FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

June 25, 2014

NDA 206162
Olaparib (Lynparza®)
AstraZeneca

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the Olaparib NDA with the Applicant's proposed indication "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" to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Executive Summary

Olaparib is an oral inhibitor of polyadenosine 5'-diphosphoribose polymerases (PARP). The applicant is seeking initial approval of this drug for the indication of 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. The efficacy of olaparib for this indication is based on the subgroup analysis of the single efficacy study D0810C00019 (Study 19) in 96 patients with deleterious germline BRCA mutation (gBRCAm)-associated, platinum-sensitive ovarian cancer. Study 19 was a multinational, randomized, double-blind, placebo-controlled trial of 265 patients with platinum-sensitive ovarian cancer who were in response to platinum-based chemotherapy. Patients were randomized 1:1 to receive either olaparib or placebo. Randomization was stratified by the time to disease progression from the completion of the penultimate platinum therapy (6-12 months vs. > 12 months), objective response to the last platinum containing regimen prior to enrollment on study (CR vs. PR), and the ethnic descent of the patient (Jewish vs. Non Jewish). The primary efficacy analysis of Study 19 was investigator-determined progression-free survival (PFS).

In a pre-specified analysis of a retrospectively identified subgroup of 96 patients with gBRCAm associated-ovarian cancer, there was an improvement (hazard ratio (HR) 0.17) in PFS for patients randomized to olaparib treatment, with median PFS of 11.2 months in the olaparib arm and 4.1 months in the placebo arm. No alpha adjustments were made for multiplicity introduced by analyzing multiple endpoints (excluding overall survival), or analyses within the BRCA subgroups. At the time of the latest interim analysis of overall survival (OS), there was no significant difference between the two arms (HR 0.85).

The safety profile of olaparib revealed that while Grade 1-2 adverse events were frequent, Grade 3-4 adverse events were rare, and deaths from treatment-emergent adverse events (TEAEs) also were rare. Common adverse events include nausea, fatigue, abdominal pain, vomiting, diarrhea and anemia. Patients treated with olaparib had higher rates of gastrointestinal events, anemia, neutropenia, fatigue, asthenia, infections and respiratory disorders than patients treated with placebo.

The Division of Oncology Products 1 seeks the advice of the Oncologic Drugs Advisory Committee regarding the pending NDA for olaparib on the following points:

1. Do the efficacy results from Study 19, namely a seven-month improvement in median progression-free survival and a hazard ratio of 0.17, along with the safety data in the gBRCAm population, demonstrate a favorable risk-benefit profile of olaparib maintenance monotherapy in gBRCAm-associated, platinum-sensitive, relapsed high-grade serous ovarian cancer that is in response to platinum-based chemotherapy?

2. The potential confirmatory trial is designed to detect a statistically significant but potentially clinically insignificant improvement in PFS. What is the appropriate

magnitude of treatment effect for median improvement and hazard ratio to be demonstrated in the SOLO-2 trial to consider olaparib to be of direct clinical benefit to this patient population?

Background

Ovarian Cancer
Ovarian cancer is the fifth leading cause of cancer mortality in women with an estimated 22,000 new cases diagnosed and 14,270 deaths from the disease in the US in 2014 (Siegel R, 2014). Standard therapy for advanced ovarian cancer consists of surgical debulking and a chemotherapy regimen consisting of a platinum agent and a taxane (Stuart G, 2011, Armstrong D, 2006, Katsumata N, 2009). Therapy for relapsed disease 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 greater than six months from the date of the last dose of platinum-based chemotherapy (Thigpen J, 1994). Therapy for platinum-sensitive disease typically consists of platinum-based chemotherapy, and a platinum doublet regimen is associated with an improvement in overall survival when compared to single agent platinum (Collaborators, 2003). The time interval between the date of the last platinum-based treatment and progression is positively correlated with the probability of responding to further platinum therapy, as those patients who have a longer platinum-free interval will have a higher response rate to further platinum treatment (Pujade-Lauraine E, 2002). Non-platinum regimens typically are not used in the platinum-sensitive setting due to the overall survival advantage seen with platinum doublets; however, intolerance to platinum agents is a clinical concern, as the risk of cumulative toxicities, particularly carboplatin allergy or neuropathy, increases over the course of continued treatments.

Several chemotherapeutic and biologic agents have been studied as maintenance therapy; however, there are currently no approved agents for the maintenance treatment in platinum-sensitive, relapsed ovarian cancer. Chemotherapeutic agents such as doxorubicin, topotecan and platinum agents are associated with increased toxicity without definitive efficacy (Pfisterer, 2006, De Placido, 2004, Bolis, 2006). A GOG study of 12 cycles of paclitaxel vs. 3 cycles of paclitaxel was associated with a seven-month improvement in PFS in the front-line maintenance setting; however, an additional study of a lower dose of paclitaxel did not replicate these findings, and paclitaxel as maintenance therapy was not widely adopted (Markman, 2003, Pecorelli, 2009). Maintenance treatment with agents targeted against VEGF and VEGFR are associated with improvements in PFS without demonstration of a survival benefit (Burger, 2011, Perren, 2011, Aghajanian, 2012, Du Bois, 2013).

BRCA
The BRCA genes, BRCA1 and BRCA2, encode proteins involved in the DNA damage repair pathway. Deleterious mutations of BRCA1 and BRCA2 are associated with an increased risk of the development of breast and ovarian cancers; however, not all mutations are considered to be

deleterious (Mik Yi, 1994, Wooster R, 1995). 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 (gBRCAm)-associated ovarian cancer is approximately 10-15% of all cases of ovarian cancer, corresponding to an annual incidence of approximately 2000 cases per year in the U.S. (Pal, 2005, Zhang, 2011).

Patients with gBRCAm-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 (Chetrit, 2008, Alsop, 2012 Bolton, 2012). Due to the increased susceptibility to chemotherapy, it is expected that the patient with gBRCAm-associated ovarian cancer will be exposed to multiple lines of various chemotherapeutic agents. Therefore, treatment-free intervals are of utmost importance to this patient population, as they allow adequate recovery from cumulative adverse reactions in preparation for the inevitable additional treatment regimen. Maintenance of a high quality of life is critical.

Approved Therapies

There are no FDA-approved therapies for the maintenance treatment of gBRCAm-associated, platinum-sensitive ovarian cancer. FDA-approved therapies for the treatment of advanced ovarian cancer include, but are not limited, to:

- Carboplatin
- Paclitaxel
- Gemcitabine
- Pegylated Liposomal Doxorubicin
- Topotecan

In 2006, a joint FDA/ASCO/AACR public workshop was held to discuss clinical trial endpoints in ovarian cancer. Overall survival was considered to be the most significant endpoint in trials of drugs for maintenance therapy, as such treatment entails additional toxicity. An improvement in PFS also was considered to be acceptable if the treatment produces “relatively few major toxicities” (Bast, 2007). Using PFS as an endpoint in trials evaluating maintenance therapy has some pitfalls, as it is difficult to recognize the magnitude of effect needed in terms of both hazard ratio and median estimates to demonstrate direct clinical benefit to the patient. In addition, the increase in the progression-free interval may not translate into the delay in the onset of symptoms, as radiographic progression most often precedes symptomatic progression of disease. There is also the concern whether the maintenance therapy will attenuate the anti-tumor activity of subsequent treatments.

Recently, a SGO/OCNA “Endpoints in clinical trials: What do our patients consider important?” survey was conducted in which patients with ovarian cancer were asked about the “minimally acceptable” difference of the median variables of PFS and OS they would accept for a new treatment. Patients were given the option of 1, 2, 3, 4 or 5+ months. The majority (>70%) desired a 5 or more month increase of either median PFS or OS, which was the largest increase that the patient could input. The true desired effect may be much larger (Herzog, 2014). The survey

results were somewhat surprising, as it was previously assumed that patients would desire an improvement in these metrics of 3-4 months. It is important to note that the survey questions did not specifically address maintenance treatment, but the results shed light on the type of magnitude of effect the surveyed patients with ovarian cancer deem acceptable for new treatments.

Major Regulatory Milestones for Olaparib Development
The major regulatory milestones for olaparib development in gBRCAm-associated ovarian cancer are depicted in Table 1 below.

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 gBRCAm associated ovarian cancer. FDA considered the gBRCAm 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	

Design of the Major Efficacy Trial (Study 19)

Study 19 is a randomized (1:1), double-blind, multicenter, placebo-controlled study 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 olaparib treatment or matching placebo.

Key Inclusion Criteria

- Patients with relapsed serous ovarian, primary peritoneal or fallopian tube cancer.
- Patients must have completed at least 2 prior courses of a platinum containing regimen.
- Patients must have disease progression greater than 6 months after the completion of their penultimate platinum regimen.
- Patients must be in partial or complete response to their last platinum regimen and patients must be treated on the study within 8 weeks of the completion of their final dose of the platinum containing regimen.
- Patients must have adequate organ function as defined by:
    - Hemoglobin ≥ 9.0 g/dL
    - Absolute neutrophil count ≥ 1.5 x 10^9/L
    - Platelet count ≥ 100 x 10^9/L
    - Total bilirubin ≤ 1.5 x institutional upper limit of normal
    - AST/ALT ≤ 2.5 x institutional upper limit of normal
    - Serum creatinine ≤ 1.5 x institutional upper limit of normal
- Patients must have an ECOG performance status ≤ 2

Key Exclusion Criteria

- Patients with low grade ovarian cancer (Grade 1)
- Patients who have had drainage of their ascites during the final 2 cycles of their last chemotherapy regimen prior to enrolment on the study.
- Persistent Grade 2 or greater toxicities caused by previous cancer therapy.
- Patients requiring treatment with potent inhibitors or inducers of CYP3A4.

Randomization

Patients were randomized 1:1 to receive olaparib treatment or matching placebo. Randomization was stratified by the time to disease progression from the completion of the penultimate platinum therapy (6-12 months vs. > 12 months), objective response to the last platinum containing regimen prior to enrollment on study (CR vs. PR), and the ethnic descent of the patient (Jewish vs. Non Jewish).

Treatment

Arm 1	olaparib 400 mg BID
Arm 2	matching placebo BID

Patients were treated until objective disease progression according to RECIST 1.0 criteria or until the patient withdrew consent. If a patient demonstrated CA-125 progression determined by a two-fold increase from the baseline CA-125 on two occasions, 7 or more days apart, a patient may have an unscheduled tumor assessment to determine progression by RECIST criteria. If progression was not demonstrated, patients would continue treatment until the next radiological assessment. If scans were performed outside of scheduled visit ± 1 week window interval and the

patient had not progressed, subsequent scans were to have been performed at their scheduled time points.

Assessments
All baseline tumor assessments using CT or MRI of the abdomen and pelvis were to be performed no more than 28 days before the start of study treatment and ideally should have been performed as close as possible to the start of study of treatment. Follow-up assessments were to be performed every 12 weeks +/-1 week after start of treatment until week 60 and every 24 weeks +/-1 week thereafter.

Safety Evaluation
The Phase 2 trial D0810C00019 (Study 19) included safety assessments at baseline, every week in the first two cycles, on day 1 ± three days of every subsequent 28-day cycle, at the end of treatment and at a follow-up visit (30 days after the last dose). All adverse events that had not recovered completely by the end of treatment were to be followed until resolution.

At baseline, safety assessments included medical, oncologic, and surgical history, vital signs, physical examination, laboratories (hematology, chemistries, liver enzymes and function, urinalysis, pregnancy test), assessment of ECOG PS and ECG. Safety assessments performed at the start of each cycle were the same as at baseline, except pregnancy tests were not required after baseline. Post-treatment follow-up for survival was to occur every 8 weeks until at least the time of the final PFS analysis.

AEs were coded by body system using a medical dictionary for regulatory authorities (MedDRA®) and were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) scale, Version 3.0.

Study Efficacy Endpoints
The primary efficacy endpoint was PFS per RECIST criteria as assessed by the investigator. Secondary endpoints included best overall response, CA-125 response (GCIG criteria), overall survival, disease related symptoms as measured by FOSI and health-related quality of life measured by the FACT-O scale.

Statistical Methods
The primary analysis for PFS was a Cox proportional hazards model with factors for time to progression (6-12 months and >12 months) after the penultimate platinum therapy before study enrolment), objective response (CR or PR, after the last platinum therapy before enrolment on the study) and Jewish decent (yes or no) in accordance with the stratification factors used at randomization. The effect of treatment was to be estimated by the adjusted HR together with its corresponding 80% and 95% confidence intervals (CIs). Kaplan-Meier plots of PFS were presented by treatment group.

The existence of any treatment-by-covariate interactions was to be investigated and the assumption of proportionality was to be assessed. The primary analysis used data

programmatically derived from the objective RECIST assessments. An exploratory analysis using the FAS that includes BRCA status in the COX model was to be performed.

No adjustments were made for multiplicity introduced by analyzing multiple endpoints (excluding OS), or analyses within the *BRCA* subgroups.

Amendments to the Statistical Analysis Plan
The primary efficacy analyses of this study were based on the ITT population. A subgroup analysis of efficacy by g*BRCA* status was performed in order to investigate the efficacy and safety of olaparib in this subgroup. This analysis was not defined in the Clinical Study Protocol (CSP) but was prospectively defined in the SAP (May 28, 2011) that was finalized prior to unblinding of the data for analysis. A summary of key changes are summarized in Table 2 below.

Table 2: Key Changes to the Analysis Plan

Analysis Change	Summary of Changes
Original Clinical Study Protocol (CSP) June 2, 2008	Co-primary population of Homologous Recombination Deficient (HRD) subset was referred to in the statistical methodology portion.
CSP Amendment 3 June 2, 2009	Analysis of PFS in the HRD population was removed as a co-primary objective
Pre-specification of BRCA subpopulation June 3, 2010	SAP amended to include a subgroup analysis by BRCA status. SAP signed off prior to unblinding of the data for the primary analysis.
Data cut off for primary PFS analysis June 30, 2010	Data were unblinded following data cut off, but investigators were not unblinded. Preliminary suggestion of differential improvement of PFS in the BRCA subpopulation (known BRCA mutation status was 37% at this time)
Analyses of blood and tumor samples for BRCA mutation status. All of 2012	All available blood samples were tested for *BRCA* status (g*BRCA*) by the Myriad laboratory developed test and PFS and OS were reanalyzed on the basis of the resulting larger data sets. After testing, the retrospective identification of gBRCA mutation status resulted in 210/265 (79%) of the study population having a known gBRCA status as defined by either the Myriad test or other local testing.

Study 19 gBRCAm Patient Demographics

A total of 265 patients at 82 sites in 16 countries were enrolled in Study 19. BRCA mutation status was known at the time of randomization in 37% of the ITT population. In 2012, the applicant tested all available blood samples for gBRCA mutations, resulting in 79% of the ITT

population having a known BRCA mutation status by either the Myriad Integrated BRACAnalysis test or local testing. Table 3 depicts the summary of BRCA mutation status. A total of 53 patients were identified as having a deleterious gBRCA mutation in the olaparib arm as compared to 43 patients in the placebo arm.

Table 3: BRCA Status

	Olaparib (N=136)	**Placebo (N=129)**
gBRCA (Rand)[1]	24%	22%
wtBRCA (Rand)	13%	16%
gBRCA (retro)[2]	15%	12%
wtBRCA (retro)	24%	34%
gBRCA (CRF+retro)[3]	**N=53** **39%**	**N=43** **33%**
wtBRCA (CRF+retro)	37%	50%
tBRCA[4]	6%	8%

1 BRCA mutation status known at the time of randomization
2 Retrospectively identified BRCA mutation status
3 Total number of patients with identified gBRCA deleterious mutation
4 Total number of patients with confirmed germline wtBRCA but with somatic BRCA mutations as detected by a different platform.

Demographic information for the gBRCAm population is depicted in Table 4 below. There were more patients on the olaparib arm who received less than or equal to 3 prior chemotherapy regimens and who had a time to progression on their penultimate platinum regiment interval of greater than 12 months as compared to the placebo arm.

Table 4: Key Demographic Parameters of the gBRCA mutation Population

	Olaparib (N=53)	**Placebo (N=43)**
Median Age	56	55
Number of Prior Chemotherapy Regimens		
≤ 3	42	31
> 3	11	12
Time to Progression Penultimate Platinum Regimen		
> 6 months; < 12 months	22	21
> 12 months	31	22
Median Time From Most Recent Disease Progression to Randomization (days)	195	189
Median Time From Completion of Final Platinum Chemotherapy to Randomization (days)	40	43
gBRCA Mutation Type		
BRCA1	40	30
BRCA2	13	13

The final platinum chemotherapy regimen prior to randomization of the gBRCAm population is depicted in Table 5 below. There were more patients on the olaparib arm who received single agent platinum prior to receiving olaparib as compared to those receiving placebo.

Table 5: Platinum-containing Regimen Immediately Prior to Randomization (gBRCAm)

Platinum Regimen Immediately Prior to Olaparib Treatment	**Olaparib (N=53)**	**Placebo (N=43)**
Platinum and Taxane	30	33
Platinum and Gemcitabine	25	33
Platinum and Anthracycline	11	14
Other Platinum Doublet	11	7
Single Agent Platinum	23	14

Study 19 Efficacy Analyses

Efficacy Outcomes

The primary efficacy outcome measure of Study 19 was investigator-assessed PFS using the data cut-off of June 30, 2010. At the time of the PFS analysis, there were 153 total events with one death in the absence of RECIST progression occurring in the olaparib arm. The remainder were progression events by RECIST criteria. Table 6 summarizes the primary efficacy outcome measure in the ITT population.

Table 6: Progression-free Survival Analysis in the ITT Population

	Olaparib (N=136)	**Placebo (N=129)**
Median PFS in months (95% CI)	8.4 (7.4, 11.5)	4.8 (4.0, 5.5)
Hazard Ratio (95% CI)	0.35 (0.25, 0.49)	
p-value (Cox proportional hazards)[1]	<0.00001	

1 - The analysis was performed using a Cox proportional hazards model with factors for treatment (olaparib vs. placebo), time to disease progression (>6-12 months and >12 months, in the penultimate platinum therapy prior to enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no)

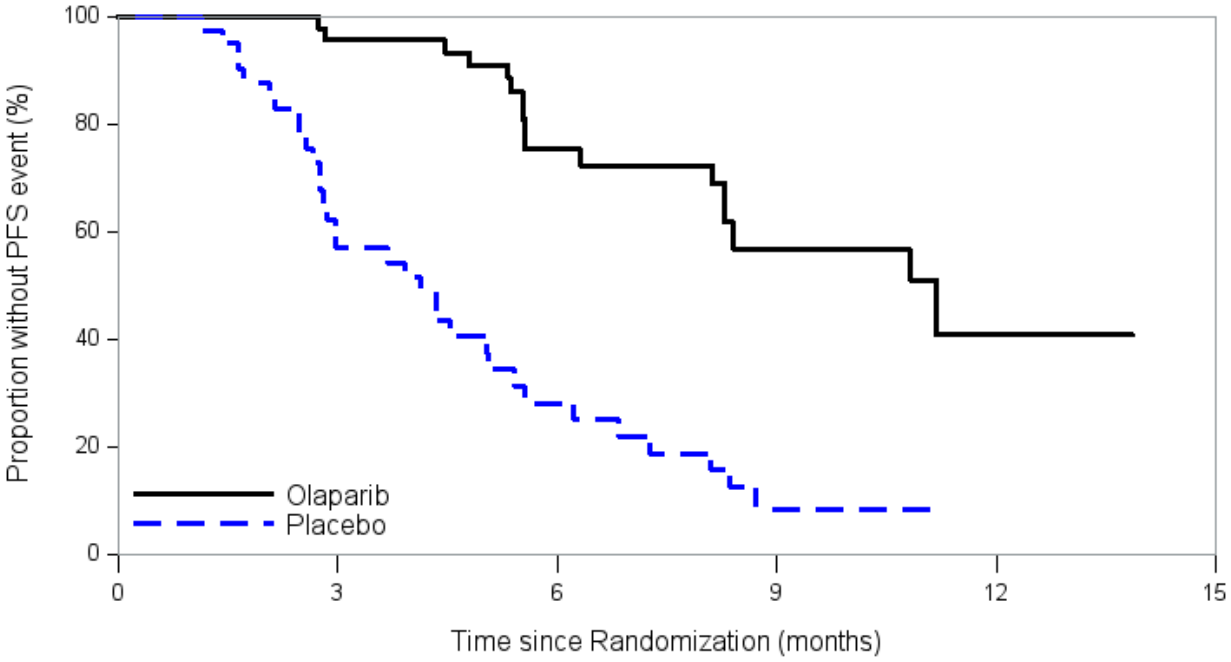
As described above, a pre-planned analysis of PFS in the known gBRCAm subpopulation suggested a differential improvement in this subset. Retrospective identification of BRCA status using patient's archived blood samples increased the gBRCAm population. Table 7 below summarizes the PFS analysis in the gBRCAm population, and Figure 1 depicts the Kaplan-Meier plot of PFS in the gBRCAm population.

Table 7: Progression-free Survival Analysis in the gBRCAm Population

	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)	

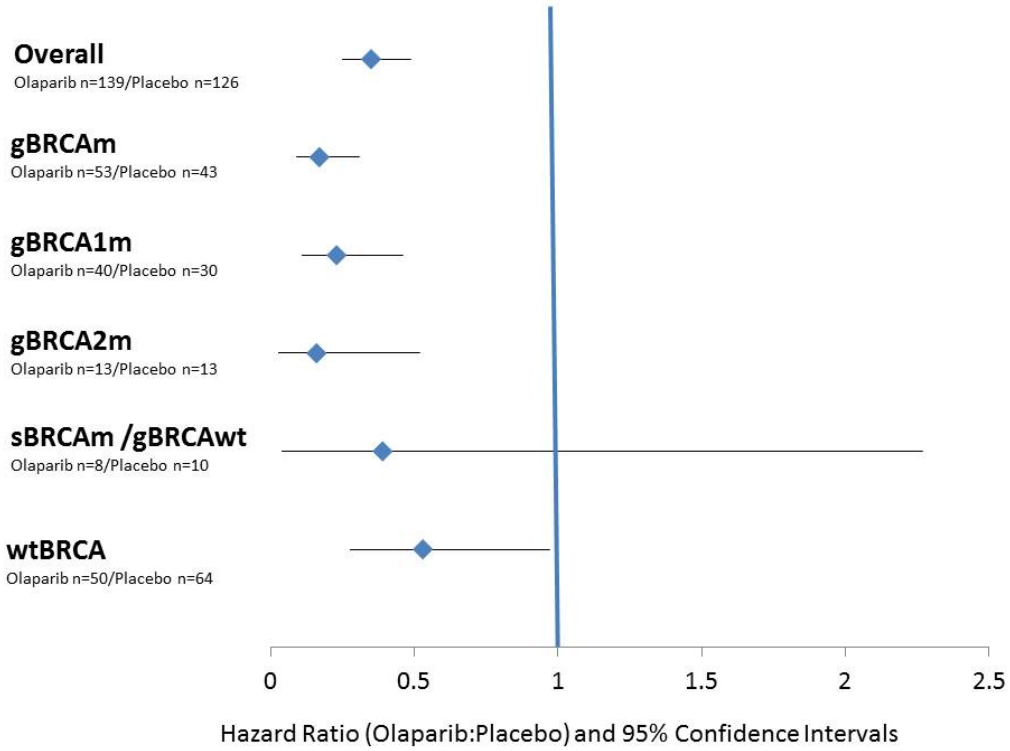
1 - The analysis was performed using a Cox proportional hazards model with factors for treatment (olaparib vs. placebo), time to disease progression (>6-12 months and >12 months, in the penultimate platinum therapy prior to enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no)

Figure 1: Kaplan-Meier Plot of Progression-free Survival in the gBRCAm Population



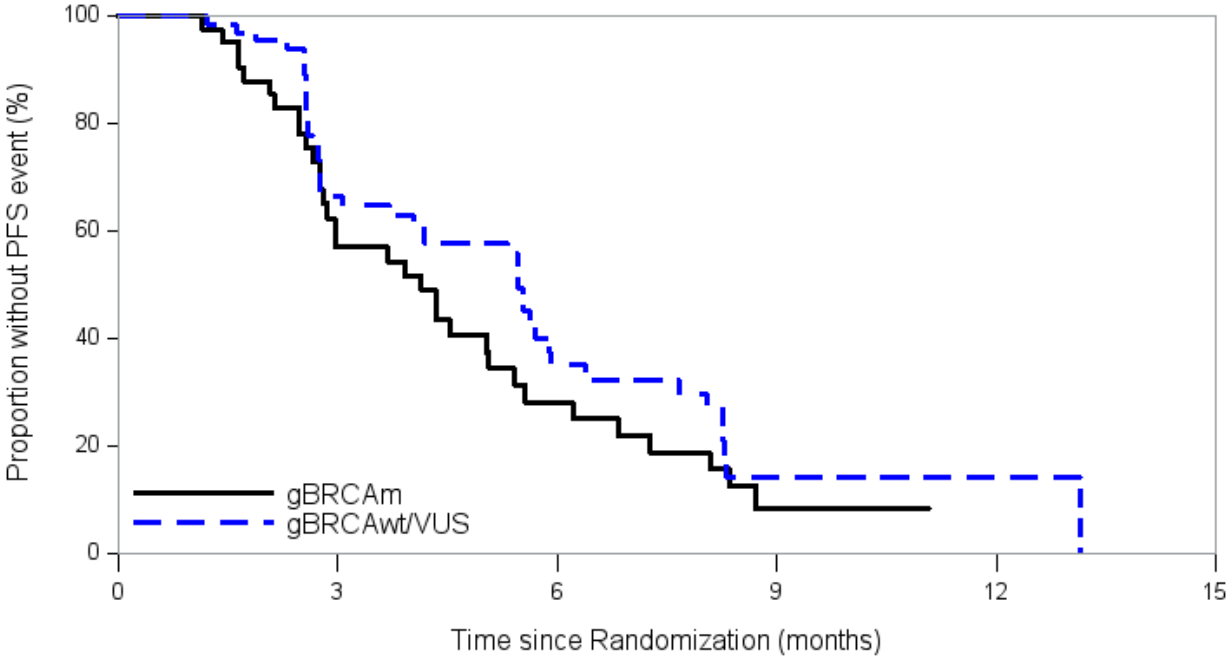
Further subgroup analyses of PFS were conducted by the FDA. These subgroups included patients with gBRCA1m, patients with gBRCA2m, and patients with tissue (somatic) BRCA mutations in the absence of germline mutations and patients with confirmed wtBRCA. As depicted in the forest plot below (Figure 2), the treatment effect was consistent in the gBRCA1m and gBRCA2m populations. There were too few patients with somatic BRCA mutations without gBRCAm to draw any conclusions regarding the efficacy of olaparib in this population. In the patients with confirmed gBRCAwt or gBRCA mutations with variations of unknown significance (n=114), the hazard ratio for PFS using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy is 0.50 (95% CI: 0.29, 0.82); however, the treatment effect of olaparib therapy in terms of PFS cannot be reliably ascertained due to the suggestion of non-proportional hazards.

Figure 2: Forest Plot of PFS Hazard Ratios by Subgroup



An additional exploratory analysis was conducted to ascertain the PFS of patients on the placebo arm as it pertains to BRCA status. In total, there were 64 patients with confirmed gBRCAwt or gBRCAvus status as opposed to 43 patients with gBRCAm status. The Kaplan-Meier curve of PFS in the placebo arm by mutation status is depicted in Figure 3 below and surprisingly suggests that the gBRCAwt/vus population may have had a slightly longer PFS. It would be expected that the gBRCAm population would have a longer PFS when compared to gBRCAwt/vus. If the time from start of platinum-based chemotherapy to progression is calculated for the placebo-treated population, this time interval (9.9 months) is consistent with the median PFS interval seen in other trials (ICON4, OCEANS, CALYPSO) in the platinum sensitive setting, suggesting that the gBRCAm placebo group “underperformed” versus an “overperforming” gBRCAwt/vus group.

Figure 3: Kaplan-Meier Plot of PFS of Placebo Treated gBRCAwt/vus vs. gBRCAm



Key Secondary Endpoints

Overall Survival

An interim analysis of OS was performed at 58% maturity. The Kaplan-Meier curve for OS in the gBRCAm population is depicted in Figure 4 and Table 8 below.

Figure 4: Kaplan-Meier Plot of Overall Survival in the gBRCAm Population

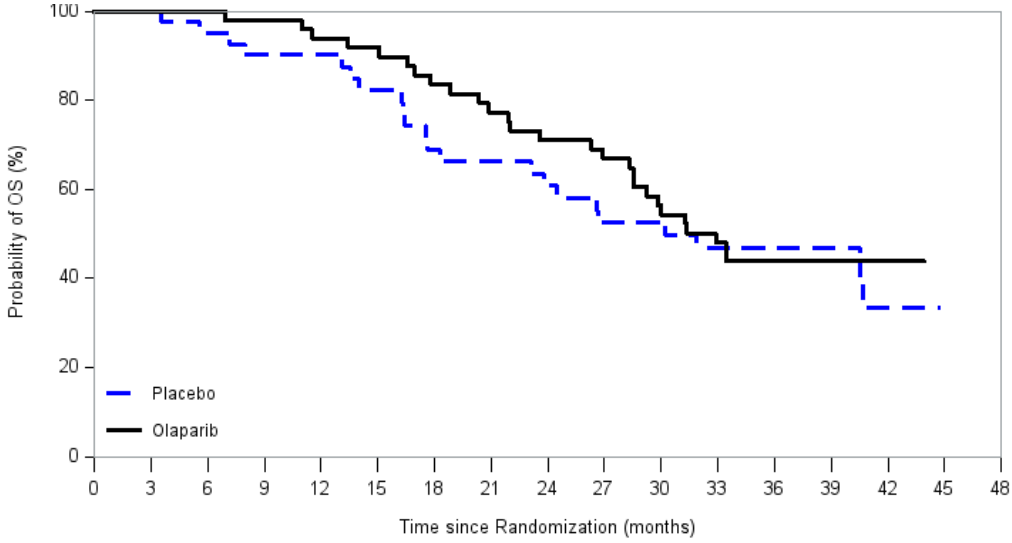


Table 8: Overall Survival Analysis in the gBRCAm Population

	Olaparib (N=136)	**Placebo (N=129)**
Median OS in months (95% CI)	32.9	30.2
Hazard Ratio (95% CI)	0.85 (0.48, 1.51)	

Patient-Reported Outcomes (PROs)
Patient-reported outcomes were assessed using the Functional Assessment of Cancer Therapy Ovarian (FACT-O) questionnaire, which was administered at baseline, every 12 weeks up to 60 weeks and then every 24 weeks until disease progression or until the patient withdrew consent. Analyses of PRO variables derived from the FACT-O consisted of the Trial Outcome Index (TOI), the total FACT-O score, and the FACT/NCCN Ovarian Symptom Index (FOSI). For each of the TOI, FOSI and total FACT-O endpoints, the proportion of patient with best responses of 'Improved', 'No Change' and "Worsened" were compared between treatments using logistic regression with factors as for the analysis of PFS. The time to worsening was compared between treatments for each of the TOI, FOSI and total FACT-O, using a Cox proportional hazards model using the same factors as for the analysis of PFS.

There were no statistically significant differences between treatment groups with respect to the TOI, FOSI, and total FACT-O score. The PRO analyses must be interpreted with caution, as an 'improved' score in any of the PRO variables may be due to recovery from the recently completed chemotherapy regimen and may not be a function of treatment with placebo or olaparib. In addition, the lack of a statistically significant improvement in these PRO measures does not sufficiently rule out a possible decrement in patient's health-related quality of life, as the adverse reaction profile of olaparib therapy may not be sufficiently captured through these instruments.

Overall Response Rate (ORR)
Patients were in either complete or partial response to platinum-based chemotherapy prior to randomization. There were few additional responses, which occurred on both treatment arms. No meaningful conclusions can be drawn from this analysis.

Supportive Efficacy Outcomes Derived From Other Trials

The anti-tumor activity of olaparib monotherapy has been assessed in multiple single-arm and randomized trials. Table 8 below depicts a summary of the overall response rates demonstrated across olaparib studies where the number of gBRCAm patients exceeded 30 and the 400 mg dose of olaparib was administered.

Table 9: Overall Response Rates of Olaparib Studies in the gBRCAm Patient Population from trials other than Study 19

Study Number and Description	N (Olaparib 400mg; gBRCAm patients)	ORR (%)	mDOR (months)
Study 12: Phase 2 monotherapy Dose Finding Study	32	31	6.8
Study 20: Phase 2 Relapsed Ovarian Cancer Study	64	41	9.1
Study 42: Phase 2 Advanced gBRCA Mutated Tumors Study	167	36	7.4
Study 9: Phase 2 gBRCA Ovarian Proof-of-Concept Study	33	33	9.5
Total N	**294**	**33**	

Safety

Safety population

Table 9 lists all studies submitted in this application from which safety data are comprised. Patients from study D0810C00019 (Study 19) form the core population for the safety analysis of olaparib.

Table 10: Summary of Olaparib Trials in Safety Analysis

Study #	Population	Design	Dose (mg B.I.D.)	# Any Olaparib	# Olaparib 400 mg B.I.D.
D0810C00001	Advanced Solid Tumors	Dose Escalation	100-400	12	6
D0810C00002	Advanced Solid Tumors	Dose Escalation	10 Q.D. to 600 B.I.D.	98	8
D0810C00004	Advanced Solid Tumors	Dose Escalation	50-400	189	12
D0810C00005	Advanced Solid Tumors	Dose Escalation	50-200	66	0
D0810C00006	Advanced Solid Tumors	Dose Escalation	50-200	19	0
D0810C00007	High-risk Breast Cancer	PD	10-400	60	12
D0810C00008	Advanced BRCAm Breast Cancer	Activity	100 and 400	54	27
D0810C00009	BRCAm Ovarian Cancer	Activity	100 and 400	58	33
D0810C00010	Advanced Solid Tumors	PK, ADME	100	6	0
D0810C00012	BRCAm Ovarian Cancer	Efficacy vs Doxil	200 and 400	64	32
D0810C00019	Platinum-sensitive Ovarian Cancer after $\geq$ 2 platinum regimens	Efficacy vs placebo	400	136	136
D0810C00020	BRCAm Ovarian and Breast Cancers	Activity	400	90	90

D0810C00021	Advanced Solid Tumors	Dose Escalation	50-200	54	0
D0810C00024	Advanced Solid Tumors	PK, BA	200-450	134	9
D0810C00039	Advanced Gastric Cancer	Efficacy in combo with chemo vs placebo	100	61	0
D0810C00041	Platinum-sensitive Ovarian Cancer	Efficacy in combo/maintenance with chemo vs chemo alone	200-400	81	81
D0810C00042	gBRCAm Advanced Solid Tumors	Activity	400	298	298
D0810L00001	Advanced Solid Tumors	Dose Escalation	50-400	44	24
D9010C00008	Advanced CRC	Activity	400	33	33
Total Exposed in AZ-sponsored trials				**1557**	**801**
ISS Total				**2618**	

Drug Modifications/Discontinuations

In study 19, dose modifications occurred in 71 (52.2%) patients on the olaparib arm versus 40 (31.3%) patients on the placebo arm. Nausea, vomiting, abdominal pain, anemia and fatigue accounted for the majority of dose modifications on the olaparib arm, while placebo patients had dose modifications mostly for abdominal pain, fatigue, small intestinal obstruction, anemia and vomiting.

More patients in the overall study population from study 19 discontinued treatment on the placebo arm (97.7%) than on the olaparib arm (83.1%). The primary reasons for treatment discontinuations were disease progression (64% on olaparib versus 85.9% on placebo); adverse events (4.4% on olaparib versus 1.6% on placebo); and patient refusing further treatment (8.1% on olaparib versus 6.3% on placebo).

Table 11: Dose Modifications and Discontinuations in Study 19

	Olaparib N=136	Placebo N=128
Dose modification (interruption or reduction)	**71**	**40**
Dose modification due to AE	53	14
Dose interruption	**49**	**21**
Dose interruption due to AE	41	11
Dose reduction (less than 800 mg/ d)	**57**	**28**
Dose reduction due to AE	31	5
Dosing permanently discontinued	**113**	**125**
Dosing permanently discontinued due to AE	6	2
Dose reductions		
Reduction to 200 mg BID	55	27
Reduction to 100 mg BID	14	2
Reduction to 50 mg BID (not allowed)	4	0

Adverse Events

The most common adverse events (≥10% on either arm) in Study 19 in all patients are shown in Table 11. Among these, the most common were nausea, fatigue, abdominal pain, vomiting, diarrhea and anemia. Patients treated with olaparib had higher rates of gastrointestinal events, anemia, fatigue, asthenia, infections and respiratory disorders than patients treated with placebo. Grade 3 and 4 adverse events were uncommon on both arms.

Table 12: Common Adverse Events on Study 19 in Overall Population

	Olaparib N=136		**Placebo N=129**	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
Blood and lymphatic system disorders				
Anemia	32 (22.8)	3 (2.2)	7 (5.4)	1 (0.8)
Gastrointestinal disorders				
Abdominal distention	17 (12.5)	0	11 (8.5)	0
Abdominal pain[1]	66 (48.5)	2 (1.5)	55 (42.6)	4 (2.9)
Constipation	28 (20.6)	0	16 (12.4)	0
Diarrhea	37 (27.2)	3 (2.2)	31 (24)	2 (1.6)
Dyspepsia	24 (17.6)	0	11 (8.5)	0
Nausea	98 (72.1)	1 (0.7)	47 (36.4)	0
Vomiting	46 (33.8)	3 (2.2)	18 (14)	1 (0.8)

	Olaparib N=136		**Placebo N=129**	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
General disorders and administration site conditions				
Asthenia	19 (14)	0	12 (9.3)	0
Fatigue	71 (52.2)	2 (1.5)	51 (39.5)	1 (0.8)
Infections				
Nasopharyingitis	22 (16.2)	0	15 (11.6)	0
Respiratory Tract Infection[2]	30 (22.1)	2 (1.5)	12 (10.9)	0
Urinary Tract Infection	14 (10.3)	0	7 (5.4)	1 (0.8)
Metabolism and nutrition disorders				
Decreased appetite	28 (20.6)	0	17(13.2)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	23 (16.9)	0	18 (14)	0
Back pain	22 (16.2)	2 (1.5)	16 (12.4)	0
Musculoskeletal pain[3]	16 (11.8)	2 (1.5)	18 (14)	0
Nervous system disorders				
Dysgeusia	22 (16.2)	0	8 (6.2)	0
Headache	28 (20.6)	0	16 (12.4)	0
Respiratory, thoracic and mediastinal disorders				
Cough	26 (19.1)	0	13 (10.1)	0
Dyspnea	17 (12.5)	2 (1.5)	8 (6.2)	0

[1]Includes preferred terms abdominal pain, upper abdominal pain and lower abdominal pain.
[2]Includes preferred terms upper respiratory tract infection, respiratory tract infection viral, lower respiratory tract infection, bronchitis, bronchopneumonia and pneumonia.
[3]Includes preferred terms musculoskeletal pain and myalgia.

The most common adverse events (≥10% on either arm) in Study 19 in patients with gBRCA mutations are shown in Table 12. As with the overall population, the most frequent adverse events were nausea, fatigue, abdominal pain, vomiting, diarrhea and anemia. In the gBRCAm population, patients treated with olaparib had higher rates of gastrointestinal events, anemia, neutropenia, fatigue, asthenia, infections and cough than patients treated with placebo.

Table 13 Common Adverse Events on Study 19 in gBRCA-mutated Population

	Olaparib N=53		**Placebo N=43**	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
Blood and lymphatic system disorders				
Anemia	14 (26.4)	1 (1.9)	2 (4.7)	1 (2.3)
Neutropenia	7 (13.2)	2 (3.8)	1 (2.3)	0

	Olaparib N=53		**Placebo N=43**	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
Gastrointestinal disorders				
Abdominal distention	6 (11.3)	0	6 (14)	0
Abdominal pain	12 (22.6)	0	16 (37.2)	1 (2.3)
Abdominal pain upper	13 (24.5)	0	3 (7)	0
Abdominal pain lower	3 (5.7)	0	6 (14)	0
Constipation	9 (17)	0	4 (9.3)	0
Diarrhea	15 (28.3)	2 (3.8)	9 (20.9)	1 (2.3)
Dyspepsia	12 (22.6)	0	4 (9.3)	0
Nausea	41 (77.4)	1 (1.9)	16 (37.2)	0
Stomatitis	6 (11.3)	0	3 (7)	0
Vomiting	17 (32.1)	2 (3.8)	4 (9.3)	0
General disorders and administration site conditions				
Asthenia	9 (17)	0	6 (14)	0
Fatigue	28 (52.8)	0	19 (44.2)	0
Peripheral edema	8 (15.1)	0	4 (9.3)	0
Pyrexia	7 (13.2)	1 (1.9)	0	0
Infections				
Nasopharyingitis	10 (18.9)	0	2 (4.7)	0
Respiratory Tract Infection[1]	17 (32.1)	1 (1.9)	6 (14)	0
Urinary Tract Infection	9 (17)	0	2 (4.7)	1 (0.8)
Metabolism and nutrition disorders				
Decreased appetite	13 (24.5)	0	6 (14)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	9 (17)	0	7 (16.3)	0
Back pain	12 (22.6)	1 (1.9)	9 (20.9)	0
Musculoskeletal pain[2]	8 (15.1)	1 (1.9)	3 (7)	0
Nervous system disorders				
Dizziness	10 (18.9)	0	3 (7)	0
Dysgeusia	11 (20.8)	0	4 (9.3)	0
Headache	12 (22.6)	0	7 (16.3)	0
Psychiatric disorders				
Depression	6 (11.3)	0	6 (14)	0
Respiratory, thoracic and mediastinal disorders				
Cough	11 (20.8)	0	6 (14)	0

[1]Includes preferred terms upper respiratory tract infection, respiratory tract infection, respiratory tract infection viral, lower respiratory tract infection, sinusitis and pneumonia.
[2]Includes preferred terms musculoskeletal pain and myalgia.

Serious Adverse Events (SAEs)

Nonfatal serious adverse events occurred in 18.4% of patients on the olaparib arm and 10.2% on the placebo arm. The most frequent treatment-related SAE was anemia, with three patients on the olaparib arm and no patients on the placebo arm. SAEs are summarized in the table below.

Table 14: Nonfatal Serious Adverse Events on Study 19 in Overall Population

Serious Adverse Events	Olaparib n=136	Placebo N=128
Any SAE	**25 (18.4%)**	**13 (10.2%)**
Anemia	3	0
Thrombocytopenia	1	0
Cardiac insufficiency	1	0
Intestinal obstruction (small or large)	3	4
Constipation	1	0
Diarrhea	1	0
Vomiting	1	0
Melena	1	0
Intra-abdominal hemorrhage	1	0
Gastritis	0	2
Abdominal pain	0	1
Impaired gastric emptying	0	1
Nausea	0	1
Hernia pain	1	0
Pyrexia	1	0
Iodine allergy	1	0
Pneumonia	1	1
Urinary tract infection	1	1
Upper respiratory tract infection	1	0
Appendicitis	1	0
Liver abscess	1	0
Endophthalmitis	0	1
Influenza	0	1
Femur fracture	1	0
Post-procedural hematoma	1	0
Dehydration	0	1
Osteoporosis	1	0
Breast cancer in situ	1	0
Myelodysplastic syndrome	1	1
Bladder cancer	0	1
Syncope	1	0
Dyspnea	2	0

Pulmonary embolism	1	0
Cough	1	0
Deep vein thrombosis	1	0
Vena cava thrombosis	1	0
Essential hypertension	0	1

Duration of Adverse Events

While the frequency of adverse events in Study 19 was comparable to many therapeutic oncology agents, there were relatively few Grade 3, 4 and 5 events. As olaparib is posed to be used in a setting where a patient typically would not be receiving treatment, the duration of adverse events was examined in Study 19. An analysis was performed for AEs where there was a difference in median duration of greater than 20 days (and no missing data for duration) in AEs that occurred in ≥10% of patients on either arm. As seen in Table 14 below, olaparib-treated patients had numerous AEs that were longer in duration than placebo-treated patients.

Table 15: Median Duration of AEs

		Olaparib N=53	**Placebo N=43**	
AE	**N**	**Median (Min-Max) Days**	**Median (Min-Max) Days**	**Δ median**
Abdominal distention	12	147 (30-613)	34 (7-71)	113
Dysgeusia	15	114.5 (16-706)	11 (2-89)	103.5
Abdominal pain upper	16	99 (4-484)	8 (1-15)	91
Nausea	57	96 (1-1174)	26 (1-85)	70
Arthralgia	16	89 (14-850)	22 (7-51)	67
Abdominal pain	28	75 (8-1061)	18 (2-109)	57
Back pain	21	57 (5-191)	8 (3-101)	49
Decreased appetite	19	66.5 (8-271)	18.5 (8-74)	48
Musculoskeletal pain	7	57 (3-194)	9.5 (4-15)	47.5
Constipation	13	44 (16-675)	4 (2-6)	40
Anemia	9	45 (8-254)	14 (14-14)	31
Asthenia	15	128 (26-165)	104 (45-130)	24
Cough	17	42 (3-835)	20 (1-92)	22

Deaths

Three olaparib-treated patients and no placebo-treated patients died due to causes other than disease progression within 30 days of the last dose of study drug. The causes of death for these patients were hemorrhagic stroke, cholestatic jaundice and myelodysplastic syndrome. While the patient who experienced cholestatic jaundice likely had progressive disease as a contributing factor to this TEAE that was unlikely to be related to olaparib, a causal relation to olaparib therapy cannot be ruled out for the other two deaths. Table 15 summarizes the deaths on Study 19.

Table 16: All Safety Population Deaths on Study 19

	Olaparib N = 136	**Placebo N = 129**
Total Deaths	77 (56.6)	77 (60.2)
Progression[#]	68 (50.0)	71 (55.5)
Deaths within 30 Days of Last Dose	3 (2.2%)	0
TEAEs	3 (2.2%)	0
Other	0	0
Deaths in follow-up*	6 (4.4%)	6 (4.7%)
TEAEs	0	0
Other	6 (3.6%)	6 (3.9%)
Unknown	2	0
Other Events[†]	4	6

[#]Includes deaths from progression both during study and in follow-up.
*More than 30 days after last dose of study drug to clinical data cutoff of November 26, 2012.
[†] Other events on the olaparib arm included euthanasia, septic shock, cerebrovascular disorder, cerebral hemorrhage.

Myelodysplastic Syndrome/Acute Myeloid Leukemia
In Study 19, three patients on olaparib treatment (2.2%) have been diagnosed with or had laboratory abnormalities suggestive of MDS or AML. One patient with wild-type gBRCA status and primary peritoneal cancer was diagnosed with MDS while on olaparib treatment at day 313. This patient died, with causes of death listed primarily as ovarian cancer and secondarily as MDS. The second patient, with gBRCAm-associated ovarian cancer, discontinued treatment after 1728 days with olaparib secondary to pancytopenia and was diagnosed 21 days later with AML. The AML was ongoing at last report. There is a third possible case of AML from the olaparib arm; this patient with gBRCAm status experienced Grade 5 hemorrhagic stroke during the course of olaparib therapy. On study day 205, olaparib was discontinued due to Grade 4 thrombocytopenia, neutropenia and leukopenia, Grade 2 anemia and 3% blasts present in the peripheral blood. At a visit two days later, a repeat peripheral blood count revealed a blast count of 16%, and a head CT revealed an intracranial hemorrhage. The patient died two days later

without further workup of the pancytopenia or peripheral blasts. However, the narrative provided is suspicious for acute leukemia.

The sponsor estimates that 2,618 patients have been treated with olaparib to date. There have been 21 total cases of MDS and/or AML reported among these patients (0.8%), not including the additional suspected case from Study 19. Of these 21 patients, 16 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=17), 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 16 patients. Among these 21 cases, nine either presented with or progressed to AML.

There is concern that the incidence of MDS/AML may be underreported. Currently, the sponsor 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 (0.03%) 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 is higher than the expected incidence in a general population or in an ovarian cancer population treated with platinum-based therapy, and this safety signal warrants further investigation. The capturing and reporting of patients experiencing MDS/AML while on or following olaparib treatment would likely be a post-marketing requirement should olaparib gain marketing approval.

Exposure Response Relationships

The pharmacokinetics of olaparib have been characterized in studies that enrolled patients with gBRCAm-associated breast and ovarian cancer. 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 5: Exposure-Response Relationship Olaparib Steady State Cmax vs. Incidence of Anemia

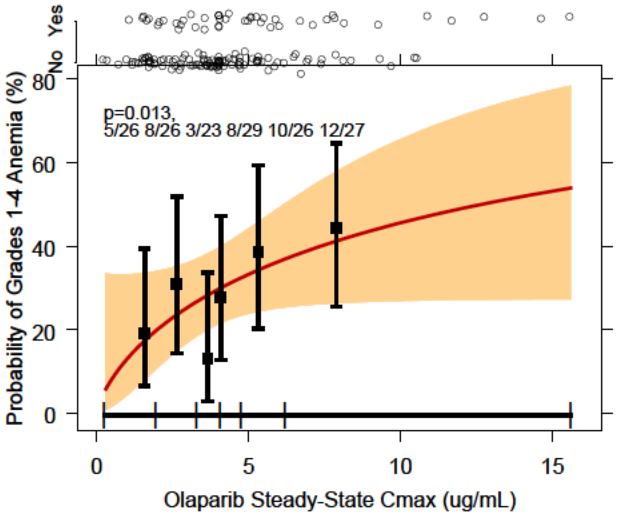
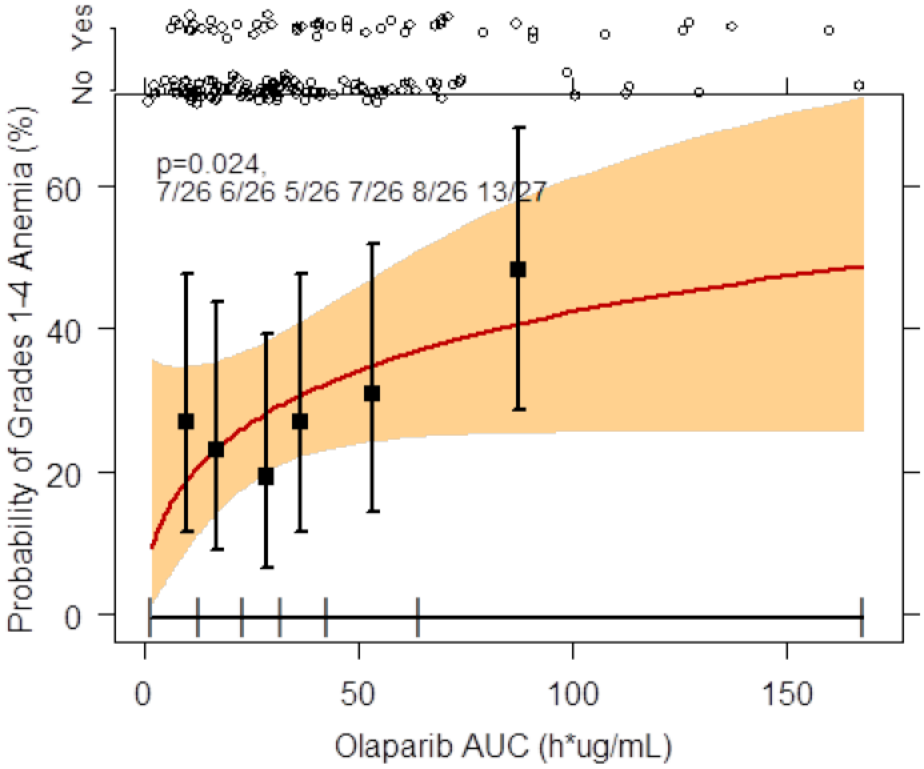


Figure 6: Exposure-Response Relationship Olaparib AUC vs. Incidence of Anemia



Confirmatory Trial

This New Drug Application is under consideration for accelerated approval under Subpart H, which stipulates that FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trial(s) establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity (CFR 314.510)). Approval under this section will be subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome (CFR 314.510).

The applicant is currently conducting a randomized, double-blind, placebo-controlled study (SOLO-2) to assess the efficacy of olaparib maintenance monotherapy in relapsed gBRCAm high-grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and / or fallopian tube cancer) or high-grade endometrioid cancer who have responded following platinum-based chemotherapy. The trial design largely mimics the design of Study 19, and approximately 264 patients will be recruited (2:1 olaparib:placebo ratio). The study is sized to give sufficient precision of the hazard ratio. This may result in a study that is powered to detect a statistically significant, but relatively small, difference in PFS between study arms. For example, with a median PFS of the control arm of 4 months and a sample size of 158 PFS events, the confirmatory study could detect a minimum statistically significant improvement in PFS of only 1.5 months, with a corresponding HR of 0.73. The results of this trial are expected to be available at the end of 2015.

A key difference between SOLO-2 and Study 19 is the formulation of olaparib administered to the patient. The dose of olaparib used in Study 19 was 400 mg PO BID of the capsule formulation. Each capsule is 50 mg, translating to a total pill count of 16 pills consumed each day. In order to facilitate olaparib dosing, a new tablet formulation was made; however, a bioequivalent dose of the tablet formulation was not established. In order to assess bioequivalence and to determine the safety and preliminary activity of the new formulation, the applicant conducted Study 24, a randomized, two-period cross-over study to determine the comparative bioavailability of two different oral formulations of olaparib in cancer patients with advanced solid tumors. Based on the totality of the efficacy and safety data generated from this study, the 300 mg tablet formulation was chosen as the most suitable dose for SOLO-2 and other randomized trials. The 300 mg tablet dose is estimated to have approximately 1.5 times the relative bioavailability of the 400 mg capsule dose. There is insufficient evidence at this point to determine if there is an exposure-response relationship for efficacy; however, there appears to be an exposure-response relationship for the incidence of anemia. This raises concerns that the overall tolerability of the new tablet formulation may be compromised in SOLO-2 as compared to Study 19. To what degree the new formulation impacts the safety and efficacy of olaparib in the gBRCAm population remains to be seen.

Summary

Risk-Benefit Considerations
Olaparib is an active treatment in gBRCAm ovarian cancer as demonstrated by a seven-month median improvement in PFS and a hazard ratio of 0.17 in the gBRCAm subgroup of Study 19. This activity is supported by an observed overall response rate of approximately 33% as monotherapy in the gBRCAm relapsed ovarian cancer setting. Safety concerns pertain to the risks of myelosuppression, fatigue and gastrointestinal disturbances such as nausea and abdominal pain. In addition, there is a small but concerning risk for the development of MDS/AML.

Given that this indication is for maintenance treatment of patients who have just completed a course of cytotoxic chemotherapy and are expected to receive multiple treatment regimens throughout their lives, tolerability and cumulative toxicities are paramount issues in determining the risk-benefit profile of olaparib therapy. The PRO assessments were uninformative in terms of characterizing whether olaparib therapy was effective in delaying disease-related symptoms, and although the toxicities resulting from olaparib therapy were generally self-limiting and reversible, the patient could have been treatment free and without therapy-related adverse reactions during this time.

The small sample size of gBRCAm patients and the retrospective identification of this patient population call into question the reliability of the estimation of treatment effect. The retrospective identification of the gBRCAm population did not appear to result in gross imbalances of known prognostic factors that could account for the treatment effect seen in Study 19, but it is important to note that the loss of randomization and the selection of a convenient sample of patients who had available whole blood sample for retrospective testing may have led inadvertently to an unequal distribution of unknown factors that may have affected the study results. The hazard ratio of 0.17 certainly suggests that most patients will have some degree of prolongation of PFS from treatment, but the data demonstrating that the placebo-treated gBRCAm performed more poorly in terms of PFS when compared to the placebo-treated gBRCAwt/vus raise the concern that the median improvement of seven months may be due in part to an “underperforming” control arm. The analysis of overall survival suggests no detriment as a result of therapy, but no survival difference was seen between treatment arms.

Study 19 demonstrated positive results in terms of an 83% reduction in the risk of progression or death and a seven-month median improvement in maintenance PFS for patients with platinum-sensitive gBRCAm associated ovarian cancer. However, there are uncertainties related to the validity and the reproducibility of the magnitude of effect seen in Study 19, and there are risks associated with olaparib therapy. Therefore, the options are to consider an accelerated approval now or wait until the results of SOLO-2 are available. The Agency asks the Oncology Drug Advisory Committee to consider the following:

Considerations for the Advisory Committee:

1. Do the efficacy results from study 19, namely a seven-month improvement in median PFS and a hazard ratio of 0.17, along with the safety data in the gBRCAm population, demonstrate a favorable risk-benefit profile of olaparib maintenance monotherapy in gBRCAm-associated, platinum-sensitive, relapsed high-grade serous ovarian cancer that is in response to the last platinum-based chemotherapy regimen?

2. The potential confirmatory trial is designed to detect a statistically significant but potentially clinically insignificant improvement in PFS. What is the appropriate magnitude of treatment effect for median improvement and hazard ratio to be demonstrated in the SOLO-2 trial to consider olaparib to be of direct clinical benefit to this patient population?

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