study 42, the trial used to support the indication in the major amendment, was whether an objective response rate of 34% is sufficient to predict a clinical benefit. Ultimately, the review team believes this is a surrogate reasonably likely to predict clinical benefit in this population, and there are two

confirmatory trials as post-marketing requirements to confirm this benefit. These issues are discussed in more detail in Section 7 of this review.

Clinical/Safety
The primary safety issue in this application is the risk of myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML) with exposure to olaparib. The rate of MDS/AML in both Study 19 and Study 42 in patients with *gBRCA*m-associated cancers was approximately 2%. This is further described in Section 8 of this review.

Product
There were two significant issues with the product review. First, the stability testing data submitted allowed for a recommended expiry for the olaparib drug product of eighteen months under long-term conditions of 25ºC. CMC requested a post-marketing commitment to conduct a stability study with the process validation batches for ICH primary stability testing to the submitted NDA specifications for the commercial product, including (b) (4) up to end of expiry.

Second, there were appearance testing reports of thermal failure (b) (4) for several batches. See Section 3.1 of this review for further details. Therefore, the following language was inserted into the PI, carton and container state: (b) (4)

Clinical/Statistical/Clinical Pharmacology/Product
The capsule that is under review in this application is no longer being used in clinical development. The applicant has changed the formulation to a tablet that has higher bioavailability than the current capsule formulation. Ultimately, the efficacy and safety of the new formulation is being tested in current and future clinical trials that are the subject of post-marketing requirements. If the risk-benefit profile of the new tablet formulation is found to be favorable, the applicant will transition to marketing only the tablet formulation.

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.

This application examines the role of olaparib 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. 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.

Ovarian cancer is diagnosed and staged by surgery and cytological or histological examination. 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.

Regulatory History

The following table from the primary clinical review describes the regulatory history of olaparib prior to this NDA submission.

Table 1: Key Regulatory Activities Related to Clinical Development

Milestone	Time	Details
IND 75,918 activated	September 2006	
Guidance Meeting	October 2012	Discussed olaparib development program for patients with *gBRCA*m-associated ovarian cancer. FDA considered the *gBRCA*m subgroup results of Study 19 to be provocative but insufficient to support an approval.
Pre-submission Meeting	March 18, 2013	Joint meeting with FDA/CDER/CDRH and AstraZeneca and Myriad Genetics Inc. to discuss regulatory pathway for the companion diagnostic assay.
Breakthrough Therapy Designation Request	March 19, 2013	Request submitted on the basis of Study 19.
Breakthrough Designation Denial	May 16, 2013	
Pre-NDA Meeting	October 2, 2013	FDA stated its expectation for a potential concurrent NDA and PMA approval and the likelihood that the application would be discussed at an advisory committee
NDA Submission	February 3, 2014	
Oncology Drug	June 25,	An Oncology Drug Advisory Committee meeting was held

Advisory Committee	2014	to discuss the benefit-risk profile of olaparib as maintenance therapy for *gBRCA*m-associated platinum sensitive ovarian cancer. The panel voted 11 versus 2 that the safety and efficacy results from Study 19 in the *gBRCA*m population DO NOT support an accelerated approval.
Post-ODAC Meeting	July 21, 2014	FDA agreed that the sponsor could submit data regarding olaparib monotherapy in patients with *gBRCA*m-associated ovarian cancer who have been treated with 3 or more lines of chemotherapy to the NDA as a major amendment to potentially support a non-maintenance indication.

3. Chemistry, Manufacturing and Control

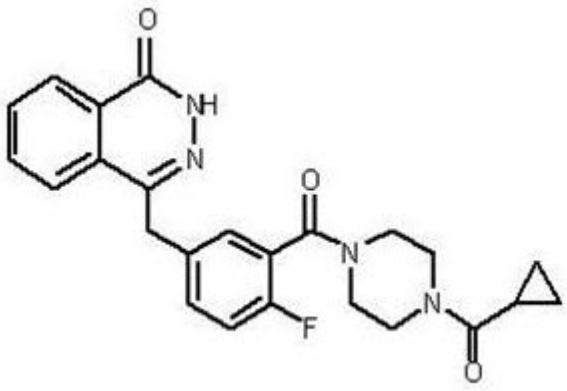
ONDQA recommended approval of olaparib from the chemistry, manufacturing, and control perspective.

3.1 General product quality considerations

3.1.1 Drug substance

Olaparib is an inhibitor of the mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme. The chemical name is 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one and has the following chemical structure:

Figure 1: Olaparib chemical structure



The empirical molecular formula for olaparib is $C_{24}H_{23}FN_4O_3$, and the relative molecular mass is 434.46. Olaparib is a crystalline solid, is non-chiral and shows pH-independent, very low solubility of approximately 0.1 mg/mL across the physiological pH range.

The following has been excerpted from the biopharmaceutics review completed by Okpo Eradiri, Ph.D.

The drug substance, olaparib, exists (b) (4). According to the Applicant, all batches of olaparib used to manufacture the capsules for

clinical trial were confirmed to be [redacted]; the Applicant has not observed [redacted] in long-term, accelerated or stressed storage conditions. However, the biopharmaceutics reviewer noted that long-term stability testing for [redacted] had not been performed.

In a teleconference with the Applicant on May 21, 2014, it was agreed that the limit of [redacted] in the dosage form will be set at ≤[redacted]%. In this scenario, the conduct of an in-vivo study to investigate the effect of [redacted] on bioavailability of olaparib in the patient population will not be required. Furthermore, the Applicant has revised the [redacted] limit in the Specification Table to "NMT [redacted]%". From a Biopharmaceutics perspective, this limit is acceptable at release and through the life cycle of the drug product.

3.1.2 Drug product

The following has been excerpted from the CMC reviews completed by Anne Marie Russell, Ph.D., and Gaetan Ladouceur, Ph.D. Refer to the CMC review for specific information pertaining to impurities, acceptance levels, and qualification based on non-clinical studies.

The olaparib drug product is a 50mg hard capsule manufactured via standard unit operations, including [redacted] of the olaparib drug substance with the single excipient and capsule fill. The specifications of the olaparib drug product include testing for appearance, identity by HPLC and UV, assay, [redacted], degradation products, dissolution, content uniformity and [redacted]. The non-compendial analytical methods were validated. Excluding [redacted] (which was not measured), satisfactory batch analysis and stability results were provided for the three primary stability batches.

Based on the stability results and analysis of clinical capsule [redacted], the recommended expiry for the olaparib drug product is eighteen months under long-term conditions of 25ºC. CMC requested a post-marketing commitment, to which the applicant agreed, to conduct a stability study with the process validation batches (minimum of 3) for ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including [redacted] up to end of expiry.

Per stability data provided for 50 mg olaparib capsules, there were appearance testing reports of thermal failure [redacted] 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] Therefore, the following language was inserted into the PI, carton and container state: [redacted]

3.2 Facilities review/inspection

The Office of Compliance issued an overall acceptable recommendation on November 21, 2014 for all manufacturing and testing facilities that were inspected during the review cycle.

4. Companion *In Vitro* Diagnostic Device

A Premarket Approval application (PMA) for the companion *in vitro* diagnostic assay has been 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 as follows:

INTENDED USE
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 (b) (4) PCR. Results of the test (b) (4) 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

The nonclinical reviewers, Tiffany K. Ricks, Ph.D., and Haw-Jyh Chiu, Ph.D., stated in their review that there were no pharmacology/toxicology issues that preclude the approval of olaparib for the requested indication.

5.1 General nonclinical pharmacology/toxicology considerations

Safety Pharmacology Assessments
The pharmacology/toxicology review contained the following conclusions based on safety pharmacology studies:

- Olaparib had no significant activity (defined as > 50% inhibition) in any of the 220 *in vitro* radioligand binding and enzyme assays when tested at a concentration of 10 μM.
- Olaparib was inactive in all seven of the human recombinant voltage-gated cardiac ion channels.
- Olaparib (10 μM) did not have any significant effects on phosphodiesterase enzyme activity, under the conditions tested.
- Olaparib inhibited the hERG tail current with an IC_{50} of 226 μM, making it a low potency or ineffective blocker.
- No statistically significant changes in cardiovascular or respiratory parameters were noted following a single intravenous administration of 1.5 or 5.0 mg/kg olaparib to anesthetized beagle dogs when compared to vehicle control-treated animals.

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.

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 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/m2 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.

5.2 Carcinogenicity

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

5.3 Reproductive toxicology

The Applicant submitted the results of embryonic fetal development studies that 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.

5.4 Other notable issues

Pharmacology/toxicology reviewers recommended that AstraZeneca adjust the acceptance criteria for impurities for the drug product as follows:
The proposed drug product acceptance criterion for the [redacted] degradant of [redacted]% is not acceptable from a pharmacology/toxicology perspective. This level of [redacted] was not qualified by nonclinical studies or clinical trials. Based on manufacturing capabilities and discussions with the CMC review team, an information request was sent to the Applicant on 10/23/2014 to reduce the proposed drug product acceptance criterion for the degradant [redacted]. AstraZeneca has agreed to lower the criterion to the ICH Q3B qualification threshold of [redacted]%.

6. Clinical Pharmacology/Biopharmaceutics

Overall, the review staff from the Office of Clinical Pharmacology found that the clinical pharmacology data in NDA 206162 were acceptable for approval.

6.1 General clinical pharmacology/biopharmaceutics considerations

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.

6.2 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 recommend that concomitant use of a strong or

moderate CYP3A inducer should be avoided. If a moderate CYP3A inducer must be co-administered, be aware that it may result in reduced efficacy.

6.3 Pathway of elimination

Olaparib is the major moiety in plasma (65% of radioactivity). 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.

6.4 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.

6.5 Demographic interactions/special populations

OCP review staff analyzed the population PK database submitted by AstraZeneca. The population PK model submitted by the Applicant 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. The Applicant did not include data from pediatric patients in this NDA.

6.6 Thorough QT study or other QT assessment

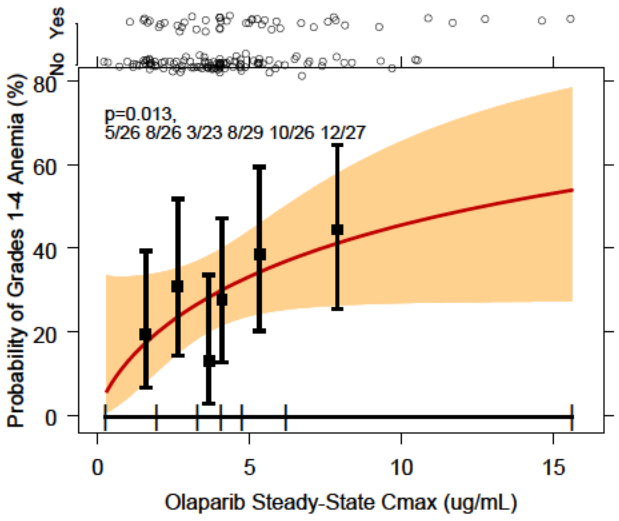
No QT signal was detected in the clinical trials. The sponsor performed QT evaluation in Trials D0816C00004 (food effect trial) and D0816C00007 (CYP3A4 inhibitor trial). The QT/IRT reviewer concluded that no large change (i.e., > 20 msec) in the QTc interval was detected at therapeutic drug exposures. The studies did not include positive control (moxifloxacin) arms.

6.7 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. Figures 5 and 6 below depict the relationship between olaparib steady-state Cmax and

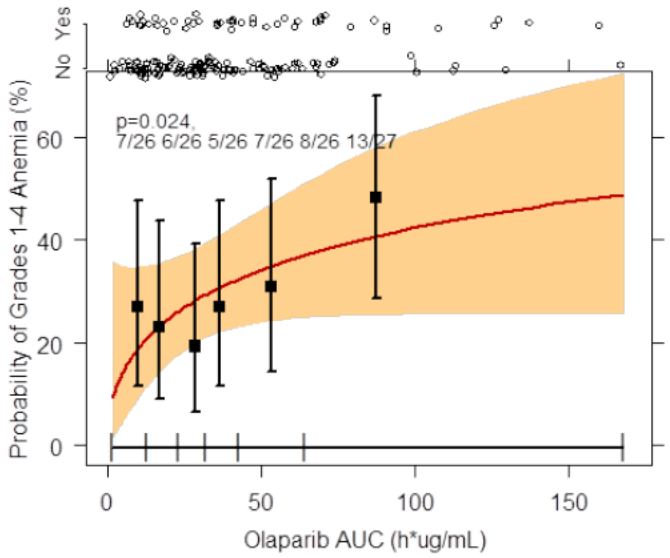
olaparib AUC and the incidence of anemia of all grades. These data, which have been derived from studies 2, 8, 9, and 12, suggest that an increased exposure to olaparib is positively correlated with the incidence of anemia.

Figure 2: Exposure-Response Relationship Olaparib Steady State Cmax vs. Incidence of Anemia



Excerpted from clinical pharmacology review

Figure 3: Exposure-Response Relationship Olaparib AUC vs. Incidence of Anemia



Excerpted from clinical pharmacology review

7. Clinical Microbiology

Not applicable.

8. Clinical/Statistical- Efficacy

Geoffrey Kim, M.D., was the primary clinical reviewer for efficacy for this application, and Gwynn Ison, M.D. was the primary clinical reviewer for safety. Hui Zhang, Ph.D., was the primary statistical reviewer. This NDA is based on the objective response rate and duration of response from the single, open-label, non-randomized trial, Study 42 titled, " A Phase II, Open-Label, Non-Randomized, Non-Comparative, Multicenter Study to Assess the Efficacy And Safety of Olaparib Given Orally Twice Daily in Patients With Advanced Cancers Who Have A Confirmed Genetic *BRCA1* And/Or *BRCA2* Mutation." This study enrolled 301 patients, of whom 137 had *gBRCA*m-associated ovarian cancer and had received three prior lines of chemotherapy. The data from these 137 patients are used for the primary efficacy analysis.

Study Design
From the primary clinical review:

Study 42 was a single-arm, open-label, multicenter study assessing the response rate of olaparib in patients with advanced cancers who have a deleterious *gBRCA* mutation. Initially, up to 150 patients with known *gBRCA*m status were to be recruited; however, after protocol amendments, this number was increased to 300 patients, with the intention that 220 patients with either breast or ovarian cancer would be enrolled with the other patients having prostate, pancreatic, or other tumor types associated with *gBRCA* deficiencies.

Patients were to be treated with olaparib capsules 400 mg twice daily until disease progression or intolerance to study medication. Tumor assessments were performed at baseline and at every 8 week intervals until objective disease progression by RECIST v1.1 criteria or until 6 months had elapsed. After 6 months, if the patient had not progressed, the scan intervals were extended to a 12 week interval.

The primary objective of the study was to assess the efficacy of oral olaparib in patients with advanced cancer who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation by assessment of tumor response. RECIST 1.1 criteria was used to assess patient response to treatment.

Other objectives were to assess the efficacy of oral olaparib in patients with advanced cancers who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation, by assessment of objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR) and disease control rate (DCR).

Changes in Study Conduct
From the primary clinical review:

There were three amendments made to the Study 42 protocol. Amendment 1 was made on March 31, 2010, and consisted of minor changes to patient eligibility and study conduct. Amendment 2 was made on August 26, 1010, and was performed to increase the amount of patients included in the study and to include an additional blood sample collection to enable confirmation of *gBRCA*m status by a central laboratory. Amendment 3 was made on August 8, 2011, and was performed to extend the final data cutoff by six months to allow for longer

safety follow up and to update recommendations for the management of hematological toxicities, including specific recommendations for the diagnosis of suspected MDS/AML.

Protocol Deviations

The table below summarizes the major protocol deviations in Study 42. A total of 15 patients had major protocol deviations defined in the study protocol.

Table 2: Major Protocol Deviations in Study 42

	N=137 (%)
Deviation from inclusion criteria	6 (4.4)
Received prohibited medication	5 (3.6)
RECIST performed more than 28 days	3 (2.2)
Medication stopped when AE worsened	1 (0.7)

Patient Disposition

The tables below from the primary clinical review provide information on patient disposition and reasons for treatment discontinuation in Study 42. Overall, there were 317 patients enrolled in six countries, and a total of 298 patients received treatment. Of the 193 patients with ovarian cancer on this trial, 137 had measurable disease and had received at least three prior lines of chemotherapy. The reason for treatment discontinuation of these 137 patients is detailed in the table below, as is the patient disposition at time of study discontinuation in the second table below.

Table 3: Reason for Treatment Discontinuation

	N = 137 (%)
Ongoing treatment	15 (11)
Adverse event	9 (7)
Development of study specific discontinuation criteria	69 (50)
Other	3 (2)
Severe non-compliance to protocol	2 (1)
Subject decision	8 (6)
Subjective disease progression	31 (23)

Table 4: Reason for Study Discontinuation

	N = 137 (%)
Ongoing Study	15 (11)
Death	81 (59)
Eligibility criteria not fulfilled	1 (1)
Subject decision	7 (5)

Patient Demographics and Disease Characteristics

The median age of the patients was 58 years, the majority were Caucasian (94%) and 93% had an ECOG PS of 0 or 1. Deleterious or suspected deleterious, germline *BRCA* mutation status was verified retrospectively in 97% (59/61) of the patients for whom blood samples were available by the companion diagnostic BRACAnalysis CDx™.

Efficacy Results

The table below displays the results of the primary endpoint in Study 42, which was tumor response. The table also shows the duration of response. The results show an ORR of 34% in this heavily pretreated population. Furthermore, the responses were durable, with the median duration at 7.9 months. As Trial 42 was designed as a single-arm study, all statistical analyses were descriptive, and no formal statistical comparisons were performed.

Table 5: 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.
Excerpted from primary clinical review

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 6: 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)**

Excerpted from the primary clinical review

Sensitivity Analyses

As there was no formal statistical testing in Study 42, no sensitivity analyses were performed.

Subgroup Analyses

As all patients in Study 42 were female and most of them (94%) were white, subgroup analyses of ORR by gender and race were not performed. Results for subgroup analyses for age and region are shown below. However, given the single-arm design of this trial and the small patient numbers, these subgroup analyses must be interpreted with caution.

Table 7: Subgroup Analyses in Study 42

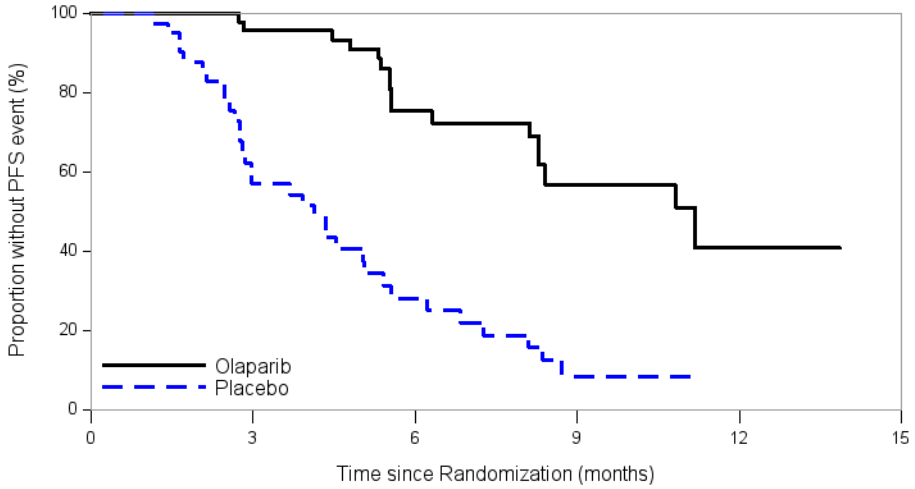
	N=137 (%)
Age	
< 50	5/26 (19.2%)
≥ 50 to < 65	32/83 (38.6%)
≥ 65	9/28 (32.1%)
Region	
US	14/40 (35.0%)
Non-US	32/97 (33.0%)

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 8: 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 4: 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, the safety profile was relatively benign, with Grade 1-2 nausea and fatigue as the most common adverse reactions.

This trial was discussed at a meeting of the Oncologic Drugs Advisory Committee (ODAC) on June 25, 2014, at which ODAC voted against recommending approval by a vote of 11-2. See the primary clincial review for the appended FDA briefing document to ODAC for more detailed analysis of this trial and Section 10 of this review for more details on the ODAC discussion.

9. Safety

9.1 Safety Database

The clinical reviewer analyzed data from a total of 2034 patients with ovarian, breast, pancreatic, gastric, and other solid tumors who received treatment with olaparib across the dose range of 10 mg daily up to 600 mg twice daily, as of May 20, 2013. Olaparib has been given as monotherapy to 1162 patients (15 studies), and in combination regimens to 872 patients (23 studies). However, she conducted the primary analysis of safety using pooled data from multiple studies in 223 patients with *gBRCA*m, advanced ovarian cancer who had received at least three prior lines of chemotherapy. Note that this number of patients is slightly higher than the pooled efficacy analysis described above in Table 6 above, as those patients had to have measurable disease as well. Supportive data from the randomized Study 19 provided context for the adverse reactions versus a control population given the primary safety analysis was conducted in a population without a concurrent control.

9.2 Safety Overview

In general, there were few Grade 3-4 adverse reactions associated with olaparib. The vast majority of adverse reactions was Grade 1-2 in severity and manifested as gastrointestinal disorders, fatigue/asthenia, anemia, infections and musculoskeletal disorders. Adverse events of special interest include myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

9.3 Deaths, discontinuations due to AEs, general AEs, and results of laboratory tests

Deaths

In the 223 patients with *gBRCA*m, advanced ovarian cancer who received three or more prior lines of chemotherapy, there were eight patients with an adverse reaction that led to death. Two of these deaths were attributed to acute leukemia, and one each was attributed to COPD, cerebrovascular accident, intestinal perforation, pulmonary embolism, sepsis, and suture rupture. The primary reviewer concluded that the AML and septic deaths may have been related to olaparib, but the other deaths likely were unrelated to olaparib.

In Study 19, there was one death in an olaparib-treated patient due to an adverse reaction. This patient had thrombocytopenia that worsened to Grade 4 and simultaneously had 16% circulating blasts noted on a peripheral smear. She suffered a hemorrhagic stroke and died. This patient may have had an underlying, undiagnosed AML, and certainly the thrombocytopenia contributed to her cause of death, thus her death likely was related to olaparib.

Discontinuations

Standardized MedDRA Query was used to characterize adverse events in the clinical trials submitted in this NDA. Adverse event grading was done according to the NCI Common Terminology Criteria for Adverse Events (CTCAE).

In the pooled analysis of 223 patients, the median exposure to olaparib was 158 days. Adverse reactions led to dose interruption in 40% of patients, dose reduction in 4%, and discontinuation in 7%. Discontinuations due to adverse events are summarized in the table below.

Table 9: Discontinuations due to adverse reactions in pooled analysis

Adverse Event	**Olaparib n=15**
Anemia/ thrombocytopenia	2
Neutropenia	1
Intestinal obstruction/ ileus	4
Nausea/ vomiting	4
Intestinal perforation	1
Abdominal pain	1
Liver enzyme elevation	1
Cerebrovascular accident	1

From the primary clinical review

In Study 19, adverse reactions led to dose interruptions in 26% of those receiving olaparib and 7% of those receiving placebo; dose reductions in 15% of olaparib and 5% of placebo patients; and discontinuation in 9% of olaparib and no placebo patients.

Grade 1-4 Adverse Events

The table below provides information on common adverse events which occurred in at least 20% of the 223 patients in the pooled analysis.

Table 10: Adverse Reactions in ≥20% of patients with *gBRCA*m advanced ovarian cancer

	3 or more lines of prior chemotherapy	
Adverse Reaction	**Grades 1-4 N=223 %**	**Grades 3-4 N=223 %**
Blood and Lymphatic disorders		
Anemia	34	18
Gastrointestinal disorders		
Abdominal pain/discomfort	43	8
Decrease appetite	22	1
Nausea	64	3

Vomiting	43	4
Diarrhea	31	1
Dyspepsia	25	0
General disorders		
Fatigue/asthenia	66	8
Infections and infestations		
Nasopharyngitis/URI	26	0
Musculoskeletal and Connective Tissue disorders		
Arthralgia/musculoskeletal pain	21	0
Myalgia	22	0

The adverse event profile was similar in the randomized Study 19, as seen in the table below.

Table 11: Adverse Reactions Reported in ≥20% of Patients with *gBRCA*-Mutated Ovarian Cancer in Study 19

Adverse Reactions	**Lynparza N=53**		**Placebo N=43**	
	Grades 1-4 %	**Grades 3-4 %**	**Grades 1-4 %**	**Grades 3-4 %**
Blood and Lymphatic disorders				
Anemia	25	4	7	2
Gastrointestinal disorders				
Abdominal pain/discomfort	47	0	58	2
Decreased appetite	25	0	14	0
Nausea	75	2	37	0
Vomiting	32	4	9	0
Diarrhea	28	4	21	2
Dyspepsia	25	0	14	0
Dysgeusia	21	0	9	0
General disorders				
Fatigue (including asthenia, lethargy)	68	6	53	2
Infections and infestations				
Nasopharyngitis/Pharyngitis/URI	43	0	16	0
Musculoskeletal and Connective tissue disorders				
Arthralgia/Musculoskeletal pain	32	4	21	0
Myalgia	25	2	12	0
Back pain	25	6	21	0
Nervous system disorder				
Headache	25	0	19	2
Respiratory, Thoracic, Mediastinal disorders				
Cough	21	0	14	0
Skin and Subcutaneous Tissue				
Dermatitis/Rash	25	0	14	0

Laboratory Tests
The most common laboratory abnormalities in the olaparib safety database are a decrease in hemoglobin and mean corpuscular volume (MCV) elevation, followed by neutropenia, thrombocytopenia and increased creatinine. The increased MCV may be a precursor to dysplasia and eventual development of MDS and/or AML. Recommended monitoring in the label is for monthly blood counts; if hematologic toxicity occurs, weekly counts are warranted. If counts do not recover within four weeks, bone marrow analysis and referral to a hematologist is recommended.

9.4 Special safety concerns

MDS/AML
AstraZeneca estimates that 2,618 patients have been treated with olaparib to date. There have been 22 total cases of MDS and/or AML identified by the primary clinical reviewer among these patients (0.8%). Of these 22 patients, 17 have died, with 12 deaths due to MDS/AML as the primary or secondary cause. Patients were receiving olaparib for ovarian/primary peritoneal/fallopian tube cancer (n=18), pancreatic cancer (n=2), or breast cancer (n=2). BRCA mutation status was wild type in two patients (ovarian cancer, primary peritoneal), unknown in three patients (ovarian cancer, ovarian cancer, pancreatic cancer) and mutated in the remaining 17 patients. Among these 22 cases, nine either presented with or progressed to AML.

The reported incidence of MDS/AML appears to be higher in the cancer population in this application. MDS/AML was confirmed in six of 298 (2%) patients with *gBRCA*m, advanced cancer in Study 42 and in three of 136 (2.2%) patients with ovarian cancer in Study 19.

There is concern that the incidence of MDS/AML may be underreported. Currently, the applicant relies on treating physicians to report the incidence of MDS/AML in those patients who have been treated with olaparib. It is conceivable that patients who were treated with olaparib at a clinical trial site can have a late development of MDS/AML while under the care of their local physician, who would not think of reporting the event back to the sponsor. Therefore, the incidence of MDS/AML associated with olaparib therapy cannot be precisely estimated. The rate of MDS in the general population according to data captured in the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) program is approximately 3.3 per 100,000; however, these data are thought to underestimate the true incidence of MDS due to underreporting to such databases (Cogle CR, 2011). The risk of MDS/AML after platinum-based chemotherapy for ovarian cancer was assessed in a case-control study in 28,971 women in North America and Europe. This study found 96 cases of MDS/leukemia (0.3%) and further noted that there was a cumulative dose-response relationship between platinum-based treatment and risk of MDS/leukemia (Travis LB, 1999).

The reported incidence in the olaparib database, and particularly in the ovarian cancer population, is higher than the expected incidence in a general population or in an ovarian cancer population treated with platinum-based therapy. Therefore, MDS/AML is the first Warning in the label, with specific instructions for hematological monitoring and early referral to a hematologist for a bone marrow analysis in case of prolonged hematologic toxicity.

Furthermore, there is a post-marketing requirement that AstraZeneca submit annual reports to FDA to collect and analyze all cases identified up until that reporting date (new cases and those reported in previous years on clinical trials and outside of clinical trials (including spontaneous safety reports).

9.5 Discussion of primary reviewer's comments and conclusions

The primary reviewer considered the safety profile of olaparib to be acceptable for the indicated population based on the overall adverse reaction profile for olaparib, which was mild in nature, 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; however, the risk of MDS/AML must be weighed against the ORR of 34%.

9.6 Differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed

There were no major differences between the CDTL and review team regarding this section of the review.

9.7 Discussion of notable safety issues (resolved or outstanding)

The major unresolved safety issue involves estimating the rate of MDS/AML in the *gBRCA*m ovarian cancer patient population. A rate of approximately 2% was observed in two small trials, thus there is a PMR for the applicant to submit annual reports for five years detailing all existing and new cases of MDS/AML identified through all means available to a pharmacovigilance team, as well as related data such as cytogenetics, *gBRCA* status (mutated or wild type) and outcome.

10. Advisory Committee Meeting

The Oncologic Drugs Advisory Committee (ODAC) met June 25, 2014, to discuss NDA 206162. The ODAC was presented data and discussion for the indication in the platinum-sensitive maintenance setting, which was supported primarily by Study 19. The key issues raised by the FDA review team 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 the reproducibility of results in a larger trial with a pre-planned analysis for this *gBRCA*m subgroup.

The first question posed to the Committee was the following:

- Do the safety and efficacy results from Study 19 in the *gBRCA*m population support an accelerated approval, or should marketing approval consideration be delayed until the results from SOLO-2 are available?

There were 11 No votes as compared to 2 Yes votes. As justification for voting against approval for olaparib at this time, committee members cited the lack of an overall survival benefit for maintenance therapy; the unreliability of the results due to loss of randomization and small sample size; the toxicity of therapy and risk of MDS/AML for patients not otherwise undergoing treatment; and the potential to hinder accrual to confirmatory study. Please see the primary clinical review for further details and for the appended FDA briefing document.

11. Pediatrics

Olaparib has been granted a full waiver for this indication.

12. Other Relevant Regulatory Issues

12.1 Application Integrity Policy (AIP)

Based on the review of the CRFs by the clinical reviewers and OSI audits, the primary data submitted to this application were found to be reliable for the primary analyses of safety and efficacy. The submission contains all required components of the eCTD. The overall quality and integrity of the application appear reasonable.

12.2 Financial disclosures

Disclosure of financial interests of the investigators who conducted the clinical trials, including statements of due diligence in cases where the applicant was unable to obtain a signed form from the investigator, was submitted in the FDA form 3454. These disclosures were certified by Darci Bertelsen, Director of Regulatory Affairs, AstraZeneca. Disclosures of financial interests were submitted for three sub-investigators, none of which were deemed to have the potential to affect the outcome of the trial.

12.3 GCP issues

The clinical study protocols for Studies 2, 9, 12, 19, 20, 24, and 42 were submitted to Independent Ethics Committees (IEC) and/or Institutional Review Boards (IRB) for review. Written approvals were required prior to initiation of the study.

The applicant provided statements that the aforementioned studies were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization/Good Clinical Practice and applicable regulatory requirements. The PI at each center ensured that the patient was given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients were also notified that they were free to discontinue from the study at any time. Patients were given the opportunity to ask questions and allowed time to consider the information provided. Informed consent was obtained from all subjects prior to the conduct of any study-related procedures.

12.4 OSI audits

The Office of Scientific Investigations chose four clinical sites from Study 19 for inspection in consultation with the clinical review division based on enrollment of large numbers of study subjects and insufficient domestic site data: Site 1801 and 1802 (Dr. Ursula Matulonis,

Massachusetts General Hospital and Dana Farber Cancer Inst, respectively, Boston, Massachusetts), Site 1703 (Dr. Charlie Gourley, Edinburgh, UK), and Site 701 (Dr. Phillip Harter, Wiesbaden, Germany). All sites received interim of final classifications of No Action Indicated, and Site 1802 received the interim classification of Voluntary Action Indicated.

After the major amendment for this NDA was submitted, Study 19 no longer was the primary source of data supporting the efficacy and safety claims for olaparib. However, the decision was made to not pursue additional clinical site inspections as there were no major conduct deficiencies at the inspected clinical sites noted above, and it is reasonable to assume that the study site conduct would not be drastically different for the other studies whose data are used to support the revised indication. In addition, a large portion of data in support of the revised indication was generated at sites in Israel. At the time of the submission of the major amendment, the State Department issued a travel warning to U.S. citizens recommending the deferral of non-essential travel to Israel.

12.5 Other discipline consults

Not applicable.

12.6 Other outstanding regulatory issues

Not Applicable.

13. Labeling

13.1 Proprietary name

The proposed proprietary name for olaparib injection is Lynparza. DMEPA notified DOP1 that the name Lynparza was acceptable from a look-alike and sound-alike perspective. Additionally, no objections to the name Lynparza were identified by DDMAC or the clinical review team during the review cycle. The proprietary name was granted in a letter to AstraZeneca dated July 31, 2014.

13.2 Labeling issues raised by OPDP

The reviewer from OPDP raised concerns regarding the companion diagnostic and whether the word “companion” and the actual name of the diagnostic BRACAnalysis CDx™ should be used in the label. The clinical team did not agree with the OPDP recommendation, as the *in vitro* diagnostic will be used to select patients who may benefit from olaparib therapy after approval.

13.3 Physician labeling

In general, all sections of the label were revised for brevity and clarity. Command language was preferred as directed by the PLR. The remainder of this section of the review will only focus on high-level issues regarding the label submitted by AstraZeneca. Numbering below is consistent with the applicable sections in product labeling. This review will not comment on all sections (for example, if only minor edits were made to a section). This CDTL agreed with the recommendations made by the review teams that are described below.

Labeling changes made in agreement with the applicant in the course of the review include the following:

- Language regarding accelerated approval was added to the indication.
- Under Warnings and Precautions (5.1), MDS/AML was moved up to the first warning. (b) (4) with recommendations for hematological monitoring folded into 5.1 under MDS/AML.
- Under Storage (16.2), the following statement was added: Lynparza should not be exposed to temperatures greater than 40ºC or 104ºF. Do not take Lynparza if it is suspected of having been exposed to temperatures greater than 40ºC or 104ºF.

13.4 Carton and immediate container labels

FDA communicated requested revisions to the Lynparza carton and container labels regarding storage conditions, specifically temperature ranges, given that there were reports of the capsule melting (b) (4) Final language stated: "Do not expose to temperatures greater than 40ºC or 104ºF."

13.5 Patient labeling/Medication guide

The PPI was revised for clarity, brevity, and understandability in conjunction with DRISK and DDMAC recommendations.

14. Recommendations/Risk Benefit Assessment

14.1 Recommended regulatory action

The recommendation of this Cross Discipline Team Leader is for approval of NDA 206162. All review teams recommended approval or reported that there were no findings that would prevent approval. DMEPA determined that the proposed proprietary name of Lynparza was acceptable.

14.2 Risk-benefit assessment

The recommendation for approval is based on the primary efficacy analysis from a single-arm trial, Study 42. This trial demonstrated 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.

The safety profile of olaparib in general is mild, with most adverse events recorded as 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, thus it appears that the safety profile can be managed in most patients. The MDS/AML signal is concerning. However, it is unclear what the true rate of MDS/AML is 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. Additionally, a post-marketing requirement for annual reports of all cases of MDS/AML from the applicant may help elucidate the true rate of MDS/AML in patients exposed to olaparib.

Overall, olaparib demonstrated an impressive ORR in a heavily pre-treated population. Ovarian cancer typically is defined by platinum sensitivity, but given that platinum sensitivity declines with each course and toxicities accumulate, olaparib provides a reasonable option for fourth-line treatment regardless of platinum sensitivity. Although the Agency has most frequently employed 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. Furthermore, as this is an accelerated approval, AstraZeneca will conduct two additional clinical trials to confirm the clinical benefit for olaparib. The first, SOLO-2, is a randomized, placebo-controlled trial being conducted in patients with *gBRCA*m-associated ovarian cancer who are in response to second-line platinum-based chemotherapy. SOLO-2 is fully enrolled, and results are expected in the first quarter of 2016. The second trial is a randomized trial of olaparib versus physician's choice single-agent chemotherapy in the treatment of platinum sensitive, relapsed ovarian cancer in patients with *gBRCA* mutations. Results from this trial are expected in 2018. Based on all of the above reasoning, I recommend approval of this application.

14.3 Recommendation for post-marketing Risk Evaluation and Management Strategies

Olaparib is indicated for the treatment of patients with life-threatening cancer. As such, additional post-market risk management activities are not necessary at this time (other than those required for all NDAs such as those described in 21 CFR 314.81). The proposed USPI contains patient counseling information for trained prescribing physicians.

14.4 Recommendation for other Post-marketing Requirements and Commitments

2824-1 Submit the progression-free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial D0818C00002, SOLO-2, the ongoing randomized double-blind, placebo-controlled, multi-center trial to assess the efficacy of olaparib maintenance monotherapy in relapsed high grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer with BRCA mutations (documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)) who have responded following platinum-based chemotherapy.

PMR Schedule Milestones	Interim report (PFS analysis)	02/2016
	Trial Completion date	12/2018
	Final report Submission (OS analysis)	03/2019

2824-2 Submit the progression-free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial D0816C00010, a randomized trial establishing the superiority of

olaparib over physician's choice single-agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying deleterious or suspected deleterious germline BRCA1/2 mutations.

PMR Schedule Milestones	Interim report (PFS analysis)	06/2018
	Trial Completion date	03/2020
	Final report submission (OS analysis)	06/2020

2824-3 Collect and analyze all cases of acute myelogenous leukemia/ myelodysplastic syndrome identified in patients treated with Lynparza (olaparib) on an annual basis. These interim reports should summarize all cases identified up until that reporting date (new cases and those reported in previous years), and should include patients treated with Lynparza on clinical trials and outside of clinical trials (including spontaneous safety reports) to provide an accurate assessment of the long-term incidence and risk of AML/MDS.

PMR Schedule Milestones	Interim Report #1	12/2015
	Interim Report #2	12/2016
	Interim Report #3	12/2017
	Interim Report #4	12/2018
	Interim Report #5	12/2019
	Final Report Submission	06/2020

2824-4 Submit the final report for trial D0816C00006 entitled, "An Open-label, Non-randomized, Multicenter, Comparative, and Phase 1 Study of the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Renal Function or Renal Impairment".

PMR Schedule Milestones	Interim report (planned primary PK analysis)	09/2015
	Trial completion	08/2016
	Final Report Submission	11/2016

2824-5 Submit the final report for trial D0816C00005 entitled, "An Open-label, Non-randomized, Multicenter, Comparative, Phase 1 Study to Determine the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Hepatic Function or Mild or Moderate Hepatic Impairment."

PMR Schedule Milestones	Interim report (planned primary PK analysis)	09/2015
	Trial Completion date	08/2016
	Final Report Submission	11/2016

2824-6 Conduct a stability study with the process validation batches (minimum of 3): ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to end of expiry.

PMC Schedule Milestones	First Interim Report (includes 6 months of data)	11/2015
	Second Interim Report (includes 12 months of data)	05/2016
	Study Completion	02/2017
	Final Report Submission	04/2017

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY E MCKEE
12/10/2014