
ODAC Briefing Book

Drug substance Olaparib (AZD2281)

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**Lynparza® for the Maintenance Treatment of Patients with
Germline *BRCA*-Mutated Metastatic Adenocarcinoma of the
Pancreas**

SPONSOR BRIEFING DOCUMENT

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this briefing book:

Abbreviation or special term	Explanation
5-FU	5-Fluorouracil
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AUC	Area under plasma concentration-time curve
AUC _{ss}	Area under plasma concentration-time curve during any dosing interval at steady state
AZD2281	The generic name olaparib is generally used when referring to the drug substance known by the laboratory code AZD2281 or KU-0059436
bid	Twice daily
BICR	Blinded independent central review
<i>BRCA</i>	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicized whereas protein is not italicized)
BRACAnalysis®	The test consists of gene sequencing and large rearrangement analysis of the <i>BRCA1</i> and <i>BRCA2</i> genes performed by Myriad Genetics, Inc in their Clinical Laboratory Improvement Amendments (CLIA) facility
BRACAnalysis CDx®	
	The test consists of gene sequencing and large rearrangement analysis of the <i>BRCA1</i> and <i>BRCA2</i> genes performed by Myriad Genetics, Inc in their Quality Systems Regulation (QSR) facility
<i>BRCAm</i>	<i>gBRCA</i> or <i>sBRCA</i> mutated
<i>BRCAwt</i>	<i>gBRCA</i> and <i>sBRCA</i> wild type
CI	Confidence interval
C _{max} (C _{max,ss})	Maximum plasma concentration (at steady state)
C _{min} (C _{min,ss})	Minimum plasma concentration (at steady state)
CR	Complete response
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DCR	Disease control rate

Abbreviation or special term	Explanation
DDR	DNA damage response
DoR	Duration of Response
DSBs	Double-strand breaks
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIGO	Fédération Internationale de Gynécologie Obstétrique (International Federation of Gynecology and Obstetrics)
<i>gBRCA</i>	Germline <i>BRCA</i>
<i>gBRCA_m</i>	Germline <i>BRCA</i> mutated
<i>gBRCA_w</i>	Germline <i>BRCA</i> wild type
G _{mean}	Geometric mean
h	Hours
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRD	Homologous recombination deficient/deficiency
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
IND	Investigational new drug
KM	Kaplan Meier
LV	Leucovorin
MATE	Human Multi-Drug And Toxin Extrusion Transporter
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mOS	Median OS
mPFS	Median PFS
MTP	Multiple testing procedure
N	Total number of patients
NED	No evidence of disease
OCT	Organic cation-transporter
ORR	Objective response rate
OS	Overall survival
PAN26	Pancreatic cancer module 26

Abbreviation or special term	Explanation
PARP	Polyadenosine 5'diphosphoribose polymerase
PARPi	PARP inhibitor
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PFS2	Time from randomization to second progression or death
PK	Pharmacokinetic
PR	Partial response
PRO	Patient reported outcomes
PSR	Platinum-sensitive relapsed
QLQ-C30	Quality of Questionnaire Core 30 item module
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
<i>sBRCA</i>	Somatic <i>BRCA</i> (<i>BRCA</i> variant found in the tumor but not in the germline)
<i>sBRCAm</i>	Somatic <i>BRCA</i> mutated
SD	Stable disease
SOC	System organ class
SSBs	single-strand breaks
std	Standard deviation
TCMD	Time to sustained clinically meaningful deterioration
TDT	Time to discontinuation of treatment or death (defined as time from randomization to discontinuation of study treatment or death)
TFST	Time from randomization to start of first subsequent therapy or death
TSST	Time from randomization to start of second subsequent therapy or death
US/USA	United States/United States of America
VUS	Variants of uncertain significance
wt	Wild type

OVERVIEW

- Metastatic pancreatic cancer has a very poor prognosis with a 5-year survival of only 3%.
- *gBRCAm* metastatic pancreatic cancer is a unique, rare (~6%), and younger subset of the disease with a large unmet medical need.
 - First-line chemotherapy may provide initial disease and symptom control, however, those are short-lived with only a 3-month time to progression or death; furthermore chemotherapy cannot be tolerated for prolonged periods of time, requiring treatment breaks and leaving the patient untreated and at high risk for early disease progression, and early re-exposure to toxic chemotherapy.
 - In the context of this highly selected biomarker-based population, a statistically significant and clinically meaningful prolongation of PFS extends the benefits achieved by chemotherapy, and it further delays the recurrence and progression of disease and the time to going on subsequent chemotherapy. PFS is a recognized regulatory endpoint and has served as the primary basis for registration in a number of patient populations in both treatment and maintenance settings, in the absence of OS.
- The pivotal Phase III POLO study investigated the efficacy of olaparib compared to placebo as maintenance therapy in *gBRCAm* metastatic pancreatic cancer patients whose disease did not progress on first-line platinum-based chemotherapy and for whom the standard practice is to stop the chemotherapy (eg, those patients who can no longer tolerate platinum-based chemotherapy or have completed the specified 6 months of chemotherapy). There was no upper limit to the duration of chemotherapy that a patient had received.
- The primary endpoint was PFS by BICR, with ORR, TFST, PFS2, OS and HRQoL as key secondary endpoints.
 - In POLO, the primary efficacy objective was met, with the risk of disease progression or death (PFS) assessed by BICR being reduced by 47% for patients on olaparib vs placebo (HR=0.53; 95% CI 0.35 to 0.82; p=0.0038) and prolonged median PFS by 3.6 months with a median PFS of 7.4 months for olaparib vs 3.8 months for placebo.
- In the 84% of patients with measurable disease at baseline, ORR by BICR was higher for patients taking olaparib vs placebo (18/78 [23.1%] vs 6/52 [11.5%]; odds ratio 2.30), including 2 patients (11.1%) on olaparib who had a CR compared with none on placebo.
 - The median DoR by BICR was much longer for patients taking olaparib (24.9 months; 95% CI 14.75, NC) vs placebo (3.7 months; 95% CI 2.10, NC).
- The primary endpoint was associated with a clinically meaningful delay in time to resumption of chemotherapy (TFST), evidence of persistence of benefit beyond first

progression (PFS2), and preservation of health-related quality of life (HRQoL) achieved by chemotherapy.

- At the time of final PFS analysis, assessment of interim OS, a key secondary endpoint, was 46% mature with an HR of 0.91 (95% CI 0.56 to 1.46).
- The manageable safety profile of olaparib in *gBRCAm* pancreatic cancer patients was generally comparable to that of other indications for which olaparib is approved.
- The benefits associated with a clinically meaningful PFS prolongation and increased prolonged durable responses in a rare and biomarker defined patient population, combined with the tolerability and convenience of oral administration, represents an overall positive benefit-risk. These results support the regular approval of olaparib in patients with *gBRCAm* metastatic pancreatic cancer whose disease has not progressed on first-line platinum-based chemotherapy.

1 EXECUTIVE SUMMARY

1.1 Introduction

Pancreatic cancer is a life-threatening disease with one of the worst prognoses of all malignancies. In 2019, it is estimated there were 56,770 newly diagnosed cases, and approximately 45,750 deaths due to pancreatic cancer in the US ([SEER Cancer Statistics Factsheets 2019](#)). The 5-year survival rates for metastatic disease are only 3% ([American Cancer Society 2019](#), [Siegel et al 2019](#)), and by 2020 pancreatic cancer is anticipated to be the 2nd leading cause of cancer death in the US.

Loss-of-function mutations of the breast cancer susceptibility genes *BRCA1* and/or *BRCA2* genes are associated with an increased risk of cancers, including ovarian, breast, prostate and pancreatic cancers. *BRCA* genes code for proteins that are involved in homologous recombination repair (HRR) of DNA double-strand breaks (DSBs) ([Murai et al 2012](#)). Cells with a deficiency in HRR, such as those with a germline *BRCA* mutations (*gBRCAm*) and loss of the second *BRCA* allele, are very sensitive to poly (adenosine diphosphate–ribose) polymerase (PARP) inhibition. Normal tissues in people with *gBRCAm* still retain one wild type *BRCA* allele (*BRCAwt*), are not deficient in HRR and are much less sensitive to PARP inhibition. PARP inhibitors act through multiple mechanisms, including trapping of PARP on DNA at sites of single-strand breaks (SSBs) and inhibiting enzymatic activity. These processes prevent repair of SSBs, which occur commonly in cancer cells, leading to the generation of DSBs, which cannot be repaired accurately in cells with defects in HRR. Thus, PARP inhibitors cause a selective accumulation of DNA damage and cancer-cell death in cells with HRR defects.

Olaparib is a first-in class potent oral PARP inhibitor (PARP-1, PARP-2 and PARP-3), that has been shown to have clinical efficacy in patients with *gBRCAm* cancers, including ovarian and breast. Olaparib was the first PARP inhibitor to be approved (December 2014 in the United States [US] and Europe) and is approved in the US for a number of indications in ovarian and breast cancer as follows:

- Treatment of patients with *gBRCAm* advanced ovarian cancer who have been treated with 3 or more prior chemotherapies
- Maintenance treatment of patients with recurrent ovarian cancer following platinum-based chemotherapy
- Maintenance treatment of patients with *gBRCAm* advanced ovarian cancer following first-line platinum-based chemotherapy
- Treatment of patients with *gBRCAm* human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer

AstraZeneca is now seeking approval of olaparib in a third tumor type, for the maintenance treatment of adult patients with deleterious or suspected deleterious *gBRCAm* metastatic adenocarcinoma of the pancreas whose disease has not progressed on first-line platinum-based chemotherapy. The proposed dosing regimen is olaparib tablets 300 mg twice daily (bid), until disease progression. This briefing document provides information in support of this indication for the Oncologic Drugs Advisory Committee.

1.2 Prevalence of *gBRCAm* metastatic pancreatic cancer

The prevalence of *gBRCAm* in unselected cases of pancreatic ductal adenocarcinoma (PDAC) has been reported to range from 1.8% to ~5% ([Blair et al 2018](#), [Holter et al 2015](#), [Shindo et al 2017](#)), with a higher prevalence in specific populations (6 to 10% in unselected Ashkenazi Jewish pancreatic patients [[Ferrone et al 2009](#), [Ozcelik et al 1997](#)] and up to 19% in patients with a family history of the disease [[Hahn et al 2003](#), [Kim et al 2012](#), [Murphy et al 2002](#)]). Pancreatic cancer is an orphan disease as defined by the FDA (<200,000 US prevalence), and *gBRCAm* pancreatic cancer patients are an even smaller segment, indicating the rarity of the intended patient population.

1.3 Natural history of *gBRCAm* metastatic pancreatic cancer following platinum-based chemotherapy

The median age of *gBRCAm* pancreatic cancer patients at diagnosis is approximately 60 years old, almost a decade younger than an unselected pancreatic cancer population reported from the Surveillance, Epidemiology, and End Results ([SEER Cancer Statistics Factsheets 2018](#)). The natural history of stage IV *gBRCAm* pancreatic cancer patients treated with platinum-based chemotherapy is markedly different from those treated with non-platinum

chemotherapies with longer overall survival (OS) in those patients treated with platinum-based chemotherapy (median OS of 15 months [n=14] versus [vs] 7 months [n=14], respectively [[Golan et al 2014](#)]). Golan et al reported median progression-free survival (PFS) results of 3 months for stage IV *gBRCAm* pancreatic cancer patients who were treated with either platinum (n=12) or non-platinum (n=18) as first-line chemotherapy ([Golan et al 2013](#)). The time interval between median PFS and OS is larger in *gBRCAm* pancreatic adenocarcinoma patients treated with platinum-based chemotherapy (~12 months) compared to what is seen in unselected pancreatic adenocarcinoma patients treated with platinum-based therapy (<5 months; [Conroy et al 2011](#)).

1.4 Unmet Need in *gBRCAm* metastatic pancreatic cancer

Over the past 40 years, there have been few advances in the treatment of metastatic pancreatic cancer; therapeutic options are generally limited to successive lines of chemotherapy. The Food and Drug Administration (FDA) has only approved five products for metastatic pancreatic cancer over the past two decades ([Ducieux et al 2015](#), [FDA](#), [Oberstein and Olive 2013](#)). Advances have consisted of the addition of chemotherapy drugs to existing regimens, resulting in small efficacy benefits but at the expense of tolerability ([Varadhachary and Wolff 2016](#)).

There are currently no precision medicine treatment options for *gBRCAm* pancreatic cancer patients. Platinum-based chemotherapy is the preferred regimen for the first-line treatment of advanced pancreatic cancer, including of *gBRCAm*, because of the evidence that overall survival is improved ([Golan et al 2014](#)) compared to that with non-platinum regimens and is advocated by national guidelines, including those for patients with known *BRCA* mutations pancreatic cancer ([NCCN 2019](#)). For *gBRCAm* patients with good performance status, NCCN guidelines recommend platinum-based regimens including the FOLFIRINOX regimen (a combination of 5-fluorouracil [5-FU], irinotecan, leucovorin [LV], and oxaliplatin) ([Conroy et al 2011](#)) and gemcitabine cisplatin ([Oliver et al 2010](#)).

There are two practice patterns that exist for these regimens. Physicians either intend to administer chemotherapy for 6 months and stop in patients who had not progressed (ie, the approach described the original FOLFIRINOX paper: [Conroy et al 2011](#)), or to administer chemotherapy until disease progression. However, in either case, many patients have to stop therapy early due to toxicity. Even when dosages are modified or when individual chemotherapy agents are dropped, platinum-based chemotherapy is difficult to tolerate due to cumulative toxicities that can be significant (eg, Grade 3/4 neutropenia [45.7% of patients] and possibly irreversible (such as sensory neuropathy [9% of patients]; [Conroy et al 2011](#), [Dahan et al 2018](#), [Kang et al 2018](#), [Ozaka et al 2018](#)). Furthermore, the need for a 46-hour infusion of fluorouracil every two weeks requires patients to carry ambulatory pumps with limitation of activities/travel and frequent visits to clinic. As a result, many patients who

receive first-line platinum-based chemotherapy do not continue that therapy until disease progression.

For those non-progressing patients who can no longer tolerate platinum-based chemotherapy, or have completed 6 months of chemotherapy, the standard practice is to stop the chemotherapy for some period of time (ie, a “chemotherapy break”), which allows the patient to recover from the challenging side effects of treatment. However, this also leaves the patient untreated and at high risk for earlier disease progression with earlier re-exposure to chemotherapy and its toxicities. This suggests a need for new treatment strategies.

1.5 Maintenance therapy may provide an option for patients who cannot tolerate prolonged intensive chemotherapy

Maintenance therapy refers to systemic therapy given to cancer patients who have achieved an objective response or disease stabilization after first-line treatment, with the aim to extend responses, delay disease recurrence or progression, and delay subsequent chemotherapy.

In addition to prolonged control of disease and delaying the time to initiation of the next line of chemotherapy, maintenance therapy must preserve a patients’ health-related quality of life (HRQoL) previously achieved on first-line chemotherapy for as long as possible ([Gourgou-Bourgade et al 2013](#)).

Maintenance therapy also needs to be tolerable, with an acceptable long-term safety profile, and be conveniently administered, eg, orally ([Pujade-Lauraine et al 2017](#)).

1.6 Pre-clinical data supported evaluation of olaparib in *gBRCAm* pancreatic adenocarcinoma

BRCAm cells which have lost both alleles lack functional *BRCA1* or *BRCA2* and therefore are unable to effectively undergo HRR. Normal cells in a person with a germline *BRCAm* retain one functional copy of *BRCA* and are not HRR deficient. DNA damage in the form of SSBs is common in cancer cells. PARP inhibitors trap PARP at the site of SSBs and prevent their repair, resulting in accumulation of DSBs. DSBs cannot be repaired accurately in cells which are HRR-deficient; an alternate error prone repair pathway is used, leading to accumulation of DNA damage and selective cancer cell death.

The sensitivity to PARP inhibition is dependent on *BRCA* mutation and is agnostic to tumor type in pre-clinical models. Pancreatic cell lines, including but not limited to a *BRCA2* mutant pancreatic cell line (CAPAN-1), have been shown to be sensitive to olaparib in vitro. Further correlations between response to olaparib and cisplatin treatment have also been demonstrated in vivo, in a pancreatic patient-derived xenograft model of *BRCAm* ([Golan et al 2018](#)).

The correlation between response to olaparib and response to platinum-based chemotherapy is explained by the mode of action of each agent; both agents lead to DSBs in DNA, which cannot be effectively repaired in *gBRCAm* cells with loss of both *BRCA* alleles. However, chemotherapy works very differently by directly inducing DNA lesions in the form of intra- and inter-strand crosslinks, irrespectively of the genetic background of the cells treated; whereas PARP inhibitors (PARPi) induce DNA damage indirectly, and the damage accumulates selectively in replicating cells with homologous recombination deficiency (HRD) (ie, *BRCA* deleterious mutations). As a consequence, platinum treatments led to cytotoxic effects that are only ~10-20-fold more selective for *BRCAm* versus *BRCAwt* cells; in contrast, olaparib is able to selectively kill *BRCAm* cells, with ~1000-fold sensitivity versus the *BRCAwt* or *BRCA+/-* heterozygote cells. This wider therapeutic window in vitro underpins the improved safety profile of olaparib compared with platinum chemotherapy ([Hucl et al 2008](#); [Tacconi et al 2019](#)).

1.7 Clinical pharmacology of olaparib

The pharmacokinetics (PK) of olaparib tablets have been well characterized in patients with advanced solid tumors, including pancreatic cancer patients. Patient age, race, gender, body weight or tumor type were not found to be predictors of olaparib plasma exposure and therefore dose adjustment on the basis of individual patient demographics is not required. Olaparib PK in patients with pancreatic cancer was similar to other cancer patients.

1.8 Phase II clinical data provided evidence of olaparib activity in *gBRCAm* pancreatic adenocarcinoma

Prior to the POLO study, clinical evidence for the activity of olaparib in pancreatic cancer patients was observed in Study D0810C00042 (Study 42; NCT01078662), a single arm Phase II basket study of olaparib in patients with *gBRCAm* malignancies across multiple tumor types ([Kaufman et al 2015](#)). The study included 23 patients with *gBRCAm* advanced pancreatic cancer who had either failed or were unsuitable for gemcitabine treatment in the advanced setting. Patients received olaparib in a second-line or above setting. Data from this study demonstrated that olaparib was active in *gBRCAm* patients with metastatic pancreatic cancer as evidenced by:

- Objective response rate (ORR): 5/23 patients (21.7%) had an ORR; of these, 1 patient had a complete response (CR) and 4 patients had a partial response (PR). No responses were observed in patients who had progressed on prior platinum therapy
- Duration of response (DoR): The median DoR was 4.4 months
- Progression free survival: The median PFS was 4.55 months, with 36.4% and 9.1% of patients remaining progression free at 6 months and 12 months, respectively

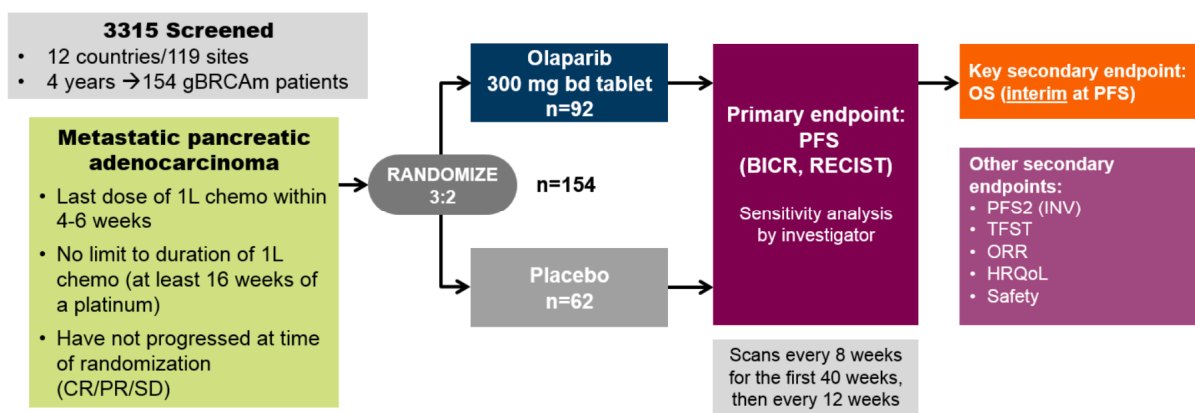
- Overall survival: The median OS was 9.81 months, with 63.6% and 40.9% of patients remaining alive at 6 months and 12 months, respectively
- Disease control rate (DCR; defined as CR, PR or stable disease [SD]): 11/23 patients (47.8%) had DCR at 16 weeks.

1.9 Olaparib efficacy as maintenance therapy in *gBRCAm* pancreatic adenocarcinoma is demonstrated in the pivotal Phase III POLO trial

1.9.1 POLO Study Design

POLO (Pancreas cancer OLaparib On-going; NCT02184195) was a robust, well-controlled, Phase III randomized, double blind, placebo-controlled multicenter study of olaparib as a maintenance therapy in *gBRCAm* patients with metastatic pancreatic adenocarcinoma (Figure 1).

Figure 1 POLO study schema



There was no upper limit to the duration of first-line chemotherapy that a patient had received and the majority of patients received more than 16 weeks (Golan et al 2019).

As stated above, many patients who receive first-line platinum-based chemotherapy do not continue that therapy until disease progression, either because their physician intended to administer chemotherapy for a maximum of 6 months (or stop sooner if they were not able to tolerate this), or their physician intended to administer chemotherapy until disease progression but treatment had to be stopped early due to toxicity. The POLO trial was intended to address an unmet need in these two practice patterns that exist for *gBRCAm* metastatic pancreatic cancer patients. A minimum duration of 16 weeks of platinum was required to ensure sufficient exposure to platinum chemotherapy in the first-line setting.

POLO was designed as a maintenance trial for metastatic pancreatic cancer patients who achieve an objective response or disease stabilization after first-line treatment, with the aim to extend response and delay recurrence or progression. PFS assessed by blinded independent central review (BICR) was chosen as the primary endpoint.

Progression-free survival is a clinically relevant endpoint to measure benefit in this subset of biomarker-selected pancreatic cancer patients because it is a direct measure of biological effect of drug on tumor growth when supported by additional endpoints reflecting patient benefit. OS is much longer in these patients when treated with platinum as first-line therapy resulting in a sizable difference between PFS and OS. This allows for patients to receive multiple subsequent therapies confounding OS. This is different than in the general pancreatic cancer population, where both PFS and OS are similarly short. The rarity of the *gBRCAm* population in addition to the longer OS makes it not feasible to power a study to reliably detect a statistically significant difference in OS. In addition, PFS is a recognized regulatory endpoint and has served as the primary basis for registration in a number of biomarker selected patient populations in both treatment and maintenance settings, in the absence of OS.

POLO was conducted in 12 countries worldwide, including the US. Patients were required to have documented evidence of a loss of function germline *BRCA* mutation (either *gBRCA1* or *gBRCA2*) to be enrolled. Evidence of a qualifying *gBRCA* mutation could be from either an existing *gBRCA* mutation result generated by local testing or from prospective testing performed by Myriad using either the Myriad *BRACAnalysis*[®] test or Myriad *BRACAnalysis CDx*[®] test. Patients randomized based on a local *gBRCA* test result were re tested post randomization prior to database lock using either the Myriad *BRACAnalysis*[®] test or Myriad *BRACAnalysis CDx*[®] test where possible, to confirm their *gBRCAm* status. The study screened 3315 patients for *gBRCAm*, enrolled 167 patients and randomized 154 patients (32 patients were randomized in the US, of whom 19 patients were randomized to olaparib). The study took 4 years to complete randomization of 154 patients, with the first patient randomized on 29 January 2015 and the last patient randomized on 06 January 2019. The study is ongoing with a final event driven overall survival analysis expected to occur in late 2020 once 106 deaths have occurred (69% maturity).

The POLO study is the first global and the largest prospective study to determine the likely prevalence of *gBRCAm* in patients with pancreatic cancer, and a total of 6.2% of patients (196/3175) with previously unknown *BRCA* status were tested and shown to be *gBRCAm* by the Myriad *BRACAnalysis*[®] test or *BRACAnalysis CDx*[®] test.

1.9.2 POLO Efficacy

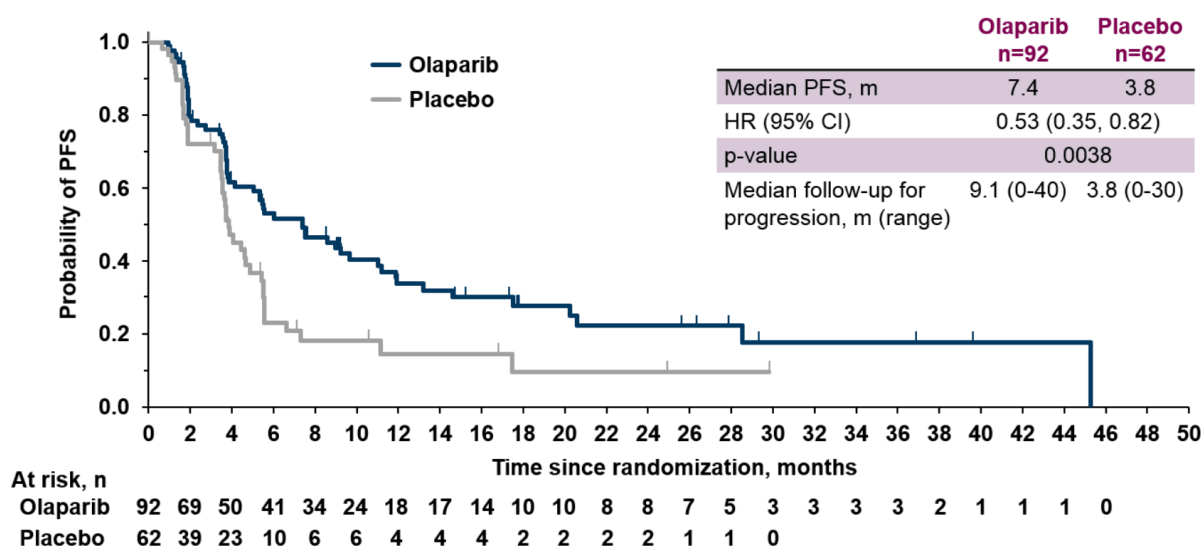
Per protocol, the primary analysis of PFS was to be undertaken once approximately 87 PFS events were observed. An interim analysis of OS was also to be performed at that time. At

the time of the data cut-off (DCO; 15 January 2019) for the primary analysis there were 104 PFS events, to permit all patients who were screened positive for *gBRCAm* to have the opportunity to be randomized.

POLO met its primary endpoint, reducing the risk of disease progression or death (PFS) assessed by BICR, by a clinically meaningful and statistically significant 47% for patients on olaparib vs placebo (HR=0.53; 95% CI 0.35 to 0.82; p=0.0038; [Figure 2](#)).

- Olaparib prolonged median PFS by 3.6 months with a median PFS of 7.4 months for olaparib vs 3.8 months for placebo.

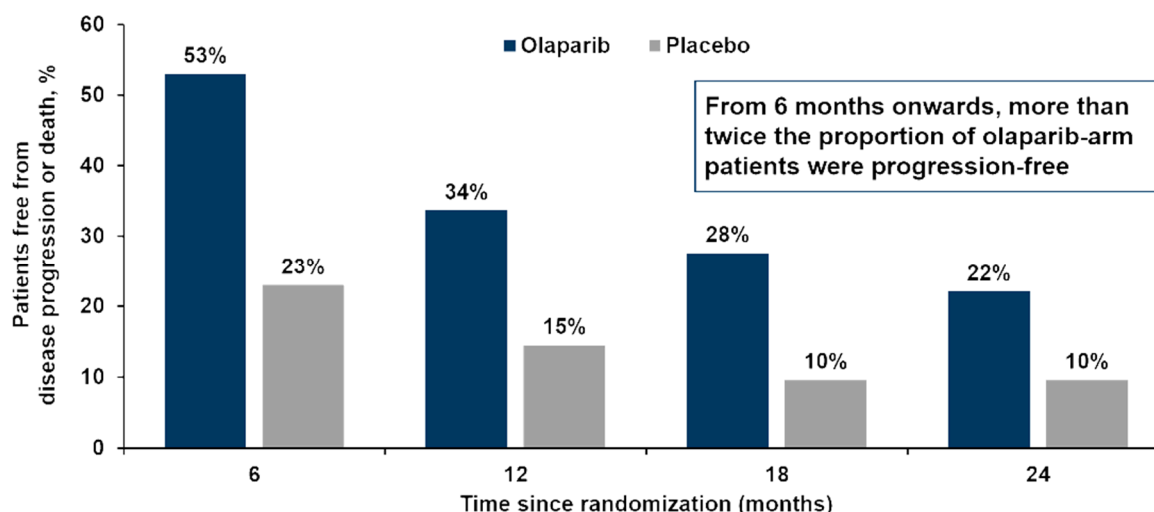
Figure 2 **Olaparib provided a clinically meaningful and statistically significant 47% reduction in the risk of disease progression or death (by BICR assessment)**



BICR Blinded independent central review; CI Confidence interval; F/U Follow-up; HR Hazard ratio; m Month; PFS Progression-free survival.

- Based on Kaplan-Meier (KM) estimates, at every timepoint beyond 6 months of treatment, the likelihood of recurrence or disease progression for patients receiving olaparib was reduced by at least half compared to placebo, which indicated that the PFS benefit was persistent ([Figure 3](#)). Furthermore, the KM plot shows sustained benefit for olaparib treated patients; 22.1% of them remaining event-free beyond 24 months.

Figure 3 Percentage of patients progression-free^a at pre-specified timepoints



^a Based on Kaplan-Meier estimates

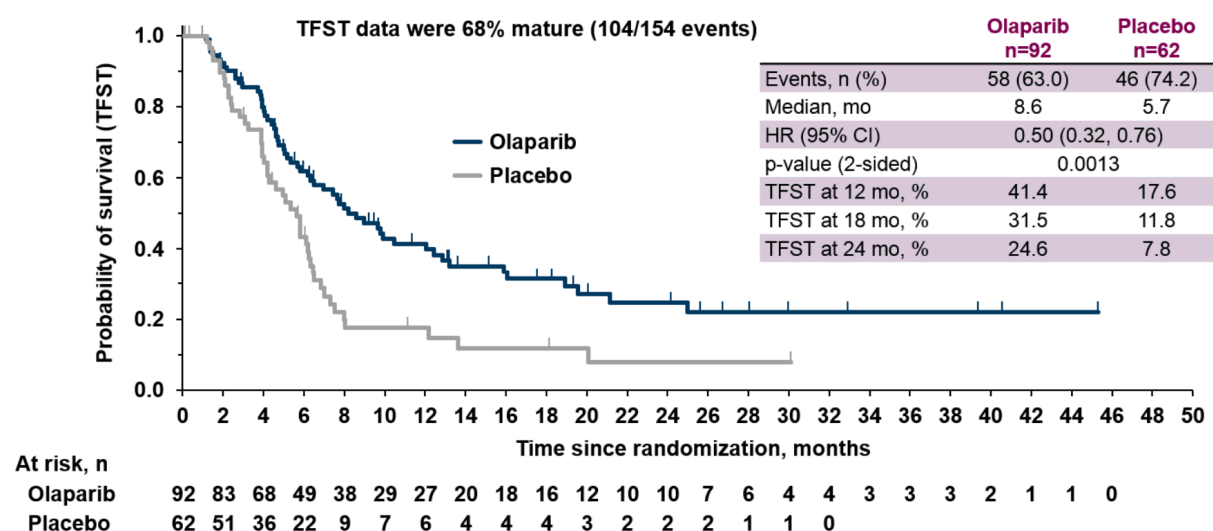
- The PFS analysis was robust: all sensitivity analyses (evaluation time bias and attrition bias) and the investigator assessment of PFS (HR=0.51; 95% CI 0.34 to 0.78; p=0.0017; median PFS 6.3 months vs 3.7 months for olaparib vs placebo, respectively) were consistent with the PFS analysis by BICR.
- The analyses of PFS were consistent across all subgroups. No subgroups derived a differential benefit compared with the overall population.
- Progression-free survival assessed at 87 events was done as a sensitivity analysis (HR=0.46; 95% CI 0.29 to 0.73; p=0.0010; median PFS 7.5 months vs 3.7 months for olaparib vs placebo, respectively) and the results were consistent with the PFS analysis conducted at the DCO of 15 January 2019 (104 events) confirming the robustness of the PFS analysis.

The additional aspects of POLO that demonstrate clinical benefit to patients were:

- In the 84% of patients with measurable disease at baseline, ORR by BICR was higher for patients taking olaparib vs placebo (18/78 [23.1%] vs 6/52 [11.5%]).
 - Of the 18 patients who had a response (CR/PR) in the olaparib arm, 2 patients (11.1%) had a CR. None of the 6 patients who had a response in the placebo arm had a CR.
- The median DoR by BICR was much longer for patients taking olaparib (24.9 months; 95% CI 14.75, NC) vs placebo (3.7 months; 95% CI 2.10, NC).

- At the DCO (15 January 2019), 9.9% of patients on olaparib were on drug for at least 2 years (compared to 3.3% on placebo) with several of them on olaparib at 3 years indicative of a cohort of patients experiencing long-term progression-free survival on olaparib.
- Olaparib extended the chemotherapy free interval and delayed the time to first subsequent therapy, which was often potentially toxic chemotherapy; a 50% reduction in the risk of first subsequent therapy or death compared with placebo treated patients (TFST HR=0.50; p=0.0013 [nominal], median TFST 8.6 months for olaparib vs 5.7 months for placebo), which was clinically meaningful to patients (Figure 4).

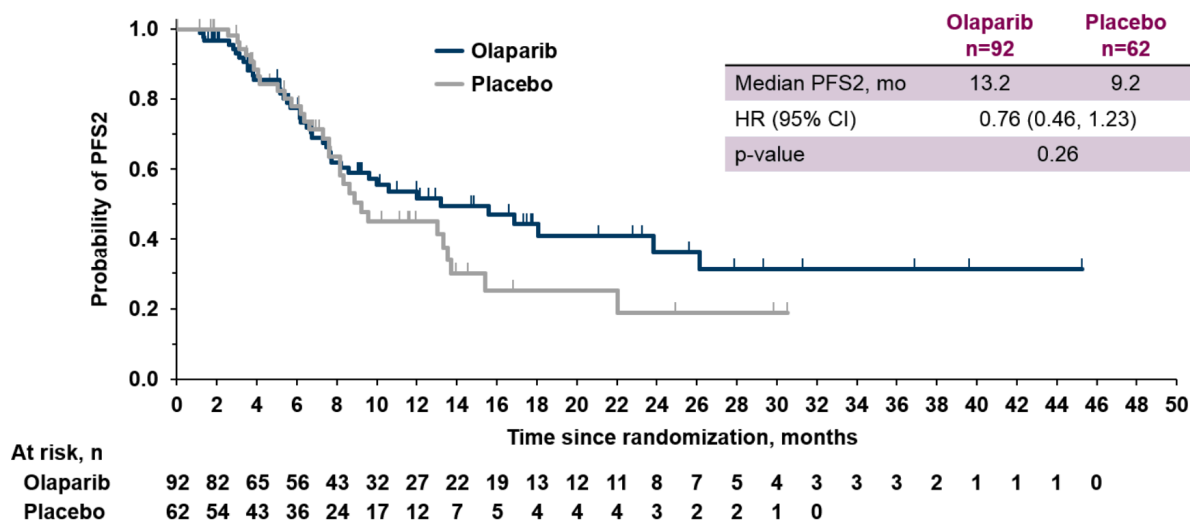
Figure 4 Olaparib provided a clinically meaningful delay in the time patients receive their first subsequent therapy



CI Confidence interval; HR Hazard ratio; mo Month; TFST time to first subsequent therapy or death.

- At the DCO (15 January 2019), more olaparib patients remained on assigned study drug (n=30, 32.6%) compared to placebo (n=8, 12.9%) and therefore were not candidates for subsequent chemotherapy (48.9% in the olaparib arm vs 74.2% in the placebo arm received subsequent therapies).
- Disease control rate (DCR; defined as CR, PR, SD or no evidence of disease [NED]) at 16 weeks was higher on the olaparib arm (53.3%) compared with the placebo arm (37.1%).
- The delay in time to second progression or death (PFS2; 46% maturity) as evidenced by Kaplan-Meier estimates, suggested a favorable trend towards benefit on olaparib (Figure 5).

Figure 5 A favorable trend towards benefit in second progression-free survival for olaparib-treated patients



CI Confidence interval; HR Hazard ratio; mo Month; PFS2 Time from randomization to second progression or death.

- The delay in TSST suggested a positive trend for the olaparib arm compared with the placebo arm, indicating that the olaparib treatment benefit is maintained over subsequent lines of therapy.
 - The clinically meaningful trend towards a delay in PFS2 and TSST demonstrate continuous benefit with olaparib beyond progression and indicates that olaparib maintenance treatment does not reduce the ability of patients to receive and respond to subsequent therapies.
- At the DCO (15 January 2019), the OS HR for olaparib-treated patients was 0.91 (95% CI 0.56 to 1.46) (interim OS maturity: 46% [71 events/154 patients]; median OS 18.9 months olaparib vs 18.1 months placebo).
 - A final event driven OS analysis is expected to occur in late 2020 once 106 deaths out of 154 patients have occurred (69% maturity). Based upon the data observed at the interim analysis and the protocol stated assumptions for the remaining data, the probability of seeing a statistically significant difference in OS at the final analysis is 9%, strongly suggesting a statistically significant result for OS is not expected. As of 17 October 2019, a total of 84 deaths have occurred.
- The HRQoL at baseline in POLO was high and comparable with expected norms for the general population, likely reflecting improvements in HRQoL for responding patients on first-line chemotherapy. Olaparib maintenance treatment preserved the HRQoL in patients, with no meaningful difference compared to placebo. The proportion of patients

with clinically meaningful improvement in global HRQoL score was 29.2% in the olaparib arm compared to 22.4% in the placebo arm.

- Olaparib appears to delay time to worsening of pain, which is a key symptom of metastatic pancreatic cancer. Longer median time (months) to deterioration intervals were observed in the olaparib arm compared to placebo (QLQ-C30 pain domain 7.4 vs 4.4; QLQ-PAN26 pancreatic pain domain 11.0 vs. 6.0). The proportion of patients who experienced deterioration in the QLQ-C30 pain domain was 23.6% in the olaparib arm and 39.7% in the placebo arm.

1.9.3 POLO Safety

The safety profile of olaparib has been well-characterized; ~12,000 subjects are estimated to have received olaparib across the clinical program, as well as >20,000 patients years exposure from post-marketing use (as of 15 June 2019). In POLO, the median total duration of exposure in the olaparib arm (6.0 months) was approximately 1.6 times longer than in the placebo arm (3.7 months). No new safety concerns were identified in POLO. The safety profile of olaparib in the POLO study was generally consistent with the known safety profile of olaparib; adverse events (AEs) with olaparib were predominantly mild or moderate in severity and, in the majority of cases, resolved without the need for any dose interventions. The 300 mg bid dose was well tolerated with the majority of patients receiving ≥ 500 to ≤ 600 mg mean daily dose of olaparib throughout the study.

Long-term tolerability to olaparib maintenance therapy was demonstrated with 25.3%, 9.9% and 3.3% of patients in the olaparib arm remaining on treatment at 1 year, 2 years and 3 years, respectively in POLO (compared with 6.7%, 3.3%, and 0%, respectively, in the placebo arm). Objective and subjective disease progression were the most common reasons for treatment discontinuation in the placebo arm (64.5% and 14.5% patients, respectively) compared with 46.7% and 12.0% of patients, respectively in the olaparib arm. Few patients in either the olaparib or placebo arms discontinued treatment due to AEs (5.5% vs 1.7%, respectively).

Hematological side effects (predominantly anemia), gastrointestinal disturbances (nausea and vomiting) and fatigue/asthenia were among the most commonly reported adverse events (reported by $\geq 15\%$ of patients) associated with olaparib treatment, were generally transient and manageable, and consistent with its known safety profile.

1.10 Benefit-Risk Discussion

gBRCAm metastatic pancreatic cancer patients represent a rare (~6% of the unselected pancreatic patient population) and relatively young patient population (median age 60 years). Despite the initial benefit that these patients may receive from first-line platinum-based chemotherapy, many patients are not able to continue therapy until disease progression due to

toxicity, which leaves them untreated and at high risk for earlier disease progression. There are currently no treatment options approved in the maintenance setting for pancreatic cancer patients and no precision medicine treatment options for the biomarker defined *gBRCAm* patients with pancreatic adenocarcinoma, reflecting a high unmet medical need in this population.

Progression-free survival is a clinically relevant endpoint to measure benefit in this rare subset of pancreatic cancer patients because it extends the time to re-initiation of chemotherapy with its associated toxicities. The rarity of the *gBRCAm* population makes it not feasible to power a study to reliably detect a statistically significant difference in OS. Additionally, the sizable difference between PFS and OS observed in *gBRCAm* pancreatic cancer patients exposed to first line platinum-based chemotherapy leads to the confounding of OS by receipt of multiple subsequent therapies.

The POLO study was a well-controlled, randomized, double blind study that met its primary endpoint, and showed that olaparib significantly maintained the benefits achieved by chemotherapy, further delayed the recurrence or progression of disease and time to going on subsequent therapy, without compromising patients' quality of life. POLO demonstrated a clinically meaningful and statistically significant 47% reduction in the risk of progression or death and a prolongation of median PFS to 7.4 months in the olaparib arm from 3.8 months in the placebo arm in *gBRCAm* patients with metastatic pancreatic adenocarcinoma, a benefit that appears to be persistent beyond 2 years based on landmark analysis. Additionally, the “tail” on PFS curve suggests that there is a cohort of patients who experience long-term progression free survival.

The median duration of response of 24.9 months for the 23% of patients who presented an objective response to olaparib (of which 2 patients had a CR), compared to 3.7 months to those patients (11%) who responded to placebo (none of whom had a CR), is remarkable in pancreatic cancer and indicative of clinical benefit.

Olaparib extended the chemotherapy-free interval and delayed the TFST, which was often potentially toxic chemotherapy by almost 9 months compared to less than 6 months on placebo.

The olaparib safety profile in POLO was consistent with the known safety profile in its approved indications (ovarian and breast cancer), and POLO demonstrated that olaparib is suitable for maintenance therapy in the proposed indication.

Based on the results of POLO, NCCN guidelines have been updated ([NCCN 2019: v3](#), dated 02 July 2019) to recommend olaparib as maintenance treatment for *gBRCAm* pancreatic cancer: “Consider olaparib as maintenance treatment for patients who have a deleterious

germline *BRCA1/2* mutation, good PS, metastatic disease, and no disease progression >16 weeks of first-line, platinum-based chemotherapy”.

Moreover, olaparib maintenance therapy has the convenience of oral administration, which allows patients to receive treatment at home, and reduces the requirement for frequent and prolonged clinic visits for intravenous administration with chemotherapy, which often requires pre- and post-chemotherapy-related monitoring and toxicity management.

Collectively the PFS benefits, ORR and DoR benefits and the additional associated secondary endpoints represent a significant advancement in the treatment of patients with *gBRCAm* pancreatic cancer, with a positive benefit-risk assessment that supports regular approval of olaparib, as maintenance for the treatment of adults with *gBRCAm* metastatic pancreatic cancer whose disease has not progressed on first-line platinum-based chemotherapy.

2 BACKGROUND

Olaparib (Lynparza[™]) is a first-in-class potent oral PARP inhibitor (PARP-1, PARP-2 and PARP-3), that exploits deficiencies in DNA repair pathways to preferentially kill cancer cells.

In the United States (US), olaparib was first approved in December 2014 and the olaparib tablet formulation is already registered for marketing for use and is indicated for:

Ovarian Cancer:

- for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (*gBRCAm* or *sBRCAm*) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.
- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.
- for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (*gBRCAm*) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Breast Cancer:

- in patients with deleterious or suspected deleterious *gBRCAm*, 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. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

On 28 June 2019 AstraZeneca submitted an efficacy supplement for a third tumor type to New Drug Application (NDA) 208,558 (S-010) for olaparib tablets in support of the following proposed indication and dose:

- Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious *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.
- A supplemental Pre-Market Approval (sPMA) for the BRACAnalysis CDx[®] assay to olaparib was submitted in July 2019.
- The recommended dose of Lynparza is 300 mg (two 150 mg tablets) taken orally twice daily, with or without food, for a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction.

Continue treatment until disease progression or unacceptable toxicity.

2.1 Metastatic pancreatic cancer

2.1.1 Disease background

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 deaths. The poor prognosis of pancreatic cancer (~90% of patients who are diagnosed will die of the disease) is due to late presentation of the disease (locally advanced or metastatic) at the time of diagnosis. For patients diagnosed with metastatic disease, 5-year survival rates are only 3% ([American Cancer Society 2019](#), [Siegel et al 2019](#)). In the US in 2019, pancreatic cancer is estimated to be the third most common cause of cancer deaths (45,750 deaths) and the ninth most commonly newly diagnosed cancer (56,770 new cases) ([American Cancer Society 2019](#), [Siegel et al 2019](#)). Pancreatic cancer is predicted to become the second most common cause of death (after lung cancer) by 2030 ([Gordon-Dseagu et al 2018](#), [Rahib et al 2014](#)) and is therefore an important public health issue.

Pancreatic cancer is an orphan disease as defined by the FDA (<200,000 US prevalence) and *gBRCAm* pancreatic cancer patients are an even smaller segment, representing up to 6% of the overall pancreatic cancer patient population indicating the rarity of the intended patient population sought in this supplemental New Drug Application (sNDA).

2.1.2 Prevalence of *gBRCA* mutations in pancreatic cancer

Although carriers of loss of function germline mutations of the *BRCA1* and *BRCA2* genes are known to have an increased risk of developing pancreatic cancer ([Breast Cancer Linkage Consortium 1999](#), [Goggins et al 1996](#)), the prevalence of *gBRCA* mutations in the unselected cases of pancreatic cancer is unclear. Holter et al reported on a prospective analysis of the prevalence of *gBRCA1/2* mutations in a cohort of 306 unselected patients with incident PDAC diagnoses and identified *gBRCA* mutations in ~5% of patients ([Holter et al 2015](#)). Shindo et al recently identified *BRCA* mutations in 1.8% of patients in a cohort of 854 patients with PDAC ([Shindo et al 2017](#)) and Blair et al identified *BRCA* mutations in 3.3% of patients in a cohort of 658 patients with resected sporadic PDAC ([Blair et al 2018](#)). There are specific populations, however, where the association is much stronger. In Ashkenazi Jewish patients with pancreatic cancer, the prevalence of *gBRCA* mutations is 6 to 10% in unselected patients ([Ferrone et al 2009](#), [Ozcelik et al 1997](#)) and 15% in patients with a family history of the disease ([Kim et al 2012](#)). In pancreatic cancer patients with a family history of the disease, prevalence of carrying a germline *BRCA2* mutation as high as 17% to 19% has been reported ([Hahn et al 2003](#), [Murphy et al 2002](#)).

2.1.3 Natural history of *gBRCAm* metastatic pancreatic cancer following platinum-based chemotherapy

The median age of *gBRCAm* pancreatic cancer patients at diagnosis is approximately 60 years old, almost a decade younger than an unselected pancreatic cancer population reported from the Surveillance, Epidemiology, and End Results ([SEER Cancer Statistics Factsheets 2018](#)). There are no direct comparisons of the natural history of *gBRCAm* metastatic pancreatic cancer with that of unselected metastatic pancreatic cancer following platinum-based chemotherapy treatment. However, recognizing the challenges with cross-study comparisons, there are literature reports where, following treatment with platinum-based chemotherapy, a longer OS was observed in *gBRCAm* metastatic pancreatic cancer patients (median OS of 15.0 months; n=14 [[Golan et al 2014](#)]) compared with the unselected population (median OS of 11.1 months; n=171 [[Conroy et al 2011](#)]).

Prior to the initiation of the POLO trial, the only published data available in *gBRCAm* metastatic pancreatic cancer patients following treatment with platinum-based chemotherapy was from the retrospective study by Golan et al ([Golan et al 2014](#)). In stage IV *gBRCAm* pancreatic cancer patients the natural history of those treated with platinum-based chemotherapy is markedly different from those treated with non-platinum chemotherapies with longer OS in those patients (median OS of 15 months [n=14] versus [vs] 7 months [n=14], respectively; [[Golan et al 2014](#)]). Golan et al reported median PFS results of 3 months for stage IV *gBRCAm* pancreatic cancer patients who were treated with either platinum (n=12) or non-platinum (n=18) as first-line chemotherapy ([Golan et al 2013](#)).

Patients analyzed in the Golan report were diagnosed between January 1994 and December 2012; no published data for PFS in *gBRCAm* metastatic pancreatic cancer patients who had received FOLFIRINOX were available prior to the initiation of the POLO trial.

Furthermore, the natural history of homologous recombination repair gene mutated (HRRm)-associated advanced (stage III and IV) pancreatic cancer patients treated with platinum-based chemotherapy is different from non-HRRm-associated pancreatic cancer patients, as reported by Pishvaian et al, with longer OS observed in HRRm patients (2.37 years vs 1.44 years [[Pishvaian et al 2019](#)]).

2.1.4 Current treatment for *gBRCAm* metastatic pancreatic cancer in the US highlights an unmet need

Over the past 40 years, there have been few advances in the treatment of metastatic pancreatic cancer; therapeutic options are generally limited to successive lines of chemotherapy. Despite significant efforts, the Food and Drug Administration (FDA) has only approved five products for metastatic pancreatic cancer over the past two decades ([Ducreux et al 2015](#), [FDA](#), [Oberstein and Olive 2013](#)). Advances have consisted of the addition of chemotherapy drugs to existing regimens, resulting in small efficacy benefits but at the expense of tolerability ([Varadhachary and Wolff 2016](#)).

There are currently no treatment options approved in the maintenance setting for pancreatic cancer patients and no precision medicine treatment options for *gBRCAm* pancreatic cancer patients.

For unselected patients, the two preferred regimens for initial treatment of metastatic disease include the platinum-based FOLFIRINOX regimen (a combination of 5-FU, irinotecan, LV, and oxaliplatin) or gemcitabine in combination with nab-paclitaxel ([Conroy et al 2011](#), [Von Hoff et al 2013](#), [Ducreux et al 2015](#), [NCCN 2019](#)). Gemcitabine alone or in combination with erlotinib may also be used in the first-line treatment setting ([Moore et al 2007](#), [NCCN 2019](#)).

Platinum-based chemotherapy is the preferred regimen for the first-line treatment of *gBRCAm* advanced pancreatic cancer because of the evidence that overall survival is markedly improved (median ~8 months from start of chemotherapy [[Golan et al 2014](#)]) compared to that with non-platinum regimens and is advocated by national guidelines in pancreatic cancer patients with known *BRCA1/2* mutations ([NCCN 2019](#)). However, many patients who receive first-line platinum-based chemotherapy do not continue that therapy until disease progression. Their physicians either intended to administer chemotherapy for 6 months (ie, the approach described in the original FOLFIRINOX paper: [Conroy et al 2011](#)), but the patients were not able to tolerate this, or their physicians intended to administer chemotherapy until disease progression but it had to be stopped prior to disease progression due to toxicity ([Dahan et al 2018](#), [Kang et al 2018](#), [Ozaka et al 2018](#)). This is because despite the initial disease control

that they may bring to patients, even when modified or drug components dropped, platinum-based regimens such as FOLFIRINOX can be very difficult to tolerate due to cumulative toxicities that can be significant and possibly irreversible. Polyneuropathy, attributable to the oxaliplatin component of FOLFIRINOX, occurs almost invariably and may not be completely reversible depending on the number of cycles received. Other components of the FOLFIRINOX regimen have their own significant issues for patients, such as diarrhea for irinotecan and the burdensome requirement for being attached to an infusion pump for 2 days every 2 weeks for fluorouracil. These cumulative toxicities can be significant (eg, Grade 3/4 neutropenia [45.7% of patients] and possibly irreversible (such as sensory neuropathy [9% of patients]; [Conroy et al 2011](#)). Patients who receive other platinum-based regimens such as gemcitabine/cisplatin also experience issues of cumulative ototoxicity and nephrotoxicity that may limit their duration of treatment. The toxicities and lifestyle effects of platinum-based regimens often limit the extent of exposure to treatment that can be given, and many patients discontinue active therapy prior to disease progression.

The original FOLFIRINOX regimen called for 6 months of platinum-based chemotherapy after which treatment should be stopped; however, the median duration of treatment on the FOLFIRINOX arm was 5 months ([Conroy et al 2011](#)). In practice, patients can typically tolerate the full regimen of FOLFIRINOX or a modified version of FOLFIRINOX for approximately 5 to 6 months, with some patients stopping for significant toxicity at 4 months ([Dahan et al 2018](#), [Kang et al 2018](#), [Ozaka et al 2018](#)).

For those patients who can no longer tolerate platinum-based chemotherapy regimens, the standard practice is to stop the chemotherapy for some period of time (ie, a “chemotherapy break”), which allows the patient to recover from the challenging side effects of treatment. However, this also leaves the patient untreated and at high risk for earlier disease progression. As many patients with pancreatic adenocarcinoma do not complete the entire course of platinum therapy due to toxicity, there is a need for new treatment strategies preventing early disease progression and maintaining the benefits that were obtained from first-line chemotherapy. This can be achieved by an effective well tolerated maintenance therapy.

2.1.5 Clinical rationale for maintenance therapy with olaparib for *gBRCAm* patients with metastatic pancreatic adenocarcinoma

Maintenance therapy refers to systemic therapy given to cancer patients who have achieved an objective response or disease stabilization after first-line treatment, with the aim to extend responses or delay recurrence or progression. While the intent of many treating physicians is to treat patients to disease progression, the cumulative toxicity that develops even with dose modification, interruptions and component drug discontinuations, can be so severe as to necessitate discontinuing therapy. This leaves patients at high risk of disease progression. However, maintenance treatment could allow for prolonged disease control and a delay in

initiation of the next line of chemotherapy (along with its associated toxicities) by a clinically meaningful duration of time, offering patients significant clinical benefit. These strategies may also help to improve recovery from toxicities of induction therapy allowing introduction of salvage therapy at a more effective dose when required.

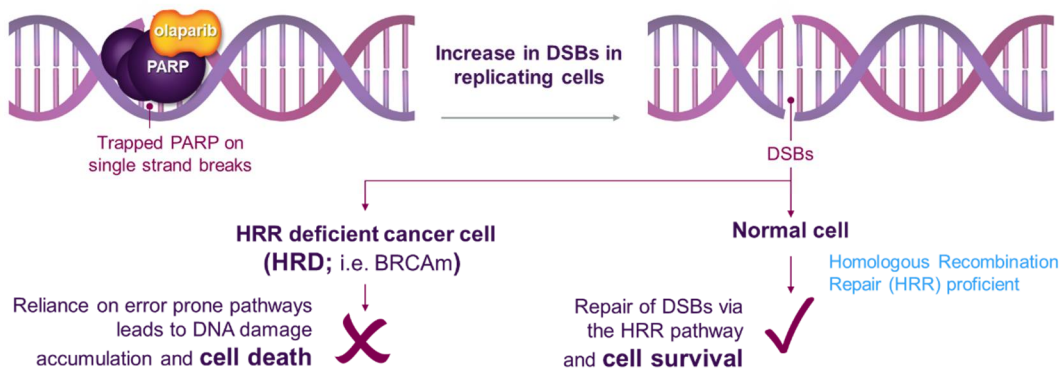
Chemotherapy may alleviate symptoms of the disease and subsequently improve patients' HRQoL; first-line treatment with FOLFIRINOX has been shown to improve overall HRQoL and lead to a decrease in some symptoms, including pain, for patients with metastatic pancreatic cancer ([Gourgou-Bourgade et al 2013](#)). In addition to prolonged control of disease, maintenance therapy must preserve patients' HRQoL previously achieved on chemotherapy for as long as possible. Maintenance therapy needs to be tolerable, with an acceptable long-term safety profile. A drug used in this setting must also be conveniently administered ([Pujade-Lauraine et al 2017](#)).

Considering there are no available treatment options for *gBRCAm* metastatic pancreatic cancer patients, there is an opportunity to introduce olaparib in the maintenance setting, a treatment with the convenience of oral administration.

2.2 Mechanism of action of olaparib

The anticancer activity of the PARP inhibitor olaparib works through a process called synthetic lethality. Olaparib inhibits and traps PARP at the sites of DNA single-strand damage, both preventing repair and during replication, leading to the generation of the more serious DNA DSBs. In HRR proficient cells, these DSBs are repaired accurately and efficiently, but in cancer cells with HRD, such as those with *BRCA1* or *BRCA2* mutations with loss of the second functional allele, repair is dependent on the inaccurate end-joining pathway that results in genome instability and preferential killing of cancer cells over normal cells ([Figure 6](#)).

Figure 6 Mechanism of action of PARPi as therapy that targets HRD



Scheme representing the mechanism of action of PARPi and the synthetic lethality with HRD (of which *BRCA* mutation is the best-known example). Inhibition and trapping of PARP selectively kills cancers that are HRR deficient. Adapted from [O'Connor 2015](#)

There are two hypotheses to explain why olaparib is predicted to be an effective maintenance treatment for pancreatic adenocarcinoma.

2.2.1 Deficiencies in homologous recombination repair

The antitumor effects of olaparib and other PARP inhibitors are dependent on an underlying defect in a cancer cell's DNA damage response (DDR) mechanisms, rather than a direct interaction with a mutated gene or protein. These defects in DDR mechanisms arise from cells with HRD, of which *BRCA* mutations are only one subtype albeit the most studied. Olaparib traps PARP at the sites of DNA single-strand damage and prevents DNA repair ([Murai et al 2012](#)). During replication, the DNA SSBs trapped with PARP are converted to DNA DSBs. Double-strand breaks are normally repaired by HRR, which is a high-fidelity process. Normal cells in a patient with a *gBRCAm* retain the second functional *BRCA* allele and are not HRR deficient, so repair DSBs normally. In cancer cells with HRD, DSBs cannot be effectively repaired resulting in preferential killing of cancer cells over normal cells. The appearance and accumulation of DNA damage in HRD cancer cells during olaparib treatment is replication-dependent. For this reason, multiple rounds of replication and cell division are required for the DNA damage to become unsupportable and to lead to selective HRD cancer cell death.

The HRR-defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo ([Hay et al 2009](#), [Rottenberg et al 2008](#), [Golan et al 2018](#)) and in the clinic ([Fong et al 2009](#), [Tutt et al 2010](#)). Clinical studies suggest that single-agent olaparib is effective in *gBRCAm* pancreatic cancer ([Kaufman et al 2015](#)).

2.2.2 Pre-selection for homologous recombination deficiency by platinum-sensitivity

PARP inhibition is an effective option for platinum-sensitive tumors (for the POLO study this was defined as patients with CR, PR or SD). Although the mechanism of platinum agent induced DNA DSBs are different to trapped PARP (platinum produce non-reversible DNA inter- and intra-strand crosslinks which distort the DNA, and inhibit DNA replication and transcription), the resulting DSBs still require HRR for effective and accurate repair. Deleterious alterations in HRR are therefore associated with a high degree of platinum sensitivity, as observed in ovarian cancer ([Bowtell 2010](#)). However, the difference in sensitivity to platinum for *BRCAm* vs *BRCAwt* cells is around 10-20-fold, in contrast to PARP inhibition which has 1000-fold difference in sensitivity in *BRCAm* compared to *BRCAwt* in vitro ([Hucl et al 2008](#), [Tacconi et al 2019](#)). Pre-clinical data show that sensitivity to platinum

agents correlates with sensitivity to olaparib in pancreatic cancer cell lines (Section 2.3), as well as cell lines derived from other tumor types in which platinum-based chemotherapy is the standard-of-care (Lowery et al 2011, Mason et al 2012). Correlations between the response to olaparib and cisplatin treatments was further demonstrated in vivo, in pancreatic patient-derived xenograft models with deleterious *BRCA* mutations (Golan et al 2018). The effect of *BRCA* mutations and response to DNA crosslinking agents in PDAC was evaluated by Lowery et al (Lowery et al 2011), who reported that 5 out of 6 *BRCAm* PDAC patients who received a platinum agent as first-line therapy demonstrated a radiographic PR or radiographic CR. In a small retrospective study in *BRCAm* patients with PDAC, a superior OS was observed for patients with stage 3/4 treated with platinum vs those treated with non-platinum chemotherapies (22 months vs 9 months; $p=0.039$) (Golan et al 2014). Clinical results from the PanCAN Know Your Tumor Program also demonstrated that HRR-related genes (DDRm) predicted OS improvement in platinum-treated pancreatic adenocarcinoma. In advanced pancreatic cancer patients who received prior platinum treatment, median OS was 2.37 years in HRRm patients compared with 1.44 years in non-DDRm patients (Pishvaian et al 2019). Maintaining a response to platinum-based chemotherapy is challenging due to their (well-known) cumulative toxicities (Conroy et al 2011).

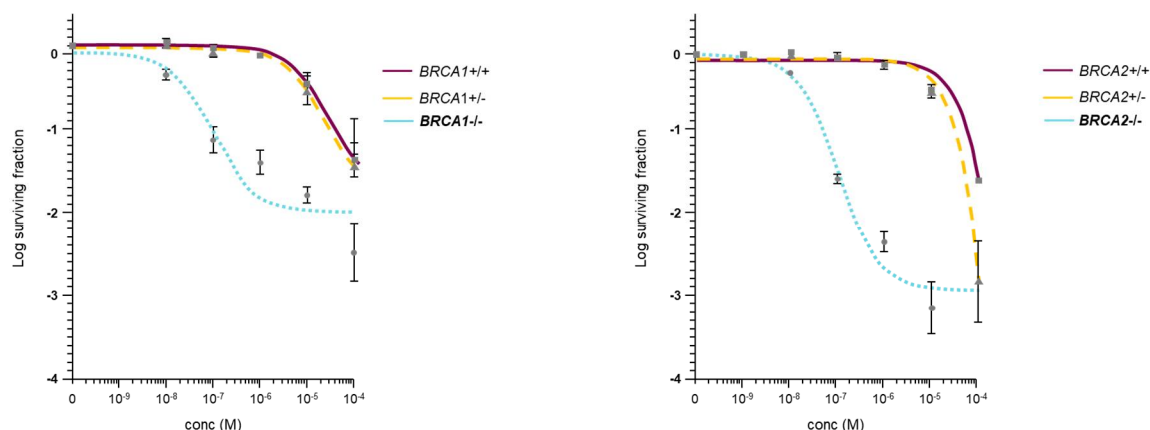
2.3 Rationale for evaluation of olaparib in pancreatic cancer

2.3.1 Pre-clinical evidence

2.3.1.1 The scientific evidence for PARP inhibitor synthetic lethality in *BRCAm* cells is not tumor type specific

The sensitivity to PARP inhibition is dependent on *BRCA* mutation (and HRD) and is agnostic to tumor type in pre-clinical models. This is evident from the very first publications of the PARPi synthetic lethality in *BRCAm* backgrounds which were demonstrated in non-cancerous cells (Farmer et al 2005, Bryant et al 2005; Figure 7) and from the fact that the efficacy of the PARP inhibitor olaparib has been observed not only in ovarian cancer models (Kortmann et al 2011) but also those of breast (Rottenberg et al 2008) and pancreatic cancer (McCabe et al 2005).

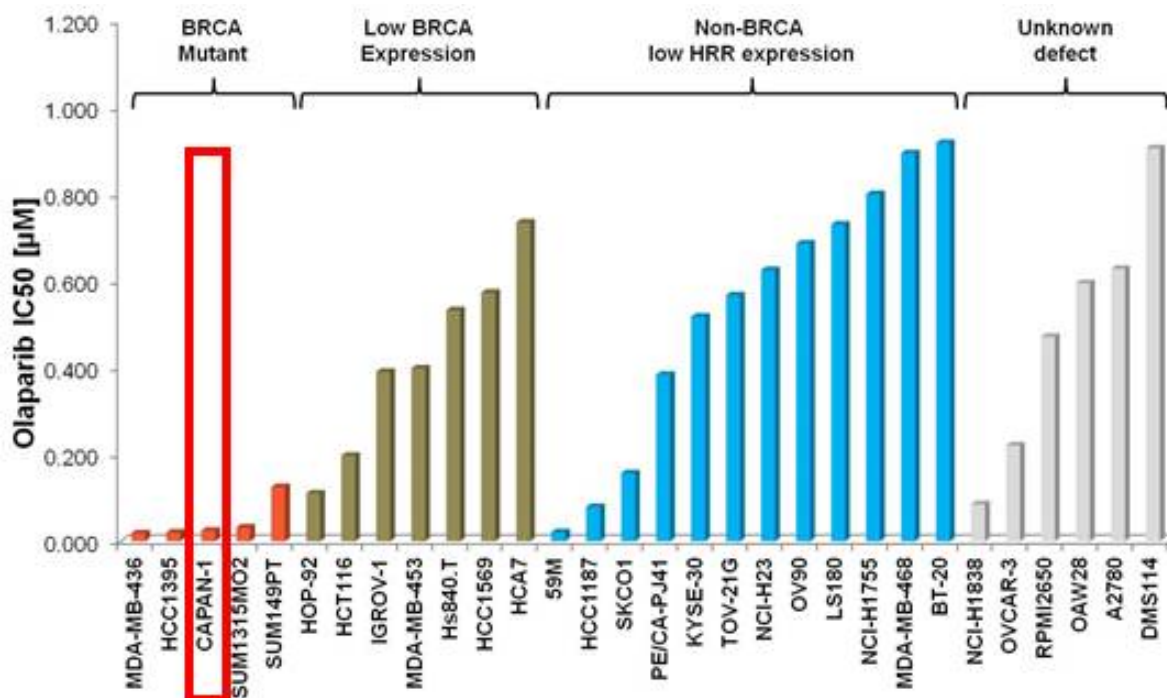
Figure 7 Differential activity of PARP inhibition with *BRCA* status



Inhibition of PARP activity selectively inhibits the survival of cells lacking wild-type *BRCA1* (left) and *BRCA2* (right). Clonogenic survival curves of *BRCA1/2* wild type, heterozygous (*BRCA1* +/- and *BRCA2* +/-) and deficient (*BRCA1* -/- and *BRCA2* -/-) mouse ES cells after 10 to 12 days continuous exposure to inhibitor. Error bars represent one standard deviation around the mean. Taken from [Farmer et al 2005](#).

The degree of sensitivity of the pancreatic cell line CAPAN-1 to olaparib is comparable to those of the most sensitive *BRCA*m breast cancer cell lines ([Figure 8](#)).

Figure 8 Olaparib activity in the *BRCA2* mutant pancreatic cancer model CAPAN-1 is comparable to the most sensitive *BRCA* mutant breast cancer cell lines



Plot of highly olaparib sensitive cell lines ($IC_{50} < 1 \mu M$) clustered by the presence known deleterious *BRCA1/2* mutations (*BRCA* Mutant), low *BRCA1/2* expression (low *BRCA* expression), low expression of one more HRR genes in the absence of *BRCA1/2* mutation/low expression (Non-*BRCA*, low HRR expression) or those without any of these defects (unknown defect).

Red rectangle indicates *BRCAm* pancreatic cancer cell line (CAPAN-1)

2.3.1.2 Generation of PARP inhibitor resistance, first demonstrated in the CAPAN-1 model, provides support that it is the *BRCA2* mutation that drives PARP inhibitor response

The first examples of PARPi resistance generation, resulted from experiments using the CAPAN-1 cell line. Characterization of the resistant clones identified secondary mutations in the *BRCA2* mutated gene that restored the reading frame and generated functional protein (Edwards et al 2008; Figure 9). This observation provides evidence that the driver of PARPi sensitivity in this model of pancreatic cancer is the *BRCA* mutation.

Figure 9 Reversion mutations in the CAPAN-1 pancreatic cancer cell line consisted of secondary mutations that restored the *BRCA2* reading frame

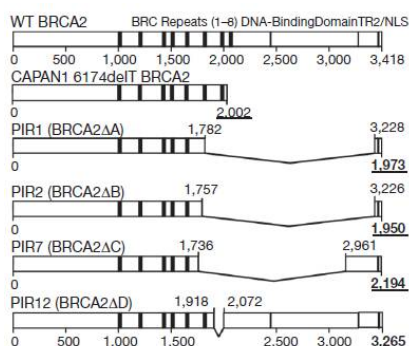
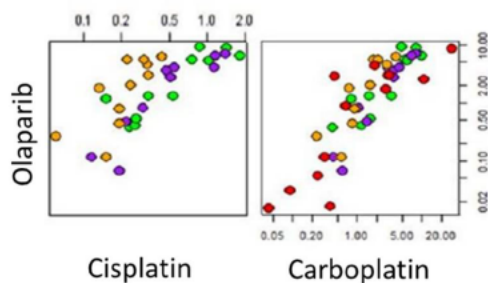


Diagram of new BRCA2 proteins in PIR1, PIR2, PIR7 and PIR12, as predicted from cDNA and genomic sequencing of *BRCA2*. The predicted number of amino acids for each new isoform is shown in bold and underlined. WT wild type

2.3.1.3 Olaparib response in cancer models correlates with platinum sensitivity in multiple tumor types including pancreatic cancer

There is a strong correlation between olaparib and platinum response in cancer models from multiple tumor indications including breast, ovarian, non-small cell lung cancer and head and neck squamous cell carcinoma cell lines (Figure 10). This correlation has a biological rationale, namely that platinum agents induce DNA DSBs that require HRR for effective and accurate repair. Consequently, cancers with HRD are highly sensitive to multiple different platinum agents. There is also a strong correlation with topoisomerase 1 inhibitors for the same reason, ie, HRR is required to effectively deal with the DNA DSBs induced by these agents.

Figure 10 Correlation of olaparib and platinum agent response in cancer cell lines

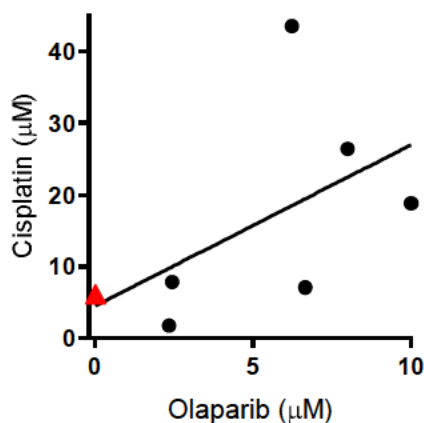


The panel shows cell line correlations of sensitivity between platinum agents and olaparib where the X-Y correlation plots compare the IC_{50} values. Different colored dots represent data points from different tumor types (red=breast, orange=ovarian, green=head and neck, purple=lung).

Left panel: olaparib vs cisplatin (IC_{50} s obtained for cisplatin are indicated on top, in μM). Right panel: olaparib vs carboplatin (IC_{50} s for carboplatin indicated at the bottom, in μM). IC_{50} s obtained for olaparib are indicated in y axis, on the right.

A similar correlation has also been observed between platinum sensitivity and olaparib sensitivity in pancreatic cancer cell lines (Figure 11).

Figure 11 Correlation of olaparib and platinum response in pancreatic cell lines



Correlation between olaparib response (IC_{50}) (x-axis) and the response to carboplatin (y-axis) in a panel of pancreatic cell lines treated with either agent. The red triangle represents CAPAN-1, the only cell line in this panel carrying a *BRCA2* deleterious mutation. Olaparib IC_{50} values were obtained in long term proliferation assay; Cisplatin IC_{50} values were provided by the Sanger Institute and are published in [Gill et al 2015](#).

Correlations between the response to olaparib and cisplatin treatments was further demonstrated in vivo, in pancreatic patient-derived xenograft models with deleterious *BRCA* mutations ([Golan et al 2018](#)).

3 CLINICAL PHARMACOLOGY OF OLAPARIB

Olaparib tablets are an oral formulation and available in two dose strengths:

- a tablet containing 150 mg of olaparib (2 x 150 mg tablets for 300 mg bid, equivalent to a total daily dose of 600 mg)
- a tablet containing 100 mg of olaparib is available to support dose reductions

To differentiate tablets strengths, a film-coat has been used for the intended commercial formulation, yellow for the 100 mg strength and green for the 150 mg strength with minor composition changes between strengths. This would not be expected to have any impact on tablet performance as demonstrated by equivalent in vitro dissolution profiles.

The PK of the olaparib tablets have been well characterized in patients with advanced solid tumors, including pancreatic cancer patients with a *gBRCA* mutation and appropriate information is included in the Lynparza US Prescribing Information ([Lynparza USPI 2018](#)).

Patient age, race, gender, body weight or tumor type were not found to be predictors of olaparib plasma exposure and therefore dose adjustment on the basis of individual patient demographics should not be required. Olaparib PK in patients with pancreatic cancer is similar to other cancer patients (Section [5.2](#)).

4 SUPPORTIVE PHASE II CLINICAL STUDY

Clinical evidence for the activity of olaparib in pancreatic cancer patients was observed in Study D0810C00042 (Study 42; NCT01078662).

4.1 Study 42 overview

Study 42 was a single arm Phase II, open-label, non-randomized, non-comparative and multicenter study to assess the efficacy and safety of olaparib (400 mg capsules) given orally bid in patients with advanced cancers, which were refractory to standard therapy and for which no suitable, effective/curative therapy existed, and who had a confirmed germline *BRCA1* and/or *BRCA2* mutation. The study included a cohort of pancreatic cancer patients who received olaparib in second-line or later setting.

- Patients had to have a confirmed documented deleterious or suspected deleterious *BRCA* mutation to be eligible for the study. The presence of a loss-of-function germline mutation in the *BRCA1* and/or *BRCA2* gene had to be confirmed prior to consent according to local practice.

- For the pancreatic cancer setting, patients had to have either failed or be unsuitable for gemcitabine treatment in the advanced setting.

Baseline characteristics for the pancreatic cancer cohort are shown in [Table 1](#). Compared with POLO, patients in Study 42 were more heavily pre-treated, with ~52% of patients receiving 2 or more prior lines of chemotherapy.

Table 1 Baseline characteristics Study 42 (pancreatic cancer cohort only)

	Olaparib 400 mg bid N=23
Age (years)	
Mean	57.1
SD	7.99
Median	58.0
Min	43
Max	73
Age group (years) n (%)	
<50	6 (26.1)
≥50 to <65	14 (60.9)
≥65	3 (13.0)
Sex n (%)	
Male	13 (56.5)
Female	10 (43.5)
Race n (%)	
White	21 (91.3)
Black or African American	1 (4.3)
Asian	1 (4.3)
ECOG performance status	
(0) Normal activity	11 (47.8)
(1) Restricted activity	9 (39.1)
(2) In bed less than or equal to 50% of the time	3 (13.0)
BRCA status	
<i>BRCA1</i>	5 (21.7)
<i>BRCA2</i>	17 (73.9)
Both	1 (4.3)
Overall disease classification	

Table 1 Baseline characteristics Study 42 (pancreatic cancer cohort only)

	Olaparib 400 mg bid N=23
Metastatic ^a	19 (82.6)
Locally Advanced ^b	4 (17.4)

^a Metastatic disease - patient has any metastatic site of disease.

^b Locally advanced - patient has only locally advanced sites of disease.

Efficacy results for pancreatic cancer cohort

This study demonstrated that olaparib was active in *gBRCAm* patients with metastatic pancreatic cancer as evidenced by:

- Objective response rate: 5/23 patients (21.7%) had an ORR; of these, 1 patient had a CR and 4 patients had a PR
- Duration of response: The median DoR was 4.4 months
- Progression-free survival: The median PFS was 4.55 months, with 36.4% and 9.1% of patients remaining progression-free at 6 months and 12 months, respectively
- Overall survival: The median OS was 9.81 months, with 63.6% and 40.9% of patients remaining alive at 6 months and 12 months, respectively
- Disease control rate (defined as CR, PR or SD): 11/23 patients (47.8%) had DCR at 16 weeks

A summary of the efficacy data from Study 42 is presented in [Table 2](#).

Table 2 Summary of efficacy from Study 42

Efficacy endpoint	Olaparib 400 mg bid capsule
	Pancreatic cohort (N=23)
ORR % (95% CI)	21.7 (7.46-43.70)
PFS	
Median PFS (months)	4.55
Progression-free at 6 months (%)	36.4
Progression-free at 12 months (%)	9.1
OS	
Median OS (months)	9.81
Alive at 6 months (%)	63.6
Alive at 12 months (%)	40.9

Table 2 Summary of efficacy from Study 42

Efficacy endpoint	Olaparib 400 mg bid capsule
	Pancreatic cohort (N=23)
Median DoR (days) [months]	134.0 days [4.4 months]
DCR % at 16 weeks (95% CI)	47.8 (26.82-69.41)

bid Twice daily; CI Confidence interval; DCR Disease control rate; DoR Duration of response; ORR Objective response rate; OS Overall survival; PFS Progression-free survival.

A retrospective analysis of data from the pancreatic cancer cohort in Study 42 (Table 3) suggested that the greatest benefit from olaparib was in the 15 patients who were not platinum resistant, either because patients had received but had not progressed on prior platinum treatment (n=7) or because they had not received prior platinum treatment (n=8) (ORR 33%; DCR 67%; median DoR 4.4 months [range 3.7 to 7.8 months]; median PFS 6.4 months; median OS 13.1 months) (AstraZeneca in-house data). In five patients (33%) who responded, 1 patient with no prior exposure to platinum had a CR, and 4 patients (1 not exposed to prior platinum and 3 exposed to prior platinum, but not resistant) had PRs. The activity of olaparib in patients who had not progressed on prior platinum therapy formed the basis for phase III POLO study.

Table 3 Efficacy results of a cohort of *gBRCAm* patients with locally advanced or metastatic pancreatic cancer who received olaparib in Study 42

Status	N	ORR	DCR	mPFS (months)	mOS (months)
		n (%)	n (%)	(95% CI)	(95% CI)
All <i>gBRCAm</i> patients with pancreatic cancer	23	5 (22) ^c	11 (48)	4.6	9.8
Not known to be platinum resistant ^a	15	5 (33) ^c	10 (67)	6.4 (1.9-8.4)	13.1 (5.8-16.6)
Exposed, non-resistant	7	3 (43)	4 (57)	7.7 (1.8-8.4)	10.6 (1.9-16.6)
Not exposed to platinum	8	2 (25) ^d	6 (75)	5.6 (1.9-NC)	13.3 (8.9-NC)
Prior platinum and resistant ^b	8	0	1 (13)	1.8	4.7

^a Not platinum resistant: non-resistant/non-exposed patients included those who discontinued their last platinum regimen due to toxicity, received only one cycle of platinum chemotherapy, progressed after their last platinum regimen (received as adjuvant therapy, or completed predetermined number of cycles, or stopped for toxicity), or who had no prior exposure to platinum therapy.

^b Prior platinum and resistant: resistant patients were defined as those patients whose tumors progressed on their last platinum regimen.

^c 1 CR and 4 PRs.

^d 1 patient had a CR and was not exposed to prior platinum.

CI Confidence intervals; CR Complete response; DCR Disease control rate; *gBRCAm* Germline breast cancer susceptibility gene mutated; mOS Median overall survival; mPFS Median progression-free survival; n Number of patients; N Total number of patients; NC Not calculable; ORR Objective response rate; PR Partial response.

5 OLAPARIB CLINICAL DEVELOPMENT PROGRAM

5.1 Regulatory history

Feedback on the POLO study was received from the FDA through an investigational new drug (IND) application and via a consultation as detailed in [Table 4](#).

Table 4 Summary of key regulatory US history (pancreatic cancer)

Date	Communication
22 August 2006	IND 75,918 submitted by KuDOS Pharmaceuticals Ltd., a wholly owned subsidiary of AstraZeneca (Serial No. 0000).
01 July 2014	AstraZeneca submitted the protocol for the Phase III POLO study under IND 121,412
25 July 2014	AstraZeneca received the Study May Proceed letter for the Phase III POLO study under IND 121,412
10 October 2014	AstraZeneca requested a Type C meeting with the FDA to discuss the pancreatic cancer development program for olaparib
03 December 2014	Type C meeting (telecon) held with FDA to discuss feedback on the pancreatic cancer development program for olaparib
07 January 2015	POLO protocol amendment 1 submitted
07 April 2015	POLO protocol amendment 2 submitted
20 May 2015	AstraZeneca submitted an Agreed initial Pediatric Study Plan (iPSP)
18 June 2015	FDA confirms agreement to the Agreed iPSP
10 August 2018	AstraZeneca submitted a request for orphan-drug designation of olaparib for “treatment of patients with pancreatic cancer.”
11 October 2018	FDA granted orphan-drug designation for olaparib for “treatment of patients with pancreatic cancer.” (Orphan Drug designation number 18-6553)
14 May 2019	Type B meeting held with FDA to discuss the clinical data from POLO and content and format of an sNDA to support expansion in labeling claim for olaparib to include maintenance treatment of adult patients with <i>gBRCA</i> -mutated metastatic pancreatic cancer whose disease has not progressed on platinum-based chemotherapy
28 June 2019	AstraZeneca submitted the sNDA application (S-010) to NDA 208,558
01 July 2019	Myriad submitted the POLO <i>gBRCA</i> sPMA application (for the Myriad BRACAnalysis CDx)
27 August 2019	FDA granted the sNDA application (NDA 208,558/S-010) a priority review classification

BRCA Breast Cancer susceptibility gene; CDx Companion diagnostic; FDA Food and Drug Administration; *gBRCA* Germline *BRCA*; IND Investigational New Drug; iPSP initial Pediatric Study Plan; NDA New Drug Application; sNDA Supplemental New Drug Application; sPMA Supplemental Pre-Market Approval; US United States

In addition, the POLO data has been filed in other regions (including Europe and Canada) and review of these applications are ongoing.

***gBRCA* mutation status testing**

AstraZeneca partnered with Myriad to develop a companion diagnostic (CDx) in pancreatic cancer. Myriad submitted a supplemental Pre-Market Approval (sPMA) for the BRACAnalysis CDx[®] assay as a CDx to olaparib in July 2019.

5.2 Clinical dose selection

300 mg bid tablet formulation

The efficacy of olaparib tablets (300 mg bid) as first-line maintenance monotherapy in patients with *gBRCAm* metastatic adenocarcinoma of the pancreas (pancreatic cancer) whose disease has not progressed on platinum-based chemotherapy was explored in a single, robust Phase III trial (POLO, NCT02184195)

The selection of the 300 mg bid tablet dose in POLO was based on the benefit risk profile established for this dose level in patients with advanced solid tumors (the majority had ovarian cancer) in Study D0810C00024 (Study 24). In this study, the 300 mg bid tablet dose was determined to be the recommended Phase III monotherapy dose, providing similar (based on noninferiority test) efficacy to the 400 mg bid capsule dose while exhibiting a safety and tolerability profile suitable for continuous long-term dosing. In addition, the tablet formulation was found to have better oral bioavailability than the capsule formulation, with olaparib steady state AUC and C_{max} values achieved at 300 mg tablet bid slightly higher than those achieved at 400 mg capsule bid.

The dose reduction and interruption rates in POLO were low (30% and 35%, respectively) and were similar to the dose reduction and interruption rates in study D0816C00002 (SOLO2; ovarian cancer: 30% and 54%, respectively) and in study D0819C00003 (OlympiAD; breast cancer: 27% and 51%, respectively), which suggests that the 300 mg bid tablet dose was well tolerated in POLO as it was in other approved indications (ovarian and breast cancer).

Sparse PK sampling was not conducted in POLO because PK exposures in pancreatic cancer patients were found to be similar to other tumor types ([Table 27](#), [Table 28](#) and [Table 29](#)). This was consistent with the finding that tumor type was not a covariate influencing the PK of olaparib in the pooled population PK report Olaparib-MS-06. In addition, with only one dose

being evaluated in POLO, it was expected that the small range in exposure would not be sufficient to characterize the exposure-response relationships in that indication.

AstraZeneca has extensive clinical experience at 300 mg bid tablet dose of olaparib across multiple tumor types (prostate cancer with D081DC00007 [PROfound], ovarian cancer with D0818C00001 [SOLO1] and SOLO2, and breast cancer with OlympiAD). To date, all efficacy trials conducted with olaparib at 300 mg bid tablet have shown favorable benefit-risk profile with positive efficacy outcomes and good tolerability profiles. In addition, the exposure-response analyses based on PFS, AEs with frequency of more than 10%, and hemoglobin concentration data pooled from studies with capsule and tablet formulation (pooled population PK report Olaparib-MS-07) showed that the 300 mg bid tablet dose provided the optimal benefit-risk ratio. Based on those data and given that tumor type is unlikely to influence the PK and safety profile of olaparib, the 300 mg bid tablet dose is an appropriate dose in the setting of maintenance treatment for pancreatic cancer patients.

5.3 POLO: the pivotal study of olaparib as maintenance treatment in *gBRCAm* patients with metastatic pancreatic adenocarcinoma who have not progressed following first-line platinum-based chemotherapy

POLO (NCT02184195) was a robust, well-controlled, Phase III randomized, double-blind, placebo-controlled multicenter study in *gBRCAm* patients with metastatic pancreatic adenocarcinoma.

Many patients who receive first-line platinum-based chemotherapy do not continue that therapy until disease progression. Their physicians either intended to administer chemotherapy for 6 months (ie, the approach described the original FOLFIRINOX paper: [Conroy et al 2011](#)), but the patients were not able to tolerate this, or to administer chemotherapy until disease progression, but it had to be stopped prior to disease progression due to toxicity. The POLO trial was intended to address an unmet need in these two practice patterns that exist for *gBRCAm* metastatic pancreatic cancer patients.

In POLO, patients with *gBRCAm* metastatic pancreatic adenocarcinoma whose tumors had not progressed on at least 16 weeks of first-line platinum-based chemotherapy were randomized (3:2 ratio) to receive either olaparib (300 mg bid tablets) or matched placebo as a maintenance treatment. There was no upper limit to the duration of chemotherapy that a patient had received and the majority of patients received more than 16 weeks ([Golan et al 2019](#)). No stratification factors were used. Patients were required to have documented evidence of a loss of function germline *BRCA* mutation (either *gBRCA1* or *gBRCA2*) to be enrolled into the POLO study. Evidence of a qualifying *gBRCA* mutation could be from either an existing *gBRCA* mutation result generated by local testing or from prospective testing performed by

Myriad using either the Myriad BRACAnalysis[®] test or Myriad BRACAnalysis CDx[®] test. Patients randomized based on a local *gBRCA* test result were re-tested post-randomization prior to database lock using either the Myriad BRACAnalysis[®] test or Myriad BRACAnalysis CDx[®] test where possible, to confirm their *gBRCAm* status.

POLO was conducted in 12 countries worldwide, including the US. The study screened 3315 patients, enrolled 167 patients and randomized 154 patients (32 patients were randomized in the US, of whom 19 patients were randomized to olaparib; [Table 7](#)). The study took 4 years to complete randomization of 154 patients, with the first patient randomized on 29 January 2015 and the last patient randomized on 06 January 2019. The primary analysis of PFS occurred once 104 PFS events had been observed. The DCO for this analysis was 15 January 2019. The study is ongoing. The planned final event driven overall survival analysis is expected to occur in late 2020 once 106 deaths have occurred (69% maturity).

POLO is the first global and the largest prospective study to determine the likely prevalence of *gBRCA* mutation in patients with adenocarcinoma of the pancreas in a post-platinum treatment setting. Of the 3175 patients successfully screened in POLO who were not tested previously, 6.2% of patients (196/3175) were shown to be *gBRCAm* by the Myriad BRACAnalysis[®] test or BRACAnalysis CDx[®] test.

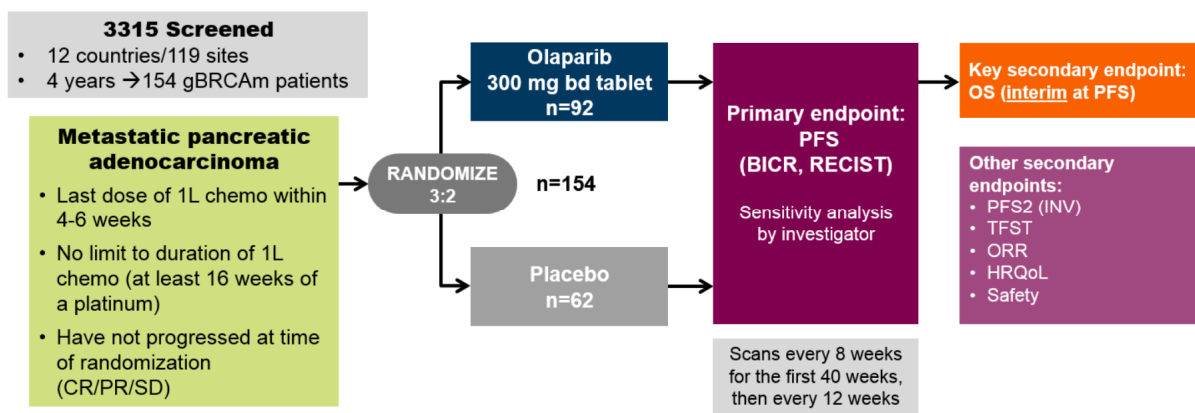
The primary objective was to determine the efficacy of olaparib compared with placebo, as assessed by PFS by BICR using modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A sensitivity analysis by investigator assessment was performed to confirm the robustness of the PFS analysis by BICR.

Progression-free survival assessed by BICR was chosen as the primary endpoint in the context of a maintenance trial of a well-tolerated oral dosage form, as it is a direct measure of the biologic effect of drug on tumor, and may also be associated with related endpoints of direct clinical value to patients such as a delay in the time to restarting subsequent more toxic chemotherapy (time to first subsequent therapy, TFST) and response rate. At the time of the initiation of POLO, there was limited data pertaining to PFS for the rare subset of *gBRCAm* pancreatic cancer patients. Golan et al reported median PFS results of 3 months for stage IV *gBRCAm* pancreatic cancer patients who were treated with either platinum (n=12) or non-platinum (n=18) as first-line chemotherapy ([Golan et al 2013](#)); these patients were diagnosed between January 1994 and December 2012. The largest study prior to POLO initiation ([Golan et al 2014](#)) found a difference in the overall survival of *gBRCAm* patients with stage IV pancreatic cancer treated with a platinum-containing regimen sometime during their clinical course, median OS of 15 months (n=14) vs 7 months (n=14) for those never receiving a platinum-containing regimen, and when stage III and IV *gBRCA* patients were pooled, this trend achieved statistical significance. Hence, although OS has historically served as basis for approval in pancreatic cancer, the short PFS but longer OS observed in *gBRCAm*

pancreatic cancer patients exposed to platinum-based chemotherapy may potentially confound OS by receipt of multiple subsequent therapies (including platinum-based therapies). In POLO patients received a median of 2 subsequent therapies, of whom around 64% included subsequent platinum chemotherapy. Additionally, the rarity of the *gBRCAm* population makes it not feasible to power a study to reliably detect a statistically significant difference in OS (to detect a clinically meaningful 3 month improvement in OS, more than 30,000 patients would need to be screened to randomize 2200 patients). For these reasons, PFS is a more practical and clinically relevant endpoint to measure benefit in this subset of pancreatic cancer patients.

Secondary endpoints included OS, PFS2, TFST, TSST, time from randomization to discontinuation of study treatment or death (TDT), ORR by BICR using RECIST version 1.1 criteria for evaluable patients, DCR by BICR using RECIST version 1.1 criteria, HRQoL, particularly global HRQoL score measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Questionnaire Core 30 item module (QLQ-C30), global health status score/QOL, safety and tolerability.

Figure 12 POLO overview



There was no upper limit to the duration of first-line chemotherapy that a patient had received and the majority of patients received more than 16 weeks (Golan et al 2019).

5.3.1 Dose reduction and interruption

Where necessary, adverse events occurring during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Study treatment could be dose reduced to 250 mg bid as a first step and to 200 mg bid as a second step.

For the management of hematological toxicity:

- CTCAE Grade 1 or 2: dose interruption as judged by the investigator; appropriate supportive treatment and causality investigation
- Repeat CTCAE Grade 1 or 2: dose interruption until recovery to CTCAE grade 1 and dose reduction to 250 mg bid as first step and 200 mg bid as second step
- CTCAE Grade 3 or 4: dose interruption until recovered to CTCAE Grade 1 for maximum of 4 weeks and dose reduction to 250 mg bid as first step and 200 mg bid as second step
- Repeat CTCAE Grade 3 or 4: Discontinue study treatment if 2 dose reductions are not able to manage the anemia

5.3.2 Schedule of assessments

Following a baseline assessment, subsequent tumor assessments using modified RECIST version 1.1 were performed every 8 weeks (± 1 week) for the first 40 weeks and then every 12 weeks (± 1 week) thereafter, relative to the date of randomization, up to objective disease progression by RECIST. Patients who were determined to have progressed according to modified RECIST version 1.1 criteria by the Investigator had scans centrally reviewed for confirmation of objective disease progression. If disease progression was not confirmed at central review an additional RECIST assessment was requested at the next scheduled RECIST visit (8 weeks from last scan). Patients were able to enter the study without measurable disease. Per the POLO protocol, RECIST 1.1 was modified to allow for assessment of patients with clinical complete response (CR) at entry who were evaluated as having No Evidence of Disease (NED). Patients with NED at baseline who were randomized in POLO were assessed according to these modified RECIST 1.1 criteria for assessment of new lesions, with responses to study treatment being either NED or progression of disease.

There was no maximum duration of study treatment. Patients continued to receive study treatment until objective radiological disease progression as per RECIST as assessed by the investigator and as long as in the investigator's opinion they were benefiting from treatment and did not meet any other discontinuation criteria. Any patient who discontinued study treatment for reasons other than objective radiological progression was to continue to undergo scheduled objective tumor assessments according to the study schedule in order to assess objective radiological progression of disease. Once a patient progressed, the patient was followed for PFS2 every 8 weeks and then survival until the final analysis. Subsequent therapy after first progression was at the investigator's discretion. Crossover to olaparib for patients on the placebo-arm was not permitted.

EORTC QLQ-C30 was administered at baseline (screening) and then every 4 weeks until progression followed by a 30-day post disease progression visit. EORTC QLQ-PAN26 (pancreas cancer specific- module 26) was administered at baseline (screening), weekly

during first 4 weeks, then every 4 weeks until progression followed by a 30-day post disease progression visit.

Patients and investigators were not routinely unblinded to study treatment and will not be unblinded prior to the final OS analysis, which is anticipated to occur by the end of 2020. Unblinding was permitted if knowledge of the treatment assignment was necessary for the management of medical emergencies.

At the time of the DCO (15 January 2019), a total of 27 patients (9 patients [9.8%] and 18 patients [29.0%] in the olaparib and placebo arms, respectively) were unblinded to randomized study treatment on the Interactive Voice Response System (IVRS). Of the 9 patients unblinded to treatment in the olaparib arm, none were unblinded prior to BICR assessed modified RECIST v1.1 progression. Of the 18 patients unblinded to treatment in the placebo arm, only 5 patients were unblinded prior to BICR-assessed modified RECIST v1.1 progression and 11 were unblinded after modified RECIST v1.1 progression (2 patients were unblinded but did not progress).

5.3.3 Statistical methods and considerations

The primary analysis was based on the programmatically derived PFS based on the BICR of the radiological scans and using all scans regardless of whether they were scheduled or not, with an event driven DCO 15 January 2019.

The effect of treatment was estimated by the hazard ratio (HR) with 95% confidence intervals (CIs). Kaplan Meier plots of PFS were presented by treatment group. Progression free survival was analyzed using a log rank test for generation of the p-value. If the observed p-value for the treatment difference was <0.025 (1-sided) then the result was regarded as statistically significant. The HR and CI were estimated from the U and V statistics obtained directly from the LIFETEST model ([Berry et al 1999](#), [Sellke and Siegmund 1983](#) and using the Breslow approach for handling ties). In addition to the investigator assessment, sensitivity analyses were performed to rule out bias resulting from different timing of scans between arms and the extent and timing of censoring. Ten subgroup factors were pre-specified in the statistical analysis plan (SAP), allowing assessment of potential differences in treatment benefit across the subgroups to be explored, as assessed by a treatment factor interaction test on the primary endpoint of PFS.

Early in the trial, the external Independent Data Monitoring Committee (IDMC) looked at the safety data. In addition, a pre-specified futility analysis for PFS was performed by a group independent of the Sponsor when 47 PFS events had occurred (11 July 2017). This analysis was not part of the alpha spending plan and the results were only shared with the IDMC. The

IDMC assessed the results against pre-specified criteria at that time and the IDMC informed the Sponsor that the study should continue without modification.

An interim analysis of OS based on 71 deaths was performed at the time of the primary analysis of PFS (104 PFS events). To strongly control the type I error at 2.5% (1-sided) for key label claims, a multiple testing procedure (MTP) was employed across the primary endpoint (PFS) and key secondary endpoint (OS). Specifically, OS was tested only after statistical significance was shown for PFS. The significance level at the OS interim analysis was determined based on the exact number of events at the time of the interim analyses and documented in the minutes of the blind data review meeting (prior to database lock). The MTP recycles the test mass to the endpoint not yet rejected in the hierarchy.

In POLO, primary HRQoL variable of interest consisted of an adjusted mean change from baseline in global HRQoL scale (global health status score/QoL items 29-30) of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 item module (EORTC QLQ-C30), which was evaluated as a secondary endpoint (not controlled for multiplicity). All other patient reported outcomes (PRO) domains were evaluated as exploratory.

Regarding HRQoL for the EORTC QLQ-C30 global health status score, descriptive statistics including change from baseline score were produced by time point, with results presented by treatment group. Adjusted mean change from baseline in global health status score were analyzed using a mixed model for repeated measures (MMRM) analysis of all the post-baseline scores for each visit and was presented by treatment group. A supportive analysis of time to sustained clinically meaningful deterioration (TCMD) was performed, using the same methodology and model as described for the analysis of PFS (log-rank test). For each type of score, the analysis was carried out for a subset of patients from the PRO set, ie, only for those patients that had the potential for a clinically meaningful deterioration to occur. Additional supportive analysis included best overall HRQoL response using a logistic regression model.

At the time POLO was designed in early 2014, there was no information available on the OS of *gBRCAm* pancreatic cancer patients who had received first-line chemotherapy on which to base the estimated OS in the control arm. With 145 patients the study was able to detect a 6 month improvement over an 8 month median OS in the placebo arm as statistically significant, with 80% power. Since the availability of the POLO results and based on information more recently published in the literature ([Golan et al 2019](#), [Pishvaian et al 2019](#)), it is acknowledged that the median OS in the *gBRCAm* pancreatic cancer patient population following receipt of first-line platinum-based chemotherapy was longer than initially predicted in both arms, and therefore, the POLO study is underpowered to meet the OS assumptions originally used to design the study. There was no prospective study of survival after maintenance therapy for *gBRCAm* pancreatic cancer at the time POLO was designed to guide

the estimate of control arm survival after stopping chemotherapy and on which to base the statistical plan.

5.3.4 Analysis populations and patient disposition

The analysis sets and the number of patients in each analysis set are summarized in [Table 5](#).

All efficacy and HRQoL data were summarized and analyzed based on randomized treatment. Three patients were excluded from the safety analysis set (SAS) (2 patients in the olaparib arm and 1 patient in the placebo arm) as they did not start study treatment. One patient who was randomized to the placebo arm was evaluated in the olaparib arm for safety, as this patient was exposed to at least 1 dose of olaparib.

Seven patients were excluded as per protocol from the PRO Analysis Set (3 patients in the olaparib arm and 4 patients in the placebo arm) as they did not have evaluable EORTC QLQ-C30 and QLQ-PAN26 forms at baseline.

Table 5 Analysis sets

	Number of patients		
	Olaparib 300 mg bid	Placebo	Total
Patients randomized	92	62	154
Patients included in FAS	92	62	154
Patients included in SAS	91 ^a	60	151
Patients excluded from SAS ^b	2	1	3
Inclusion/exclusion criteria not met	1	0	1
Did not receive treatment	1	1	2
Patients included in PRO analysis set	89	58	147
Patients excluded from PRO analysis set ^a	3	4	7
No evaluable baseline EORTC QLQ-C30 and QLQ-PAN26 form	3	4	7

^a One patient was randomized to placebo but evaluated in olaparib treatment arm for safety, as this patient was exposed to at least 1 dose of olaparib.

^b An individual patient could have been excluded for more than 1 reason.

bid twice daily; EORTC European Organization for Research and Treatment of Cancer; FAS Full Analysis Set; PRO patient reported outcome; QLQ-C30 quality of life questionnaire for cancer patients; QLQ-PAN26 quality of life questionnaire for pancreatic cancer patients; SAS Safety Analysis Set.

Patient disposition is summarized in [Table 6](#). The majority of patients (103/113 [91.2%]) who discontinued study treatment did so due to objective and subjective disease progression.

Table 6 Patient disposition (All patients)

	Number (%) of patients		
	Olaparib 300 mg bid	Placebo	Total
Patients screened			3315
Patients enrolled ^a			167
Patients randomized	92 (100)	62 (100)	154 (100)
Patients who were not randomized ^b			13 (7.8)
Patient decision			2 (1.2)
Eligibility criteria not fulfilled			11 (6.6)
Full Analysis Set ^c	92 (100)	62 (100)	154 (100)
Patients who received study treatment	90 (97.8)	61 (98.4)	151 (98.1)
Patients who did not receive study treatment and terminated the study	2 (2.2)	1 (1.6)	3 (1.9)
Patients ongoing study treatment at DCO ^c	30 (32.6)	8 (12.9)	38 (24.7)
Patients continuing study off-treatment at DCO ^c	19 (20.7)	19 (30.6)	38 (24.7)
Patients who discontinued study treatment ^{c,i}	60 (65.2)	53 (85.5)	113 (73.4)
Adverse event	4 (4.3) ^d	2 (3.2) ^d	6 (3.9)
Objective disease progression	43 (46.7)	40 (64.5)	83 (53.9)
Patient decision	1 (1.1)	1 (1.6)	2 (1.3)
Subjective disease progression ^e	11 (12.0)	9 (14.5)	20 (13.0)
Other ^f	1 (1.1)	1 (1.6)	2 (1.3)
Patients who withdrew from the study ^c	43 (46.7)	35 (56.5)	78 (50.6)
Patient decision ^g	3 (3.3)	1 (1.6)	4 (2.6)
Eligibility criteria not fulfilled	0	1 (1.6)	1 (0.6)
Death	40 (43.5)	29 (46.8)	69 (44.8)
Patient lost to follow-up	0	2 (3.2)	2 (1.3)
Other	0	2 (3.2)	2 (1.3)
Patients who were unblinded ^c	9 (9.8)	18 (29.0)	27 (17.5)
Unblinded prior to disease progression (BICR) ^h	0	5 (8.1)	5 (3.2)
Unblinded and received PARP inhibitor as subsequent therapy	1 (1.1)	6 (9.7)	7 (4.5)

^a Main study informed consent received.

^b Percentages were calculated from number of patients signing the main ICF.

^c Percentages were calculated from number of patients randomized.

- ^d Note: The adverse event leading to discontinuation of study treatment table reports that 5/91 (5.4%) olaparib-treated patients vs 1/60 (1.6%) placebo-treated patients in the SAS discontinued treatment due to AEs. The adverse event leading to discontinuation of study treatment table does not include one patient (placebo arm) who had an AE of back pain which occurred prior to study treatment. This event was ongoing during treatment and resulted in the discontinuation of study drug, however, as the event occurred prior to treatment it was not captured in the adverse event leading to discontinuation of study treatment table. In the patient disposition table, one patient (olaparib arm) was reported to have discontinued study drug due to subjective disease progression, however, the patient also discontinued treatment on the same day due to an AE of decreased appetite; the AE of decreased appetite is captured in the adverse event leading to discontinuation of study treatment table.
- ^e Subjective progression was based on investigator local disease assessment as recorded on the CRF.
- ^f Any reason not specifically recorded, for example patient died.
- ^g One patient in the olaparib arm and one patient in the placebo arm voluntarily withdrew from the study. Post follow-up these patients were subsequently reported to have died.
- ^h Includes unblinding prior to death in the absence of BICR progression.
- ⁱ Only one main reason is presented for patients who discontinue study treatment, hence the number of patients discontinuing for an AE will not match those in the AE safety tables
- AE adverse event; bid twice daily; BICR blinded independent central review; CRF case report form; DCO data cut-off; ICF informed consent form; PARP polyadenosine 5'diphosphoribose polymerase; SAS Safety Analysis Set.

5.3.5 Study population

The patient population treated in POLO is a prospectively defined population with a high unmet medical need, in line with clinical practice. The entry criteria were designed to define a study population who could receive benefit from olaparib treatment. Baseline, demographic and tumor characteristics were generally well balanced between the arms (Table 7).

POLO was conducted in 12 countries worldwide. The first subject enrolled (ie, screened) in POLO was in December 2014. Given the low prevalence of *gBRCA* mutations in pancreatic cancer, and the lack of *BRCA* screening of pancreatic cancer patients as part of standard clinical practice, extensive screening was required to enroll POLO (a total of 3315 patients were screened, 3175 patients of whom were submitted to Myriad for prospective determination of their *gBRCA* mutation status). In total, 154 patients were randomized (92 olaparib and 62 placebo): 57.2% in Europe, 22.7% in the US, 3.9% in Asia, and 16.2% in the Rest of World. Of the 154 patients randomized, 48 patients (31.2%) were randomized based on a local *gBRCAm* test result, with the remainder (106 patients) randomized based on a prospectively conducted Myriad *BRCAAnalysis*[®] or *BRCAAnalysis CDx*[®] test result. There were some differences in the percentage of patients in age groups between the arms; of note the percentage of patients in the olaparib arm who were ≥65 years old was higher than the placebo arm. As a percentage, there were more males in the olaparib arm than in the placebo arm. The majority of patients were White. There was a higher percentage of patients who were non-White in the olaparib arm compared with the placebo arm (10.9% vs 4.8%, respectively) (Table 7). It is acknowledged that there are more limited data in non-White patients and patients of other ethnic descent (including Black or African American, Asian,

etc), however given the mode of action of olaparib, it is not expected that racial or ethnic origin would have a major impact on either the efficacy or safety profile of olaparib ([Table 7](#)).

The median age of patients in POLO (57.0 years in the olaparib arm vs 57.0 years in the placebo arm) was younger than the median age at initial diagnosis of 70 years in the unselected US pancreatic cancer population ([SEER Cancer Statistics Factsheets 2018](#)). The mean age of patients randomized in POLO, and the low proportion of patients in the ≥ 65 years age category, are consistent with reports in the literature that *gBRCAm* pancreatic cancer is diagnosed at a younger age, with a mean age of pancreatic cancer diagnosis for *BRCA1* and *BRCA2* mutation carriers of 60.3 years ([Golan et al 2014](#)).

The proportion of patients whose best response to first-line (platinum) chemotherapy was either CR/PR or SD was well balanced between the arms. The majority of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of ‘normal activity’ (0) in both treatment arms; more patients in the olaparib arm had an ECOG performance status of ‘normal activity’ (0) compared with the placebo arm. There were no locally advanced patients enrolled in the study (patients had general [sites not specified] or specific sites of metastasis prior to the first-line chemotherapy). Four patients (2 in the olaparib arm and 2 in the placebo arm) had NED at baseline (ie, no target lesion and no non-target lesion) because they had responded completely to first-line platinum-based chemotherapy.

Table 7 **Summary of selected demographic and disease characteristics at baseline (Full Analysis Set)**

	FAS	
	Olaparib 300 mg bid (N=92)	Placebo (N=62)
Demographics		
Age (years)		
Mean (std)	58.2 (10.27)	56.4 (9.07)
Median (range)	57.0 (37-84)	57.0 (36-75)
Age group (years), n (%)		
<35	0	0
35 to 44	8 (8.7)	7 (11.3)
45 to 54	27 (29.3)	20 (32.3)
55 to 64	29 (31.5)	22 (35.5)
65 to 74	24 (26.1)	12 (19.4)
75 to 84	4 (4.3)	1 (1.6)
≥ 85	0	0

Table 7 **Summary of selected demographic and disease characteristics at baseline (Full Analysis Set)**

	FAS	
	Olaparib 300 mg bid (N=92)	Placebo (N=62)
Sex, n (%)		
Male	53 (57.6)	31 (50.0)
Female	39 (42.4)	31 (50.0)
Race, n (%)		
White	82 (89.1)	59 (95.2)
Black or African American	5 (5.4)	0
Asian	4 (4.3)	2 (3.2)
Native Hawaiian or other Pacific Islander	0	0
American Indian or Alaskan Native	1 (1.1)	0
Other	0	1 (1.6)
Disease characteristics		
Time from original diagnosis to randomization (months)		
Median	6.87	6.97
Min, Max	3.6, 38.4	4.1, 30.2
Histology type		
Adenocarcinoma (not otherwise specified)	53 (57.6)	37 (59.7)
Adenocarcinoma: acinar	0	4 (6.5)
Adenocarcinoma: papillary	0	1 (1.6)
Adenocarcinoma: solid with mucous formation	0	1 (1.6)
Pancreas adenocarcinoma	38 (41.3)	17 (27.4)
Not affected	0	1 (1.6)
Missing	1 (1.1)	1 (1.6)
Primary tumor location		
Pancreas	91 (98.9)	61 (98.4)
Missing	1 (1.1)	1 (1.6)
Any general or specific site of metastasis prior to chemotherapy ^a		
No	0	0
Yes	89 (96.7)	61 (98.4)
Missing	3 (3.3)	1 (1.6)
Site of metastasis prior to chemotherapy ^b		

Table 7 **Summary of selected demographic and disease characteristics at baseline (Full Analysis Set)**

	FAS	
	Olaparib 300 mg bid (N=92)	Placebo (N=62)
Ascites	1 (1.1)	1 (1.6)
Bone	2 (2.2)	2 (3.2)
Gastrointestinal system	1 (1.1)	2 (3.2)
Liver	61 (66.3)	48 (77.4)
Brain	0	0
Lung	10 (10.9)	5 (8.1)
Adrenal gland	2 (2.2)	1 (1.6)
Lymph node	22 (23.9)	13 (21.0)
Mediastinum	1 (1.1)	1 (1.6)
Peritoneum	10 (10.9)	5 (8.1)
Other	8 (8.7)	5 (8.1)
Extent of disease at Baseline		
Metastatic ^c	87 (94.6)	55 (88.7)
Best response on first-line treatment		
CR/PR	46 (50.0)	30 (48.4)
SD	45 (48.9)	31 (50.0)
Missing	1 (1.1)	1 (1.6)
Biliary stent		
Presence of biliary stent	1 (1.1)	4 (6.5)
Absence of biliary stent	91 (98.9)	58 (93.5)
ECOG performance status		
(0) Normal activity	65 (70.7)	38 (61.3)
(1) Restricted activity	25 (27.2)	23 (37.1)
Missing	2 (2.2)	1 (1.6)
<i>BRCA</i> status previously known (local result available) ^d		
Known	30 (32.6)	17 (27.4)
Unknown	62 (67.4)	45 (72.6)
Locally reported <i>BRCA</i> status		
<i>BRCA</i> mutated	30 (32.6)	16 (25.8)
<i>BRCA1</i>	10 (10.9)	5 (8.1)

Table 7 Summary of selected demographic and disease characteristics at baseline (Full Analysis Set)

	FAS	
	Olaparib 300 mg bid (N=92)	Placebo (N=62)
<i>BRCA2</i>	19 (20.7)	11 (17.7)
Both <i>BRCA1</i> and <i>BRCA2</i>	1 (1.1)	0
Missing ^{e,f}	62 (67.4)	46 (74.2)
Myriad reported <i>BRCA</i> status		
<i>BRCA</i> mutated	89 (96.7)	61 (98.4)
<i>BRCA1</i>	29 (31.5)	16 (25.8)
<i>BRCA2</i>	59 (64.1)	45 (72.6)
Both <i>BRCA1</i> and <i>BRCA2</i>	1 (1.1)	0
<i>BRCA</i> VUS	0	0
<i>BRCA</i> wildtype	0	0
Missing	3 (3.3)	1 (1.6)

- ^a Any general or specific site of metastasis prior to chemotherapy – patients were to have general or specific sites of metastases for study enrolment.
- ^b Patients could have one or more sites of disease.
- ^c Sites of metastases at baseline assessed post patient response to first-line chemotherapy, prior to study treatment.
- ^d One patient was randomized based on local *gBRCA* results which were subsequently confirmed by Myriad. This patient should have been included in the “*BRCA* status previously known” cohort but were inadvertently mis-assigned to the “Unknown” cohort. One patient (olaparib treated) had incomplete local *gBRCA* results recorded in the eCRF, leading to missing local *gBRCA* information (ie, *BRCA* variant classification information) in the analysis dataset. Therefore, there should be 31 (33.7%) patients in the “known” and 61 (66.3%) patients in the “unknown” group for the FAS and 28 (31.5%) and 61 (68.5%) for the Myriad group.
- ^e Patients with a previously unknown *gBRCA* mutation status at study entry.
- ^f Two patients were randomized based on local *gBRCA* results which were subsequently confirmed by Myriad. These patients were included in the “missing” group as 1 patient has only information on which *BRCA* gene was mutated and 1 patient had neither information on which *BRCA* gene was mutated nor which *BRCA* variant was detected was reported in the eCRF.

bid Twice daily; *BRCA* Breast cancer susceptibility gene; CR Complete response; ECOG Eastern Cooperative Oncology Group; FAS Full Analysis Set; *gBRCAm* Germline *BRCA* mutated; PR Partial response; SD Stable disease; std Standard deviation; VUS Variants of uncertain significance.

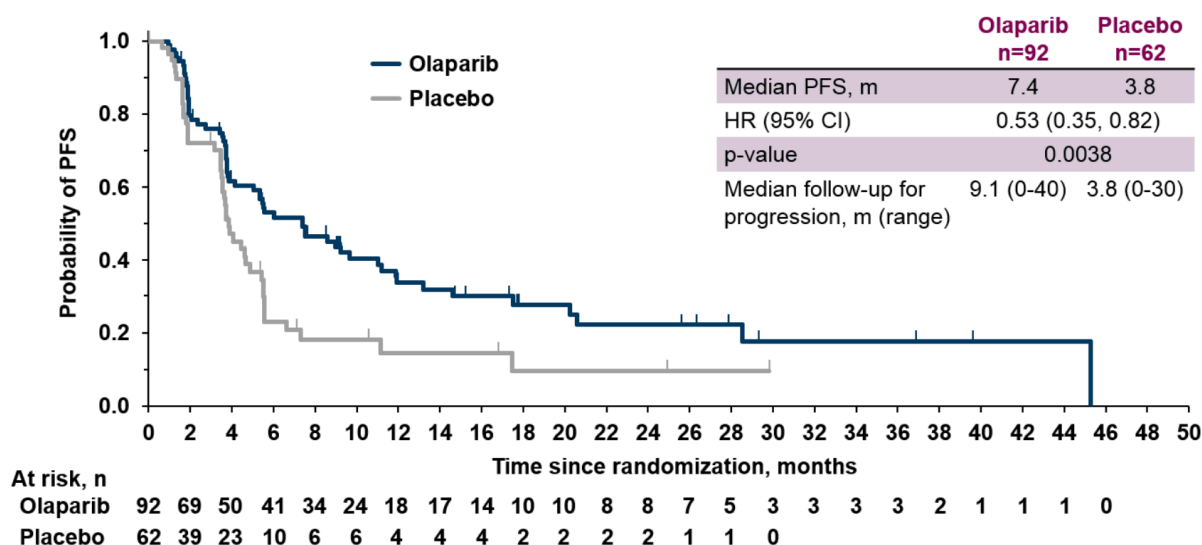
5.4 POLO: key efficacy data

Per protocol, the primary analysis of PFS was to be undertaken once approximately 87 PFS events were observed. An interim analysis of OS was also to be performed at that time. At the time of the data cut-off (DCO; 15 January 2019) for the primary analysis there were

104 PFS events, to permit all patients who were screened positive for *gBRCAm* to have the opportunity to be randomized.

POLO met its primary endpoint, reducing the risk of disease progression or death (PFS) assessed by BICR, by a clinically meaningful and statistically significant 47% for patients on olaparib vs placebo (HR=0.53; 95% CI 0.35 to 0.82; p=0.0038; [Figure 13](#)).

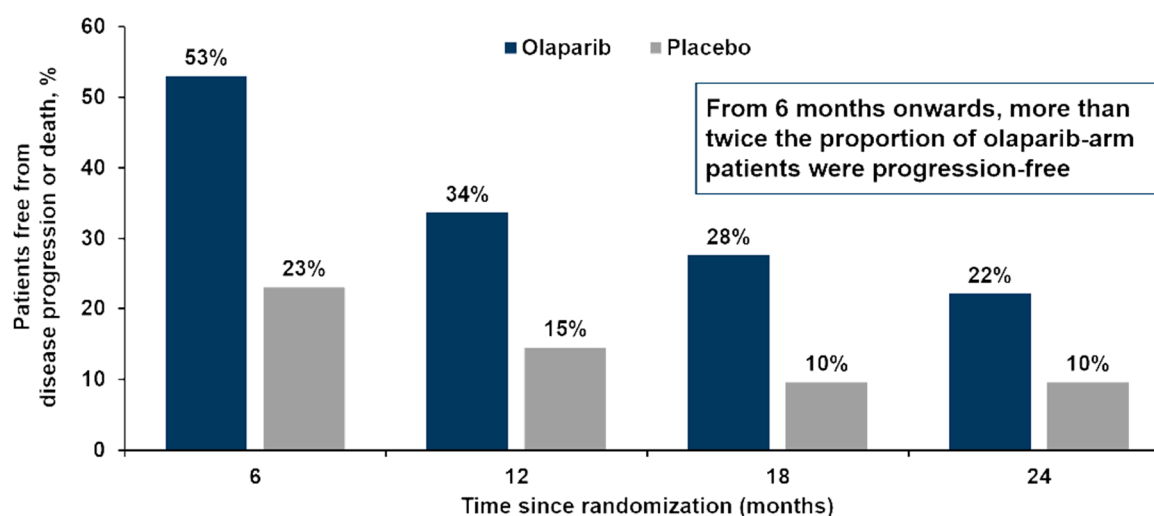
Figure 13 **Olaparib provided a clinically meaningful and statistically significant 47% reduction in the risk of disease progression or death (by BICR assessment)**



BICR Blinded independent central review; CI Confidence interval; F/U Follow-up; HR Hazard ratio; m Month; PFS Progression-free survival.

- Olaparib prolonged median PFS by 3.6 months with a median PFS of 7.4 months for olaparib vs 3.8 months for placebo ([Table 8](#)).
- At every timepoint beyond 6 months of treatment, the likelihood of recurrence or disease progression for patients receiving olaparib reduced by at least half compared to placebo, which indicated that the PFS benefit was persistent ([Figure 14](#)). Furthermore, the KM plot shows sustained benefit for olaparib treated patients; over 20% of them remaining event-free beyond 24 months. Several patients remain on drug at 3 years. The ‘tail’ on the olaparib KM curve suggests the possibility of a cohort of patients on drug with long-term progression free survival.

Figure 14 Percentage of patients progression-free^a at pre-specified timepoints



^a Based on Kaplan-Meier estimates

A summary of the efficacy data from POLO is presented in [Table 8](#).

Table 8 Summary of key efficacy outcome variables (Full Analysis Set) (DCO 15 January 2019)

	FAS	
	Olaparib 300 mg bid	Placebo
	(N=92)	(N=62)
PFS by BICR (maturity 68%)		
Number of events/total number of patients (%)	60/92 (65.2)	44/62 (71.0)
Median PFS (95% CI) [months]	7.4 (4.14-11.01)	3.8 (3.52-4.86)
HR (95% CI)	0.531 (0.346-0.815)	
P-value (2-sided)	0.0038	
Patients progression-free at 6 months (%)	53.0	23.0
Patients progression-free at 12 months (%)	33.7	14.5
Patients progression-free at 18 months (%)	27.6	9.6
Patients progression-free at 24 months (%)	22.1	9.6
Patients progression-free at 36 months (%)	17.7	NC
Interim OS (maturity 46%)		
Number of events/total number of patients (%)	41/92 (44.6)	30/62 (48.4)
Median OS (95% CI) [months]	18.9 (14.85-26.15)	18.1 (12.62-26.12)

**Table 8 Summary of key efficacy outcome variables (Full Analysis Set)
(DCO 15 January 2019)**

	FAS	
	Olaparib 300 mg bid	Placebo
	(N=92)	(N=62)
HR (95% CI)	0.906 (0.563-1.457)	
P-value (2-sided)	0.6833	
Overall survival rate at 6 months (%)	87.5	92.9
Overall survival rate at 12 months (%)	70.0	66.5
Overall survival rate at 18 months (%)	54.0	51.6
Overall survival rate at 24 months (%)	37.9	35.3
Overall survival rate at 36 months (%)	34.7	24.7
PFS2 (maturity 46%)		
Number of events/total number of patients (%)	41/92 (44.6)	30/62 (48.4)
Median PFS2 (95% CI) [months]	13.2 (7.75-26.15)	9.2 (7.62-13.54)
HR (95% CI)	0.755 (0.464-1.230)	
P-value (2-sided) [nominal]	0.2597	
TDT (maturity 73%)		
Number of events/total number of patients (%)	60/92 (65.2)	53/62 (85.5)
Median time (95% CI) [months]	7.2 (5.52-10.84)	3.8 (3.55-4.80)
HR (95% CI)	0.446 (0.297-0.670)	
P-value (2-sided) [nominal]	0.0001	
TFST (maturity 68%)		
Number of events/total number of patients (%)	58/92 (63.0)	46/62 (74.2)
Median time (95% CI) [months]	8.6 (6.21-12.45)	5.7 (4.17-6.34)
HR (95% CI)	0.496 (0.324-0.760)	
P-value (2-sided) [nominal]	0.0013	
TSST (maturity 58%)		
Number of events/total number of patients (%)	50/92 (54.3)	39/62 (62.9)
Median time (95% CI) [months]	13.2 (8.84-20.04)	9.2 (8.34-13.14)
HR (95% CI)	0.678 (0.437-1.051)	
P-value (2-sided) [nominal]	0.0825	
ORR by BICR		
Number of objective responders:total number of patients with measurable disease at baseline (%)	18/78 (23.1)	6/52 (11.5)

**Table 8 Summary of key efficacy outcome variables (Full Analysis Set)
(DCO 15 January 2019)**

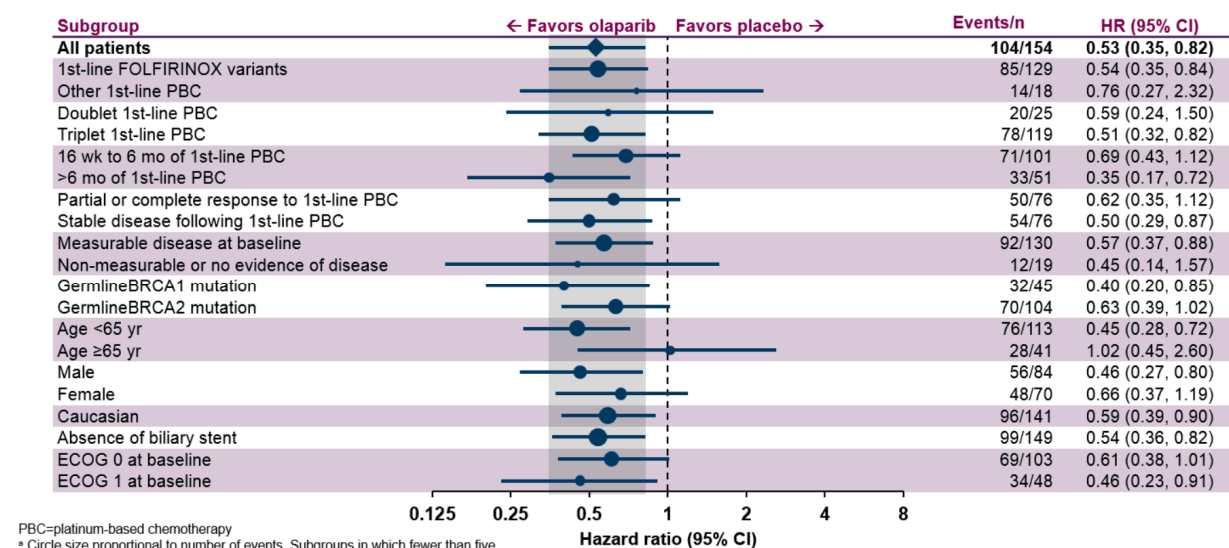
	FAS	
	Olaparib 300 mg bid	Placebo
	(N=92)	(N=62)
Complete response (%)	2 (2.6)	0
Partial response (%)	16 (20.5)	6 (11.5)
Odds ratio (95% CI)	2.300 (0.886-6.761)	
P-value (2-sided) [nominal]	0.1028	
DoR by BICR		
n	18	6
Median (95% CI) [months]	24.9 (14.75-NC)	3.7 (2.10-NC)
DCR by BICR		
Patients with DCR at 16 weeks n, (%)	49 (53.3)	23 (37.1)

Note: In the POLO study, in order to strongly control the Type I error at 2.5% 1-sided, a multiple testing procedure was employed across the primary endpoint (PFS) and key secondary endpoint (OS). All other variables that were tested (PFS2, TFST, TSST, and TDT) at a 1-sided significance level of 2.5% but not adjusted for multiplicity.

bid Twice daily; BICR Blinded independent central review; CI Confidence interval; DCO Data cut-off; DCR Disease control rate; DoR Duration of response; HR Hazard ratio; NC not calculable; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PFS2 Time from randomization to second progression or death; TDT Time from randomization to study treatment discontinuation or death; TFST Time from randomization to start of first subsequent therapy or death; TSST Time from randomization to start of second subsequent therapy or death.

- The sensitivity analysis of PFS by investigator assessment (HR=0.51; 95% CI 0.34 to 0.78; p=0.0017; median PFS 6.3 months vs 3.7 months for olaparib vs placebo, respectively) was consistent with the PFS analysis by BICR. All other pre-specified sensitivity analyses (evaluation time bias [HR=0.553] and attrition bias [HR=0.505]) were also consistent with the BICR assessment of PFS, confirming the robustness of the primary analysis.
- The analyses of PFS were consistent across all pre-specified subgroups. No subgroups derived a differential benefit compared with the overall population (Figure 15). The global interaction test was not statistically significant (p=0.2106, 2-sided) at the 10% level. Overall, these results indicate that olaparib is an effective maintenance treatment option irrespective of potential or expected prognostic factors.

Figure 15 A consistent PFS benefit was observed across all subgroups



Hazard ratios and CIs are not displayed for subgroup categories with <5 events in either treatment group.

Progression is determined using modified RECIST version 1.1 and BICR.

A hazard ratio <1 favors olaparib 300 mg bid to be associated with a longer progression-free survival than placebo.

The size of the circle is proportional to the number of events.

The grey band represents the 95% confidence interval for the overall (all patients) hazard ratio, calculated using U and V statistics obtained from log rank test.

BICR Blinded independent central review; *BRCA* Breast cancer susceptibility gene; CI Confidence interval;

ECOG Eastern Cooperative Oncology Group; HR Hazard ratio; PBC Platinum-based chemotherapy;

PFS Progression free survival; RECIST Response Evaluation Criteria in Solid Tumors.

Early censoring (<2 months of randomization)

Additional efficacy analyses were conducted to evaluate the early censoring of patients in POLO. Early censoring was defined as occurring within the first 2 months after randomization. Two months was selected as the cut-off as the first response assessment occurred at Week 8 (±1 week). A total of 12 patients were censored within the first 2 months, with 5 patients (5%) on the olaparib arm and 7 patients (11%) on the placebo arm, as shown in [Table 9](#).

Table 9 **Progression-free survival by BICR, reasons for early censoring (FAS)**
(DCO 15 January 2019)

	Olaparib 300 mg bid (N=92)	Placebo (N=62)
Within 2 months, n (%)		
Alive & progression free	4 (4.3)	3 (4.8)
Censored death	0	1 (1.6)
Discontinued study	0	2 (3.2)
Lost to follow-up	0	1 (1.6)
Withdrawn consent	1 (1.1)	0

bid Twice daily; BICR Blinded independent central review; DCO data cut-off; FAS Full Analysis Set.

Of the patients who were censored within the first 2 months, the majority (7/12, 58%) were alive and progression-free (without BICR confirmed progressive disease) within the first 2 months after randomization (4 patients [4.3%] in the olaparib arm and 3 patients [4.8%] in the placebo arm). All of these patients were randomized at the end of the study (~6 months before DCO).

A post hoc multivariate analysis showed the primary analysis result was not impacted by any of the baseline factors (selected key prognostic baseline factors of: best response to first-line treatment [CR/PR vs SD], time on first-line treatment [≤ 6 months, > 6 months], age group (< 65 years, ≥ 65 years], ECOG PS [0,1], and type of previous chemotherapy [FOLFIRINOX, gemcitabine/cisplatin, other]) (Table 10).

Table 10 **Progression-free survival (by BICR) unadjusted and adjusted Cox proportional hazards model (FAS) (DCO 15 January 2019)**

	Number (%) of patients with events/number of patients	HR	95% CI	p-value (2-sided)
Unadjusted model ^a	Olaparib: 60/92 (65.2) Placebo: 44/62 (71.0)	0.56	0.37-0.83	0.0038
Adjusted model ^b	Olaparib: 59/90 (65.6) Placebo: 44/61 (72.1)	0.59	0.39-0.88	0.0096

^a Cox proportional hazards model using only the treatment term as covariate.

^b Cox proportional hazards model containing the treatment term and the subgroups defined by best response on first-line treatment (CR/PR, SD), time on first-line treatment (≤ 6 months, > 6 months), age group (< 65 years, ≥ 65 years), ECOG status at baseline (0 Normal activity, 1 Restricted activity), and previous chemotherapy (FOLFIRINOX variants, Gemcitabine/Cisplatin, Other) as covariates.

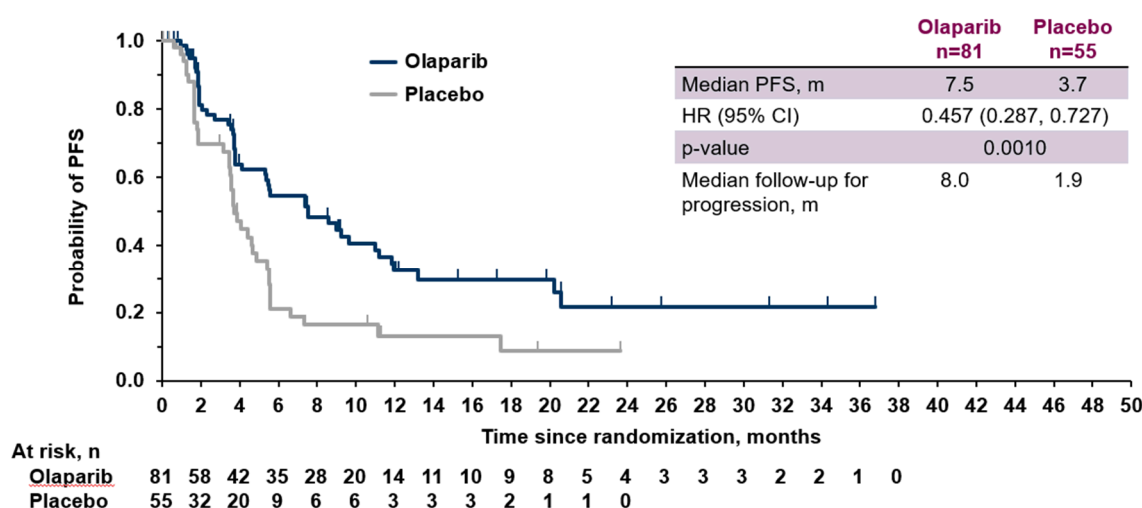
The CIs are calculated using a profile likelihood approach.

A hazard ratio < 1 favors olaparib to be associated with a longer progression-free survival than placebo.

BICR Blinded independent central review; CI Confidence interval; CR Complete response; DCO Data cut-off; ECOG Eastern Cooperative Oncology Group; FAS Full Analysis Set; FOLFIRINOX Folinic acid, fluorouracil, irinotecan and oxaliplatin; HR Hazard ratio; PR Partial response; SD Stable disease.

Progression-free survival assessed at 87 events (as described in the SAP) was done as an additional sensitivity analysis. A KM plot of PFS including events up to the 87th event is presented in [Figure 16](#). Results were consistent with the PFS analysis conducted at the DCO of 15 January 2019 (104 events) ([Figure 13](#)), confirming the robustness of the PFS analysis.

Figure 16 Kaplan-Meier plot of PFS (by BICR assessment) in the FAS - Sensitivity analysis up to the 87th progression event



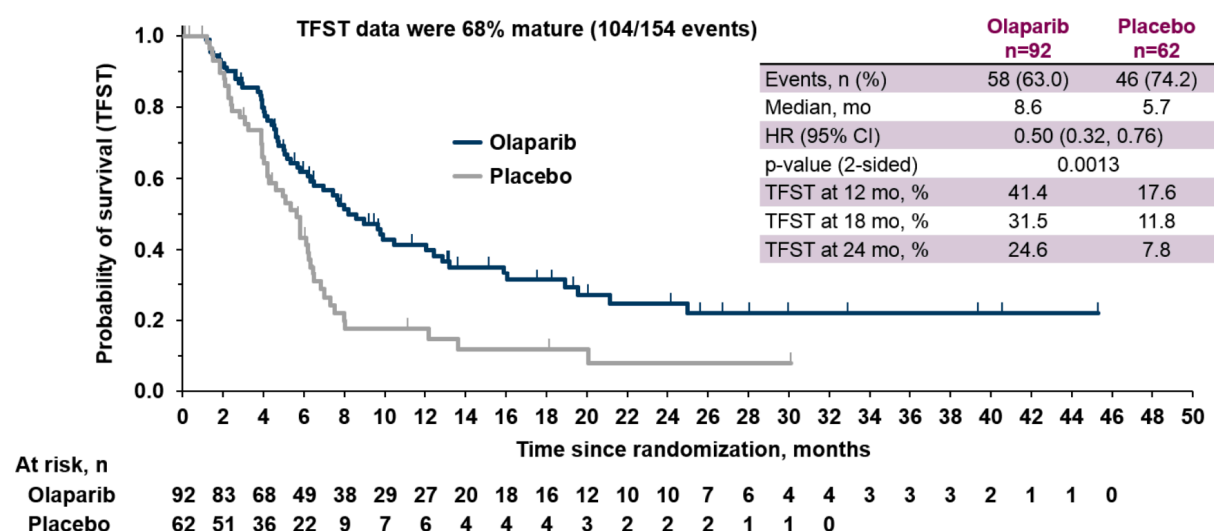
BICR Blinded independent central review; CI Confidence interval; DCO Data cut-off; FAS Full analysis set; HR Hazard ratio; m Month; PFS Progression-free survival.

The additional aspects of POLO that demonstrate clinical benefit to patients were:

- In the 84% of patients with measurable disease at baseline, ORR by BICR was higher for patients taking olaparib vs placebo (23.1% vs 11.5%) ([Table 8](#)).
 - Of the 18 patients who had a response in the olaparib arm, 2 patients (11.1%) had a CR. None of the 6 patients who had a response in the placebo arm had a CR.
- The median DoR by BICR was much longer for patients taking olaparib (24.9 months; 95% CI 14.75, NC) vs placebo (3.7 months; 95% CI 2.10, NC) ([Table 8](#)).
- At the DCO (15 January 2019), more patients remained on study treatment with olaparib (n=30, 32.6%) compared with placebo (n=8, 12.9%) ([Table 6](#)) and therefore were not eligible for subsequent therapy at the time of DCO, as evidenced by the use of subsequent therapies (48.9% in the olaparib arm vs 74.2% in the placebo arm).

- Olaparib extended the chemotherapy free- duration and delayed the time to first subsequent therapy, often based on treatment with potentially toxic chemotherapy; a 50% reduction in the risk of first subsequent therapy or death compared with placebo treated patients (TFST HR=0.50; p=0.0013 [nominal], median TFST 8.6 months for olaparib vs 5.7 months for placebo; [Table 8](#), [Figure 17](#)), which is clinically meaningful to patients.
 - The most commonly reported subsequent treatments included platinum-containing regimens.

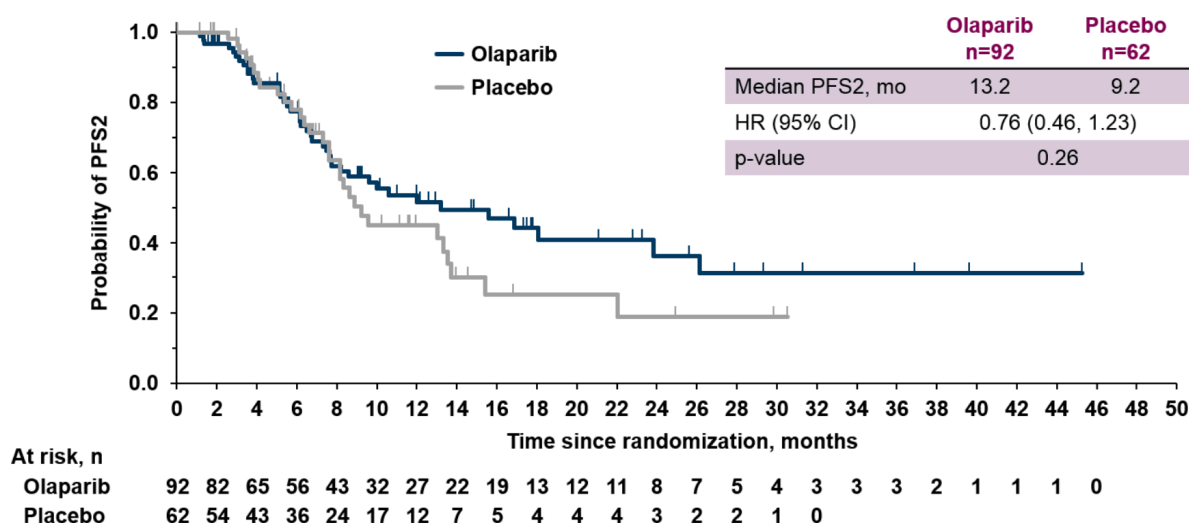
Figure 17 **Olaparib provided a clinically meaningful delay in the time patients receive their first subsequent therapy**



CI Confidence interval; HR Hazard ratio; mo Month; TFST time to first subsequent therapy or death.

- The delay in PFS2 (46% maturity) as evidenced by Kaplan-Meier estimates, suggested a favorable trend towards benefit on olaparib ([Table 8](#), [Figure 18](#)). PFS2 is an indicator of treatment benefit extending beyond first progression.

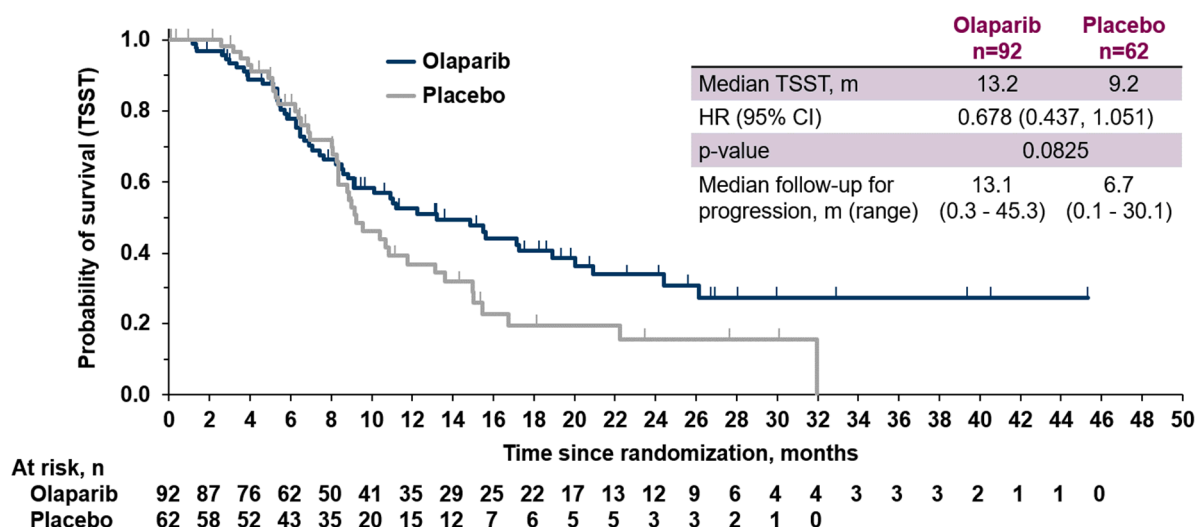
Figure 18 A favorable trend towards benefit in second progression-free survival for olaparib-treated patients



CI Confidence interval; HR Hazard ratio; mo Month; PFS2 Time from randomization to second progression or death.

- The delay in TSST suggested a positive trend for the olaparib arm compared with the placebo arm (Table 8, Figure 19), and data indicated that the olaparib treatment benefit is maintained over subsequent lines of therapy.
 - The clinically meaningful trend towards a delay in PFS2 and TSST demonstrate continuous benefit with olaparib beyond progression and indicates that olaparib maintenance treatment does not reduce the ability of patients to receive and respond to subsequent platinum-based chemotherapy, when the disease progresses.

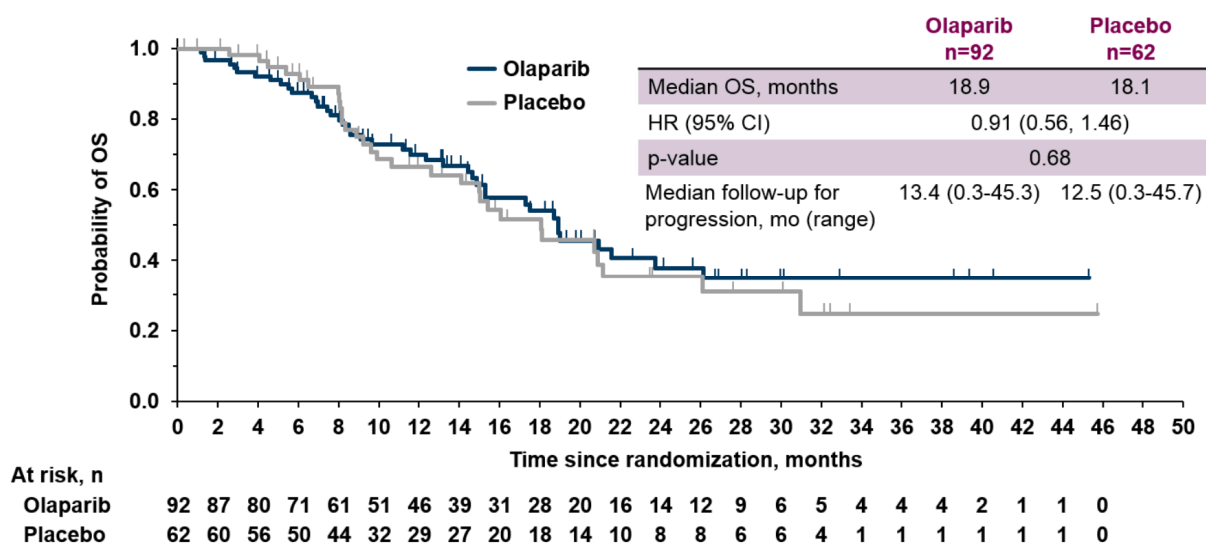
Figure 19 **Olaparib delayed the time patients receive their second subsequent therapy**



CI Confidence interval; HR Hazard ratio; m Month; TSST time to second subsequent therapy or death

- At the DCO (15 January 2019), the OS HR for olaparib-treated patients was 0.91 (95% CI 0.56 to 1.46) (interim OS maturity: 46% [71 events/154 patients]; median OS 18.9 months olaparib vs 18.1 months placebo). As of 17 October 2019, a total of 85 deaths have occurred. A final event driven OS analysis is expected to occur in late 2020 once 106 deaths have occurred (69% maturity). Based upon the data observed at the interim OS analysis and the protocol specified assumptions for the remaining data (6-month OS improvement over placebo), the probability of seeing a statistically significant difference in OS at the final analysis is 9%, strongly suggesting a significant result is not expected. With more modest assumptions the probability is lower.

Figure 20 OS for olaparib-treated patients



OS data were 46% mature

CI Confidence interval; HR Hazard ratio; mo Month; OS Overall survival.

- At the DCO of 15 January 2019, the percentage of patients who remained on treatment over time in the olaparib arm was 25.3% at 1 year, 9.9% at 2 years, and 3.3% at 3 years, compared with 6.7%, 3.3%, and 0%, respectively, in the placebo arm.
- Health-Related Quality of Life:
 - Baseline HRQoL scores were high, indicating a relatively good quality of life and consistent with the patient population that responded to first-line platinum-based treatment such as FOLFIRINOX ([Gourgou-Bourgade et al 2013](#)).
 - Olaparib maintenance treatment preserved the HRQoL, with no meaningful differences observed compared to placebo ([Table 11](#)). This is important as olaparib significantly improved PFS without compromising HRQoL despite comparison versus placebo, which is not expected to introduce any treatment-related symptoms. Additionally, olaparib appeared to maintain HRQoL benefits achieved during first-line platinum-based chemotherapy ([Figure 21](#), [Gourgou-Bourgade et al 2013](#)).
 - Olaparib appears to delay time to worsening of pain, which is a key symptom of metastatic pancreatic cancer.
 - For the EORTC QLQ-C30 pain domain, median time to sustained clinically meaningful deterioration was longer in olaparib arm compared to placebo (7.4 months vs. 4.4 months; HR=0.699; p=0.1335). Similarly, a longer median time to deterioration was observed for olaparib arm compared to placebo in the pancreatic pain domain of the QLQ-PAN26 (11.0 months vs. 6.0 months;

HR=0.810; p=0.4220). These results suggest potential benefit of olaparib in delaying time to worsening of pain ([Table 8](#)).

- The proportion of patients who experienced deterioration in the QLQ-C30 pain domain was 23.6% in the olaparib arm and 39.7% in the placebo arm. Deterioration was similar in the QLQ-PAN26 pancreatic pain domain for both arms.
- Disease control rate (defined as CR, PR, SD or NED) at 16 weeks was higher on the olaparib arm (53.3%) compared with the placebo arm (37.1%).
- Other secondary endpoints included TDT, with data supportive of the primary findings in favor of olaparib over placebo.
- Efficacy outcomes (PFS, OS, PFS2, TFST, TSST and TDT) for the confirmed Myriad *gBRCAm* subset (n=150) were consistent with those in the full analysis set (FAS).

5.4.1 Health-Related Quality of Life

Patients with metastatic pancreatic cancer have worse quality of life compared with the general cancer patient population ([Müller-Nordhorn et al 2006](#)). Therapies that preserve or improve HRQoL may provide meaningful patient-centered benefits in patients with pancreatic cancer.

Metastatic pancreatic cancer patients that derive clinical benefit on first-line chemotherapy have an improved HRQoL as a result of improved disease-related symptoms such as pain ([Gourgou-Bourgade et al 2013](#)). For example, in patients treated with first-line FOLFIRINOX, the mean EORTC QLQ-C30 global HRQoL score was 68.3 out of 100 based on PRODIGE4/ACCORD11 trial data (a higher score = better quality of life) ([Gourgou-Bourgade et al 2013](#)). Of note, this score is relatively high as it is similar to available normative data among the general population in the United States, Canada, and Europe (EORTC QLQ-C30 global HRQoL norm value=66.1 out of 100; n=15,386 in the United States, Canada, and 11 European countries) ([Nolte et al 2019](#)).

Thus, POLO sought to ensure preservation of HRQoL for as long as possible to patients who responded to first-line platinum-based treatment.

5.4.1.1 Olaparib maintenance treatment significantly prolonged PFS while preserving HRQoL compared to placebo

A pre-specified secondary objective of the POLO study was to assess global HRQoL using the EORTC QLQ-C30 global health status/QoL domain, a single measure of overall patient global health status and HRQoL. All other PRO domains were evaluated as exploratory. The PRO questionnaires were administered per schedule of assessments (see [Section 5.3.2](#)). Of note, patients were not followed beyond the 30-day post progression visit in either arm.

Patient Reported Outcomes Questionnaires: In POLO, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 item module (EORTC QLQ-C30) and the EORTC QLQ-PAN26 (pancreas cancer-specific module 26) questionnaires were administered to evaluate the effect of olaparib and placebo on HRQoL, functioning, and cancer-related symptoms from the patient perspective. These questionnaires are designed to capture key aspects of patient experience that reflect how a patient feels or functions in relation to the condition and/or treatment.

The EORTC QLQ-C30 and QLQ-PAN26 questionnaires are validated, reliable, and sensitive to assess the pancreatic cancer patient experience ([Aronson et al 1993](#), [Eaton et al 2017](#), [Fitzsimmons et al 1999](#), [Herman et al 2019](#), [Vanagas et al 2006](#)). These questionnaires were scored using scoring manuals provided by the developer ([EORTC QLQ-C30 scoring manual 2001](#), [QLQ-PAN scoring algorithm 2007](#)). Raw scores were transformed on to a scale ranging from 0 to 100. For global HRQoL and functioning scales, a higher score is indicative of better quality of life whereas for symptom scales a higher score is indicative of more severe symptoms.

The overall compliance rates for the PRO questionnaires were high in both treatment arms; 96.6% in the olaparib arm and 94.8% in the placebo arm. The treatment arms were balanced in terms of baseline scores. Baseline scores for the QLQ-C30 global HRQoL score were high in both arms (means for the olaparib and placebo groups, respectively, were 70.4/100 points and 74.3/100 points).

Compared to available normative data, the baseline PRO scores indicated good functioning and low symptom burden ([Nolte et al 2019](#), [Scott et al 2008](#)). This is expected in the maintenance treatment setting, such as POLO study, as the disease burden at baseline may be attenuated in patients who responded to first-line treatment ([Conroy et al 2011](#), [Gourgou-Bourgade et al 2013](#)).

Given high baseline HRQoL scores, on par with general population normative values, and minimal to low symptom burden in patients enrolled in POLO, a significant improvement in HRQoL or symptoms cannot be expected.

Adjusted mean change from baseline global HRQoL score was the primary analysis of the QLQ-C30 questionnaire and was evaluated using a mixed-model for repeated measures (MMRM) analysis of all of the post-baseline HRQoL scores by treatment group and visit. As shown in [Table 11](#), there was no statistically significant or clinically meaningful difference between the treatment arms in the overall adjusted mean change from baseline in global

HRQoL score¹. The adjusted mean change from baseline in global HRQoL score across all time points up to 6 months was -1.20 in the olaparib group and 1.27 in the placebo group, well within the pre-defined 10-point change from baseline that is defined as being clinically meaningful. This corresponded to an estimated difference between the treatment arms of 2.47 points, in the context of an EORTC scale of 100 points. For a plot of mean scores for QLQ-C30 global HRQoL over time see [Figure 21](#).

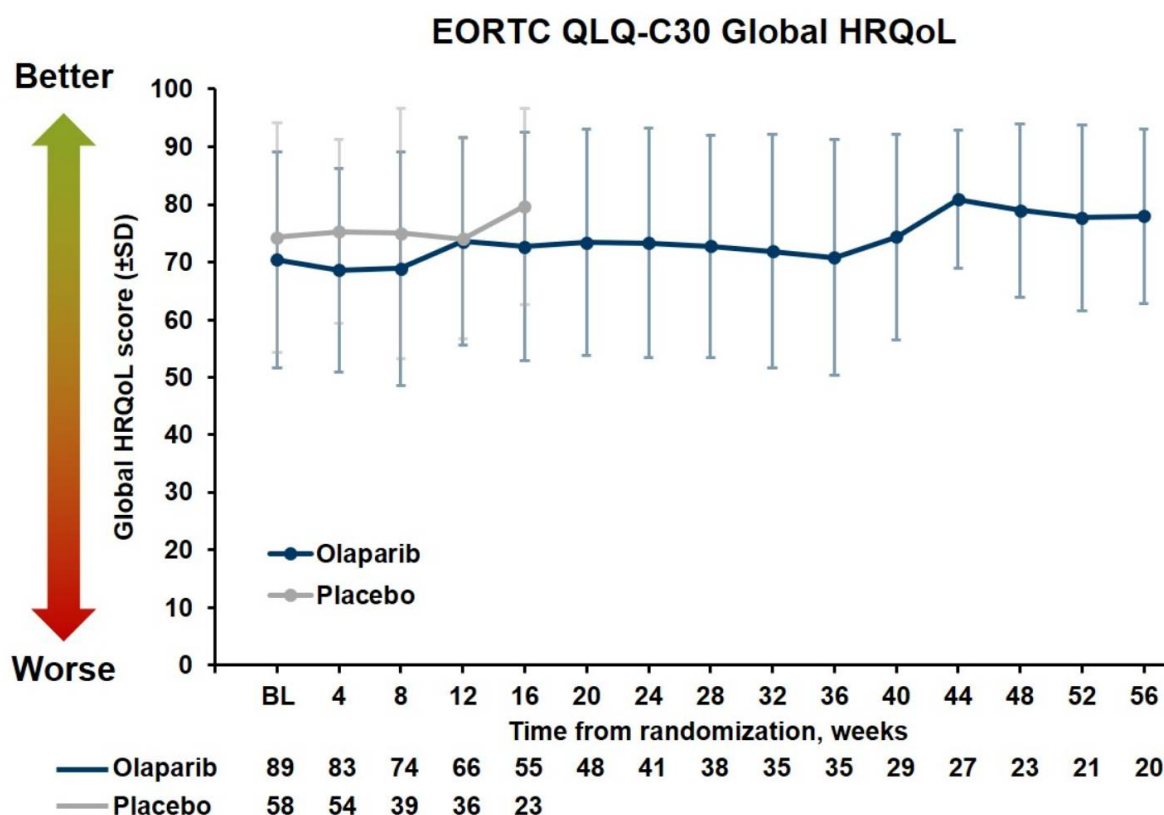
Table 11 Overall adjusted mean change from baseline up to 6 months in EORTC QLQ-C30 global health status/QoL, MMRM (PRO analysis set)

	Olaparib 300 mg bid (N=89)	Placebo (N=58)
n	84	54
Adjusted mean change estimate ^a	-1.20	1.27
Standard error	1.422	1.948
95% CI ^a	-4.014, 1.618	-2.580, 5.124
Estimated difference (olaparib minus placebo)	-2.47	
95% CI ^a	-7.267, 2.327	
Nominal p-value (2-sided)	0.310	

^a Calculated using a mixed model for repeated measures analysis of all of the post-baseline scores for each visit. Only visits with at least 25% of available samples in both treatment arms (calculated separately by treatment arm) were included in the model to ensure a sufficient sample for a reliable estimate. Global health status/QoL score consists of item 29 and 30 of QLQ-C30. The HRQoL score ranges from 0 to 100. A higher score indicates better QoL. A score change of 10 points was pre-defined as clinically meaningful. bid twice daily; CI confidence interval; EORTC European Organization for Research and Treatment of Cancer; HRQoL health-related quality of life; MMRM mixed model for repeated measures; PRO patient reported outcomes; QLQ-C30 quality of life questionnaire for cancer patients; QoL quality of life.

¹ A 10-point change from baseline was pre-defined as clinically meaningful change [Osoba et al 1998](#).

Figure 21 Mean ($\pm$ standard deviation) EORTC QLQ-C30 global health status/QoL across timepoints, by treatment group (PRO analysis set)



EORTC QLQ-C30 global health status/QoL score ranged from 0 to 100. A higher score indicated high functioning/QoL. Mean scores were pre-specified for calculation up to sample ≥ 20 .
 30 D F/U 30-day follow-up; C cycle; EORTC European Organization for Research and Treatment of Cancer; EOT End of treatment; PRO patient reported outcomes; QLQ C30 Quality of life questionnaire for cancer patients; W week.

Pre-specified exploratory analyses evaluating time to sustained clinically meaningful deterioration and best overall QoL response were also conducted.

- Olaparib maintenance appears to prolong the median TCMD in global HRQoL score compared to the placebo arm; however statistical significance was not reached (Table 12 and Figure 23).
- Olaparib appears to delay time to worsening of pain, which is a key symptom of metastatic pancreatic cancer. For the EORTC QLQ-C30 pain domain, time to sustained clinically meaningful deterioration was longer in olaparib arm compared to placebo (7.4 months vs. 4.4 months; HR=0.699; p=0.1335). Similarly, a longer median time to deterioration was observed for olaparib arm compared to placebo in the pancreatic pain

domain of the QLQ-PAN26 (11.0 months vs. 6.0 months; HR=0.810; p=0.4220) (Table 12).

- Figure 22 and Table 31 shows EORTC QLQ-C30/PAN26 global HRQoL, physical function, and symptoms best overall QoL response. Most patients experienced ‘improved’ or ‘no change’ responses in both arms.
 - The proportion of patients with an improvement in global HRQoL score was 29.2% in the olaparib arm compared to 22.4% in the placebo arm.
 - The proportion of patients who experienced a deterioration in the QLQ-C30 pain domain was 23.6% in the olaparib arm and 39.7% in the placebo arm. Deterioration was similar in the QLQ-PAN26 pancreatic pain domain for both arms.
 - The proportion of patients with a deterioration was similar in both arms for the fatigue domain. Furthermore, the proportion of patients with a deterioration in nausea/vomiting domain was 23.6% in the olaparib arm vs. 8.6% in the placebo arm.

Table 12 Summary of time to sustained clinically meaningful deterioration for EORTC QLQ-C30/PAN26 global health status/QoL and pain domains in patients with baseline score of ≥ 10 (PRO analysis set)

	Olaparib 300 mg bid (N=89)	Placebo (N=58)
QLQ-C30 Global health status/QoL domain		
No. of patients with baseline score ≥10	89	57
n (%) of patients with sustained clinically meaningful deterioration	33 (37.1)	22 (38.6)
Treatment effect		
Median TCMD (95% CI) [months] ^{a,b}	21.2 (8.21, NC)	6.0 (3.71, NC)
HR (95% CI) ^c	0.717 (0.405, 1.270)	
Nominal 2-sided p-value ^c	0.2535	
QLQ-C30 Pain domain		
No. of patients with baseline score ≥10	87	58
n (%) of patients with sustained clinically meaningful deterioration	47 (54.0)	33 (56.9)
Treatment effect		
Median TCMD (95% CI) [months] ^{a,b}	7.4 (3.61, 11.33)	4.4 (2.83, 5.82)
HR (95% CI) ^c	0.699 (0.437, 1.116)	
Nominal 2-sided p-value ^c	0.1335	
QLQ-PAN26 Pancreatic pain domain^d	88	58
n (%) of patients with sustained clinically meaningful deterioration	42 (47.7)	25 (43.1)
Treatment effect		
Median TCMD (95% CI) [months] ^{a,b}	11.0 (4.96, 16.56)	6.0 (3.02, 11.04)
HR (95% CI) ^c	0.810 (0.484, 1.355)	
Nominal 2-sided p-value ^c	0.4220	

^a TCMD was defined as time from randomization to ≥ 10 -point decrease in global health status/HRQoL score or ≥ 10 -point increase in symptom score that is confirmed at the subsequent assessment or death (death included if it occurred within 2 assessment time points). The analysis was carried out for a subset of patients from the PRO set, ie, only for those patients that had the potential for a clinically meaningful deterioration to occur. Any patient not known to have experienced a sustained clinically meaningful deterioration and not known to have died at the time of the analysis were censored at the time of their last assessment where the score could be evaluated.

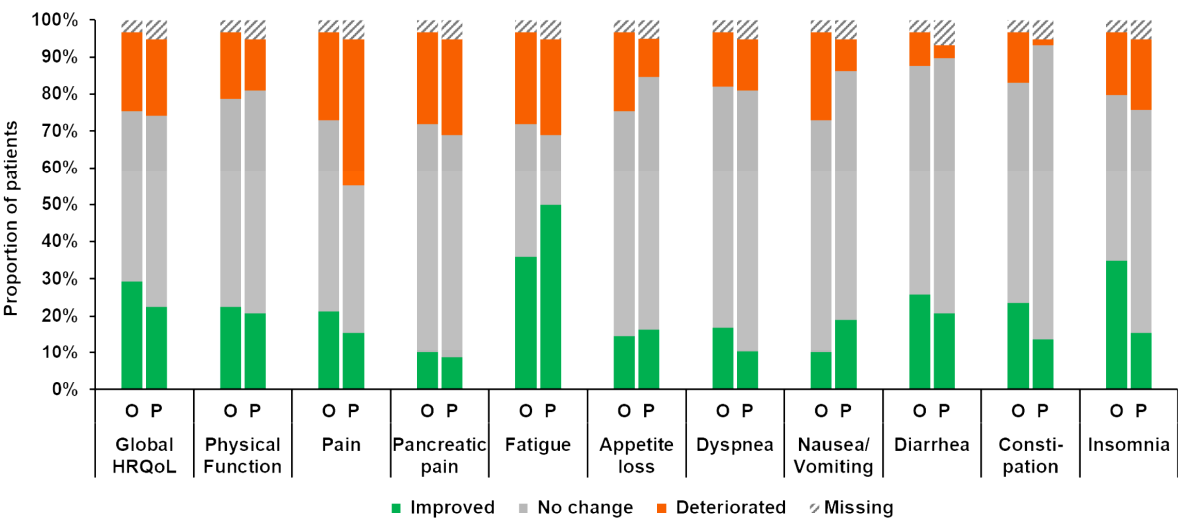
^b Calculated using KM techniques.

^c The analysis was performed using a log-rank test. The HR and CI were calculated using U and V statistics obtained from the log-rank test.

^d Pancreatic pain domain is part of the QLQ-PAN26 questionnaire, this multi-item domain consisted of 4 questions assessing abdominal discomfort, back pain, pain during night, and discomfort lying down.

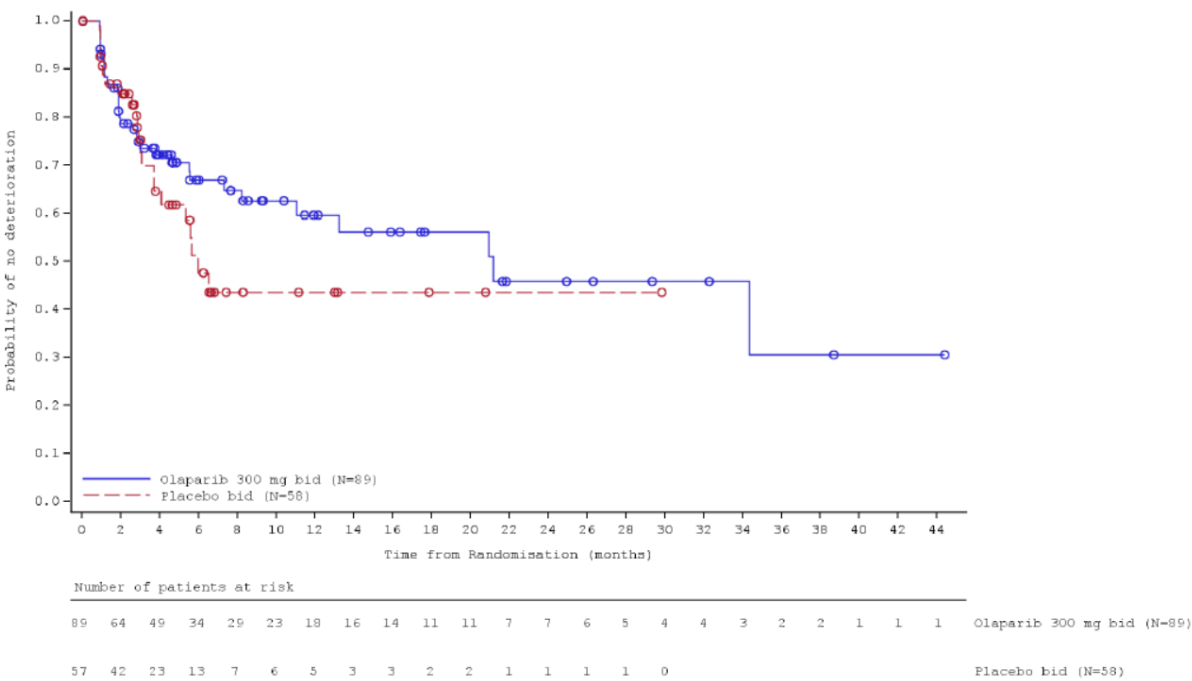
bid twice daily; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; KM Kaplan-Meier; TCMD time to sustained clinically meaningful deterioration. NC not calculated

Figure 22 EORTC QLQ-C30/PAN26 global HRQoL, physical function and symptoms: best overall QoL response (PRO analysis set)



O Olaparib; P Placebo

Figure 23 Time to sustained clinically meaningful deterioration Kaplan-Meier plot for EORTC QLQ-30 Global Health Status (PRO analysis set)



- In the POLO study, patients discontinued study treatment at disease progression per investigator, any other reasons including toxicity, or death (whichever occurred first) and were only followed for PRO assessment 30-day post progression. Therefore, follow-up for HRQoL was considerably shorter in the placebo arm and the impact of disease progression, or any subsequent treatments, on HRQoL was not taken into account.
- Adjusted mean change from baseline analyses only included visits at which $\geq 25\%$ of patients in each treatment arm had evaluable questionnaires; for the global HRQoL analysis this equated to the first 6 months of treatment.
- As such, it is likely these analyses underestimate the overall impact of olaparib treatment in comparison with placebo, since disease progression and associated subsequent therapies would be expected to result in further deterioration in HRQoL.

Overall, HRQoL was preserved with olaparib maintenance therapy in *gBRCAm* patients with metastatic pancreatic cancer whose disease had not progressed during first-line platinum-based chemotherapy, with no meaningful difference observed compared with placebo. Additionally, olaparib appears to provide benefit to patients by delaying time to worsening of pain, which is a key symptom of metastatic pancreatic cancer.

5.4.1.2 Olaparib maintenance treatment significantly prolonged PFS while appearing to maintain HRQoL gains achieved after first-line treatment (eg, FOLFIRINOX)

The POLO study enrolled *gBRCAm* patients with metastatic pancreatic adenocarcinoma who had not progressed following first-line platinum-based chemotherapy. Over 80% of patients enrolled had previously received first-line treatment with FOLFIRINOX or variants of FOLFIRINOX, which have been shown to improve survival and HRQoL ([Gourgou-Bourgade et al 2013](#)) in the first-line setting. [Figure 24](#) shows HRQoL scores of the first-line FOLFIRINOX treatment arm from the PRODIGE4/ACCORD11 trial followed by olaparib arm scores from the POLO study. While caution should be exercised when making cross-trial comparisons, [Figure 24](#) shows cross-trial longitudinal mean EORTC QLQ-C30 scores at baseline prior to first-line FOLFIRINOX treatment, end of FOLFIRINOX (6 months), at baseline prior to olaparib maintenance, and then throughout olaparib maintenance up to Week 48.

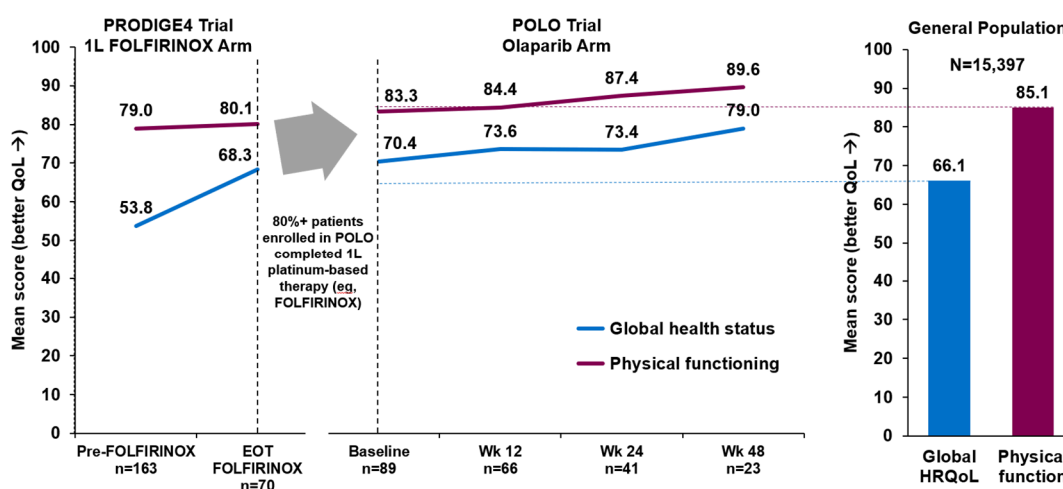
Olaparib maintenance appeared to preserve HRQoL improvements achieved following first-line FOLFIRINOX treatment while significantly prolonging PFS ([Figure 24](#)).

- Based on FOLFIRINOX arm baseline scores, first-line treatment population appeared to have generally higher disease-related symptom burden (eg, pain, fatigue, appetite loss, constipation), which is reduced after successful completion of treatment.

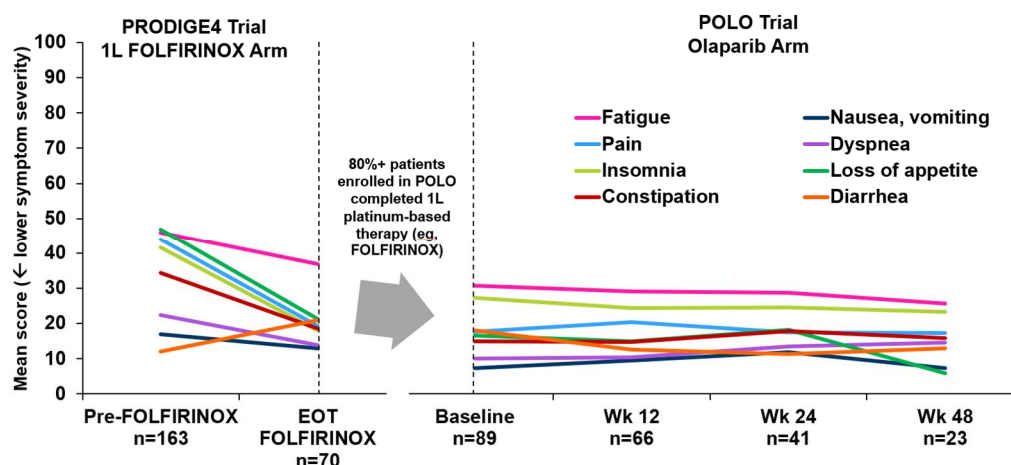
- Patients who enrolled in POLO olaparib arm experienced minimal to low baseline symptom burden, which is generally maintained throughout the treatment (eg, fatigue, nausea/vomiting, pain, insomnia, loss of appetite, constipation, and diarrhea). Global HRQoL and physical function scores were high at baseline and maintained throughout the treatment.

Figure 24 EORTC QLQ-C30 Global health status/QoL, physical function, and symptoms scores during first-line FOLFIRINOX treatment (PRODIGE4/ACCORD11) and olaparib maintenance (POLO)

a) Overall global health status/QoL and physical function (higher score = better QoL)



b) Patient-reported symptoms (lower score = lower symptom severity)



Pre-FOLFIRINOX and EOT FOLFIRINOX (6 months) scores were obtained from [Gourgou-Bourgade et al 2013](#). EORTC scale score ranged 0-100 where higher score on global health status/QoL represent better QoL while lower scores on symptom scale represent lower symptom severity.

This figure shows cross-trial longitudinal patient reported outcomes mean scores pre FOLFIRINOX, end of treatment FOLFIRINOX (6 months), olaparib baseline and olaparib maintenance (Weeks 12, 24, 48) [EORTC QLQ-C30]. Panel (a) shows global health status/QoL (global HRQoL) and physical function scores while panel (b) shows patient-reported symptom scores from EORTC QLQ-C30. Caution should be exercised when making cross-trial comparisons.

6 CLINICAL SAFETY

Across the entire clinical program, as of 15 June 2019, approximately 11,919 patients are estimated to have received treatment with olaparib.

The 300 mg bid dose of olaparib has demonstrated a consistent and well-defined tolerability profile suitable for use as a long-term maintenance therapy. Hematological side effects (predominantly anemia), gastrointestinal disturbances (nausea and vomiting) and fatigue/asthenia are the most commonly reported adverse events (reported by $\geq 15\%$ of patients) with olaparib treatment. These adverse events are predominantly mild to moderate in severity and infrequently lead to discontinuation of treatment.

Evaluation of olaparib safety for the proposed indication is based on the 151 patients randomized and treated in the pivotal POLO (olaparib 300 mg bid maintenance therapy n=91; matching placebo n=60), supported by a large pooled dataset of 1329 patients intended to receive the tablet formulation of olaparib at a dose of 300 mg bid as a monotherapy and who received olaparib treatment from 14 studies in the clinical trial program (including POLO).

In the olaparib 300 mg bid pool dataset, the contributing studies have differing patient populations; therefore, these safety data are considered supplementary to the presentation of data from POLO. The majority of patients in the 300 mg bid pool had either ovarian, fallopian tube or primary peritoneal cancer (818/1329 patients [61.6%]) or breast cancer (268/1329 patients [20.8%]). There were 103 patients with pancreatic adenocarcinoma (12 patients were recruited outside of POLO in Phase I/II studies that recruited any patient with advanced cancer). Patients with other advanced solid tumors, including colon/colorectal (n=23 patients) or prostate (n=11 patients) cancers were also treated in these studies. Patients were being treated for different stages of their disease. The median treatment duration in the 300 mg bid pool was generally longer than in POLO, due to the large number of patients in the 300 mg bid pool recruited in ovarian cancer studies where time to disease progression and hence treatment duration is longer than for pancreatic cancer.

Summaries of the key demographic and baseline patient characteristics for the 14 studies contributing to the pooled dataset are provided in [Table 30](#). It is important to note that these

data are for all patients in these studies and not just those in the olaparib 300 mg bid tablet dose cohorts.

The exposure of patients in the 300 mg bid olaparib pool, at the time of the sNDA DCO of 15 January 2019 is summarized in [Table 13](#).

6.1 Exposure and tolerability in POLO

The median total duration of exposure in the olaparib arm (182 days [6.0 months]) was approximately 1.6 times longer than the duration of exposure in the placebo arm (113 days [3.7 months]). In the olaparib arm, the median total treatment duration (182 days [6.0 months]) was similar to the actual treatment duration (168 days [approximately 5.5 months]), which shows that most patients were able to receive the assigned treatment and that the duration of any treatment interruptions was short.

The cumulative exposure to treatment over time, including treatment interruptions, is presented in [Table 13](#). A higher proportion of patients in the olaparib arm received treatment for a period of at least 6 months compared with the placebo arm. At 6 months, approximately half of patients in the olaparib arm (48.4%) vs less than a fifth of patients in the placebo arm (15.0%) were still on treatment. Furthermore, the percentage of patients remaining on treatment over time in the olaparib arm was 25.3% at 1 year, 9.9% at 2 years and 3.3% at 3 years, compared with 6.7%, 3.3% and 0%, respectively, in the placebo arm. Divergence between arms occurred after approximately 3 months on study.

Table 13 Cumulative exposure over time in POLO and the 300 mg bid pool – including treatment interruptions (SAS)

Treatment month	Number (%) of patients		
	POLO		Olaparib 300 mg bid pool
	Olaparib 300 mg bid (N=91)	Placebo (N=60)	Olaparib 300 mg bid (N=1329)
>0	91 (100.0)	60 (100.0)	1329 (100.0)
≥1 month	87 (95.6)	55 (91.7)	1248 (93.9)
≥3 months	70 (76.9)	37 (61.7)	1032 (77.7)
≥6 months	44 (48.4)	9 (15.0)	819 (61.6)
≥9 months	34 (37.4)	6 (10.0)	NA
≥12 months	23 (25.3)	4 (6.7)	547 (41.2)
≥18 months	13 (14.3)	3 (5.0)	407 (30.6)
≥24 months	9 (9.9)	2 (3.3)	285 (21.4)
≥36 months	3 (3.3)	0	22 (1.7)
≥48 months	NA	NA	6 (0.5)

Duration of treatment was collected in days. A month is defined as 365.25/12=30.4375 days.

Rows are cumulative and patients are counted if the actual treatment duration is greater than or equal to the stated duration.

bid twice daily; SAS Safety Analysis Set; NA not available.

Dose interruptions and reductions were permitted in the protocol to manage AEs. A total of 35.2% of patients in the olaparib arm and 5.0% of patients in the placebo arm had AEs leading to dose interruption. A total of 16.5% of patients in the olaparib arm and 3.3% of patients in the placebo arm had an AE leading to dose reduction. Despite these dose modifications, the majority (ranging from 69% to 90% across time periods) of patients received ≥500 to ≤600 mg mean daily dose of olaparib throughout the study ([Table 14](#)).

Table 14 Total daily dose of olaparib by time period in POLO (SAS)

Olaparib daily dose (mg)	Number (%) of patients by time period				
	Up to 3 months (N=91)	>3 to ≤6 months (N=71)	>6 to ≤9 months (N=45)	>9 to ≤12 months (N=35)	>12 months (N=23)
>500 to ≤600	82 (90.1)	55 (77.5)	35 (77.8)	28 (80.0)	16 (69.6)
>400 to ≤500	5 (5.5)	8 (11.3)	4 (8.9)	3 (8.6)	1 (4.3)
≤400	4 (4.4)	8 (11.3)	6 (13.3)	4 (11.4)	6 (26.1)

Patients were included once in each relevant time period.

SAS Safety Analysis Set.

6.2 Adverse events

The patients experiencing AEs in any category are summarized in [Table 15](#). The majority of patients experienced 1 or more AEs during the course of the study. There was a higher incidence in all AE categories in the olaparib arm, compared with the placebo arm. Most AEs were mild or moderate in severity, non-serious and did not lead to treatment discontinuation. Where necessary, AEs were generally well managed with dose modifications, as evidenced by the low incidence of discontinuations due to an AE (5.5%). Findings were generally consistent with the larger 300 mg bid pool ([Table 15](#)).

Table 15 Number (%) of patients^a with adverse events in any category in POLO and the 300 mg bid pool – patient level (SAS)

AE category	POLO		Olaparib 300 mg bid pool
	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	Olaparib 300 mg bid (N=1329)
Any AE	87 (95.6)	56 (93.3)	1298 (97.7)
Any AE of CTCAE Grade 3 or higher	36 (39.6)	14 (23.3)	528 (39.7)
Any AE with outcome = death	0 ^b	0	9 (0.7)
Any SAE (including events with outcome = death)	22 (24.2)	9 (15.0)	274 (20.6)
Any AE leading to discontinuation of olaparib/placebo	5 (5.5)	1 (1.7)	102 (7.7)
Any AE leading to dose interruption	32 (35.2)	3 (5.0)	515 (38.8)
Any AE leading to dose reduction	15 (16.5)	2 (3.3)	282 (21.2)

^a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.

^b One patient in the olaparib arm had an SAE of duodenal perforation that became fatal after DCO and after the 30-day follow up period (reported as Grade 5 on study).

Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo. CTCAE v4.03. MedDRA v21.1.

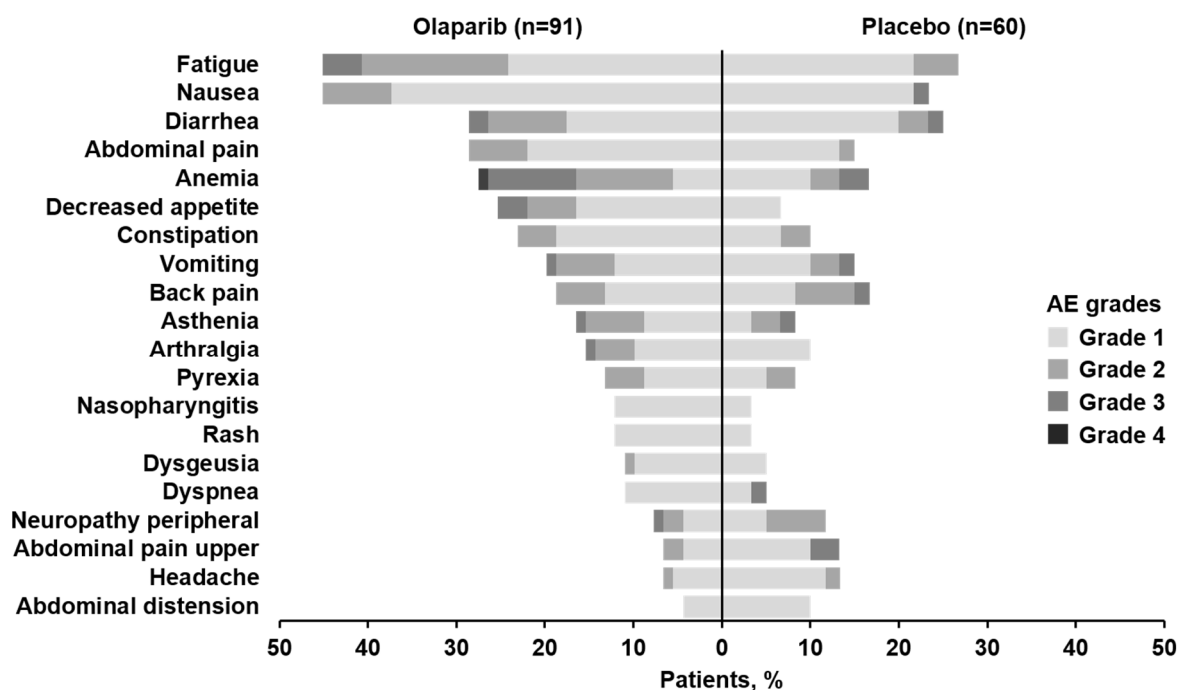
AE adverse event; bid twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO data cut-off; MedDRA Medical Dictionary for Regulatory Activities; SAE serious adverse event; SAS Safety Analysis Set.

6.2.1 Most common adverse events by preferred term (any grade) and Grade ≥ 3

In the olaparib arm, the most common AEs (reported by $\geq 20\%$ patients) were fatigue, nausea, abdominal pain, diarrhea, anemia, decreased appetite and constipation ([Figure 25](#)). Except for constipation, all of these AEs are known adverse drug reactions (ADRs) for olaparib as monotherapy. These common AEs were mainly low grade (CTCAE Grade 1 or 2) and did not

generally require dose modification or lead to discontinuation of study treatment. The nature and type of common AEs were broadly consistent with the larger 300 mg bid pool ([Table 16](#)).

Figure 25 POLO: Most common AEs >10% and CTCAE 3/4



A higher percentage of all patients in the olaparib group reported AEs of CTCAE Grade ≥ 3 (39.6%) compared with the placebo group (23.3%) ([Table 16](#)). The incidence of CTCAE Grade ≥ 3 AEs was largely driven by the incidence of AEs of anemia (10 of the 91 olaparib-treated patients [11.0%] had CTCAE Grade ≥ 3 AEs of anemia). AEs of fatigue were reported in 4 olaparib-treated patients (4.4%) and AEs of alanine aminotransferase (ALT) increased, decreased appetite, gamma glutamyl transferase (GGT) increased and neutropenia were each reported in 3 olaparib-treated patients (3.3%); all other CTCAE Grade ≥ 3 AEs were reported in ≤ 2 patients in either treatment arm. The ALT and GGT elevations were reported in patients with plausible alternative explanations for these events, such as new or worsening liver metastases, stent dysfunction and biliary obstruction (section [6.2.7](#)). Findings were generally consistent with the larger 300 mg bid pool ([Table 16](#)).

Table 16 **Number (%) of patients^a with most common AEs in POLO (all grades reported in ≥10% of patients in POLO [either olaparib or placebo arms]) and the 300 mg bid pool – Safety Analysis Set**

Preferred term ^b	POLO				Olaparib 300 mg bid pool	
	Any grade		Grade ≥3		Any grade	Grade ≥3
	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	Olaparib 300 mg bid (N=1329)	
Patients with any AE	87 (95.6)	56 (93.3)	36 (39.6)	14 (23.3)	1298 (97.7)	528 (39.7)
Fatigue	41 (45.1)	16 (26.7)	4 (4.4)	0	521 (39.2)	37 (2.8)
Nausea	41 (45.1)	14 (23.3)	0	1 (1.7)	838 (63.1)	13 (1.0)
Abdominal pain	26 (28.6)	15 (25.0)	2 (2.2)	1 (1.7)	236 (17.8)	18 (1.4)
Diarrhea	26 (28.6)	9 (15.0)	0	0	358 (26.9)	15 (1.1)
Anemia	25 (27.5)	10 (16.7)	10 (11.0)	2 (3.3)	513 (38.6)	228 (17.2)
Decreased appetite	23 (25.3)	4 (6.7)	3 (3.3)	0	294 (22.1)	9 (0.7)
Constipation	21 (23.1)	6 (10.0)	0	0	243 (18.3)	1 (0.1)
Vomiting	18 (19.8)	9 (15.0)	1 (1.1)	1 (1.7)	467 (35.1)	16 (1.2)
Back pain	17 (18.7)	10 (16.7)	0	1 (1.7)	161 (12.1)	8 (0.6)
Asthenia	15 (16.5)	5 (8.3)	1 (1.1)	1 (1.7)	222 (16.7)	24 (1.8)
Arthralgia	14 (15.4)	6 (10.0)	1 (1.1)	0	177 (13.3)	3 (0.2)
Pyrexia	12 (13.2)	5 (8.3)	0	0	159 (12.0)	2 (0.2)
Nasopharyngitis	11 (12.1)	2 (3.3)	0	0	107 (8.1)	0
Rash	11 (12.1)	2 (3.3)	0	0	76 (5.7)	0
Dysgeusia	10 (11.0)	3 (5.0)	0	0	218 (16.4)	0
Dyspnea	10 (11.0)	3 (5.0)	0	1 (1.7)	170 (12.8)	11 (0.8)
Neuropathy peripheral	7 (7.7)	7 (11.7)	1 (1.1)	0	43 (3.2)	3 (0.2)
Abdominal pain upper	6 (6.6)	8 (13.3)	0	2 (3.3)	144 (10.8)	1 (0.1)

Table 16 **Number (%) of patients^a with most common AEs in POLO (all grades reported in ≥10% of patients in POLO [either olaparib or placebo arms]) and the 300 mg bid pool – Safety Analysis Set**

	POLO				Olaparib 300 mg bid pool	
	Any grade		Grade ≥3		Any grade	Grade ≥3
Preferred term ^b	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	Olaparib 300 mg bid (N=1329)	
Headache	6 (6.6)	8 (13.3)	0	0	228 (17.2)	4 (0.3)
Abdominal distension	4 (4.4)	6 (10.0)	0	0	73 (5.5)	0

^a Table ordered by incidence of events in POLO.

^b Multiple occurrences of a system organ class/preferred term for a patient are counted only once for the patient.

Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

AE Adverse event; bid Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients

6.2.2 Serious adverse events

During POLO, a higher proportion of patients reported SAEs in the olaparib arm compared with the placebo arm (Table 17). The most common system organ class (SOC) for reported SAEs was Gastrointestinal disorders. Most SAE preferred terms were reported in fewer than 2 patients in each arm. The most commonly reported SAE ($\geq 5\%$) was anemia (7 events in 6 patients in the olaparib arm versus no events in the placebo arm). No new safety concerns were identified from the review of these events.

In the olaparib arm, the majority of the SAEs reported occurred whilst on treatment. A total of 3 olaparib treated patients (3.3%) and 4 placebo treated patients (6.7%) had SAEs with a date of onset during the safety follow-up period. The majority of SAEs had resolved with either no action taken, or following a temporary dose interruption or dose reduction, or were resolving. Five patients (all 5 in the olaparib arm) had SAEs that were ‘not recovered/not resolved’ at the DCO date for this analysis.

A similar proportion of patients (20.6%) in the 300 mg bid pool reported SAEs compared to those who received olaparib in POLO (24.2%). The SOC where SAEs were most commonly reported were Blood and lymphatic system disorders, Gastrointestinal disorders and Infections and infestations and this was consistent for POLO data (Table 17). A higher proportion of patients in POLO reported SAEs in the SOC of Hepatobiliary disorders compared with the 300 mg bid pool, indicative of the high proportion of patients in POLO with hepatic metastases at study entry.

Table 17 **Number (%) of patients with SAEs (reported by ≥ 2 patients in POLO [either olaparib or placebo arms] and/or reported by ≥ 5 patients in 300 mg bid pool) (SAS)**

	POLO		Olaparib 300 mg bid pool
MedDRA SOC Preferred term	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	Olaparib 300 mg bid (N=1329)
Patients with any SAE	22 (24.2)	9 (15.0)	274 (20.6)
Gastrointestinal disorders	10 (11.0)	3 (5.0)	53 (4.0)
Abdominal pain	3 (3.3)	1 (1.7)	11 (0.8)
Vomiting	1 (1.1)	3 (5.0)	8 (0.6)
Intestinal obstruction	0	0	6 (0.5)
Ileus	0	0	5 (0.4)
Small intestinal obstruction	0	0	5 (0.4)
Blood and lymphatic system disorders	6 (6.6)	1 (1.7)	82 (6.2)

Table 17 **Number (%) of patients with SAEs (reported by ≥ 2 patients in POLO [either olaparib or placebo arms] and/or reported by ≥ 5 patients in 300 mg bid pool) (SAS)**

	POLO		Olaparib 300 mg bid pool
MedDRA SOC Preferred term	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	Olaparib 300 mg bid (N=1329)
Anemia	6 (6.6)	0	67 (5.0)
Neutropenia	0	0	7 (0.5)
Thrombocytopenia	0	0	5 (0.4)
Hepatobiliary disorders	4 (4.4)	1 (1.7)	10 (0.8)
Cholangitis	2 (2.2)	1 (1.7)	3 (0.2)
Infections and infestations	4 (4.4)	0	54 (4.1)
Urinary tract infection	1 (1.1)	0	10 (0.8)
Pneumonia	1 (1.1)	0	9 (0.7)
Sepsis	0	0	6 (0.5)
Gastroenteritis	0	0	5 (0.4)
General disorders and administration site conditions	1 (1.1)	2 (3.3)	23 (1.7)
Pyrexia	0	2 (3.3)	8 (0.6)
Respiratory, thoracic and mediastinal disorders	1 (1.1)	0	20 (1.5)
Pleural effusion	1 (1.1)	0	6 (0.5)
Pulmonary embolism	0	0	5 (0.4)
Investigations	1 (1.1)	0	11 (0.8)
Platelet count decreased	1 (1.1)	0	5 (0.4)
Vascular disorders	1 (1.1)	0	10 (0.8)
Deep vein thrombosis	0	0	5 (0.4)

Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

bid Twice daily; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

6.2.3 Adverse events leading to discontinuation of study treatment

The incidence of AEs leading to discontinuation of study treatment was low (5.5% in the olaparib arm vs 1.7% in the placebo arm; [Table 18](#)). The only AE leading to discontinuation of olaparib that was reported in ≥ 2 olaparib-treated patients was fatigue. Approximately half

of the AEs leading to discontinuation of study treatment resolved after treatment was stopped; decreased appetite, duodenal perforation, proteinuria and 1 event of fatigue were unresolved at the time of the DCO for the primary analysis. The DAE of duodenal perforation was fatal (death occurred after the DCO).

AEs leading to discontinuation of olaparib in POLO occurred at a similar frequency compared with the 300 mg bid pool. Anemia and nausea were the most common AE leading to discontinuation in the 300 mg bid pool.

Table 18 **Number (%) of patients with adverse events leading to discontinuation (reported by all patients in POLO and/or reported by ≥ 5 patients in 300 mg bid pool) (SAS)**

	POLO		Olaparib 300 mg bid pool
MedDRA SOC Preferred term	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	Olaparib 300 mg bid (N=1329)
Patients with any AE leading to discontinuation	5 (5.5)	1 (1.7)	102 (7.7)
General disorders and administration site conditions	2 (2.2)	1 (1.7)	16 (1.2)
Fatigue	2 (2.2)	0	8 (0.6)
Pyrexia	0	1 (1.7)	2 (0.2)
Gastrointestinal disorders	2 (2.2)	0	20 (1.5)
Duodenal perforation ^a	1 (1.1)	0	1 (0.1)
Nausea	0	0	10 (0.8)
Vomiting	1 (1.1)	0	8 (0.6)
Musculoskeletal and connective tissue disorders	1 (1.1)	0	4 (0.3)
Arthralgia	1 (1.1)	0	2 (0.2)
Myalgia	1 (1.1)	0	1 (0.1)
Metabolism and nutrition disorders	1 (1.1)	0	4 (0.3)
Decreased appetite	1 (1.1)	0	3 (0.2)
Renal and urinary disorders	1 (1.1)	0	1 (0.1)
Proteinuria	1 (1.1)	0	1 (0.1)
Blood and lymphatic system disorders	0	0	32 (2.4)
Anemia	0	0	22 (1.7)
Thrombocytopenia	0	0	6 (0.5)

^a Following database lock, study site confirmed the patient had an AE of gastric fistula which lead to discontinuation of study treatment.

Multiple occurrences of a system organ class/preferred term for a patient were counted only once for the patient. Sorted by decreasing order of frequency in the olaparib arm and then by order of frequency in the placebo arm.

Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo.

AE Adverse event; bid Twice daily; MedDRA Medical Dictionary for Regulatory Activities (v21.1);

SAS Safety analysis set; SOC System organ class.

6.2.4 Deaths

In POLO, at the time of the DCO for the primary PFS analysis there were a total of 71 deaths in the 154 randomized patients (41/92 patients [44.6%] in the olaparib arm and 30/62 patients [48.4%] in the placebo arm). The majority of deaths (97%) were due to the disease under investigation only ([Table 19](#)).

Details of the 3 olaparib-treated patients whose deaths were not related to disease under investigation only are summarized below:

- One patient was admitted to hospital 15 days after their last dose of olaparib with hematemesis; an SAE of duodenal perforation was reported. The patient was discharged on study Day 144 with “deterioration of general conditions with adequate symptom control”. The patient died after the DCO date. The event of duodenal perforation was considered unrelated to olaparib by the reporting investigator.
- Two patients had deaths in the category “other”. The “other” causes were refractory septic shock/septic shock and cause unknown; both deaths occurred approximately 2 months after olaparib treatment has been discontinued. The patient who had refractory septic shock/septic shock receiving a subsequent anticancer therapy (cisplatin/gemcitabine) after they had discontinued olaparib.

Deaths in the 300 mg bid pool

In the 300 mg bid pool there were a total of 365 deaths out of 1329 patients (27.5%), with the majority (92%) due to the disease under investigation only ([Table 19](#)).

Details for all patients who had AEs leading to death in the 300 mg bid pool (excluding deaths in POLO) are summarized below:

Ten patients of 1329 patients (excluding deaths in POLO) had ‘death related to disease under investigation and an AE outcome of death’ (5 patients), ‘AE with outcome of death only’ (3 patients) or ‘death not related to disease and AE with outcome of death only (AE start date falling >30 days after last treatment dose)’ (2 patients) reported: acute myeloid leukemia (4) [1 patient also had subarachnoid hemorrhage], sepsis (2), MDS, ophthalmic herpes zoster, hepatic failure and cardiopulmonary failure (1 each).

Seventeen patients (excluding deaths in POLO) had the reason for death recorded as ‘other’, the reported terms (primary cause of death) were: death (7 patients), disease progression (2 patients), breast cancer (2 patients), ovarian cancer, septic shock, intestinal obstruction, intentions overdose, right ventricular failure and pulmonary hypertension (1 patient each).

Table 19 **Number (%) of patients who died in POLO and the 300 mg bid pool**

Category	POLO (FAS)		Olaparib 300 mg bid pool (SAS)
	Olaparib 300 mg bid (N=92)	Placebo bid (N=62)	Olaparib 300 mg bid (N=1329)
Total number of deaths	41 (44.6)	30 (48.4)	365 (27.5)
Death related to disease under investigation only ^a	39 (42.4)	30 (48.4)	335 (25.2)
Death related to disease under investigation and with AE outcome = death	0	0	5 (0.4)
AE with outcome of death only	0 ^b	0	4 (0.3)
AE with outcome of death only (AE start date falling >30 days after last treatment dose)	0	0	2 (0.2)
Patients with unknown/other reason for death ^c	2 (2.2) ^d	0	19 (1.4)

^a Deaths on or after the date of first dose and up to 30 days following the last dose of study medication.

^b One patient in the olaparib arm had an SAE of duodenal perforation which started 15 days after the last dose of olaparib (reported as Grade 5 AE) that became fatal after the 30-day safety follow-up period and after the DCO. Since this patient died after the DCO date the SAE outcome at the DCO was reset programmatically to not recovered/not resolved, however, Grade 5 (fatal) was maintained as reported. The patient had a past medical history of duodenal perforation prior to entry in the study.

^c Patients who died and are not captured in the earlier categories.

^d Patients who died and are not captured in the earlier categories. In POLO, one patient had the primary cause of death reported as unknown and one patient had their primary cause of death reported as refractory septic shock (the event occurred 75 days after the last dose of olaparib and is therefore not reported as an AE [after the 30-day safety follow-up period only events that are AESIs were reported as AEs]).

Note: One patient in the olaparib arm and one patient in the placebo arm voluntarily withdrew from the study. Post follow-up these patients were subsequently reported to have died.

AE Adverse event; bid Twice daily; DCO Data cut-off; FAS Full analysis set; N Total number of patients; SAE Serious adverse event, SAS Safety analysis set.

6.2.5 Characterization of the most common adverse events

Olaparib has a well characterized safety profile and the ADRs previously identified by AstraZeneca for olaparib tablets were: anemia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, fatigue and asthenia, nausea and vomiting, diarrhea, stomatitis, dyspepsia, upper abdominal pain, decreased appetite, increase in blood creatinine, mean corpuscular volume increased, headache, dizziness, dysgeusia, cough, hypersensitivity, dermatitis, rash, and

dyspnea. Data from POLO and the 300 mg bid pool were consistent with data from other olaparib monotherapy studies.

6.2.5.1 Anemia

Anemia is the most common hematological toxicity reported with olaparib treatment and has been identified as an ADR. In general, reported events of anemia were manageable by dose modifications, standard supportive therapies and rarely led to treatment discontinuation.

In POLO AEs of anemia (grouped term) were reported for a higher percentage of patients in the olaparib arm compared with the placebo arm (Table 20). These events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment. The AE category table for the 300 mg bid pool showed that a higher proportion of patients in the 300 mg bid pool had AEs, CTCAE Grade ≥ 3 AEs, DAEs and a lower proportion of patients had SAEs of anemia (grouped term) when compared with olaparib data from POLO (Table 20). Within the context of a shorter duration of exposure in POLO, the incidence and severity of anemia events following olaparib treatment in POLO are consistent with the known safety profile of olaparib.

Onset was early, generally in the first 3 months of starting olaparib although the risk of developing anemia remained fairly constant throughout exposure with no evidence of cumulative effect.

Table 20 POLO and the 300 mg bid pool: Number (%) of patients who had at least one adverse event of anemia (grouped term) reported in any category

AE category ^a	POLO SAS		Olaparib 300 mg bid pool (N=1329)
	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	
Any AE	25 (27.5)	10 (16.7)	526 (39.6)
Any AE of CTCAE Grade 3 or higher	10 (11.0)	2 (3.3)	231 (17.4)
Any AE with outcome = death	0	0	0
Any SAE	6 (6.6)	0	71 (5.3)
AEs leading to dose reduction	4 (4.4)	0	153 (11.5)
AEs leading to treatment interruption	9 (9.9)	0	220 (16.6)
Any AE leading to discontinuation	0	0	22 (1.7)

Grouped term consisting of the preferred terms of anemia, anemia macrocytic, erythropenia, hematocrit decreased, hemoglobin decreased, normochromic anemia, normochromic normocytic anemia, normocytic anemia, red blood cell count decreased.

^a Patients with multiple events reported in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

AE Adverse event; bid Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

Unlike other olaparib trials which required a hemoglobin ≥ 10 g/dL, in recognition of the effects of prior chemotherapy, POLO allowed patients to have a hemoglobin level of ≥ 9.0 g/dL (CTCAE Grade ≤ 2) for eligibility. In total, 20/154 patients (13.0%) reported anemia at study entry, with 7.7% of patients on olaparib and 5.2% on placebo having grade 2 laboratory hemoglobin values at baseline, and 1.7% of patients on placebo having a grade 3 laboratory hemoglobin value at baseline.

No patients in POLO had CTCAE Grade 4 hemoglobin values during the study; 11.0% of olaparib-treated patients had increases to CTCAE Grade 3 hemoglobin values.

Laboratory data showed 11/91 olaparib-treated patients (12.1%) in POLO had ≥ 2 grade decreases in hemoglobin, compared with 1/58 patients (1.7%) in the placebo arm.

In the olaparib arm, 14/25 patients (56.0%) with AEs of anemia (grouped term) were treated for the AE compared with 4/10 patients (40.0%) in the placebo arm. Additionally, one patient had 2 packed red-blood cell (PBRC) transfusions for treatment of an AE of anemia, the first of which started the day after the patient discontinued treatment.

In the olaparib arm of POLO, 15 patients (16.5%) in the olaparib arm received at least 1 blood or PBRC transfusion as a concomitant medication. The majority of patients received ≤ 3 transfusions; however, 1 patient who had concurrent AEs of anastomotic hemorrhage and melaena received 18 PBRC transfusions over a 7-month period. One olaparib-treated patient (1.1%) had treatment with an erythropoiesis stimulating agent (epoetin beta). In the placebo arm of POLO, no patients received a blood transfusion or other antianemic preparation on treatment; 3 patients (0.5%) in the placebo arm received at least 1 PBRC transfusion on treatment or within 30 days of discontinuation of study treatment; 2 of these 3 patients had a single transfusion and 1 patient had 2 transfusions. One patient had a transfusion of PBRCs the day before randomization. No patient on placebo received treatment with an erythropoiesis stimulating agent.

Anemia is a common AE routinely managed by physicians treating cancer patients. When clinically indicated, blood transfusions may be required to treat patients developing anemia on olaparib treatment. Dose interruptions and dose reductions can also be used in the management of patients developing anemia on olaparib therapy.

6.2.5.2 Neutropenia

Neutropenia has been identified as an ADR with olaparib treatment. In general, reported events of neutropenia are mild or moderate in severity, do not lead to treatment discontinuation, are manageable and generally resolve whilst on treatment.

AEs of neutropenia (grouped term) were reported for a higher percentage of patients in the olaparib arm compared with the placebo arm ([Table 21](#)). These events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment. One placebo-treated patient had an AE of febrile neutropenia (the patient had an CTCAE Grade 3 SAE that started in follow-up, [11 days after the last dose of placebo], lasted 10 days and recovered). There were no patients with AEs of neutropenic infection or neutropenic sepsis in POLO.

In the olaparib arm, none of the 4 patients with CTCAE Grade ≥ 3 AEs of neutropenia (grouped term) were SAEs. The AE category table for the 300 mg bid pool showed that a higher proportion of patients in the 300 mg bid pool had AEs, CTCAE Grade ≥ 3 AEs, SAEs and DAEs of neutropenia (grouped term) when compared with olaparib data from POLO ([Table 21](#)).

There was no association between the development of neutropenia and the length of time on olaparib treatment; AEs of neutropenia (grouped term) were reported throughout the study period in the olaparib-treated arm (median time to onset of first event was 2.17 months); the majority (9/11 patients) of events with olaparib resolved (median time to resolution of 0.33 months for first event).

Table 21 POLO and the 300 mg bid pool: Number (%) of patients who had at least one adverse event of neutropenia (grouped term) reported in any category

AE category ^a	POLO SAS		Olaparib 300 mg bid pool (N=1329)
	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	
Any AE	11 (12.1)	5 (8.3)	269 (20.2)
Any AE of CTCAE Grade 3 or higher	4 (4.4)	2 (3.3)	99 (7.4)
Any AE with outcome = death	0	0	0
Any SAE	0	0	14 (1.1)
AEs leading to dose reduction	1 (1.1)	0	40 (3.0)
AEs leading to treatment interruption	3 (3.3)	0	104 (7.8)
Any AE leading to discontinuation	0	0	6 (0.5)

Grouped term consisting of: agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased.

^a Patients with multiple events reported in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

AE Adverse event; bid Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

The majority (69/71 patients [97.2 %]) of olaparib-treated patients in POLO had a maximum CTCAE Grade ≤ 2 reported for absolute neutrophil count (ANC) values; all 50 patients with data in the placebo arm also had CTCAE Grade ≤ 2 ANC during the POLO study.

Laboratory data for POLO showed 9/71 olaparib-treated patients (12.7%) in POLO had ≥ 2 grade decreases in ANC, compared with 2/50 patients (4.0%) in the placebo arm.

Of the patients in the olaparib arm with AEs of neutropenia, 1/11 patients (9.1%) were treated for the AE compared with 3/5 patients (60.0%) in the placebo arm. Colony stimulating factor use in the olaparib arm was rare: 1 olaparib-treated patient (1.1%) received a colony stimulating factor.

6.2.5.3 Thrombocytopenia

Thrombocytopenia has been identified as an ADR with olaparib treatment. In general, reported events of thrombocytopenia are mild or moderate in severity, do not lead to treatment discontinuation, are manageable and generally resolve whilst on treatment.

AEs of thrombocytopenia (grouped term) were reported for a higher percentage of patients in the olaparib arm compared with the placebo arm (Table 22). These events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment. The AE category table for the 300 mg bid pool (Table 22) showed a consistent pattern of AEs when compared with olaparib data from POLO. The incidence and severity of thrombocytopenia events following olaparib treatment in POLO are consistent with the known safety profile of olaparib.

There was no association between the development of thrombocytopenia and the length of time on olaparib treatment. First onset of AEs of thrombocytopenia (grouped term) were reported throughout the first 12 months of study period in the olaparib-treated arm (median time to first onset was 0.49 months); the majority (10 of 13 patients) of events with olaparib resolved (median time to resolution of first event of 1.05 month).

Table 22 POLO and the 300 mg bid pool: Number (%) of patients who had at least one adverse event of thrombocytopenia (grouped term) reported in any category

AE category ^a	POLO SAS		Olaparib 300 mg bid pool (N=1329)
	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	
Any AE	13 (14.3)	4 (6.7)	166 (12.5)
Any AE of CTCAE Grade 3 or higher	3 (3.3)	0	36 (2.7)
Any AE with outcome = death	0	0	0
Any SAE	1 (1.1)	0	10 (0.8)
AEs leading to dose reduction	2 (2.2)	0	18 (1.4)
AEs leading to treatment interruption	4 (4.4)	0	44 (3.3)
Any AE leading to discontinuation	0	0	9 (0.7)

Grouped term consisting of thrombocytopenia, platelet production decreased, platelet count decreased and plateletcrit decreased.

^a Patients with multiple events reported in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

AE Adverse event; bid Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

The majority of patients had a worst CTCAE Grade of ≤ 2 reported for platelet values throughout treatment. A low proportion of olaparib-treated patients (2 patients [2.3%]) had CTCAE Grade ≥ 3 reductions in platelet count during the study; no patients in the placebo arm had a CTCAE Grade ≥ 3 reduction in platelet count.

Only 1/13 olaparib-treated patients (7.7%) and none of the placebo-treated patients were treated for AEs of thrombocytopenia.

6.2.5.4 Nausea and vomiting

Nausea and vomiting have both been identified as ADRs with olaparib treatment. In general, reported events of nausea and vomiting are mild or moderate in severity, do not lead to treatment discontinuation, are manageable and generally resolve whilst on treatment.

As shown in [Table 23](#), AEs of nausea and vomiting were reported for a higher percentage of patients in the olaparib arm compared with the placebo arm in POLO. These events were predominantly Grade 1 or 2 in severity and rarely led to permanent discontinuation of treatment in the olaparib arm. AE category tables for the 300 mg bid pool showed a fairly consistent pattern of AEs when compared with olaparib data from POLO ([Table 23](#)). Within the context of the shorter duration of treatment exposure in POLO, the incidence and severity of nausea and vomiting events following olaparib treatment in POLO are consistent with the known safety profile of olaparib. Events of nausea and vomiting in POLO were generally reported early in the treatment period (median time to onset was 0.16 months and 0.95 months, respectively).

Table 23 POLO and the 300 mg bid pool: Number (%) of patients who had at least one adverse event of nausea or vomiting reported in any category

AE category ^a	Nausea			Vomiting		
	POLO SAS		Olaparib 300 mg bid pool (N=1329)	POLO SAS		Olaparib 300 mg bid pool (N=1329)
	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)		Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	
Any AE	41 (45.1)	14 (23.3)	838 (63.1)	18 (19.8)	9 (15.0)	467 (35.1)
Any AE of CTCAE Grade 3 or higher	0	1 (1.7)	13 (1.0)	1 (1.1)	1 (1.7)	16 (1.2)
Any AE with outcome = death	0	0	0	0	0	0
Any SAE	0	0	4 (0.3)	1 (1.1)	3 (5.0)	8 (0.6)
Any AE leading to a dose reduction	0	0	25 (1.9)	2 (2.2)	0	10 (0.8)
Any AE leading to a dose interruption	1 (1.1)	0	69 (5.2)	4 (4.4)	1 (1.7)	79 (5.9)
Any AE leading to discontinuation	0	0	10 (0.8)	1 (1.1)	0	8 (0.6)

^a Patients with multiple events reported in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

AE Adverse event; bid Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Date cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

Nausea and vomiting are routinely managed by oncologists treating pancreatic cancer. The low grade events occurring on olaparib treatment can be effectively treated empirically using standard anti-emetic treatment and prophylaxis is not required. Temporary dose interruptions or dose reductions of olaparib may be required in a small number of patients.

6.2.5.5 Fatigue and asthenia

Fatigue and asthenia have both been identified as ADRs with olaparib treatment. AEs of fatigue/asthenia were reported in a higher percentage of patients in the olaparib arm compared with the placebo arm (Table 24). These events were generally Grade 1 or 2 in severity and rarely resulted in permanent discontinuation of treatment. The AE category table for the 300 mg bid pool showed a consistent pattern of AEs when compared with olaparib data from POLO (Table 24). The incidence and severity of fatigue and asthenia events following olaparib treatment in POLO are consistent with the known safety profile of olaparib.

Table 24 POLO and the 300 mg bid pool: Number (%) of patients who had at least one adverse event of fatigue or asthenia reported in any category

AE category ^a	POLO SAS		Olaparib 300 mg bid pool (N=1329)
	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	
Any AE	55 (60.4)	21 (35.0)	716 (53.9)
Any AE of CTCAE Grade 3 or higher	5 (5.5)	1 (1.7)	59 (4.4)
Any AE with outcome = death	0	0	0
Any SAE	0	0	4 (0.3)
AEs leading to dose reduction	5 (5.5)	1 (1.7)	52 (3.9)
AEs leading to treatment interruption	4 (4.4)	1 (1.7)	51 (3.8)
Any AE leading to discontinuation	2 (2.2)	0	10 (0.8)

^a Patients with multiple events reported in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

AE Adverse event; bid Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

Fatigue and asthenia on olaparib treatment were generally reported early, with the majority of first events with olaparib reported within the first 3 months of treatment. Median time to onset was 0.49 months. A similar percentage of patients in the olaparib arm (3/55 [5.5%]) and placebo arm (1/21 [4.8%]) were reported by the investigator to have received treatment for the event of fatigue and asthenia.

6.2.5.6 Diarrhea

Diarrhea has been identified as an ADR with olaparib treatment. In general, reported events of diarrhea were mild or moderate in severity, do not lead to treatment discontinuation, are manageable and generally resolve whilst on treatment.

Table 25 shows that AEs of diarrhea (single preferred term) were reported for a higher percentage of patients in the olaparib arm compared with the placebo arm in the POLO study. These events were all Grade 1 or 2 in severity and none led to permanent discontinuation of treatment. Events of diarrhea were generally reported early in the treatment period (median time to onset was 0.54 months) and the majority (19 of 26 patients) of first events with olaparib resolved, (median time to resolution of first event of 0.31 months). A similar proportion of patients in the olaparib arm with diarrhea were treated for the AE (9 [34.6%] of 26 patients) compared with the placebo arm (3 [33.3%] of 9 patients). The AE category table for the 300 mg bid pool showed a consistent pattern of AEs when compared with olaparib data

from POLO (Table 25). The incidence and severity of diarrhea events following olaparib treatment in POLO are consistent with the known safety profile of olaparib.

Table 25 POLO and the 300 mg bid pool: Patients who had at least one AE of diarrhea reported in any category

AE category ^a	Number (%) of patients		
	POLO SAS		Olaparib 300 mg bid pool (N=1329)
	Olaparib 300 mg bid (N=91)	Placebo bid (N=60)	
Any AE	26 (28.6)	9 (15.0)	358 (26.9)
Any AE of CTCAE Grade 3 or higher	0	0	15 (1.1)
Any AE with outcome = death	0	0	0
Any SAE	0	0	1 (0.1)
AEs leading to dose reduction	0	0	2 (0.2)
AEs leading to treatment interruption	1 (1.1)	0	34 (2.6)
Any AE leading to discontinuation	0	0	0

^a Patients with multiple events reported in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

AE Adverse event; bid Twice daily; CTCAE Common Terminology Criteria for Adverse Events; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

6.2.6 Adverse events of special interest

Important potential risks for olaparib treatment include MDS/AML, new primary malignancies, and pneumonitis.

Myelodysplastic syndrome /Acute myeloid leukemia

In POLO, there were no reports of MDS/AML in either treatment arm.

At the DCO for the sNDA, 30/2527 patients from a monotherapy “all doses” pool reported an event of MDS/AML, giving a cumulative incidence rate of 1.2%. Across the entire olaparib clinical trial program (10682 patients [largely composed of ovarian and breast cancer patients] as of 15 December 2018), there have been 64 reports of MDS/AML, giving an estimated cumulative incidence of 0.6%, which includes events of MDS/AML from placebo-controlled, blinded monotherapy studies in which the treatment arm is unknown.

A causal relationship between olaparib treatment and the development or acceleration of MDS/AML has not been established and POLO data provides important reassurance that this

conclusion is applicable to the patient population studied. The important potential risk of MDS/AML is closely monitored as part of routine pharmacovigilance practices. Appropriate information on MDS/AML is also detailed in Section 5.1 of the USPI.

New primary malignancies

In POLO, there were no reports of new primary malignancies in either treatment arm during study treatment and the 30-day follow-up period. Two patients randomized to the placebo arm had events of new primary malignancies reported after the 30-day follow-up period (1 patient had an AE of rectal cancer [Grade 2] and occurred 339 days after the last dose of placebo treatment; 1 patient died of metastatic ovarian cancer 469 days after their last dose of placebo).

At the DCO for the sNDA, 35/2527 patients from a monotherapy “all doses” pool reported a new primary malignancy, giving a cumulative incidence rate of 1.4%. Across the entire olaparib clinical trial program (10682 patients [largely composed of ovarian and breast cancer patients] as of 15 December 2018), there have been 69 reports of new primary malignancies, giving an estimated cumulative incidence of 0.6%, which includes events of new primary malignancies from placebo-controlled, blinded monotherapy studies in which the treatment arm is unknown.

A causal relationship between olaparib treatment and the development of new primary malignancies has not been established. The benefits that patients may expect to receive from olaparib for the treatment of metastatic pancreatic adenocarcinoma are considered to outweigh the risk of the potential development of a new primary malignancy. New primary malignancies will be monitored actively in the Phase III program and post-marketing. Routine pharmacovigilance practices, signal identification and review for new primary malignancies will also be conducted.

Pneumonitis

At the time of the DCO for POLO (15 January 2019), it was reported that 1 patient (1.1%) in the olaparib arm and no patients in the placebo arm had an AE of pneumonitis on treatment, and no patients had AEs of pneumonitis in the post-follow-up period.

The AE of pneumonitis in the olaparib-treated patient was a non-serious event (CTCAE Grade 1) that started on Day 411 of study (12 December 2017), when the patient was receiving a dose of 250 mg bid. The dose was not changed and no treatment was given. The event was not considered related to olaparib treatment. The AE was reported as unresolved at the DCO date of 15 January 2019.

At the DCO for the sNDA, 15/2095 patients from a “therapeutic dose pool” reported an event of pneumonitis, giving a cumulative incidence rate of 0.7%.

The incidence of AEs of pneumonitis in the POLO study was low and comparable with that in the olaparib monotherapy combined therapeutic dose pool. The majority of patients reporting pneumonitis in olaparib studies had received prior radiotherapy and/or chemotherapy and had other risk factors within the medical histories including pneumonitis, interstitial lung fibrosis, dyspnea, hemoptysis, chest infection, allergic asthma, pleural effusion, pleural metastases, and smoking.

A causal relationship between olaparib treatment and the development of pneumonitis has not been established. Therefore, the benefits that patients may expect to receive from olaparib treatment are considered to outweigh the potential risk of developing pneumonitis. Appropriate information on pneumonitis is provided in Section 5.2 of the USPI.

6.2.7 Clinical chemistry, renal and hepatic function

No new safety concerns were identified from the clinical chemistry results. In POLO, mild elevations in creatinine with no apparent sequelae have been observed in the absence of an elevation in urea or blood urea nitrogen. Any increase observed remained consistent over the dosing period with levels returning to baseline at the 30-day follow-up/post follow-up visits. The small increases in creatinine observed with olaparib and the rapid onset of the mild changes observed, with a return to baseline after olaparib discontinuation, are consistent with the in vitro finding that olaparib is known to be an OCT2 and MATE1 inhibitor. There were no clinically relevant findings for urinalysis.

The incidence of CTCAE Grade 3 or 4 clinical chemistry parameter values (albumin, alanine aminotransferase [ALT], alkaline phosphatase, aspartate aminotransferase, bilirubin, creatinine and gamma-glutamyl transferase) was low in both treatment arms. An apparent numerical imbalance in ALT elevations between olaparib and placebo arms was caused by patients with plausible alternative explanations, such as new or worsening liver metastases, stent dysfunction and biliary obstruction. There is no indication of an underlying effect on the liver.

Based on all available data there is no evidence to suggest that olaparib causes drug-induced liver injury. There were no confirmed Hy's Law cases in POLO.

Based on all the available data there is no evidence to suggest that olaparib impairs renal function.

6.2.8 ECG

In POLO, there were no clinically relevant trends in ECG observations were evident during the study for those patients who had on-treatment ECGs.

6.2.9 Adverse events in special populations: age and race

Effect of age

In POLO, the majority of olaparib-treated patients were younger than 65 years old (63 patients); 28 patients were aged ≥ 65 years. In the olaparib-treated patients, there was a similar proportion of patients reporting AEs, CTCAE Grade ≥ 3 , SAEs and AEs requiring a dose interruption in patients aged < 65 years and ≥ 65 years. Dose reductions were reported more frequently in patients aged < 65 years (20.6%) than patients aged ≥ 65 years (7.1%) and there was a numerically lower proportion of patients who discontinued treatment due to AEs in the < 65 years age category (4.8%) compared to the ≥ 65 years age category (7.1%). In the context of the small group sizes, the safety and tolerability profile of olaparib in POLO is comparable between the age groups.

The safety profile in the 300 mg bid pool showed that there was a similar proportion of patients for olaparib that had AEs and SAEs in all age categories. There was a slightly higher proportion of patients who discontinued treatment due to AEs in the ≥ 65 years age category compared with < 65 years. Four fatal AEs were reported in the < 65 years and 5 in the ≥ 65 years age category. There were no significant difference in the safety profile of olaparib in patients < 65 years vs those ≥ 65 years; no dose adjustment is required based on patient age.

Table 26 POLO and the 300 mg bid pool: Number (%) of patients^a with adverse events in any category by age group

	POLO (SAS)				Olaparib 300 mg bid pool	
	<65 years		≥65 years		<65 years	≥65 years
AE category	Olaparib 300 mg bid (N=63)	Placebo bid (N=48)	Olaparib 300 mg bid (N=28)	Placebo bid (N=12)	Olaparib 300 mg bid (N=1060)	Olaparib 300 mg bid (N=269)
Any AE	59 (93.7)	44 (91.7)	28 (100.0)	12 (100.0)	1034 (97.5)	264 (98.1)
Any AE of CTCAE Grade 3 or higher	24 (38.1)	10 (20.8)	12 (42.9)	4 (33.3)	413 (39.0)	115 (42.8)
Any AE with outcome = death	0	0	0	0	4 (0.4)	5 (1.9)
Any SAE	16 (25.4)	7 (14.6)	6 (21.4)	2 (16.7)	210 (19.8)	64 (23.8)
AEs leading to dose reduction	13 (20.6)	1 (2.1)	2 (7.1)	1 (8.3)	229 (21.6)	53 (19.7)
AEs leading to treatment interruption	22 (34.9)	2 (4.2)	10 (35.7)	1 (8.3)	416 (39.2)	99 (36.8)
Any AE leading to discontinuation	3 (4.8)	1 (2.1)	2 (7.1)	0	76 (7.2)	26 (9.7)

^a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories

Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of study treatment.

Effect of race

The safety profile in the 300 mg bid pool for olaparib in White and non-White patients was generally similar. A review of the safety data in the 293 non-White patients (293/1329 [22.0%]) showed that the safety profile was consistent with that observed in all patients receiving olaparib.

Although there appears to be some variability in the reporting of individual terms, particularly with respect to reporting of laboratory values as AEs, no clinically meaningful differences in the safety profile of olaparib in White vs Asian or other non-White patients have been observed and no effect of race on the PK of olaparib has been identified. No dose adjustment is required based on racial origin.

Effect of gender

In POLO 54.5% (84/154) of patients were male and 45.5% (70/154) of patients were female. No clinically meaningful gender related differences in the safety profile of olaparib have been identified. No dose adjustment is required on the basis of gender.

7 BENEFIT-RISK ASSESSMENT

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 deaths in the US. Pancreatic cancer is an orphan disease in the US, as defined by the FDA. Pancreatic cancer patients with a *gBRCA* mutation are an even smaller segment, representing up to 6% of the overall pancreatic cancer patient population, indicating the rarity of this biomarker-defined subpopulation. There are currently no treatment options approved in the maintenance setting for pancreatic cancer patients and no precision medicine treatment options for *gBRCAm* patients with pancreatic cancer, reflecting a high unmet medical need in this population.

Platinum-based chemotherapy is the preferred regimen for the first-line treatment of *gBRCAm* advanced pancreatic cancer because of the evidence that overall survival is improved compared to that with non-platinum regimens and is advocated by national guidelines for patients with *BRCAm* pancreatic cancer. There are two practice patterns that exist for these regimens. Physicians either intend to administer chemotherapy for 6 months and stop in patients who had a response (ie, the approach described the original FOLFIRINOX paper: [Conroy et al 2011](#)), or to administer chemotherapy until disease progression. However, the standard platinum-based FOLFIRINOX regimen, even when dosages are modified or when individual chemotherapy agents are dropped, is difficult to tolerate due to cumulative toxicities that can be significant and possibly irreversible. Polyneuropathy, attributable to the oxaliplatin component of FOLFIRINOX, occurs almost invariably and may not be completely reversible depending on the number of cycles received. Other components of the

FOLFIRINOX regimen have their own significant issues for patients, such as diarrhea for irinotecan and the burdensome requirement for being attached to an infusion pump for 2 days every 2 weeks for fluorouracil. Patients who receive other platinum-based regimens such as gemcitabine/cisplatin also experience issues of cumulative ototoxicity and nephrotoxicity that may limit their duration of treatment.

For those patients who can no longer tolerate platinum-based chemotherapy, or have completed the specified 6 months of chemotherapy, the standard practice is to stop the chemotherapy for some period of time (ie, a “chemotherapy break”), which allows the patient to recover from the challenging side effects of treatment. However, this also leaves the patient untreated and at high risk for earlier disease progression resulting in a need for new treatment strategies preventing early disease progression and maintaining the benefits that were obtained from first-line chemotherapy.

Therefore, there is a need for new treatment strategies (such as maintenance therapies) preventing early disease progression, and thus delaying time to resumption of chemotherapy, which allows the patient more time to recover from the toxicities of prior chemotherapy. The availability of olaparib would address this high unmet need and would be the first targeted PARP inhibitor in the first-line maintenance treatment setting for *gBRCAm* patients with metastatic pancreatic adenocarcinoma whose disease has not progressed on first-line platinum-based chemotherapy.

Results from the Phase III, randomized, double-blind, placebo-controlled POLO study, support a positive benefit-risk profile for olaparib, with a clinically meaningful and statistically significant 47% reduction in the risk of progression or death and a prolongation of median PFS to 7.4 months in the olaparib arm from 3.8 months in the placebo arm in *gBRCAm* patients with metastatic pancreatic adenocarcinoma. Additionally, at every timepoint including and beyond 6 months of treatment, the likelihood of recurrence or disease progression for patients receiving olaparib reduced by at least half compared to placebo, which suggested that the PFS benefit was persistent. Over twenty percent of patients remain progression-free on olaparib at two years and several patients at three years suggesting that there is a cohort of patients who experience long-term progression-free survival.

The median duration of response of 24.9 months for the 23% of patients who presented an objective response to olaparib (of which 2 patients had a CR), compared to 3.7 months to those patients (11%) who responded to placebo (none of whom had a CR), is remarkable in pancreatic cancer and indicative of clinical benefit.

In the context of maintenance treatment setting for a well-tolerated and convenient oral dosage form, the clinically meaningful delays in TFST and PFS2 for olaparib treated patients compared with placebo treated patients further support the PFS benefit observed with

olaparib. The prolongation of the time off chemotherapy while still in response presents an unequivocal benefit to patients, which is best measured by the delay to the start of the next subsequent treatment. Olaparib extended the chemotherapy free duration and delayed the time to subsequent potentially toxic chemotherapy (median TFST 8.6 months for olaparib vs 5.7 months for placebo), which in the majority of cases (63%) was again a platinum containing regimen. This ~9 month break in resuming chemotherapy is clinically meaningful to patients as it constitutes about half of the median life expectancy of patients randomized into POLO (~18 months). Although the data were 46% mature, the prolongation of PFS2, trended towards benefit for olaparib. This indicates extension of benefit on olaparib beyond first progression in patients who receive subsequent therapies. There was also no detriment in OS at the time of interim analysis in olaparib treated patients.

Although OS has historically served as the basis for approval in pancreatic cancer, the rarity of the *gBRCAm* population makes it not feasible to power a study to reliably detect a statistically significant difference in OS. Randomization of 2200 patients is needed to show a 3-month improvement in survival vs placebo (18 months to 21 months) with 80% power, which would require screening of 37,000 patients assuming a *gBRCAm* prevalence of 6%. Furthermore, the longer OS observed in *gBRCAm* pancreatic cancer patients exposed to platinum-based chemotherapy and the confounding of OS by receipt of multiple subsequent therapies makes OS a challenging endpoint for primary assessment of benefit in this patient subset.

In addition, PFS is a recognized regulatory endpoint and has served as the primary basis for registration in a number of biomarker selected patient populations in both treatment and maintenance settings, in the absence of OS. For these reasons, PFS is a more practical and clinically relevant endpoint to measure benefit in this subset of pancreatic cancer patients.

Pancreatic cancer patients who achieved disease control on first-line chemotherapy have a relatively high HRQoL, which was also observed in POLO (~70 out of the 100-point EORTC QLQ-C30 instrument). Olaparib maintenance treatment preserved HRQoL compared to placebo, while significantly prolonging PFS, suggesting that the benefits, including those in HRQoL, achieved during first-line platinum-based chemotherapy are maintained. There was also a trend for olaparib maintenance treatment to prolong the median time to clinically meaningful deterioration in global HRQoL score compared to the placebo arm, although this was not statistically significant (21.2 months vs 6.0 months, respectively). Additionally, olaparib appears to delay time to worsening of pain, which is a key symptom of metastatic pancreatic cancer. For the EORTC QLQ-C30 pain domain, time to sustained clinically meaningful deterioration was longer in olaparib arm compared to placebo (7.4 months vs. 4.4 months; HR=0.699; p=0.1335). Similarly, a longer median time to deterioration was observed for olaparib arm compared to placebo in the pancreatic pain domain of the QLQ-

PAN26 (11.0 months vs. 6.0 months; HR=0.810; p=0.4220). These data demonstrate that olaparib maintenance treatment provides clinically meaningful patient-centered benefit.

The safety profile of olaparib has been well-characterized; ~12,000 subjects are estimated to have received olaparib across the clinical program, as well as >20,000 patients-years exposure from post-marketing use (as of 15 June 2019). No new safety concerns were identified in the POLO study. In POLO, the safety profile of olaparib was generally consistent with the known safety profile of olaparib; adverse events with olaparib were predominantly mild or moderate in severity and, in the majority of cases, resolved without the need for any dose interventions. Where interventions were required for olaparib AEs, these were generally manageable through dose interruptions and dose reductions, with few subjects experiencing AEs that led to drug discontinuation (5.5%). Long-term tolerability to olaparib maintenance therapy was demonstrated with 25.3%, 9.9% and 3.3% of patients in the olaparib arm remaining on treatment at 1 year, 2 years and 3 years, respectively in POLO (compared with 6.7%, 3.3%, and 0%, respectively, in the placebo arm). Most patients remained on treatment until disease progression, indicating that olaparib is an overall well-tolerated therapy, and supports the suitability of olaparib as a maintenance treatment option for patients with *gBRCAm* metastatic pancreatic adenocarcinoma following first-line platinum-based chemotherapy.

The widely followed NCCN guidelines have been updated ([NCCN 2019](#): v3, dated 02 July 2019) to recommend olaparib as maintenance treatment for *gBRCAm* pancreatic cancer based on the results of POLO: “Consider olaparib as maintenance treatment for patients who have a deleterious germline *BRCA1/2* mutation, good PS, metastatic disease, and no disease progression >16 weeks of first-line, platinum-based chemotherapy”.

Moreover, olaparib maintenance therapy has the convenience of oral administration, which allows patients to receive treatment at home, and reduces the requirement for frequent and prolonged clinic visits for intravenous administration with chemotherapy, which often requires pre- and post-chemotherapy-related monitoring and toxicity management.

Collectively these outcomes represent a significant advancement in the treatment of patients with *gBRCAm* pancreatic cancer, and an overall positive benefit-risk assessment that supports regular approval of olaparib for the maintenance treatment of adults with *gBRCAm* metastatic pancreatic cancer whose disease has not progressed on first-line platinum-based chemotherapy.

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Appendix A Additional data presentations

Table 27 Comparison of steady state exposure parameters of olaparib in patients with pancreatic cancer (Study D0810C00005) and patients with advanced solid tumors (Study D0810C00002)

Treatment regimen	Statistic	D0810C00005	D0810C00002	D0810C00005	D0810C00002
		AUC ₀₋₇ (µg h/mL)	AUC ₀₋₁₂ (µg h/mL)	C _{max,ss} (µg/mL)	C _{max,ss} (µg/mL)
50 mg	N	7	4 ^a	8	4 ^a
	Gmean	11.7	11.5 ^a	2.31	2.08 ^a
	GCV%	79.7	54 ^a	76.7	12 ^a
	Range	6.74-42.0	7.46-20.0 ^a	0.945-7.27	1.90-2.37 ^a
100 mg	N	2	9	2	9
	Gmean	20.9 ^b	20.5	4.95 ^b	3.67
	%CV	NC	52	NC	31
	Range	16.0-27.2	10.7-48.9	4.05-6.04	2.81-5.86
200 mg	N	2	33	2	33
	Gmean	24.0 ^b	31.6	4.96 ^b	5.84
	%CV	NC	75	NC	58
	Range	23.5-24.4	6.22-162	4.33-5.69	1.69-17.1

^a Dosed at 60 mg

^b Amean

NC Not calculated

Table 28 **Pharmacokinetic parameters after single dose of 100 mg tablet in patients with pancreatic cancer and in all patients in Study D0816C00007**

Parameter	Summary statistics	Patients with pancreatic cancer	All patients
$C_{\max}$ (µg/mL)	N	7	56
	Gmean	2.52	2.99
	GCV(%)	41.6	48.2
	Range	1.23-3.88	0.980-9.04
AUC (µg h/mL)	N	6	53
	Gmean	12.40	14.8
	GCV(%)	81.1	75.4
	Range	4.89-42.0	4.89-86.3
$t_{\max}$ (h)	N	7	56
	Median	1.48	1.03
	Range	0.48-4	0.48-8.25
$t_{1/2}$ (h)	N	6	53
	Amean	14.14	15.0
	SD	4.79	8.23
	Range	9.22-22.9	5.75-57.9
CL/F (L/h)	N	6	53
	Amean	9.72	8.16
	SD	6.12	4.61
	Range	2.38-20.5	1.16-20.5
V_z/F (L)	N	6	53
	Amean	205	192
	SD	142	172
	Range	37.9-428	18.3-809

Table 29 Pharmacokinetic parameters after multiple dose of 300 mg tablet in patients with pancreatic cancer and in all patients in Study D0816C00007

Parameter	Summary statistics	Patients with pancreatic cancer	All patients
$C_{\max,ss}$ (µg/mL)	N	5	45
	Gmean	7.66	8.44
	GCV(%)	37.2	37.3
	Range	4.35-11.3	4.35-19.3
$C_{\min,ss}$ (µg/mL)	N	5	45
	Gmean	2.02	1.61
	GCV(%)	149.5	109.5
	Range	0.652-6.93	0.292-8.26
AUC_{ss} (µg h/mL)	N	4	42
	Gmean	67.8	55.5
	GCV(%)	43.6	52.6
	Range	44.2-112	19.6-164
$t_{\max}$ (h)	N	5	45
	Median	3.01	1.5
	Range	1.01-6.02	1.00-8.02

Table 30 Key demographic and baseline characteristics by study: studies in olaparib 300 mg bid pool

Study Number of patients randomized/ treated Number of US patients	Age/sex/race	Performance status	Tumor type	Prior anticancer treatment	BRCA mutation status
D081FC00001 (POLO) N=154/151 (91 in the pooled dataset) N=32 US patients	36 to 84 years (mean age 57.5 years) 70 (45.5%) Female 84 (54.5%) Male 141 (91.6%) White, 6 (3.9%) Asian, 5 (3.2%) Black, African American and 2 (1.3%) Other	ECOG PS ≤1 103 (66.9%) PS0 48 (31.2%) PS1 (data were missing for 3 patients)	Metastatic pancreatic adenocarcinoma	All pre-treated Median number of prior chemotherapies for metastatic disease was 1.0	All <i>gBRCAm</i>
D0816C00010 (SOLO3) N=266/254 (178 in the pooled dataset) N=41 US patients	39 to 79 years (mean age 58.5 years) All Female 148 (83.1%) White, 24 (13.5%) Asian, 6 (3.4%) Black, African American and Other	ECOG PS ≤2 (177 [99.4%] patients were ECOG PS ≤1)	Advanced (FIGO Stage III-IV) Ovarian Cancer	All pre-treated Median number of prior chemotherapies was 3.0	All <i>gBRCAm</i>
SOLO1 N=391/390 (260 n the pooled dataset) N=110 US patients	29 to 84 years (mean age 53.5 years) All Female 320 (81.8%) White, 59 (15.1%) Asian, 12 (3.1%) Black, African American and Other	ECOG PS ≤1 305 (78.0%) PS0 85 (21.7%) PS1	Advanced (FIGO Stage III-IV) Ovarian Cancer	All pre-treated Median number of prior chemotherapies was 1.0	389 <i>gBRCAm</i> 2 <i>sBRCAm</i>

Table 30 **Key demographic and baseline characteristics by study: studies in olaparib 300 mg bid pool**

Study Number of patients randomized/ treated Number of US patients	Age/sex/race	Performance status	Tumor type	Prior anticancer treatment	BRCA mutation status
SOLO1 China cohort N=64/64 (44 ² in the pooled dataset) N=0 US patients	33 to 67 years (mean age 51.0 years) All Female 64 (100%) Asian.	ECOG PS ≤1 33 (51.6%) PS0 31 (48.4%) PS1	Advanced (FIGO Stage III-IV) Ovarian Cancer	All pre-treated Median number of prior chemotherapies was 1.0	All <i>gBRCAm</i>
OlympiAD N=302/296 (205 in the pooled dataset) N=64 US patients	22 to 76 years (mean age 45.3 years) 295 (97.7%) Female, 7 (2.3%) Male 197 (65.2%) White, 94 (31.1%) Asian, 11 (3.6%) Black, African American and Other	ECOG PS ≤1 210 (69.5%) PS0 92 (30.5%) PS1	Metastatic breast cancer	All pre-treated Median number of prior chemotherapies was 1.0	All <i>gBRCAm</i>

² Please note that 4 of the patients in the China cohort were counted as part of the SOLO1 SAS and are not counted again in the 300 mg bid pool.

Table 30 **Key demographic and baseline characteristics by study: studies in olaparib 300 mg bid pool**

Study Number of patients randomized/ treated Number of US patients	Age/sex/race	Performance status	Tumor type	Prior anticancer treatment	BRCA mutation status
SOLO2 N=295/294 (195 in pooled dataset) N=26 US patients	28 to 83 years (mean age 57.0 years) All female 173 (88.3%) White, 22 (11.2%) Asian, 1 (0.5%) Black or African American.	ECOG PS ≤1 239 (81.0%) PS0 54 (18.3%) PS1	PSR ovarian cancer	All treated patients had prior chemotherapy Median number of prior regimens was 2.0 (range 2 – 7)	All <i>gBRCAm</i>
SOLO2 China Cohort N=32/32 (22 in pooled dataset) N=0 US patients	33 to 67 years (mean age 49.6 years) All female 32 (100%) Asian.	ECOG PS ≤1	PSR ovarian cancer	All treated patients had prior chemotherapy Median number of prior regimens was 2.0 (range 2 – 4)	All <i>gBRCAm</i>
Study 24 bioavailability (groups 4 and 6) N=197 in whole study/24 in groups 4 and 6 (24 in pooled dataset) N=0 US patients	40 to 78 years (mean age 56 years) 23 (95.8%) Female, 1 (4.2%) Male 23 (95.8%) White, 1 (4.2%) Asian.	ECOG PS ≤2	Breast or ovarian cancer	All had prior chemotherapy Median number of prior regimens in groups 4 and 6 was 4.0	All <i>gBRCAm</i>

Table 30 **Key demographic and baseline characteristics by study: studies in olaparib 300 mg bid pool**

Study Number of patients randomized/ treated Number of US patients	Age/sex/race	Performance status	Tumor type	Prior anticancer treatment	BRCA mutation status
Study 04 Food effect (Part C) N=60/55 (57 in pooled dataset, including 2 patients from Part B) N=0 US patients	36 to 79 years (mean age 60.0 years) 42 (76.3%) Female, 13 (23.6%) Male 54 (98.2%) White, 1 (1.8%) other.	ECOG PS $\leq$ 2 (54 [98.2%] patients were ECOG PS $\leq$ 1 and data for 1 patient was missing)	Patients with advanced solid tumors. The most common primary tumor locations were: ovary (19 [34.5%] patients), breast (9 [16.3%] patients), lung (4 [7.3%] patients), colorectal (3 [5.5%] patients), peritoneum (2 [3.6%] patients), and prostate (2 [3.6%] patients).	All pre-treated	5 <i>BRCAm</i> ; 8 <i>BRCAwt/VUS</i> , 47 patients not tested
Study 06: renal impairment study (Part B only) N=44/43 (43 in pooled dataset) N=0 US patients	32 to 76 years (mean age 61.9 years) 19 (44.2%) male, 24 (55.8%) female 42 (97.7%) White/ 1 (2.3%) Asian	41 (95.3%) patients were ECOG PS $\leq$ 1; data for 2 patients were missing	Patients with advanced solid tumors and normal renal function or mild or moderate renal impairment. Most common locations were ovary (12 [27.9%] patients), renal (5 [11.6%] patients) and breast (4 [9.3%] patients).	All pre-treated	3 <i>BRCAm</i> ; 4 <i>BRCAwt</i> , 35 patients not tested

Table 30 Key demographic and baseline characteristics by study: studies in olaparib 300 mg bid pool

Study Number of patients randomized/ treated Number of US patients	Age/sex/race	Performance status	Tumor type	Prior anticancer treatment	BRCA mutation status
Study 07 itraconazole interaction study (Part C) N=59/54 (56 in pooled dataset including 2 patients from Part B) N=0 US patients	34 to 82 years (mean age 61.0 years) 38 (70.4%) Female, 16 (29.6%) Male 51 (94.4%) White, 1 (1.9%) each of Asian, Black or African American, and other race	ECOG PS ≤2 (53 [98.1%] patients were ECOG PS ≤1; 1 patient was PS 2)	Patients with advanced solid tumors. The most common primary tumor locations were: ovary (20 [37.0%] patients), pancreas (6 [11.1%] patients), rectal (4 [7.4%] patients), breast, cervix, and head/neck, cervix (3 patients [5.6%] each), biliary tract, colon, colorectal, lung, peritoneum, and uterus (2 [3.7%] patients each).	All pre-treated	6 <i>BRCAm</i> ; 8 <i>BRCAwt/VUS</i> , 45 patients not tested
Study 08 rifampicin interaction study (Part B only) N=22/19 (19 in pooled dataset) N=0 US patients	31 to 79 years (mean age 58.0 years) 16 (84.2%) Female, 3 (15.8%) Male 19 (100.0%) White	ECOG PS ≤2 (16 [84.2%] patients were ECOG PS ≤1; 3 patients were PS 2)	Patients with advanced solid tumors. The most common primary tumor locations were: breast and ovary (each with 6 patients [26.3%]); colon (2 patients [10.5%]).	All pre-treated	Unknown

Table 30 Key demographic and baseline characteristics by study: studies in olaparib 300 mg bid pool

Study Number of patients randomized/ treated Number of US patients	Age/sex/race	Performance status	Tumor type	Prior anticancer treatment	BRCA mutation status
D081BC00001 Japan Phase I study (Part B only) N=23/23 (19 in pooled dataset) N=0 US patients	34 to 77 years (mean age 54.1 years) 15 (65.2%) Female, 8 (34.8%) Male 23 (100.0%) Asian	ECOG PS ≤ 2 (18 [78.3%] patients were ECOG PS 0)	Patients with advanced solid malignancies. The primary tumor locations in most of the patients were breast (5 [21.7%] patients), ovary (4 [17.4%] patients), cervix and uterus (2 [8.7%] patients each).	The median number of previous chemotherapy regimens at baseline was 3.	
D081CC00001: Anti-hormonal PK interaction study (Part B only) N=79/79 (69 in pooled dataset) N=0 US patients	29 to 79 years (mean age 58.3 years) 64 (81.0%) Female, 15 (19.0%) Male 73 (92.4%) White, 2 (2.5%) Asian, 2 (2.5%) Black or African American, 2 (2.5%) other	ECOG PS ≤ 2 (78[98.7%] patients were ECOG PS ≤ 1 ; 1 patient was PS 2)	Patients with advanced solid cancer. The most common primary tumor locations were: ovary (36 patients [45.6%]), and breast (16 patients [20.3%]).	All pre-treated	21 <i>BRCAm</i> ; 9 <i>BRCAwt</i> , 46 patients not tested, 3 missing

Table 30 Key demographic and baseline characteristics by study: studies in olaparib 300 mg bid pool

Study Number of patients randomized/ treated Number of US patients	Age/sex/race	Performance status	Tumor type	Prior anticancer treatment	BRCA mutation status
D0816C00005 Hepatic impairment study N=31/31 (30 in pooled dataset) N=0 US patients	41 to 78 years (mean age 59.7 years) 14 (45.2%) Female, 17 (54.8%) Male 30 (96.8%) White, 1 (3.2%) Asian.	ECOG PS ≤2 (12[38.7%] patients were ECOG PS 0; 17 [54.8%] patients were PS1 and 2 patients were PS 2 at the start of Part B of the study)	Patients with advanced solid cancer. The most common primary tumor locations were: liver (8 patients); ovary, colon and pancreas were also common sites (each in 4 patients). Hepatic function was normal in 13 (41.9%) patients; mild impairment in 10 (32.3%) patients; moderate impairment in 8 (25.8%) patients.	All pre-treated	BRCA status was not a requirement for study entry
D081BC00002 China PK study; N=47/36 (20 in pooled dataset) N=0 US patients	32 to 67 years (mean age 48.4 years). 8 (22.2% male, 28 (77.8%) female. 36 (100%) Asian	35 [97.2%] patients were ECOG PS ≤1; 1 patient was PS 2	Patients with advanced solid tumors. Most common locations were breast (21 [58.3%] patients) ovary (6 [16.7%] patients), and gastric (5 [13.9%] patients).	All pre-treated. Median number of regimens of previous chemotherapy at baseline was 4.0	Patients were not tested for BRCA mutation status.

bid Twice daily; *BRCA*: Breast cancer susceptibility gene; *BRCA_m* *BRCA*-mutated; *BRCA/VUS* *BRCA* variant of uncertain significance; *BRCA_{wt}* *BRCA* wild type; ECOG Eastern Cooperative Oncology Group; FIGO International Federation of Gynecology and Obstetrics; PK Pharmacokinetics; PS Performance status; PSR platinum sensitive relapsed

Table 31 EORTC QLQ-C30/PAN26 global HRQoL, physical function and symptoms: best overall QoL response (PRO analysis set)

	Number (%) of patients			
	Improved ^a	No change ^b	Deteriorated ^c	Missing ^d
Global HRQoL				
Olaparib (N=89)	26 (29.2)	41 (46.1)	19 (21.3)	3 (3.4)
Placebo (N=58)	13 (22.4)	30 (51.7)	12 (20.7)	3 (5.2)
Physical Function				
Olaparib (N=89)	20 (22.5)	50 (56.2)	16 (18.0)	3 (3.4)
Placebo (N=58)	12 (20.7)	35 (60.3)	8 (13.8)	3 (5.2)
Pain				
Olaparib (N=89)	19 (21.3)	46 (51.7)	21 (23.6)	3 (3.4)
Placebo (N=58)	9 (15.5)	23 (39.7)	23 (39.7)	3 (5.2)
Pancreatic pain^e				
Olaparib (N=89)	9 (10.1)	55 (61.8)	22 (24.7)	3 (3.4)
Placebo (N=58)	5 (8.6)	35 (60.3)	15 (25.9)	3 (5.2)
Fatigue				
Olaparib (N=89)	32 (36.0)	32 (36.0)	22 (24.7)	3 (3.4)
Placebo (N=58)	29 (50.0)	11 (19.0)	15 (25.9)	3 (5.2)
Appetite loss				
Olaparib (N=89)	13 (14.6)	54 (60.7)	19 (21.3)	3 (3.4)
Placebo (N=58)	9 (16.5)	40 (69.0)	6 (10.3)	3 (5.2)
Dyspnea				
Olaparib (N=89)	15 (16.9)	58 (65.2)	13 (14.6)	3 (3.4)
Placebo (N=58)	6 (10.3)	41 (70.7)	8 (13.8)	3 (5.2)
Nausea/vomiting				
Olaparib (N=89)	9 (10.1)	56 (62.9)	21 (23.6)	3 (3.4)
Placebo (N=58)	11 (19.0)	39 (67.2)	5 (8.6)	3 (5.2)
Diarrhea				
Olaparib (N=89)	23 (25.8)	55 (61.8)	8 (9.0)	3 (3.4)
Placebo (N=58)	12 (20.7)	40 (69.0)	2 (3.4)	4 (6.9)
Constipation				
Olaparib (N=89)	21 (23.6)	53 (59.6)	12 (13.5)	3 (3.4)
Placebo (N=58)	8 (13.8)	46 (79.3)	1 (1.7)	3 (5.2)

Insomnia				
Olaparib (N=89)	31 (34.8)	40 (44.9)	15 (16.9)	3 (3.4)
Placebo (N=58)	9 (15.5)	35 (60.3)	11 (19.0)	3 (5.2)

- ^a Patients had 2 consecutive visit responses of "improved" a minimum of 21 days apart, or had 1 visit response of "improvement" with no further assessments, and did not die within 2 PRO assessment visits.
- ^b Patients did not qualify for overall response of "improved". Patients had 2 consecutive visit responses of "no change" a minimum of 21 days apart, or had 1 visit response of "no change" with no further assessments, and did not die within 2 PRO assessment visits.
- ^c Patients did not qualify for overall response of "improved" or "no change". Patient had 2 consecutive visit responses of "deterioration" a minimum of 21 days apart, or had 1 visit response of "deterioration" and no further assessments, or had 1 visit response of "improvement" or "no change" followed by death within 2 PRO assessment visits.
- ^d Patients had no evaluable baseline or post-baseline PRO assessments.
- ^e Pancreatic pain domain is part of the QLQ-PAN26 questionnaire, this multi-item domain consisted of 4 questions assessing abdominal discomfort, back pain, pain during night, and discomfort lying down.
- EORTC European Organization for Research and Treatment of Cancer; PRO patient reported outcomes; QLQ-C30 quality of life questionnaire for cancer patients; QoL quality of life.