EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 May 2020
EMA/195425/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lynparza

International non-proprietary name: olaparib

Procedure No. EMEA/H/C/003726/II/0033

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation or special term	Explanation
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AML	Acute myeloid leukaemia
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic classification
Bd	Twice daily
BICR	Blinded independent central review
BoR	Best objective response
BRAC*Analysis*®	The test consists of gene sequencing and large rearrangement analysis of the *BRCA1* and *BRCA2* genes performed by Myriad Genetics, Inc in their Clinical Laboratory Improvement Amendments facility
BRACAnalysis CDx®	The test consists of gene sequencing and large rearrangement analysis of the *BRCA1* and *BRCA2* genes performed by Myriad Genetics, Inc in their Quality Systems Regulation (QSR) facility
BRCA	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicised whereas protein is not italicised)
BRCAm	*gBRCA or sBRCA* mutated
CI	Confidence interval
CR	Complete response
CRO	Clinical Research Organisation
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events.
CYP	Cytochrome P450
d	Day
DAE	Discontinuation of study drug due to an AE (adverse event).
DCO	Data cut-off
DCR	Disease control rate
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer

EQ-5D	EuroQoL five dimensions
EQ-5D-5L	EuroQoL five dimensions, five level
FAS	Full Analysis Set
GCP	Good Clinical Practice
gBRCA	Germline BRCA
gBRCAm	Germline BRCA mutated
GGT	Gamma-glutamyl transferase
HDPE	High density polyethylene
HR	Hazard ratio
HRD	Homologous recombination repair deficiency
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for
ID	Identification
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	International normalised ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
Max	Maximum
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities.
Min	Minimum
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
NA	Not applicable
NC	Not calculable
NED	No evidence of disease
OAE	Other significant adverse event (ie, significant AEs, other than SAEs and
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose polymerase
PD	Progressive disease
PDAC	Pancreatic ductal adenocarcinoma

PFS	Progression-free survival
PFS2	Time from randomisation to second progression
PR	Partial response
PRO	Patient reported outcomes
PT	Preferred term
Q	Quartile
Q4W	Every 4 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
QLQ-C30	Quality of life questionnaire for cancer patients
QLQ-PAN26	Quality of life questionnaire for pancreatic cancer patients
QoL	Quality of life
ORR	Objective response rate
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumours. This study used modified
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Stable disease
SSB	Single-strand break
SUSAR	Suspected unexpected serious adverse reaction
TCMD	Time to sustained clinically meaningful deterioration
TDT	Time to discontinuation of treatment or death (defined as time from
TFST	Time to first subsequent therapy or death (defined as time from
TSST	Time to second subsequent therapy or death (defined as time from
UK	United Kingdom
ULN	Upper limit of normal
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose polymerase
PD	Progressive disease
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
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SUSAR	Suspected unexpected serious adverse reaction
TCMD	Time to sustained clinically meaningful deterioration
TDT	Time to discontinuation of treatment or death (defined as time from
TFST	Time to first subsequent therapy or death (defined as time from
TSST	Time to second subsequent therapy or death (defined as time from
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
V	Visit
WHO	World Health Organisation

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 2 July 2019 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to support the use of Lynparza tablets (100mg and 150 mg) for the maintenance treatment of gBRCAm metastatic pancreatic cancer based on the results from the pivotal Phase 3 study, POLO; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.8 for lynparza hard capsules (50 mg) to revise list of ADR based on the pooled safety data analysis. The RMP version 18 has also been submitted. Furthermore, the PI is brought in line with the latest guideline regarding the sodium content. The MAH also took the occasion to include some minor editorial changes in the PI.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0262/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0262/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau   Co-Rapporteur: Koenraad Norga

Timetable	Actual dates
Submission date	2 July 2019
Start of procedure:	20 July 2019
CHMP Rapporteur Assessment Report	13 September 2019
CHMP Co-Rapporteur Assessment Report	18 September 2019
PRAC Rapporteur Assessment Report	20 September 2019
PRAC Outcome	3 October 2019
CHMP members comments	07 October 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2019
Request for supplementary information (RSI)	17 October 2019
PRAC Rapporteur Assessment Report	6 January 2020
CHMP Rapporteur Assessment Report	16 January 2020
PRAC Outcome	16 January 2020
CHMP members comments	20 January 2020
Updated CHMP Rapporteur Assessment Report	24 January 2020
Request for supplementary information (RSI)	30 January 2020
PRAC Rapporteur Assessment Report	02 April 2020
PRAC members comments	07 April 2020
Updated PRAC Rapporteur Assessment Report	10 April 2020
CHMP Rapporteur Assessment Report	10 April 2020
PRAC Outcome	17 April 2020
CHMP members comments	20 April 2020
Updated CHMP Rapporteur Assessment Report	24 April 2020
Request for supplementary information (RSI)	30 April 2020
CHMP Rapporteur Assessment Report	14 May 2020
PRAC Rapporteur Assessment Report	14 May 2020
PRAC members comments	17 May 2020

Timetable	Actual dates
CHMP members comments	17 May 2020
Updated CHMP Rapporteur Assessment Report	18 May 2020
Updated PRAC Rapporteur Assessment Report	18 May 2020
Opinion	28 May 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Pancreatic cancer is a malignant neoplasm of the pancreas (ICD-9, 2014). More than 80% of exocrine pancreatic cancers are infiltrating ductal adenocarcinomas, a majority of which exhibit KRAS mutations, predominantly G12V or G12D mutations (Seufferlein, et al, 2012), and the remaining types include adenosquamous carcinomas, squamous cell carcinomas, signet ring cell carcinomas, acinar cell carcinomas, undifferentiated carcinomas, undifferentiated carcinomas with giant cells, and solid pseudopapillary neoplasms of the pancreas. Exocrine pancreatic tumors are far more common than pancreatic neuroendocrine tumors, which make up about 3-5% of all pancreatic malignancies (Krampitz, 2013). Hereditary conditions account for ~5-10% of pancreatic cancer (Seufferlein et al., 2012).

Epidemiology and risk factors, screening tools/prevention

Pancreatic cancer was the thirteenth most frequent cancer worldwide with an estimated 458,918 new cases diagnosed in 2018 (Globocan 2018). Globally, age-standardised incidence rates (per 100,000 per year) were lowest in Africa (2.2) and highest in Europe (7.7) and North America (7.6) (Globocan 2018). In the US in 2019, pancreatic cancer is estimated to be the ninth most common newly diagnosed cancer (56,770 new cases) (American Cancer Society 2019, Siegel et al 2018). In Europe in 2018, pancreatic cancer was estimated to be the ninth most common newly diagnosed cancer (132,559 new cases) (Globocan 2018). Current trends show increasing incidence in the US and Europe, particularly for younger adults (Wu et al 2018, Rawla et al 2019). At least 50% of newly diagnosed pancreatic tumours are staged as metastatic (SEER Cancer Fact Sheet).

Due to the very poor prognosis of pancreatic cancer with nearly as many deaths as new cases annually, the disease prevalence is low (Bray et al 2018). The estimated 5-year prevalence of pancreatic cancer in 2018 was 282,574 worldwide, with 32,692 prevalent cases in the US and 79,268 cases in Europe (Globocan 2018).

With a life expectancy of ~5% at 5 years, the prognosis of this cancer has not improved over the past 20 years, and incidence and mortality rates are very similar. Death due to pancreatic carcinoma is increasing in Europe. It usually arises in elderly patients with a mean age at onset of 71 years for men and 75 years for women. The majority of patients with pancreatic cancer progress to either metastatic or locally advanced disease in the asymptomatic phase. Surgical excision is the definitive treatment with a 5-year survival rate (after resection) of ~20%, but it is only possible in 15%–20% of the patients.

The opportunity to detect pancreatic cancer, while it remains curable, depends on the ability to identify and screen high-risk populations before their symptoms arise. Defining the treatment strategy for patients suffering from pancreatic carcinoma requires a specialised multidisciplinary team that includes: surgeons, medical oncologists, gastroenterologists, radiation therapists, radiologists, and supportive and palliative care specialists. (Ducreaux et al, 2015, ESMO guidelines)

The causes of pancreatic cancer are not well understood. The main risk factors are tobacco, and factors related to dietary habits (BMI, red meat intake, low fruit and vegetables intake, diabetes, alcohol intake) (Ducreaux et al, 2015, ESMO guidelines) and Helicobacter pylori infection (Maisonneuve et al 2015, Rawla et al 2019). Additional potential risk factors include obesity, diabetes, non-O blood type, exposure to chemicals, chronic pancreatitis, and genetic predisposition, including BRCA germline mutations (Iqbal et al 2012, Maisonneuve et al 2015, Rawla et al 2019). BRCA mutated cancer is more common among patients with a personal history of cancer or family history of several cancers, including pancreatic, or those of Ashkenazi Jewish heritage (Bannon et al 2018; Chaffee et al 2018, Holter et al 2015).

Although carriers of loss of function germline mutations of the BRCA1 and particularly BRCA2 gene 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 recently reported on a prospective analysis of the prevalence of gBRCA1/2 mutations in a cohort of 306 unselected patients with incident pancreatic ductal adenocarcinoma (PDAC) diagnoses and identified gBRCA mutations in ~5% of patients (Holter et al 2015). Furthermore, 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).

Pancreatic cancer incidence is higher for men than women and increases with age; the median age at diagnosis in the US is 70 years (Ferlay et al 2018, SEER Cancer Fact Sheet). There is some evidence that patients carrying BRCA mutations are diagnosed at a younger age; however, results are not consistent (Bannon et al 2018, Holter et al 2015, Hu et al 2018, Toss et al 2019).

Biologic features

About 95% of pancreatic cancers are adenocarcinomas. Mucinous lesions of the pancreas have potential for malignant progression. Multiple combinations of genetic mutations are commonly found in pancreatic cancers. The vast majority (>80%) of pancreatic carcinomas are due to sporadically occurring mutations. Only a small proportion (<10%) are due to inherited germline mutations.

Germline mutations in BRCA2, p16, ATM, STK11, PRSS1/PRSS2, SPINK1, PALB2, and DNA mismatch repair genes are associated with varying degrees of increased risk for pancreatic carcinoma.

Familial pancreatic cancers, defined as at least two first-degree relatives with pancreatic cancer, account for only 5%–10% of all pancreatic cancer cases. Mutation in BRCA2 is probably the most common inherited disorder in familial pancreatic cancer.

Other familial syndromes linked to pancreatic cancer are: hereditary pancreatitis, hereditary non-polyposis colorectal cancer, hereditary breast and ovarian cancers, Peutz–Jeghers syndrome, ataxia telangiectasia, familial atypical multiple mole melanoma syndrome and Li–Fraumeni syndrome. (Ducreaux et al, 2015, ESMO guidelines).

Clinical presentation, diagnosis <and stage/prognosis>>

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.

Early symptoms of pancreatic cancer result from a mass effect. Common presenting symptoms include jaundice, pain, weight loss, steatorrhoea.

Staging of the patient is initially done by CT scan. Endoscopic ultrasound (EUS) is now largely used in the staging of adenocarcinoma.

According to the American Hepato-Pancreato-Biliary Association consensus report, pancreatic ductal adenocarcinoma (when metastases are absent) is classified as resectable, borderline resectable or unresectable. At the time of diagnosis, pancreatic ductal adenocarcinoma is deemed resectable in only 15%–20% of patients. (Ducreaux et al, 2015, ESMO guidelines)

There is some evidence that prognosis for BRCA mutation carriers is worse compared to those without mutations (Blair et al 2018, Ferrone et al 2009). The poor outcomes observed for pancreatic cancer are largely due to the late presentation of the disease as optimum screening tests have yet to be identified (McGuigan et al 2018). However, platinum-based chemotherapy regimens were associated with markedly improved survival in patients with gBRCA1/2 mutations, with survival differences no longer appreciated with wild-type patients (Blair et al, 2018; Golan et al, 2017).

Management

There are several treatment options available for patients with metastatic pancreatic cancer as first line therapy, including platinum based chemotherapy. The two preferred regimens for initial treatment of metastatic disease include the combination of 5 fluorouracil (5 FU), irinotecan, leucovorin (LV), and oxaliplatin (FOLFIRINOX) or gemcitabine in combination with nab paclitaxel (Ducreux et al 2015, NCCN 2019). Gemcitabine alone or in combination with either capecitabine or erlotinib may also be used in the first line treatment setting (Sohal et al 2018).

However, exacerbated toxicities are associated with combination platinum based chemotherapy regimens (eg, Grade 3 or 4 neutropenia and sensory neuropathy; Conroy et al 2011) which generally limit the number of cycles of treatment that can be given, meaning chemotherapy cannot generally be continued until disease progression.

Furthermore, few second line regimens are available for the treatment of patients with pancreatic cancer (American Cancer Society 2019), and these agents offer modest benefit (Rahma et al 2013). In 2015 in the US and 2016 in the EU, liposomal irinotecan (Onivyde™) was approved in combination with 5-FU and LV, as second line treatment after progression following gemcitabine-based therapy for patients with metastatic adenocarcinoma of the pancreas. 5-FU/LV plus oxaliplatin may be considered as second line treatment under certain circumstances, for patients who received gemcitabine plus nab paclitaxel as first line treatment, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a relatively favourable co morbidity profile (Ducreux et al 2015, Sohal et al 2018).

2.1.2. About the product

Olaparib (Lynparza®) is a potent inhibitor of polyadenosine 5'diphosphoribose polymerase (PARP) which is being developed in a range of tumours as a monotherapy as well as in combination. PARP inhibition targets tumours that have homologous recombination DNA repair pathway deficiencies (HRD).

Lynparza, 50 mg capsule formulation, was approved on 16 December 2014 in monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Subsequently a tablet formulation (100 mg and 150 mg) was approved on 8 May 2018 as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. In the frame of the type II variations II-20 and II-23, tablet formulation was approved for the treatment of patients with breast cancer and first line maintenance treatment of the ovarian cancer.

The aim of this application is to provide the clinical data to support the extension of the Lynparza indication to include (initial MAH proposed indication):

Lynparza (olaparib) is indicated as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2 mutated metastatic adenocarcinoma of the pancreas whose disease has not progressed following first line platinum-based chemotherapy

The proposed application is based on data from study D081FC00001 (POLO), a Phase III, randomized, double blind, placebo controlled, multicenter study of olaparib maintenance treatment (300 mg [2 x 150 mg tablets] twice daily [bd]) in patients with metastatic adenocarcinoma of the pancreas with gBRCAm (documented germline mutation in BRCA1 or BRCA2) that were loss of function mutations (deleterious or suspected deleterious), whose tumours had not progressed following at least 16 weeks of first line platinum based chemotherapy.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

An updated ERA covering this extension of indication has been submitted.

The addition of the pancreatic cancer indication suggests environmental exposure will increase. In line with the environmental risk assessment guideline, the MAH submitted an updated ERA. Of note, an ERA was previously assessed during the original application for marketing authorisation for olaparib and subsequent type II variations and the conclusions remain the same.

The total PEC value (sum of the PEC for each indication (ovarian (Latvia), breast (Belgium), and pancreatic cancers (Hungary)) was recalculated and is still based on a different worst case scenario. The highest recent disease prevalences in Europe were taken into account. Published data are presented to support these data and the refined Fpen calculations are considered acceptable. This worst case scenario total PEC is above the Phase I action limit of 0.01 µg/L as in previous ERA. Updated PEC/PNEC ratios are provided and do not raise concerns.

It is agreed that olaparib is very persistent. However, the Kow value (correct determination) indicates a low potential for bioaccumulation. Olaparib is thus not classified as a PBT or vPvB compound.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable.

An updated ERA covering this extension of indication has been submitted.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of olaparib.

Considering the above data, olaparib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Clinical studies that contributed to the overall assessment of clinical efficacy of olaparib

Type of study	Study identifier, status	Objective(s) of the study	Study design/type of control	Test product, dosage regimen, route of administration	No. of subjects randomised or enrolled/ treated	Patient population	Location of Study Report
Pivotal study (POLO)							
Efficacy, Safety	D081FC00001 **Ongoing; primary PFS analysis completed**	Determine the efficacy of olaparib maintenance monotherapy compared to placebo by assessment of PFS	Phase III, double-blind, randomized, placebo-controlled, multicentre	Olaparib 300 mg bd tablet (oral) Matching placebo	154 (92 olaparib; 62 placebo)	Patients with *gBRCAm* metastatic pancreatic adenocarcinoma whose tumours have not progressed after receiving a minimum of 16 weeks of first-line platinum-based chemotherapy (there was no upper limit to the duration of chemotherapy that a patient had received).	Module 5.3.5.1

Type of study	Study identifier, status	Objective(s) of the study	Study design/type of control	Test product, dosage regimen, route of administration	No. of subjects randomised or enrolled/ treated	Patient population	Location of Study Report
Supportive study (Study 42)							
Efficacy, safety	D0810C00042 Complete	Assess the efficacy of oral olaparib in patients with advanced cancer who had confirmed genetic *BRCA1* and/or *BRCA2* mutation by assessment of tumour response	Phase II, open-label, non-randomized, non-comparative, multicentre	Olaparib 400 mg bd capsule (oral)	317/298 (23 with pancreatic cancer)	Patients with advanced cancers with confirmed *gBRCA1*- and/or *gBRCA2*-mutations	Module 5.3.5.2

bd Twice daily; *BRCA* Breast cancer susceptibility gene; *gBRCA* Germline *BRCA*; *gBRCAm* Germline *BRCA* mutated; OS Overall survival; PFS Progression-free survival.

2.3.2. Pharmacodynamics

No new studies have been provided to support this application.

<u>Platinum sensitivity</u>

PARP inhibition is an effective option for platinum-sensitive tumors. Non clinical data show that sensitivity to platinum agents correlates with sensitivity to olaparib in pancreatic cancer cell lines, as well as cell lines derived from other tumor types in which platinum-based chemotherapy is the standard of care (Mason et al 2012).

The effect of BRCA mutations and response to DNA crosslinking agents in pancreatic ductal adenocarcinoma (PDAC) was evaluated by Lowery et al 2011 (Lowery et al 2011), who reported that 5 out of 6 BRCA-associated PDAC patients who received a platinum agent as first-line metastatic therapy demonstrated a radiographic partial response (PR) or radiographic complete response (CR). In a small retrospective study in BRCAm patients with pancreatic adenocarcinoma, a superior OS was observed for patients with Stage III/IV treated with platinum versus those treated with non platinum chemotherapies (22 months vs 9 months; p=0.039) (Golan et al 2014). Treatment of 23 patients with germline BRCA1/2 or PALB2 mutations and PDAC with gemcitabine-cisplatin combination resulted in 65.2% response rate (O'Reilly et al, 2020).

Patients randomised in POLO trial has received a prior platinum-containing regimen. There is no established criteria to define platinum-sensitive disease or associated platinum-free interval.

<u>Germline BRCA1/2 testing and concordance</u>

Only germline testing has been conducted. Tumour BRCA testing has not been performed.

Central germline BRCA1/2 testing and concordance with local germline testing

The entry criteria for patients in POLO included the requirement to have a loss of function gBRCA1 or gBRCA2 mutation, determined prior to study entry from an existing local gBRCA test (51 patients, of which 48 patients have been randomised) or from prospective testing using either the Myriad BRACAnalysis® CLIA test (216 patients tested, of which 13 patients have been randomised as gBRCAm, 5 patients had VUS and 197 patients were gBRCAwt) or the Myriad BRACAnalysis CDx® test (2978 patients tested of which 100 patients have been randomised with gBRCAm, 73 patients had VUS, 2702 patients were gBRCAwt and two inconclusive interpretation).

Patients randomised on to POLO using a local gBRCA result were retested post randomisation prior to database lock with either the Myriad BRACAnalysis® or the BRACAnalysis CDx® test where possible. Out of 154 randomised patients, 150 had a sample available to test using a Myriad gBRCA test. Fifty-one patients had a local BRCA result. Out of those 51 patients, blood sample was available and could be tested in 44 out of 48 patients retested by Myriad gBRCA test.
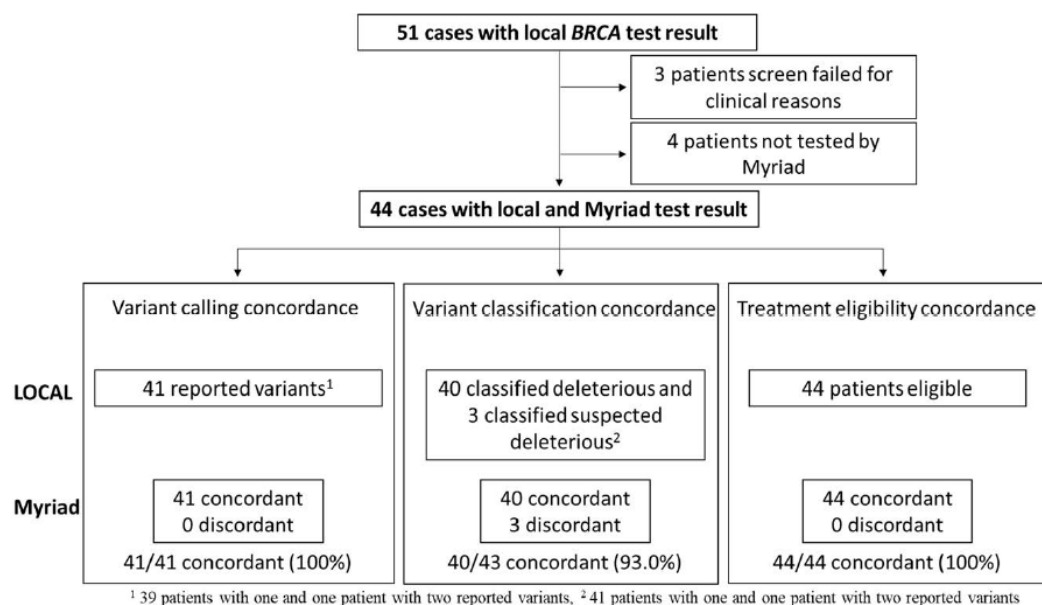
Figure 1: Summary of concordance analysis between test results and Myriad gBRCA test results in POLO

The concordance between the local BRCA test and the Myriad gBRCA for classification concordance was 93.0%. The observed classification discordance was limited to the classification of mutants to be Suspected Deleterious or Deleterious mutations, which were both eligible for the POLO study.

Within the 150 patients who were randomised, and tested by Myriad (106 prospectively and 44 retrospectively) the following mutations were reported

- 147(98.0%) carried a Deleterious mutation

- 1 (0.7%) carried 2 Deleterious mutations

- 2 (1.3%) carried a Suspected Deleterious mutation

Table Distribution of gBRCA1 and gBRCA2 mutations in POLO study

| | Pancreatic cancer (N=155 variants) | | | |
| | *BRCA1* (N=46 variants) | | *BRCA2* (N=109 variants) | |
	N	%	N	%
Frameshift (%)	32	69.6	77	70.6
Nonsense (%)	3	6.5	19	17.4
Missense (%)	4	8.7	5	4.6
Splice site variant (%)	2	4.3	4	3.7
In-frame InDel (%)	0	0.0	1	0.9

	Pancreatic cancer (N=155 variants)			
	BRCA1 (N=46 variants)		BRCA2 (N=109 variants)	
	N	%	N	%
Large rearrangement (%)	5	10.9	3	2.8
Additional variant types (%)	0	0.0	0	0.0

The Myriad gBRCAm subset represents cases who were confirmed as carrying a loss of function (deleterious or suspected deleterious) mutation in either gBRCA1 or gBRCA2 by the Myriad BRACAnalysis® or BRACAnalysis CDx® tests. Efficacy results are summarised in the relevant section.

Patients who were either not confirmed as carrying a loss of function (deleterious or suspected deleterious) mutation by the Myriad BRACAnalysis® or BRACAnalysis CDx® tests, or who could not be tested by these tests were excluded from the Myriad gBRCAm subset.

Study 42 relied on prior local gBRCA testing to guide eligibility, as recorded on the case report forms [CRFs] at the time of enrolment to the study. The gBRCA status of pancreatic patients was not reconfirmed centrally with the Myriad gBRCA test.

The results of exploratory analysis of tumour samples have been provided from two subsets: FMI analysis (47 samples) and HLI analysis (140 samples). The results for sBRCAm detection are not consistent between two analyses and the proposed rate of 2% of sBRCAm cannot be confirmed at this point. It is noticed that ATM mutations occur concomitantly with gBRCAm mutations with reported frequency of about 5 – 6%.

For patients enrolled in POLO study, tumour sample sequencing data from the above exploratory analysis have been available only for 8 patients precluding meaningful analysis of HRD biomarkers.

Therefore, the MAH is recommended to further investigate tissue biomarkers to better define patients with likelihood to derive a benefit from treatment.

2.3.3. Discussion on clinical pharmacology

No new clinical pharmacology data were submitted as part of this application. The current clinical pharmacology package provides sufficient characterisation of the key pharmacokinetics characteristics of olaparib. When combined with in vitro drug metabolism and PK profiling data and in vivo DDI studies, it provides sufficient data supporting adequate information for special populations and DDI in the product information.

2.3.4. Conclusions on clinical pharmacology

Overall, there is in general sufficient information available on the pharmacokinetics and pharmacodynamics of olaparib tablets to support the use in the applied indication.

The MAH is recommended to further investigate tissue biomarkers to better define patients with likelihood to derive a benefit from treatment.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The dose of olaparib in POLO (300 mg bd tablets) was selected based on data from the Phase I study, D0810C00024 (Study 24) in an advanced gBRCA mutated ovarian cancer population. Study 24 was a formulation comparison study and the findings provided information on the efficacy, pharmacokinetic (PK)/pharmacodynamic, safety and tolerability profiles of the olaparib tablet (EPAR Lynparza-H-C-3726-X-16-G.

2.4.2. Main study

Title of Study

Study D081FC00001 (POLO): A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First-Line Platinum-Based Chemotherapy.

Methods

This was a Phase III, randomised, double-blind, placebo-controlled, multicentre study to assess the efficacy of olaparib maintenance monotherapy in metastatic pancreatic adenocarcinoma patients with *gBRCA* mutations (documented mutation in *gBRCA1* or *gBRCA2*) that were predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) whose disease had not progressed after receiving a minimum of 16 weeks of first-line platinum-based chemotherapy. There was no upper limit to the duration of chemotherapy that a patient had received.

Patients have been selected based on the inclusion/exclusion criteria reported below and were to be randomised within 6 weeks after their last dose of chemotherapy (last dose was the day of the last infusion) and treatment started as soon as possible but no less than 4 weeks and no more than 8 weeks after the last chemotherapy dose. At the time of starting study treatment, all previous chemotherapy treatment was to be discontinued.

Patients were to continue to receive study treatment until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (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. Crossover to olaparib was not permitted within the design of the study but patients were able to access PARP inhibitors outside of the study and subsequent PARP inhibitor use was documented.

The primary endpoint assessment of PFS was based on BICR of objective radiological findings as per the modified RECIST guidelines. For medical decisions, progression was based on investigator assessment. A number of secondary endpoints were selected to provide further support for the clinical benefit of

olaparib in this patient population, and included OS, PFS2 (as assessed by the investigator) and patient reported outcome (PRO) measures.

The primary analysis of the study was planned to occur when approximately 87 progression events had occurred. The primary analysis was based on a BICR of disease progression by modified RECIST; however, a sensitivity analysis was performed using the investigator-recorded assessment. All efficacy variables including OS were analysed at the time of the primary analysis (providing sufficient events were available to make the analyses meaningful).

Figure 1 shows the design of the study.

Figure 2. Flow chart of study design
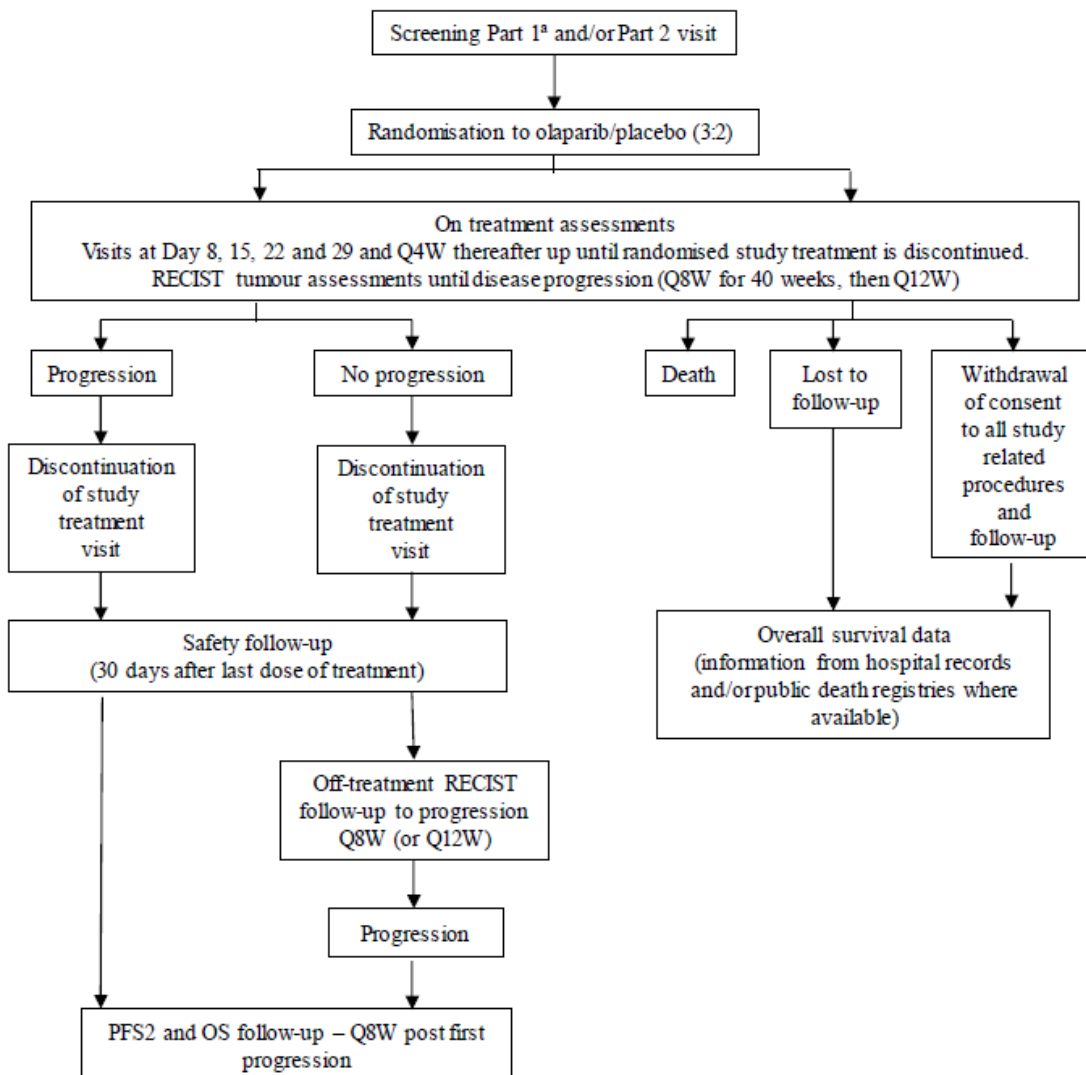
^a   Screening Part 1 only required if a patient's *gBRCAm* status was unknown.
BRCA breast cancer susceptibility gene; *gBRCAm* germline *BRCA* mutated; OS overall survival; PFS2 time from randomisation to second progression; Q4W every 4 weeks; Q8W every 8 weeks; Q12W every 12 weeks; RECIST Response Evaluation Criteria in Solid Tumours.

Study participants

A total of 154 patients were enrolled and randomised to olaparib (92 patients) or to placebo (62 patients). The study randomised patients at a total of 59 study centres worldwide; United States of America (USA; 13 centres), Germany (8 centres), France (7 centres), Israel (7 centres), Spain (7 centres), United Kingdom (UK; 6 centres), Italy (4 centres), Belgium (2 centres), Republic of Korea (2 centres), Australia (1 centre), Canada (1 centre) and Netherlands (1 centre);

Key inclusion criteria included:

- Patients must have been ≥18 years of age.

- Histologically or cytologically confirmed pancreatic adenocarcinoma receiving initial chemotherapy for metastatic disease and without evidence of disease progression on treatment.

- Patients with measurable disease and/or non-measurable or NED assessed at baseline by computed tomography (CT) (or magnetic resonance imaging where CT is contraindicated) were to be entered in this study. RECIST 1.1 had been modified to allow the assessment of progression due to new lesions in patients with NED at baseline.

- Documented mutation in *gBRCA1* or *gBRCA2* that was predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function).

- Patients who were on treatment with a first-line platinum-based (cisplatin, carboplatin or oxaliplatin) regimen for metastatic pancreatic cancer, had received a minimum of 16 weeks of continuous platinum treatment and had no evidence of progression based on investigator's opinion. Patients who had received at least 16 weeks of a platinum regimen but had the platinum discontinued for toxicity but continued on the remaining drugs of their regimen were also eligible if they had no evidence of disease progression within 4 weeks of their last dose of chemotherapy.

- Patients who had received platinum as potentially curative treatment for a prior cancer (eg, ovarian cancer) or as adjuvant/neoadjuvant treatment for pancreatic cancer were eligible provided at least 12 months had elapsed between the last dose of platinum-based treatment and initiation of the platinum-based chemotherapy for metastatic pancreatic cancer.

- Patients must have had normal organ and bone marrow function measured within 4 weeks prior to administration of study treatment.

- ECOG PS 0-1 at date signing of informed consent.

- Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test.

Key exclusion criteria for POLO included:

- *gBRCA1* and/or *gBRCA2* mutations that were considered to be non-detrimental (eg, "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favour polymorphism" or "benign polymorphism" etc.).

- Progression of tumour between start of first-line platinum-based chemotherapy for metastatic pancreatic cancer and randomisation.

- Cytotoxic chemotherapy or non-hormonal targeted therapy within 28 days of Cycle 1 Day 1 was not permitted. Palliative radiotherapy must have been completed 14 or more days before Cycle 1 Day 1. The patient could have received a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study as long as these were started at least 2 weeks prior to study treatment.

- Exposure to an investigational product within 30 days or 5 half-lives (whichever was longer) prior to randomisation.

- Any previous treatment with a PARP inhibitor, including olaparib.

- Patients with second primary cancer, EXCEPTIONS: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, ductal carcinoma in situ , stage 1 grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with NED for ≥5 years prior to study entry.

- Resting electrocardiogram (ECG) with corrected QT interval (QTc) ≥450 msec detected on 2 or more time points within a 24 hour period or family history of long QT syndrome. If ECG demonstrates QTc ≥450 msec, patient will only be eligible if repeat ECG demonstrates QTc ≤450 msec.

- Major surgery within 2 weeks of starting study treatment: patients must have recovered from any effects of any major surgery.

- Patients with a history of treated central nervous system (CNS) metastases were eligible, provided they meet all of the following criteria: Disease outside the CNS is present. No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study. No history of intracranial haemorrhage or spinal cord haemorrhage. Minimum of 2 weeks between completion of radiotherapy and Cycle 1 Day 1 and recovery from significant (Grade ≥3) acute toxicity with no ongoing requirement for ≥10 mg of prednisone per day or an equivalent dose of other corticosteroid.

- Patients with a known hypersensitivity to olaparib or any of the excipients of the product.

- Whole blood transfusions in the last 120 days prior to enrolment to the study which may interfere with gBRCA testing (packed red blood cells and platelet transfusions were acceptable).

Treatments

The details of the study drugs are given in **Table 2. Study treatments**.

Table 2. Study treatments

Study treatment	Olaparib	Placebo to match olaparib
Dosage formulation	150 mg and 100 mg green, film coated tablet	Tablet, with the appearance to match each strength of olaparib
Route of administration:	Oral	Oral
Dosing instructions	Planned dose of 300 mg bd were made up of 2 x 150 mg tablets bd with 100 mg tablets used to manage dose reductions. Tablets were to be taken at the same times every morning and evening of each day, approximately 12 hours apart with approximately 240 mL of water. The olaparib/placebo tablets should have been swallowed whole and not chewed, crushed, dissolved or divided. Olaparib/placebo tablets could be taken with a light meal/snack (eg, 2 pieces of toast or a couple of biscuits).	
Packaging and labelling	Olaparib and placebo were packed in HDPE bottles with child-resistant closures.	

bd: twice daily; HDPE: high density polyethylene.

Objectives

Primary objective

The primary objective of POLO was to determine the efficacy of olaparib maintenance monotherapy compared to placebo by PFS.

Key secondary objectives

The secondary objectives of POLO included: OS, PFS2, TFST, TSST, TDT, ORR by BICR, DCR by BICR, HRQoL as measured by the EORTC QLQ-C30 global QoL scale, safety and tolerability.

Outcomes/endpoints

Table 3. Objectives and endpoints

Objective	Endpoint/variable
Primary objective:	
• To determine the efficacy of olaparib maintenance monotherapy compared to placebo by PFS.	• PFS by BICR using modified RECIST v1.1
Secondary objectives:	
• To determine the efficacy of olaparib maintenance monotherapy compared to placebo.	• OS (observed and predicted using observed PFS and OS data) • Time from randomisation to second progression (PFS2) • Time from randomisation to first subsequent therapy or death (TFST) • Time from randomisation to second subsequent therapy or death (TSST) • Time from randomisation to study treatment discontinuation or death (TDT) • ORR by BICR using modified RECIST v1.1 criteria for evaluable patients • DCR at 16 weeks by BICR using modified RECIST v1.1 criteria
• To assess the effect of olaparib on HRQoL as measured by the EORTC QLQ-C30 global QoL scale.	• Adjusted mean change from baseline in global QoL score from the EORTC-QLQ-C30 questionnaire
Safety objective:	
• To assess the safety and tolerability of olaparib maintenance monotherapy.	• AEs, physical examination, vital signs including blood pressure, pulse, ECG and laboratory findings including clinical chemistry and haematology

Objective	Endpoint/variable
Exploratory objectives:	
• To assess the effect of olaparib on functioning as measured by the EORTC QLQ-C30 functioning domains (physical, role, cognitive, emotional and social). • To assess the effect of olaparib on pancreatic adenocarcinoma symptoms as measured by the EORTC QLQ-PAN26 items and scales. • To assess clinically relevant symptoms as measured by the EORTC QLQ-C30 and PAN26, including pain, fatigue, nausea, weight loss (or difficulty gaining weight/loss of appetite), jaundice. • To assess change in performance status as measured by the ECOG performance status scale.	• Adjusted mean change from baseline on EORTC-QLQ-C30 functioning domains (physical, role, cognitive, emotional, social), on EORTC-QLQ-C30 and PAN26 symptom scales and items (pain, fatigue, nausea, weight loss [difficulty gaining weight/loss of appetite], jaundice) and on performance status measured by the ECOG performance status scale
• To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility.	• Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay. • Health state utility derived from the HRQoL instrument, the EuroQoL EQ-5D
• To explore methods of estimating OS adjusting for the impact of the control arm receiving subsequent PARP inhibitors or imbalances between the treatment arms for other potentially active agents.[a]	• OS adjusted for impact of subsequent PARP inhibitors (or other potentially active investigational agents, if appropriate, to support reimbursement appraisals)
• To determine the frequency of and describe the nature of *BRCA* mutation/s in tumour samples and to compare this with germline *BRCA* mutation status.[a]	• *BRCA1* and/or *BRCA2* mutation status in tumour
• To identify tumour tissue based biomarkers (including but not limited to somatic *BRCA1/2* mutations, *BRCA* methylation and/or other HRD biomarkers) that could be used to guide future patient segmentation approaches for development.[a] • Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (if available), blood samples at Day 1 and on disease progression or on residual tissue material collected as part of the study.[a]	• Potential tissue biomarkers identified

[a]   This objective will be analysed outside of the CSR and will be reported separately.

AE adverse event; BICR blinded independent central review; *BRCA* Breast cancer susceptibility gene; CSR clinical study report; DCR disease control rate; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D EuroQoL five

dimensions; HRD homologous recombination repair deficiency; HRQoL health-related quality of life; ORR objective response rate; OS overall survival; PARP polyadenosine 5'diphosphoribose polymerase; PFS progression-free survival; QLQ-C30 quality of life questionnaire for cancer patients; QLQ-PAN26 quality of life questionnaire for pancreatic cancer patients; QoL quality of life; RECIST Response Evaluation Criteria in Solid Tumours.

Primary outcome variable

Progression free survival
Progression-free survival is defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to disease progression (i.e. date of RECIST progression/death or censoring – date of randomisation + 1). Patients who have not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progressed or died after two or more missed visits, the patient were censored at the time of the latest evaluable RECIST assessment (prior to the missing visits).

Main secondary outcome variables

Overall survival
Overall Survival was defined as the time from the date of randomisation until death due to any cause (i.e. date of death or censoring – date of randomisation + 1). Any patient not known to have died at the time of analysis was supposed to be censored based on the last recorded date on which the patient was known to be alive.

Time from randomisation to second progression
The time from randomisation to second progression (PFS2) was defined as the time from the date of randomisation to the earliest of the second progression event as assessed by the investigator or death (ie date of PFS2 event or censoring – date of randomisation + 1).

Time to first subsequent therapy or death

The TFST was defined as the time from randomisation to the earlier of first subsequent cancer therapy start date following study treatment discontinuation, or death (i.e. date of first subsequent cancer therapy/death or censoring – date of randomisation + 1).

Time to second subsequent therapy or death
The TSST was defined as the time from randomisation to the earlier of the second subsequent cancer therapy start date following study treatment discontinuation, or death (i.e. date of second subsequent cancer therapy/death or censoring – date of randomisation + 1).

Time to study treatment discontinuation or death
The TDT was defined as the time from randomisation to the earlier of the date of study treatment discontinuation or death (i.e. date of study treatment (olaparib/placebo) discontinuation/death or censoring – date of randomisation + 1).

Best objective response
BoR was the best response a patient has had following randomisation but prior to starting any subsequent cancer therapy and prior to RECIST progression or the last evaluable assessment in the absence of RECIST progression.

Objective response rate

For each treatment group, the ORR was the number of patients with a BoR of CR and PR according to the BICR data divided by the number of patients in the treatment group with measurable disease at baseline where 'measurable' is defined by the BICR data. Only patients with measurable disease at baseline could achieve an objective response of CR or PR.

Disease control rate

The DCR was defined as the percentage of patients who had at least one confirmed visit response of CR or PR or had demonstrated SD or NED for at least 15 weeks (ie, 16 weeks minus 1 week to allow for an early assessment within assessment window) prior to any evidence of progression.

Patient Reported Outcome Variables

The EORTC QLQ-C30/PAN26, validated PRO questionnaires in the target patient population, will be used to evaluate disease symptoms, functional impacts (e.g., physical functioning), and HRQoL and characterise clinical benefit from the patient perspective. The EORTC QLQ-C30 / QLQ-PAN26 will be scored according to the EORTC scoring manual (Fayers et al 2001) and the draft scoring procedure for QLQ-PAN26 (Johnson 2007).

Sample size

The primary endpoint of the study was PFS. Approximately 145 patients would be randomised (3:2 ratio of olaparib:placebo) and the final PFS analysis was to occur once approximately 87 PFS events (confirmed via a central review) have occurred. A single interim PFS analysis for futility was to be performed when 50% of the PFS events required for the final analysis (approximately 44 PFS events) based on BICR have occurred.

The study was sized assuming a true treatment effect that was a PFS hazard ratio (HR) of 0.54 at the final analysis, assuming 80% power and 2.5% alpha (1-sided), with 3:2 randomisation (olaparib:placebo). Assuming PFS was exponentially distributed, a PFS HR of 0.54 equates to a 3.4 month improvement in median PFS over an assumed 4 month median PFS for placebo.

Patients were to be followed for the final analysis of OS and PFS2 (when approximately 106 death events have occurred). With 106 OS events the study had 80% power to show a statistically significant difference in OS at the 1-sided 2.5% level if the assumed true treatment effect was a HR 0.57; this translated to an approximate 6-month improvement in median OS over an assumed 8 month median OS on placebo, assuming OS was exponentially distributed.

Assuming that the study accrual period was approximately 15 months, 87 PFS events were anticipated to be observed approximately 18 to 19 months after the first patient is randomised in the study. It was estimated that 44 PFS events would have occurred approximately 13 to 14 months after first patient in. It was estimated that 106 deaths would have occurred approximately 31 months after first patient in.

Randomisation

Patients were randomised using an Interactive Voice Response System (IVRS)/Interactive Web Response System in a 3:2 ratio to the treatments as specified below:

- Olaparib tablets orally 300 mg bd

- Placebo tablets orally bd

No stratification factors were included in the randomisation.

Blinding (masking)

This was a double-blind study and the medication was labelled using a unique Kit ID number, which was linked to the randomisation scheme. The active and placebo tablets were identical and presented in the same packaging to ensure blinding of the study medication.

Unblinding was permitted for management of medical emergencies or if considered necessary in order to make further treatment decisions for individual patients.

Statistical methods

The primary outcome variable was PFS assessed by BICR. The PFS analysis was performed with a DCO of 15 January 2019.

PFS was analysed using a log-rank test for generation of the p-value and using the Breslow approach for handling ties. The HR and confidence interval (CI) were estimated from the U and V statistics obtained directly from the LIFETEST model.

Subgroup analyses of PFS were conducted to assess the consistency of treatment effect across potential or expected prognostic factors. Sensitivity analyses were conducted to assess the possible presence of evaluation-time, attrition and ascertainment (BICR vs investigator).

The secondary efficacy endpoints of overall survival (OS), time from randomisation to second progression or death (PFS2, as assessed by the investigator), time from randomisation to first subsequent therapy or death (TFST), time from randomisation to second subsequent therapy or death (TSST) and time from randomisation to study treatment discontinuation or death (TDT) were analysed using the same methodology and model as used for the primary analysis of PFS. Best objective response (BoR) was also a secondary efficacy endpoint and was calculated based on the overall visit responses from each RECIST assessment. BoR was summarised based on the RECIST by BICR criteria using the following response categories: complete response (CR), partial response (PR), stable disease (SD), no evidence of disease (NED), progressive disease (PD) and not evaluable. Disease control rate (DCR) was defined as the percentage of patients who have at least one visit response of CR or PR or had demonstrated SD or NED for at least 15 weeks.

The impact of olaparib on health-related quality of life (HRQoL) was assessed through an analysis of the global health status/quality of life (QoL) gathered from Items 29 and 30 of European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30, a questionnaire developed to assess general cancer related symptoms, functional impacts (eg, physical functioning) and HRQoL. Change from baseline score was the primary analysis of the questionnaire and was analysed

using a mixed model for repeated measures analysis of all of the post-baseline scores each visit.

In order to describe the nature of the benefits of olaparib maintenance treatment, a multiple testing procedure was also employed across the primary endpoint (PFS) and the secondary endpoint of OS. All other variables (PFS2, TFST, TSST, TDT and HRQoL) were tested at a 2-sided significance level of 5% but not adjusted for multiplicity; thus, p-values are treated as nominal.

The impact of olaparib on HRQoL was repeated as an exploratory analysis for selected EORTC QLQ-C30 functional and symptom scales as well as for selected EORTC QLQ-PAN26 scales (a questionnaire developed specifically to assess pancreatic cancer-specific symptoms [eg, pancreatic pain] and their impact). Descriptive statistics including change from baseline, arithmetic mean (±standard deviation) plots of scores over time, adjusted mean change from baseline (95% CI) over time (summary tables and plots) and frequency tables of best overall quality of life (QoL) response were presented by treatment group. In addition an exploratory analysis of the EuroQoL five dimensions, five level (EQ-5D-5L) index which comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) was conducted. Descriptive statistics, graphs and listings were reported for health state utility values and visual analogue scale by visit as well as change in these scores from baseline, and was summarised by treatment group.

Sensitivity analyses

As a sensitivity analysis to the primary endpoint of PFS, the primary analysis was repeated excluding patients who did not have a gBRCA mutation status confirmed by the central Myriad test. The same methodology and model as used for the primary analysis was applied and the HR and associated 95% CI were reported. A KM plot of PFS for this subset of patients was presented by treatment group.

Sensitivity analyses of PFS were performed to assess for possible attrition bias, evaluation time bias and ascertainment bias (see Section 1.3.6.1 for further details). A sensitivity analysis for deviation bias was to be conducted if the proportion of patients with deviations that could specifically affect efficacy was >10%; however the criteria for this analysis were not met.

Results

Participant flow

Figure 3. Patient disposition (All patients)
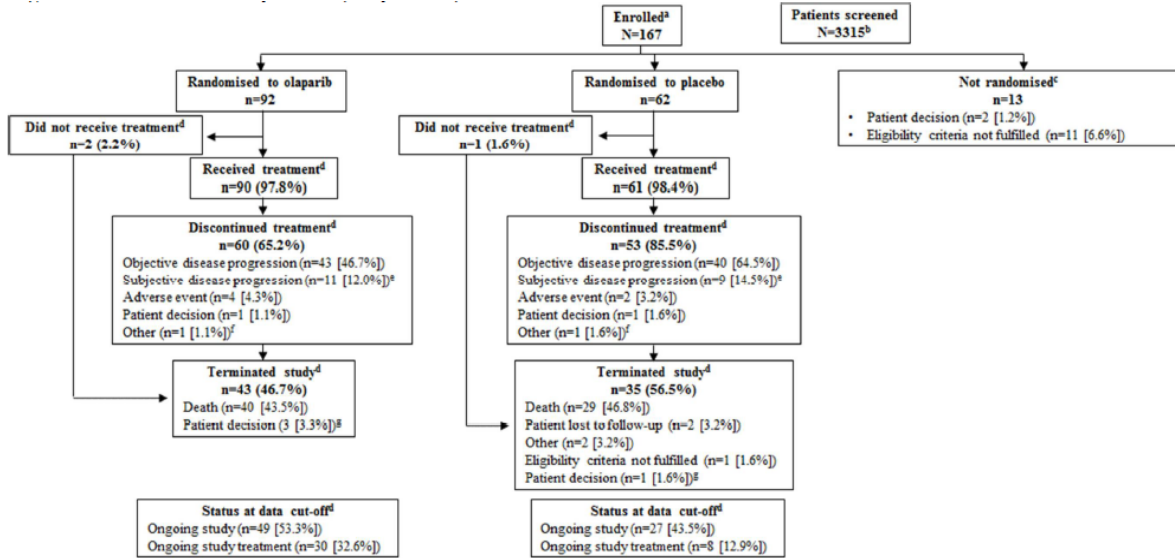
^a   Main study informed consent received.
^b   A total of 3315 patients screened. Of the 247 patients determined to have a gBRCA mutation (AstraZeneca data on file), 167 were enrolled in the study.
^c   Percentages are calculated from the number of patients signing the main ICF.
^d   Percentages are calculated from the number of patients randomised.
^e   Subjective progression is based on investigator local disease assessment as recorded on the CRF.
^f   Any reason not specifically recorded, for example patient died.
^g   Patient E1001007 in the olaparib arm and Patient E7835002 in the placebo arm voluntarily withdrew from the study. Post follow-up these patients were subsequently reported to have died.

BRCA breast cancer susceptibility gene; CRF case report form; gBRCA germline BRCA; ICF informed consent form.
Data derived from Table 11.1.1, Table 11.1.9.3, Table 11.3.3.2.1 and Appendix 12.2.1.1.

Table 4. Patient disposition (All patients)

	Number (%) of patients		
	Olaparib 300 mg bd	**Placebo**	**Total**
Patients screened			3315
Patients enrolled^a			167
Patients randomised	92 (100)	62 (100)	154 (100)
Patients who were not randomised^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]	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 randomised.

d.   Note: Table 11.3.5.1.1 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. Table 11.3.5.1.1 does not include one patient (placebo arm) who had an AE of back pain which occurred prior to study treatment (see Appendix 12.2.7.6). 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 Table 11.3.5.1.1. In Table 11.1.1, 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 Table 11.3.5.1.1.

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.

AE adverse event; bd 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.

Data derived from Table 11.1.1, Table 11.1.9.3, Table 11.3.3.2.1 and Appendix 12.2.1.1.
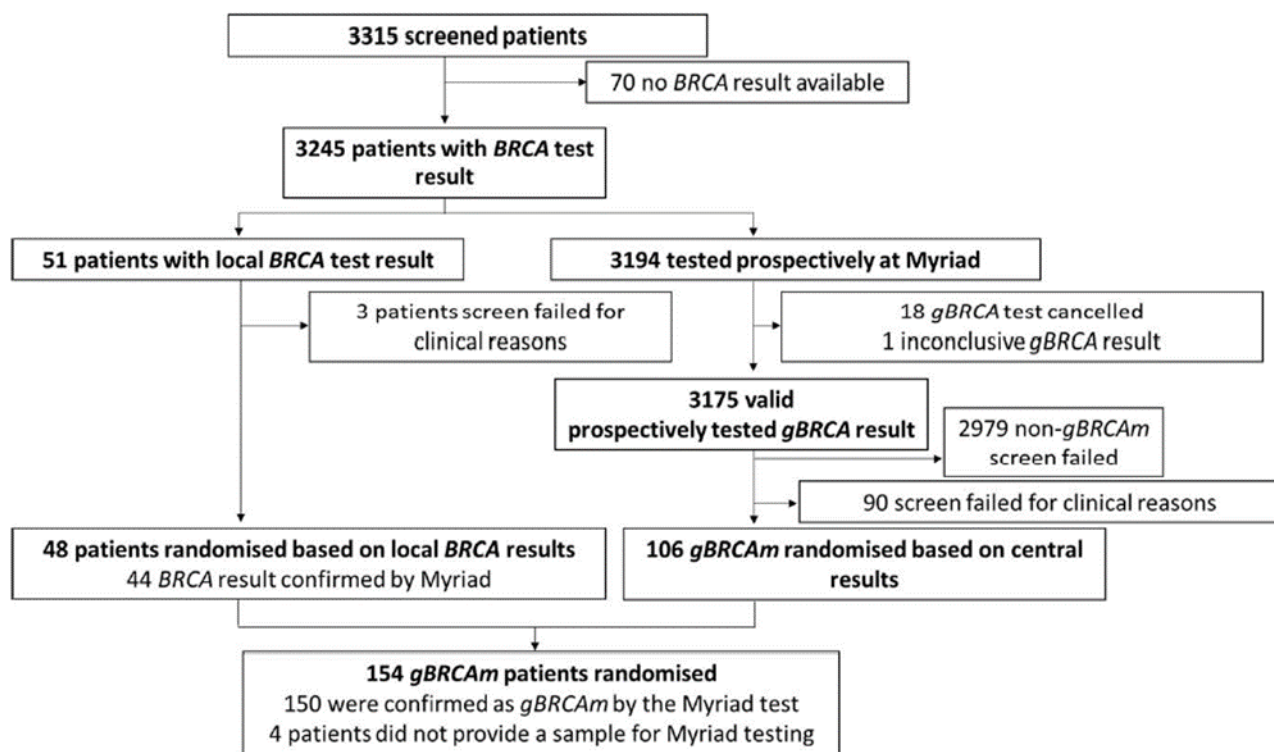
Figure: Routes to randomisation (All patients)

Recruitment

First subject enrolled: 16 December 2014

Data cut-off date: 15 January 2019

Conduct of the study

Protocol Amendments

Important amendments to the original study protocol, including when those amendments came into effect with respect to the recruitment of patients, and other significant changes to study conduct are shown in table below. The original CSP was dated 31 March 2014. The last protocol amendment 2 was dated 28 February 2015.

Table 5: Protocol amendments and other significant changes to study conduct

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment
Amendments made before the start of subject recruitment		
Protocol Amendment 1 14 October 2014	Frequency of safety assessments for MDS/AML changed from every 3 weeks after the first cycle to every 4 weeks after the first cycle (Not applicable).	To ensure protocol consistency and to correct a typographical error
	Haematology and clinical chemistry assessments were changed from Day 1 during the first cycle to Days 1, 8, 15 and 22 during the first cycle (Section 5.1).	To ensure protocol consistency and to correct a typographical error
Amendments made after the start of subject recruitment		
Protocol Amendment 2 28 February 2015	Decreased the number of events that should have occurred at the interim and primary PFS analysis and increased the size of the alpha from 2.26% to 2.5% (Section 5.1, Section 5.8.1.1, Section 5.8.3 and Section 5.8.4).	Removal of the interim superiority analysis per FDA recommendation meant that the 2.5% significance level did not need to be shared between the interim and final analysis so fewer events were required
	Analysis of OS and PFS2 at the time of interim PFS analysis was removed (Section 5.8.1.2 and Section 5.8.1.3).	Removal of the superiority analysis at the time of the interim analysis as per FDA recommendation, therefore OS and PFS2 did not need to be analysed at this time.
	Time to global QoL and pancreatic pain scale deterioration was removed and replaced with adjusted mean change from baseline in global QoL score using MMRM analysis. Addition of the exploratory analysis of HRQoL (Section 5.8.1.8, Section 5.8.1.9 and Section 5.8.2.3).	To change the type of analysis used to MMRM analysis of adjusted mean change from baseline, which is independent of minimal important differences values that are not well-defined, and is suitable for analysing continuous responses measured repeatedly over time. An exploratory analysis was performed to examine adjusted mean change from baseline on EORTC QLQ-C30 and QLQ-PAN26 functioning domains and symptom scales/items.
	Addition of data from the QT study (Section 3.4).	To provide additional data on the QT study that has been conducted.

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment
Protocol Amendment 2 28 February 2015	Changed time of initial ECG from within 7 days before starting to treatment if patient was eligible following completion of all other Part 2 screening assessments to 14 days (Section 5.1 and Section 5.8.1.10).	To ensure that the patient could start treatment within 8 weeks of their last chemotherapy dose instead of 7 weeks.
	Clarified that SAEs only relating to blood sampling for Myriad *gBRCA* will be collected during Part 1 of screening (Section 5.1).	To clarify the SAE reporting requirements in the screening Part 1 phase
	Changed the resting QTc in the exclusion criteria from >470 msec to ≥450 msec (Section 5.3.1).	To be consistent with the ICH E14 guideline as requested by the German Ethics committee.
	Clarified that patients could enter the study with a haemoglobin value of >9 g/dL and clarified dose reductions for the management of anaemia (Section 6.7.1 of the CSP)	To make the management of haematological toxicity clearer.
	Clarified that BoR should only be calculated using data up to the point of any subsequent therapies being used and that BoR will also be reported using investigator-recorded assessment (Section 5.8.1.6).	To bring text in line with current AstraZeneca oncology statistical guidance
	Updated the subgroups of the FAS that were analysed for PFS (Section 5.8.1.1).	To include additional subgroup analyses of PFS; previous chemotherapy (FOLFIRINOX variants versus gemcitabine/cisplatin), and presence/absence of biliary stent were analysed in Cox proportional hazards models.

[a]   All protocol amendments were approved by AstraZeneca before being submitted to a regulatory authority and/or an IRB/IEC.

AML acute myeloid leukaemia; BoR best objective response; *BRCA* breast cancer susceptibility gene; CSP clinical study protocol; ECG electrocardiogram; EORTC European Organisation for Research and Treatment of Cancer; FAS Full Analysis Set; FDA Food and Drug Administration; *gBRCA* germline *BRCA*; HRQoL health-related quality of life; ICH International Council for Harmonisation; IEC Independent Ethics Committee; IRB Institutional Review Board; MDS myelodysplastic syndrome; MMRM mixed model for repeated measures; OS overall survival; PFS progression-free survival; PFS2 time from randomisation to second progression; QLQ-C30 quality of life questionnaire for cancer patients; QLQ-PAN26 quality of life questionnaire for pancreatic cancer patients; QoL quality of life; QTc corrected QT interval; SAE serious adverse event.

Table 6: Changes to planned analyses

Key details of change (Section of this report affected)	Reason for change
Changes made before unblinding of study data	
The definition of the Patient Reported Outcome analysis set was changed from requiring a patient to have "evaluable baseline EORTC QLQ-C30 and QLQ-PAN26 forms" to specify this in more detail by stating that it must be possible to determine at least 1 sub-scale baseline score from at least 1 of the 2 forms.	For clarity
Analysis of time to sustained clinically meaningful deterioration in HRQoL was added.	A supportive analysis of QoL using this end-point was of interest
Changes made after unblinding of study data	
A new source table was generated to present the prevalence of patients with *gBRCAm* in the pancreatic adenocarcinoma population (Table 11.1.9.3).	Data were collected as part of the study and needed to be reported.
ECOG performance status (0 or 1) was added in to the subgroup analysis of PFS by BICR and OS (data included in Table 11.1.17, Table 11.2.3.1, Table 11.2.4.2, Table 11.2.3.4, Figure 11.2.3.2 and Figure 11.2.4.3, and new KM plots were generated as source figures [Figure 11.2.3.3.11 and Figure 11.2.4.6.11]).	ECOG performance status was included as a baseline covariate in the Cox analysis as an imbalance in patients with ECOG performance status 0 at baseline was observed between the 2 treatment arms.
Table 11.2.3.1.1 generated to present median PFS and 95% CI data for the subgroup analysis of PFS by BICR.	Data were collected as part of the study and needed to be reported.
Table 11.2.3.1.2 generated to present unadjusted and adjusted Cox proportional hazards model data for PFS.	Cox proportional hazards models were run containing the treatment term only or the treatment term and the subgroups as covariates to assess for any impact of imbalances at baseline.
Table 11.2.9.3.1 and Table 11.2.9.3.2 "Duration and onset of objective response" by BICR and Investigator assessment, respectively, updated to include 95% CI data.	Data were collected as part of the study and needed to be reported.
New source tables generated for QLQ-C30 symptoms of dyspnoea, constipation and diarrhoea.	Data were collected as part of the study and needed to be reported.

Protocol deviations

The number of patients with important protocol deviations in each treatment group are summarised in **Table 5. Important protocol deviations (FAS)**

This section describes important protocol deviations that could have affected the interpretation of the primary efficacy analysis or the analysis related to the secondary safety objectives. The FAS population was used for the summaries of efficacy data, and no patients were excluded from this population for important protocol deviations.

The important protocol deviations and those important protocol deviations identified as having the potential to affect efficacy outcomes and trigger a pre-planned sensitivity analysis if they occurred in >10% patients were identified and classified prior to database lock, in a blinded manner, for the primary DCO (15 January 2019).

The 2 treatment arms were balanced with respect to the percentage of patients with important protocol deviations. In total, 2.6% of patients (2.2% in the olaparib arm and 3.2% in the placebo arm) had protocol deviations that could have triggered a sensitivity analysis; however, this analysis was not conducted as the SAP pre-defined 10% threshold was not reached.

Table 7. Important protocol deviations (FAS)

	Number (%) of patients		
	Olaparib 300 mg bd (N=92)	Placebo (N=62)	Total (N=154)
Number of patients with at least 1 important deviation triggering a sensitivity analysis[a, b]	**2 (2.2)**	**2 (3.2)**	**4 (2.6)**
Inclusion criterion not met (histologically or cytologically confirmed pancreatic adenocarcinoma could not be determined)	0	1 (1.6)	1 (0.6)
Patient did not take any study medication	2 (2.2)	1 (1.6)	3 (1.9)
Number of patients with at least 1 important deviation[a]	**21 (22.8)**	**13 (21.0)**	**34 (22.1)**
RECIST scans outside of a scheduled visit window on >2 occasions	9 (9.8)	9 (14.5)	18 (11.7)
Use of prohibited concomitant medication	3 (3.3)	1 (1.6)	4 (2.6)
Severe non-compliance to protocol; study drug not discontinued	3 (3.3)	0	3 (1.9)
Baseline RECIST scan of target lesions >28 days before study treatment was started	1 (1.1)	2 (3.2)	3 (1.9)
Patient did not take any study medication	2 (2.2)	1 (1.6)	3 (1.9)
Study enrolment >8 weeks since last dose of chemotherapy	1 (1.1)	1 (1.6)	2 (1.3)
Exclusion criterion met (cancer therapy stop date within 28 days of Cycle 1 Day 1)	1 (1.1)	1 (1.6)	2 (1.3)
Inclusion criterion not met (histologically or cytologically confirmed pancreatic adenocarcinoma could not be determined)	0	1 (1.6)	1 (0.6)
Inclusion criterion not met (white blood cell not available at baseline)	1 (1.1)	0	1 (0.6)
Inclusion criterion not met (blood transfusion <28 days prior to study treatment)	0	1 (1.6)	1 (0.6)
Inclusion criterion not met (patient on treatment with a first-line platinum-based regimen for <16 weeks)	1 (1.1)	0	1 (0.6)
Use of CYP inducers	1 (1.1)	0	1 (0.6)
SAE/AE not reported within required timeline	1 (1.1)	0	1 (0.6)
Baseline RECIST scan of non-target lesions >28 days before study treatment was started	0	1 (1.6)	1 (0.6)

Baseline laboratory value (ALT) missing	1 (1.1)	0	1 (0.6)

Important deviations before the start of treatment and during treatment. The same patient may have had more than 1 important protocol
         deviation.
b.   A sensitivity analysis for primary efficacy was to be conducted if >10% of the FAS did not fulfil the relevant inclusion or exclusion criteria
         or did not receive any study medication.
   Note that the same patient may have had more than 1 important protocol deviation. AE adverse event; ALT alanine aminotransferase; bd twice daily;
   CYP cytochrome P450; FAS Full Analysis Set; RECIST Response Evaluation Criteria in Solid Tumours; SAE serious adverse event. Data derived
   from Table 11.1.2 and Appendix 12.2.2.1.

Baseline data

Demographic characteristics

The demographic and key baseline characteristics of study patients are summarised in **Table 6. Demographic characteristics (FAS)**

Demographic characteristics in the Myriad confirmed *gBRCAm* subset were consistent with the FAS.

Table 8. Demographic characteristics (FAS)

		Olaparib 300 mg bd (N=92)	Placebo (N=62)	Total (N=154)
Age (years)	n	92	62	154
	Mean	58.2	56.4	57.5
	Standard deviation	10.27	9.07	9.81
	Median	57.0	57.0	57.0
	Min	37	36	36
	Max	84	75	84
Age group (years), n (%)	35 to 44	8 (8.7)	7 (11.3)	15 (9.7)
	45 to 54	27 (29.3)	20 (32.3)	47 (30.5)
	55 to 64	29 (31.5)	22 (35.5)	51 (33.1)
	65 to 74	24 (26.1)	12 (19.4)	36 (23.4)
	75 to 84	4 (4.3)	1 (1.6)	5 (3.2)
Sex, n (%)	Male	53 (57.6)	31 (50.0)	84 (54.5)
	Female	39 (42.4)	31 (50.0)	70 (45.5)
Race, n (%)	White	82 (89.1)	59 (95.2)	141 (91.6)
	Black or African American	5 (5.4)	0	5 (3.2)
	Asian	4 (4.3)	2 (3.2)	6 (3.9)
	American Indian or Alaskan Native	1 (1.1)	0	1 (0.6)
	Other	0	1 (1.6)	1 (0.6)
Ethnic group, n (%)	Hispanic or Latino	4 (4.3)	2 (3.2)	6 (3.9)
	Not Hispanic or Latino	88 (95.7)	60 (96.8)	148 (96.1)

bd twice daily; FAS Full Analysis Set; Max maximum; Min minimum. Data derived from Table 11.1.4.

Disease characteristics

The disease characteristics of the patients at baseline are summarised in **Table 7. Disease characteristics at baseline (FAS)**. Baseline characteristics of the target population of patients with *gBRCAm* metastatic pancreatic adenocarcinoma whose disease had not progressed following first-line platinum-based chemotherapy were generally well balanced between the 2 treatment groups.

Of the patients tested by Myriad who had an unknown *BRCA* mutation status at study entry, the prevalence of confirmed *gBRCAm* patients was 6.2% (198/3175 patients). Two patients were incorrectly identified as having unknown *BRCA* mutation status and were inadvertently included in the original analysis. Correcting for this error the prevalence of confirmed *gBRCAm* patients should be 6.2% (196/3175).

The primary tumour location in the majority of patients in both arms was the pancreas; One Patient in the olaparib arm and one Patient in the placebo arm did not receive treatment and did not have their primary tumour location recorded. A n o t h e r Patient had histology type at diagnosis recorded as "cannot be determined", however had a primary tumour location specified as the pancreas.

There were no locally advanced patients enrolled in the study (patients had general [sites not specified] or specific sites of metastasis prior to first-line chemotherapy). In both treatment arms, the most frequently reported site of disease for patients with evidence of metastatic disease at baseline was the liver. 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).

Table 9. Disease characteristics at baseline (FAS)

	Olaparib 300 mg bd (N=92)	Placebo (N=62)	Total (N=154)
Time from original diagnosis to randomisation (months)			
n	91	61	152
Median	6.87	6.97	6.93
Minimum, Maximum	3.6, 38.4	4.1, 30.2	3.6, 38.4
Histology type at diagnosis, n (%)			
Adenocarcinoma (not otherwise specified)	53 (57.6)	37 (59.7)	90 (58.4)
Pancreatic adenocarcinoma	38 (41.3)	17 (27.4)	55 (35.7)
Adenocarcinoma: acinar	0	4 (6.5)	4 (2.6)
Adenocarcinoma: papillary	0	1 (1.6)	1 (0.6)
Adenocarcinoma: solid with mucus formation	0	1 (1.6)	1 (0.6)
Not affected[a]	0	1 (1.6)	1 (0.6)
Missing	1 (1.1)	1 (1.6)	2 (1.3)
Primary tumour location at diagnosis			
Pancreas	91 (98.9)	61 (98.4)	152 (98.7)
Missing	1 (1.1)	1 (1.6)	2 (1.3)
Any general or specific site of metastasis prior to chemotherapy[b]			

No	0	0	0
Yes	89 (96.7)	61 (98.4)	150 (97.4)
Missing	3 (3.3)	1 (1.6)	4 (2.6)
Site of metastasis prior to chemotherapy			
Liver	61 (66.3)	48 (77.4)	109 (70.8)
Lymph node	22 (23.9)	13 (21.0)	35 (22.7)
Lung	10 (10.9)	5 (8.1)	15 (9.7)
Peritoneum	10 (10.9)	5 (8.1)	15 (9.7)
Other	8 (8.7)	5 (8.1)	13 (8.4)
Bone	2 (2.2)	2 (3.2)	4 (2.6)
Adrenal gland	2 (2.2)	1 (1.6)	3 (1.9)
Gastrointestinal system	1 (1.1)	2 (3.2)	3 (1.9)
Ascites	1 (1.1)	1 (1.6)	2 (1.3)
Mediastinum	1 (1.1)	1 (1.6)	2 (1.3)
Extent of disease at baseline			
Metastatic[c]	87 (94.6)	55 (88.7)	142 (92.2)
Biliary stent at baseline			
Presence of biliary stent	1 (1.1)	4 (6.5)	5 (3.2)
Absence of biliary stent	91 (98.9)	58 (93.5)	149 (96.8)
ECOG performance status at baseline			
(0) Normal activity	65 (70.7)	38 (61.3)	103 (66.9)
(1) Restricted activity	25 (27.2)	23 (37.1)	48 (31.2)
Missing	2 (2.2)	1 (1.6)	3 (1.9)
BRCA status previously known (local result available) at baseline			
Known	30 (32.6)[d]	17 (27.4)	47 (30.5)[d]
Unknown	62 (67.4)[d]	45 (72.6)	107 (69.5)[d]
Locally reported *BRCA* status at baseline			
BRCA mutated[e]	30 (32.6)	16 (25.8)	46 (29.9)
BRCA1	10 (10.9)	5 (8.1)	15 (9.7)
BRCA2	19 (20.7)	11 (17.7)	30 (19.5)
Both *BRCA1* and *BRCA2*	1 (1.1)	0	1 (0.6)
Missing[f]	62 (67.4)	46 74.2)	108 (70.1)
Myriad reported *BRCA* status at baseline			
BRCA mutated[e]	89 (96.7)	61 (98.4)	150 (97.4)
BRCA1	29 (31.5)	16 (25.8)	45 (29.2)
BRCA2	59 (64.1)	45 (72.6)	104 (67.5)
Both *BRCA1* and *BRCA2*	1 (1.1)	0	1 (0.6)
Missing	3 (3.3)	1 (1.6)	4 (2.6)

a.　Relates to Patient with histology type at diagnosis recorded as "cannot be determined".

b.　Patients were to have general or specific sites of metastases for study enrolment.

c.　Summary includes sites of disease where the extent is recorded as metastatic or both (ie, locally advanced and metastatic). Sites of metastases at baseline assessed post patient response to first-line chemotherapy, prior to study treatment.

d.　Overall, 48 patients were randomised on the basis of a locally available *BRCA* testing result.
One Patient(in the olaparib arm) should have been included in the "*BRCA* status previously known" cohort but was inadvertently mis-assigned to the "unknown" cohort. This patient 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, in the olaparib arm and total columns

respectively, there should be 31 (33.7%) and 48 (31.2%) patients in the "known" group and 61 (66.3%) and 106 (68.8%) patients in the "unknown" group in the FAS (see Table 11.1.9).

e. Contains 'deleterious mutation' and 'genetic variant, suspected deleterious'.
f. Missing locally confirmed *gBRCA* status included patients with no local test result available who consented to provide blood samples for *gBRCA* testing by Myriad as per protocol. Also includes 2 patients with incomplete reporting of the local result in the eCRF. These patients were included in the "missing" group as one Patient had only information on which *BRCA* gene was mutated and one Patient had neither information on which *BRCA* gene was mutated nor which *BRCA* variant was detected, reported in the eCRF.
bd twice daily; *BRCA* breast cancer susceptibility gene; ECOG Eastern Cooperative Oncology Group; eCRF electronic case report form; FAS Full Analysis Set; *gBRCA* germline *BRCA*.
Data derived from Table 11.1.9, Table 11.1.10 and Table 11.1.17 and Appendix 12.2.2.1.

All patients who received study treatment had received 1 prior regimen of disease-related chemotherapy at baseline (**Table *8*. Summary of previous disease-related chemotherapy at baseline (FAS)**). Two patients were not known to have received a prior chemotherapy treatment for metastatic pancreatic adenocarcinoma; these 2 patients did not receive study treatment. Another one patient received 2 previous treatment regimens of FOLFIRINOX as neo-adjuvant and adjuvant treatment for pancreatic adenocarcinoma. The time between the patient receiving the last dose of adjuvant treatment and initiation of the platinum-based chemotherapy for metastatic pancreatic adenocarcinoma was approximately 10 months; this did not meet the criteria for important or major protocol deviations.

A further patient did not receive a minimum of 16 weeks of continuous treatment with a first-line platinum-based regimen; the patient received 10 weeks of treatment and was recorded as having an important protocol deviation.

Table 10. Summary of previous disease-related chemotherapy at baseline (FAS)

Number of regimens	Number (%) of patients		
	Olaparib 300 mg bd (N=92)	Placebo (N=62)	Total (N=154)
Number of regimens received			
1	90 (97.8)	61 (98.4)	151 (98.1)
2	1 (1.1)	0	1 (0.6)
Unknown[a]	1 (1.1)	1 (1.6)	2 (1.3)
Summary statistics[a]			
n	91	61	152
Mean	1.0	1.0	1.0
Standard deviation	0.10	0.00	0.08
Median	1.0	1.0	1.0

   a   Patients in the unknown category are not included in the calculation of 'n' or the associate summary statistics.
bd twice daily; FAS Full Analysis Set. Data derived from Table 11.1.12.2.

Previous disease-related chemotherapy treatments are summarised in **Table *9*. Previous disease-related chemotherapy information (FAS)**.

Table 11. Previous disease-related chemotherapy information (FAS)

Baseline subgroup	Number (%) of patients		
	Olaparib 300 mg bd (N=92)	Placebo (N=62)	Total (N=154)
Previous chemotherapy			

FOLFIRINOX variants	79 (85.9)	50 (80.6)	129 (83.8)
Gemcitabine/cisplatin	2 (2.2)	3 (4.8)	5 (3.2)
Other	10 (10.9)	8 (12.9)	18 (11.7)
Missing	1 (1.1)	1 (1.6)	2 (1.3)
Type of previous chemotherapy			
Doublets	15 (16.3)	10 (16.1)	25 (16.2)
Triplets	73 (79.3)	46 (74.2)	119 (77.3)
Other	3 (3.3)	5 (8.1)	8 (5.2)
Missing	1 (1.1)	1 (1.6)	2 (1.3)
Time on first-line treatment until randomisation			
≤6 months	61 (66.3)	40 (64.5)	101 (65.6)
>6 months	30 (32.6)	21 (33.9)	51 (33.1)
Missing	1 (1.1)	1 (1.6)	2 (1.3)
Best response on first-line treatment			
SD	45 (48.9)	31 (50.0)	76 (49.4)
PR/CR	46 (50.0)	30 (48.4)	76 (49.4)
Missing	1 (1.1)	1 (1.6)	2 (1.3)

bd twice daily; CR complete response; FAS Full Analysis Set; PR partial response; SD stable disease. Data derived from Table 11.1.17.

Table 12   **"Other" first-line chemotherapy regimens for metastatic pancreatic cancer (non-FOLFIRINOX variants/gemcitabine/cisplatin; Full Analysis Set)**

	Number (%) of patients		
First-line treatment regimen	**Olaparib 300 mg bd (N=92)**	**Placebo bd (N=62)**	**Total (N=154)**
GEMOX	5 (5.4)	1 (1.6)	6 (3.9)
Oxaliplatin	1 (1.1)	1 (1.6)	2 (1.3)
FOLFOX/nab-paclitaxel	0	1 (1.6)	1 (0.6)
Gemcitabine/nab-paclitaxel /capecitabine/cisplatin	2 (2.2)	2 (3.2)	4 (2.6)
Gemcitabine/epirubicine/capecitabine/cisplatin	0	2 (3.2)	2 (1.3)
FOLF/cisplatin	1 (1.1)	0	1 (0.6)
FOLFIRI/cisplatin	0	1 (1.6)	1 (0.6)
5FU/carboplatin	1 (1.1)	0	1 (0.6)

Only the initial first-line treatment regimens were shown; the continuous treatment regimens with platinum discontinued for toxicity were not captured in this table.

Patients are counted once per type of regimen.

5FU 5-fluorouracil; bd Twice daily; CSR Clinical study report.

Source data: Table 11.1.12.1.1, POLO CSR.

For any type of regimen, the most common individual regimen by far was FOLFIRINOX (2-week cycle) given to 75% (115) of randomised patients followed by FOLFOX (2-week cycle) (10 patients). The

median (range) number of FOLFIRINOX cycles was 9 (4:61) in the olaparib and 9 (4:21) in the placebo arm.

For platinum-containing regimens, data on the number of cycles could be determined for 71 patients. FOLFIRINOX was the most common therapy (47 patients). The median (min:max) number of cycles of FOLFIRINOX was 9 (6:58) in the olaparib and 9 (6:12) in the placebo arm. The table excludes subsequent cycles where the platinum was dropped.

Table **Distribution of the number of cycles of first line chemotherapy, including cycles where the platinum was dropped, and the remaining drugs continued (Full Analysis Set; DCO: 15 January 2019)**

Regimen (cycle length)	Treatment group	n	Mean	Median	SD	Min	Max
FOLFIRINOX (2-week cycle)	Olaparib	71	10.9	9.0	7.11	5	61
	Placebo	44	9.9	9.0	2.99	4	21
	Both	115	10.5	9.0	5.88	4	61
FOLFOX (2-week cycle)	Olaparib	5	6.8	7.0	2.59	3	10
	Placebo	5	9.4	10.0	1.95	7	12
	Both	10	8.1	8.0	2.56	3	12
GEMOX (2-week cycle)	Olaparib	5	10.2	8.0	3.49	8	16
	Placebo	1	8.0	8.0	-	8	8
	Both	6	9.8	8.0	3.25	8	16
Gemcitabine/cisplatin (4-week cycle)	Olaparib	2	5.5	15.5	12.02	7	24
	Placebo	3	22.0	8.0	26.89	5	53
	Both	5	19.4	8.0	20.26	5	53
Gemcitabine/ nab-paclitaxel /capecitabine/cisplatin (4-week cycle)	Olaparib	2	6.0	6.0	0.00	6	6
	Placebo	2	5.5	5.5	0.71	5	6
	Both	4	5.8	6.0	0.50	5	6
XELOX (3-week cycle)	Olaparib	2	6.0	6.0	2.83	4	8
	Placebo	1	8.0	8.0	-	8	8
	Both	3	6.7	8.0	2.31	4	8
Gemcitabine/epirubicin/ capecitabine/cisplatin (3-week cycle)	Placebo	2	8.0	8.0	2.83	6	10
	Both	2	8.0	8.0	2.83	6	10
Oxaliplatin (2-week cycle)	Olaparib	1	27.0	27.0	-	27	27
	Placebo	1	13.0	13.0	-	13	13
	Both	2	20.0	20.0	9.90	13	27
5FU/carboplatin (3-week cycle)	Olaparib	1	5.0	5.0	-	5	5
	Both	1	5.0	5.0	-	5	5
Etoposide/carboplatin (3-week cycle)	Olaparib	1	6.0	6.0	-	6	6
	Both	1	6.0	6.0	-	6	6
FOLFIRI/cisplatin (2-week cycle)	Placebo	1	8.0	8.0	-	8	8
	Both	1	8.0	8.0	-	8	8
FOLFOX/ nab-paclitaxel (3-week cycle)	Placebo	1	12.0	12.0	-	12	12
	Both	1	12.0	12.0	-	12	12

Table   **Distribution of the number of cycles of first line chemotherapy, including cycles where the platinum was dropped, and the remaining drugs continued (Full Analysis Set; DCO: 15 January 2019)**

Regimen (cycle length)	Treatment group	n	Mean	Median	SD	Min	Max
LV5FU/cisplatin (2-week cycle)	Olaparib	1	8.0	8.0	-	8	8
	Both	1	8.0	8.0	-	8	8
Any regimen	Olaparib	91	10.5	8.0	6.91	3	61
	Placebo	61	10.2	9.0	6.27	4	53
	Both	152	10.4	9.0	6.64	3	61

The regimen listed is the regimen on which the patient started therapy and does not reflect subsequent modifications such as dropping a platinum after 16 weeks.

5FU 5-Fluorouracil; DCO Data cut-off; LV Leucovorin; Max Maximum; Min Minimum; SD Standard deviation.

Source data: IEMT 1934.1.

Table   **Distribution of the number of cycles of first line chemotherapy, platinum-containing regimens, excluding cycles where the platinum was dropped, and the remaining drugs continued (Full Analysis Set; DCO: 15 January 2019)**

Regimen (cycle length)	Treatment group	n	Mean	Median	SD	Min	Max
FOLFIRINOX (2-week cycle)	Olaparib	29	10.9	9.0	9.34	**6**	**58**
	Placebo	18	9.4	9.0	1.69	6	12
	Both	47	10.3	9.0	7.40	6	58
GEMOX (2-week cycle)	Olaparib	4	8.8	8.0	1.50	8	11
	Placebo	1	6.0	6.0	-	6	6
	Both	5	8.2	8.0	1.79	6	11
Gemcitabine/ cisplatin (4-week cycle)	Olaparib	2	15.5	15.5	12.02	7	24
	Placebo	3	22.0	8.0	26.89	5	53
	Both	5	19.4	8.0	20.26	5	53
Gemcitabine/ nab-paclitaxel/ capecitabine/cisplatin (4-week cycle)	Olaparib	2	6.0	6.0	0.00	6	6
	Placebo	2	5.5	5.5	0.71	5	6
	Both	4	5.8	6.0	0.50	5	6
FOLFOX (2-week cycle)	Olaparib	2	4.5	4.5	2.12	3	6
	Placebo	1	12.0	12.0	-	12	12
	Both	3	7.0	6.0	4.58	3	12
Gemcitabine/ epirubicin/ capecitabine/cisplatin (3-week cycle)	Placebo	2	8.0	8.0	2.83	6	10
	Both	2	8.0	8.0	2.83	6	10
Oxaliplatin (2-week cycle)	Olaparib	1	27.0	27.0	-	27	27
	Placebo	1	13.0	13.0	-	13	13
	Both	2	20.0	20.0	9.90	13	27
	Olaparib	1	5.0	5.0	-	5	5

Table   **Distribution of the number of cycles of first line chemotherapy, platinum-containing regimens, excluding cycles where the platinum was dropped, and the remaining drugs continued (Full Analysis Set; DCO: 15 January 2019)**

Regimen (cycle length)	Treatment group	n	Mean	Median	SD	Min	Max
5FU/carboplatin (3-week cycle)	Both	1	5.0	5.0	-	5	5
FOLFIRI/cisplatin (2-week cycle)	Placebo	1	8.0	8.0	-	8	8
	Both	1	8.0	8.0	-	8	8
LV5FU/cisplatin (2-week cycle)	Olaparib	1	8.0	8.0	-	8	8
	Both	1	8.0	8.0	-	8	8
Any regimen	Olaparib	42	10.5	8.0	8.68	3	58
	Placebo	29	10.4	9.0	8.49	5	53
	Both	71	10.5	8.0	8.54	3	58

This does not include subsequent cycles where the platinum was dropped and the remaining drugs continued.

5FU 5-Fluorouracil; DCO Data cut-off; LV Leucovorin; Max Maximum; Min Minimum; SD Standard deviation.

Source data: IEMT 1934.2.

There were 32 (20.8%) patients (24 [26.1%] in the olaparib arm and 8 [12.9%] in the placebo arm) who received previous non disease-related chemotherapy treatment, and 14 (9.1%) patients (10 [10.9%] in the olaparib arm and 4 [6.5%] in the placebo arm) who received previous non disease-related "other" treatments (eg, hormonal therapy) for any cancer excluding metastatic pancreas cancer.

Table. Distribution of the number of cycles of first-line chemotherapy, complete regimen, sensitivity analysis excluding a Patient with 61 cycles, (Full analysis set), DCO: 15 January 2019

Regimen (cycle length)	Treatment group	n	Mean	Median	StdDev	Min	Max
FOLFIRINOX (2-week cycle)	Olaparib	70	10.2	9.0	3.78	5	23
	Placebo	44	9.9	9.0	2.99	4	21
	Both	114	10.1	9.0	3.49	4	23

The regimen listed is the regimen on which the patient started therapy and does not reflect subsequent modifications such as dropping a platinum after 16 weeks.
DCO data cut-off; Max maximum; Min minimum; StdDev standard deviation.
Source data: Table 2185.1.

Table Distribution of the number of cycles of first-line chemotherapy platinum treatment, sensitivity analysis excluding a Patient with 58 cycles, (Full analysis set), DCO: 15 January 2019

Regimen (cycle length)	Treatment group	n	Mean	Median	StdDev	Min	Max
FOLFIRINOX (2-week cycle)	Olaparib	28	9.2	**9.0**	2.32	**6**	**14**
	Placebo	18	9.4	**9.0**	1.69	**6**	**12**
	Both	46	9.3	9.0	2.07	6	14

This does not include subsequent cycles where the platinum was dropped, and the remaining drugs continued.
DCO data cut-off; Max maximum; Min minimum; StdDev standard deviation.
Source data: Table 2185.2.

Table. Summary of length of time (days) between end of first-line chemotherapy and start of study treatment, (Full analysis set), DCO: 15 January 2019

Regimen (cycle length)	Treatment group	n	Mean	StdDev	Median	Min	Max
Complete regimen	Olaparib	90	**40.7**	32.79	35.0	16	337[a]
	Placebo	61	**38.4**	11.85	36.0	16	93[a]
	Both	151	39.8	26.37	35.0	16	337
Platinum treatment	Olaparib	42	**72.4**	75.92	36.5	25	337
	Placebo	28	**45.7**	38.14	36.5	16	232
	Both	70	61.7	64.56	36.5	16	337

[a] Four patients who randomized 8 weeks after their last dose of first-line regimen (Day 62, Day 71, Day 93 and Day 337) and reported as protocol deviation. Length of time was calculated in days as : Study treatment start date – first-line chemotherapy end date + 1. DCO Data cut-off; Max Maximum; Min Minimum; StdDev Standard deviation. Source data: Table 2053.1

Concomitant medication after study entry

The most commonly received concomitant medications were generally received by a higher proportion of patients in the olaparib group.

In total, 4 (4.3%) patients in the olaparib arm and 2 (3.2%) patients in the placebo arm received disallowed concomitant medication (**Table *10.* Disallowed concomitant medications during study treatment (FAS)**). The use of disallowed concomitant medication did not raise concerns about the conduct of the study.

Table 13. Disallowed concomitant medications during study treatment (FAS)

ATC classification Generic term	Number (%) of patients		
	Olaparib 300 mg bd (N=92)	Placebo (N=62)	Total (N=154)
Number of patients with disallowed concomitant medication	4 (4.3)	2 (3.2)	6 (3.9)
Centrally acting sympathomimetics	1 (1.1)	1 (1.6)	2 (1.3)
Modafinil	1 (1.1)	1 (1.6)	2 (1.3)
Imidazole and triazole derivatives	1 (1.1)	1 (1.6)	2 (1.3)
Ketoconazole	1 (1.1)	1 (1.6)	2 (1.3)
Anti-oestrogens	1 (1.1)	0	1 (0.6)
Tamoxifen citrate	1 (1.1)	0	1 (0.6)
Macrolides	1 (1.1)	0	1 (0.6)
Clarithromycin	1 (1.1)	0	1 (0.6)

A patient can have 1 or more Generic term reported under a given ATC text.

Includes medication 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. Also includes medication with an onset date prior to the date of first dose but continued after the date of first dose.

Medications coded using WHO coding.

ATC anatomical therapeutic classification; bd twice daily; FAS Full Analysis Set; WHO World Health Organisation.
Data derived from Table 11.1.8.

Treatment compliance

Compliance was derived from the actual administration days (total planned days - days of interruption) divided by the total planned administration days (last dose date - first dose date + 1); mean treatment compliance was high in both treatment arms; 96.3% in the olaparib arm and 97.9% in the placebo arm.

Numbers analysed

The analysis sets and the number of patients in each analysis set are summarised in **Table 11. Analysis sets**.

Table 14. Analysis sets

	Number (%) of patients		
	Olaparib 300 mg bd	Placebo	Total
Patients randomised	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 randomised to placebo but evaluated in olaparib treatment arm for safety, as this patient was exposed to at least 1 cycle of olaparib.
b. An individual patient could have been excluded for more than 1 reason.

bd twice daily; EORTC European Organisation 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. Data derived from Table 11.1.3.c

Outcomes and estimation

The DCO for the analysis of PFS (15 January 2018) took place when 104 PFS events (67.5% maturity) had occurred, approximately 48 months after the first patient was randomised. At this time 71 deaths had also occurred and were included in a planned OS interim analysis. At this DCO, all efficacy, quality of life (QoL) and safety variables were analysed, as appropriate, based on the amount of data available at that time. No further analyses of PFS are planned unless requested by Health Authorities.

Primary outcome variable: progression-free survival by BICR

PFS (based on BICR) was the primary variable for the study and was analysed at the primary DCO (15 January 2019) based on the FAS analysis population. The progression status based on BICR at the time of PFS analysis is presented in **Table *12*. Progression status (BICR) at the time of progression-free survival**

At the time of DCO there were 104 PFS events (67.5% maturity) with a higher proportion on the placebo arm than the olaparib arm (71.0% placebo vs 65.2% olaparib, respectively). Five of the PFS events were deaths in the absence of RECIST progression (excluding censoring due to 2 or more missed RECIST visits); all of which occurred in the olaparib arm. Approximately an equal percentage of patients in both arms had PD due to progression of a target or non-target lesion, or developing new lesions. Overall, 30 (32.6%) patients in the olaparib arm vs 12 (19.4%) patients in the placebo arm were progression-free at the time of analysis. Thirty (32.6%) patients in the olaparib arm and 8 (12.9%) patients randomised to placebo were still taking their assigned study treatment at the time of DCO.

Table 15. Progression status (BICR) at the time of progression-free survival

Progression status	Type of event	Number (%) of patients	
		Olaparib 300 mg bd (N=92)	Placebo (N=62)
Progression	Total	60 (65.2)	44 (71.0)
	RECIST progression	55 (59.8)	44 (71.0)
	Target lesions[a]	23 (25.0)	18 (29.0)
	Non-target lesions[a]	23 (25.0)	17 (27.4)
	New lesions[a]	24 (26.1)	20 (32.3)
	Death in the absence of progression	5 (5.4)	0
Censored patients	Total[b]	32 (34.8)	18 (29.0)
	Censored death[c]	1 (1.1)	3 (4.8)
	Progression-free at time of analysis[d]	30 (32.6)	12 (19.4)
	Lost to follow-up	0	1 (1.6)
	Withdrawn consent	1 (1.1)	0
	Discontinued study[e]	0	2 (3.2)

a. Target lesions, non-target lesions and new lesions are not necessarily mutually exclusive categories.
b. Patients who had not progressed or had died at the time of analysis, or who progressed or died after 2 or more missed visits, were censored at the last evaluable RECIST assessment, or Day 1 if there were no evaluable visits.
c. Death which occurred after 2 or more missed visits in the absence of RECIST progression.
d. Includes patients, known to be alive and censored at the last evaluable RECIST assessment, or alive with no evaluable baseline or post-baseline RECIST assessment (and censored at Day 1).
   e. Does not include patients that withdrew consent or were lost to follow-up. This analysis is based on blinded independent central review of radiological scans.
  bd twice daily; BICR blinded independent central review; FAS Full Analysis Set; RECIST Response Evaluation Criteria in Solid Tumours.

  Data derived from Table 11.2.1.1.

As shown in **Table 13. Summary of analysis of progression-free survival based on BICR (FAS)** POLO met its primary endpoint, demonstrating a clinically meaningful and statistically significant improvement in PFS as assessed by BICR for patients treated with olaparib 300 mg bd maintenance therapy compared with placebo. There was a 47% reduction in the risk of disease progression or death

with a median PFS of 7.4 months for olaparib vs 3.8 months for placebo. This equates to a prolongation of median progression-free interval of 3.6 months with olaparib versus placebo.

Progression occurred on treatment for 90.0% of the patients on olaparib compared with 93.2% of the patients on placebo.

Table 16. Summary of analysis of progression-free survival based on BICR (FAS)

	Olaparib 300 mg bd (N=92)	Placebo (N=62)
n (%) of events	60 (65.2)	44 (71.0)
Treatment effect		
Median PFS (95% CI) [months][a]	7.4 (4.14, 11.01)	3.8 (3.52, 4.86)
HR (95% CI)[b]	0.531 (0.346, 0.815)	
2-sided p-value[a]	0.0038	
Progression free at 6 months (%)[a]	53.0	23.0
Progression free at 12 months (%)[a]	33.7	14.5
Progression free at 18 months (%)[a]	27.6	9.6
Progression free at 24 months (%)[a]	22.1	9.6
Progression free at 36 months (%)[a]	17.7	NC
Progression free at 48 months (%)[a]	NC	NC

a.   Calculated using the KM technique.
b.   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.
  bd twice daily; BICR blinded independent central review; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; KM Kaplan-Meier; NC not calculable; PFS progression-free survival.

  Data derived from Table 11.2.1.1.

The KM plot for the BICR-assessed PFS by modified RECIST v1.1 is presented in Figure 3.

Figure 4. Progression-free survival by BICR, Kaplan-Meier plot (FAS)
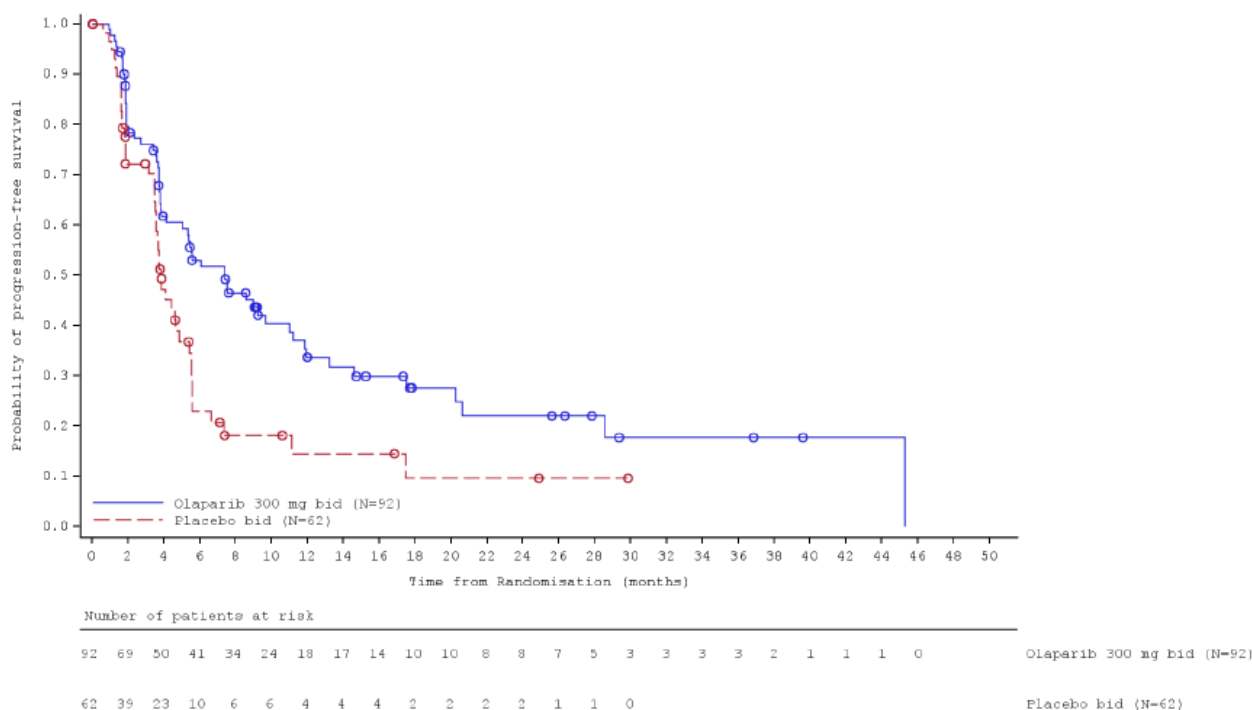
BICR blinded independent central review; FAS Full Analysis Set. Data derived from
Figure 11.2.1.2.

Sensitivity analysis of progression-free survival

Table 14. Sensitivity analysis of progression-free survival by investigator assessment (FAS)
and **Table 16. Other sensitivity analysis of progression-free survival (FAS).** present the results of
the sensitivity analyses of PFS performed at DCO (evaluation time bias, attrition bias and ascertainment
bias [hereafter referred to as investigator assessment]). Analysis of deviation bias was not performed as
specified in the protocol due to ≤10% of patients having the specified deviations.

Sensitivity analysis of progression-free survival by investigator assessment

The sensitivity analysis of PFS by investigator assessment confirmed the analysis by BICR assessment
with a HR of 0.51 (95% CI 0.34, 0.78; Table 18). The median PFS of 6.3 months for olaparib vs 3.7
months for placebo, was consistent with that of the PFS analysis by BICR. The KM plot for PFS by
investigator assessment is presented in Figure 4.

Table 17. Sensitivity analysis of progression-free survival by investigator assessment (FAS)

	Olaparib 300 mg bd (N=92)	Placebo (N=62)
Investigator assessment		
n (%) of events	54 (58.7)	48 (77.4)
Median PFS (months)[a]	6.3	3.7
HR (95% CI)[b]	0.514 (0.339, 0.780)	
2-sided p-value	0.0017	

a.   Progression was determined by investigator assessed RECIST data.
b.   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.
 bd twice daily; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; PFS progression-free survival; RECIST Response
 Evaluation Criteria in Solid Tumours.
 Data derived from Table 11.2.2.1.

Figure 5. Progression-free survival by investigator assessment, Kaplan-Meier plot (FAS)
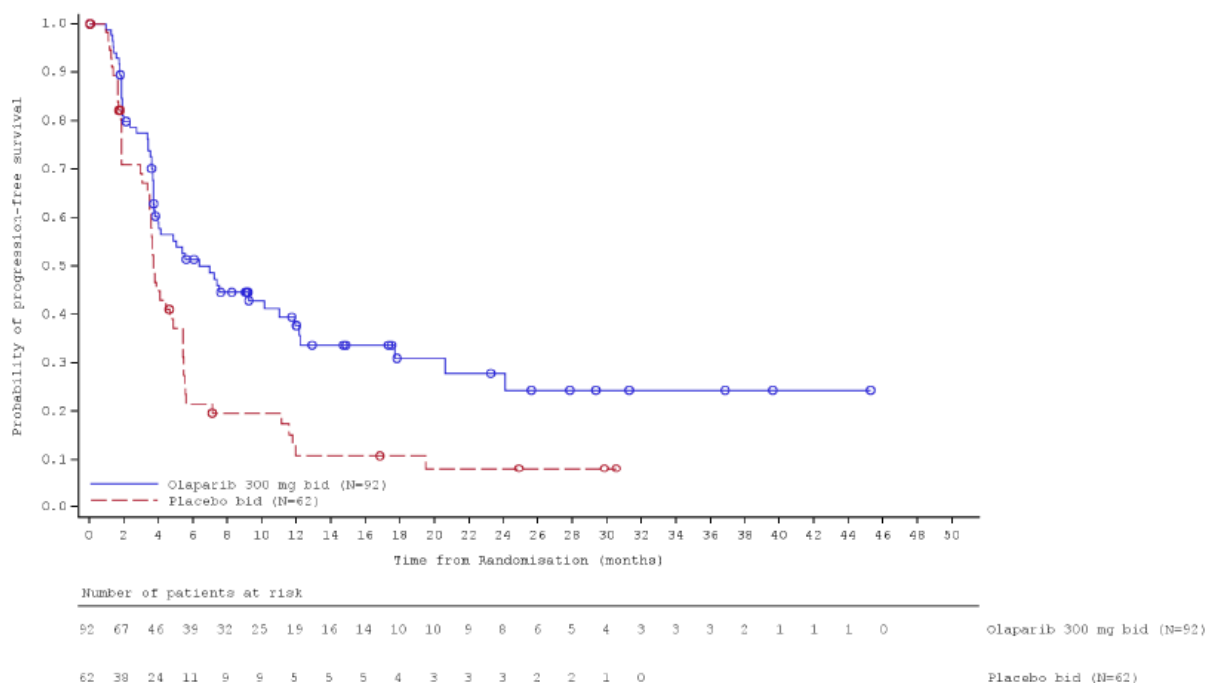
FAS Full Analysis Set.

Data derived from Figure 11.2.2.7.

Disagreement between investigator and BICR on RECIST progression

Disagreement between investigator and BICR assessment of RECIST v1.1 progression is presented in **Table 15. Disagreement between investigator and central reviews of RECIST v1.1 progression (FAS)**. Overall, 28 (18.2%) patients were discordant between investigator and BICR based progression ([6+12+7+3]/154). As the difference between treatment arms in early discrepancy rate was positive and the difference between treatment arms in late discrepancy rate was negative, there was no suggestion of bias in the investigator favouring the olaparib arm.

Table 18. Disagreement between investigator and central reviews of RECIST v1.1 progression (FAS)

	Number (%) of patients		Difference
	Olaparib 300 mg bd (N=92)	Placebo (N=62)	Olaparib 300 mg bd - Placebo
RECIST progression[a] declared by:			
Investigator and central review	48 (52.2)	41 (66.1)	NA
Progression date agreement (within 2 weeks)	30 (32.6)	26 (41.9)	NA
Progression date ≥2 weeks earlier by central review than by investigator	9 (9.8)	13 (21.0)	NA
Progression date ≥2 weeks earlier by investigator than by central review	9 (9.8)	2 (3.2)	NA
Investigator but not central review	6 (6.5)	7 (11.3)	NA
Central review but not investigator	12 (13.0)	3 (4.8)	NA

No progression by both	26 (28.3)	11 (17.7)	NA
Early discrepancy rate[b]	0.28	0.19	0.09
Late discrepancy rate[c]	0.58	0.64	-0.06

a. Patients who had not progressed or died at the time of analysis, or who had progressed or died after 2 or more missed visits, were censored at the latest evaluable RECIST assessment, or Day 1 if there were no evaluable visits. Patients with a RECIST progression within 2 visits of baseline who did not have any evaluable visits or did not have a baseline assessment were censored at Day 1.

b. Early discrepancy rate is the frequency of investigator declared progressions before central review as a proportion of all investigator progressions.

c. Late discrepancy rate is the frequency of investigator declared progressions after central review as a proportion of all discrepancies. Modified RECIST v1.1.

bd twice daily; FAS Full Analysis Set; NA not applicable; RECIST Response Evaluation Criteria in Solid Tumours. Data derived from Table 11.2.2.4.

Other sensitivity analyses of progression-free survival

Table 16. Other sensitivity analysis of progression-free survival (FAS). presents the results of the other sensitivity analyses of PFS performed at the PFSDCO (evaluation time bias and attrition bias).

All other sensitivity analyses (evaluation time bias and attrition bias) were consistent with the BICR assessment of PFS confirming the robustness of the primary analysis.

Table 19. Other sensitivity analysis of progression-free survival (FAS).

	Number (%) of patients with events	Median PFS (months)[a]	HR[b]	95% CI[b]	p-value
Sensitivity analysis: evaluation time bias	Olaparib: 60 (65.2)	6.5	0.553	0.362, 0.846	0.0063
	Placebo: 44 (71.0)	3.0			
Sensitivity analysis: attrition bias	Olaparib: 58 (63.0)	7.5	0.505	0.326, 0.783	0.0023
	Placebo: 43 (69.4)	3.8			

a. Progression was determined by BICR assessment.

b. 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. BICR blinded independent central review; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; PFS progression-free survival. Data derived from Table 11.2.2.1.

Days between RECIST assessments

There was good compliance with the CSP-required RECIST assessments scheduled Q8W (±1 week) for the first 40 weeks and subsequently Q12W (±1 week) relative to the date of randomisation, until objective disease progression as defined by modified RECIST v1.1.

Secondary outcome variables

Overall survival

At the time of the DCO, 53.3% of olaparib-treated patients and 43.5% of patients in the placebo arm were alive and in survival follow-up. At the time of the PFS analysis, the interim OS data were 46% mature (71/154 events; **Table 17. Summary of overall survival (FAS)**). The median OS was 18.9 months in the olaparib arm and 18.1 months in the placebo arm. The HR suggested no OS detriment for olaparib-treated patients. Based on KM estimates, in the olaparib arm, the percentage of patients who remained alive were 70.0% at 12 months, 54.0% at 18 months, 37.9% at 24 months and 34.7% at 36 months

(n=46, 28, 14 and 4, respectively), compared with 66.5%, 51.6%, 35.3% and 24.7% in the placebo arm (n=29, 18, 8 and 1, respectively).

The KM plot for OS is presented in **Figure 5. Overall survival, Kaplan-Meier plot (FAS)**Final OS analysis will be conducted when approximately 106 deaths have occurred (69% maturity).

The percentage of patients whose subsequent therapy included a PARP inhibitor was 14.5% (9/62) patients in the placebo arm and 1.1% (1/92) patients in the olaparib arm.

Table 20. Summary of overall survival (FAS)

	Olaparib 300 mg bd (N=92)	Placebo (N=62)
n (%) of deaths[a]	41 (44.6)	30 (48.4)
Treatment effect		
Median OS (95% CI) [months][b]	18.9 (14.85, 26.15)	18.1 (12.62, 26.12)
HR (95% CI)[c]	0.906 (0.563, 1.457)	
2-sided p-value[c]	0.6833	
OS at 6 months (%)[b]	87.5	92.9
OS at 12 months (%)[b]	70.0	66.5
OS at 18 months (%)[b]	54.0	51.6
OS at 24 months (%)[b]	37.9	35.3
OS at 36 months (%)[b]	34.7	24.7
OS at 48 months (%)[b]	NC	NC

a. OS was defined as time from randomisation until death.

[a]   Calculated using the KM technique.

[b]   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.

bd twice daily; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; KM Kaplan-Meier; NC not calculable; OS overall survival. Data derived from Table 11.2.4.1.

Figure 6. Overall survival, Kaplan-Meier plot (FAS)

FAS Full Analysis Set. Data derived from Figure 11.2.4.4.
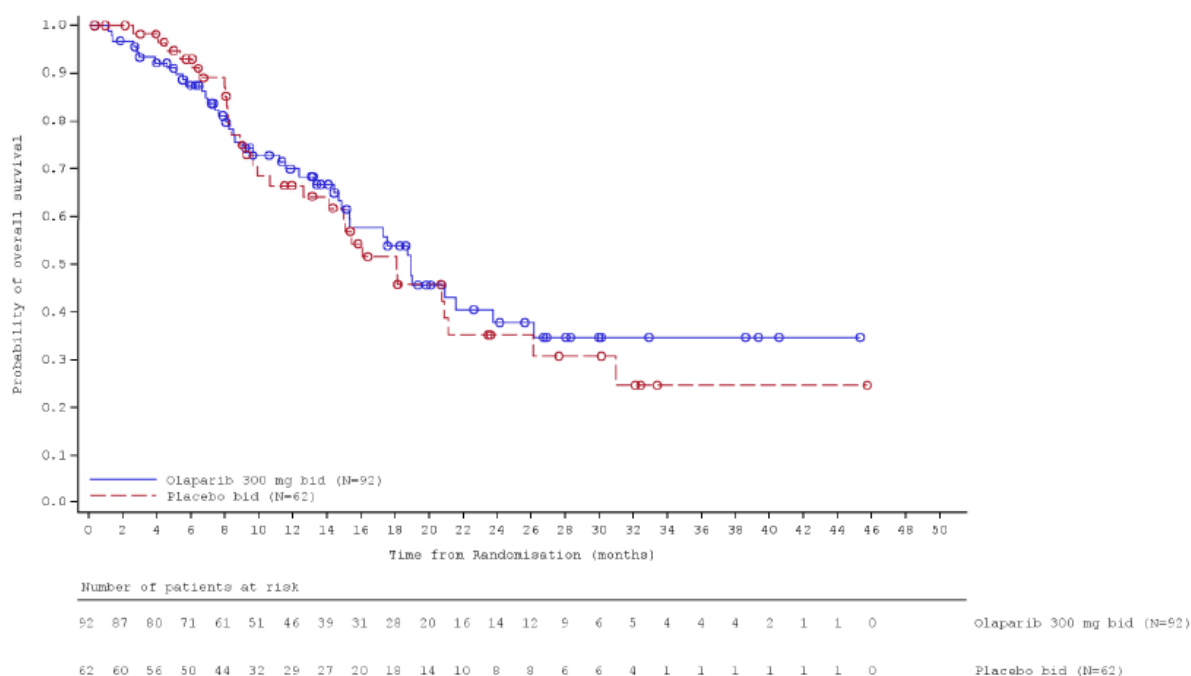
Time from randomisation to second progression

The date of second progression was recorded by the investigator and defined according to local standard clinical practice and could involve any of objective radiological or symptomatic progression or death. At the time of DCO there were 71 PFS2 events (46% maturity) with a higher proportion in the placebo arm than the olaparib arm. Overall, 55.4% of patients in the olaparib arm vs 51.6% of patients in the placebo arm were second progression free at the time of analysis (includes censored patients, patients lost to follow-up and patients who discontinued from study).

	Olaparib 300 mg bid (N=92)	Placebo bid (N=62)
Second progression, n (%)	41 (44.6)	30 (48.4)
Symptomatic progression	1 (1.1)	1 (1.6)
Objective radiological progression	25 (27.2)	21 (33.9)
Other progression	0	1 (1.6)
Death [a]	15 (16.3)	7 (11.3)
No second progression, n (%)	51 (55.4)	32 (51.6)
Censored second progression [b]	2 (2.2)	4 (6.5)
Censored death in the absence of any progression [c]	2 (2.2)	1 (1.6)
Censored death after first progression [d]	2 (2.2)	0
Progression-free at time of analysis [e]	32 (34.8)	10 (16.1)
Subject with first progression [f]	11 (12.0)	12 (19.4)
Lost to follow-up	0	2 (3.2)
Withdrawn consent	2 (2.2)	0
Discontinued the study for other reasons [g]	0	3 (4.8)

The median PFS2 in the olaparib arm was 13.2 months compared with 9.2 months in the placebo arm; a median difference of 4 months. While there was no statistically significant difference, the delay in time from randomisation to second progression or death (PFS2) suggested a trend in favour of olaparib treatment (**Table *18*. Summary of second progression-free survival (FAS)**). The KM plot for PFS2 is presented in **Figure *6*. Second progression-free survival, Kaplan-Meier plot (FAS)**.

Table 21. Summary of second progression-free survival (FAS)

	Olaparib 300 mg bd (N=92)	Placebo (N=62)
n (%) of events[a]	41 (44.6)	30 (48.4)
Treatment effect		
Median PFS2 (95% CI) [months][b]	13.2 (7.75, 26.15)	9.2 (7.62, 13.54)
HR (95% CI)[c]	0.755 (0.464, 1.230)	
Nominal 2-sided p-value[c]	0.2597	
Second progression free at 6 months (%)[b]	77.5	78.0
Second progression free at 12 months (%)[b]	53.7	45.1
Second progression free at 18 months (%)[b]	44.4	25.1
Second progression free at 24 months (%)[b]	36.4	18.8
Second progression free at 36 months (%)[b]	31.2	NC
Second progression free at 48 months (%)[b]	NC	NC

a.   PFS2 was defined as time from randomisation until date of second RECIST progression or death.
  b.   Calculated using the KM technique.
  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.
bd twice daily; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; KM Kaplan-Meier; NC not calculable; PFS2 time from randomisation to second progression; RECIST Response Evaluation Criteria in Solid Tumours. Data derived from Table 11.2.5.1.

Figure 7. Second progression-free survival, Kaplan-Meier plot (FAS)
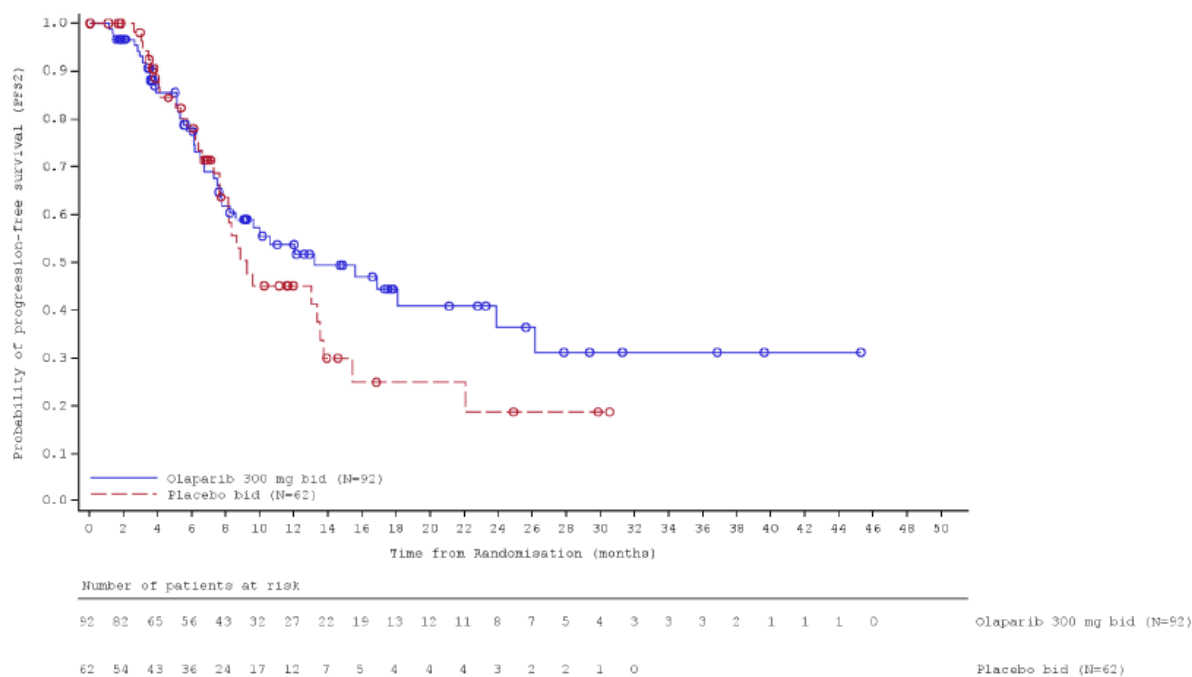
FAS Full Analysis Set; PFS2 time from randomisation to second progression. Data derived from Figure 11.2.5.2.

Time from randomisation to first subsequent therapy or death

The median TFST in the olaparib arm was 8.6 months compared with 5.7 months in the placebo arm (**Table 19. Summary of time from randomisation to first subsequent cancer therapy or death (FAS)**). Although not controlled for multiplicity, the delay in TFST was statistically significant in the olaparib arm compared with the placebo arm. This was consistent with the benefit observed in the PFS analysis (Section 7.1.1). The KM plot for TFST is presented in **Figure 7. Time from randomisation to first subsequent cancer therapy or death, Kaplan-Meier plot (FAS)**

Table 22. Summary of time from randomisation to first subsequent cancer therapy or death (FAS)

	Olaparib 300 mg bd (N=92)	Placebo (N=62)
n (%) of events[a]	58 (63.0)	46 (74.2)
Treatment effect		
Median TFST (95% CI) [months][b]	8.6 (6.21, 12.45)	5.7 (4.17, 6.34)
HR (95% CI)[c]	0.496 (0.324, 0.760)	
Nominal 2-sided p-value[c]	0.0013	

a.   TFST was defined as the time from randomisation to the earlier of first subsequent cancer therapy start date following study treatment discontinuation, or death.

b.   Calculated using the KM technique.

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.

Figure 8. Time from randomisation to first subsequent cancer therapy or death, Kaplan-Meier plot (FAS)

FAS Full Analysis Set; TFST time to first subsequent therapy or death. Data derived from
Figure 11.2.6.2.

Time from randomisation to second subsequent therapy or death

The median TSST in the olaparib arm was 13.2 months compared with 9.2 months in the placebo arm (**Table *20.* Summary of time from randomisation to second subsequent cancer therapy or death (FAS)**). The delay in TSST suggests a positive trend for the olaparib arm compared with the placebo arm.The KM plot for TSST is presented in **Figure 8. Time from randomisation to second subsequent cancer therapy or death, Kaplan-Meier plot (FAS)**.
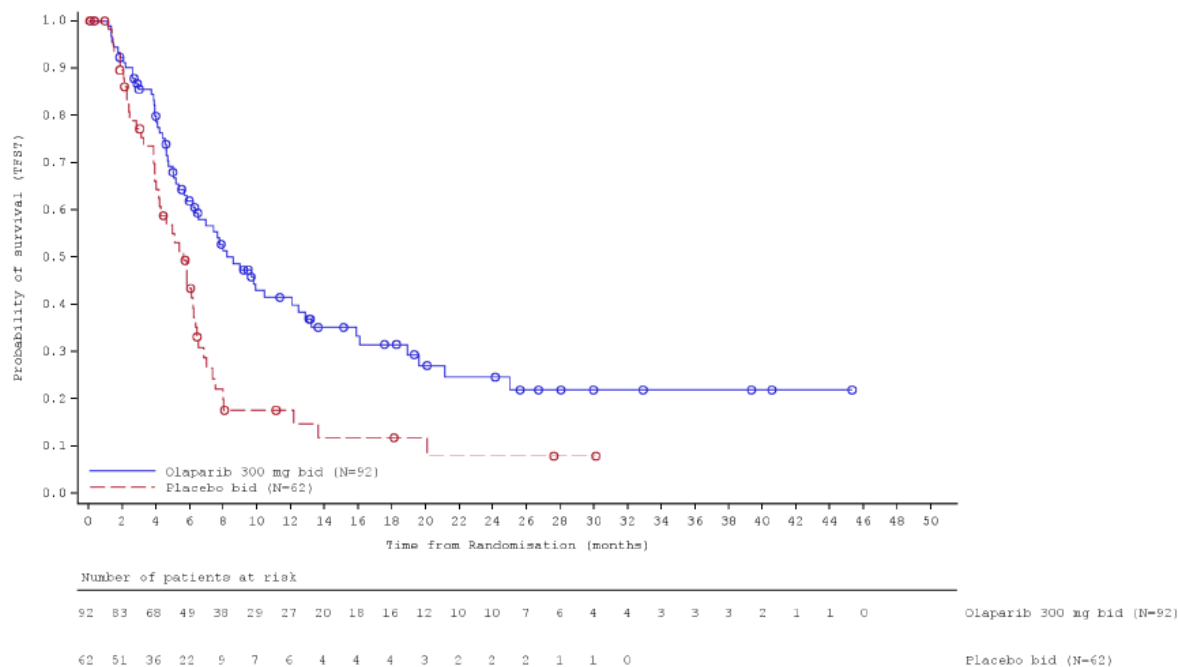
Table 23. Summary of time from randomisation to second subsequent cancer therapy or death (FAS)

	Olaparib 300 mg bd (N=92)	Placebo (N=62)
n (%) of events[a]	50 (54.3)	39 (62.9)
Treatment effect		
Median TSST (95% CI) [months][b]	13.2 (8.84, 20.04)	9.2 (8.34, 13.14)
HR (95% CI)[c]	0.678 (0.437, 1.051)	
Nominal 2-sided p-value[c]	0.0825	

a.   TSST was defined as the time from randomisation to the earlier of second subsequent cancer therapy start date following study treatment discontinuation, or death.

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.

bd twice daily; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; KM Kaplan-Meier; TSST time to second subsequent therapy or death. Data derived from Table 11.2.7.1.1.

Figure 9. Time from randomisation to second subsequent cancer therapy or death, Kaplan-Meier plot (FAS)

FAS Full Analysis Set; TSST time to second subsequent therapy or death. Data derived from Figure 11.2.7.2.

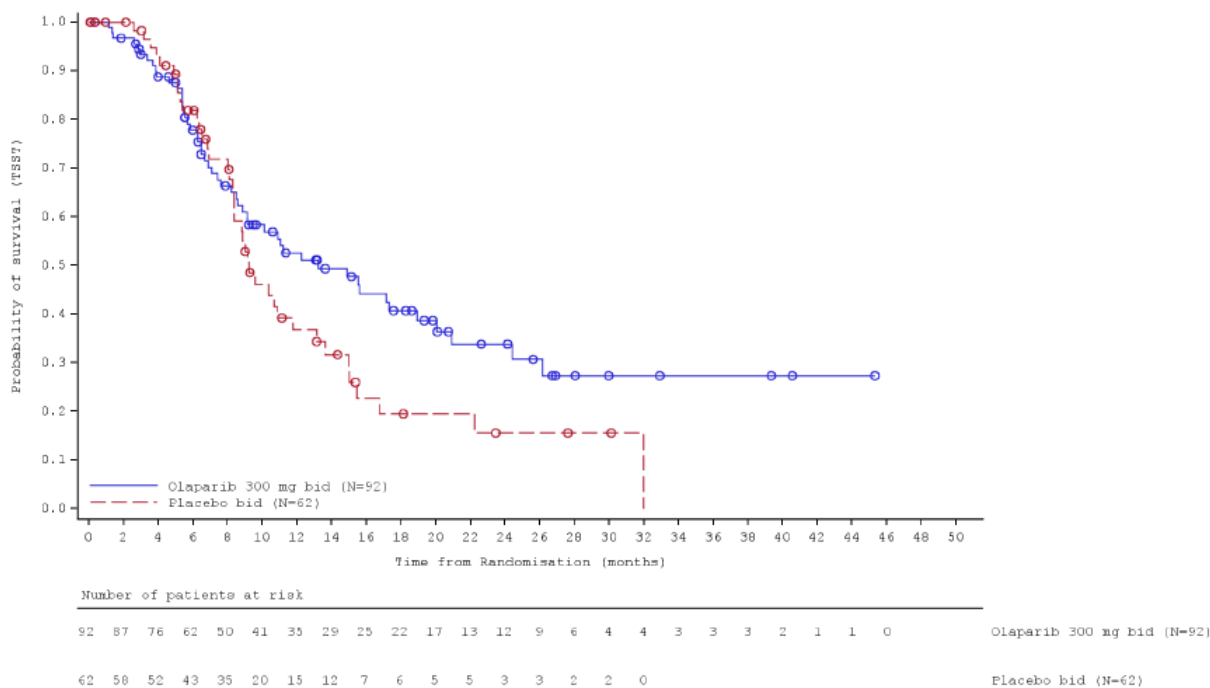**Time from randomisation to study discontinuation or death**

The median TDT in the olaparib arm was 7.2 months compared with 3.8 months in the placebo arm (**Table 21. Summary of time from randomisation to study treatment discontinuation or death (FAS)**). Although not controlled for multiplicity, the delay in TDT was statistically significant in the olaparib arm compared with the placebo arm. This is consistent with the benefit observed in the PFS analysis. The KM plot for TDT is presented in **Figure 9. Time from randomisation to study treatment discontinuation or death, Kaplan-Meier plot (FAS)**.

Table 24. Summary of time from randomisation to study treatment discontinuation or death (FAS)

	Olaparib 300 mg bd (N=92)	Placebo (N=62)
n (%) of events[a]	60 (65.2)	53 (85.5)
Treatment effect		
Median TDT (95% CI) [months][b]	7.2 (5.52, 10.84)	3.8 (3.55, 4.80)
HR (95% CI)[c]	0.446 (0.297, 0.670)	
Nominal 2-sided p-value[c]	0.0001	

a.   Time to treatment discontinuation or death was defined as the time from randomisation to the earlier of the date of study treatment discontinuation or death.
b.   Calculated using the KM technique.
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.

Figure 10. Time from randomisation to study treatment discontinuation or death, Kaplan-Meier plot (FAS)
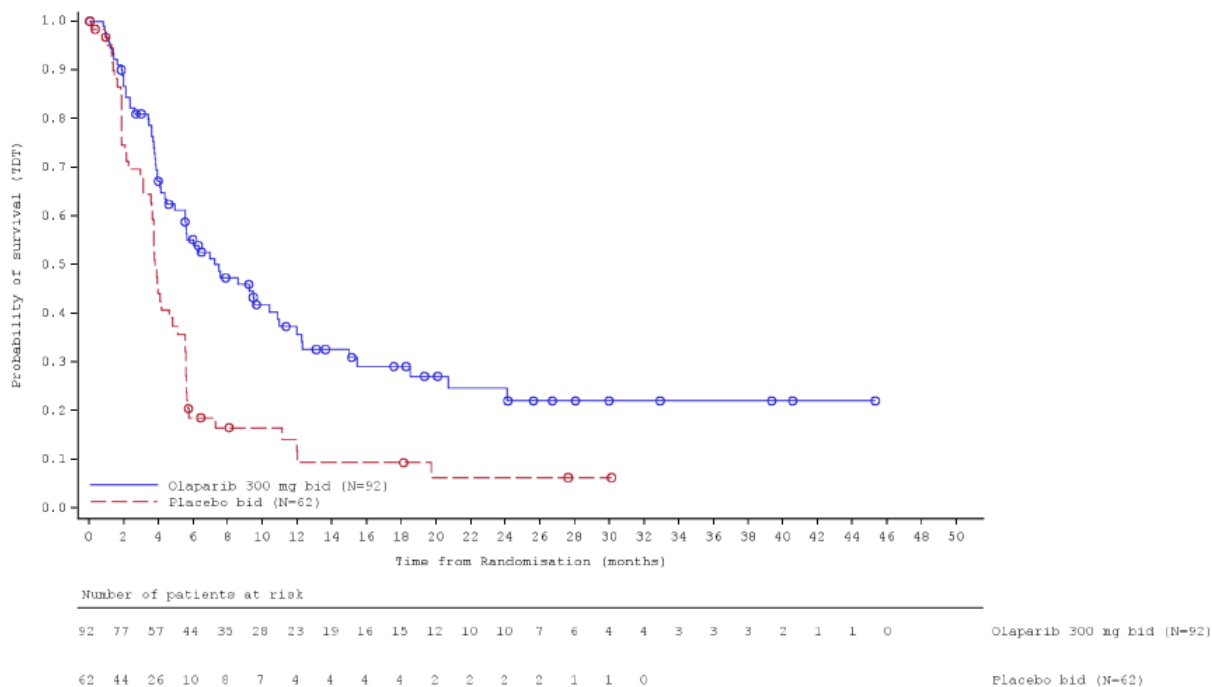
FAS Full Analysis Set; TDT time to study treatment discontinuation or death. Data derived from Figure 11.2.8.2.

Subsequent therapies

Fewer patients in the olaparib arm compared with the placebo arm received 1 or more subsequent cancer therapies, up to the time of last DCO (**Table 22. Subsequent cancer therapies (FAS)**). The most commonly reported treatments included platinum-containing regimens (see Table 11.1.14.1).

Table 25. Subsequent cancer therapies (FAS)

	Number (%) of patients		
	Olaparib 300 mg bd (N=92)	**Placebo (N=62)**	**Total (N=154)**
Total[a]	45 (48.9)	46 (74.2)	91 (59.1)
Platinum chemotherapy	20 (21.7)	18 (29.0)	38 (24.7)
PARP inhibitor	1 (1.1)	9 (14.5)	10 (6.5)
Other chemotherapy regimen (including platinum combination regimens)[b]	45 (48.9)	45 (72.6)	90 (58.4)
Gemcitabine/cisplatin	1 (1.1)	1 (1.6)	2 (1.3)
Gemcitabine/oxaliplatin	1 (1.1)	0	1 (0.6)
FOLFIRINOX[c]	17 (18.5)	18 (29.0)	35 (22.7)

FOLFOX[d]	2 (2.2)	5 (8.1)	7 (4.5)
Other investigational agents	2 (2.2)	3 (4.8)	5 (3.2)
Hormonal agent	0	0	0

a.   Subsequent therapies could be reported as regimens or as individual drugs and in some instances are reported both ways.
 b.   "Other chemotherapy regimen" included platinum-based combinations and non-platinum-containing chemotherapy regimens. The platinum-based combinations in this category are presented.
 c.   FOLFIRINOX: folinic acid/fluorouracil/irinotecan/oxaliplatin.
 d.   FOLFOX: folinic acid/fluorouracil/oxaliplatin.
 bd twice daily; FAS Full Analysis Set; PARP polyadenosine 5'diphosphoribose polymerase. Data derived from Table 11.1.14.1.

Subsequent PARP inhibitors were received by 1 (2.2%) of the 45 olaparib treated patients who received a subsequent therapy, and 9 (19.6%) of the 46 placebo treated patients who received a subsequent therapy. PARP inhibitors were received as the first subsequent therapy in 0 patients in the olaparib arm and 2 patients in the placebo arm (**Table 23. Subsequent PARP inhibitors by line of subsequent therapy (FAS)**).

Table 26. Subsequent PARP inhibitors by line of subsequent therapy (FAS)

	Number (%) of patients		
	Olaparib 300 mg bd (N=92)	Placebo (N=62)	Total (N=154)
Received PARP inhibitor	1 (1.1)	9 (14.5)	10 (6.5)
Second-line	0	2 (3.2)	2 (1.3)
Third-line	0	6 (9.7)	6 (3.9)
Fourth-line	0	1 (1.6)[a]	1 (0.6)
Fifth-line	1 (1.1)	1 (1.6)	2 (1.3)
Patients in placebo arm who subsequently received olaparib		7 (11.3)	7 (4.5)

  a   Patient was incorrectly recorded on the eCRF as receiving a PARP inhibitor as both third- and fourth-line treatment, see Appendix 12.2.4.12.5 and Appendix 12.2.6.6.2.

bd twice daily; eCRF electronic case report form; FAS Full Analysis Set; PARP polyadenosine 5'diphosphoribose polymerase. Data derived from Table 11.1.15.

Best objective response and objective response rate

BoR based on BICR data is summarised in **Table 24. Best overall response (BICR) (FAS)**. Of the patients in the FAS, a BoR (either CR or PR) by BICR was achieved by 19.6% of patients in the olaparib arm vs 9.7% of patients in the placebo arm. Of the patients who had a response, 2/18 (11.1%) patients in the olaparib arm experienced CR compared with 0 patients in the placebo arm; 16/18 (88.9%) patients in the olaparib arm and 6/6 (100%) patients in the placebo arm had PR.

Results for BoR based on investigator assessment were consistent with those based on BICR assessment.

Table 27. Best overall response (BICR) (FAS)

Response status	Best objective response	Number (%) of patients	
		Olaparib 300 mg bd (N=92)	Placebo (N=62)
Response	Total	18 (19.6)	6 (9.7)

	CR[a]	2 (2.2)	0
	PR[a]	16 (17.4)	6 (9.7)
Non-response	Total	74 (80.4)	56 (90.3)
	SD ≥7 weeks	45 (48.9)	34 (54.8)
	Progression	20 (21.7)	17 (27.4)
	RECIST progression	19 (20.7)	17 (27.4)
	Death	1 (1.1)	0
	No evidence of disease[b]	5 (5.4)	0
	Not evaluable	4 (4.3)	5 (8.1)
	SD <7 weeks[c]	2 (2.2)	1 (1.6)
	Incomplete baseline assessments	1 (1.1)	0
	No valid baseline assessment	1 (1.1)	4 (6.5)

a. Response did not require confirmation.
b. Applies only to those patients entering the study with no disease at baseline according to BICR.
c. Patients in the not evaluable category with SD <7 weeks recorded as the reason were: one Patient(randomised to the olaparib arm and immediately withdrawn prior to treatment due to disease progression); one Patient (started treatment with olaparib on the 12 June 2018 and had objective disease progression assessed by the Investigator on the 27 July 2018, 45 days after starting treatment); another Patient (started treatment with placebo on the 5 December 2017 and had objective disease progression assessed by the Investigator on the 18 January 2018, 44 days after starting treatment).
Response is determined by BICR. Modified RECIST v1.1. bd twice daily; BICR blinded independent central review; CR complete response; FAS Full Analysis Set; PR partial response; RECIST Response Evaluation Criteria in Solid Tumours; SD stable disease. Data derived from Table 11.2.9.1.1, Appendix 12.2.2.2, Appendix 12.2.1.5 and Appendix 12.2.6.2.2.

ORR based on BICR data for patients in the FAS with measurable disease at baseline was higher for patients in the olaparib arm compared with the placebo arm (23.1% vs 11.5%, respectively; odds ratio=2.30; 95% CI 0.89, 6.76; p=0.1028 [nominal]). Results for ORR based on investigator assessment were consistent with those based on BICR assessment.

The median DoR based on BICR data was longer in the olaparib arm (24.9 months; 95% CI 14.75, not calculable) than in the placebo arm (3.7 months; 95% CI 2.10, not calculable), with a longer median time to onset of response (5.4 months [95% CI 3.65, 5.55] for olaparib and 3.6 months [95% CI 1.58, 7.13] for placebo). Results for DoR based on investigator assessment were consistent with those based on BICR assessment.

Disease control rate

Based on BICR data a greater proportion of patients in the olaparib arm (53.3%) compared with the placebo arm (37.1%) had disease control at 16 weeks following randomisation. Results for disease control at 16 weeks based on investigator assessment were consistent with those based on BICR assessment.

Table 28   POLO D081FC00001: Disease control rate at 16 weeks (BICR assessment; Full Analysis Set)

	Number (%) of patients	
Disease control rate at 16 weeks	**Olaparib 300 mg bd (N=92)**	**Placebo bd (N=62)**
Disease control		
CR	1[a] (1.1)	0
PR	7 (7.6)	4 (6.5)
SD	36 (39.1)	19 (30.6)

Table 28   POLO D081FC00001: Disease control rate at 16 weeks (BICR assessment; Full Analysis Set)

Disease control rate at 16 weeks	Number (%) of patients	
	Olaparib 300 mg bd (N=92)	Placebo bd (N=62)
NED	5 (5.4)	0
No disease control	41 (44.6)	35 (56.5)
Not evaluable/missing	2 (2.2)	4 (6.5)

Efficacy variables in Myriad confirmed gBRCAm patients

Table *25*. Summary of key efficacy outcome variables for Myriad gBRCAm patients (FAS) presents a summary of key efficacy outcome variables for Myriad *gBRCAm* patients.

PFS in the Myriad confirmed *gBRCAm* patients was consistent with the results of the FAS. The KM plot for PFS in the Myriad confirmed *gBRCAm* subset is presented.

Overall, OS, PFS2, TDT, TFST and TSST, outcomes in the Myriad *gBRCAm* subset were consistent with those in the FAS.

Table 29. Summary of key efficacy outcome variables for Myriad gBRCAm patients (FAS)

	Olaparib 300 mg bd (N=89)	Placebo (N=61)
PFS by BICR		
Total number of events (%)	59 (66.3)	44 (72.1)
Median PFS (months)[a]	7.4	3.8
HR (95% CI)[b]	0.550 (0.358, 0.842)	
2-sided p-value[b]	0.0060	
OS		
Total number of events (%)	41 (46.1)	29 (47.5)
Median OS (95% CI) [months][a]	18.9 (14.65, 23.75)	18.1 (14.09, 26.12)
HR (95% CI)[b]	0.973 (0.604, 1.568)	
2-sided p-value[b]	0.9113	
PFS2		
Total number of events (%)	41 (46.1)	30 (49.2)
Median PFS2 (95% CI) [months][a]	13.2 (7.75, 23.85)	9.2 (7.62, 13.54)
HR (95% CI)[b]	0.792 (0.488, 1.287)	
Nominal 2-sided p-value[b]	0.3470	
TDT		
Total number of events (%)	58 (65.2)	52 (85.2)
Median TDT (95% CI) [months][a]	7.0 (4.47, 10.97)	3.9 (3.61, 5.09)
HR (95% CI)[b]	0.463 (0.308, 0.697)	
Nominal 2-sided p-value[b]	0.0002	

	Olaparib 300 mg bd (N=89)	Placebo (N=61)
TFST		
Total number of events (%)	56 (62.9)	45 (73.8)
Median TFST (95% CI) [months][a]	8.2 (5.82, 12.85)	5.7 (4.01, 6.24)
HR (95% CI)[b]	0.502 (0.327, 0.773)	
Nominal 2-sided p-value[b]	0.0017	
TSST		
Total number of events (%)	50 (56.2)	38 (62.3)
Median TSST (95% CI) [months][a]	12.3 (8.61, 18.92)	9.2 (8.34, 13.14)
HR (95% CI)[b]	0.722 (0.465, 1.121)	
Nominal 2-sided p-value[b]	0.1464	

a.　　Calculated using KM techniques.

b.　　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.

bd twice daily; BICR blinded independent central review; *BRCA* breast cancer susceptibility gene; CI confidence interval; FAS Full Analysis Set; *gBRCAm* germline *BRCA* mutated; HR hazard ratio;

KM Kaplan-Meier; OS overall survival; PFS progression-free survival; PFS2 time from randomisation to second progression; TDT time from randomisation to study treatment discontinuation or death; TFST time to first subsequent therapy or death; TSST time to second subsequent therapy or death. Data derived from Table 11.2.2.1, Table 11.2.4.7.1, Table 11.2.5.4, Table 11.2.6.1.2, Table 11.2.7.1.2 and Table 11.2.8.1.2.

Secondary and exploratory variables: Patient-reported outcomes

Global HRQoL was the key PRO variable of interest in this study. The overall compliance rates for the EORTC QLQ-C30 were high in both treatment arms. The treatment arms were balanced at baseline. Baseline scores for the EORTC QLQ-C30 global HRQoL score (global health status/QoL, items 29 and 30) were high and balanced for all patients (means for the olaparib and placebo arms, respectively, were 70.4/100 and 74.3/100).

Change from baseline in global HRQoL score was analysed using a mixed-effects model for repeated measures (MMRM) analysis of all of the post-baseline HRQoL scores by treatment group and visit. As shown in Table 26, there was no statistically significant difference between the treatment arms in the overall adjusted mean change from baseline in global HRQoL score. The adjusted mean change from baseline in global HRQoL score across all time points up to 6 months was -1.20 in the olaparib arm and 1.27 in the placebo arm. This corresponded to an estimated difference between the treatment arms of -2.47 points, in the context of an EORTC scale of 100 points.

Overall patient-reported outcome data demonstrated olaparib maintenance treatment preserved overall HRQoL as no statistically significant or clinically meaningful worsening was observed in global HRQoL score compared with placebo.

Table 30 **Overall adjusted mean change from baseline up to 6 months in EORTC QLQ-C30 global health status/QoL, MMRM (PRO analysis set) (DCO 15 January 2019)**

	Olaparib 300 mg bd (N=89)	Placebo (N=58)
N	84	54
Adjusted mean estimate	-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 non-missing values in both treatment arms (calculated separately by treatment arm) were included in the model.

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-point was pre-defined as clinically meaningful.

bd Twice daily; CI Confidence interval; CSR Clinical study report; Data cut-off; EORTC European Organisation for Research and Treatment of Cancer; HR Health-related quality of life; MMRM Mixed-effects model for repeated measures; PRO Patient reported outcomes; QLQ-C30 Quality of Life Questionnaire Core 30 item module; QoL Quality of life.

Data derived from Table 11.2.12.1.2, POLO CSR, Module 5.3.5.1.

Ancillary analyses

Subgroup analyses of progression-free survival

Analyses for the primary endpoint (PFS by BICR) for 11 subgroups (10 pre-defined and ECOG performance status included as an additional exploratory subgroup) were conducted to assess the consistency of treatment effect across potential or expected prognostic factors. The forest plot of PFS by subgroup is presented in

Figure 11. Forest plot of **progression-free survival by subgroup (FAS)**. Acknowledging that the study was not powered to assess efficacy within individual subgroups and due to the multiple testing, the analyses should be interpreted with caution.

Figure 11. Forest plot of progression-free survival by subgroup (FAS)
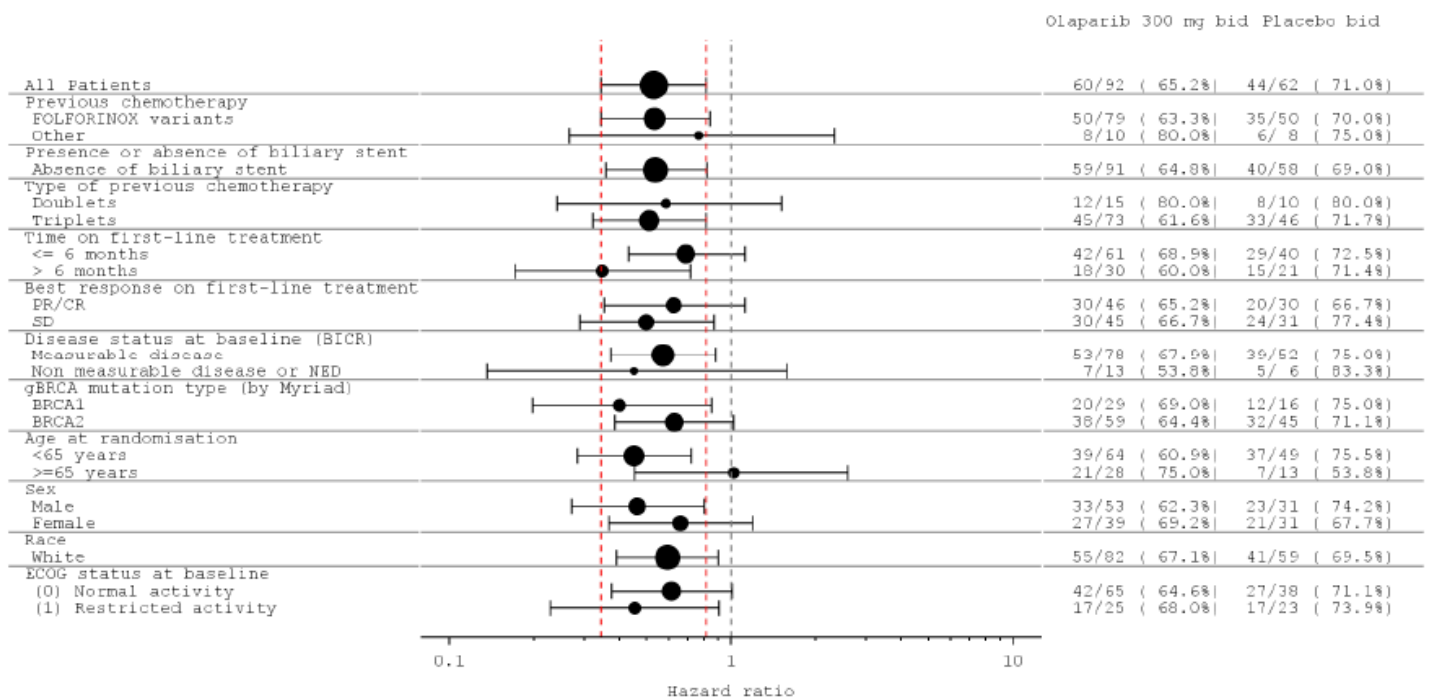
Progression was determined by BICR using modified RECIST v1.1.

A HR <1 favoured olaparib to be associated with a longer PFS than placebo.

Cox proportional hazards model included terms for randomised treatment, subgroup and treatment-by-subgroup interaction term.

Size of circle is proportional to the overall number of events.

Grey band represents the 95% CI for the overall (all patients) HR, calculated using U and V statistics obtained from the log-rank test.

HRs and CIs are not displayed for subgroup categories with <5 events in either treatment group. bd twice daily; BICR blinded independent central review; BRCA breast cancer susceptibility gene; CI confidence interval; CR complete response; ECOG Eastern Cooperative Oncology Group; FAS Full Analysis Set; gBRCA germline BRCA; HR hazard ratio; NED no evidence of disease; PFS progression-free survival; PR partial response; RECIST Response Evaluation Criteria in Solid Tumours; SD stable disease.

Data derived from Figure 11.2.3.2

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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Figure 12. Forest plot of overall survival, forest plot, by subgroup (Full Analysis Set)
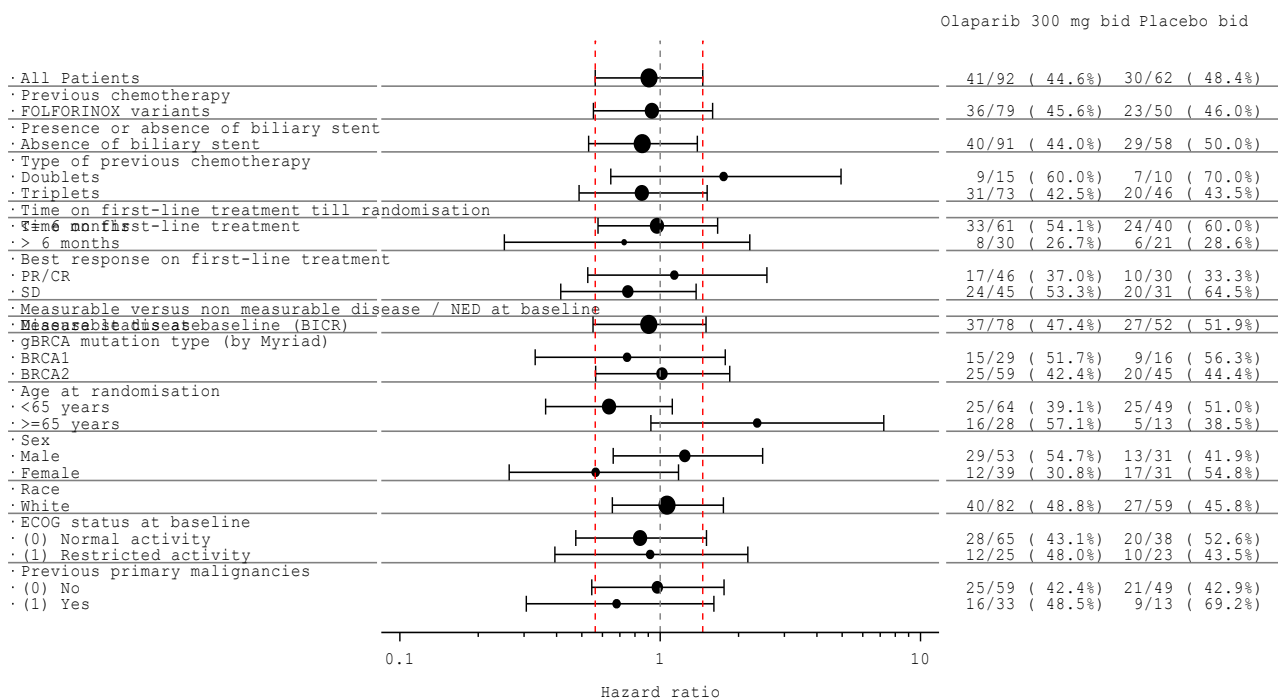
BICR Blinded independent central review; bid Twice daily; *BRCA* Breast cancer susceptibility gene; CR Complete response; ECOG Eastern Cooperative Oncology Group; *gBRCA* Germline *BRCA*; PR Partial response; SD Stable disease.

Source figure: IEMT 1962b.

The analyses of PFS were consistent across all subgroups. No subgroups derived a differential benefit compared with the overall population. The PFS HR in patients with a baseline best response to first-line treatment of CR/PR (HR 0.62; 95% CI 0.35, 1.12) was similar to that observed for patients with SD (HR 0.50; 95% CI 0.29, 0.87;

Table 41   Hazard ratios and confidence intervals for progression-free survival and overall survival, by subgroup (Full Analysis Set)

Subgroup variable	Subgroup level	Progression-free survival (BICR)			Overall survival		
		Lower	HR	Upper	Lower	HR	Upper
All patients		0.346	0.531	0.815	0.563	0.906	1.457
Previous chemotherapy	FOLFORINOX variants	0.345	0.535	0.838	0.554	0.929	1.159
	Other	0.265	0.763	2.323	NC	NC	NC

Table 41   Hazard ratios and confidence intervals for progression-free survival and overall survival, by subgroup (Full Analysis Set)

| Subgroup variable	Subgroup level	Progression-free survival (BICR)			Overall survival		
		Lower	HR	Upper	Lower	HR	Upper
Presence or absence of biliary stent	Absence	0.358	0.538	0.817	0.531	0.853	1.389
Type of previous chemotherapy	Doublets	0.241	0.586	1.504	0.656	1.752	4.951
	Triplets	0.323	0.511	0.815	0.488	0.850	1.515
Time on first-line treatment	≤6 months	0.431	0.690	1.121	0.577	0.972	1.662
	>6 months	0.171	0.348	0.716	0.252	0.727	2.209
Best response on first-line treatment	CR/PR	0.353	0.623	1.121	0.527	1.133	2.570
	SD	0.289	0.498	0.866	0.415	0.751	1.374
Disease status at baseline (BICR)	Measurable disease	0.374	0.570	0.875	0.552	0.904	1.500
	Non-measurable	0.136	0.452	1.571	NC	NC	NC
gBRCA mutation type (by Myriad)	*BRCA1*	0.197	0.401	0.848	0.331	0.746	1.778
	BRCA2	0.387	0.627	1.019	0.565	1.016	1.850
Age	<65 years	0.284	0.452	0.718	0.363	0.636	1.113
	≥65 years	0.454	1.021	2.596	0.921	2.358	7.226
Sex	Male	0.270	0.461	0.801	0.660	1.243	2.476
	Female	0.368	0.658	1.190	0.263	0.565	1.176
Race	White	0.392	0.592	0.899	0.655	1.062	1.749
ECOG status at baseline	(0) Normal activity	0.376	0.610	1.007	0.474	0.837	1.506
	(1) Restricted activity	0.228	0.455	0.905	0.394	0.915	2.171
Previous primary malignancies	No	0.348	0.550	0.871	0.563	0.987	1.750
	Yes	0.276	0.611	1.490	0.291	0.680	1.703

BICR Blinded independent central review; *BRCA* Breast cancer susceptibility gene; CR Complete response; CSR Clinical study report; ECOG Eastern Cooperative Oncology Group; *gBRCA* Germline *BRCA*; HR Hazard ratio; NC Not calculated; PR Partial response; SD Stable disease.

Source Table 11.2.3.1 and Table 11.2.4.2, POLO CSR, Module 5.3.5.1.

Figure 12. Progression-free survival per best response on first-line treatment, Kaplan-Meier plot (FAS)). The median PFS in olaparib-treated patients in the PR/CR and SD subgroups was 7.4 months compared with 3.8 and 3.9 months in placebo-treated patients, respectively.

The global interaction test was not statistically significant at the 10% level (p=0.2106; see Table 11.2.3.4). Overall, these results indicate that olaparib is an effective maintenance treatment option irrespective of potential or expected prognostic factors. In addition, an exploratory post hoc multivariate Cox analysis (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 performance status [0, 1], and type of previous chemotherapy [FOLFIRINOX, gemcitabine/cisplatin, other] were included in the model) illustrated that the primary analysis result was not impacted by any imbalances in the baseline factors (HR 0.59; 95% CI 0.39, 0.88).

Figure 13. Progression-free survival per best response on first-line treatment, Kaplan-Meier plot (FAS)
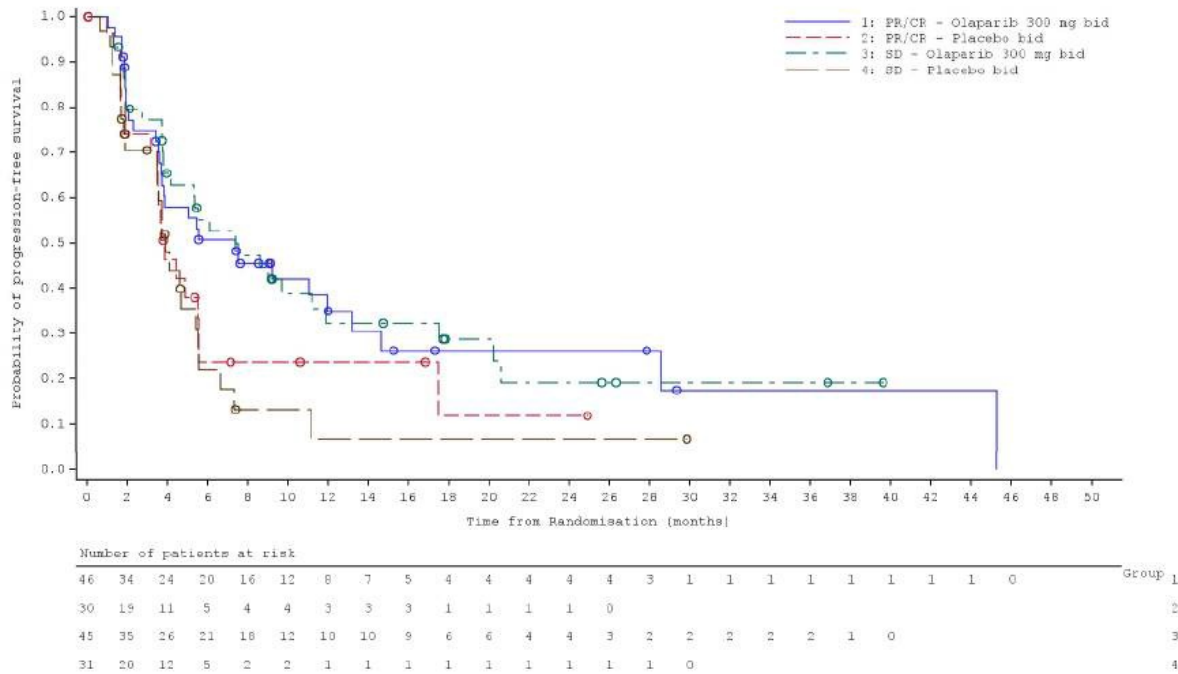
Progression was determined by BICR using modified RECIST v1.1.

BICR blinded independent central review; CR complete response; FAS Full Analysis Set; PR partial response; RECIST Response Evaluation Criteria in Solid Tumours; SD stable disease.

Data derived from Figure 11.2.3.3.4.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present

application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 31. Summary of Efficacy for POLO trial

Title: A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First-Line Platinum-Based Chemotherapy			
Study identifier	Study Code - D081FC00001 EudraCT Number - 2014-001589-85 NCT Number - NCT02184195		
Design	Phase III, randomised, double blind, placebo controlled, multicentre, parallel study		
	Duration of main phase: Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	not applicable	
Hypothesis	Superiority		
Treatments groups	Olaparib	300 mg (2 x 150 mg tablets) orally bd N= 92	
	Placebo	300 mg (2 x 150 mg tablets) orally bd N= 62	
Endpoints and definitions	Primary endpoint	PFS	The time from randomisation until the date of objective radiological disease progression according to modified RECIST v1.1 or death (by any cause in the absence of disease progression) regardless of whether the patient withdrew from randomised therapy or received another anticancer therapy prior to disease progression.
	Secondary endpoint	OS	The time from the date of randomisation until death due to any cause.
	Secondary endpoint	PFS2	The time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death.
	Secondary endpoint	TFST	time to first subsequent therapy or death.
	Secondary endpoint	TSST	time to second subsequent therapy or death.

	Secondary endpoint	TDT	time to study treatment discontinuation or death.
	Secondary endpoint	ORR by BICR	the number of with a BoR of CR and PR according to the BICR data divided by the number of patients in the treatment group with measurable disease at baseline.
	Secondary endpoint	DCR	the percentage of patients who have at least 1 confirmed visit response of CR or PR or have demonstrated SD for at least 16 weeks prior to any evidence of progression.
	Secondary endpoint	mean change in global QoL score	EORTC QLQ-C30: a questionnaire (30 questions) used to evaluate disease symptoms, functional impacts (eg, physical functioning), and HRQoL and to characterise clinical benefit from the patient perspective.
Database lock			

Results and Analysis

Analysis description	Primary Analysis
Analysis population and time point description	ITT: The primary statistical analysis of the efficacy of olaparib included all randomised patients and compared the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment were included in the FAS. Therefore, all efficacy data were summarised and analysed using the FAS on an ITT basis.

Descriptive statistics and estimate variability	Treatment group	Olaparib	Placebo
	Number of subject	92	62
	Median PFS by BICR (months) 95% CI	7.4 (4.14, 11.01)	3.8 (3.52, 4.86)
	Median OS (months) 95% CI	18.9 (14.85, 26.15)	18.1 (12.62, 26.12)
	Median PFS2 (months) 95% CI	13.2 (7.75, 26.15)	9.2 (7.62, 13.54)
	Median TFST (months) 95% CI	8.6 (6.21, 12.45)	5.7 (4.17, 6.34)
	Median TSST (months) 95% CI	13.2 (8.84, 20.04)	9.2 (8.34, 13.14)

	Median TDT (months) 95% CI	7.2 (5.52, 10.84)	3.8 (3.55, 4.80)
	ORR by BICR	23.1%	11.5%
	Median DCR (months) 95% CI	24.9 (14.75, not calculable)	3.7 (2.10, not calculable)
	Mean change in global QoL score	-1.20 (-4.014-1.618)	1.27 (-2.580-5.124)

Effect estimate per comparison	Primary endpoint PFS (67.5% maturity)	Comparison groups	Olaparib vs placebo
		Hazard ratio	0.531
		95% CI	(0.346, 0.815)
		2 sided P-value	0.0038
	Secondary endpoint OS (46% maturity)	Comparison groups	Olaparib vs placebo
		Hazard ratio	0.906
		95% CI	(0.563, 1.457)
		2 sided P-value	0.6833
	Secondary endpoint PFS2 (30.9% maturity)	Comparison groups	Olaparib vs placebo
		Hazard ratio	0.755
		95% CI	(0.464, 1.230)
		2 sided P-value	0.2597
	TFST (49.4% maturity)	Comparison groups	Olaparib vs placebo
		Hazard ratio	0.496
		95% CI	(0.324, 0.760)
		2 sided P-value	0.0013
	TSST (36.3% maturity)	Comparison groups	Olaparib vs placebo
		Hazard ratio	0.678
		95% CI	(0.437, 1.051)
		2 sided P-value	0.0825
	TDT (96.4% maturity)	Comparison groups	Olaparib vs placebo
		Hazard ratio	0.446
		95% CI	(0.297, 0.670)
		2 sided P-value	0.0001
Notes			

Supportive study

Study D0810C00042. A Phase II, Open-Label, Non-Randomised, Non-Comparative, Multicentre Study to Assess the Efficacy And Safety of Olaparib Given Orally Twice Daily in Patients With Advanced Cancers Who Have A Confirmed Genetic *BRCA1* And/Or *BRCA2* Mutation

Supportive efficacy data (utilising the capsule formulation) are provided by 23 *gBRCAm* patients from the Phase II study D0810C00042 (Study 42) that investigated response of patients with g*BRCAm* advanced solid malignances, including pancreatic cancer. This study did not have a comparator arm and was not conducted in the maintenance treatment setting. In Study 42, confirmation of gBRCA mutated disease was required at study entry and patients were also to be gBRCAm and were to have either failed standard treatment or no standard of care existed for their advanced cancer. Patients in the pancreatic cohort had either failed or were unsuitable for gemcitabine treatment in the advanced setting. Unlike POLO which recruited only patients with metastatic pancreatic adenocarcinoma in the maintenance setting, Study 42 included patients with solid tumours other than pancreatic cancer and treated patients with olaparib monotherapy at the time of relapse.

Primary objective: To assess the efficacy of oral olaparib in patients with advanced cancer who had a confirmed *gBRCA1* and/or *gBRCA2* mutation by assessment of tumour response.

Key secondary objectives: To assess the efficacy of oral olaparib in patients with advanced cancers who had a confirmed *gBRCA1* and/or *gBRCA2* mutation, by assessment of ORR, PFS, OS, DoR and DCR. To determine the safety and tolerability of oral olaparib in patients with advanced cancers who had a confirmed *gBRCA1* and/or *gBRCA2* mutation.

Design: This was a single-arm (ie, no comparator arm), open-label study. After starting treatment with olaparib 400 mg bd orally, patients attended periodic clinic visits for assessment of safety and efficacy until confirmed objective disease progression occurred according to RECIST 1.1. Following confirmed disease progression, patients discontinued olaparib treatment but could receive any other cancer treatment at the investigator's discretion.

Patients: A total of 298 patients (62 breast cancer patients, 193 ovarian cancer patients, 23 pancreatic cancer patients, 8 prostate cancer patients, and 12 patients with another type of cancer) received olaparib at 13 sites in 6 countries (Israel, United States of America [USA], Australia, Germany, Spain, and Sweden).All 298 patients were included in the safety analysis set. Patients were ≥18 years of age with histologically and/or cytologically confirmed malignant solid tumours that were refractory to standard therapy and for which no suitable, effective/curative therapy existed. Patients had to have a confirmed documented deleterious or suspected deleterious *gBRCA* mutation. The demographic characteristics of this heavily pre-treated advanced disease study population were generally representative of each tumour type, independent of *gBRCA* status.

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

Twenty-three patients with pancreatic cancer were enrolled and received olaparib in Study 42; of these, 21 patients had discontinued as of the DCO for the CSR, 14 patients due to development of study specific discontinuation criteria, 5 patients due to disease progression, 1 patient due to subject decision and 1 patient with a reason of "other" (2 patients were ongoing at DCO).

The mean age of the patients with pancreatic cancer in Study 42 was 57.1 (standard deviation [std] 7.99) years and 13 (56.5%) patients were male and 10 (43.5%) were female. The majority of patients were White (21 [91.3%] patients) followed by Black or African American and Asian (1 patient each). The mean weight of the patients with pancreatic cancer was 68.7 kg. ECOG PS at baseline was "0" for 11 (47.8%) patients, "1" for 9 (39.1%) patients and "2", for 3 (13.0%) patients. Five (21.7%) patients were *BRCA1* positive and 17 (73.9%) patients were *BRCA2* positive; 1 patient was positive for both *BRCA1* and *BRCA2*. Nineteen (82.6%) patients had metastatic pancreatic cancer and 4 (17.4%) patients had locally advanced pancreatic cancer disease prior to commencing chemotherapy. The time from diagnosis to first dose was ≤2 years for 20 (87.0%) patients and >2 to ≤5 years for 3 (13.0%) patients. A total of 21 (91.3%) patients with pancreatic cancer had received prior gemcitabine based chemotherapy (see Table 11.1.3.4, Study 42 CSR Module 5.3.5.2), and 12 (52.2%) patients had received 2 or more prior lines of chemotherapy (see Table 11.1.3.2, Study 42 CSR Module 5.3.5.2).

Patients were to receive olaparib until confirmed objective disease progression occurred according to RECIST 1.1. Following confirmed disease progression, patients discontinued olaparib treatment but could receive any other cancer treatment at the investigator's discretion.

The median total treatment duration in patients with pancreatic cancer in Study 42 was 170.0 days (range: 9 to 723 days; approximately 5.6 months). The median actual treatment duration was 167 days in the pancreatic cancer group.

There were 7 (30.4%) patients in the pancreatic cancer group patients who had dose interruptions in the study and 2 (8.7%) patients in the pancreatic cancer group had dose reduction in the study. Dose modifications (an interruption and/or reduction) were reported in a total of 7 (30.4%) patients in the pancreatic cancer group. AE was the most common reason for dose interruptions, dose reductions, and dose modifications.

Summary of efficacy

A summary of the efficacy data from Study 42 is presented in **Table 28.** Summary of efficacy across olaparib studies: other supportive study (Study 42). Study 42 investigated a different dose and formulation of olaparib and did not include a comparator.

Table 32. Summary of efficacy across olaparib studies: other supportive study (Study 42)

Efficacy endpoint	Olaparib 400 mg bd capsule
	Pancreatic cohort **(N=23)**
ORR % (95% CI)	21.7 (7.46-43.70)
PFS	
Median PFS (95% CI for median) (months)	4.55 (1.84-7.72)
Progression-free at 6 months (%)	36.4
Progression-free at 12 months (%)	9.1
OS	
Median OS (95% CI for median) (months)	9.81 (5.62-16.36)
Alive at 6 months (%)	63.6
Alive at 12 months (%)	40.9
Median DoR (days)	134.0 (4.4 months)
DCR % at 16 weeks (95% CI)	47.8 (26.82-69.41)

bd Twice daily; CI Confidence interval; CSR Clinical study report; DCR Disease control rate; DoR Duration of response; ORR Objective response rate; OS Overall survival; PFS Progression-free survival. Data derived from Tables 11.2.1.2, 11.2.2.4, 11.2.2.5, 11.2.2.8, and 11.2.4.1, Study 42 CSR, Module 5.3.5.2.

Objective response rate

ORR was a secondary outcome in Study 42. In Study 42, 5 patients (21.7%) (95% CI: 7.46 to 43.70) out of the 23 patients with measurable disease in the pancreatic cancer group showed a response; 4 showed a PR and 1 patient showed a CR.

Progression-free survival

PFS was a secondary outcome in Study 42. The median PFS was 4.55 months in patients with *gBRCAm* pancreatic cancer (Table 28. Summary of efficacy across olaparib studies: other supportive study (Study 42)). Additionally, 36.4% of patients in the pancreatic cancer cohort remained progression-free at 6 months.

Overall survival

OS was a secondary outcome in Study 42 and was defined as the time from the start date of study treatment until death due to any cause. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the subject was known to be alive. In Study 42 the median OS was 9.81 months in the *gBRCAm* pancreatic cancer cohort, with a survival rate at 6 months of 63.6% and 40.9% at 12 months (Table 28. Summary of efficacy across olaparib studies: other supportive study (Study 42)).

Subsequent therapy use was documented for 12/23 (52.2%) of patients with pancreatic cancer in Study 42.

Other efficacy endpoints

Median DoR (134.0 days) and DCR (47.8% of patients at 16 weeks) also supported the findings from POLO that olaparib demonstrates activity in patients with *gBRCAm* pancreatic cancer (Table 28. Summary of efficacy across olaparib studies: other supportive study (Study 42)).

2.4.3. Discussion on clinical efficacy

The MAH submitted a type II variation application to the current marketing authorisation of Lynparza seeking a new therapeutic indication as maintenance treatment of gBRCAm metastatic pancreatic cancer.

The main evidence of the efficacy of olaparib in the pancreatic setting came from the study D081FC00001 (POLO). POLO is a 3:2 randomised, double blind, placebo controlled, multicentre phase III trial designed to assess the efficacy of olaparib maintenance monotherapy in patients with gBRCA mutated metastatic pancreatic cancer. Eligible patients presented gBRCAm metastatic pancreatic adenocarcinoma and not disease progression after receiving a minimum of 16 weeks of first-line platinum-based chemotherapy. There were no maximum of cycles of chemotherapy and patients should have started treatment between 4 and 8 weeks from last chemotherapy treatment. Crossover to olaparib arm was not permitted. The primary endpoint of the study is PFS.

Design and conduct of clinical studies

According to clinical guidelines for pancreatic cancer (NCCN GL v3.2019 and ESMO 2015), metastatic patients with good PS (ECOG 0-2) are eligible for chemotherapy; preferred regimens are FOLFIRINOX or Gemcitabine + albumin-bound paclitaxel. In the presence of known BRCA 1/2 mutations, preferred regimens are FOLFIRINOX or Gemcitabine + cisplatin (recommendation category 2A - NCCN GL v3.2019 for pancreatic cancer). Currently, there is no approved therapy indicated for the maintenance of adult patients with metastatic pancreatic cancer in first line setting. Nevertheless, the complete chemotherapy regimen is usually continued until disease progression or unacceptable toxicity, for which its components can be discontinued.

The inclusion and exclusion criteria are considered acceptable and seemed to define a specific population of pancreatic cancer. The patients randomised in this study were representative of the intended target population. Nevertheless, very little is known about the prognostic and predictive value of germline BRCA1/2 mutations in the metastatic pancreatic cancer setting and whether the presence of these mutations designate a different subpopulation among unselected pancreatic cancer patients. There are only a few publications that describe the natural history after receiving standard of care therapy, treatment response and other outcomes in the gBRCAm pancreatic cancer patient population.

The largest study prior to POLO was from Golan et al who reported a retrospective study investigating the impact of gBRCA1 and gBRCA2 mutations on the natural history of gBRCAm pancreatic adenocarcinoma and therapeutic outcome following the use of platinum agents (Golan et al 2014). In patients with Stage IV disease, median OS of platinum treated patients (n=14 patients) was 15 months compared with 7 months for those treated with non-platinum chemotherapy (n=14 patients, P=0.276). When combining data for Stages III and IV ("advanced disease"), the median OS was 22 months for the platinum-exposed patients (n=22 patients) compared with 9 months for the non-platinum exposed patients (n=21 patients, P=0.039). 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 patients) or non-platinum (n=18 patients) as first-line chemotherapy (Golan et al 2013).

In a retrospective survival analysis of patients with advanced pancreatic adenocarcinoma and gBRCA or PALB2 mutations (Reiss et al 2018), 29 patients with advanced PDAC (Stage III n=5 patients, Stage IV n=24 patients) were matched to patients who were non-carrier or untested by age at diagnosis, year of diagnosis, stage and sex. The median OS was 21.8 months for patients with BRCA1/2 or PALB2 mutations compared to an OS of 8.1 months for patients without mutations (HR 0.35; 95% CI 0.2 to 0.62; P <0.001). For patients with mutations who received platinum treatment, the median OS was not reached (median follow-up, 20.1 months), versus an OS of 6.1 months for the patients with no platinum exposure. When the patients with mutations who had received no systemic therapy at all were eliminated (n=4 patients), the median OS increased to 15.3 months for patients with no platinum exposure.

There are two relatively large studies while not directly looking at gBRCA-associated pancreatic cancer that assessed the natural history of the disease in related populations.

Pishvaian et al 2019 reported the clinical results from the 'Know Your Tumor Program' and demonstrated that DNA damage repair (DDR) deficiencies (which includes BRCA1 and BRCA2) predict OS improvement in platinum-treated advanced pancreatic adenocarcinoma (Stage III unresectable and Stage IV). In advanced pancreatic cancer patients with a DDR mutation, median OS was 2.37 years (28.4 months; n=54 patients) for those who received prior platinum treatment compared to 1.08 years (13.0 months; n=19 patients) for those who did not receive platinum treatment. In contrast, in the DDR-proficient patients (patients without DDR mutations), median OS was 1.44 years (17.3 months; n=258 patients) with prior platinum treatment compared to 1.08 years (13.0 months; n=114 patients) with prior non-platinum treatment.

Fogelman et al 2015 reviewed cases of metastatic pancreatic adenocarcinoma from patients at two institutions (John Hopkins University and MD Anderson Cancer Center) who had a family history of tumours associated with BRCA mutation (breast, ovarian and pancreatic). The hypothesis was that patients with a strong family history might have DDR defects and would preferentially benefit from DNA damaging agents such as platinum based therapy. The use of platinum chemotherapy was found to be associated with superior survival in patients with a strong family history of these cancers. In patients

with three or more relatives harboring such cancers, individuals who received platinum therapy at any point (n=16 patients) presented a superior survival benefit compared to those patients (n=6 patients) with no history of platinum therapy (median OS 21.7 months vs 12 months, HR 0.41, 95% CI 0.22 to 0.76, p=0.004). However, no such trend was observed in patients who had no family history of these tumours and who received either platinum (n=190 patients) or non-platinum (n=151 patients) chemotherapy (median OS 8.3 months vs 7.5 months, respectively).

These results indicate that at least some patients with germline BRCA1/2 mutations may survive 2 years or more after diagnosis (depending on clinical stage at presentation) whereas median OS reported for non-selected pancreas cancer is 9 to 12 month in patients treated with FOLFIRINOX (Conroy et al 2011, Von Hoff et al 2013).

Patients with deleterious or suspected deleterious germline mutation in BRCA1 and/or BRCA2 genes were eligible based on local and central testing, with retrospective confirmation of the mutation status. The high number of screened patients (more than 3000) needed to select a sufficient number of patients (about 250) for further screening illustrates the rarity of condition and potential difficulties in detecting patients eligible for the intended treatment in clinical practice.

Eligible patients should have received a minimum of 16 weeks of first-line platinum-based chemotherapy for metastatic disease with no maximum number of cycles. POLO trial was designed for patients who could not be treated successfully with platinum-based chemotherapy until disease progression, with enrolment of patients corresponding to 2 patterns: patients who are non-progressing, but who can no longer tolerate platinum-based chemotherapy and patients who have completed 6 months of chemotherapy per the original FOLFIRINOX treatment. In case patients discontinued platinum component (oxaliplatin, cisplatin, carboplatin) due to toxicity after at least 16 weeks of treatment and continued to be treated with the remaining drugs of the initial regimen, they were still eligible if no evidence of disease progression within 4 weeks after their last dose of chemotherapy. No objective criteria seemed to have been used to start olaparib apart from toxicity. If therapy is reasonably tolerated, platinum-containing regimens are usually continued beyond 16 weeks (Ducreux et al, Sem in Onc, 2019; Dahan et al, 2018; Controy et al, 2011). It is not clear how the number of cycles for chemotherapy components, and in particular platinum, was balanced beyond the minimal 16–week period and recorded to ensure a similar exposure between two arms as the information on previous therapies was not comprehensively collected.

The initially proposed indication concerned germline BRCA mutated patients with metastatic adenocarcinoma of the pancreas whose disease has not progressed on a first-line platinum-based chemotherapy regimen. It was requested to specify according to eligibility criteria that threshold of 16 weeks concerning minimal duration of the platinum component has been considered and not the duration of the complete platinum-containing chemotherapy regimen, for which there was no upper limit imposed.

PFS was the primary endpoint in POLO study supported by OS, PFS2, TFST, TSST, TDT, BoR, DCR, and PRO as secondary endpoints. Regrettably, a scientific advice has not been sought for the POLO study.

The primary endpoint of PFS does not correspond to usual requirement for a study design in patients with metastatic pancreatic cancer where OS is highly recommended as primary endpoint (EMA/CHMP/205/95 Rev. 5).

Even if prolonged PFS might be considered to be of benefit to the patients, the selection of PFS as primary endpoint would not be entirely sufficient. In the context of maintenance therapy, PFS2 is considered highly valuable to evaluate the impact on tumour's drug resistance profile affected by therapy and the activity of next-line therapies.

All efficacy variables were calculated using the ITT population. The PFS is analysed using a log-rank test for generation of the p-value and using the Breslow approach for handling ties using BICR data. Several sensitivity analyses are performed to evaluate potential bias effect due to attrition and ascertainment, and the influence of the implemented censoring results

The comparisons between olaparib and placebo arms on all other variables (PFS2, TFST, TSST, TDT and HRQoL) in this study are not confirmatory, because there was no multiplicity adjustment plan for secondary endpoints in this study.

A multiple testing procedure was also employed across the primary endpoint (PFS) and the secondary endpoint of OS. The interpretation of the subgroup results is difficult, since the sample size in each subgroup was not planned to power such analyses for detecting the same magnitude of the treatment effect. The study was not designed for the identification and confirmation of subgroups of patients benefiting from treatment.

Two protocol amendments and 5 versions of the SAP (plus supplementary SAP after the DCO) have been issued. Among changes introduced, those in regard to interim PFS analysis are discussed below.

The important deviations necessitating sensitivity analysis above the threshold of 10% have been reported in 2.6% of patients. However, other types of important deviations occurred overall in 22.8% and 21% of patients in olaparib and placebo arm, respectively.

Efficacy data and additional analyses

Pivotal study

A total of 3315 patients were screened for POLO study. From these, 247 patients were determined to have a gBRCA mutation and 167 patients were finally enrolled in the study; 92 were allocated to olaparib arm, 62 to placebo arm and 13 were not randomized. From the FAS/ITT population (154 patents), only 3 patients did not receive study medication; 2 in the olaparib arm and 1 in the placebo arm.

At the time of DCO (approximately 49 months after the first patient was enrolled), more patients were still on treatment on the olaparib arm (32.6%) than in the placebo arm (12.9%). In both arms, the main cause of study treatment discontinuation was objective disease progression with a higher incidence in the placebo arm (46.7% vs 64.5%, olaparib vs placebo, respectively). Further, 12.0% (11/92) of the patients in the olaparib arm and 14.5% (9/62) in the placebo arm discontinued due to disease progression by investigator local disease assessment. The main cause of study withdrawal was death (43.5% vs 46.8%, olaparib vs placebo, respectively).

In the FAS, baseline patient demographic and disease/tumour characteristics were in general well balanced between treatment arms. Disease characteristics at baseline in the Myriad confirmed gBRCAm subset were consistent with the FAS and well balanced between the 2 treatments arms . The median age of the enrolled patients is 57.0 years old in both arms. There is evidence suggesting that BRCA mutated patients may present an early onset of the disease (Holter et al 2015, Toss et al 2019). There was a higher percentage of patients aged ≥65 year patients in the olaparib arm (30.4%) compared with the placebo arm (21.0%).

Overall, there were proportionally 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% versus 4.8%, respectively).

Related to disease characteristics at baseline, median time from original diagnosis to randomisation was 6.87 months in the olaparib arm and 6.97 months in the placebo arm. However, there were patients for which this time was of 38.4 months in the olaparib arm and 30.6 months in the placebo arm. The main histology type was pancreatic adenocarcinoma. All the patients were metastatic and the main site of metastasis prior to chemotherapy was liver (70.8%), followed to a lesser extent by lymph node (22.7%), lung (9.7%) and peritoneum (9.7%). Slight differences on the presence of biliary stent (1.1% olaparib vs 6.6%placebo) and extent of disease at baseline (metastatic 94.6% for olaparib vs 88.7% for placebo) were also observed. Patients were in relatively good condition as the majority of patients presented an ECOG PS of 0; more patients in the olaparib arm had an ECOG performance status of 'normal activity' (0) compared with the placebo arm (65 [70.7%] and 38 [61.3%] patients, respectively).

Overall, 48 (31.2%) patients were randomised on the basis of a prior locally determined BRCA mutation; 2 patients did not provide sufficient details of the local test in the eCRF. Overall, 46 patients with sufficient details of the locally determined BRCA mutation were reported, 15 (9.7%) patients had BRCA1 mutations, 30 (19.5%) patients had BRCA2 mutations and 1 (0.6%) patient was reported to carry both BRCA1 and BRCA2 mutations. In total, 150 (97.4%) patients were confirmed to be gBRCAm by Myriad; of those, 45 (30.0%) had BRCA1 mutations, 104 (69.3%) had BRCA2 mutations and 1 (0.7%) patient carried both BRCA1 and BRCA2 mutations. Four (2.6%) patients were not reviewed by Myriad and were excluded from the subset of Myriad confirmed gBRCAm patients; these patients were reported as gBRCAm by local testing. The proportion of BRCA1 and BRCA2 mutations was well balanced in both groups with a higher incidence of total BRCA2 mutations (67.5%) compared to total BRCA1 mutations (29.2%) which is not unexpected.

Almost all the patients received only one regimen (98.1% - 151/154) of previous chemotherapy which in the majority of the cases were FOLFIRINOX variants (83.8%). Considering that 20.8% patients received the previous non disease-related chemotherapy treatment and 9.1% patients with non disease-related "other" treatments (eg, hormonal therapy) for another cancer, there is and indirect indication that at least 1/5 patients could suffer from previous primary malignancy before occurrence of the pancreatic cancer. Several primary malignancies often occur in gBRCAm patients during their life course. The time on first-line treatment until randomisation was equal or inferior to six months in 65.6% (101/154) of the total cases. The best response to the first-line treatment were well balance in both arms being stable disease in most of the total cases (49.4% - 76/154). Overall, the concomitant treatments administered were representative of those commonly prescribed for patients of the target population and were not considered to have impacted the study results. The use of concomitant medication was balanced between groups.

From the 154 randomized patients in the FAS population (92 in the olaparib arm and 62 in the placebo arm), 3 patients were excluded from SAS population as they did not start study treatment (2 from the olaparib arm and 1 from the placebo arm). A total of 7 patients (3 in the olaparib arm and 4 in the placebo arm) were excluded from the PRO analysis set population due to the lack of evaluable forms at baseline. The demographics and baseline characteristics of the Myriad gBRCAm subset (n=150 patients) was similar to the FAS (n=154 patients).

POLO study demonstrated a statistically significant improvement in **PFS** by BICR in FAS population among metastatic gBRCAm patients with pancreatic adenocarcinoma after a platinum base first-line treatment. At the time of DCO (15 January 2019), 65.2% (60/92) of the patients in the olaparib arm had progressed compared to 71.0% (44/62) of the patients in the placebo arm (data maturity, 67.5%). Five of the PFS events were deaths in the absence of RECIST progression (excluding censoring due to 2 or

more missed RECIST visits); all of which occurred in the olaparib arm. Thirty (32.6%) patients in the olaparib arm and 8 (12.9%) patients randomised to placebo were continuing study treatment at the time of DCO.Results showed a 47% lower risk of disease progression or death with olaparib than with placebo (HR 0.531, 95% IC 0.346 – 0.815, p-value 0.0038). The median of PFS showed a difference of 3.6 months favouring olaparib arm (7.4 months vs 3.8 months). Regarding the Kaplan-Meier plot, a marked separation of the curves favouring olaparib arm was seen from the 4th month of treatment.

In line with the protocol changes and per the SAP amendment 2, the interim superiority analysis (change to futility only) was deleted. This included recalculation of the number of events needed for the primary PFS analysis and change to the method used for Type 1 error adjustment for the interim and final analyses of overall survival. The futility analysis supervised by an IDMC should have been conducted according to the protocol and SAP when 44 PFS events have been recorded.

According to the CSR, a single interim PFS analysis for futility was performed when 50% of the final number of progression events required for the primary PFS analysis had been reached (46 PFS events from 74 randomised patients) based on BICR. The interim analysis was performed by an IDMC. The futility assessment was based on the probability of eventually showing statistical significance for the primary endpoint when the final number of PFS events (n=87) was reached. If the observed HR for PFS at the interim was more than 1.02, the IDMC would have considered the option of declaring futility. The interim PFS analysis was conducted by another independent CRO to ensure the study integrity. The results of the analysis at 87 PFS events have been provided and are consistent with the primary analysis at 104 PFS events. PFS was 7.5 months in the olaparib arm and 3.7 months in the placebo arm, with HR of 0.457 (95%CI 0.287,; 0.727, p-value 0.0010).

Sensitivity analysis of PFS by investigator assessment showed similar results and still statistically significant with a HR of 0.514 (95% IC 0.339 – 0.780, p-value 0.0017). The median PFS values were of 6.3 months vs 3.7 months for olaparib vs placebo, showing therefore a gain of PFS of 2.6 months for olaparib arm which is one month less than results obtained by BICR. This discrepancy seemed not be driven by bias. Other PFS results for sensitivity analysis (attrition and evaluation time bias) were in line with PFS by BICR assessment.

Subgroup analysis of PFS across various particular subgroups did not reveal an obvious differential benefit across pre-defined subgroups compared with the overall population.

OS results did not show a statistical significance in OS improvement with a HR of 0.906 (95% IC 0.563 – 1.457, p value = 0.6833) (maturity, 46%). Median OS were of 18.9 months vs 18.1, favouring olaparib vs placebo. Kaplan-Meier plot showed a clear separation of OS curves at month 26. It is unlikely that further maturation of the data would evidence a trend in OS. Further, similar proportion of patients in both arms presented a second progression at DCO (44.6% vs 48.4%) showing a HR for **PFS2** of 0.755 (95% CI 0.464 - 1.230, p value = 0.2597, median 13.2 months for olaparib and 9.2 months for placebo).

Results showed a statistically significant delay in **TFST** for olaparib arm compared with placebo in the FAS population (HR 0.496, 95% IC 0.324 – 0.760, p value = 0.0013, median of 8.6 months for olaparib vs 5.7 months for placebo). Even if the positive trend of the curves was observed in **TSST**, the difference seen in the median of these results (13.2 vs 9.2 months, olaparib vs placebo) did not demonstrated a statistical significance (HR 0.678, 95% IC 0.437 - 1.051, p value = 0.0825). Results for **TDT** were in line with those from PFS, showing a statistical significance with a value of HR of 0.446 (95% IC 0.297 – 0.670, p value = 0.0001) and median results of 7.2 months for olaparib compared to 3.8 months for

placebo. The most common subsequent therapy reported after progression were platinum-based chemotherapy and PARP inhibitors.

The subsequent treatment after progression, especially PARP inhibitors use, has to be considered for long-term survival data analysis interpretation. Overall, 45/92 patients (48.9%) in the olaparib arm and 46/62 patients (74.2%) in the placebo arm received subsequent cancer therapies. Even if no cross-over was allowed in POLO trial, subsequent PARP inhibitors were received by 1 (1.1%) and 9 (14.5%) of the olaparib-treated and placebo-treated patients, respectively. PARP inhibitors were received as the first subsequent therapy in 0 patients in the olaparib arm and 2 patients in the placebo arm.

Related to results for **BoR**, a higher proportion of patients in olaparib arm reached a response (CR or PR) (19.6% - 18/92) compared to placebo arm (9.7% - 6/62). Most of these responses were PR in both arms (17.4% - 16/92 vs 9.7% - 6/62, olaparib vs placebo, respectively). CR was reached by two patients (2.2%) in the olaparib arm compared to none in the placebo arm (0.0%). Of note, patients that entered in the study with no measurable disease were classified under 'non-response'. **ORR** by BICR was higher for patients in the olaparib arm compared with the placebo arm (23.1% vs 11.5%). Results for ORR based on investigator assessment were in line. A longer **duration of the response** was seen in olaparib arm (24.9 months) compared to placebo arm (3.7 months). As previously seen in other studies of olaparib, patients in placebo arm seemed to present a quicker **onset of the response** than those in olaparib arm (5.4 months vs 3.6 months).

Overall, results from efficacy variables for Myriad gBRCAm patients are in line with those from the FAS population.

The main PRO variable for HRQoL analysis was Global HRQoL score (global health status/QoL items 29 and 30) of the EORTC QLQ-C30. The overall compliance rates for the QLQ-C30 were high in both treatment arms. The treatment arms were balanced in terms of baseline scores. This is expected in the maintenance treatment setting as disease burden at baseline is minimal post chemotherapy. Only visits with at least 25% of non-missing values in both treatment arms were included in the mixed model for repeated measures (MMRM). The study treatment discontinuation visit and the safety follow-up visit were excluded from the analysis, but the rationale has not been provided. There was no collection of data foreseen beyond progression. There was no statistically significant difference between the treatment arms in the overall adjusted mean change from baseline in global HRQoL score. The adjusted mean change from baseline in EORTC QLQ-C30 global HRQoL score across all time points up to 6 months was -1.20±1.42 in the olaparib group (84 evaluable patients) and 1.27±1.95 in the placebo group (54 evaluable patients), with a corresponding estimated difference of −2.47 points (95% CI −7.27 to 2.33; p=0.310 [nominal]).

The analysis of time to pain progression using the QLQ-C30 pain domain suggested a trend in benefit for olaparib treatment compared with placebo (HR= 0.70; 95% CI: 0.437, 1.116), with a delay in time to worsening of pain. This is a patient- relevant outcome as metastatic pancreatic cancer patients frequently require help from a pain specialist for pain control and the use of potent narcotics (Ducreux et al 2015).

Supportive study

Supportive data from the pancreatic patients from study 42 were also provided. Study 42 was a phase II, open-label, non-randomised, non-comparative study to assess the efficacy and the safety of olaparib in advanced cancer who have confirmed a genetic BRCA1/ BRCA2 mutation. This study was not conducted in the maintenance setting. Patients in the pancreatic cohort had either failed or were unsuitable for gemcitabine treatment in the advanced setting. The dose was 400mg bd orally.

Twenty-three patients with pancreatic cancer were finally enrolled and received olaparib in Study 42. The mean age of the patients with pancreatic cancer in Study 42 was 57.1 (standard deviation [std] 7.99) years. The majority of patients were White (21 [91.3%] patients) followed by Black or African American and Asian (1 patient each). ECOG PS at baseline was "0" for 11 (47.8%) patients, "1" for 9 (39.1%) patients and "2", for 3 (13.0%) patients. Five (21.7%) patients were BRCA1 positive and 17 (73.9%) patients were BRCA2 positive; 1 patient was positive for both BRCA1 and BRCA2. Nineteen (82.6%) patients had metastatic pancreatic cancer and 4 (17.4%) patients had locally advanced pancreatic cancer disease prior to commencing chemotherapy.

Patients were supposed to receive olaparib until confirmed objective disease progression. The median actual treatment duration was 167 days in the pancreatic cancer group.

Results showed a ORR of 21.7% (7.46-43.70), a median PFS of 4.55 months (1.84-7.72), a median OS of 9.81 months (5.62-16.36), a median DoR of 4.4 months and a DCR rate at 16 weeks of 47.8 (26.82-69.41).

Even if Study 42 investigated a different dose and formulation of olaparib and did not include a comparator, results supported the demonstration of olaparib activity in metastatic pancreatic cancer patients with gBRCA1/2 mutations. Its magnitude appears to be less important (ORR 22%) than in patients with breast or ovarian cancer harbouring gBRCAm.

Additional expert consultation

The Scientific Advisory Group in Oncology agreed that olaparib maintenance treatment was associated with activity and clinical effects in the proposed indication. The trial was robust in terms of internal and external validity.

The clinical effect has been shown on the basis of prolongation of PFS. There was also improvement in some individual symptoms and a trend in delaying pain progression. There was no clear improvement but also no apparent detriment on other important clinical endpoints like HRQoL, PFS2, and OS, compared to placebo. However, OS data are still immature.

According to a majority of SAG members, the benefit observed in the PFS in the overall population is relevant when put into context of the very poor prognosis, the deterioration in pain and other symptoms that is generally expected after progression (as evidence by the post-PD HRQoL analysis), the small population with gmBRCA pancreatic cancer, the lack of therapies with demonstrated effect in this subset, and the good tolerability. Also, some members pointed out quite impressive duration of survival without progression in some patients of about two years without the need for additional platinum-based chemotherapy. Delaying toxic second-line chemotherapy that is associated with very modest activity was in itself considered a benefit. According to this view, although direct comparison with prolonged chemotherapy before progression or second-line chemotherapy after progression was not available, these relative-efficacy considerations do not detract from the efficacy shown. An additional efficacious regimen in this disease with very limited options and dismal prognosis was considered a major therapeutic advantage at least in some patients.

However, a minority of SAG members disagreed, and considered that the effect on PFS was too modest to represent a clinical benefit in the overall population. Some members also questioned why the gain in PFS did not translate into OS, given that dilution of the effect post-progression was considered unlikely considering available options. Some members also regretted that no active comparator was used and that

it was not clear what would have happened if patients in the control group would have received treatment with platinum salts etc. This would be important to understand the added therapeutic value of olaparib over available treatment options as continued chemotherapy before, or second-line treatment after progression. Admittedly, though, the efficacy of such regimens in this molecular subgroup is not known precisely although it can be assumed to be similar. They also considered that delaying subsequent chemotherapy, like gemcitabine + nab-paclitaxel could potentially lead to loss of benefits, although the risks are mainly theoretical. Thus, the added value, or detriment, of olaparib over available treatment options was unknown.

The internal validity is supported based on consistent results in subgroup analyses and broadly concordant results across efficacy endpoints, although the OS data are clearly immature. The external validity is corroborated by the mechanism of action and the results observed in ovarian cancer.

The SAG agreed that the OS data were very immature, and this was unfortunate as an effect on OS would have been expected given the observed effect on PFS. The SAG agreed that updated/final analyses should be submitted given the very early cut-off especially for OS. The company has agreed to provide with the data in the post approval setting.

Although the subgroup analyses showed consistent benefits by type of mutation, a comprehensive evaluation of other molecular markers should be conducted to better define likelihood to derive a benefit from treatment and further enrich the indication. To some extent, it is unclear whether the results of the ancillary molecular study have been exhaustively analysed and presented. It should be clarified what molecular analyses have been conducted in the study and what material is available for further analyses.

Apparent under-representation of elderly patients was discussed. However, based on individual patient data, there were no big concerns about possible differential activity in elderly patients.

Safety profile has been discussed as well and result of this consultation is reported in the safety section.

2.4.4. Conclusions on the clinical efficacy

Olaparib in monotherapy as maintenance treatment in gBRCAm patients produced a statistically significant prolongation of PFS of 3.6 months on top of 3.8 months in placebo arm. OS results showed a non-statistically significant small difference favouring olaparib. The Applicant was recommended to provide updated OS and PFS2 data in the post approval setting.

2.5. Clinical safety

Introduction

Across the entire clinical programme, as of 15 December 2018, approximately 10682 patients are estimated to have received treatment with olaparib. The focus of this analysis is the POLO study (POLO) where olaparib 300 mg (or placebo) bd was given as a maintenance monotherapy in the first-line maintenance treatment of *gBRCAm* patients with metastatic pancreatic adenocarcinoma whose disease has not progressed following platinum-based chemotherapy. Supportive safety data, for olaparib 300 mg bd as a monotherapy, are

provided by a pool of 1329 patients who were intended to receive this dose and received olaparib in the Applicant-sponsored studies.

Study 42 (pancreatic cancer patients only)

Supportive safety data from an additional 23 patients with pancreatic cancer who were recruited in Study 42 are presented, which used the capsule formulation of olaparib. The DCO for the analysis of tumour response (primary analysis) for Study 42 was 31 July 2012. At the time of the DCO, the majority of patients in the pancreatic SAS had discontinued study treatment (21 [91.3%] of 23 olaparib-treated pancreatic cancer patients).

Patient exposure

Overall extent of exposure: POLO

A total of 151 patients were randomised in POLO, 91 were randomised to the olaparib arm and 60 to the placebo arm. A higher proportion of olaparib-treated patients received treatment for a period of at least 6 months compared with the placebo arm.

Long term exposure to olaparib is shown in the table below

Table 33. Overall extent of exposure in POLO (SAS)

Month (approximate)	Number (%) of patients	
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)
≥Day 1	91 (100.0)	60 (100.0)
≥1 month (30.4 days)	87 (95.6)	55 (91.7)
≥3 months (91.3 days)	70 (76.9)	37 (61.7)
≥6 months (182.6 days)	44 (48.4)	9 (15.0)
≥9 months (273.9 days)	34 (37.4)	6 (10.0)
≥12 months (365.3 days)	23 (25.3)	4 (6.7)
≥18 months (547.9 days)	13 (14.3)	3 (5.0)
≥24 months (730.5 days)	9 (9.9)	2 (3.3)
≥36 months (1095.8 days)	3 (3.3)	0

Rows are cumulative and patients were counted if the actual treatment duration was greater than or equal to the stated duration. A month was defined as 365.25/12 = 30.4375 days.

Duration of treatment

The number of patients still on treatment began to diverge between arms after 3 months (in favour of olaparib). Duration of exposure to study treatment in POLO is summarised in Table below

Table 34. Duration of Olaparib/placebo exposure in POLO (SAS)

Treatment duration (days)	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)
Total treatment duration[a]		
Mean (std)	290.3 (289.27)	156.6 (174.06)
Median	182.0	113.0
Minimum; Maximum	23; 1379	2; 915
Total treatment days	26419	9393
Actual treatment duration[b]		
Mean (std)	283.8 (284.46)	154.7 (173.95)
Median	168.0	112.5
Minimum; Maximum	17; 1367	2; 915
Total treatment days	25826	9281

[a]   Total treatment duration (days) = (last dose date - first dose date +1) for each phase.
[b]   Actual treatment duration (days) = (last dose date - first dose date +1) excluding dose interruptions.
Note: Dose interruptions include those where the patient forgot to take a dose. If a patient was ongoing at the data-cut-off (DCO) date, the DCO date was used to calculate duration.
bd Twice daily; SAS Safety analysis set; std Standard deviation.

Study 42 (pancreatic cancer patients only)

Median duration of treatment was 170.0 days (5.6 months); range 9 to 723 days (0.3 to 23.8 months).

Dose modification

Dose modifications (interruptions or reduction) were reported in 41.8% patients on olaparib and 16.7% placebo patients.

Interruptions and reductions to planned dosing of olaparib and placebo

		Number (%) of patients	
		Olaparib 300mg bd (N=91)	Placebo bd (N=60)
No interruption		59 (64.8)	53 (88.3)
Number of patients with an interruption	Any	32 (35.2)	7 (11.7)
	1 interruption	16 (17.6)	6 (10.0)
	2 interruptions	10 (11.0)	1 (1.7)
	3 interruptions	3 (3.3)	0
	4 interruptions	3 (3.3)	0
Reason for interruption:	Adverse event	30 (33.0)	3 (5.0)
	Lab abnormality not reported as an AE	0	1 (1.7)
	Surgery	1 (1.1)	1 (1.7)
	Other	1 (1.1)	2 (3.3)
No dose reduction		64 (70.3)	56 (93.3)
Number of patients with a dose reduction	Any	27 (29.7)	4 (6.7)
	1 reduction	9 (9.9)	2 (3.3)
	2 reductions	10 (11.0)	0
	3 reductions	4 (4.4)	0
	4 reductions	2 (2.2)	1 (1.7)
	5 reductions	2 (2.2)	0
	33 reductions	0	1 (1.7)
Reason for reduction:	Adverse event	21 (23.1)	3 (5.0)
	Surgery	1 (1.1)	0
	Other	8 (8.8)	1 (1.7)

		Number (%) of patients	
		Olaparib 300mg bd (N=91)	Placebo bd (N=60)
Number of patients with both an interruption and dose reduction	Any	21 (23.1)	1 (1.7)
	2 interruptions and reductions	3 (3.3)	1 (1.7)
	3 interruptions	6 (6.6)	0
	4 interruptions and reductions	5 (5.5)	0
	5 interruptions and reductions	4 (4.4)	0
	6 interruptions and reductions	2 (2.2)	0
	9 interruptions and reductions	1 (1.1)	0

Overall extent of exposure: 300 mg bd pool

As shown in table below, long-term exposure to olaparib therapy was demonstrated in the 300 mg bd pool; 547 (41.2%) and 285 (21, 4%) of all patients remained on treatment for ≥1 year and ≥2 years, respectively.

Table 35. Overall extent of exposure in the 300 mg bd pool

Month (days)	Number (%) of patients
	Olaparib 300 mg bd N=1329
≥Day 1	1329 (100.0)
≥1 month (30.4 days)	1248 (93.9)
≥3 months (91.3 days)	1032 (77.7)
≥6 months (182.6 days)	819 (61.6)
≥12 months (365.3 days)	547 (41.2)
≥18 months (547.9 days)	407 (30.6)
≥24 months (730.5 days)	285 (21.4)
≥36 months (1095.8 days)	22 (1.7)
≥48 months (1461.1 days)	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 were counted if the actual treatment duration is greater than or equal to the stated duration.

bd Twice daily; DCO Data cut-off.

The median total treatment duration in the 300 mg bd pool was 284 days (approximately 9.3 months).

Demographics:

POLO

The demographic and disease characteristics of patients in POLO are summarised previously in Table 5 *(See 'Baseline data' at 'Main study' – 'Clinical efficacy').*

Olaparib 300 mg bd pool

Demographic data have not been pooled, as the group of studies contributing to the 300 mg bd pooled dataset have different patient populations of varying stages of disease.

Adverse events

An overview of adverse events in POLO is shown in the table below.

Table 36. POLO: Number (%) of patients who had at least 1 AE in any category (SAS)

AE category[a]	Number (%) of patients	
	Olaparib 300 mg bd N=91	Placebo bd N=60
Any AE	87 (95.6)	56 (93.3)
Any AE of CTCAE Grade 3 or higher	36 (39.6)	14 (23.3)
Any AE with outcome = Death	0[b]	0
Any SAE (including events with outcome = death)	22 (24.2)	9 (15.0)
Any AE leading to discontinuation of study treatment	5 (5.5)	1 (1.7)
Any AE leading to dose reduction of study treatment	15 (16.5)	2 (3.3)
Any AE leading to interruption of study treatment	32 (35.2)	3 (5.0)

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

b   one Patient in the olaparib arm had an SAE of duodenal perforation which started during the 30 day follow-up period (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.

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; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events (v4.03); SAE Serious adverse event; SAS Safety analysis set.

Table 37. Number (%) of patients who had at least 1 AE in any category (olaparib treatment groups) in POLO and the 300 mg bd pool.

AE category[a]	Number (%) of patients	
	POLO SAS olaparib 300 mg bd (N=91)	Olaparib 300 mg bd pool (N=1329)
Any AE	87 (95.6)	1298 (97.7)
Any AE of CTCAE Grade 3 or higher	36 (39.6)	528 (39.7)
Any AE with outcome = Death	0[b]	9 (0.7)
Any SAE (including events with outcome = death)	22 (24.2)	274 (20.6)
Any AE leading to discontinuation of study treatment	5 (5.5)	102 (7.7)
Any AE leading to dose reduction of study treatment	15 (16.5)	282 (21.2)
Any AE leading to interruption of study treatment	32 (35.2)	515 (38.8)

a   Patients with multiple events 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.

b   one Patient in the olaparib arm had an SAE of duodenal perforation which started during the 30 day follow-up period (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.

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; bd Twice daily; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE serious adverse event; SAS Safety analysis set.

Common adverse events: POLO

All AEs reported in at least 10% of patients in either treatment arm of POLO are summarised in table 34 taking into consideration the overall frequencies of the most commonly reported AEs adjusted for patient years' exposure.

Table 38. Most common AEs (reported by ≥10% patients in either arm exposure) and adjusted by patient years' exposure in POLO (SAS)

Preferred term[a]	Olaparib 300 mg bd (N=91)		Placebo bd (N=60)	
	Number (%) of patients with events[b]	Event rate[c] (per 1000 patient years)	Number (%) of patients with events[b]	Event rate[c] (per 1000 patient years)
Any AE	87 (95.6)	16593.60	56 (93.3)	21086.60
Fatigue	41 (45.1)	863.03	16 (26.7)	659.22
Nausea	41 (45.1)	987.29	14 (23.3)	596.54
Abdominal pain	26 (28.6)	496.81	15 (25.0)	557.18
Diarrhoea	26 (28.6)	494.58	9 (15.0)	346.28
Anaemia	25 (27.5)	427.05	10 (16.7)	382.46
Decreased appetite	23 (25.3)	362.21	4 (6.7)	137.21
Constipation	21 (23.1)	329.90	6 (10.0)	230.05
Vomiting	18 (19.8)	270.79	9 (15.0)	333.29

Back pain	17 (18.7)	270.71	10 (16.7)	383.67
Asthenia	15 (16.5)	245.92	5 (8.3)	171.05
Arthralgia	14 (15.4)	231.33	6 (10.0)	232.62
Pyrexia	12 (13.2)	168.62	5 (8.3)	169.93
Nasopharyngitis	11 (12.1)	169.48	2 (3.3)	67.85
Rash	11 (12.1)	169.25	2 (3.3)	69.20
Dysgeusia	10 (11.0)	139.51	3 (5.0)	103.31
Dyspnoea	10 (11.0)	150.02	3 (5.0)	101.77
Pruritus	9 (9.9)	129.26	4 (6.7)	149.42
Neuropathy peripheral	7 (7.7)	95.97	7 (11.7)	252.67
Abdominal pain upper	6 (6.6)	84.55	8 (13.3)	292.73
Headache	6 (6.6)	83.16	8 (13.3)	301.02
Abdominal distension	4 (4.4)	54.38	6 (10.0)	210.42

[a]   Multiple occurrences of a preferred term for a patient were counted only once for the patient.

[b]   Sorted by decreasing order of frequency in the olaparib arm and then by order of frequency in the placebo arm.

[c]   Number of patients with the AE divided by the sum of total duration of follow-up (for patients without the event) and the time to the first occurrence of the AE (for patients with the event) in each group, multiplied by 1000 and converted to patient years.

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.

Comparative analysis of adverse events for the Olaparib treatment group in POLO and Study *42*

Table 39. Number (%) of patients who had at least 1 AE in any category (POLO SAS and Study 42 pancreatic cancer cohort only)

AE category[a]	Number (%) of patients	
	Olaparib capsule 400 mg bd Study 42 pancreatic cancer cohort only N=23	Olaparib tablet 300 mg bd POLO SAS N=91
Any AE	23 (100)	87 (95.6)
Any AE of CTCAE Grade 3 or higher	15 (65.2)	36 (39.6)
Any AE with outcome = Death	0	0[b]
Any SAE (including events with outcome = death)	7 (30.4)	22 (24.2)
Any AE leading to discontinuation of study treatment	0	5 (5.5)

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

b   One Patient in the olaparib arm had an SAE of duodenal perforation which started during the 30-day follow-up period (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.

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.
AE Adverse event; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Event; SAE Serious adverse event; SAS Safety analysis set.

Common adverse events: tablet pool

AEs of fatigue, nausea, abdominal pain, anaemia, vomiting, back pain, rash, dysgeusia, neutropenia, headache and dizziness were reported at a higher incidence (≥5% difference) in the POLO SAS compared with the 300 mg tablet pool.

An overview of adverse events in POLO and 300 mg bd pool is shown in the table below

Table 40. : Most common AEs (reported in ≥10% in the Olaparib treatment arm of POLO or the 300 mg bd pool)

Preferred term	Number (%) of patients[a]	
	POLO SAS olaparib 300 mg bd (N=91)	Olaparib 300 mg bd pool N=1329
Patients with any AE	87 (95.6)	1298 (97.7)
Fatigue	41 (45.1)	521 (39.2)
Nausea	41 (45.1)	838 (63.1)
Diarrhoea	26 (28.6)	358 (26.9)
Abdominal pain	26 (28.6)	236 (17.8)
Anaemia	25 (27.5)	513 (38.6)
Decreased appetite	23 (25.3)	294 (22.1)
Constipation	21 (23.1)	243 (18.3)
Vomiting	18 (19.8)	467 (35.1)
Back pain	17 (18.7)	161 (12.1)
Asthenia	15 (16.5)	222 (16.7)
Arthralgia	14 (15.4)	177 (13.3)
Pyrexia	12 (13.2)	159 (12.0)
Nasopharyngitis	11 (12.1)	107 (8.1)
Rash	11 (12.1)	76 (5.7)
Dysgeusia	10 (11.0)	218 (16.4)
Dyspnoea	10 (11.0)	170 (12.8)
Cough	8 (8.8)	179 (13.5)
Neutropenia	7 (7.7)	184 (13.8)
Headache	6 (6.6)	228 (17.2)
Dizziness	6 (6.6)	164 (12.3)
Abdominal pain upper	6 (6.6)	144 (10.8)
Dyspepsia	5 (5.5)	137 (10.3)

[a] Table ordered by incidence of events in POLO.
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; bd Twice daily; CSR Clinical study report; DCO Data cut-off; N Total number of patients; SAS Safety analysis set.

Adverse events by treatment period: POLO

An assessment of AEs by treatment period of AE onset is presented in Table below.

Table 41. Onset of AE in the first 3 months and 3-6 months of treatment for the most common AEs (reported in ≥10% of patients in either arm) in POLO (SAS)

Preferred term	Number (%) of patients			
	Onset in 0-3 months		Onset in 3-6 months	
	Olaparib 300 mg bd N=91	Placebo bd N=60	Olaparib 300 mg bd N=76	Placebo bd N=43
Fatigue	36 (39.6)	16 (26.7)	4 (5.3)	1 (2.3)
Nausea	37 (40.7)	10 (16.7)	3 (3.9)	3 (7.0)
Diarrhoea	19 (20.9)	7 (11.7)	5 (6.6)	1 (2.3)
Abdominal pain	16 (17.6)	7 (11.7)	4 (5.3)	6 (14.0)
Anaemia	18 (19.8)	7 (11.7)	9 (11.8)	2 (4.7)
Decreased appetite	21 (23.1)	2 (3.3)	2 (2.6)	3 (7.0)
Constipation	11 (12.1)	5 (8.3)	8 (10.5)	2 (4.7)
Vomiting	12 (13.2)	5 (8.3)	2 (2.6)	4 (9.3)
Back pain	10 (11.0)	6 (10.0)	2 (2.6)	4 (9.3)
Asthenia	13 (14.3)	3 (5.0)	4 (5.3)	1 (2.3)
Arthralgia	11 (12.1)	5 (8.3)	2 (2.6)	1 (2.3)
Pyrexia	6 (6.6)	2 (3.3)	2 (2.6)	3 (7.0)
Nasopharyngitis	4 (4.4)	1 (1.7)	1 (1.3)	1 (2.3)
Rash	7 (7.7)	2 (3.3)	2 (2.6)	0
Dysgeusia	10 (11.0)	3 (5.0)	0	0
Dyspnoea	8 (8.8)	3 (5.0)	2 (2.6)	0
Neuropathy peripheral	5 (5.5)	7 (11.7)	1 (1.3)	0
Abdominal pain upper	4 (4.4)	5 (8.3)	1 (1.3)	2 (4.7)
Headache	6 (6.6)	7 (11.7)	0	1 (2.3)
Abdominal distention	3 (3.3)	5 (8.3)	0	1 (2.3)

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; ALT Alanine aminotransferase; AST Aspartate aminotransferase; bd Twice daily; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

Causally-related adverse events: POLO

Table 42. Most common AEs of CTCAE Grade ≥3 AEs (reported in ≥2 patients in either treatment arm) in POLO (SAS)

MedDRA SOC preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)
Patients with any CTCAE Grade ≥3 AE	36 (39.6)	14 (23.3)
Blood and lymphatic system disorders	14 (15.4)	3 (5.0)
Anaemia	10 (11.0)	2 (3.3)
Neutropenia	3 (3.3)	1 (1.7)
Investigations	7 (7.7)	0
ALT increased	3 (3.3)	0
GGT increased	3 (3.3)	0
AST increased	2 (2.2)	0
Platelet count decreased	2 (2.2)	0
Gastrointestinal disorders	7 (7.7)	4 (6.7)
Abdominal pain	2 (2.2)	1 (1.7)
Abdominal pain upper	0	2 (3.3)
General disorders and administration site conditions	6 (6.6)	1 (1.7)
Fatigue	4 (4.4)	0
Metabolism and nutrition disorders	4 (4.4)	4 (6.7)
Decreased appetite	3 (3.3)	0
Hyperglycaemia	1 (1.1)	2 (3.3)
Nervous system disorders	4 (4.4)	1 (1.7)
Polyneuropathy	2 (2.2)	0
Vascular disorders	3 (3.3)	2 (3.3)
Hypertension	2 (2.2)	1 (1.7)
Hepatobiliary disorders	3 (3.3)	1 (1.7)
Cholangitis	2 (2.2)	1 (1.7)

[a]   Multiple occurrences of a system organ class/preferred term for a patient were counted only once for the patient.

[b]   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.

Table 43. The most commonly-reported Grade 3 and 4 AEs for the Olaparib treatment arm in POLO and Study 42

MedDRA SOC preferred term[b]	Number (%) of patients[a]	
	Olaparib capsules 400 mg bd Study 42 pancreatic cancer cohort N=23	Olaparib tablet 300 mg bd POLO SAS N=91
Patients with any CTCAE Grade ≥3 AE	15 (65.2)	36 (39.6)
Blood and lymphatic system disorders	**4 (17.4)**	**14 (15.4)**
Anaemia	4 (17.4)	10 (11.0)
Neutropenia	0	3 (3.3)
Investigations	**2 (8.7)**	**7 (7.7)**
ALT increased	1 (4.3)	3 (3.3)
GGT increased	1 (4.3)	3 (3.3)
AST increased	0	2 (2.2)
Platelet count decreased	0	2 (2.2)
Gastrointestinal disorders	**3 (13.0)**	**7 (7.7)**
Abdominal pain	1 (4.3)	2 (2.2)
Abdominal pain upper	0	0
General disorders and administration site conditions	**3 (13.0)**	**6 (6.6)**
Fatigue	3 (13.0)	4 (4.4)
Metabolism and nutrition disorders	**3 (13.0)**	**4 (4.4)**
Decreased appetite	0	3 (3.3)
Nervous system disorders	**2 (8.7)**	**4 (4.4)**
Polyneuropathy	0	2 (2.2)
Vascular disorders	**0**	**3 (3.3)**
Hypertension	0	2 (2.2)
Hepatobiliary disorders	**1 (4.3)**	**3 (3.3)**
Cholangitis	1 (4.3)	2 (2.2)

[a]   Multiple occurrences of a system organ class/preferred term for a patient were counted only once for the patient.

[b]   Sorted by decreasing order of frequency in the POLO 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.

Comparison of CTCAE Grade ≥3 adverse events: tablet pool

Table 44. Most common AEs of CTCAE Grade 3 or higher (reported in ≥2% patients in Olaparib treatment arm of POLO and the 300 mg bd pool)

System organ class Preferred term[b]	Number (%) of patients[a]	
	POLO SAS olaparib 300 mg bd (N=91)	Olaparib 300 mg bd pool (N=1329)
Patients with any CTCAE Grade ≥3 AE	36 (39.6)	528 (39.7)
Blood and lymphatic system disorders	14 (15.4)	278 (20.9)
Anaemia	10 (11.0)	228 (17.2)
Neutropenia	3 (3.3)	62 (4.7)
Investigations	7 (7.7)	89 (6.7)
ALT increased	3 (3.3)	9 (0.7)
GGT increased	3 (3.3)	12 (0.9)
AST increased	2 (2.2)	11 (0.8)
Platelet count decreased	2 (2.2)	16 (1.2)
Neutrophil count decreased	1 (1.1)	38 (2.9)
Gastrointestinal disorders	7 (7.7)	87 (6.5)
Abdominal pain	2 (2.2)	18 (1.4)
General disorders and administration site conditions	6 (6.6)	72 (5.4)
Fatigue	4 (4.4)	37 (2.8)
Metabolism and nutrition disorders	4 (4.4)	35 (2.6)
Decreased appetite	3 (3.3)	9 (0.7)
Nervous system disorders	4 (4.4)	26 (2.0)
Polyneuropathy	2 (2.2)	2 (0.2)
Vascular disorders	3 (3.3)	18 (1.4)
Hypertension	2 (2.2)	5 (0.4)
Hepatobiliary disorders	3 (3.3)	11 (0.8)
Cholangitis	2 (2.2)	3 (0.2)

[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.

Serious adverse event/deaths/other significant events

Deaths in POLO

A summary of patients who died in the POLO study is presented in table below.

Table 45. patients who died in POLO (FAS)

Category	Number (%) of patients	
	Olaparib 300 mg bd (N=92)	Placebo bd (N=62)
Total number of deaths	41 (44.6)	30 (48.4)
Death related to disease under investigation only[a]	39 (42.4)	30 (48.4)
Death related to disease under investigation and with AE outcome = death	0	0
AE with outcome of death only	0[b]	0
AE with outcome of death only (AE start date falling >30 days after last treatment dose)	0	0
Patients with unknown/other reason for death	2 (2.2)[c]	0

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 during the 30 day follow-up period (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 were 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 74 days after the last dose of olaparib and was therefore not reported as an AE [after the 30-day safety follow-up period only events that are AESIs were reported as AEs]).

AE Adverse event; AESI Adverse event of special interest; bd Twice daily; FAS Full analysis set.

Patients in POLO whose deaths were not considered due to disease progression only are listed in Table below with relevant data on their treatment history in the study, and the investigator's opinion on the likelihood of a causal relationship between death and study treatment

Table 46. POLO: Key information for deaths not due to disease progression (FAS)

Time from first dose to death (days)	Time from last dose to death (days)	Treatment period[b]	Primary cause of death (investigator text/ MedDRA preferred term)	Secondary cause of death (investigator text/ MedDRA preferred term)	Autopsy performed	Comments, including causal relationship to olaparib[b]
186	55	Safety follow-up	Duodenal perforation		NR	The patient died after the DCO date. The event of duodenal perforation was considered unrelated to olaparib.
90	61	Post safety follow-up	Unknown/Death	Unknown/Death	NR	The patient discontinued olaparib and withdrew from the study on Day 30; disease progression was reported on Day 52.
637	75	Post safety follow-up	Refractory septic shock/Septic shock[c]	NR	No	The patient discontinued olaparib and withdrew from the study on Day 563 and subsequently received 2 cycles (14 days) of cisplatin/gemcitabine as second line chemotherapy (from Day 596 to Day 610).

[a]   Note: The safety follow-up period was specified as 30 days post-treatment discontinuation. Patients were still in follow-up for overall survival.

[b]   As assessed by the investigator.

[c]   The event of septic shock was not recorded as an AE as it occurred after the 30-day safety follow up period (after the 30-day safety follow-up period only events that are AESIs were reported as AEs).

AE Adverse event; AESI Adverse event of special interest; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events (v4.0); DCO Data cut-off; FAS Full analysis set; MedDRA Medical Dictionary for Regulatory Activities (v21.1); NR Not reported; SAE Serious adverse event.

Comparison of deaths: POLO and Study 42

Eighteen (78.3%) of the 23 pancreatic cancer patients in Study 42 died. The cause of death for all 18 patients was related to the disease under investigation only.

Comparison of deaths: tablet pool

Table 47. Number of deaths in the Olaparib treatment arm in POLO and the 300 mg bd pool.

Category	Number (%) of patients	
	POLO FAS olaparib 300 mg bd (N=91)	Olaparib 300 mg bd pool (N=1329)
Total number of deaths	41 (44.6)	365 (27.5)
Death related to disease under investigation only[a]	39 (42.4)	335 (25.2)
Death related to disease under investigation and with AE outcome = death	0	5 (0.4)
Death not related to disease and AE with outcome of death only	0[b]	4 (0.3)
Death not related to disease and AE with outcome of death only (AE start date falling >30 days after last treatment dose)	0	2 (0.2)
Patients with unknown reason for death[c]	2 (2.2)[d]	19 (1.4)[e]

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 during the 30 day follow-up period (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]). See Section 2.1.4 for mini narratives for these patients.

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; bd Twice daily; CSR Clinical study report; DCO Data cut-off.; FAS Full analysis set; N Total number of patients; SAE Serious adverse event.

A listing for all patients in POLO whose deaths were not related to disease under investigation only is presented in Table below; a listing for all patients who had AEs leading to death in the 300 mg bd pool (excluding deaths in POLO) is presented in Table below**.**

Table 48. Listing of key information for AEs leading to death in the 300 mg bd pool (excluding POLO)

Sex/Age (years)	AE (MedDRA preferred term)	Causally related to olaparib[a]	Time from start of treatment to AE onset (days)	Dose last taken before death (mg/day)	Time from last dose to death (days)	Time from start of treatment to death(days)
F/71	Acute myeloid leukaemia	Yes	526	300	177	680
M/63	Ophthalmic herpes zoster	No	68	600	31	89
M/77	Hepatic failure	No	23	400	2	24
F/49	Sepsis	No	72	400	1	704
F/73	Cardiopulmonary failure	No	63	600	4	63
F/68	Myelodysplastic syndrome	Yes	249	500	82	313
F59	Acute myeloid leukaemia	Yes	748	500	21	767
	Subarachnoid haemorrhage	No	761			
F/52	Acute myeloid leukaemia	Yes	807	300	328	1084
F/64	Acute myeloid leukaemia	Yes	571	300	308	825
F/39	Sepsis	No	138	600	16	139

[a]   As assessed by the investigator
AE: Adverse event; bd: Twice daily; CSR: Clinical study report; DCO: Data cut-off; F: Female; M: Male; MedDRA: Medical Dictionary for Regulatory Activities.

Serious adverse events: POLO

Only SAEs reported in >2 patients in either treatment arm are shown in Table below

Table 49. Most common SAEs (occurring in ≥2 patients in either treatment group) in POLO (SAS)

MedDRA SOC Preferred term	Number (%) of patients	
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)
Patients with any SAE	22 (24.2)	9 (15.0)
Gastrointestinal disorders	10 (11.0)	3 (5.0)
Abdominal pain	3 (3.3)	1 (1.7)
Vomiting	1 (1.1)	3 (5.0)
Blood and lymphatic system disorders	6 (6.6)	1 (1.7)
Anaemia	6 (6.6)	0
Hepatobiliary disorders	4 (4.4)	1 (1.7)
Cholangitis	2 (2.2)	1 (1.7)
General disorders and administration site conditions	1 (1.1)	2 (3.3)
Pyrexia	0	2 (3.3)

bd Twice daily; MedDRA Medical Dictionary for Regulatory Activities (v21.1); SAE Serious adverse event; SAS Safety analysis set; SOC System organ class.
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.

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.

Comparison of serious adverse events in POLO and Study 42

Seven pancreatic cancer patients in Study 42 had a total of 12 on-treatment SAEs (SAEs were anaemia, cerebrovascular accident, cholangitis, device related sepsis, fatigue, groin pain hypokalaemia, intestinal mass, obstruction gastric, pneumonia, pulmonary embolism and vomiting; each SAE was reported by a single patient only. Of the 12 AEs, only 3 SAEs were unresolved at the DCO date (groin pain, intestinal mass and pulmonary embolism;

Table 50. POLO: Most common SAEs (occurring in ≥2 patients) in either POLO SAS or Study 42 pancreatic cancer cohort only

MedDRA SOC Preferred term	Number (%) of patients	
	Olaparib capsules 400 mg bd Study 42 pancreatic cancer cohort N=23	Olaparib tablet 300 mg bd POLO SAS N=91
Patients with any SAE	7 (30.4)	22 (24.2)
Gastrointestinal disorders	3 (13.0)	10 (11.0)
Abdominal pain	0	3 (3.3)
Blood and lymphatic system disorders	1 (4.3)	6 (6.6)
Anaemia	1 (4.3)	6 (6.6)
Hepatobiliary disorders	1 (4.3)	4 (4.4)
Cholangitis	1 (4.3)	2 (2.2)

bd Twice daily; MedDRA Medical Dictionary for Regulatory Activities (v21.1); SAE Serious adverse event; SAS Safety analysis set; SOC System organ class.

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.

Comparison of serious adverse events in POLO and the 300 mg bd pool

Most SAEs were reported by single patients in POLO, but the SOCs where SAEs were most commonly reported were Blood and lymphatic system disorders, gastrointestinal disorders and Infections and infestations and this was consistent for 300 mg bd pool data (see Table 47).

Table 51. Most common SAEs (reported by ≥2 patients in the Olaparib treatment arm of POLO and/or reported by ≥5 patients in the 300 mg bd pool)

System organ class Preferred term	Number (%) of patients	
	POLO SAS olaparib 300 mg bd (N=91)	Olaparib 300 mg bd pool (N=1329)
Patients with any SAE	**22 (24.2)**	**274 (20.6)**
Gastrointestinal disorders	**10 (11.0)**	**53 (4.0)**
Abdominal pain	3 (3.3)	11 (0.8)
Vomiting	1 (1.1)	8 (0.6)
Intestinal obstruction	0	6 (0.5)
Ileus	0	5 (0.4)
Small intestinal obstruction	0	5 (0.4)
Blood and lymphatic system disorders	**6 (6.6)**	**82 (6.2)**
Anaemia	6 (6.6)	67 (5.0)
Neutropenia	0	7 (0.5)
Thrombocytopenia	0	5 (0.4)
Hepatobiliary disorders	**4 (4.4)**	**10 (0.8)**
Cholangitis	2 (2.2)	3 (0.2)
Infections and infestations	**4 (4.4)**	**54 (4.1)**
Urinary tract infection	1 (1.1)	10 (0.8)
Pneumonia	1 (1.1)	9 (0.7)
Sepsis	0	6 (0.5)
Gastroenteritis	0	5 (0.4)
General disorders and administration site conditions	**1 (1.1)**	**23 (1.7)**
Pyrexia	0	8 (0.6)

System organ class Preferred term	Number (%) of patients	
	POLO SAS olaparib 300 mg bd (N=91)	Olaparib 300 mg bd pool (N=1329)
Respiratory, thoracic and mediastinal disorders	1 (1.1)	20 (1.5)
Pleural effusion	1 (1.1)	6 (0.5)
Pulmonary embolism	0	5 (0.4)
Investigations	1 (1.1)	11 (0.8)
Platelet count decreased	1 (1.1)	5 (0.4)
Vascular disorders	1 (1.1)	10 (0.8)
Deep vein thrombosis	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.

bd Twice daily; CSR Clinical study report; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

Data derived from Table 11.3.4.1.1, POLO CSR, Module 5.3.5.1 (DCO: 15 January 2019); Table 2.7.4.1.3.1, 300 mg bd pool, Module 5.3.5.3 (DCO: 15 January 2019).

Adverse Drug Reactions (ADR)

The ADRs previously identified for olaparib tablets were: anaemia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, fatigue and asthenia, nausea and vomiting, diarrhoea, stomatitis, dyspepsia, upper abdominal pain, decreased appetite, increase in blood creatinine, mean corpuscular volume (MCV) increased, headache, dizziness, dysgeusia, cough, hypersensitivity, dermatitis, rash, and dyspnoea.

All the ADRs are generally of mild or moderate severity (CTCAE grade 1 or 2) and rarely require treatment discontinuation.

The frequencies of ADRs based the POLO study are shown in table 48.

Table 52. Frequency of AEs in POLO for events identified as ADRs associated with olaparib treatment

System organ class/PT	Olaparib 300 mg bd N=91		Placebo N=60	
	All CTCAE grades n (%)	CTCAE grades ≥3 n (%)	All CTCAE grades n (%)	CTCAE grades ≥3 n (%)
Blood and lymphatic system disorders	32 (35.2)	14 (15.4)	16 (26.7)	3 (5.0)
Anaemia[a]	25 (27.5)	10 (11.0)	10 (16.7)	2 (3.3)
Neutropenia[a]	11 (12.1)	4 (4.4)	5 (8.3)	2 (3.3)
Thrombocytopenia[a]	13 (14.3)	3 (3.3)	4 (6.7)	0
Lymphopenia[a]	2 (2.2)	1 (1.1)	1 (1.7)	0
Leukopenia[a]	5 (5.5)	1 (1.1)	2 (3.3)	0
Respiratory, thoracic and mediastinal disorders	23 (25.3)	2 (2.2)	7 (11.7)	1 (1.7)
Cough[a]	8 (8.8)	0	2 (3.3)	0
Dyspnoea[a]	12 (13.2)	0	3 (5.0)	1 (1.7)
Gastrointestinal disorders	69 (75.8)	7 (7.7)	38 (63.3)	4 (6.7)
Nausea	41 (45.1)	0	14 (23.3)	1 (1.7)
Vomiting	18 (19.8)	1 (1.1)	9 (15.0)	1 (1.7)
Diarrhoea	26 (28.6)	0	9 (15.0)	0
Dyspepsia	5 (5.5)	0	5 (8.3)	0
Abdominal pain upper	6 (6.6)	0	8 (13.3)	2 (3.3)
Stomatitis[a]	9 (9.9)	0	3 (5.0)	0
General disorders and administration site conditions	59 (64.8)	6 (6.6)	28 (46.7)	1 (1.7)
Fatigue (including asthenia)[a]	55 (60.4)	5 (5.5)	21 (35.0)	1 (1.7)
Investigations	25 (27.5)	7 (7.7)	13 (21.7)	0
Increase in creatinine	6 (6.6)	0	1 (1.7)	0
Metabolism and nutrition disorders	32 (35.2)	4 (4.4)	12 (20.0)	4 (6.7)
Decreased appetite	23 (25.3)	3 (3.3)	4 (6.7)	0

System organ class/PT	Olaparib 300 mg bd N=91		Placebo N=60	
	All CTCAE grades n (%)	CTCAE grades ≥3 n (%)	All CTCAE grades n (%)	CTCAE grades ≥3 n (%)
Nervous system disorders	40 (44.0)	4 (4.4)	27 (45.0)	1 (1.7)
Headache	6 (6.6)	0	8 (13.3)	0
Dysgeusia	10 (11.0)	0	3 (5.0)	0
Dizziness	6 (6.6)	0	3 (5.0)	0
Skin and subcutaneous tissue disorders	30 (33.0)	0	12 (20.0)	0
Hypersensitivity[a]	2 (2.2)	0	0	0
Rash[a]	14 (15.4)	0	3 (5.0)	0
Dermatitis[a]	0	0	0	0

[a] Anaemia includes PTs of anaemia, erythropenia, haemoglobin decreased, red blood cell count decreased, haematocrit decreased, anaemia macrocytic, normochromic anaemia, normochromic normocytic anaemia, and normocytic anaemia; Neutropenia includes PTs of agranulocytosis, granulocyte count decreased, granulocytopenia, neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic infection, neutropenic sepsis, and idiopathic neutropenia; Thrombocytopenia includes PTs of thrombocytopenia, platelet count decreased, platelet production decreased, and plateletcrit decreased; Lymphopenia includes PTs of lymphocyte count decreased, lymphopenia, B-lymphocyte count decreased, and T-lymphocyte count decreased; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Cough includes PTs of cough and productive cough; Stomatitis includes PTs of stomatitis, mouth ulceration, and aphthous ulcer; Fatigue and Asthenia includes PTs of asthenia and fatigue; Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity; Rash includes PTs of exfoliative rash, generalised erythema, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, and rash pruritic; Dermatitis includes PTs of dermatitis, dermatitis allergic, and dermatitis exfoliative; Dyspnoea includes PTs of dyspnoea and dyspnoea exertional.

Analysis of main adverse drug reactions

Hematologic toxicities

Anaemia

AEs of anaemia were reported for a higher percentage of patients in the olaparib arm (27, 5%) compared with the placebo arm (16, 7%). These events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment.

Onset of anaemia was early, generally in the first 3 months of starting olaparib (median time to first onset was 1.25 months; although the risk of developing anaemia remained fairly constant throughout exposure with no evidence of cumulative effect. AEs of anaemia were manageable by interrupting or reducing the olaparib dose or giving blood transfusions or other blood preparations in accordance with local practice. The majority of patients who developed anaemia resolved on treatment.

Blood transfusions were reported in 16.5% of the patients treated with olaparib. No patients discontinued treatment due to AEs of anaemia.

Table 53. POLO and the 300 mg bd pool: Patients who had at least one AE of anaemia (grouped term) reported in any category

AE category[a]	Number (%) of patients		
	POLO SAS		Olaparib 300 mg bd pool (N=1329)
	Olaparib 300 mg bd (N=91)	Placebo bd (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 anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia, 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.

Table 54. Blood products use (SAS)

	Number (%) of patients	
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)
Number of patients with a blood transfusion[a]	15 (16.5)	0
Other antianemic preparations	**1 (1.1)**	**0**
Epoetin beta	1 (1.1)	0
Number of patients with a blood transfusion and/or another antianemic preparation	15 (16.5)	0
Patients with a blood transfusion and/or another antianemic preparation and CTCAE Grade ≥2 haemoglobin	16 (17.6)	0
Patients with a blood transfusion and/or another antianemic preparation and an AE of Anaemia (grouped term)	16 (17.6)	0

[a]   Whole blood (n=4) or red blood cells, concentrated (n=12) and includes concomitant medications taken at any time during the continuous dosing phase.

bd Twice daily; SAS Safety analyis set.

Neutropenia

Table 55. POLO and the 300 mg bd pool: Patients who had at least one AE of neutropenia (grouped term) reported in any category

AE category[a]	Number (%) of patients		
	POLO SAS		Olaparib 300 mg bd pool (N=1329)
	Olaparib 300 mg bd (N=91)	Placebo bd (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; bd Twice daily; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

AEs of neutropenia were reported for a higher percentage of patients in the olaparib arm (12.1%) compared with the placebo arm (8.3%). These events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment

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 of 11 patients) of events with olaparib resolved (median time to resolution of 0.33 months for first event

Lymphopenia

Table 56. POLO and the 300 mg bd pool: Patients who had at least one AE of lymphopenia (grouped term) reported in any category

AE category[a]	Number (%) of patients		
	POLO SAS		Olaparib 300 mg bd pool (N=1329)
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)	
Any AE	2 (2.2)	1 (1.7)	63 (4.7)
Any AE of CTCAE Grade 3 or higher	1 (1.1)	0	17 (1.3)
Any AE with outcome = death	0	0	0
Any SAE	0	0	0
AEs leading to dose reduction	0	0	2 (0.2)
AEs leading to treatment interruption	0	0	9 (0.7)
Any AE leading to discontinuation	0	0	1 (0.1)

Grouped term consisting of the preferred terms of: B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia and T-lymphocyte 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.

AEs of lymphopenia were reported for a similar percentage of patients in the olaparib arm (2.2%) compared with the placebo arm (1.7%). These events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment.

Thrombocytopenia

Table 57. POLO and the 300 mg bd pool: Patients who had at least one AE of thrombocytopenia (grouped term) reported in any category

AE category[a]	Number (%) of patients		
	POLO SAS		Olaparib 300 mg bd pool (N=1329)
	Olaparib 300 mg bd (N=91)	Placebo bd (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; bd Twice daily; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

AEs of thrombocytopenia were reported for a higher percentage of patients in the olaparib arm (14.3%) compared with the placebo arm (6.7%). These events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment. These were 4 patients in the olaparib arm (with AEs including anastomotic haemorrhage, epistaxis, gastric varices haemorrhage and upper gastrointestinal haemorrhage) and 2 patients in the placebo arm (with AEs of pancreatic haemorrhage and rectal haemorrhage).

There was 1 (1.1%) CTCAE Grade 4 SAE and 2 (2.2%) Grade 3 AEs of thrombocytopenia (grouped term) in the olaparib arm, compared with no patients in the placebo arm

Leukopenia

Table 58. POLO and the 300 mg bd pool: Patients who had at least one AE of leukopenia (grouped term) reported in any category

AE category[a]	Number (%) of patients		
	POLO SAS		Olaparib 300 mg bd pool (N=1329)
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)	
Any AE	5 (5.5)	2 (3.3)	203 (15.3)
Any AE of CTCAE Grade 3 or higher	1 (1.1)	0	45 (3.4)
Any AE with outcome = death	0	0	0
Any SAE	0	0	4 (0.3)
AEs leading to dose reduction	0	0	22 (1.7)
AEs leading to treatment interruption	0	0	61 (4.6)
Any AE leading to discontinuation	0	0	4 (0.3)

Grouped term consisting of: agranulocytosis, granulocyte count decreased, granulocytopenia, leukopenia and white 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.

Nausea and vomiting

In POLO study, the reported incidence was higher for olaparib-treated patients compared with placebo-treated patients (nausea: 45.1% vs 23.3% and vomiting: 19.8% vs 15.0%, respectively. Events were predominantly Grade 1 or 2 in severity and resolved in the majority of patients while continuing treatment with olaparib.

A total of 15 (36.6%) olaparib-treated patients reported both nausea and vomiting. Approximately half of the olaparib-treated patients with nausea (19 [46.3%] of 41 patients) were treated for the AE and 5 (27.8%) of 18 patients with vomiting received treatment; similar proportions of patients received treatment for nausea and vomiting in the placebo arm (5 [35.7%] of 14 patients and 4 [44.4%] of 9 patients, respectively.

Events of nausea and vomiting were generally reported early in the treatment period (median time to onset was 0.16 months and 0.95 months, respectively.

Table 59. POLO and the 300 mg bd pool: Patients who had at least one AE of nausea or vomiting reported in any category

AE category[a]	Number (%) of patients					
	Nausea			Vomiting		
	POLO SAS		Olaparib 300 mg bd pool (N=1329)	POLO SAS		Olaparib 300 mg bd pool (N=1329)
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)		Olaparib 300 mg bd (N=91)	Placebo bd (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; bd Twice daily; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; DCO Date cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

Diarrhoea

In polo study, AEs of diarrhoea (single preferred term) were reported for a higher percentage of patients in the olaparib arm (28.6%) compared with the placebo arm (15%). These events were all Grade 1 or 2 in severity and none led to permanent discontinuation of treatment.

Events of diarrhoea 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.

Table 60. POLO and the 300 mg bd pool: Patients who had at least one AE of diarrhoea reported in any category

AE category[a]	Number (%) of patients		
	POLO SAS		Olaparib 300 mg bd pool (N=1329)
	Olaparib 300 mg bd (N=91)	Placebo bd (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; bd Twice daily; CSR Clinical study report; 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

In polo study, AEs of fatigue/asthenia were reported in a higher percentage of patients in the olaparib arm (60.4%) compared with the placebo arm (35%).

These events were generally Grade 1 or 2 in severity and rarely resulted in permanent discontinuation of treatment. 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.

Table 61. POLO and the 300 mg bd pool: Patients who had at least one AE of fatigue or asthenia reported in any category

AE category[a]	Number (%) of patients		
	POLO SAS		Olaparib 300 mg bd pool (N=1329)
	Olaparib 300 mg bd (N=91)	Placebo bd (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; bd Twice daily; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety analysis set.

Grouped term analysis of all abdominal pain events

Because the incidence of upper abdominal pain (all events and CTCAE Grade 3 events) in olaparib-treated patients in POLO was low an analysis used grouped term for abdominal pain was conducted (abdominal pain, abdominal pain lower, abdominal pain upper and gastrointestinal pain).

The results of this analysis showed the proportion of patients with AEs of abdominal pain (all events, CTCAE Grade ≥3 events) was similar for the olaparib-treated arm compared with the placebo-treated arm in POLO.

Table 62. POLO and the 300 mg bd pool: Patients who had at least one AE of abdominal pain (grouped term analysis) reported in any category

AE category[a]	Number (%) of patients		
	POLO SAS		Olaparib 300 mg bd pool (N=1329)
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)	
Any AE	31 (34.1)	22 (36.7)	373 (28.1)
Any AE of CTCAE Grade 3 or higher	2 (2.2)	3 (5.0)	21 (1.6)
Any AE with outcome = death	0	0	0
Any SAE	3 (3.3)	1 (1.7)	11 (0.8)
AEs leading to dose reduction	0	0	3 (0.2)
AEs leading to treatment interruption	4 (4.4)	0	31 (2.3)
Any AE leading to discontinuation	0	0	2 (0.2)

The grouped term consisted of the following individual PTs: abdominal pain, abdominal pain lower, abdominal pain upper, and gastrointestinal pain.

[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; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; N Total

Cough

In the POLO study, AEs of cough (grouped term consisting of cough and productive cough) were reported for a higher percentage of patients in the olaparib arm (8.8%) than the placebo arm (3.3%)

There were no CTCAE Grade 3 events in the POLO study and no AEs led to permanent discontinuation of treatment.

A higher proportion of patients in the olaparib arm with an AE of cough received treatment for the AE (4 [50.0%] of 8 patients) compared with no patients in the placebo arm.

In POLO, AEs of cough (grouped term analysis) in the olaparib arm were reported throughout the study period (median time to first onset was 4.42 months); the majority (6 of 8 patients) of events with olaparib resolved (median time to resolution of first event of 0.72 months).

Table 63. POLO and the 300 mg bd pool: Patients who had at least one AE of cough (grouped term) reported in any category

AE category[a]	Number (%) of patients		
	POLO SAS		Olaparib 300 mg bd pool (N=1329)
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)	
Any AE	8 (8.8)	2 (3.3)	196 (14.7)
Any AE of CTCAE Grade 3 or higher	0	0	2 (0.2)
Any AE with outcome = death	0	0	0
Any SAE	0	0	1 (0.1)
AEs leading to dose reduction	0	0	0
AEs leading to treatment interruption	0	0	8 (0.6)
Any AE leading to discontinuation	0	0	0

Grouped term consisting of cough and productive cough

[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. Hypersensitivity grouped term consisting of hypersensitivity and drug hypersensitivity.

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

Data derived from Table 2.7.4.1.5.2.22a and Table 2.7.4.1.5.2.22b, Module 5.3.5.3 (DCO: 15 January 2019).

Dyspnoea

In POLO, AEs of dyspnoea (grouped term consisting of AEs of bendopnoea, bergman's triad, dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal, laryngeal dyspnoea, nocturnal dyspnoea, orthopnoea, platypnoea, transfusion-associated dyspnoea and trepopnoea) were reported for a higher percentage of patients in the olaparib arm (13.2%) than the placebo arm (5%).

There were no CTCAE Grade 3 AEs, SAEs or DAE for dyspnoea (grouped term) in the POLO study.

Table 64. POLO and the 300 mg bd pool: Patients who had at least one AE of dyspnoea (grouped term analysis) reported in any category

AE category[a]	Number (%) of patients		
	POLO SAS		Olaparib 300 mg bd pool (N=1329)
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)	
Any AE	12 (13.2)	3 (5.0)	188 (14.1)
Any AE of CTCAE Grade 3 or higher	0	0	11 (0.8)
Any AE with outcome = death	0	0	0
Any SAE	0	0	4 (0.3)
AEs leading to dose reduction	0	0	1 (0.1)
AEs leading to treatment interruption	1 (1.1)	0	13 (1.0)
Any AE leading to discontinuation	0	0	2 (0.2)

Grouped term consisting of bendopnoea, bergman's triad, dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal, laryngeal dyspnoea, nocturnal dyspnoea, orthopnoea, platypnoea, transfusion-associated dyspnoea and trepopnoea.

[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.

Adverse events of special interest

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), pneumonitis and new primary malignancies have been classified in the RMP as important potential risks supported by pharmacovigilance activities. Reports for events of MDS/AML and new primary malignancies continue to be collected beyond 30 days after the last dose of olaparib, by use of targeted safety questionnaire, and can be reported at any point in OS follow-up.

Since MDS/AML, pneumonitis and new primary malignancies occur at low frequency, to improve the sensitivity and precision of estimates to characterize these important potential risks, information has been drawn from larger pools of olaparib studies; Summaries of all reports for each safety topic up to the DCO of 15 December 2018 are provided in summary, these are:

- Olaparib monotherapy all doses pool (n=2527 patients) consists of all patients who have received at least 1 dose of olaparib as a monotherapy treatment (tablet or capsule formulation) at any dose. In addition, 23 patients from Study 42 are included. All patients from the olaparib monotherapy combined therapeutic dose pool are included in the olaparib monotherapy all doses pool

- Entire clinical programme as of 15 December 2018 (n=10682 patients) This pool includes, any studies where olaparib is given in combination with other anticancer treatments, investigator-sponsored studies (ISSs) and data from the managed access programme (MAP)

Myelodysplastic syndrome/acute myeloid leukaemia

Table *63*. Summary of AEs of MDS/AML occurring across the olaparib programme shows the AEs of MDS/AML in the olaparib all doses monotherapy pool and across the entire olaparib clinical programme, and provides incidence rates.

Table 65. Summary of AEs of MDS/AML occurring across the olaparib programme

| Data source | TEAEs[a] + AEs after 30-day follow-up | | | |
| | Olaparib | | Placebo | |
	Number of AEs	Incidence	Number of AEs	Incidence
POLO N=91 olaparib N=60 placebo	0	0	0	0
Olaparib monotherapy, all doses pool N=2527 olaparib	30	1.2%	NA	NA
Entire clinical programme pool N=10682 olaparib	64	0.6%	NA	NA

[a]   TEAEs are events occurring on-study or during 30-day follow-up. Note, in the POLO study, AEs of MDS/AML were not actively solicited beyond 30 days after the last dose of olaparib; when these AEs were reported as occurring after the 30-day follow-up period, they were captured on the AstraZeneca Patient Safety database.

AEs Adverse events; AML Acute myeloid leukaemia; CSR Clinical study report; DCO Data Cut-off;

In POLO, there were no patients with reported events of MDS or AML in the olaparib or placebo treatment arms, which occurred on treatment or within the 30-day follow-up.

The incidence of events of MDS/AML in the olaparib arm of POLO (no events) was consistent with the incidence for olaparib in other studies in breast cancer (no AEs of MDS/AML were reported in the OlympiAD study) and lower than that seen for olaparib in studies in ovarian cancer (SOLO1 [1.9%], SOLO2 [2.1%], Study 19 [1.5%]) and the larger monotherapy pool population for the olaparib clinical programme (1.0%).

Incidence rates of MDS/AML in other pivotal studies, in the olaparib all doses monotherapy pool and across the entire olaparib clinical programme

Including all patients exposed to olaparib during clinical development (ie, including data from monotherapy studies, blinded studies, combination studies, investigator sponsored studies [ISSs] and the managed access programme [MAP]) provides data for 10682 patients (as of 15 December 2018). In this population, largely composed of ovarian and breast cancer patients, there have been 64 reports of MDS/AML out of a total of 10682 patients estimated to have received olaparib in the clinical study programme, giving an estimated cumulative incidence of 0.6% for MDS/AML. The 64 reports of MDS/AML comprise the 30 reports from the olaparib monotherapy all doses pool, plus reports from ongoing open label monotherapy studies, the ongoing MAP programme, combination studies with olaparib (including ISSs) and events from placebo-controlled, blinded monotherapy studies. Events in patients which are still on blinded treatment have been considered as olaparib cases in the calculation of incidence rates.

Most of the 30 patients with events of MDS/AML in the olaparib monotherapy all doses pool were receiving treatment for ovarian, peritoneal or fallopian tube cancer (n=24), with 2 other events occurring in patients with breast cancer. Twenty-two patients had a documented *BRCA* mutation, 2 patients were *gBRCA* wildtype and in 2 patients, the *BRCA* mutation status was unknown.

In 18 of the 30 cases of MDS/AML in the monotherapy pool a fatal outcome was reported, with MDS/AML noted as the primary or secondary cause of death. The duration of therapy with olaparib in patients who developed MDS/AML varied from <4.2 months to >4.9 years

In 6 cases, MDS/AML was ongoing at the time of reporting and in 1 case of chronic myelomonocytic leukaemia, outcome was reported as recovered following allogeneic transplantation 320 days after diagnosis. There have also been reports of MDS/AML from post marketing surveillance, consistent with the characterisation of the events reported from monotherapy clinical studies.

New primary malignancy

In POLO, there were no events of new primary malignancy reported in either arm on treatment or during the 30-day follow-up period. Two patients in the placebo arm reported new primary malignancies (one rectal cancer and one ovarian cancer) which occurred after the 30-day follow-up period.

Table *64*. Summary of AEs of new primary malignancies occurring across the olaparib programme shows the AEs of new primary malignancies in POLO compared with other studies in the clinical programme, and provides incidence rates. When larger populations of olaparib-treated patients are considered the incidence remains below 1.5%.

Table 66. Summary of AEs of new primary malignancies occurring across the olaparib programme

Data source	TEAEs[a] + AEs after 30-day follow-up			
	Olaparib		Placebo[b]	
	Number of AEs	Incidence	Number of AEs	Incidence
POLO N=91 olaparib N=60 placebo	0	0	0	NA
Olaparib monotherapy, all doses pool N=2527 olaparib	35	1.4	NA	NA
Entire clinical programme pool N=10682 olaparib	69	0.6	NA	NA

[a]   TEAEs are events occurring on-study or during 30-day follow-up. Note, in the POLO study, AEs of new primary malignances were not actively solicited beyond 30 days after the last dose of olaparib; when these AEs were reported as occurring after the 30-day follow-up period, they were captured on the AstraZeneca Patient Safety database.

[b]   A review of AEs that started >30 days following the last dose of study treatment showed that 2 placebo treated patients had AEs that were potential new primary malignancies (1 patient had an AE of rectal cancer that was CTCAE Grade 2 and 1 patient was reported to have metastatic ovarian cancer as primary cause of death; both events occurred more than 300 days after the last dose of placebo treatment). These AEs are not included in the table as they were not actively solicited.

Other

Pneumonitis

AEs of pneumonitis are collected on-treatment and during the 30-day follow-up period only; there is no additional follow-up for pneumonitis events beyond the end of the 30-day follow up period.

Table 67. Summary of AEs of pneumonitis occurring across the olaparib programme

Data source	TEAEs[a]			
	Olaparib		Placebo	
	Number of AEs	Incidence	Number of AEs	Incidence
POLO N=91 olaparib N=60 placebo	1	1.1	0	0
Olaparib monotherapy, combined therapeutic dose pool N=2095 olaparib	15	0.7	NA	NA

[a]   TEAEs are events occurring on-study or during 30-day follow-up.
AEs Adverse events; CSR Clinical study report; DCO Data Cut-off; N Total number of patients; NA Not applicable; TEAE Treatment emergent adverse event.

In POLO, there was 1 Grade 1 pneumonitis case reported in olaparib-treated patients and no cases in placebo-treated patients.

Overall, the majority of pneumonitis AEs reported in the olaparib monotherapy therapeutic dose pool were mild or moderate, non-serious and resolved without treatment discontinuation. None of the 15 pneumonitis AEs had a fatal outcome

Pneumonitis AEs received from post-marketing spontaneous reports and other solicited sources with olaparib monotherapy are consistent with the characterisation of the events reported from olaparib monotherapy clinical studies. The reports of pneumonitis from post-marketing surveillance are consistent with the characterisation of the events reported from monotherapy clinical studies.

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.

Laboratory findings

Haematology

Table 68. POLO - Number (%) of patients with maximum overall CTCAE grades during treatment for key haematological parameters (SAS)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin					
Olaparib 300 mg bd	13/91 (14.3%)	50/91 (54.9%)	18/91 (19.8%)	10/91 (11.0%)	0
Placebo bd	21/58 (36.2%)	35/58 (60.3%)	2/58 (3.4%)	0	0
Platelets					
Olaparib 300 mg bd	39/88 (44.3%)	42/88 (47.7%)	5/88 (5.7%)	2/88 (2.3%)	0
Placebo bd	36/59 (61.0%)	23/59 (39.0%)	0	0	0
Leukocytes					
Olaparib 300 mg bd	40/80 (50.0%)	24/80 (30.0%)	14/80 (17.5%)	1/80 (1.3%)	1/80 (1.3%)
Placebo bd	44/57 (77.2%)	10/57 (17.5%)	3/57 (5.3%)	0	0
Neutrophils					
Olaparib 300 mg bd	53/71 (74.6%)	9/71 (12.7)%	7/71 (9.9%)	1/71 (1.4%)	1/71 (1.4%)
Placebo bd	45/50 (90.0%)	1/50 (2.0%)	4/50 (8.0%)	0	0
Lymphocytes					
Olaparib 300 mg bd	29/75 (38.7%)	21/75 (28.0%)	18/75 (24.0%)	5/75 (6.7%)	2/75 (2.7%)
Placebo bd	38/52 (73.1%)	11/52 (21.2%)	3/52 (5.8%)	0	0

bd Twice daily; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; SAS Safety analysis set.
Derived from local laboratory assessments using local reference ranges

Clinical chemistry

Based on data provided there were no new clinical chemistry changes observed during POLO (Table 65).

Table 69. POLO: Number (%) of patients with maximum overall CTCAE grades during treatment for key clinical chemistry parameters (SAS)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT					
Olaparib 300 mg bd	56/89 (62.9%)	25/89 (28.1%)	4/89 (4.5%)	4/89 (4.5%)	0
Placebo bd	31/59 (52.5%)	23/59 (39.0%)	4/59 (6.8%)	1/59 (1.7%)	0
AST					
Olaparib 300 mg bd	52/89 (58.4%)	30/89 (33.7%)	4/89 (4.5%)	3/89 (3.4%)	0
Placebo bd	34/59 (57.6%)	23/59 (39.0%)	1/59 (1.7%)	1/59 (1.7%)	0
ALP					
Olaparib 300 mg bd	32/89 (36.0%)	49/89 (55.1%)	5/89 (5.6%)	3/89 (3.4%)	0
Placebo bd	24/59 (40.7%)	31/59 (52.5%)	2/59 (3.4%)	2/59 (3.4%)	0
Albumin					
Olaparib 300 mg bd	73/88 (83.0%)	15/88 (17.0%)	0	0	0
Placebo bd	51/57 (89.5%)	5/57 (8.8%)	1/57 (1.8%)	0	0
Bilirubin					
Olaparib 300 mg bd	71/88 (80.7%)	9/88 (10.2%)	7/88 (8.0%)	1/88 (1.1%)	0
Placebo bd	55/59 (93.2%)	4/59 (6.8%)	0	0	0
Creatinine					
Olaparib 300 mg bd	1/68 (1.5%)	59/68 (86.8%)	7/68 (10.3%)	1/68 (1.5%)	0
Placebo bd	7/46 (15.2%)	37/46 (80.4%)	2/46 (4.3%)	0	0

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
GGT					
Olaparib 300 mg bd	22/84 (26.2%)	29/84 (34.5%)	19/84 (22.6%)	12/84 (14.3%)	2/84 (2.4%)
Placebo bd	18/55 (32.7%)	13/55 (23.6%)	16/55 (29.1%)	6/55 (10.9%)	2/55 (3.6%)

ALP Alkaline phosphatase; ALT Alanine aminotransferase; AST Aspartate aminotransferase; bd Twice daily; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; GGT gamma glutamyl transerase; SAS: Safety analysis set.
Derived from laboratory assessments using local reference ranges after start of treatment up to the last dose of study medication.

Comparative analysis of clinical laboratory evaluations

In general, the laboratory evaluations for POLO and the 300 mg bd pool were comparable. Changes in haemoglobin, neutrophils, lymphocytes, platelets and mean corpuscular volume were the only significant haematological parameters with clinically relevant changes; these parameters are recognised ADRs for olaparib. Anaemia is the only one important identified risk in the RMP, whereas neutropenia and thrombocytopenia are no longer considered as important identified risk in the RMP.

Increase in creatinine

Most of the laboratory values for creatinine were CTCAE Grade 1 or 2 throughout the study; a single patient in the olaparib arm had a laboratory value of CTCAE Grade 3.

AEs of increased creatinine were reported for a higher percentage of patients in the olaparib Arm (6.6%) compared with the placebo arm (1.7%), although overall numbers were low. These events were predominantly Grade 1 in severity and none led to permanent discontinuation of treatment.

•*Assessment of the potential for drug-induced liver injury*

Based on all available data there is no evidence to suggest that olaparib causes DILI. There were no confirmed Hy's Law cases. Two (2) (2.2%) olaparib-treated patients in POLO had suspected Hy's law (ie, concurrent elevations of ALT, AST and bilirubin; see Table 34): both patients had hepatic metastases at study entry, and disease progression on the same day that the abnormal hepatic enzymes were reported, which provides an explanation for their elevated liver enzymes.

•*Laboratory abnormalities for ALT and AST (POLO)*

In POLO, there were no patients who had CTCAE Grade 4 laboratory values for ALT and AST; the proportion of patients with on-treatment CTCAE Grade 3 elevations was low in both treatment arms.

- There were 4 (4.5%) of 89 patients in the olaparib arm who had a laboratory value of ALT elevation of CTCAE Grade 3 (worst grade), and 3 (3.4%) of 89 patients with CTCAE Grade 3 elevated AST during treatment. No liver diagnostic investigations data were reported for these 4 patients.

- A single placebo-treated patient had on-treatment laboratory values of ALT and AST elevations of CTCAE Grade 3 (worst grade).

•*Concomitant elevations of ALT/AST by maximal total bilirubin (POLO)*

An assessment of ALT, AST maximal elevations during treatment by maximal total bilirubin elevation showed that 6 (6.6%) patients in the olaparib arm and 4 (6.6%) patients in the placebo.

•*Laboratory abnormalities for ALT and AST (300 mg bd pool)*

In the 300 mg bd pool, 24 (1.8%) patients had an ALT increased laboratory value (worst grade) of CTCAE Grade 3 and 2 patients (0.2%) had an ALT increased laboratory value of CTCAE Grade 4; 33 (2.5%) patients had a CTCAE Grade 3 laboratory value of AST increased; no patients had an AST increased laboratory value of CTCAE Grade 4. The proportion of patients with these abnormal laboratory values in the 300 mg bd pool (1.8% and 2.5%, respectively), which was lower than that in the olaparib arm of the

POLO study (4.5% and 3.4%, respectively); no patients in POLO had CTCAE Grade 4 abnormal laboratory values

•*Concomitant elevations of ALT/AST and bilirubin (300 mg bd pool)*

An assessment of combined elevations of ALT and bilirubin was conducted for all patients in the 300 mg bd pool. Of these 1329 patients, 20 patients reported elevations of both AST or ALT >3 × ULN and total bilirubin >2 × ULN, irrespective of ALP, at any point during their study treatment

•*Assessment of potential for renal impairment*

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

The median change in creatinine from baseline to Cycle 3 for olaparib-treated patients was an increase of 11.7 µmol/L compared with 8.8 µmol/L for placebo-treated patients. Median creatinine levels for olaparib-treated patients then remained consistent over time (maximum median change 14.1 µmol/L, median change at the majority of time points between 8.8 and 13.6 µmol/L) with levels returning to baseline at the 30 day follow-up/post follow-up visits

Data from all patients in the 300 mg bd pool showed that a similar proportion of patients in the 300 mg bd pool had CTCAE grade shifts in creatinine, compared with POLO. In the 300 mg bd pool, 91.5% of olaparib-treated patients had normal creatinine at baseline, 7.8% had CTCAE Grade 1 at baseline and 0.5% had CTCAE Grade 2 at baseline. A total of 1018/1325 (76.8%) patients had a single change in CTCAE Grade (changes were normal to Grade 1 in 980 of the 1018 patients) and 203/1325 (15.3%) had 2 CTCAE grade shifts (all were normal to Grade 2); 3 patients (0.2%) had a 3 grade shift in creatinine (from Grade 0 to Grade 3).

Safety in special populations

The 300 mg bd pool has largely been used as the data source for this section rather than POLO however, as the POLO study is the first Phase III study with olaparib in a tumour type that was not strongly associated with female patients, an analysis of AEs by patient gender in the POLO study has also been included. The pooled dataset includes patients with a range of solid tumours, including breast cancer.

Effect of age

***Table 69. Number of patients reporting at least one adverse event by age group in* the 300 mg bd pool**

MedDRA term	Number (%) of patients			
	Age ≤65 years N=1060	Age 65 to 74 years N=221	Age 75 to 84 years N=48	Age ≥85 years N=0
Any AE	1034 (97.5)	217 (98.2)	47 (97.9)	0
Any AE CTCAE grade 3 or higher	413 (39.0)	95 (43.0)	20 (41.7)	0
Any AE with outcome = death	4 (0.4)	4 (1.8)	1 (2.1)	0
Any SAE (including events with outcome = death)	210 (19.8)	53 (24.0)	11 (22.9)	0
Fatal	3 (0.3)[b]	4 (1.8)	1 (2.1)	0
Hospitalisation/prolong existing hospitalisation	194 (18.3)	47 (21.3)	11 (22.9)	0
Life-threatening	24 (2.3)	12 (5.4)	1 (2.1)	0
Other (disability incapacity)	5 (0.5)	2 (0.9)	0	0
Other (medically significant)	59 (5.6)	13 (5.9)	3 (6.3)	0
Any AE leading to dose interruption of treatment	416 (39.2)	83 (37.6)	16 (33.3)	0
Any AE leading to dose reduction of treatment	229 (21.6)	44 (19.9)	9 (18.8)	0
Any AE leading to discontinuation of treatment	76 (7.2)	20 (9.0)	6 (12.5)	0

a   The total is not equal to the sum of the events across the seriousness criteria because investigators are asked to indicate each seriousness criterion valid for the event.
b   One patient (in Study D0816C00005; a patient with moderate hepatic impairment) had a fatal AE that was not reported as an SAE. The reported AE of was of terminal hepatic failure that led to discontinuation of olaparib and death.

AE Adverse event; bd Twice daily; DCO Data cut-off; MedDRA Medical Dictionary for Regulatory Activities; SAEs Serious adverse events.

An analysis of AEs by the SOCs most relevant to elderly patients, and age is provided in table below.

Table 70. Number of patients with, and reports of adverse events within the SOCs/SMQs of most relevance to elderly patients, by age in the 300 mg bd pool

Category	Number (%) of patients			
	Age ≤65 years N=1060	Age 65 to 74 years N=221	Age 75 to 84 years N=48	Age ≥85 years N=0
Total number of patients with AEs	1034 (97.5)	217 (98.2)	47 (97.9)	0
Psychiatric disorders (SOC)	192 (18.1)	36 (16.3)	8 (16.7)	0
Accidents and injuries (SMQ)	72 (6.8)	14 (6.3)	4 (8.3)	0
Cardiac disorders (SOC)	63 (5.9)	15 (6.8)	2 (4.2)	0
Vascular disorders (SOC)	117 (11.0)	28 (12.7)	4 (8.3)	0
Central nervous system vascular disorders (SMQ)	8 (0.8)	3 (1.4)	0	0
Infections and infestations (SOC)	471 (44.4)	106 (48.0)	21 (43.8)	0
Quality of life decreased (PT)	0	0	0	0
Sum of orthostatic hypertension and loss of consciousness, falls, black outs, syncope, dizziness, ataxia, fractures	156 (14.7)	40 (18.1)	5 (10.4)	0

AE Adverse event; bd Twice daily; DCO Data cut-off; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred term; SMQ Standardised MedDRA query; SOC System organ class.

Effect of race

The safety profile in the 300 mg bd pool for olaparib in White, Asian and other non-White patients was generally similar.

Table 71. Number (%) of patients who had at least 1 AE in any category by race (White patients, Asian patients and other non-White patients) in the 300 mg bd pool

AE category[a]	Number (%) of patients		
	White patients (N=1036)	Asian patients (N=262)	Other non-White patients (N=31)
Any AE	1013 (97.8)	256 (97.7)	29 (93.5)
Any AE of CTCAE Grade ≥3	397 (38.3)	120 (45.8)	11 (35.5)
Any AE with outcome = death	7 (0.7)	2 (0.8)	0
Any SAE (including events with outcome = death)	215 (20.8)	53 (20.2)	6 (19.4)
AE leading to dose reduction of study treatment	223 (21.5)	50 (19.1)	9 (29.0)
Any AE leading to interruption of study treatment	398 (38.4)	105 (40.1)	12 (38.7)
AE leading to discontinuation of study treatment	82 (7.9)	20 (7.6)	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.

[b]   Of the 293 Non-White patients, 262 patients were Asian; 12 patients were Black, and 19 patients were 'other'.

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.

The most common (≥10% of either White or Asian patients) AEs by race are shown in

Table 72. Most common AEs (≥10% of either White or Asian patients) by race in the olaparib 300 mg bd pool

Preferred term[a]	Number (%) of patients		
	White patients (N=1036)	Asian patients (N=262)	Other non-White patients (N=31)
Any AE	1013 (97.8)	256 (97.7)	29 (93.5)
Nausea	662 (63.9)	161 (61.5)	15 (48.4)
Anaemia	372 (35.9)	123 (46.9)	18 (58.1)
Vomiting	373 (36.0)	86 (32.8)	8 (25.8)
Fatigue	435 (42.0)	79 (30.2)	7 (22.6)
Decreased appetite	216 (20.8)	71 (27.1)	7 (22.6)

Preferred term[a]	Number (%) of patients		
	White patients (N=1036)	Asian patients (N=262)	Other non-White patients (N=31)
White blood cell count decreased	34 (3.3)	64 (24.4)	3 (9.7)
Neutrophil count decreased	32 (3.1)	58 (22.1)	2 (6.5)
Upper respiratory tract infection	72 (6.9)	45 (17.2)	6 (19.4)
Neutropenia	134 (12.9)	43 (16.4)	7 (22.6)
Diarrhoea	307 (29.6)	42 (16.0)	9 (29.0)
ALT increased	38 (3.7)	40 (15.3)	1 (3.2)
Constipation	204 (19.7)	35 (13.4)	4 (12.9)
AST increased	32 (3.1)	33 (12.6)	0
Platelet count decreased	29 (2.8)	33 (12.6)	0
Leukopenia	73 (7.0)	31 (11.8)	3 (9.7)
Headache	191 (18.4)	30 (11.5)	7 (22.6)
Dizziness	128 (12.4)	31 (11.8)	5 (16.1)
Dysgeusia	183 (17.7)	29 (11.1)	6 (19.4)
Abdominal pain	205 (19.8)	27 (10.3)	4 (12.9)
Cough	148 (14.3)	27 (10.3)	4 (12.9)
Thrombocytopenia	79 (7.6)	26 (9.9)	4 (12.9)
Pyrexia	133 (12.8)	26 (9.9)	0
Dyspepsia	112 (10.8)	24 (9.2)	1 (3.2)
Back pain	138 (13.3)	18 (6.9)	5 (16.1)
Abdominal pain upper	123 (11.9)	18 (6.9)	3 (9.7)
Dyspnoea	149 (14.4)	17 (6.5)	4 (12.9)
Arthralgia	157 (15.2)	16 (6.1)	4 (12.9)
Asthenia	210 (20.3)	8 (3.1)	4 (12.9)

[a]   Table ordered by incidence of preferred terms in the population of Asian patients.
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.
ALT Alanine aminotransferase; AST Aspartate aminotransferase; bd Twice daily; WBC White blood cell.
Data derived from Table 2.7.4.1.11.2, 300 mg bd pool, Module 5.3.5.3 (DCO: 15 January 2019).

Effect of gender

Table 71 shows the distribution of AEs in the POLO study by patient sex.

Table 73. POLO: Number of patients reporting at least one adverse event by gender (SAS)

AE Category	Number (%) of patients[a]			
	Olaparib 300 mg bd (N=91)		Placebo bd (N=60)	
	Male patients N=52	Female patients N=39	Male patients N=30	Female patients N=30
Any AEs	50 (96.2)	37 (94.9)	29 (96.7)	27 (90.0)
Any AE CTCAE grade 3 or higher	22 (42.3)	14 (35.9)	8 (26.7)	6 (20.0)
Any AE with outcome = death	0	1 (2.6)[b]	0	0
Any SAE (including events with outcome = death)	13 (25.0)	9 (23.1)	6 (20.0)	3 (10.0)
Any AE leading to dose interruption of treatment	18 (34.6)	14 (35.9)	2 (6.7)	1 (3.3)
Any AE leading to dose reduction of treatment	8 (15.4)	7 (17.9)	2 (6.7)	0
Any AE leading to discontinuation of treatment	2 (3.8)	3 (7.7)	0	1 (3.3)

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.

b   One Patient in the olaparib arm had an SAE of duodenal perforation which started during the 30 day follow-up period (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.

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; bd Twice daily; DCO Data cut-off; SAE Serious adverse event; SAS Safety analysis set.

Effect of hepatic impairment at baseline

The current dosing recommendations included in the product data sheet are:

"Lynparza can be administered to patients with mild or moderate hepatic impairment (Child Pugh classification A or B) with no dose adjustment. Lynparza is not recommended for use in patients with severe hepatic impairment (Child Pugh classification C), as safety and pharmacokinetics have not been studied in these patients."

Effect of renal impairment at baseline

The current dosing recommendations included in the product data sheet are:

'For patients with moderate renal impairment (creatinine clearance 31 to 50 mL/min) the recommended dose of Lynparza is 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg). Lynparza is not recommended for patients with severe renal impairment or end-stage renal disease

(creatinine clearance ≤30 ml/min) as safety and pharmacokinetics have not been studied in these patients. Lynparza can be administered to patients with mild renal impairment (creatinine clearance 51 to 80 mL/min) with no dose adjustment.

Discontinuation due to adverse events

AE leading to discontinuation (DAEs)

In Polo, the incidence of AEs leading to discontinuation of study treatment was higher in the Olaparib arm (5.5%) than in the placebo arm (1.7%). The most common AEs leading to discontinuation of study treatment (reported for ≥2 patients) was fatigue (reported for 2 patients each [2.2%]) in the olaparib arm.

Table 74. Adverse events leading to discontinuation of study treatment in ≥2 patients by system organ class and preferred term (SAS)

MedDRA SOC preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)
Patients with any AE leading to discontinuation	5 (5.5)	1 (1.7)
General disorders and administration site conditions	2 (2.2)	1 (1.7)
Fatigue	2 (2.2)	0
Pyrexia	0	1 (1.7)
Gastrointestinal disorders	2 (2.2)	0
Duodenal perforation[c]	1 (1.1)	0
Vomiting	1 (1.1)	0
Musculoskeletal and connective tissue disorders	1 (1.1)	0
Arthralgia	1 (1.1)	0
Myalgia	1 (1.1)	0
Metabolism and nutrition disorders	1 (1.1)	0
Decreased appetite	1 (1.1)	0
Renal and urinary disorders	1 (1.1)	0
Proteinuria	1 (1.1)	0

[a] Multiple occurrences of a system organ class/preferred term for a patient were counted only once for the patient.

[b] Sorted by decreasing order of frequency in the olaparib arm and then by order of frequency in the placebo arm.

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

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.

Comparison of adverse events leading to discontinuation in 300 mg pool

The table above summarises these data, which show that although fatigue was the only DAE reported by ≥ 2 patients in POLO, anaemia and nausea were the most common AE leading to discontinuation in the 300 mg bd pool.

AEs leading to treatment interruption

The most commonly reported AEs (≥2 patients in either treatment group) leading to interruption of olaparib dosing are presented in **Table *75*. AEs leading to treatment interruption occurring in ≥2 patients in either treatment group (SAS)**.

The most common AEs leading to dose interruption (reported in ≥5% of patients) in the olaparib arm were anaemia, vomiting, neutropenia, and nausea. The most common AEs leading to dose delay (reported in ≥ 5% of patients) in the chemotherapy arm were neutropenia, thrombocytopenia, and pyrexia

Table 75. AEs leading to treatment interruption occurring in ≥2 patients in either treatment group (SAS)

Preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)
Patients with any AE leading to dose interruption	32 (35.2)	3 (5.0)
Anaemia	9 (9.9)	0
Vomiting	4 (4.4)	1 (1.7)
Abdominal pain	4 (4.4)	0
ALT increased	3 (3.3)	0
Asthenia	2 (2.2)	1 (1.7)
Arthralgia	2 (2.2)	0
AST increased	2 (2.2)	0
Constipation	2 (2.2)	0
Fatigue	2 (2.2)	0
GGT increased	2 (2.2)	0
Neutropenia	2 (2.2)	0
Platelet count decreased	2 (2.2)	0
Thrombocytopenia	2 (2.2)	0

[a] Multiple occurrences of a preferred term for a patient are counted only once for the patient.
[b] Sorted by decreasing order of frequency in the olaparib arm and then by order of frequency in the placebo arm.
AE Adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; bd Twice daily; GGT: Gamma-glutamyltransferase; MedDRA Medical Dictionary for Regulatory Activities (v21.0); SAS Safety analysis set

AEs leading to dose reduction

Table 76. Adverse events leading to dose reduction of study treatment in ≥2 patient in either group

Preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=91)	Placebo bd (N=60)
Patients with any AE leading to dose reduction	15 (16.5)	2 (3.3)
Anaemia	4 (4.4)	0
Asthenia	3 (3.3)	1 (1.7)
Fatigue	2 (2.2)	0
Vomiting	2 (2.2)	0

[a] Multiple occurrences of a preferred term for a patient are counted only once for the patient.
[b] Sorted by decreasing order of frequency in the olaparib arm and then by order of frequency in the placebo arm.

AE Adverse event; bd Twice daily; MedDRA Medical Dictionary for Regulatory Activities (v21.0);
SAS Safety analysis set.

Post marketing experience

No new safety findings have been reported from post-marketing data in the frame of this procedure. Pharmacovigilance of the product is well established.

2.5.1. Discussion on clinical safety

This application for a new indication in patients with pancreatic cancer is supported by safety data from a randomised POLO study in which 91 patients received olaparib in tablet formulation at a dose of 300 mg bd and 60 patients – placebo. This comparative data remains limited in the intended indication and is supported by non-comparative data in 12 patients with pancreatic cancer recruited in Phase I/II studies.

This safety data in pancreatic cancer patients have been compared with pooled safety data with tablet formulation at a dose of 300 mg bd as a monotherapy from additional 12 monotherapy studies providing a database of about 1329 patients (101 of whom had pancreatic cancer).

Supportive safety data from an additional 23 patients with pancreatic cancer who were recruited in Study 42 are submitted, which used the capsule formulation. This study was a Phase II, open-label, basket study of olaparib capsules 400 mg oral bd as treatment of patients with *gBRCAm* malignancies across multiple tumour types. The 23 patients in the pancreatic cancer cohort had to have either failed or be unsuitable for gemcitabine treatment in the advanced setting.

Taking into account the small number of patients in the pancreatic cohort of Study 42, the differences in patient population and the inherent limitations on interpretation of safety information from a single arm study, the safety data for the 23 patients with pancreatic cancer in Study 42 are generally supportive of the safety profile of olaparib patients with pancreatic cancer in the POLO study.

Across the entire clinical programme, as of 15 December 2018, an estimated 10682 patients have received treatment with olaparib.

Overall, the safety profile of olaparib observed in POLO study was consistent with previously reported profile for the olaparib tablet formulation.

Safety findings in POLO and tablet pooled safety datasets

- The majority of patients exposed to olaparib reported adverse events (AEs), which were generally mild to moderate in severity and did not lead to discontinuation. The toxicity of olaparib was thus most often manageable, including by dose interruptions, dose reductions and standard supportive treatment as required. The safety findings in olaparib arm of POLO were consistent with the 300 mg bd pool.

- The median total treatment duration to olaparib was approximately 1.6 times longer than duration of exposure to placebo (approximately 6.0 months) compared with the placebo arm (approximately 3.7 months). Overall, 25.3% of patients in the olaparib arm remained on treatment for ≥1 year compared with 6.7% of patients in the placebo arm. Compared with the olaparib arm of POLO, median treatment duration in the 300 mg bd pool was generally longer, due to the large number of patients in the 300 mg bd pool recruited in ovarian cancer studies where time to disease progression and hence treatment duration is longer than for pancreatic cancer.

- The majority of AEs occurred within the first 3 months of treatment. The most common (reported by ≥20% of patients) AEs in the olaparib arm were fatigue (45.1%), nausea (45.1%), diarrhoea (28.6%), abdominal pain (28.6%), anaemia (27.5%), decreased appetite (25.3%) and constipation (23.1%). These results were numerically similar for the 300 mg bd pool population; except for nausea (63.1%), vomiting (35.1%), abdominal pain (17.8%) and anaemia (38.6%).

- Dose interruptions or delay and dose reductions were reported respectively in 41.8% patients on olaparib and 16.7% placebo patients.

- The proportion of patients who reported AEs leading to discontinuation of treatment was low in both treatment arms and was higher in the olaparib arm (5.5%) compared with the placebo arm (1.1%). Fatigue (2.2%) was the only AEs leading to discontinuation of olaparib in more than one patient in the olaparib arm.

- Grade ≥3 AEs had a higher incidence in the olaparib arm (39.6% of the patients) than in the placebo arm (23.3%). Anaemia was the only AEs Grade ≥3 reported in ≥5% of patients in the olaparib arm (reported in 11% of olaparib arm versus 3.3% of placebo arm). AEs of CTCAE Grade 3 or higher were similar and occurred at similar frequencies in olaparib between treatment arm of POLO and the 300 mg bd pool (17, 2%).

- SAEs were reported in 24.2% (22/91 patients) of the olaparib-arm compared to 15% (9/60) of the placebo arm. The most common reported SAE was anemia (6.6% olaparib *vs* 0% placebo). The highest frequency of reported SAEs at the system organ class (SOC) level were gastrointestinal disorders (11% olaparib vs. 3% placebo) and blood and lymphatic system disorders (6.6% olaparib vs.1.7% placebo). The most common SAE in both arms was abdominal pain (3.3% olaparib vs 1.7% placebo), vomiting (1.1% olaparib vs 5.0% placebo) and cholangitis (2.2% vs 1.7%). The majority of SAEs had resolved with either no action taken or following a temporary dose interruption or delay/dose change or were recovering. SAEs were reported at a similar frequency in POLO and in the 300 mg bd pooled dataset.

- Most deaths occurring on study were related to the disease under investigation. A total of 3 patients died with causes unrelated to disease progression: one duodenal perforation, one refractory septic shock and one unknown cause. All 3 patients were in the olaparib arm and in all cases, death occurred after the patient had discontinued olaparib treatment and completed the 30-day follow up period. The frequency of deaths for any reason was similar for olaparib-treated patients over patients in the placebo arm (44.6% vs. 48.4% respectively). The frequency of deaths for any reason was higher for olaparib-treated patients (44.6%) in POLO over the 300 mg bd pool (27.5%).

- The adverse drug reactions (ADRs) identified for olaparib tablets are the same as before described in the SmPC of olaparib (ie, anaemia; neutropenia; leukopenia; thrombocytopenia; lymphopenia; fatigue and asthenia; nausea and vomiting; diarrhoea; dyspepsia; stomatitis; upper abdominal pain; decreased appetite; dizziness; headache; dysgeusia; cough; dyspnoea increase in blood creatinine; mean corpuscular volume elevation; rash; hypersensitivity; and dermatitis).

- Anaemia appears as the most prominent AE among Grade ≥3, SAEs and events leading to dose adjustments. Haematological toxicity overall was similar to other indications. As regards concomitant treatment, 15 (16.5%) patients in the olaparib arm received at least 1 blood or PBRC transfusion. The majority of patients received ≤3 transfusions; however, 1 patient received 18 PBRC transfusions over a 7 month period. One (1.1%) olaparib-treated patient had treatment with an erythropoiesis stimulating agent (epoetin beta). In the placebo arm of POLO, no patients received a blood transfusion or other antianaemic preparation on treatment or treatment with an erythropoiesis stimulating agent.

- The adverse events of special interest (AESIs) for olaparib are Myelodysplastic syndrome (MDS)/AML, pneumonitis and new primary malignancies. Investigators in POLO were required to record MDS/AML and new primary malignancies events beyond 30 days after the last dose of olaparib at any point in OS follow-up. A causal relationship between olaparib treatment and the development or acceleration of MDS/AML, new primary malignancies and pneumonitis has not been established.

  o There were no reports of MDS or AML in either treatment arm of POLO, either on treatment, or within the 30-day follow-up period. The incidence of MDS/AML AEs The incidence of MDS/AML AEs, in the pool of patients who received olaparib in monotherapy studies (tablet and capsule formulations; all doses of olaparib) showed an incidence of 1.2% for olaparib (30 patients with AEs of MDS/AML in a total of 2527 patients).

  o There were no reports of new primary malignancies in POLO. The incidence of new primary malignancies in the pool of patients who received olaparib in monotherapy studies (tablet and capsule formulations; all doses of olaparib) is 1.4% for olaparib (35 patients in a total of 2527 patients, of whom 12 patients had skin cancers. The non-skin cancer events were essentially: breast cancers (n=9), gastrointestinal (GI) cancers (n=5), thyroid cancer (n=2), plasma cell myeloma (n=2), lung cancer (n=2), and other (n= 3)).

  o In POLO, 1 event of pneumonitis was reported (1.1% incidence). The incidence for the pooled data of olaparib in monotherapy combined therapeutic dose (N=2095 olaparib-treated patients) is 0.7%. These events were mild or moderate, non-serious and resolved without treatment discontinuation; none of them had a fatal outcome.

- Regarding to laboratory parameters

- o Changes in the laboratory values for the haematology parameters of haemoglobin, neutrophils, platelets and lymphocytes showed a decrease on olaparib treatment. At the exception of anaemia and neutropenia (see above, paragraph on AEs grade ≥ 3) these changes were reported in low numbers of patients with a maximum CTCAE Grade of 3 or 4 (leukopenia 2.6%, neutrophil count 2.3%, % and platelet count decreased 2.3%). These changes in haematological parameters are generally mild or moderate, manageable, and reversible.

- o Increases in creatinine have been identified as an ADR with olaparib treatment. AEs of increased creatinine were predominantly Grade 1 in severity and none led to permanent discontinuation of treatment. The lab observations of elevated serum creatinine were not associated with renal impairment and had apparently no clinical sequelae.

- o No hepatobiliary or renal safety concerns were identified from a review of laboratory and AE data.

- Special populations: Although there are limited data in elderly patients ≥75 years of age, assessment of the safety of olaparib in patient subgroups has demonstrated an acceptable safety profile regardless of age, race, gender, or body weight. No dose adjustment is required on the basis of patient age, racial origin, and gender or body weight.

Additional expert consultations

After consultation with Scientific Advisory Group in Oncology the toxicity is considered generally manageable given the low frequency of treatment discontinuation due to toxicity. The toxicity profile is well characterised based on extensive experience in the breast and ovarian cancer settings.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of olaparib tablet formulation is considered acceptable for the intended population. In a relatively limited number of gBRCAm patients with metastatic pancreatic adenocarcinoma, olaparib had a safety profile similar to other previously approved indications and pooled safety data.

Nevertheless, its tolerability profile in terms of substantial proportion of dose adjustments should be considered in the context of a maintenance therapy and patients experiencing ADRs need to be carefully followed by physicians .

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The PRAC considered that the risk management plan version 18.3 is acceptable. The CHMP endorsed this advice without changes.

The olaparib RMP covers both the Capsules and Tablet formulations, however the addition of a new therapeutic indication has been proposed only for the Tablet licence, for the hard capsules the variation modifies the safety information only, by incorporating the pooled olaparib safety data.

Safety concerns

Important identified risks	None
Important potential risks	Myelodysplastic syndrome/acute myeloid leukaemia
	New primary malignancies
	Pneumonitis
	Medication errors associated with dual availability of capsules and tablets
	Effects on embryofoetal survival and abnormal development
Missing information	Long term exposure to/potential toxicity to olaparib

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance activities for olaparib.

Risk minimisation measures

Table V-77   Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
MDS/AML	Routine risk communication in: • SmPC Section 4.4 • PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.4**: Guidance is provided for monitoring and management. **PL Section 2**: Advice regarding low blood counts and the signs and symptoms to look out for. **PL Section 4**	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire • Cumulative review (provided concurrent with each annual PBRER)
New primary malignancy	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire
Pneumonitis	Routine risk communication in: • SmPC Section 4.4 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.4**: Guidance is provided for monitoring and management. **PL Section 2**: Advice on the signs and symptoms of possible pneumonitis.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire

Table V-77   **Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Medication errors associated with dual availability of capsules and tablets	Routine risk communication in: • SmPC Section 4.2 • PL Section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.2:** ~~Statement informing that olaparib is available as tablets and capsules which are not to be used interchangeably due to differences in the dosing and bioavailability of each formulation.~~ **PL Section 3**~~: Statement informing that olaparib is available as tablets and capsules which are not the same and not to be used interchangeably.~~ **Additional risk minimisation measures:** Distribution of a DHPC to prescribers and pharmacists providing clear information on the 2 formulations.	Routine
Effects on embryofoetal survival and abnormal development	Routine risk communication in: • SmPC Sections 4.4, 4.6 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.4, 4.6:** ~~Advice on contraception and pregnancy.~~ **PL Section 2:** ~~Advice on contraception and pregnancy.~~	Routine
Long term exposure to/potential toxicity to olaparib	None	Routine

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1of the SmPC have been updated to include data on the new claimed indication in pancreatic cancer.

The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable because the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The purpose of the current submission was to seek marketing approval for olaparib as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2- mutations who have metastatic adenocarcinoma of the pancreas whose disease has not progressed after a minimum of 16 weeks on first-line platinum-based chemotherapy.

3.1.2. Available therapies and unmet medical need

According to clinical guidelines for pancreatic cancer (NCCN GL v1.2020 and ESMO 2015), metastatic patients with good PS (ECOG 0-2) are eligible for at least 4-6 months of chemotherapy. In the presence of known BRCA 1/2 mutations, preferred regimens are FOLFIRINOX or modified FOLFIRINOX or Gemcitabine + cisplatin (recommendation category 2A - NCCN GL v1.2020 for pancreatic cancer). Currently, there is no approved therapy indicated for the first line maintenance treatment of adult patients with metastatic pancreatic cancer specifically in patients with germline BRCA1/2 mutations.

3.1.3. Main clinical studies

This application is based on results from the Study D081FC00001 (POLO): A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First-Line Platinum-Based Chemotherapy.

3.2. Favourable effects

POLO demonstrated a statistically significant improvement in **PFS** by BICR in FAS population, with HR of 0.531, 95% IC 0.346 – 0.815, p-value 0.0038. The median of PFS showed a difference of 3.6 months favouring olaparib arm (7.4 months *vs*. 3.8 months). The sensitivity analysis of PFS by investigator assessment (HR 0.51; 95% CI 0.34, 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. Other sensitivity analyses were also consistent with the BICR assessment of PFS, supporting the robustness of the primary analysis.

A higher proportion of patients in olaparib arm reached a <u>response</u> (CR or PR as **BoR**) (19.6% - 18/92) compared to placebo arm (9.7% - 6/62). Most of these responses were PR in both arms (17.4% - 16/92

vs 9.7% - 6/62, olaparib *vs*. placebo, respectively). CR was reached by two patients (2.2%) in the olaparib arm compared to none in the placebo arm (0.0%).

A higher rate of **ORR** by BICR was seen in the olaparib arm compared to placebo arm (23.1% vs 11.5%). A longer **duration of the response** in olaparib arm (24.9 months, n=18) compared to placebo arm (3.7 months, n=6) was reported.

3.3. *Uncertainties and limitations about favourable effects*

In line with clinical practice, the study population enrolled is heterogeneous with regard to types of first-line chemotherapy regimens, the duration of treatment with platinum and other components and potential reasons for their discontinuation (unacceptable toxicity, completion of the planned number of cycles, patient choice). Patients who could tolerate complete platinum-containing chemotherapy regimen until progression have not been consequently considered for olaparib/placebo treatment necessitating interruption of successive chemotherapy courses.

OS results did not show a statistical significance at 46% maturity with a HR of 0.906 (95% IC 0.563 – 1.457, p value = 0.6833, median OS of 18.9 months vs 18.1 for olaparib *vs*. placebo). It is unlikely that further maturation of the data would result in substantial OS gain. In this context, the supportive value of OS data remains limited.

In terms of **PFS2**, similar proportion of patients in both arms presented a second progression (44.6% *vs*. 48.4%). Results for PFS2 showed a HR of 0.755 (95% CI 0.464 - 1.230, p value = 0.2597, median 13.2 months for olaparib and 9.2 months for placebo), indicating that olaparib treatment effect is preserved at least during the first subsequent line of treatment.

Although no statistically significant improvement could be shown for PFS2 and OS, numerically higher median estimates have been observed in the olaparib arm at this timepoint.

Final analysis of OS and PFS2 data will become available in Q4 2020.

There are few long-term survivors that appeared to derive benefit from olaparib maintenance treatment but characteristics of these patients could not be identified based on the analyses conducted. Therefore, the MAH is recommended to further investigate tissue biomarkers to better define patients with likelihood to derive a benefit from treatment.

3.4. *Unfavourable effects*

Overall, the safety profile of olaparib is well characterised.

The safety profile of olaparib in the proposed first-line maintenance indication is based mainly from the phase III POLO Study where patients were dosed olaparib (or placebo) 300 mg bd as a monotherapy. The POLO data have been pooled with the data from patients receiving olaparib 300 mg bd tablet in additional 12 monotherapy studies providing a pooled safety database about 1329 patients (101 of whom had pancreatic cancer).

The most common (reported by ≥20% of patients) AEs in the olaparib arm were fatigue (45.1%), nausea (45.1%), diarrhoea (28.6%), abdominal pain (28.6%), anaemia (27.5%), decreased appetite (25.3%) and constipation (23.1%).

Grade ≥3 AEs had a higher incidence in the olaparib arm (39.6% of the patients) than in the placebo arm (23.3%). Anaemia was the only AEs Grade ≥3 reported in ≥5% of patients in the olaparib arm (reported in 11% of olaparib arm versus 3.3% of placebo arm).

SAEs were reported in 24.2% (22/91 patients) of the olaparib-arm compared 15% (9/60) of the placebo arm. The most common reported SAE was anaemia (6.6% olaparib *vs.* 0% placebo). The highest frequency of reported SAEs at the system organ class (SOC) level were gastrointestinal disorders (11% olaparib vs. 3% placebo) and blood and lymphatic system disorders (6.6% olaparib vs.1.7% placebo).

The median total treatment duration to olaparib was approximately 1.6 times longer than duration of exposure to placebo (approximately 6.0 months) compared with the placebo arm (approximately 3.7 months). Overall, 25.3% of patients in the olaparib arm remained on treatment for ≥1 year compared with 6.7% of patients in the placebo arm.

Dose interruptions or delay and dose reductions were reported respectively in 41.8% patients on olaparib and 16.7% placebo patients.

One olaparib treated patient developed an AE of duodenal perforation during the 30 day follow-up period which became fatal after the DCO for the analysis.

Anaemia appears as the most prominent AE among Grade ≥3, SAEs and events leading to dose adjustments. Haematological toxicity overall was similar to other indications. As regards concomitant treatment, 15 (16.5%) patients in the olaparib arm received at least 1 blood or PBRC transfusion. The majority of patients received ≤3 transfusions; however, 1 patient received 18 PBRC transfusions over a 7 month period. One (1.1%) olaparib-treated patient had treatment with an erythropoiesis stimulating agent (epoetin beta). In the placebo arm of POLO, no patients received a blood transfusion or other antianaemic preparation on treatment or treatment with an erythropoiesis stimulating agent.

There were no cases of AML/MDS reported on treatment or 30 days after treatment.

It was reported that 1 (1.1%) patients 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. This AE did not require modification of the olaparib dose and no treatment was given.

3.5. Uncertainties and limitations about unfavourable effects

The most important uncertainties about unfavourable effects are related to the risk of AML/MDS, new primary malignancies and pneumonitis, which will continue to be closely monitored (especially relevant for long-survivors). Data for long-term exposure remain limited.

3.6. Effects Table

Table 78. Effects Table for Lynparza - Pancreatic cancer (15 December 2018)

Effect	Short description	Unit	Olaprib	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS (HR)	From randomizatio n to		0.53	1	(95% CI 0.35, 0.82) p= 0.0038	POLO

Effect	Short description	Unit	Olaprib	Placebo	Uncertainties / Strength of evidence	References
	progression or death.					
Unfavourable Effects						
AEs	TEAEs regardless causality	%	95.6	93.3		
Grade ≥ AEs	TEAEs grade 3-4 regardless causality	%	39.6	23.3		
Serious AEs	Serious TEAEs regardless causality	%	24.2	15		
AEs leading to discontinuat ion of study treatment		%	5.5	1.1		
AEs leading to reduction and interruption of study treatment		%	41.8	16.7		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The maintenance treatment for a metastatic pancreatic cancer is a new paradigm. **PFS** results showed a 47% lower risk of disease progression or death with olaparib than with placebo in rare selected patients with germline BRCA1/2 mutations. This gain in PFS could be considered meaningful taking into account the natural evolution of metastatic adenocarcinoma of the pancreas. **PFS2** results were supportive of the PFS results showing numerically positive trend with 4 months PFS2 gain in the olaparib arm at the time of assessment. **OS** results showed a non-statistically significant small difference favouring olaparib.

Overall, olaparib was well tolerated with a manageable safety profile which is sufficiently characterised, although data for long-term safety remain limited. While ADRs of hematologic and lymphatic system occurred at a high frequency, they are generally of low grade and easily manageable. Safety results of POLO seem to be in line with the safety profile of olaparib from other studies and post-marketing information. Measures to minimize the risk are well addressed in the RMP submitted by the MAH.

3.7.2. Balance of benefits and risks

To support the new intended indication of olaparib:

Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.

clinical data from POLO study were submitted.

Related to results, a statistically significant gain in median PFS of 3.6 months was shown and supported by a positive trend in PFS2 outcome. **OS** results showed a non-statistical significant small difference favouring olaparib. Considering the manageable safety profile, it can be concluded that the benefits outweigh the risks.

3.8. Conclusions

The overall B/R of Lynparza in the intended indication:

Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.

 is positive.

4. **Recommendations**

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 26 out of 30 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to support the use of Lynparza tablets (100mg and 150 mg) for the maintenance treatment of gBRCAm metastatic pancreatic cancer based on the results from the pivotal Phase 3 study, POLO; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.8 for lynparza hard capsules (50 mg) to revise list of ADR based on the pooled safety data analysis. The RMP version 18.3 has also been submitted. Furthermore, the PI is brought in line with the latest guideline regarding the sodium content. The MAH also took the occasion to include some minor editorial changes in the PI.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Lynparza is not similar to Onivyde pegylated liposomal within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

Divergent position to the CHMP recommendation

Divergent position to the majority recommendation is appended to this report.

5. Appendix

1.   Divergent positions to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 28 May 2020

DIVERGENT POSITION DATED 28 May 2020

Lynparza EMEA/H/C/003726/II/0033

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the   granting of an extension of indication for Lynparza Tablets (100mg and 150mg) indicated as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.

The reason for divergent opinion was the following:

Considering the patient population and the treatment setting at hand, i.e. the maintenance setting in BRCA mutated pancreas carcinoma, we consider that benefit should be shown in terms of OS. Such data have not been provided. As a consequence, while the safety profile is deemed manageable, clinical efficacy cannot be considered established and the B/R is negative.

Alexandre Moreau

Martina Weise

Johann Lodewijk Hillege

Simona Stankevičiūtė