FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

December 17, 2019

NDA 208558/Supplement 10
Lynparza (olaparib) tablets
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 supplemental NDA to this Advisory Committee in order to gain the Committee's insights and opinions, and 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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1. PROPOSED INDICATION

The Applicant, AstraZeneca Pharmaceuticals LP (AstraZeneca), is seeking approval for the following indication:

Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA mutated (gBRCAm) metastatic adenocarcinoma of the pancreas whose disease has not progressed on first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

2. EXECUTIVE SUMMARY

This supplemental application to NDA 208558 contains the results of a single, randomized, placebo-controlled trial (POLO) assessing the safety and efficacy of olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor. POLO enrolled 154 patients with germline (g)*BRCA*-mutant(m) metastatic pancreatic adenocarcinoma receiving first-line chemotherapy for metastatic disease and whose disease had not progressed after receiving a minimum of 16 weeks of treatment with a first-line platinum-based chemotherapy. Patients were randomized (3:2) to receive olaparib or placebo. The primary endpoint is progression-free survival (PFS) by blinded independent centralized review (BICR) using a modification of Response Evaluation Criteria in Solid Tumours (RECIST) that accounts for patients with clinical complete response (CR) at study entry. This trial demonstrated a statistically significant improvement in PFS [hazard ratio (HR): 0.53 (95% confidence interval (CI): 0.35, 0.81); p=0.0035] corresponding to a 3.6-month improvement in median PFS, and evidence of tumor shrinkage as indicated by the difference in overall response rate (ORR) of 9.9% (95% CI: 1.1%, 20.8%) as compared to the placebo arm. No effect on OS was observed.

Based on these data, AstraZeneca seeks approval for the indication cited above.

The specific issues identified by FDA are summarized below:

<u>Has an accurate and reliable treatment effect on PFS been demonstrated?</u>

As stated in FDA's *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry (December 2018)*[1], "endpoints based on tumor

[1] https://www.fda.gov/media/71195/download

assessments should be evaluated for the potential of bias or uncertainty. When the primary study endpoint is based on tumor measurements (e.g., PFS or ORR), tumor assessments generally should be verified by central reviewers blinded to study treatments to ascertain lack of assessment bias." Additionally, FDA noted that "[A]ccuracy in measuring tumors can differ among tumor settings. Tumor measurements used in ORR determinations can be imprecise in locations where there is a lack of demarcated margins (e.g., pleural or peritoneal mesothelioma, pancreatic cancer, brain tumors)."

In POLO, one potential source of uncertainty, which is independent of the primary endpoint, is whether the trial is adequately controlled, given the small size of the trial. Given the limited sample size, randomization alone may not have ensured balance for all important prognostic factors. Additionally, the impact of imputation in patients with missing data is greater in small trials. FDA notes that while the baseline demographics and tumor characteristics appear generally similar between the treatment and control arms in POLO, there is an imbalance between arms for some known baseline factors that may affect prognosis. For example, there was a higher proportion of patients with ECOG performance status of 0 (71% vs. 61%) and no evidence of disease at study entry (5% vs. 0) in the olaparib arm, while there were fewer patients 65 years of age and older (21% vs. 30%) in the placebo arm. In addition, there was more missing data for disease burden at baseline in the placebo arm (1% vs. 6%), resulting in a higher rate of earlier censoring in the placebo arm. FDA conducted several exploratory subgroup analyses to assess for effects of such imbalances; in these exploratory subgroup analyses, treatment effects generally favored the experimental arm.

Another source of uncertainty in the detection of an effect on PFS in pancreatic cancer, is the limitation of current imaging technology to accurately measure locoregional tumors. This is an important consideration since 60% and 80% of patients with disease progression in the olaparib and placebo arms, respectively, were identified solely or in part based on progressive disease in the pancreas. The POLO trial required serial imaging with computerized tomography (CT) or magnetic resonance imaging (MRI) scans at baseline and for serial assessment of tumor measurements; 18-fluorodeoxy glucose (FDG)-positron emission tomography (PET) scans were permitted for identification of new lesions only if a baseline FDG-PET scan had been performed and correlation was required by either CT or MRI imaging; however no patients were determined to have progressed based on PET scans. In a review containing a meta-analysis of up to 7 studies enrolling 333 patients with pancreatic cancer that assessed the diagnostic performance of imaging technologies in detection of recurrent disease, contrast-enhanced CT scans demonstrated "moderate" diagnostic accuracy

(sensitivity of 0.70 and specificity of 0.80).[2] Sensitivity was improved (0.95) but specificity was not (0.80) with the addition of FDG-PET/CT to contrast enhanced CT. In a retrospective review, pre-operative staging (American Joint Committee on Cancer 8th edition) by imaging by CT, MRI, and/or ultrasound (US) was compared with staging based on surgical specimens among 286 patients who underwent attempted curative resection between 2007 and 2017 at a single center.[3] Discordant tumor (T) stage was identified in 106 (39.6%) of cases, with underestimation of tumor size in 80 cases (29.9%) and overestimation of tumor size in 26 cases (9.7%) by imaging as compared with measurement of tumor in the surgical specimen. Finally, FDA notes that concern regarding the accuracy of assessment of pancreatic cancer tumor status is supported by the 10% response rate observed in the placebo arm, although it is possible that responses to placebo (as well as a similar proportion in the olaparib arm) may be attributable to "delayed" treatment effects of chemotherapy.

Given these concerns regarding the accuracy of tumor measurement in pancreatic cancer, FDA approval of all previous drugs for the treatment of pancreatic cancer has been based on effects on OS, an endpoint for which assessment bias and limitations in the accuracy of tumor measurement by imaging technology are not present. However, FDA has stated that treatment effects on tumor-based endpoints that are very large in magnitude can be considered less likely to be affected by both assessment bias and limitations in the trial design. Furthermore, effects that are large in magnitude and statistically robust may support a conclusion that the direct clinical benefit has been demonstrated for the first-line treatment settings in metastatic solid tumors. This approach was used in prior approval of olaparib for maintenance treatment following first-line chemotherapy for ovarian cancer and has been used for first-line treatment of biomarker-defined non-small cell lung cancer for targeted therapies (i.e., EGFR, ALK, ROS1 inhibitors).

FDA acknowledges that a difference in PFS favoring the olaparib arm has been demonstrated in the POLO trial. However, there is uncertainty that the observed magnitude of the treatment effect on PFS accurately represents the true treatment effect, given potential issues with the reliability and accuracy of imaging technologies in this disease setting, the limited patient experience, and

[2] Daaman LA, Groot VP, Goense L, et al. The diagnostic performance of CT versus FDG PET-CT for the detecton of recurrent pancreatic cancer: a systematic review and meta-analysis. Eur J Radiol 106 (2018) 128-136.

[3] Kassardjian A, Stanzione N, Wang, H. Comparative Accuracy of Tumor Size Assessment and Stage Analysis by Imaging Modalities Versus Gross Examination for Pancreatic Ductal Adenocarcinoma. Pancreas 48(2), February 2019, 223-227.

potential for imbalances in prognostic factors affecting tumor response between arms.

What is the clinical significance of the observed effect on PFS?

In the analysis of PFS based on the protocol pre-specified number of PFS events (87), there was a statistically significant effect on PFS [HR: 0.46 (95% CI: 0.29, 0.73); p=0.0009 by an unstratified log-rank test]. However, this treatment effect was clinically modest, corresponding to a modest difference in median PFS of 3.8 months. In the final analysis of PFS conducted by AstraZeneca based on 104 PFS events, the results were similar [HR 0.53 (95% CI: 0.35, 0.81)] with a difference of 3.6 months in median PFS based on the difference in observed point estimates. Based on 10,000 bootstrap iterations using a basic non-parametric bootstrap, the estimated median difference in PFS is 3.2 months (95% CI: 0.3, 7.3). The lower bound of the 95% confidence interval indicates that the true difference in median PFS between arms may be as small as 0.3 months (9 days).

There was no evidence of a treatment effect in the interim OS analysis performed at the time of the final PFS analysis [HR 0.91 (95% CI: 0.56, 1.46)], reflecting a 67% information fraction (representing 71 of the 106 OS events planned for the final analysis of OS). FDA notes that while the trial may have been inadequately sized to detect small differences in survival, it was of adequate size to detect an effect on survival similar to that claimed for PFS. Specifically, there was adequate power to detect an effect on OS corresponding to a HR of 0.57, with a sample size of 145 patients and 106 required OS events. The estimated difference in ORR is 9.9% (95% CI: 1.1%, 20.8%) based on the estimated ORR of 19.6% (95%CI: 12.0%, 29.1%) in the olaparib arm and 9.7% (95% CI: 3.6%, 19.9%) in the placebo arm.

Issues to be discussed by the committee

Issue #1:
Given the following limitations of the POLO trial design, discuss whether there is compelling evidence of an accurate and reliable treatment effect for olaparib on PFS, given that:

- it is a small trial in which the control arm contains 58 patients with measurable (n=52) or non-measurable (n=6) disease and 4 patients with missing data regarding disease burden at baseline;
- there are imbalances in known prognostic factors between treatment arms and this may suggest potential imbalances in unknown factors; and

- there are limitations of imaging technology in accurately measuring tumor burden, particularly at the site of primary disease.

Issue #2:
If the Committee finds there is compelling evidence that there is a treatment effect on PFS, is the observed effect on PFS clinically meaningful in that the benefits outweigh the risks, given that:

- the treatment effect may correspond to a difference in median PFS as small as 9 days;
- there is no evidence of an effect on OS;
- treatment with olaparib results in an increase in Grade 3 to 5 adverse reactions (39% vs. 23%) and serious adverse reactions (24% vs. 15%)?

3. BACKGROUND

Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor that was first approved under the provisions of accelerated approval on December 19, 2014 as monotherapy for patients with deleterious or suspected deleterious g*BRCA*m advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

3.1 Pancreatic Cancer

Pancreatic cancer is a life-threatening disease, with one of the worst prognoses of all malignancies and is one of the leading causes of cancer death in the US. For patients diagnosed with metastatic pancreatic ductal adenocarcinoma (PDAC), the 5-year survival rate is only 3%. In 2019, pancreatic cancer is estimated to be the fourth most common cause of cancer death (45,750 deaths) and the ninth most common newly diagnosed cancer (56,770 new cases) in the US.[4] The clinical course of patients with pancreatic cancer is usually aggressive and surgery remains the only option for cure, although the percentage of patients who have resectable disease is low. Advanced stage of disease at the time of diagnosis confers a poor prognosis and low 5-year survival rates. Even when diagnosed and treated at an early stage, 80% of patients have disease that will eventually progress.

[4] Siegel RL, Miller KD, Jemal A. Cancer Statistics 2019. CA Cancer J Clinical 2109; 69(1):7-34.

3.2 Germline *BRCA*-mutated (g*BRCA*m) Pancreatic Cancer

Carriers of loss of function germline mutations of the *BRCA1* and *BRCA2* genes are known to have an increased risk of developing pancreatic cancer.[5,6] The prevalence of germline *BRCA* mutations in patients with pancreatic cancer is reported to range between 2 to 5 percent.[7,8]

The natural history and prognosis of patients with g*BRCA*-mutated PDAC is not well characterized. One report suggested a better prognosis in patients with pancreatic cancer carrying *BRCA1*, *BRCA2*, or *PALB2* mutations, with an OS improvement in carriers compared with non-carriers (median OS of 21.8 vs 8.1 months; [HR 0.35 (95%CI: 0.2, 0.62; p<0.001)] based on a retrospective analysis of 29 patients.[9] No well-controlled studies have been conducted to compare outcomes of patients with g*BRCA*m versus unselected pancreatic cancer. There are notable epidemiological differences; patients with germline mutations in *BRCA1* and *BRCA2* tend to be diagnosed with pancreatic cancer at a younger median age (approximately 62 years) compared to the unselected population (70 years). In addition, patients with g*BRCA*m-associated metastatic PDAC may derive more benefit from first-line platinum-based chemotherapy; one meta-analysis showed an improvement in median OS of over 10 months [23.7 months vs. 12.2 months; (95% CI: 5.05, 15.37); p<0.001] in 85 patients treated with a platinum-based therapy versus 32 patients treated with a non-platinum based chemotherapy.[10]

3.3 Available Therapies for g*BRCA*m Metastatic Pancreatic Cancer

There are no approved therapies specifically indicated for treatment of the subpopulation of patients with PDAC who have g*BRCA*m. Additionally, there are no approved therapies for the maintenance treatment of patients with metastatic PDAC, irrespective of g*BRCA*m status.

[5] Cavanagh H, Rogers KM. The role of *BRCA*1 and *BRCA*2 mutations in prostate, pancreatic and stomach cancers. Hereditary Cancer in Clinical Practice 2015; 13(1):16.
[6] Ferrone CR, Levine DA, Tang LH, et al. *BRCA* germline mutations in Jewish patients with pancreatic adenocarcinoma. Journal of Clinical Oncology 2009; 27(3):433–438.
[7] Shindo K, Yu J, Suenaga M, et al. Deleterious germline mutations in patients with apparently sporadic pancreatic adenocarcinoma. J Clin Oncol 2017; 35(30):3382-90.
[8] Holter S, Borgida A, Dodd A, Grant R, Semotiuk K, Hedley D, et al. Germline *BRCA* mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol 2015; 33(28):3124-9.
[9] Reiss KA, Yu S, Judy R, et al. Retrospective Survival Analysis of Patients With Advanced Pancreatic Ductal Adenocarcinoma and Germline *BRCA* or *PALB2* Mutations. JCO Precision Oncology 2018; published online.
[10] Rebellato TF, Falavigna M, Pozzari M et al. Should platinum-based chemotherapy be preferred for germline Breast Cancer genes (*BRCA* 1 and 2-mutated pancreatic ductal adenocarcinoma (PDAC) patients? A systematic review and meta-analysis.

The following drugs are considered available therapy for the first-line treatment of patients with unselected metastatic PDAC:

- Gemcitabine (Gemzar) is approved for the first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) PDAC. Gemzar is also indicated for patients previously treated with fluorouracil. Approval was based on the results of a multi-center, single-blind, randomized (1:1) trial conduct in 126 patients with locally advanced or metastatic pancreatic cancer who had received no prior treatment with chemotherapy. The trial demonstrated statistically significant improvements in clinical benefit response (22% vs. 4.8%), survival (median survival 5.7 vs. 4.2 months), and time to disease progression (median TTP 2.1 vs. 0.9) for those randomized to gemcitabine as compared to fluorouracil.

- Paclitaxel protein-bound (Abraxane) is approved for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine. Approval was based on the results of a multicenter, randomized, open-label study conducted in 861 patients receiving first-line treatment of metastatic adenocarcinoma of the pancreas; patients were randomized (1:1) to receive Abraxane/gemcitabine (N=431) or gemcitabine as a single agent (N=430). The trial demonstrated statistically significant improvements in OS [HR 0.72 (95% CI: 0.62, 0.83); p<0.0001] with a median of 8.5 vs. 6.7 months, PFS [HR 0.69 (95% CI: 0.58, 0.82); p<0.0001] with a median of 5.5 vs. 3.7 months, and ORR (23% vs. 7%; p<0.0001).

- Erlotinib (Tarceva) is approved, in combination with gemcitabine, for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer. Approval was based on the results of a randomized, double-blind, placebo-controlled trial in 569 patients with locally advanced, unresectable or metastatic pancreatic cancer who were randomized (1:1) to receive gemcitabine and erlotinib or gemcitabine and matching placebo. The trial demonstrated a statistically significant improvement in OS [HR 0.81 (95% CI: 0.68, 0.97); p=0.028] with a median of 6.5 vs. 6.0 months; PFS [0.76 (95% CI: 0.64, 0.92)] with a median of 3.8 vs. 3.6 months; and ORR (8.6% vs. 7.9%) were similar between the arms.

The National Comprehensive Cancer Network (NCCN) practice guidelines (version 3.2019 dated July 2, 2019) recommend the following regimens for initial treatment of locally advanced (including metastatic) pancreatic ductal carcinoma:

- FOLFIRINOX (for those with ECOG performance status [PS] 0-1) with or without subsequent chemoradiation;
- FOLFIRINOX with or without subsequent chemoradiation; or
- gemcitabine and paclitaxel protein-bound with or without radiation;

- gemcitabine and cisplatin administered for ≥ 2 to 6 cycles for patients with *BRCA*1/2 or *PALB2* mutations.

These recommendations are based on evidence of improved survival in published studies.

The NCCN practice guidelines recommend gemcitabine plus cisplatin for patients with *BRCA1/2* or *PALB2* mutations based on a retrospective study of patients with pancreatic cancer with a family history of breast, ovarian, or pancreatic cancers. In this retrospective study, there was a longer survival (median 22.9 months vs. 6.3 months) for those who received platinum-based chemotherapy.[11] Additionally, the NCCN practice guidelines rely on a case series in which 5 of 6 patients with g*BRCA*m metastatic pancreatic cancer achieved a partial response.[12]

FOLFIRINOX was identified as an appropriate treatment option based on the results of a randomized trial comparing FOLFIRINOX with single agent gemcitabine.[13] In a meta-analysis that included 11 studies that enrolled 315 patients with locally advanced pancreatic cancer where survival outcomes were captured and available for patient-level meta-analysis, the median survival ranged from 10.0 to 32.7 months across studies and the median survival using patient-level data was 24.2 months (95% CI: 21.6, 26.8 months).[14] In this meta-analysis, the median PFS ranged from 3.0 to 20.4 months across studies and the median PFS using patient-level data was 15.0 months (95% CI: 13.8, 16.2). The authors concluded that the median survival results compare very favorably to those reported in clinical studies administering gemcitabine alone.

3.4 Regulatory History of Olaparib

Prior Approvals of Olaparib

The original New Drug Application (NDA) for Lynparza (olaparib) capsules was approved under the provisions of accelerated approval on December 19, 2014. This accelerated approval was based on the observed overall response rate of

[11] Oliver GR, Sugar E, Laheru D, Diaz LA. Family history of cancer and sensitivity to platinum chemotherapy in pancreatic adenocarcinoma [abstract]. Gastrointestinal Cancers Symposium 2010:180.
[12] Lowery MA, Kelsen DP, Stadler ZK, et al. An emerging entity: pancreatic adenocarcinoma associated with a known *BRCA* mutation: clinical descriptors, treatment implications, and future directions. Oncologist 2011; 16:1397-1402.
[13] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. NEJM 2011; 364:1817-1825.
[14] Suker A, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. The Lancet Oncology 2016; 17(6):801-810.

34% (95% CI: 26, 42) and Kaplan-Meier estimated median duration of response of 7.9 months (95% CI: 5.6, 9.6), which supported the following indication:

> *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.*

On August 17, 2017, FDA approved Lynparza tablets (NDA 208558) for:

- the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy; and
- the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

The approval for the first indication was based on the results of the SOLO-2 trial, a double-blind, placebo-controlled trial in which 295 patients with germline *BRCA*-mutated (g*BRCA*m) ovarian, fallopian tube, or primary peritoneal cancer who had received at least two prior platinum-containing regimens and had a response (complete or partial) to their most recent platinum-based regimen were randomized (2:1) to receive Lynparza tablets 300 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. The approval was based on demonstration of a statistically significant and clinically compelling improvement in investigator-assessed PFS at a pre-specified interim analysis. The hazard ratio (HR) for PFS was 0.30 (95% CI: 0.22, 0.41); p <0.0001, corresponding to a 13.6-month improvement in median PFS (from 5.5 to 19.1 months). At the time of the analysis of PFS, OS data were not mature with 24% of events. Based on these data, FDA also determined that the results verified the clinical benefit of olaparib 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.

The second indication under NDA 208558 was based on the results of “Study 19” (NCT00753545), a double-blind, placebo-controlled trial in which patients (N=265) with platinum-sensitive ovarian cancer who had received two or more previous platinum-containing regimens were randomized (1:1) to receive olaparib or placebo until unacceptable toxicity or progressive disease. This trial demonstrated a highly statistically significant but clinically modest improvement in investigator-assessed PFS [HR 0.35 (95% CI: 0.25, 0.49); p<0.001], corresponding to a 3.6-month improvement in median PFS (from 4.8 to 8.4 months) and no suggestion of detrimental effect on OS.

On January 12, 2018, Lynparza tablets were approved for the treatment of "patients with deleterious or suspected deleterious g*BRCA*m, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy." This approval was based on the results of the OlympiAD trial, a randomized, open-label, active-controlled study in 302 patients with g*BRCA*m HER2- negative metastatic breast cancer randomized (2:1) to Lynparza or healthcare provider's choice of chemotherapy. The trial showed a highly statistically significant but clinically modest improvement in BICR-assessed PFS [HR 0.58 (95% CI: 0.43, 0.80); p=0.0009], corresponding to a 2.8-month improvement in median PFS (from 4.2 to 7.0 months) supported by an approximate doubling of the overall response rate (52% vs. 23%). Data submitted in a subsequent supplement indicated that there was no improvement in OS [HR 0.90 (95% CI: 0.66, 1.23)].

On December 19, 2018, Lynparza tablets were approved for the "maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy." This approval was based on the results of the SOLO-1 trial, a randomized, double-blind, placebo-controlled trial conducted in 391 patients with *BRCA*-mutated (*BRCA*m) advanced ovarian, fallopian tube, or primary peritoneal cancer following first-line platinum-based chemotherapy who were randomized (2:1) to receive Lynparza or placebo until disease progression or unacceptable toxicity. The approval was based on demonstration of a highly statistically significant and clinically compelling improvement in investigator-assessed PFS [HR 0.30 (95% CI: 0.23, 0.41); p<0.0001] corresponding to a median PFS in the placebo arm of 13.8 months with the median not reached after nearly 3 years of follow-up in the Lynparza arm.

<u>Pertinent Regulatory History for this Supplemental New Drug Application</u>
Table 1 summarizes the pertinent regulatory history related to this supplemental NDA.

Table 1. Regulatory Milestones

Jul 1, 2014	AstraZeneca submitted IND 121412 containing the POLO trial protocol.
Jul 23, 2014	FDA issued correspondence regarding the design of POLO: • FDA stated that the POLO trial was inadequately designed as a single trial intended to support a marketing application given the challenges of accurate tumor measurements in pancreatic cancer in assessing the primary endpoint of PFS. • FDA expressed concerns regarding the interpretability of the trial as it might not enroll a homogenous population based on failure to limit the prior platinum-based chemotherapy to one or a few regimens. • FDA recommended that AstraZeneca revise the primary endpoint to OS and limit the number of prior therapies.
Jul 25, 2014	The IND was allowed to proceed.
Dec 3, 2014	A meeting between AstraZeneca and FDA was held to discuss the olaparib development program in pancreatic cancer and the adequacy of the design of the POLO trial to provide data to support accelerated approval. • FDA expressed concern that the targeted magnitude of improvement in PFS, corresponding to a 3.4-month improvement in median PFS would not be likely to predict an effect on OS. • FDA also expressed concern with AstraZeneca's plan to use the final analysis of OS in the POLO trial to confirm the clinical benefit of olaparib, because the study might be underpowered to detect a realistic effect on OS.
Oct 11, 2018	Olaparib was granted orphan designation for pancreatic cancer.
May 14, 2019	A pre-NDA meeting was held between AstraZeneca and FDA to discuss the high-level results and adequacy of the POLO study to support a marketing application. • FDA stated that whether the magnitude of the observed treatment effect on PFS is clinically meaningful and statistically robust to support the proposed indication would be a review issue and depend on the risk/benefit assessment of olaparib. • FDA again expressed concern that the study was underpowered to detect an effect on OS and therefore the POLO trial was not adequately designed to verify and confirm the clinical benefit of olaparib.
Jun 28, 2019	AstraZeneca submitted the sNDA application (S-010) to NDA 208558.
Jul 1, 2019	Myriad submitted the POLO g*BRCA* sPMA application for the Myriad BRACAnalysis CDx.
Aug 27, 2019	FDA granted priority review to this sNDA.

4. CLINICAL STUDY SUPPORTING THE APPLICATION

4.1 Design of the Major Efficacy Trial (Study POLO)

Study POLO was a randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy of olaparib maintenance monotherapy in metastatic pancreatic adenocarcinoma patients with g*BRCA 1* or g*BRCA2* mutations that were predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) whose disease had not progressed after receiving a minimum of 16 weeks of first-line platinum-based chemotherapy. Although the reasons for discontinuation of platinum-based chemotherapy were not captured in the case report forms for POLO, patients who had received at least 16 weeks of a platinum regimen and had the platinum discontinued for toxicity but continued on the remaining chemotherapy agent(s) were also eligible if they had no evidence of disease progression within 4 weeks of their last dose of chemotherapy. Other key eligibility criteria included ECOG performance status of 0 or 1 and normal organ and bone marrow function.

Patients were randomly assigned in a 3:2 ratio to one of the following two treatment arms:

- Experimental: Olaparib 300 mg orally twice daily
- Control: Matched placebo.

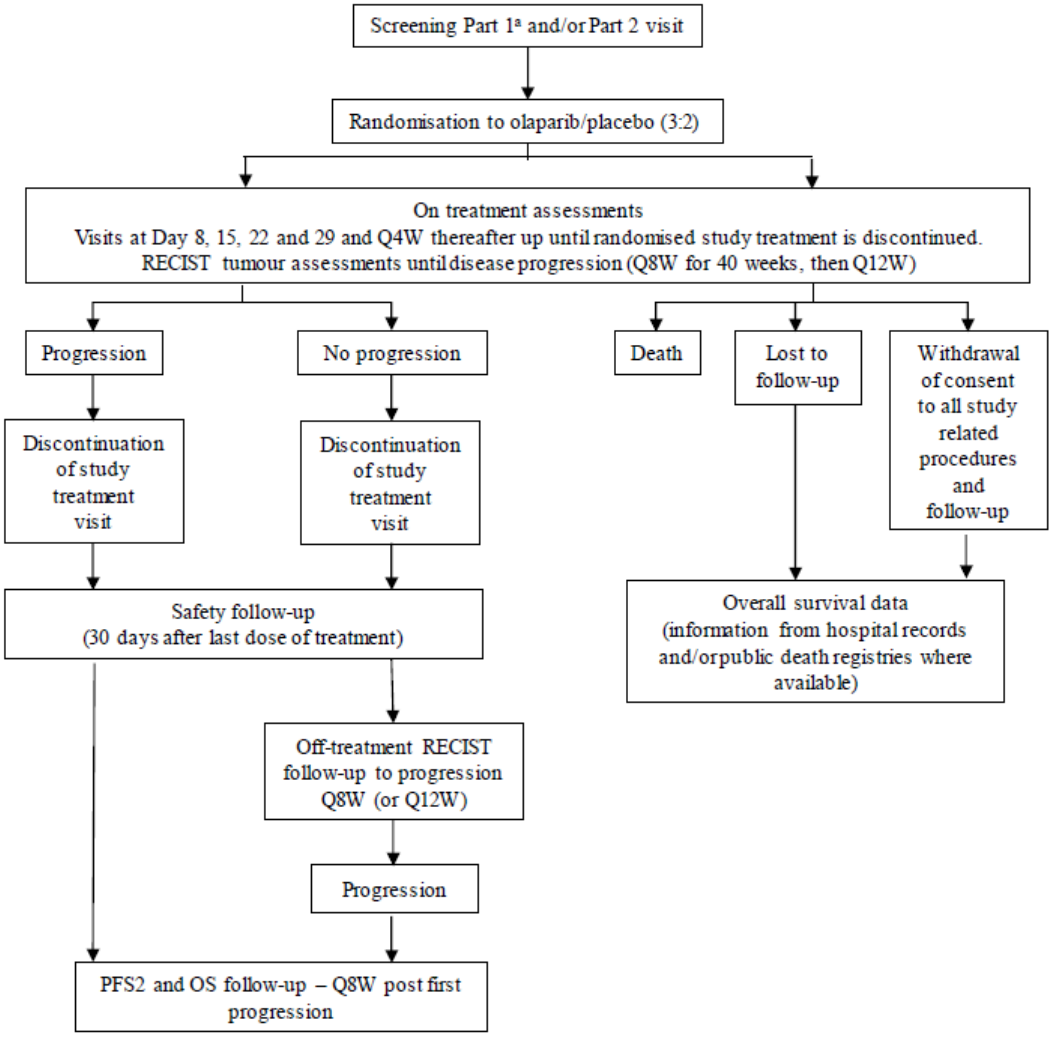
Randomization was not stratified by any factor.

Treatment continued until disease progression as assessed by the investigator and as long as, in the investigator's opinion, the patient was benefiting from treatment and did not meet any other discontinuation criteria. Patients with centrally unconfirmed progression were permitted to continue until the next disease assessment and discontinued if progression was subsequently confirmed. Patients on the placebo arm who experienced disease progression were not permitted to crossover to the olaparib arm.

Follow-up assessment of disease by CT of chest, abdomen and pelvis (or MRI where CT was contraindicated) was required for all patients. Tumor assessments occurred at baseline, every 8 weeks until Week 40, and then every 12 weeks.

Figure 1 depicts the POLO study design.

Figure 1. POLO Study Design



[a] Screening Part 1 only required if a patient's *gBRCAm* status was unknown.

BRCA breast cancer susceptibility gene; *gBRCAm* germline *BRCA* mutated; OS overall survival; PFS2 time from randomisation to second progression; Q4W every 4 weeks; Q8W every 8 weeks; Q12W every 12 weeks; RECIST Response Evaluation Criteria in Solid Tumours.

[Source: Clinical Study Report]

Statistical Analysis Plan

The primary endpoint of POLO was progression free survival (PFS) as assessed by blinded independent central review (BICR) using a modified version of Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. PFS was defined as the time from randomization until the date of objective radiological disease

progression according to RECIST or death (by any cause in the absence of disease progression) regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy prior to disease progression (i.e., date of RECIST progression/death or censoring – date of randomization + 1). In general, the rules for censoring of PFS were consistent with FDA Guidance for Industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (December 2018)*, except that PFS was not censored at the time of the subsequent anti-cancer treatment.

The primary analysis of PFS was a log-rank test performed on the intent-to-treat (ITT) population. The PFS hazard ratio (HR) and its associated 95% confidence interval (CI) were to be estimated using the log-rank test (U and V statistics).[15,16]

The pre-specified sample size was 145 patients. Assuming that the median PFS was 4.0 months in the control arm and 7.4 months in the experimental arm, a total of 87 events were needed to detect a HR of 0.54 with 80% power at a 2-sided alpha level of 5%. One PFS interim analysis for futility was planned to be performed when 44 (50%) PFS events were observed.

The key secondary endpoint of POLO was OS. The statistical analysis plan included a gatekeeping procedure specifying that PFS would be tested first, followed by OS. OS was defined as the time from the date of randomization until death due to any cause (i.e., date of death or censoring – date of randomization + 1). Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive. A total of 106 events were needed to detect a HR of 0.57 with 80% power at a 2-sided alpha level of 5% assuming that the median PFS was 8.0 months in the control arm and 14.0 months in the experimental arm. OS was to be analysed using the same method as for PFS, and the final analysis of OS would be conducted when 106 events had occurred. A pre-specified interim analysis of OS was to be conducted when the final PFS analysis had occurred. The multiplicity adjustment for analyses of OS was based on the O'Brien-Fleming method.

The statistical analysis plan (SAP) for POLO also included a plan for exploratory analyses of clinical outcome assessment endpoints using descriptive statistics evaluating the change from baseline by time point in the EORTC QLQ-C30 global health status / quality of life (QoL) score for items 29-30 and adjusted

[15] Berry G, Kitchin RM, Mock PA. A comparison of two simple hazard ratio estimators based on the logrank test. Statistics in Medicine 1991; 10:749-7.
[16] Sellke, T., Siegmund, D. Sequential analysis of the proportional hazards model. Biometrika 1983; 70:315-326.

mean change from baseline (95% CI) over time. Due to their exploratory nature, these analyses were not controlled for multiplicity.

4.2 Results

4.2.1 Study Population

At the time of the final PFS analysis based on a January 30, 2019 data cut-off date, a total of 154 patients (92 in olaparib arm and 62 in placebo arm) were randomized. All but one patient (olaparib arm) met the eligibility criteria for exposure to a minimum of 16 weeks of a platinum-based therapy. Tables 2 and 3 summarize the baseline demographic and tumor characteristics of randomized patients in POLO.

Table 2. Study Population

Demographic Group	Olaparib 300 mg twice daily N=92 (%)	Placebo twice daily N=62 (%)
Age		
< 65	64 (70)	49 (79)
≥ 65	28 (30)	13 (21)
Sex		
Female	39 (42)	31 (50)
Male	53 (58)	31 (50)
Race		
White	82 (90)	59 (95)
Asian	4 (4.3)	2 (3.2)
Black or African-American	5 (5.4)	0
Other	1 (1.1)	1 (1.7)
Region		
North America	21 (23)	12 (21)
Western Europe	49 (54)	39 (61)
Middle East (Israel)	17 (16)	8 (12)
Asia (Korea)	4 (4.4)	2 (3.3)
Other	1 (1.1)	1 (1.6)
ECOG Performance Status (baseline)		
0	65 (71)	38 (61)
1	25 (27)	23 (37)
Missing	2 (2.2)	1 (1.6)

Table 3. Baseline Disease Characteristics

	Olaparib 300 mg twice daily N=92 (%)	Placebo twice daily N=62 (%)
First-line Treatment Regimen		
FOLFIRINOX	71 (77)	44 (71)
≥ 8 cycles	58 (63)	40 (65)
Gemcitabine plus a platinum	9 (10)	8 (13)
≥ 8 cycles	6 (7)	3 (5)
FOLFOX or CapeOX	7(8)	6(10)
≥ 8 cycles	2 (2)	5 (8)
Other platinum-containing regimen	4 (4)	3 (5)
Missing	1 (1.1)	1 (1.6)
Best response on first-line treatment		
CR	6 (7)	3 (5)
PR	40 (43)	27 (43)
Stable Disease	45 (49)	31 (50)
Missing	1 (1.1)	1 (1.6)
Disease burden at randomization		
Measurable disease	78 (85)	52 (84)
Non-measurable disease	8 (9)	6 (10)
No evidence of disease	5 (5)	0
Missing	1 (1.1)	4 (6)

Table 4 summarizes patient disposition information in POLO.

Table 4: Patient Disposition

	Olaparib 300 mg twice daily N=92 (%)	Placebo twice daily N=62 (%)
Randomized	92 (100)	62 (100)
Untreated	1 (1)	2 (3)
Treated	91 (99)	60 (97)
End of Study Treatment Status		
Ongoing	30 (33)	8 (13)
Discontinued	60 (65)	53 (85)
Reasons for discontinuing study treatment		
Adverse event	4 (4.3)	2 (3)
Objective disease progression	43 (47)	40 (65)
Reasons for withdrawing from the study	43 (47)	35 (57)
Death	41 (45)	30 (48)
Patient choice	3 (3.3)	1 (1.6)
Lost to follow-up	0	2 (3.2)

4.2.2 Efficacy Results

Although the statistical analysis plan specified that the final analysis of PFS was to occur after 87 BICR-assessed PFS events, AstraZeneca performed this analysis after occurrence of 104 PFS events. Due to the magnitude of the difference in the number of PFS events, reflecting a 20% increase over the pre-specified number of PFS events required for the final analysis, FDA conducted an exploratory retrospective analysis of PFS based on the pre-specified 87 PFS events. Based on 87 BICR-assessed PFS events among 136 randomized patients, POLO demonstrated a highly statistically significant effect on PFS that was modest in magnitude. Results of AstraZeneca's final analysis of PFS based on occurrence of 104 PFS events in 154 randomized patients were consistent with FDA's retrospective analysis of PFS based on the pre-specified 87 PFS events (Table 5).

As summarized in Table 5, the interim analysis of OS, which was based on a 67% information fraction (71 of the 106 OS events planned for the final analysis;

Figure 3), did not to show a statistically significant difference between the treatment arms. Based on the FDA statistician's calculation, the predictive power, the probability of rejecting the null hypothesis (no difference in OS between the two arms) under the posterior distribution with a noninformative prior given the observed statistic in the OS interim analysis, is 16%.

At the time of the data cut-off (Jan 2019), 30 patients (33%) in the olaparib arm and 8 patients in the placebo arm (13%) remained on protocol specified therapy, and 49% in the olaparib arm and 74% in the placebo arm had initiated post-progression therapy. Although crossover was not permitted in POLO, subsequent PARP inhibitor use was documented in 9 (15%) patients in the placebo arm. Of these, 7 (11%) patients received olaparib.

Table 5: Efficacy Results of Study POLO

	Olaparib n = 81	**Placebo n = 55**	**Olaparib n = 92**	**Placebo n = 62**
	Pre-specified Analysis[a]		**Final Analysis[b]**	
Progression Free Survival				
Number of Events n (%)	47 (58.0)	40 (72.7)	60 (65.2)	44 (71.0)
Progression	43	40	55	44
Death	4	0	5	0
Median PFS in months (95% CI)	7.5 (5.3, 11.2)	3.7 (3.5, 4.9)	7.4 (4.1, 11.0)	3.8 (3.5, 4.9)
Hazard ratio[c] (95% CI)	0.46 (0. 29, 0.73)		0.53 (0.35, 0.81)	
p-value (log-rank)	0.0009[d]		0.0035[f]	
			Interim Analysis	
Overall Survival (OS)				
Number of Events (%)			41 (44.6)	30 (48.4)
Median OS in months (95% CI)			18.9 (14.9, 26.2)	18.1 (12.6, 26.1)
Hazard ratio[c](95% CI)			0.91 (0.56, 1.46)	
p-value (log-rank)			0.6832[c]	
Overall Response Rate			19.6% (12%, 29%)	9.7% (4%, 20%)
Duration of Response (DOR)[e]			n=18	n=6
% of DOR ≥ 6 months			72%	33%
% of DOR ≥12 months			56%	33%

[a] Based on the prespecified 87 BICR- assessed PFS events in the SAP. At the time of the analysis, 136 patients (81 in Lynparza arm and 55 in the placebo arm) had been randomized.

This analysis was conducted by FDA and is considered a retrospective analysis performed after the results of the final analysis of PFS conducted by AstraZeneca was provided to FDA.
[b] At the time of AstraZeneca's final PFS analysis (considered the primary analysis of PFS by the Applicant), 104 BICR- assessed PFS events had occurred and a total of 154 patients had been randomized (92 in the olaparib arm and 62 in the placebo arm).
[c]Hazard ratio, 95% CI, and p-value calculated from a log-rank test (Peto method)
[d] Nominal p-value
[e] Based on observed durations of response rather than Kaplan-Meier estimated durations
[f] As compared to a significance level of 0.0452

Because the results of the pre-specified and final analyses of PFS are comparable, subsequent PFS analyses presented in this briefing document are based upon the final analysis based on 104 PFS events in 154 randomized patients.

Figure 2. Kaplan-Meier Curves of PFS

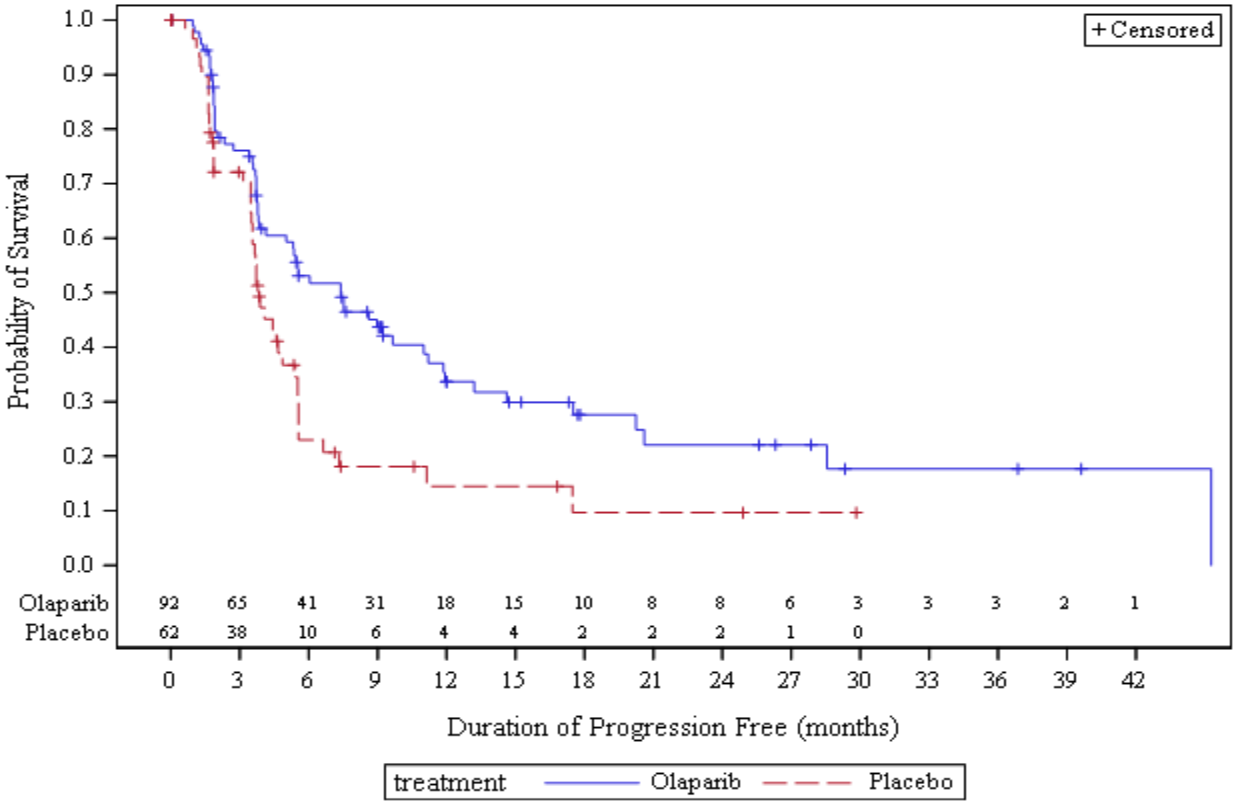
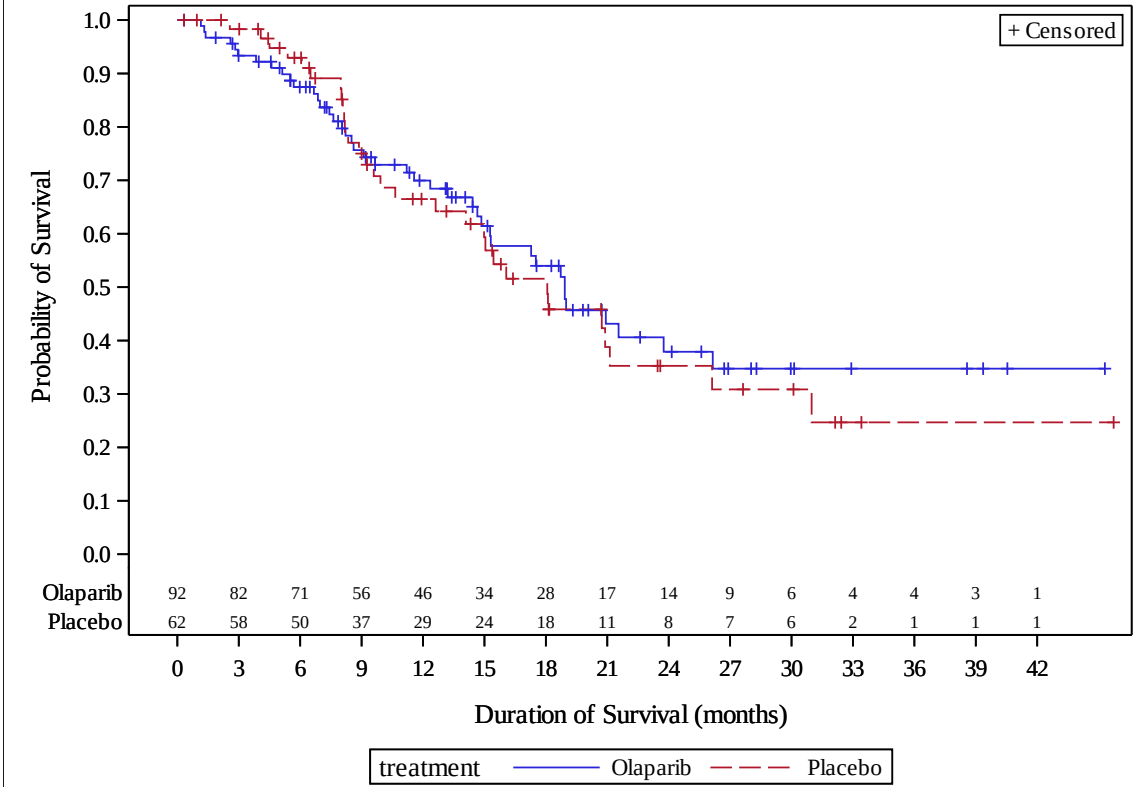


Figure 3. Kaplan-Meier Curves of OS



Interpretation of PFS Results

Due to concerns that the radiologic assessment of PFS can be challenging in this disease setting, both FDA and AstraZeneca conducted several sensitivity analyses of PFS to evaluate the robustness of the estimated PFS treatment effect and assess bias introduced from different sources. The sensitivity analyses were conducted by using different estimating methods (e.g. Cox model, Pike estimator), different censoring schemes (e.g., no censoring death, censoring PFS for patients who receiving subsequent cancer therapy, etc.), and different data sources (e.g., investigator assessment). The results of those sensitivity analyses were consistent with the final analysis of PFS.

Table 6 below shows concordance of progressive disease (PD) status between the BICR and investigator (INV) assessment.

Table 6: Concordance between Blinded Independent Committee Review and Investigator Assessment per RECIST v1.1

PD Status by Investigator	PD Status by BICR			
	Olaparib (n=92)		Placebo (n=62)	
	PD	No PD	PD	No PD
PD	42	6	41	7
No PD	12	26	3	11
Concordance Rate	74%		84%	

Notwithstanding potential challenges in the measurement of tumor-based endpoints in PDAC, FDA requests advice from the Committee regarding whether the observed treatment effect on PFS represents a benefit to patients. As shown in Table 5, the observed effect on PFS did not result in any effects on OS.

FDA notes that the sample size for POLO was small, resulting in wide confidence intervals around the estimated treatment effects. In order to estimate the difference in median PFS between arms, a bootstrap method was used to estimate the 95% confidence interval for the difference in median PFS. Based on 10,000 bootstrap iterations, the estimated median difference in PFS and its 95% CI based on a basic non-parametric bootstrap is 3.2 months (95% CI: 0.3 months, 7.3 months). Given that the lower bound of this confidence interval is 0.3 months (or approximately 9 days), FDA requests advice from the Committee regarding whether the observed effect on PFS is clinically meaningful.

FDA performed a test to evaluate whether the proportional hazard assumption was met. This test failed to detect evidence of non-proportionality; however, such a test may lack power to detect non-proportionality due to the small sample size. The Kaplan-Meier curves of PFS appear to show some degree of nonproportionality. The curves did not show separation until approximately 4 months, after approximately 53% of patients either had events or were censored. FDA performed additional sensitivity analyses by applying the restricted mean survival time (RMST) method using different truncation points (15 months and 18 months). The truncated time was selected (15 or 18 months) such that approximately 8-12% patients remained at risk. Based on the truncation times, the estimated RMST difference in PFS between arms ranged from 2.6 months (95% CI: 0.9, 4.3) to 3.1 months (95% CI: 1.0, 5.2). The range of the RMST differences again demonstrated great variation in the difference in PFS and the lower ends did not suggest that there was a clinically meaningful difference.

FDA noted that within 4 months of randomization, 60 (39%) of the 154 randomized patients had developed progression according to RECIST and 2 patients had died. Among the 60 patients with RECIST-defined progression within 4 months of randomization, 68% had previously received triplet combination chemotherapy, 72% had an ECOG performance status of 0, 72% received less than 6 months of first-line therapy, and 72% had a germline *BRCA*2 mutation. To evaluate whether the PFS result from POLO were driven by a subgroup of patients, FDA conducted several exploratory analyses to identify factors that might have impacted the PFS results. FDA's exploratory analyses included evaluation of PFS in subgroups by *BRCA* mutation type (*BRCA1* vs. *BRCA2*), best response on first-line treatment (complete response/partial response vs. stable disease), and baseline ECOG PS (0 vs. 1). These exploratory analyses did not identify a clear relationship between any of these factors and the treatment effect of olaparib.

4.2.3 Safety Overview

The POLO study provides the primary evidence of clinical safety for olaparib in patients with g*BRCA*m metastatic pancreatic adenocarcinoma. The safety population excluded 3 patients who did not receive study drug, 2 on the olaparib arm and 1 on the placebo arm. One patient who was randomized to placebo was treated with olaparib and this patient was included in the olaparib safety population. Table 7 provides a summary of safety for the POLO study. Table 8 summarizes the adverse reactions in POLO occurring in ≥ 10% of patients. Adverse events of special interest in POLO include myelodysplasia/acute myeloid leukemia (MDS/AML), new primary malignancies, and pneumonitis. No events of MDS/AML or new primary malignancy were observed in the olaparib arm. One patient in the olaparib arm had a Grade 1 adverse reaction of pneumonitis.

Table 7. Study POLO Safety Overview (Safety Analysis Set)

	Olaparib 300 mg twice daily N=91 (%)	Placebo twice daily N=60 (%)
Median Exposure	6 months	4 months
Patient with ≥ 1 AE	87 (95)	56 (93)
Patients with Grade 3-5 AE	36 (39)	14 (23)
Patients with SAE	22 (24)	9 (15)
Deaths not due to progression	4 (4.4)	1 (1.7)
Treatment discontinuation due to AE	4 (4.4)	1 (1.7)
Dose modifications due to AE	33 (36)	4 (6)

AE= adverse events; SAE= serious adverse events

Table 8. Adverse Reactions in POLO in ≥ 10% of patients

	Olaparib 300 mg twice daily N=91[a]		Placebo twice daily N=60[a]	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
General Disorders and Administration Site Conditions				
Fatigue	42 (46)	4 (4.4)	19 (32)	0
Asthenia	15 (16)	1 (1.1)	5 (8)	1 (1.7)
Pyrexia	12 (13)	0	5 (8)	0
Peripheral edema	8 (9)	1 (1.1)	7 (12)	0
Blood and Lymphatic System Disorders				
Anemia	25 (27)	11 (12)	10 (17)	2 (3.3)
Gastrointestinal Disorders				
Nausea	42 (46)	0	15 (25)	1 (1.7)
Abdominal pain[b]	32 (35)	1 (1.1)	25 (42)	0
Diarrhea	26 (29)	0	9 (15)	0
Constipation	22 (24)	0	7 (12)	0
Vomiting	18 (20)	1 (1.1)	11 (18)	1 (1.7)
Dyspepsia	5 (5.5)	0	6 (10)	0
Abdominal distension	4 (4.4)	0	6 (10)	0

	Olaparib 300 mg twice daily N=91[a]		Placebo twice daily N=60[a]	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Metabolism and Nutrition Disorders				
Decreased appetite	23 (25)	3 (3.3)	5 (8)	0
Skin and Subcutaneous Tissue Disorders				
Rash[c]	12 (13)	0	3 (5)	0
Pruritis	10 (11)	0	4 (7)	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	10 (11)	0	3 (5)	1 (1.7)
Nervous System Disorders				
Peripheral neuropathy	10 (11)	1 (1.1)	7 (12)	0
Dysgeusia	10 (11)	0	3 (5)	0
Headache	6 (7)	0	8 (13)	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	18 (20)	0	12 (20)	1 (1.7)
Arthralgia	14 (15)	1 (1.1)	6 (10)	0
Infections and Infestations				
Nasopharyngitis	11 (12)	0	2 (3.3)	0

[a] Three randomized patients did not receive treatment (two in the olaparib arm and one in the placebo arm). One patient who was randomized to the placebo arm received olaparib and is included here in the olaparib group.
[b] Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort
[c] Includes preferred terms of rash and rash erythematous

One death occurred in the olaparib arm due to an unknown cause. The patient was a 63-year old man who experienced a serious adverse event of stroke while on therapy resulting in discontinuation of olaparib, and died 61 days later. A causal relationship between this patient's death and olaparib cannot be ruled out based upon the information submitted by AstraZeneca.

5. SUMMARY OF FDA REVIEW ISSUES

In general, FDA has recommended OS as the primary endpoint of randomized trials intended to demonstrate the safety and effectiveness of new drugs for the treatment of pancreatic cancer, because it is a direct measure of clinical benefit, it is a feasible endpoint to assess in cancers such as advanced PDAC that have a short life expectancy, and based on FDA's concerns regarding the accuracy of radiological assessment of tumor status in pancreatic cancer, particularly at the primary tumor site and in metastatic locations such as the peritoneum and lymph nodes. An OS benefit was demonstrated for the three drugs approved for the first-line treatment of pancreatic cancer, gemcitabine, gemcitabine in combination with paclitaxel protein-bound, and gemcitabine in combination with erlotinib.

Although FDA has approved drugs that have an acceptable risk-benefit profile to treat some types of cancers based upon demonstration of substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, the magnitude of improvement in PFS and reliability of assessment of PFS are important factors in determining whether an observed improvement in PFS is clinically meaningful and likely to translate into a clinical benefit for patients.

The final analysis of PFS in the POLO trial demonstrated a persuasive, statistically significant effect on PFS [HR: 0.53 (95% CI: 0.35,0.81); p=0.0035 by an unstratified log-rank test]. However, this treatment effect was clinically modest. The PFS curves separated after approximately 53% of patients had PFS events or were censored and corresponded to a modest difference in median PFS of 3.6 months. Based on 10,000 bootstrap iterations using a basic non-parametric bootstrap, the estimated median difference in PFS at the final PFS analysis was 3.2 months (95% CI: 0.3, 7.3). The lower bound of the 95% confidence interval indicates that the true difference in median PFS may be as small as 0.3 months (9 days).

There was no evidence of an effect on OS for olaparib in the POLO trial in the interim analysis, with an upper limit of the 95% confidence interval for the estimated HR for OS of 1.46. FDA notes that while the trial may have been inadequately sized to detect small differences in survival, it was of adequate size and power to detect an effect on survival that is similar to that claimed for PFS. Specifically, there was adequate power (80%) to detect an effect on OS corresponding to a HR 0.57, with the pre-specified sample size of 145 patients and 106 OS events needed for the final analysis of OS. Additionally, given that PARP inhibitor use was documented in 9 (15%) patients in the placebo arm (including 7 patients who received olaparib), it does not appear likely that the lack

of demonstration of an OS benefit can be solely attributed to subsequent use of a PARP inhibitor in patients randomized to the placebo arm.

The safety profile of olaparib in patients with g*BRCA*m metastatic PDAC appears similar to the known safety profile of olaparib for its currently approved indications. However, in POLO, patients treated with olaparib experienced an increase in Grade 3 through 5 adverse reactions (39% vs. 23%) and serious adverse reactions (24% vs. 15%) compared to those receiving placebo.

When making a risk:benefit assessment for use of olaparib in the maintenance treatment of patients with g*BRCA*m pancreatic adenocarcinoma, FDA will consider the totality of evidence, including prior clinical experience with olaparib and the demonstration of effectiveness supporting previous approvals. As illustrated in Table 8, FDA has accepted PFS as the primary endpoint supporting approval of olaparib for other indications; however, in such cases, the Kaplan-Meier curves tended to separate early; in most cases, the PFS curves separated prior to Month 3 following randomization when 10% or fewer randomized patients experienced a PFS event or were censored. Additionally, except for the breast cancer trial, the 95% CI around the estimated HR for PFS were substantially narrower than the observed 95% CI for the proposed pancreatic cancer indication, and the magnitude of improvement in median PFS was larger (or supported by an improvement in OS).

Table 9: Summary of Basis of Efficacy Results for Olaparib Indications

Indication	PFS HR (95% CI); p-value	Median PFS Olaparib (mos)	Median PFS Control (mos)	Shape of K-M PFS Curves	OS HR (95% CI) p-value
Pancreatic cancer (proposed)					
Maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*m metastatic adenocarcinoma of the pancreas whose disease has not progressed on first-line platinum-based chemotherapy.	0.53 (0.35,0.81); p<0.0035	7.4	3.8	• PFS curves separate at ≈ Month 4 • ≈53% of patients either had a PFS event or were censored prior to curve separation • curves do not appear proportional	Interim Analysis 0.91 (0.56, 1.46) p=0.6833[a]
Ovarian Cancer					
First-Line maintenance treatment of *BRCA*-mutated advanced epithelial, ovarian cancer, fallopian tube, or primary peritoneal cancer[b]	0.30 (0.23-0.41) p<0.0001	NR[c]	13.8	• PFS curves separated before Month 3 • ≈5% of patients either had a PFS event or were censored prior to curve separation • curves appear proportional	NT; data not mature
Maintenance treatment of recurrent epithelial, ovarian, fallopian tube, or primary peritoneal cancer[d,e]	0.30[d] (0.22, 0.41); p <0.0001	19.1	5.5	• PFS curves separated before Month 3 • <10% patients either had a PFS event or were censored prior to curve separation • curves appear proportional	NT; data not mature
	0.35[e] (0.25, 0.49) p<0.0001	8.4	4.8	• PFS curves separates at Month 2.	0.73 (0.55, 0.95)[f]

Indication	PFS HR (95% CI); p-value	Median PFS Olaparib (mos)	Median PFS Control (mos)	Shape of K-M PFS Curves	OS HR (95% CI) p-value
				• ≈5% of patients either had a PFS event or were censored prior to curve separation Curves appear proportional	
Advanced g*BRCA*-mutated ovarian cancer after 3 or more lines of chemotherapy[g]	NT	NT	NT	NT	NT
Breast Cancer					
Germline *BRCA*-mutated HER2-negative metastatic breast cancer[h]	0.58 (0.43, 0.80) p=0.0009	7.0	4.2	• PFS curves separate at Month 2. • ≈10% of patients either had a PFS event or were censored prior to curve separation curves appear proportional	0.90 (0.66, 1.23)

Source: Lynparza product labeling
HR = hazard ratio K-M = Kaplan-Meier; NT = not tested (single arm study; approval based on ORR); OS = overall survival; PFS = progression-free survival
[a] nominal p-value [b] SOLO-1 trial [c] KM-estimated median PFS >36 months
[d] SOLO-2 trial [e] Study 19 [f] Not formally tested for survival
[g] Study 42; accelerated approval based on durable overall response rate, with confirmation of clinical benefit based on results of the SOLO-2 trial
[h] OlympiAD trial

6. ISSUES FOR THE COMMITTEE

- Discuss whether the demonstrated magnitude of benefit in progression free survival (PFS) with no evidence of effect on overall survival (OS) over placebo constitutes a clinically meaningful treatment effect in patients with metastatic g*BRCA*m pancreatic adenocarcinoma who have not had progression following at least 16 weeks of platinum-based chemotherapy.

- Is the risk-benefit assessment for maintenance olaparib in patients with g*BRCA*m PDAC favorable?