26 April 2019
EMA/330530/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lynparza

International non-proprietary name: olaparib

Procedure No. EMEA/H/C/003726/II/0023

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

AE(s)	Adverse event(s)
BICR	Blinded Independent Central Review
BRCA	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicised whereas protein is not italicised)
Integrated BRAC*Analysis*	The test consists of gene sequencing and large rearrangement analysis of the *BRCA1* and *BRCA2* genes performed by Myriad Genetics, Inc
BRACAnalysis CDx	The test consists of gene sequencing and large rearrangement analysis of the *BRCA1* and *BRCA2* genes performed by Myriad Genetics, Inc
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
BRCAwt/VUS	*gBRCA* and *sBRCA* wild type/variant of uncertain significance
CA-125	Cancer antigen-125 (tumour biomarker)
CCR	Clinical complete response
CDx	Companion diagnostic
CHMP	Committee for Medicinal Products for Human Use, formerly known as the Committee for Proprietary Medicinal Products (CPMP)
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
30DFUP	30 day follow-up period
DCO	Data cut-off
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EMA	European Medicines Agency
EoT	End of treatment
EU	European Union
FACT-O	Functional Assessment of Cancer Therapy – Ovarian
FAS	Full Analysis Set
FDA	Food and Drug Administration
FMI	Foundation Medicine Inc

g*BRCA*	Germline *BRCA*
g*BRCA*m	Germline *BRCA* mutated
HR	Hazard ratio
HRD	Homologous recombinant deficiency
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
HRRm	Homologous recombination repair mutation
ICH	International Council for Harmonisation
IVRS	Interactive Voice Response System
MMRM	Mixed models for repeated measures
MTP	Multiple testing procedure
NC	Not calculated
NR	Not reported
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose polymerase
PFS	Progression-free survival
PFS2	Time from randomisation to second progression or death
PK	Pharmacokinetic
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
s*BRCA*	Somatic *BRCA* (*BRCA* variant found in the tumour but not in the
s*BRCA*m	Somatic *BRCA* mutated
s*BRCA* VUS	Somatic *BRCA* variant of uncertain significance
t*BRCA*	Tumour *BRCA* (mutations detected in the tumour)
t*BRCA*m	Tumour *BRCA* mutated
t*BRCA*wt	Tumour *BRCA* wild type
TDT	Time from randomisation to study treatment discontinuation or death
	Time to first subsequent therapy (defined as time from randomisation
TOI	Trial outcome index
	Time to second subsequent therapy (defined as time from
ULN	Upper limit of normal
US (USA)	United States (of America)
VUS	Variant of uncertain significance
wt	Wild type

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 29 August 2018 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 include the use of Lynparza film-coated tablets as monotherapy for the maintenance treatment of adult patients with newly diagnosed advanced *BRCA*-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy, based on the results of a single pivotal Phase 3 study (D0818C00001, referred to as SOLO 1); as a consequence, sections 4.1, 4.2 and 4.8 of the SmPC are updated. The Package Leaflet is updated in accordance. The updated pooled safety information for this submission has also been incorporated and aligned in the Lynparza capsules SmPC and PL.

The requested variation proposed 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) and the granting of a (product-specific) waiver.

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant 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: Bart Van der Schueren

Timetable	Actual dates
Submission date	29 August 2018
Start of procedure:	15 September 2018
CHMP Rapporteur Assessment Report	13 November 2018
CHMP Co-Rapporteur Assessment Report	15 November 2018
PRAC Rapporteur Assessment Report	19 November 2018
PRAC Outcome	29 November 2018
CHMP members comments	3 December 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	6 December 2018
Request for supplementary information (RSI)	13 December 2018
PRAC Rapporteur Assessment Report	4 February 2019
CHMP Rapporteur Assessment Report	14 February 2019
PRAC Outcome	14 February 2019
CHMP members comments	18 February 2019
Request for supplementary information (RSI)	28 February 2019
CHMP Rapporteur Assessment Report	11 April 2019
CHMP members comments	15 April 2019
Updated CHMP Rapporteur Assessment Report	18 April 2019
Opinion	26 April 2019
The CHMP adopted a report on similarity of Lynparza to Yondelis and Zejula on (Appendix 1)	26 April 2019
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Lynparza in comparison with existing therapies (Appendix 2) on	26 April 2019

2. Scientific discussion

2.1. Introduction

Disease or condition

Ovarian cancer is the leading cause of death from gynaecological cancers in the US and Europe, ranking as the fifth most common cause of cancer death in women (American Cancer Society 2018, Ferlay et al 2013).

Epidemiology and risk factors, screening tools/prevention

In 2018, it is estimated that there will be 22,240 newly diagnosed ovarian cancer cases in the US and approximately 14,070 people will die from ovarian cancer (American Cancer Society 2018). Across Europe, the age standardised rate in 2018 was 16.7/100,000 and the mortality was 10.7/100,000 (ECIS 2018).

Ovarian cancer remains one of the most difficult cancers to diagnose at an early curable stage. 75% of patients present with advanced disease (Stage III or IV) (Hennessy et al 2009). The majority of patients die from their disease, with 5-year survival rates only 29% for advanced stages (Siegel et al 2018).

Biologic features

Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasm (about 90%) (Chan JK et al 2006; Jelovac D et al. 2011). The World Health Organization (WHO) classification of surface epithelial ovarian tumours includes six major histotypes - serous, mucinous, endometrioid, clear cell, transitional cell and epithelial-stromal. The serous subtype of ovarian carcinoma accounts for approximately 60-80% of ovarian cancer cases and is the most aggressive type of ovarian cancer.

Grade is an additional prognostic determinant and a number of grading systems currently exist which are derived from reviewing the following tumour characteristics: architectural features, mitotic counts and nuclear atypia (ESMO Clinical Practice Guidelines, 2013). Low grade (grade 1, well differentiated) serous ovarian carcinoma is considered a distinct type of disease compared with high grade (grade 2 and 3 – moderately and poorly differentiated) serous carcinoma based on a number of clinical and molecular features, thus forming a 2 tier classification of low and high grade disease widely accepted and used in clinical practice (Levanon et al 2008; Vang et al 2009).

The classification based on molecular pathogenesis divides epithelial tumours into type 1 and type 2 ovarian carcinomas. While Type 1 tumours are characterized by specific mutations in *KRAS*, *BRAF*, *ERBB2*, *PTEN* and *PIK3CA* but rarely *TP53* and are relatively genetically stable, type 2 tumours are characterised by nearly universal *TP53*, which makes them genetically highly unstable (Cancer Genome Atlas Research Network 2011, Ledermann et al, 2013). Moreover, recent evidence suggests that serous and endometrioid carcinomas arise from the tubal fimbrae, suggesting similar biology and origin for the high grade epithelial histologies (Jayson et al 2014). Pennington et al (2014) reported DNA repair deficiencies in carcinomas with serous and non-serous histology.

Platinum predominantly causes large-scale DNA intra-strand cross-links which require a competent homologous recombination pathway for effective repair. Given that platinum sensitivity and PARP inhibitor sensitivity may converge at the homologous recombination pathway, it was possible that platinum responsiveness may be also enrich for PARP inhibitor sensitivity (Mukhopadhyay et al 2010). Clinical data support the hypothesis that platinum sensitive tumours are more sensitive to PARP inhibitors than platinum resistant tumours (Matulonis et al 2016). Thus, while *BRCA* mutations and HRD might represent biological markers of sensitivity to PARP inhibitors, platinum responsiveness may be a clinical indicator of sensitivity to these compounds.

New emerging data suggest that PARP inhibitor sensitivity is broader than *BRCA1/2* and HRR deficiencies and may extend to non-HRR DNA damage response deficiencies and pathways as well (Postel-Vinay et al

2013, Cerrato et al, 2016, Murata et al, 2016, Lu et al 2017). Moreover, it has been reported that 51% of high-grade serous ovarian cancer have compromised homologous recombination-based repair (Cooke et al. 2011). It is assumed that somatic *BRCA* and homologous repair deficiency (HRD) status refer to samples at time of diagnosis/primary surgery. Advanced tumours are normally heterogeneous and may be so also for somatic *BRCA* mutations/HRD. The selective pressure of platinum therapy is at least partly reflected in time to recurrence so that late recurrences may increase the likelihood of positive findings with respect to s*BRCA*/HRD. In addition reversion of g*BRCA* mutations is a well described mechanism associated with resistance development.

Clinical presentation, diagnosis and stage / prognosis

Early stage ovarian cancer is often asymptomatic and therefore difficult to detect. For women who do experience symptoms in the early stages, ovarian cancer is sometimes misdiagnosed because the majority of symptoms are nonspecific. These symptoms may overlap those of gastrointestinal and other diseases, and as a result, many patients may be treated incorrectly for months or years.

The definitive diagnosis and staging of ovarian cancer is by surgery, and cytological or histological examination of tissue samples.

The Federation of Gynecology and Obstetrics (FIGO) surgical staging system is used for epithelial ovarian cancer and primary peritoneal adenocarcinoma. Because the disease tends to be asymptomatic in early stages, or associated with vague, non-specific symptoms, the majority of patients are diagnosed with advanced stage disease.

The advanced stage at which ovarian cancer is generally detected is reflected in the 5-year survival rates; 46% across all stages and 29% for advanced stages (Siegel et al 2017). Even though, over 80% of patients respond to initial platinum-based chemotherapy treatment, the majority subsequently relapse (Colombo et al 2010).

Despite best current standard of care for newly diagnosed advanced ovarian cancer patients, approximately 70% of patients relapse within the first three years and become largely incurable (Ledermann et al 2013).

Recurrent disease is classified as platinum resistant or platinum sensitive, depending on whether the disease recurred less than or greater than 6 months following previous platinum therapy, and this classification is highly prognostic and is important in determining optimal chemotherapeutic treatment options.

Recurrent disease is incurable, and the challenge is to balance aggressive treatment in an effort to prolong disease-free time, while maintaining a tolerable side-effect profile and quality of life (Lancet 2009). Most patients will die within 3 to 4 years of diagnosis [Coleman et al 2013].

Management

The current standard of care for newly diagnosed advanced ovarian cancer, including those patients with *BRCA*m high-risk ovarian cancer, consists of radical debulking surgery followed by post-operative platinum-based first line chemotherapy (NCCN Ovarian 2019).

In terms of impact on clinical outcome of residual disease post cytoreductive surgery, based on prospective analysis of 3 multicentre Phase III randomised, controlled clinical studies, it has been shown that patients with complete surgical resection have improved prognosis as compared to patients in optimal resection (1-10 mm) or those with residual macroscopic disease (> 1 cm) (du Bois et al 2009). As a result, ESMO clinical guidelines as well as other international guidelines stipulate that in advanced epithelial ovarian cancer, the aim is complete cytoreduction of all macroscopic visible disease, since this has been shown to be associated with a significantly increased OS and PFS (Ledermann et al 2013).

For patients for whom upfront surgery is unlikely to achieve a complete resection, treatment consists of neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy (NCCN

Ovarian 2019). First line chemotherapy is generally given for a maximum of 6 cycles. It cannot be continued until progression as it is associated with cumulative neurological, renal, and haematological toxicities. Moreover, clinical outcomes do not improve if chemotherapy is extended beyond 6 cycles (Ledermann et al 2013). Since chemotherapy is not a viable treatment option in the maintenance setting, there is a need for a well-tolerated maintenance treatment option in the first line setting. The vascular endothelial growth factor inhibitor bevacizumab (Avastin) in combination with carboplatin and paclitaxel followed by bevacizumab maintenance is the only treatment approved in the first line maintenance ovarian cancer setting.

Several PARP inhibitors including olaparib are approved for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. However there is currently no PARP inibitors approved for the first line maintenance treatment.

There are currently no first line maintenance treatments approved specifically for *BRCA*m patients with advanced ovarian cancer and these patients receive the same treatment options as all other ovarian cancer patients. Bevacizumab is an available maintenance treatment option regardless of *BRCA* status however, subgroup analyses from the GOG-218 study based on mutation in homologous recombination repair (HRR) genes, the majority of which (74%) were *BRCA*m (*BRCA*1 148 [12.4%] patients, *BRCA*2 78 [6.5%] patients, other HRR genes 81 [6.8%] patients) demonstrated no significant interaction for the effect of bevacizumab based on HRR mutational status, with modest benefit observed in both subgroups: PFS in the subgroup of patients with HRRm (n=228): HR 0.95, 95% CI 0.71-1.26, and PFS in the subgroup of patients with no HRR mutation (n=581): HR 0.71, 95% CI 0.60 0.85. In both the GOG-218 and ICON7 trials, bevacizumab treatment was shown to be associated with significant toxicity, including but not limited to hypertension, neutropenia, venous thromboembolic events, febrile neutropenia, wound healing complication, and gastrointestinal perforation/fistula/abscess (Gonzalez et al 2013).

About the product

The active substance of Lynparza is olaparib, a potent oral human PARP inhibitor (PARP-1, PARP-2, and PARP-3) that exploits deficiencies in DNA repair pathways to preferentially kill cancer cells with these deficits compared to normal cells.

Olaparib was initially approved in December 2014 as a capsule formulation 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. The recommended dose of Lynparza is 400 mg (eight capsules) taken twice daily, equivalent to a total daily dose of 800 mg.

The tablet formulation was subsequently approved in May 2018 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. The recommended dose of Lynparza is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction.

Lynparza tablet formulation has also recently been approved as monotherapy for the treatment of adult patients with germline *BRCA*1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer (see SmPC section 4.1).

In the present application, the MAH is applying for a new indication for olaparib (tablet formulation) as follows: Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with newly diagnosed advanced *BRCA*1/2-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first line platinum-based chemotherapy.

The recommendation indication is: Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA1/2*-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first line platinum-based chemotherapy. (see SmPC section 4.1).

Before Lynparza treatment is initiated for first-line maintenance treatment of high-grade epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC), patients must have confirmation of deleterious or suspected deleterious germline or somatic mutations in the breast cancer susceptibility genes (*BRCA*) 1 or 2 using a validated test.

There is no requirement for *BRCA*1/2 testing prior to using Lynparza for the maintenance treatment of relapsed EOC, FTC or PPC who are in a complete or partial response to platinum-based therapy.

Genetic counselling for patients tested for mutations in *BRCA*1/2 genes should be performed according to local regulations.

The recommended dose of Lynparza is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction.

Patients should start treatment with Lynparza no later than 8 weeks after completion of their final dose of the platinum containing regimen.

Patients can continue treatment until radiological disease progression, unacceptable toxicity or for to 2 years if there is no radiological evidence of disease after 2 years of treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years (see SmPC section 4.2).

While for patients with platinum sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (already approved indication), it is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

Treatment may be interrupted or dose may be reduced to manage adverse reactions such as nausea, vomiting, diarrhoea and anaemia and dose reduction can be considered (see sections 4.4 and 4.8).

2.2. Non-clinical aspects

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

An updated ERA covering this extension of indication and the extension of indication in the breast cancer setting was submitted. Details of the assessment of this updated ERA are reflected in the AR of variation II/20. The ERA was considered acceptable.

2.3. *Clinical aspects*

2.3.1. Introduction

GCP

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

The applicant 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: Pivotal clinical study (SOLO1) contributing to the 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/ treated	Patient population	Location of study report
Pivotal study							
Efficacy and Safety	D0818C00001 SOLO1 Ongoing for extended OS follow-up	Determine the efficacy (assessed by PFS) of olaparib compared to placebo in *BRCAm* patients	Phase III, randomised, double-blind, placebo-controlled, multicentre	Olaparib 300 mg bd tablet (oral) Matching placebo	391/390	Newly diagnosed, advanced (FIGO Stage III-IV) *BRCA*-mutated high grade serous or high grade endometrioid ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer who are in CR or PR following completion to first line platinum-based chemotherapy.	Module 5.3.5.1

bd Twice daily; *BRCAm BRCA* mutated; CR Complete response; FIGO Fédération Internationale de Gynécologie Obstétrique (International Federation of Gynaecology and Obstetrics); OS Overall survival; PFS Progression-free survival; PR Partial response.

2.3.2. Pharmacodynamics

Mechanism of action

No new study was provided in support of this application.

<u>*BRCA*1/2 testing and concordance</u>

Central germline *BRCA*1/2 testing and concordance with local germline testing

The methodology to classify *BRCA*1 or *BRCA*2 variants and to define those that lead to loss of function was based upon the American College of Medical Genetics and Genomics (ACMG) recommendations for standards for interpretation and reporting of sequence variants (Richards et al 2015). A variety of classifications is currently used taking into account these recommendations. Criteria and evidence used to classify variants at Myriad have been established in accordance with ACMG guidelines and standards. *BRCA*1 and *BRCA*2 variants are classified into one of the five categories, with deleterious or suspected deleterious variants corresponding to class 1 or 2 of the ACMG classification. Patients with variants corresponding to other categories, including variants of uncertain significance (VUS) have not been considered for eligibility.

Patients randomised to SOLO1 using a local germline *BRCA*1/2 result were retested post-randomisation prior to database lock using mainly the Myriad Integrated BRACAnalysis test. Of the 383 patients confirmed to have deleterious (95.3%) or suspected deleterious (4.7%) status, 253 and 130 were randomised to the olaparib and placebo arm, respectively. Large rearrangements in the *BRCA*1/2 genes were detected in 5.5% (21/383) of the randomised patients.

In patients where *BRCA*1/2 mutation status was determined by local *BRCA* and Myriad germline testing, the results were highly concordant (only 3 patients with discordant results between local and Myriad confirmed subset). One patient entered the study with a local g*BRCA*m result and was later classified by Myriad as *BRCA* VUS.

The Myriad g*BRCA*m population represents patients who were determined either prospectively or retrospectively as carrying deleterious or suspected deleterious mutation in either *BRCA*1 or *BRCA*2 (please refer to the efficacy data in the ancillary analyses part).

Retrospective central tumour testing and concordance with central germline testing

Archival tumour tissue samples were requested for all randomised patients and were profiled retrospectively tested prior to database lock using the FoundationOne CDx Clinical Trial Assay performed at Foundation Medicine (FMI). Variant classification at FMI is conducted according to defined criteria into 4 classification categories, including the eligible known or likely pathogenic variants.

In total, for 87.2% (341/391) of patients representing the Foundation Medicine t*BRCA*m population tumour samples were successfully tested (no tumour sample was available for testing in 5 patients and the t*BRCA* result was not reported in 45 patients with available tumour samples). Among these 341 patients 95% had an eligible mutation (known [n=47] or likely pathogenic [n=277]) and 2 g*BRCAwt* patients were confirmed to have s*BRCAm* only. (please refer to the efficacy data in the ancillary analyses part)

The overall concordance between the FMI t*BRCA* test and the Myriad g*BRCA* for reporting of germline variants was 95%. The FMI t*BRCA* test reported an extra 2 eligible patients (35 variants). The majority of discordant cases (55.5%, 10 out of 18) were due to large rearrangements reported by Myriad that were not detected by the FMI *tBRCA* test. Of note 2 of the 18 discordant cases carry true somatic mutations that entered the study with a local t*BRCA*m result and could not be detected by the Myriad germline test (Table below). These 2 patients were both in the olaparib arm.

Table 2: SOLO1: Summary of *BRCA* mutation status by Myriad germline and Foundation Medicine tumour (FAS)

Treatment	Myriad germline status	Foundation Medicine tumour status			
		BRCAm[a]	*BRCA* VUS	*BRCAwt*[b]	Missing
Olaparib (tablet) 300 mg bd (N=260)	*BRCAm*[a]	212 (81.5)	2 (0.8)	10 (3.8)	29 (11.2)
	BRCA VUS	0	1 (0.4)	0	0
	BRCAwt[b]	2 (0.8)	0	0	0
	Missing	0	0	0	4 (1.5)
Placebo (N=131)	*BRCAm*[a]	110 (84.0)	2 (1.5)	2 (1.5)	16 (12.2)
	BRCA VUS	0	0	0	0
	BRCAwt[b]	0	0	0	0
	Missing	0	0	0	1 (0.8)
Total (N=391)	*BRCAm*[a]	322 (82.4)	4 (1.0)	12 (3.1)	45 (11.5)
	BRCA VUS	0	1 (0.3)	0	0
	BRCAwt[b]	2 (0.5)	0	0	0
	Missing	0	0	0	5 (1.3)

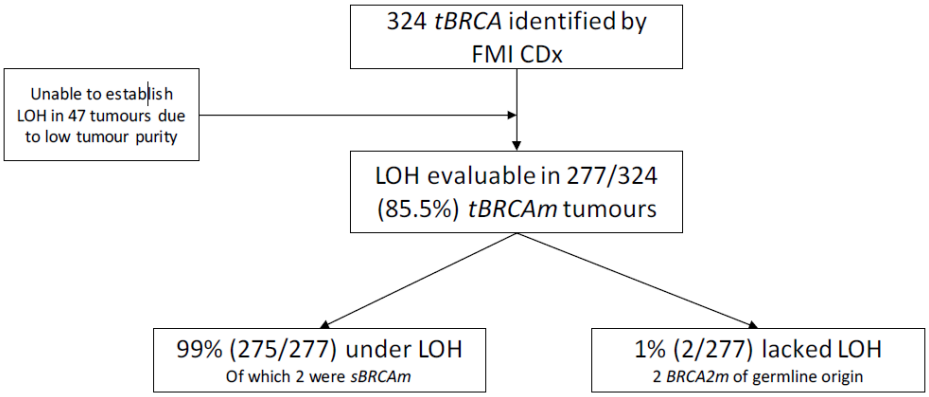
[a] Contains *BRCA* loss of function mutations.
[b] Contains *BRCA* polymorphism and *BRCA* wild type (no mutation detected).
bd Twice daily; *BRCA* Breast cancer susceptibility gene; *BRCAm* *BRCA* mutated; CSR Clinical Study Report; FAS Full Analysis Set; VUS Variant of uncertain significance; wt Wild type.
Source: Table 11.1.9.1.2, SOLO1 CSR, Module 5.3.5.1.

Exploratory analyses of tumour samples

The analysis of the available tumour samples from SOLO1 has been provided.

Locus specific loss of heterozygosity (LOH)

Using the SGZ ((somatic-germline-zygosity) computational method to predict somatic vs. germline origin and homozygous vs. heterozygous or sub-clonal state of variants (Sun et al, 2018), the results of *BRCA*-locus specific LOH have been provided in the F1CDx CTA *tBRCAm* cohort.



BRCA Breast cancer susceptibility gene; FMI Foundation Medicine Inc., LOH Loss of heterozygosity; *sBRCA* Somatic *BRCA*; *tBRCA* Tumour *BRCA*

Figure 1: Locus-specific LOH analysis of Foundation One CDx cohort in SOLO1

Table 3: Locus-specific LOH status in study 19, TCGA, SOLO1 and SOLO2

Study	Population		N[a]	% LOH (n)
Study 19 (Dougherty et al 2017)	High grade serous or endometrioid ovarian cancer, primary peritoneal and/or fallopian tube cancer. PSR. 2+ prior lines of platinum treatment.	*gBRCAm*	71	100 (71/71)
		sBRCAm	18	83 (15/18)
		BRCAm	89	97 (86/89)
TCGA (TCGA 2011)	High grade serous ovarian tumours representative of patients at diagnosis	*gBRCAm*	57	97 (55/57)
		sBRCAm	32	100 (32/32)
		BRCAm	89	98 (87/89)
SOLO1	High grade serous or endometrioid ovarian cancer, primary peritoneal and/or fallopian tube cancer. CR/PR after 1st line platinum chemotherapy	*gBRCAm*	275	99 (273/275)
		sBRCAm	2	100 (2/2)
		BRCAm	277	99 (275/277)
SOLO2 (Hodgson et al 2017)	High grade serous or endometrioid ovarian cancer, primary peritoneal and/or fallopian tube cancer. PSR. 2+ prior lines of platinum treatment.	*gBRCAm*	210	99.5 (209/210)

[a] Number of samples where LOH can be determined.
BRCA Breast cancer susceptibility gene; *BRCAm* *BRCA* mutated; CR Complete response; *gBRCAm* Germline *BRCA* mutated; LOH Loss of heterozygosity; PR Partial response; *sBRCA* Somatic *BRCA* mutated; PSR Platinum sensitive relapsed; TCGA The Cancer Genome Atlas

Homologous recombination deficiency (HRD) tests

The Foundation Medicine LOH score reflects a measure of % genomic LOH ('the LOH score'), without combination with additional measures of genomic instability (telomeric allelic imbalance and large-scale state transitions).

A high proportion of SOLO1 tumours with an evaluable FMI LOH score, had a score above or equal to 14% (84%, 237/283) or 16% (77%, 218/283).

The PFS of patients in SOLO1 considered to be HRD negative according to the FMI LOH test (with both the 14% and 16% cut-offs) were explored (IEMT1546).

Table 4: SOLO1: PFS by HRD subgroup

LOH score subgroup	Treatment arm	N	Number (%) of events	PFS hazard ratio and 95% confidence interval
LOH score <14	Olaparib Placebo	27 19	9 (33.3) 14 (73.7)	0.2 (0.06, 0.45)
LOH score ≥14	Olaparib Placebo	165 72	63 (38.2) 56 (77.8)	0.32 (0.22, 0.46)
LOH score <16	Olaparib Placebo	43 22	18 (41.9) 16 (72.2)	0.29 (0.15, 0.58)
LOH score ≥16	Olaparib Placebo	149 69	54 (36.2) 54 (78.3)	0.29 (0.2, 0.43)

HRD Homologous recombination deficiency; LOH Loss of heterozygosity; PFS Progression free survival

TP53 mutations

Sequencing data for TP53 was available for all SOLO1 tumour samples analysed using the F1CDx CTA. 96% (329/341) of SOLO1 tumour samples sequenced at FMI harboured a mutation in TP53 predicted to affect protein function.

Using the same classification schemes as described for Study 19 (Molina-Vila et al 2014; Poeta et al 2007) 52% (170/329) of TP53 mutations in SOLO1 were predicted to be disruptive and 48% (159/329) non-disruptive in nature.

Table 5: SOLO1: PFS by TP53 mutation status

TP53 status subgroup	Treatment arm	N	Number (%) events	PFS hazard ratio	95% Confidence interval
Disruptive	Olaparib Placebo	112 58	42 (37.5) 39 (67.2)	0.39	0.25. 0.61
Non-disruptive	Olaparib Placebo	108 51	44 (40.7) 42 (82.4)	0.27	0.18, 0.42

PFS Progression free survival
Data derived from Table 1447

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.

The pharmacodynamics of olaparib was investigated in studies with the capsule formulation and some additional data is also available from studies conducted with the tablet formulation.

Exploratory genetic analysis of tumour samples from the study 19 was provided in previous applications and biomarkers of HRD will be further studied in planned and ongoing studies, including the requested OPINION study (see current Annex II) and ORZORA study (see current Annex II). In line with previous recommendations in relation to Lynparza, the MAH is recommended to further investigate the prognostic and predictive value of tests that would allow quantitative assessment of genomic instability and homologous recombination deficiencies in patients with specific mutations in *BRCA*1/*BRCA*2 and other HRR-related genes. The assessment of data in patients with large genomic rearrangements in *BRCA*1 and *BRCA*2 genes is also recommended. Further, the MAH is recommended to investigate tumour heterogeneity and mechanisms of resistance in patients with *BRCA*-mutated tumours and tumours harbouring mutations in HRR-related genes. In addition to the above-mentioned studies, data will become available from the LIGHT study (NCT02983799), a Phase II, open-label, non-randomized, multi-center study assessing the efficacy and safety of olaparib tablets in subjects with platinum-sensitive or partially platinum-sensitive, relapsed, high-grade serous or high-grade endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received at least 1 prior line of platinum-based chemotherapy.

The MAH presented results from the analysis of the tumour samples from SOLO1. An FMI LOH score cut-off of 14% was determined to identify HRD high tumours, using survival data from the TCGA high-grade serous ovarian cancer dataset and tested prospectively as part of the ARIEL2 study (Swisher et al 2017). Subsequently, on the basis of retrospective analysis of data from ARIEL2 part 1, a cut-off of 16% or greater was determined as being the optimal discriminator for high genomic LOH in the ARIEL3 study (Coleman et al 2017). As the tumour samples from SOLO1 patients have been tested using the Foundation One Clinical Trial Assay (F1CDx CTA), a % genomic LOH score was provided as part of the advanced analytics from FMI.

Data showed that (i) from evaluable tumours, 99% have been reported to harbour *BRCA*1/2 locus-specific LOH, (ii) the benefit of olaparib over placebo was similar in both the HRD positive and negative subgroups by LOH score. The MAH is recommended to provide the OS data by HRD score and TP53 mutation status in comparison with available data from previous studies (Study 19 and SOLO2) at the time when the updated OS analysis at higher maturity rates is available.

The SmPC adequately reflects that local or central testing of blood or tumour samples for *BRCA1/2* mutations has been used in different studies. Depending on the test used and the international classification consensus, the *BRCA1/2* mutations have been identified as deleterious/suspected deleterious or pathogenic/likely pathogenic. Genetic testing should be conducted by an experienced laboratory using a validated test.

2.3.4. Conclusions on clinical pharmacology

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

2.4. Clinical efficacy

2.4.1. Main study

Study D0818C00001 (SOLO 1)

Methods

This was a Phase III, randomised, double blind, placebo controlled, multicentre study to assess the efficacy of olaparib maintenance monotherapy in advanced (FIGO Stage III-IV) ovarian cancer patients (including patients with primary peritoneal and/or fallopian tube cancer) with *BRCA* mutations (documented mutation in *BRCA*1 or *BRCA*2) that were predicted to be loss of function mutations (known or predicted to be detrimental/lead to loss of function) who had responded following first-line platinum-based chemotherapy.

Study participants

Inclusion criteria

1- Patients must have been ≥18 years of age.

2- Female patients with newly diagnosed, histologically confirmed, advanced (FIGO Stage III or IV) *BRCA* mutated high grade serous or high grade endometrioid (based on local histopathological findings) ovarian cancer, primary peritoneal cancer and/or fallopian-tube cancer who had completed first-line platinum-based chemotherapy (intravenous or intraperitoneal).

3-Stage III patients must have had 1 attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery.

4-Documented mutation in *BRCA*1 or *BRCA*2 that was predicted to be a loss of function mutation (known or predicted to be detrimental/lead to loss of function).

5-Patients who had completed first-line platinum (eg, carboplatin or cisplatin), containing therapy (intravenous or intraperitoneal) prior to randomisation:

-Patients had, in the opinion of the investigator, clinical CR or PR and had no clinical evidence of disease progression on the post-treatment scan or a rising CA-125 level, following completion of this chemotherapy course. Patients with stable disease (SD) on the post-treatment scan at completion of first line platinum-containing therapy were not eligible for the study.

-Platinum-based chemotherapy course must have consisted of a minimum of 6 treatment cycles and a maximum of 9, however if platinum-based therapy was discontinued early as a result of toxicities specifically related to the platinum regimen, patients must have received a minimum of 4 cycles of the platinum regimen.

-Patients must not have received bevacizumab during their first-line course of treatment, either in combination or as maintenance therapy following combination therapy.

-Patients must not have received an investigational agent during their first-line course of chemotherapy.

-Patients were to be randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion).

6-Pre-treatment CA-125 measurements must have met a criterion specified below:

- If the first value was less than or equal to the upper limit of normal (ULN) the patient was eligible to be randomised and a second sample was not required.

- If the first value was greater than ULN a second assessment was performed at least 7 days after the first. If the second assessment was ≥15% more than the first the patient was not eligible.

7- Patients must have had normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined in the protocol.

8- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.

9- Patients must have had a life expectancy ≥16 weeks.

10- Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test prior to Myriad *BRCA* test during screening Part 1, within 28 days of study treatment and confirmed prior to treatment on Day 1*.

11- Patient was willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations*.

12 A formalin fixed, paraffin embedded tumour sample from the primary cancer was to be available for central testing. If there was no written confirmation of the availability of an archived tumour sample prior to enrolment the patient was not eligible for the study*.

BRCA status

This study was designed to recruit g*BRCA*m based on local or central testing or s*BRCA*m patients based on local testing. Patients known to have *BRCA* mutations (g*BRCA* ie, blood or t*BRCA* ie, tumour) prior to randomisation could enter the study based on this result providing that all such testing had been undertaken in appropriately accredited laboratories (ie, testing done for research only was not acceptable). In addition, the patients must have consented to provide 2 blood samples. One sample was used for a confirmatory g*BRCA* test post randomisation using either the Myriad Integrated BRACAnalysis, the Myriad BRACAnalysis CDx (gene sequencing and large rearrangement analysis) or BGI test (patients in China). The second blood sample was collected to enable any bridging study to validate the companion diagnostic test for olaparib, if needed.

Patients with unknown *BRCA* status must have consented to provide 2 blood samples for g*BRCA* testing and followed all local ethical procedures for genetic testing. When the result from the Myriad/BGI test indicated the patient did have a loss of function (deleterious or suspected deleterious) *BRCA* mutation, the patient was randomised into the study (provided they had fulfilled all other screening requirements). There was no prospective central testing of tumour samples at randomisation, only retrospective analysis (see pharmacodynamics part).

Main exclusion criteria

1-*BRCA*1 and/or *BRCA*2 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).

2-Patients with early stage disease (FIGO Stage I, IIA, IIB or IIC).

3-SD or progressive disease (PD) on the post-treatment scan or clinical evidence of progression at the end of the patient’s first line chemotherapy treatment.

4-Patients where more than 1 debulking surgery had been performed before randomisation to the study. (Patients who, at the time of diagnosis, were deemed to be unresectable and underwent only a biopsy or oophorectomy but then went on to receive chemotherapy and interval debulking surgery were eligible).

5-Patients who had previously been diagnosed and treated for earlier stage ovarian, fallopian tube or primary peritoneal cancer.

6-Patients who had previously received chemotherapy for any abdominal or pelvic tumour, including treatment for prior diagnosis at an earlier stage for their ovarian, fallopian tube or primary peritoneal cancer. (Patients who had received prior adjuvant chemotherapy for localised breast cancer may have been eligible, provided that it was completed more than three years prior to registration, and that the patient remained free of recurrent or metastatic disease).

7-Patients with synchronous primary endometrial cancer unless both of the following criteria were met:

(a) Stage <2

(b) Less than 60 years old at the time of diagnosis of endometrial cancer with Stage IA or IB Grade 1 or 2, or Stage IA Grade 3 endometrioid adenocarcinoma OR ≥60 years old at the time of diagnosis of endometrial cancer with Stage IA Grade 1 or 2 endometrioid adenocarcinoma. Patients with serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium were not eligible.

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

-Other malignancy within the last 5 years except: 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. Patients with a history of localised breast cancer may have been eligible, provided they completed their adjuvant chemotherapy more than 3 years prior to registration, and remained free of recurrent or metastatic disease.

-Resting electrocardiogram (ECG) with correct QT interval (QTc) >470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome.

-Patients who received any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used).

-Patients with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML).

-Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases was not required. The patient could receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically SD for 28 days.

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

-Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection.

-Previous allogeneic bone marrow transplant

Treatments

Table 6: Details of study drugs

Study drug	Dosage form and strength	Manufacturer	Batch number
Olaparib	150 mg and 100 mg green, film-coated tablet	AbbVie on behalf of AstraZeneca	1000088520, 1000118082, 1000127647, 1000127650, 1000073054, 1000073096, 1000073208, 1000086264, 25170B900, 25171B900, 27176B900, 31187B900, 31188B900, 34194B900, 34196B900, 37203B900, 37204B900, 39209B900, 39212B900, 39215B900, 44232B900, 48246B900
Placebo to match olaparib	Tablet, with the appearance to match each strength of olaparib	Penn Pharma on behalf of AstraZeneca	007131, 007132, 007236, 007279, 007284, 007624, 009142, 009143, 009510, 009511, 009671, 009936

Patients will be administered their randomised study treatment tablets orally at a dose of 300mg twice daily. This tablet dose has been approved in a number of countries for use in patients with ovarian and metastatic breast cancers. Doses of study treatment should be taken at the same times each day approximately 12 hours apart.

Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. A decision about continuing treatment with the study drug beyond 2 years was made after assessing the patient's disease status according to modified RECIST guidelines at Week 108, and/or by assessing the patient's clinical condition. Patients should continue with study treatment to RECIST progression despite rises in CA- 125. Patients who continue to have evidence of stable disease at two years may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued.

Objectives

Primary objective

To determine the efficacy by PFS (using investigator assessment of scans according to modified Response Evaluation Criteria in Solid Tumours [RECIST] 1.1 for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria) of olaparib maintenance monotherapy compared with placebo in *BRCA* mutated high risk advanced ovarian cancer patients who are in clinical CR or PR following first line platinum-based chemotherapy.

Secondary objectives

-To determine the efficacy of olaparib maintenance monotherapy compared with placebo by assessment of OS, time to earliest progression by RECIST or cancer antigen-125 (CA-125), or death, and time from randomisation to second progression (PFS2).

-To determine the efficacy of olaparib maintenance monotherapy compared with placebo by assessment of 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).

-To compare the effects of olaparib maintenance monotherapy with placebo on Health-Related Quality of Life (HRQoL) as assessed by the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O).

-To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the *BRCA* genes using variants identified with current and potential future *BRCA* mutation assays (gene sequencing and large rearrangement analysis).

Safety objective

The safety objective of this study was to assess the safety and tolerability of olaparib maintenance monotherapy in *BRCA* mutated high risk advanced ovarian cancer patients who are in clinical CR or PR following first line platinum-based chemotherapy.

Outcomes / endpoints

Primary outcome variable

Progression free survival

PFS was defined as the time from randomisation until the date of objective radiological disease progression according to RECIST or death (by any cause in the absence of progression) regardless of whether the patient discontinued randomised therapy or received another anticancer therapy prior to progression (ie, date of RECIST progression/death or censoring date of randomisation+1).

Secondary outcome variables

Time from randomisation to second progression

PFS2 was defined as the time from the date of randomisation to the earliest of the progression event (radiological, CA-125 or symptomatic progression) subsequent to that used for the primary variable PFS or death.

Overall survival

OS was defined as the time from the date of randomisation 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 patient was known to be alive.

Time from randomisation to start of first subsequent therapy or death and time from randomisation to start of second subsequent therapy or death

TFST was defined as the time from the date of randomisation to the earlier of the date of therapy start date following study treatment discontinuation, or death and indicates clinical deterioration requiring further treatment.

TSST was defined as the time from the date of randomisation to the earlier of the date of second subsequent therapy start date following study treatment discontinuation, or death and was assessed to improve understanding of the longer term benefit of olaparib maintenance therapy in the proposed target population.

Time to study discontinuation or death

TDT was defined as the time from the date of randomisation to the earlier of the date of study treatment discontinuation or death.

Time to earliest progression by RECIST 1.1, CA-125 or death

Time to progression by RECIST or CA-125 progression or death was defined as the time from randomisation to the earlier date of RECIST or CA-125 progression or death by any cause.

Investigators were instructed to continue scans until RECIST progression even in the presence of a clinical CA-125 progression.

Best overall RECIST response

It was the best response a patient had during their time in the study 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.

Patient-reported outcomes

The main endpoint for HRQoL analysis was the TOI, an established single targeted index derived from the FACT-O questionnaire.

Sample size

The primary endpoint of the study was PFS. In total, 206 PFS events in the study would have 90% power to show statistically significant PFS at the 2-sided 5% level if the assumed true treatment effect were HR 0.62; this translates to a 8 months benefit in median PFS over 13 months on placebo (estimated from data reported by Alsop et al 2012) if PFS is exponentially distributed. Approximately 344 patients were planned to be recruited (2:1 ratio) so that data maturity for the PFS analysis was approximately 60%. No further analyses of PFS were planned beyond this point unless requested by Health Authorities. An initial analysis of OS was performed at the time of the PFS analysis. PFS was analysed when approximately 198 events had occurred (approximately 50% maturity) or after the last patient randomised had the opportunity to have been on the study for at least 36 months, whichever came first as emerging data suggested that the original assumptions that were used to design the study were likely to have been underestimated.

Randomisation

Patients were randomised using an Interactive Voice Response System (IVRS)/Interactive Web Response System in a 2:1 ratio to the treatments as specified below:

-Olaparib tablets orally 300 mg bd

-Placebo tablets orally bd

Patients were to be randomised within 8 weeks after their last dose of chemotherapy (last dose was the day of the last infusion).

Randomisation was stratified by:

-Response to first line platinum chemotherapy (in the opinion of the investigator, clinical CR or PR).

Clinical CR was defined as no evidence of RECIST measurable or non-measurable disease on the end of chemotherapy scan and a normal CA-125. PR was defined as ≥30% reduction in RECIST measurable or non-measurable disease demonstrated from the start to finish of previous chemotherapy OR no radiological evidence of disease on the end of chemotherapy scan with a CA-125 which had not decreased to within the normal range.

Blinding (masking)

The study was double blinded.

Statistical methods

The primary endpoint PFS was analysed using a log-rank test stratified by response to first-line platinum chemotherapy (in the opinion of the investigator, clinical CR or PR) for generation of the p-value and using the Breslow approach for handling ties. The hazard ratio (HR) and confidence interval (CI) were estimated from a Cox Proportional Hazards model (with ties=Efron and the stratification variable as a covariate); the CI was calculated using a profile likelihood approach. Stratification variables were defined according to data from the interactive voice/web response system (IVRS/IWRS) as per the version 4 of the protocol.

A Kaplan-Meier (KM) plot of PFS was presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST or death) were provided along with median PFS and corresponding 95% CI for each treatment. The proportion and corresponding 95% CI of patients alive and progression free at 6 monthly intervals was summarised (using the KM plot) and presented by treatment group.

In addition, the following analyses were performed:

-Sensitivity analyses to the main analyses of PFS, PFS2, OS, TDT, TFST, and TSST were performed in those patients whose g*BRCA*m status was determined by the Myriad test or t*BRCA*m status was determined by the Foundation Medicine tumour test.

-Further sensitivity analyses for PFS:

- Stratified log-rank tests were used to assess for possible evaluation time bias, attrition bias, and ascertainment bias (PFS based on BICR assessment).
- Investigator-reported PFS using eCRF stratification variables.
- Potential impact of informative censoring (using BICR).
- A stratified log-rank test using U and V statistics to calculate HR and CI was performed, based on investigator data, to assess the robustness of the primary analysis methodology with regards to the derivation of the HR and associated CI.
- A sensitivity analysis for the proportion of patients progression-free at 24 months was performed.

-Additional analysis for PFS:

- The earliest of investigator/BICR assessment of progression.

PFS, PFS2, TDT, TFST, TSST, change from baseline in trial outcome index (TOI) score and OS were tested at a 2-sided significance level of 5%. In order to strongly control the type I error at 2.5% 1-sided, a multiple testing procedure (MTP) was employed across the primary endpoint (PFS) and key secondary endpoints (PFS2 and OS). Specifically, PFS2 was tested only after statistical significance was shown for PFS. OS was tested only after the null hypotheses were rejected for PFS and PFS2. The MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy.

Interim analyses of PFS2 and OS were carried out at the time of the PFS analysis, and the same methodology and model was used. At the time of the PFS analysis, statistical significance was declared for PFS2 since statistical significance was shown for PFS and the 1-sided p-value for PFS2 was $p<0.0125$. No further PFS2 comparison was planned to be conducted. Statistical significance for OS was not declared at this time and the final OS analysis is planned to occur at approximately 235 OS events, when approximately 60% of deaths have occurred.

The primary statistical analysis of the efficacy of olaparib included all patients who were randomised as part of the global enrolment. The primary analysis compared the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised as part of the global enrolment but did not subsequently go on to receive study treatment were included in the Full Analysis Set (FAS). The analysis population for HRQoL data is the subset of the FAS (ITT set).

There was no pre-specified hypothesis and alpha allocation for the HRQoL analysis. Change from baseline in TOI score was analysed using a mixed model for repeated measures (MMRM) analysis of the change from baseline (defined as prior to first dose) in TOI scores for each visit. The main analysis was the comparison of the average treatment effect from the point of randomisation for the first 24 months (include analysis of data obtained within the first 24 months unless there is excessive missing data (defined as >75% missing data). For each subscale of FACT-O, if at least 50% of the items are missing, that subscale also will be treated as missing. It was expected that the stability in "HRQoL" over the 24 months following start of randomised treatment would be longer for patients randomised to olaparib than placebo.

Results

Participant flow

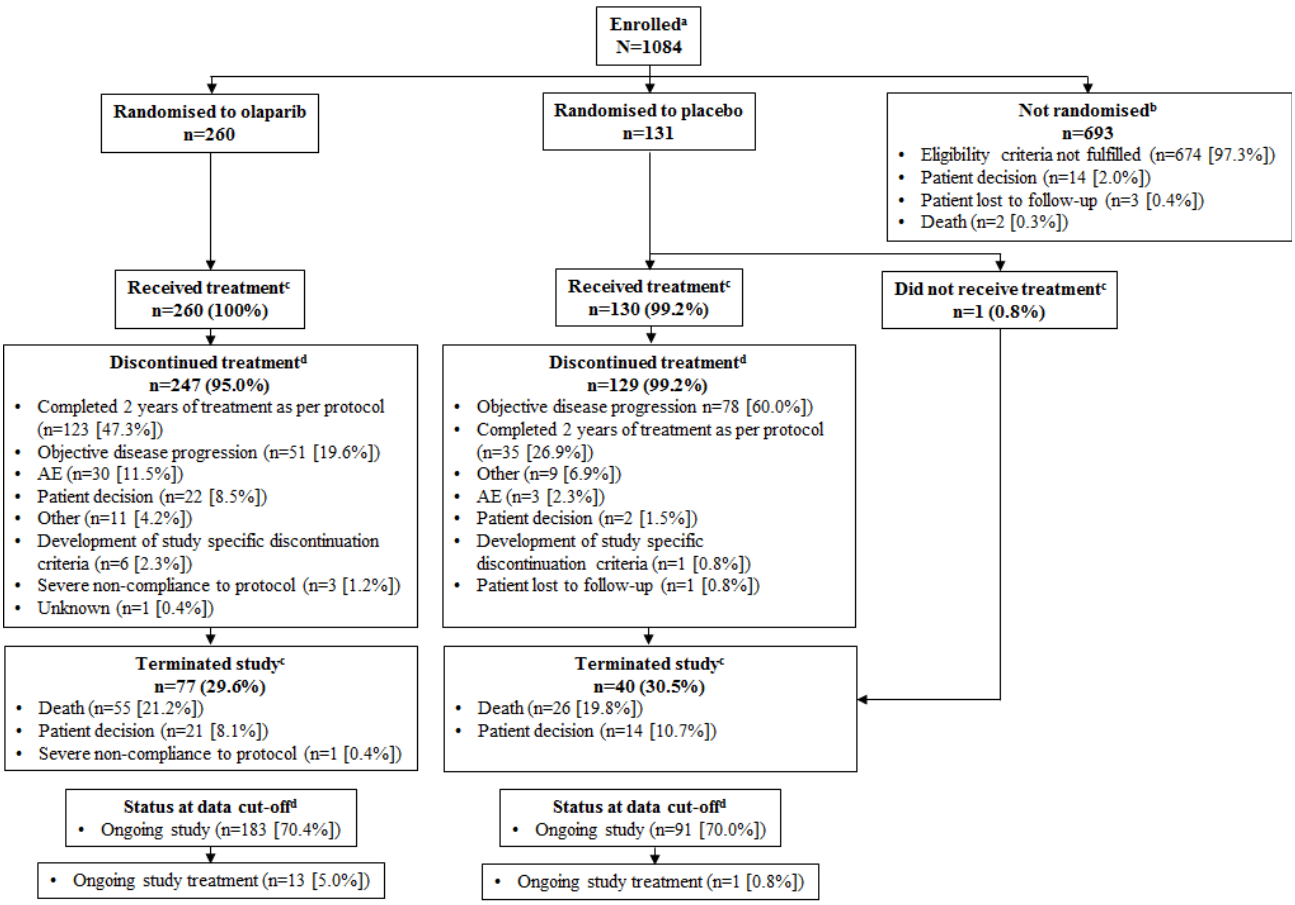


Figure 2: Patient disposition (all patients), SOLO1

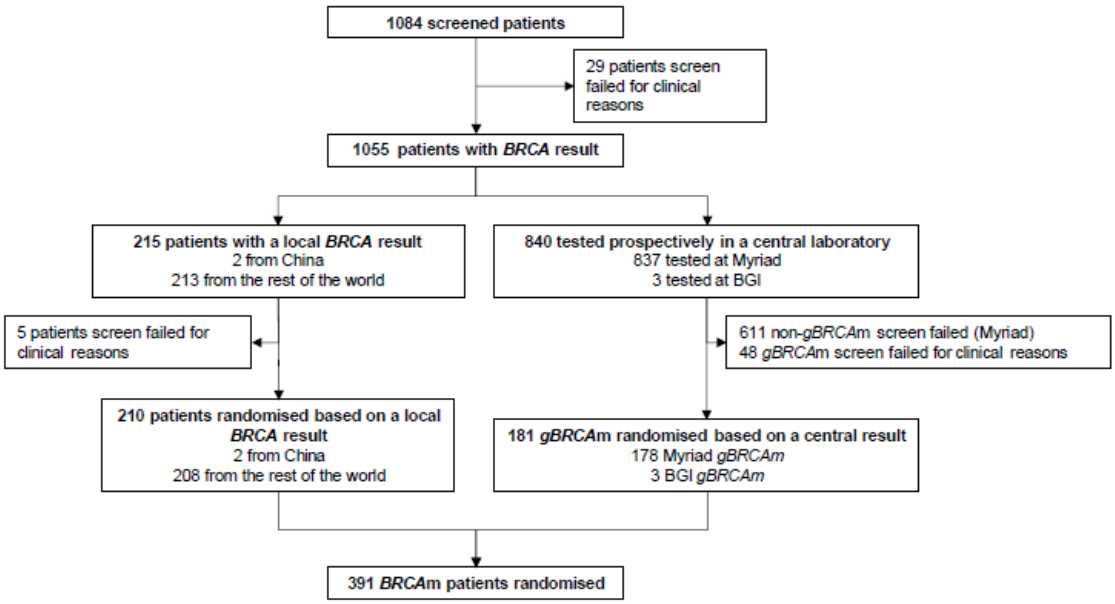


Figure 3: Routes to randomisation (All patients)

In total, 1084 patients underwent clinical screening for entry onto the SOLO1 global study and 391 patients were randomised, 210 (53.7%) with a local *BRCA* result (blood or tumour, including 2 patients from China) and 181 (46.3%) following central g*BRCA*m determination based on a prospectively conducted Myriad Integrated BRAC Analysis (n=178) or BGI (n=3) g*BRCA*m test result. In total, 387 (99.0%) patients were randomised on the basis of a germline result, 2 (0.5%) patients on the basis of a tumour result and 2 (0.5%) patients for which the site did not report the sample of origin.

Table 7: SOLO1: Summary of patient disposition (DCO 17 May 2018)

	FAS			Myriad *gBRCAm*			FMI *tBRCAm*		
	Olaparib 300 mg bd n (%)	Placebo n (%)	Total n (%)	Olaparib 300 mg bd n (%)	Placebo n (%)	Total n (%)	Olaparib 300 mg bd n (%)	Placebo n (%)	Total n (%)
Patients enrolled[a]			1084			431			324
Patients randomised	260	131	391	253	130	383	214	110	324
Patients who received treatment[b]	260 (100)	130 (99.2)	390 (99.7)	253 (100)	129 (99.2)	382 (99.7)	214 (100)	110 (100)	324 (100)
Patients ongoing study treatment at DCO[c]	13 (5.0)	1 (0.8)	14 (3.6)	12 (4.7)	1 (0.8)	13 (3.4)	11 (5.1)	1 (0.9)	12 (3.7)
Patients who discontinued study treatment[c,e,f]	247 (95.0)	129 (99.2)	376 (96.4)	241 (95.3)	128 (99.2)	369 (96.6)	203 (94.9)	109 (99.1)	312 (96.3)
Completed 2 years of treatment as per protocol	123 (47.3)	35 (26.9)	158 (40.5)	120 (47.4)	35 (27.1)	155 (40.6)	106 (49.5)	27 (24.5)	133 (41.0)
Objective disease progression	51 (19.6)	78 (60.0)	129 (33.1)	49 (19.4)	78 (60.5)	127 (33.2)	41 (19.2)	70 (63.6)	111 (34.3)
Adverse event	30 (11.5)	3 (2.3)	33 (8.5)	31 (12.3)	3 (2.3)	34 (8.9)	22 (10.3)	1 (0.9)	23 (7.1)
Patient decision	22 (8.5)	2 (1.5)	24 (6.2)	24 (9.5)	2 (1.6)	26 (6.8)	20 (9.3)	2 (1.8)	22 (6.8)
Development of study-specific discontinuation criteria	6 (2.3)	1 (0.8)	7 (1.8)	81 (32.0)	22 (17.1)	103 (27.0)	72 (33.6)	18 (16.4)	90 (27.8)
Severe non-compliance to protocol	3 (1.2)	0	3 (0.8)	3 (1.2)	0	3 (0.8)	2 (0.9)	0	2 (0.6)
Patient lost to follow-up	0	1 (0.8)	1 (0.3)	0	1 (0.8)	1 (0.3)	0	1 (0.9)	1 (0.3)
Other	11 (4.2)	9 (6.9)	20 (5.1)	52 (20.6)	22 (17.1)	74 (19.4)	45 (21.0)	17 (15.5)	62 (19.1)
Unknown	1 (0.4)	0	1 (0.3)	1 (0.4)	0	1 (0.3)	1 (0.5)	0	1 (0.3)
Patients continuing treatment post 2 years as per protocol[c]	15 (5.8)	2 (1.5)	17 (4.4)	14 (5.5)	2 (1.6)	16 (4.2)	11 (5.1)	2 (1.8)	13 (4.0)

	FAS			Myriad *gBRCAm*			FMI *tBRCAm*		
	Olaparib 300 mg bd n (%)	Placebo n (%)	Total n (%)	Olaparib 300 mg bd n (%)	Placebo n (%)	Total n (%)	Olaparib 300 mg bd n (%)	Placebo n (%)	Total n (%)
Patients continuing study off treatment at DCO[b,d]	170 (65.4)	90 (68.7)	260 (66.5)	167 (66.0)	90 (69.2)	257 (67.1)	141 (65.9)	79 (71.8)	220 (67.9)
Patients who withdrew from the study[b,d]	77 (29.6)	40 (30.5)	117 (29.9)	74 (29.2)	39 (30.0)	113 (29.5)	62 (29.0)	30 (27.3)	92 (28.4)
Death	55 (21.2)	26 (19.8)	81 (20.7)	52 (20.6)	25 (19.2)	77 (20.1)	46 (21.5)	20 (18.2)	66 (20.4)
Patient decision	21 (8.1)	14 (10.7)	35 (9.0)	21 (8.3)	14 (10.8)	35 (9.1)	15 (7.0)	10 (9.1)	25 (7.7)
Severe non-compliance to protocol	1 (0.4)	0	1 (0.3)	1 (0.4)	0	1 (0.3)	1 (0.5)	0	1 (0.3)

[a] Informed consent received.
[b] Percentages are calculated from number of patients randomised.
[c] Percentages are calculated from number of patients who received treatment.
[d] May include patients who never received study treatment (1 randomised placebo patient withdrew from the study before receiving any study treatment).
[e] Note that in the FAS, the discontinuation reason "Completed 2 years of treatment as per protocol" is derived programmatically; all other reasons are taken as reported on the eCRF.
[f] Note that in the Myriad *gBRCAm* and FMI *tBRCAm* subsets, the categories of "Completed 2 years of treatment as per protocol", "Development of study-specific discontinuation criteria" and "Other" are not mutually exclusive; hence patients can be included in more than 1 of these categories.

bd Twice daily; CSR Clinical Study Report; DCO Data cut-off; eCRF Electronic case report form; FAS Full Analysis Set; FMI Foundation Medicine Inc; *gBRCAm* Germline *BRCA* mutated; *tBRCAm* Tumour *BRCA* mutated.

Patient disposition: reasons for discontinuation for patients who withdrew from study before completing 2 years on treatment

Table 8: Patient disposition: reasons for discontinuation for patients who withdrew from study before completing 2 years on treatment

	Number (%) patients		
	Olaparib 300 mg bd (N=260)	Placebo (N=131)	Total (N=391)
Patients who discontinued study treatment	111 (42.7)	92 (70.8)	203 (52.1)
Subject decision	22 (8.5)	2 (1.5)	24 (6.2)
Adverse event	30 (11.5)	3 (2.3)	33 (8.5)
Severe non-compliance to protocol	3 (1.2)	0	3 (0.8)
Objective disease progression	46 (17.7)	76 (58.5)	122 (31.3)
Development of study-specific discontinuation criteria	3 (1.2)	1 (0.8)	4 (1.0)
Patient lost to follow-up	0	1 (0.8)	1 (0.3)
Other	7 (2.7)	9 (6.9)	16 (4.1)

bd twice daily.
Data derived from Table 1504.1.

Recruitment

In the Full Analysis Set, patients were randomised at 118 sites in 15 countries worldwide across Europe (39%), North America (36%), Asia (12%), and Rest of World (13%) (Australia, Brazil, Canada, China, France, Israel, Italy, Japan, the Netherlands, Poland, Russia, South Korea, Spain, United Kingdom, United States). The top 5 recruiting countries were US, Italy, Spain, Canada and South Korea. Five patients were randomised in sites in China during the global trial recruitment period and are included in both the global cohort as well as the China cohort.

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 9. The last protocol amendment 4 was dated 21 February 2018.

Table 9: 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 after the start of patient recruitment		
Protocol Amendment 1 5 December 2013	Changed text to include patients who progressed could remain on study treatment (Section 5.1).	Updated to allow patients who had progressed to continue to receive study treatment if, in the opinion of the investigator, it was in the patient's best interest.
	Increased the approximate number of centres participating in this study (Section 2.1).	To clarify the approximate number of centres
	Inclusion of an additional secondary objective of assessing efficacy by TFST, TSST and TDT (Section 4.2, Section 5.5 and Section 5.7.4)	To further assess efficacy
	Clarified that AstraZeneca will pay for Myriad testing and specified that the tumour specimen could only be diagnostic in order to determine the mutation result removed (Section 5.1).	To clarify who was to pay for confirmatory *BRCA* testing for patients during/post screening and to allow tumour samples to come from a wider range of tumour material collected after original diagnosis was made.
	Table 1 of CSP updated (Not applicable)	Clarification to collection of Myriad *gBRCA* sample timing. Clarification to urinalysis during screening Part 1. No requirement for BP and pulse to be measured in a supine position. Addition of footnote q to concomitant medications. Clarification to collection of SAE and AE data during screening Part 1.

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment
Protocol Amendment 1 5 December 2013	Table 2 of CSP updated (Not applicable)	No requirement for BP and pulse to be measured in a supine position. Clarification of text and location of all required laboratory tests.
	Table 3 of the CSP updated (Section 5.1, Table 2)	No requirement for BP and pulse to be measured in a supine position. Removed duplicated and unnecessary footnotes from urinalysis. Updated to clarify procedures for patients who had progressed and continued to receive study treatment.
	Table 4 of the CSP updated (Section 5.1, Table 3)	Addition of text to clarify visits to take place for patients who remained on treatment post progression and then subsequently discontinued treatment. Addition of resource use in PFS2 and OS follow up to collect data to ensure accurate economic assessment of olaparib. Clarification of subsequent anti-cancer treatment collection.
	Specification that other platinum agents may have been administered to inclusion criterion 5 (Section 5.3.1)	Clarification that other platinum agents may have been administered beside carboplatin or cisplatin.
	Clarification to exclusion criterion 8 (Section 5.3.2)	Clarification of which patients with synchronous endometrial cancer were eligible.
	Revision of methods of statistical analyses (Section 5.7.3, Section 5.7.4.1, Section 5.7.4.2, Section 5.7.4.3, Section 5.7.4.4)	Revised to highlight the key sensitivity analyses in patients whose *gBRCAm* status was confirmed by the central Myriad test.
	Revision of the analysis of the PFS2 endpoint (Section 5.7.4.1)	Revised to remove the text relating to time to subsequent therapy as a supportive analysis to PFS2.

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment
Protocol Amendment 2 19 December 2014	Addition of the China cohort (Section 2.1, Section 5.1 and Section 5.7.2)	Addition of China patient cohort to allow the originally allocated patients from China to be recruited to the study.
	Changed the type of analysis for FACT-O scores (Section 4.2, Section 4.4, Section 5.5 and Section 5.7.4.7)	Changed to MMRM analysis which is independent of minimal important differences values.
	Revised wording associated with the use of blood samples (Section 5.1)	Revised to correct an inconsistency in wording associated with the use of blood samples collected for *gBRCA* testing.
	Table 2 of CSP updated (Not applicable)	Clarification for bridging study requirement. Addition of the explanation about necessity of blood samples collection from all consented patients, including *BRCA* known patients who did not reach randomisation visit.
	Removal of survival and time to second progression assessments from study schedule (Section 5.1)	Clarification of the study design by removal of an assessments added by an error.
	Change in study design to allow continuous collection of Quality of Life data beyond disease progression (Section 5.1)	Additional data collected was to allow more comprehensive comparison of the changes in HRQoL on both arms.
	Clarification to exclusion criterion 17 (Section 5.3.2)	Clarified that patients with persistent toxicities ≥CTCAE Grade 2 (rather than >CTCAE Grade 2) were to be excluded.
	Section 6.4.3 of the CSP (recording of adverse events – post follow-up adverse events) was updated (Not applicable)	To further clarify post follow-up adverse event reporting.

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment
Protocol Amendment 2 19 December 2014	Text regarding evaluation of best overall modified RECIST 1.1 response revised (Section 5.7.4.6)	Text revised for consistency with current AstraZeneca oncology statistical guidance, which states that ORR should only be calculated using data up to the point of any subsequent therapies being used. Text regarding the DCR also removed as the inclusion of this endpoint was no longer required and was not consistent with current AstraZeneca oncology statistical guidance. In addition, the confirmed visit response text was not consistent with modified RECIST 1.1.
	Text regarding the multiplicity strategy for primary and key secondary endpoints revised (Section 12.2.1 of the CSP and Section 5.7)	To clarify the multiple testing procedure.
	Revised text regarding analysis of primary endpoint (Section 5.7.3)	To ensure that the primary analysis is based on stratification data from the randomisation system following the intent-to-treat principle, irrespective of mis-stratification issues, and to include a sensitivity analysis based on eCRF data.
	Revised text regarding analysis of efficacy endpoints PFS and OS (Section 5.7.3 and Section 5.7.4.2)	To correct an error in the text that did not cover the action to be taken if exactly 20 events are observed.
Protocol Amendment 3 19 February 2016	Changed the assessment of PFS in the primary objective from BICR to investigator assessment (Section 4.1, Section 5.5 and Section 5.7.3)	Emerging data suggested that the assumed median PFS for patients with *BRCAm* ovarian cancer used to design this study may have been underestimated. This in conjunction with the discrepancy rate observed between investigator confirmed progression and the BICR results suggested it may not be possible to obtain the events required for the protocol specified primary endpoint without a change in the protocol design. The assessment of PFS by BICR was added as a sensitivity analysis.

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment
Protocol Amendment 3 19 February 2016	Changed frequency of RECIST assessments and clarified treatment decision point at 108 weeks (Section 5.1 and Section 5.3.4).	Changed frequency of RECIST assessments from up to 120 weeks to 156 weeks (3 years) and added text to clarify the decision to continue treatment at Week 108.
	Revised text describing TOI analyses (Section 5.7.4.7).	TOI improvement rate analysis and time to worsening analysis will no longer be performed.
	Revised text regarding required contraception in female patients and their partners. New Appendix added ("Acceptable Birth Control Methods") (Section 5.3.3)	Reduction of the required period of contraception for females after stopping study treatment from '3 months' to '1 month'.
	Revised wording describing potential clinical interactions of olaparib (Section 5.4.5.2)	To describe possible clinical effects of olaparib on CYP3A4 and UGT1A1.
	Revised text related to storage of biological samples (none)	Adjustment of wording to reflect transition of long-term biological sample storage responsibility from AstraZeneca United Kingdom Biobank to Fisher Bioservices.

a All protocol amendments were approved by AstraZeneca before being submitted to a regulatory authority and/or an IRB/IEC. BICR blinded independent central review; BP blood pressure; *BRCA*m breast cancer susceptibility gene mutated; CSP clinical study protocol; CTCAE Common Terminology Criteria for Adverse Events; DCR disease control rate; eCRF electronic case report form; IEC Independent Ethics Committee; IRB Institutional Review Board; HRQoL Health-Related quality of life; MMRM mixed model for repeated measures; ORR objective response rate; OS overall survival; PFS progression-free survival; PFS2 time from randomisation to second progression; RECIST Response Evaluation Criteria in Solid Tumours; TDT time from randomisation to study treatment discontinuation or death; TFST time to first subsequent therapy or death; TOI Trial Outcome Index; TSST time to second subsequent therapy or death.

SAP amendments

SAP Version	Major Changes	Rationale for change
2	• Change of assessment of primary endpoint (PFS) from BICR to investigator assessment • Inclusion of details of China cohort analysis • Inclusion of HRQoL patient centric endpoints and further exploratory HRQoL analyses and general considerations for visit windows regarding HRQoL • Removal of proposed statistical analysis of HRQoL improvement • Removal of proposed pooled analyses of Overall Survival data that included study D0810C00019 • Inclusion of rules for handling partial missing dates • Modification/removal of certain adverse event summaries	• During interactions with EMA and FDA, due to the slower than expected event rate it was agreed that as the study is double-blind it was reasonable to make the primary endpoint assessment be based on investigator rather than BICR, with BICR analysis being a key sensitivity analysis. • China cohort analysis described in protocol amendment and thus transferred to SAP • Addition of patient centric HRQoL endpoints to allow further investigation on PRO data • As the study is a maintenance study in patients who are in complete or partial response, thus in a good state of health, it is not anticipated that patients could show any significant improvement. Therefore, this analysis was removed. • No pooled analyses are reported at the individual study level which is the purpose of this SAP • Clarification of how partial or missing dates should be handled. • Following review by the AstraZeneca study team, the planned safety analyses were updated.
3	• Clarification of rules for handling two missed visits when analysing progression free survival • Removal of HRQoL patient centric endpoints • Inclusion of analysis of progression free survival rate at 24 months	• Due to change in RECIST assessment after 3 years from 12 weekly to 24 weekly, further clarification was required for handling two missed visits at the time of the change from 12 to 24 weekly assessments. • Following the interpretation of the results of the patient centric endpoints in SOLO2, it was decided that these would no longer be required. • An analysis at the time point when for the majority of patients who had not yet progressed were to stop treatment it was decided to include a landmark analysis.

4	• Revision of text describing time of analysis of primary endpoint • Inclusion of analyses of data for subset of subjects confirmed as being *tBRCAm* • Inclusion of summaries of specific grouped adverse event terms	• During interactions with the EMA and FDA, due to the slower than expected progression rate it was agreed that the data cut off could be modified • Retrospective tumour testing was included in protocol and thus relevant analyses by the patients confirmed to have a tumour *BRCA* mutation were required. • In order to better describe certain safety data, summaries of grouped preferred terms for certain adverse events were included.

BICR Blinded Independent Central Review; *BRCA* breast cancer susceptibility gene; EMA European Medicines Agency; FDA Food and Drug Administration; HRQoL Health Related Quality of Life; PFS Progression free survival; PRO Patient reported outcome; RECIST Response evaluation criteria in solid tumours; SAP Statistical Analysis Plan.

Protocol deviations

Table 10: Important protocol deviations (FAS)

	Number (%) of patients		
	Olaparib 300 mg bd (N=260)	**Placebo (N=131)**	**Total (N=391)**
Number of patients with at least 1 important deviation[a]	37 (14.2)	10 (7.6)	47 (12.0)
RECIST scans outside of a scheduled visit window on >2 occasions	19 (7.3)	2 (1.5)	21 (5.4)
Baseline RECIST scan >28 days before study treatment was started	5 (1.9)	1 (0.8)	6 (1.5)
Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment (or longer period depending on defined characteristics of agents used)	2 (0.8)	3 (2.3)	5 (1.3)
Severe non-compliance with treatment	5 (1.9)	0	5 (1.3)
Method of tumour assessment other than MRI or CT scan used	2 (0.8)	1 (0.8)	3 (0.8)
Patients must have normal organ and bone marrow function measured within 28 days of randomisation	1 (0.4)	2 (1.5)	3 (0.8)
The subject took concomitant medications or therapies prohibited whilst subject was receiving study medication	1 (0.4)	2 (1.5)[b]	3 (0.8)
Patients did not complete 1st line platinum-containing therapy (intravenous or intraperitoneal) prior to randomisation, and did not meet the further conditions described in the protocol	2 (0.8)	0	2 (0.5)
Pre-treatment CA-125 criterion - 1st value within ULN, patient eligible for randomisation, 2nd sample not required. - 1st value >ULN then 2nd assessment performed ≥7 days after 1st. If ≥15% of 1st, patient not eligible	2 (0.8)	0	2 (0.5)
ECOG performance status not 0-1	1 (0.4)	0	1 (0.3)

[a] Important deviations before the start of treatment and during treatment.

[b] Patient E7855015, who was randomised to the placebo arm, is included in this category in error as she withdrew before receiving any study medication.

Note that the same patient may have had more than 1 important protocol deviation.

Baseline data

Table 11: SOLO1: Summary of demographic and patient characteristics at baseline (FAS, Myriad g*BRCA*m subset, FMI t*BRCA*m subset) (DCO 17 May 2018)

	FAS		Myriad *gBRCAm*		FMI *tBRCAm*	
	Olaparib 300 mg bd (N=260)	Placebo (N=131)	Olaparib 300 mg bd (N=253)	Placebo (N=130)	Olaparib 300 mg bd (N=214)	Placebo (N=110)
Demographics						
Age (years)						
Mean (SD)	53.6 (9.38)	53.4 (9.79)	53.5 (9.41)	53.4 (9.82)	53.1 (9.14)	53.3 (9.49)
Median (range)	53.0 (29-82)	53.0 (31-84)	53.0 (29-82)	53.0 (31-84)	53.0 (29-80)	53.0 (35-84)
Age group (years), n (%)						
<50	94 (36.2)	48 (36.6)	91 (36.0)	48 (36.9)	78 (36.4)	40 (36.4)
≥50 to <65	131 (50.4)	64 (48.9)	128 (50.6)	63 (48.5)	110 (51.4)	55 (50.0)
≥65	35 (13.5)	19 (14.5)	34 (13.4)	19 (14.6)	26 (12.1)	15 (13.6)
Race, n (%)						
White	214 (82.3)	106 (80.9)	211 (83.4)	106 (81.5)	177 (82.7)	91 (82.7)
Asian	39 (15.0)	20 (15.3)	35 (13.8)	19 (14.6)	31 (14.5)	15 (13.6)
Black or African American	2 (0.8)	2 (1.5)	2 (0.8)	2 (1.5)	1 (0.5)	2 (1.8)
American Indian or Alaska Native	0	1 (0.8)	0	1 (0.8)	0	1 (0.9)
Native Hawaiian or other	1 (0.4)	1 (0.8)	1 (0.4)	1 (0.8)	1 (0.5)	1 (0.9)
Other	4 (1.5)	1 (0.8)	4 (1.6)	1 (0.8)	4 (1.9)	0
Ethnicity, n (%)						
Hispanic or Latino	11 (4.2)	7 (5.3)	11 (4.3)	7 (5.4)	8 (3.7)	6 (5.5)
Not Hispanic or Latino	249 (95.8)	124 (94.7)	242 (95.7)	123 (94.6)	206 (96.3)	104 (94.5)

	FAS		Myriad *gBRCAm*		FMI *tBRCAm*	
	Olaparib 300 mg bd (N=260)	Placebo (N=131)	Olaparib 300 mg bd (N=253)	Placebo (N=130)	Olaparib 300 mg bd (N=214)	Placebo (N=110)
Disease characteristics						
ECOG PS, n (%)						
(0) Normal activity	200 (76.9)	105 (80.2)	196 (77.5)	105 (80.8)	167 (78.0)	88 (80.0)
(1) Restricted activity	60 (23.1)	25 (19.1)	57 (22.5)	24 (18.5)	47 (22.0)	22 (20.0)
Missing	0	1 (0.8)	0	1 (0.8)	0	0
Myriad/BGI or locally reported *BRCA* gene name, n (%)[a]						
BRCA1	191 (73.5)	91 (69.5)	188 (74.3)	91 (70.0)	160 (74.8)	75 (68.2)
BRCA2	66 (25.4)	40 (30.5)	62 (24.5)	39 (30.0)	52 (24.3)	35 (31.8)
BRCA1 and *BRCA2*	3 (1.2)	0	3 (1.2)	0	2 (0.9)	0
Tumour characteristics						
Primary tumour location, n (%)						
Ovary	220 (84.6)	113 (86.3)	213 (84.2)	112 (86.2)	179 (83.6)	94 (85.5)
Fallopian tubes	22 (8.5)	11 (8.4)	22 (8.7)	11 (8.5)	21 (9.8)	11 (10.0)
Primary peritoneal	15 (5.8)	7 (5.3)	15 (5.9)	7 (5.4)	12 (5.6)	5 (4.5)
Other	3 (1.2)	0	3 (1.2)	0	2 (0.9)	0
Tumour grade at diagnosis, n (%)						
Well differentiated (G1)	0	0	0	0	0	0
Moderately differentiated (G2)	26 (10.0)	12 (9.2)	26 (10.3)	12 (9.2)	22 (10.3)	10 (9.1)
Poorly differentiated (G3)	215 (82.7)	105 (80.2)	208 (82.2)	104 (80.0)	175 (81.8)	87 (79.1)
Undifferentiated (G4)	5 (1.9)	4 (3.1)	5 (2.0)	4 (3.1)	4 (1.9)	3 (2.7)

	FAS		Myriad *gBRCAm*		FMI *tBRCAm*	
	Olaparib 300 mg bd (N=260)	Placebo (N=131)	Olaparib 300 mg bd (N=253)	Placebo (N=130)	Olaparib 300 mg bd (N=214)	Placebo (N=110)
Unassessable (GX)	14 (5.4)	10 (7.6)	14 (5.5)	10 (7.7)	13 (6.1)	10 (9.1)
Missing	0	0	0	0	0	0
FIGO Staging, n (%)						
III	5 (1.9)	2 (1.5)	5 (2.0)	2 (1.5)	5 (2.3)	2 (1.8)
IIIA	10 (3.8)	5 (3.8)	10 (4.0)	5 (3.8)	6 (2.8)	5 (4.5)
IIIB	27 (10.4)	7 (5.3)	26 (10.3)	7 (5.4)	22 (10.3)	7 (6.4)
IIIC	178 (68.5)	91 (69.5)	173 (68.4)	91 (70.0)	148 (69.2)	74 (67.3)
IV	40 (15.4)	26 (19.8)	39 (15.4)	25 (19.2)	33 (15.4)	22 (20.0)
CA-125 status at baseline, n (%)						
CA-125 levels ≤ULN	247 (95.0)	123 (93.9)	240 (94.9)	122 (93.8)	203 (94.9)	103 (93.6)
CA-125 levels >ULN	13 (5.0)	7 (5.3)	13 (5.1)	7 (5.4)	11 (5.1)	7 (6.4)
Missing[b]	0	1 (0.8)	0	1 (0.8)	0	0
Histology type, n (%)						
Serous	245 (94.2)	130 (99.2)	238 (94.1)	129 (99.2)	199 (93.0)	109 (99.1)
Endometrioid	9 (3.5)	0	9 (3.6)	0	9 (4.2)	0
Mixed, Epithelial	5 (1.9)	1 (0.8)	5 (2.0)	1 (0.8)	5 (2.3)	1 (0.9)
Other	1 (0.4)	0	1 (0.4)	0	1 (0.5)	0
Serous papillary	1 (0.4)	0	1 (0.4)	0	1 (0.5)	0

[a] *gBRCAm* patients reported using Myriad/BGI test were considered first before then considering locally reported *BRCA* gene name. The 5 randomised patients from China had a BGI test rather than a Myriad test.

[b] This patient was randomised but did not receive treatment.

Table 12: History of debulking surgery (FAS)

Debulking Surgery	Surgery Performed	Surgery timing	Outcome	Number (%) of patients: Olaparib 300 mg bd (N=260)	Placebo bd (N=131)	Total (N=391)
Prior to randomisation [a]	No			4 (1.5)	3 (2.3)	7 (1.8)
	Yes	Any	Residual Macroscopic Disease	55 (21.2)	29 (22.1)	84 (21.5)
			No Residual Macroscopic Disease	200 (76.9)	98 (74.8)	298 (76.2)
			Unknown	1 (0.4)	1 (0.8)	2 (0.5)
			Total	256 (98.5)	128 (97.7)	384 (98.2)
		Upfront	Residual Macroscopic Disease	37 (14.2)	22 (16.8)	59 (15.1)
			No Residual Macroscopic Disease	123 (47.3)	62 (47.3)	185 (47.3)
			Unknown	1 (0.4)	1 (0.8)	2 (0.5)
			Total	161 (61.9)	85 (64.9)	246 (62.9)
		Interval	Residual Macroscopic Disease	18 (6.9)	7 (5.3)	25 (6.4)
			No Residual Macroscopic Disease	76 (29.2)	36 (27.5)	112 (28.6)
			Total	94 (36.2)	43 (32.8)	137 (35.0)

Table 13: Summary of last platinum chemotherapy prior to randomisation (Full analysis set)

Number of cycles	Olaparib 300 mg bd (N=260)	Placebo bd (N=131)
<4	0	0
4	2 (0.8)	0
5	2 (0.8)	1 (0.8)
6	198 (76.2)	106 (80.9)
7	17 (6.5)	10 (7.6)
8	18 (6.9)	7 (5.3)
9	23 (8.8)	7 (5.3)
>9	0	0

Table 14: Stratification factors (Full analysis set)

Response to previous platinum chemotherapy	Number (%) of patients: Olaparib 300 mg bd (N=260)	Placebo bd (N=131)	Total (N=391)
As randomised			
CR	213 (81.9)	107 (81.7)	320 (81.8)
PR	47 (18.1)	24 (18.3)	71 (18.2)
Recorded on eCRF			
CR	189 (72.7)	101 (77.1)	290 (74.2)
PR	71 (27.3)	30 (22.9)	101 (25.8)

Numbers analysed

Table 15: Analysis sets

	Number (%) of patients		
	Olaparib 300 mg bd	Placebo bd	Total
Patients randomised	260	131	391
Patients included in full analysis set	260 (100)	131 (100)	391 (100)
Patients included in safety analysis set	260 (100)	130 (99.2)	390 (99.7)
Patients excluded from safety analysis set [a]	0	1 (0.8)	1 (0.3)
Did not meet inclusion/exclusion criteria	0	1 (0.8)	1 (0.3)

Outcomes and estimation

The DCO for the analysis of PFS (17 May 2018) took place when 198 progression events had occurred (~50% maturity), approximately 56 months after the first patient was randomised. At this DCO, all efficacy, QoL and safety variables were analysed, as appropriate, based on the amount of data available at that time.

Primary variable: progression-free survival by investigator assessment

PFS (based on investigator assessment) was the primary variable for the study and was analysed at the primary DCO (17 May 2018) on the FAS population. The progression status based on investigator assessment at the time of PFS analysis is presented below.

Table 16: Progression status at the time of progression-free survival analysis based on investigator assessment (FAS)

Progression status	Type of event	Number (%) of patients	
		Olaparib 300 mg bd (N=260)	Placebo (N=131)
Progression	Total	102 (39.2)	96 (73.3)
	RECIST progression[a]	100 (38.5)	95 (72.5)
	Target lesions[b]	2 (0.8)	4 (3.1)
	Non-target lesions[b]	7 (2.7)	7 (5.3)
	New lesions[b]	94 (36.2)	90 (68.7)
	Death[c]	2 (0.8)	1 (0.8)
No progression	Total	158 (60.8)	35 (26.7)
	Censored RECIST progression[d]	2 (0.8)	0
	Censored death[e]	1 (0.4)	0
	Progression free at time of analysis[f]	134 (51.5)	32 (24.4)
	Lost to follow-up[g]	0	0
	Withdrawn consent[g]	21 (8.1)	3 (2.3)
	Discontinued study[g]	0	0

[a] Does not include RECIST progression events that occurred after 2 or more missed visits or within 2 visits of baseline where the patient had no evaluable visits or did not have a baseline assessment.
[b] Not necessarily mutually exclusive categories.
[c] Death in the absence of RECIST progression or death that occurred within 2 visits of baseline where the patient had no evaluable visits or did not have a baseline assessment. Does not include deaths that occurred after 2 or more missed visits.
[d] RECIST progression event occurred after 2 or more missed visits or within 2 visits of baseline where the patient had no evaluable visits or did not have a baseline assessment.
[e] Death which occurred after 2 or more missed visits in the absence of RECIST progression.
[f] Patients known to be alive and without RECIST progression.
[g] Patients at last evaluable RECIST assessment.
This analysis was based on investigator review of radiological scans.
bd twice daily; FAS Full Analysis Set; RECIST Response Evaluation Criteria in Solid Tumours.

Table 17: Summary of analysis of progression-free survival based on investigator assessment (FAS)

	Olaparib 300 mg bd (N=260)	Placebo (N=131)
n (%) of events[a]	102 (39.2)	96 (73.3)
Treatment effect		
HR[b]	0.30	
95% CI[b]	0.23, 0.41	
2-sided p-value[c]	<0.0001	
Median PFS, months[d]	NR	13.8
Progression free at 6 months (%)[d]	93.9	80.6
Progression free at 12 months (%)[d]	87.7	51.4
Progression free at 24 months (%)[d]	73.6	34.6
Progression free at 36 months (%)[d]	60.4	26.9
Progression free at 48 months (%)[d]	52.6	11.4

[a] PFS was defined as time from randomisation until date of RECIST progression or death.
[b] Estimated from Cox proportional hazards model including the stratification variable as a covariate.
[c] Determined using log-rank test stratified by response to previous platinum chemotherapy.
[d] Calculated using Kaplan-Meier techniques.
bd twice daily; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; NR not reached; PFS progression-free survival; RECIST Response Evaluation Criteria in Solid Tumours.
Data derived from Table 11.2.1.2.

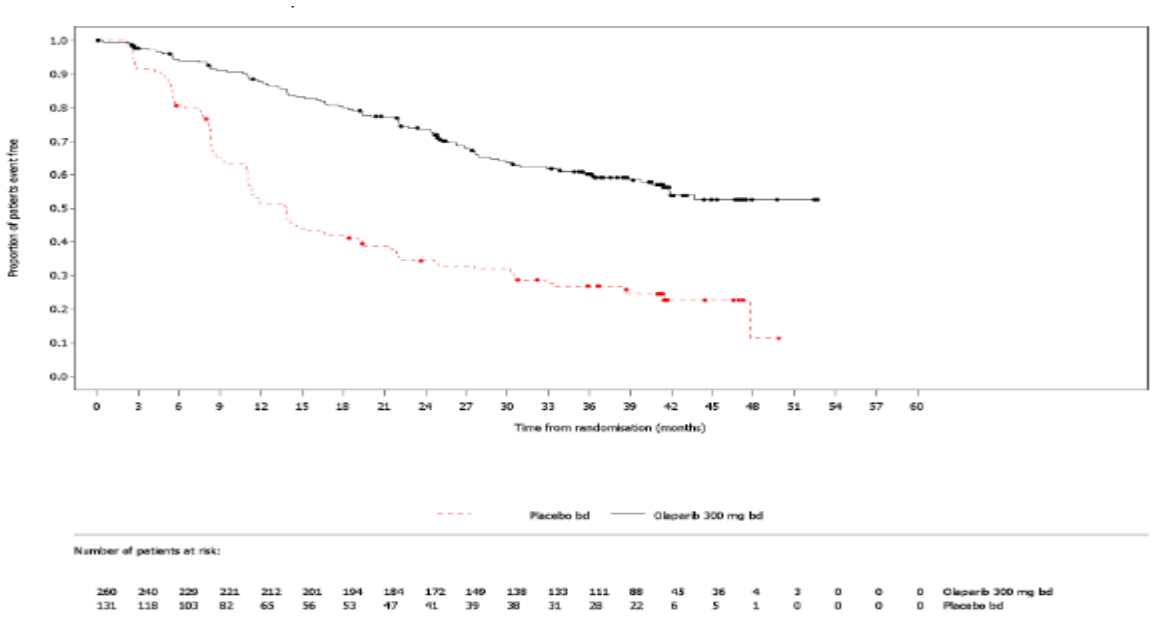


Figure 4: Progression-free survival by investigator assessment, Kaplan-Meier plot (FAS)

Secondary variables

Time from randomisation to second progression or death

PFS2 events were based on radiological, CA-125 or symptomatic progression as assessed by the investigator or death. Of the patients who had a second progression, in both treatment arms the majority were based on radiological assessment. At the time of DCO there were 121 PFS2 events (30.9% maturity) with a higher proportion in the placebo arm than the olaparib arm.

Table 18 Second progression-free survival status (FAS)

Progression status	Type of Event	Number (%) of patients: Olaparib 300 mg bd (N=260)	Number (%) of patients: Placebo bd (N=131)
Second progression	Total	69 (26.5)	52 (39.7)
	RECIST progression [a]	47 (18.1)	39 (29.8)
	Progression by CA-125 [a]	6 (2.3)	3 (2.3)
	Symptomatic progression [a]	2 (0.8)	2 (1.5)
	Other progression [a]	1 (0.4)	2 (1.5)
	Death [b]	13 (5.0)	6 (4.6)
No second progression	Total	191 (73.5)	79 (60.3)
	Censored second progression [c]	6 (2.3)	11 (8.4)
	Censored death [c]	4 (1.5)	4 (3.1)
	Progression free at time of analysis [c]	159 (61.2)	53 (40.5)
	Lost to follow-up [d]	0	0
	Withdrawn consent [d]	21 (8.1)	11 (8.4)
	Discontinued study [d]	1 (0.4)	0

[a] RECIST progression, Progression by CA-125, Symptomatic progression and Other progression are not necessarily mutually exclusive categories. [b] Death in the absence of second progression event. [c] Patients who have not had a second disease progression or died at the time of analysis, or who have second progression or die after two or more missed visits, are censored at the latest evaluable assessment where they are known to be alive and without a second disease progression. [d] Patients at last evaluable assessment.

Table 19: Summary of second progression-free survival (FAS)

	Olaparib 300 mg bd (N=260)	Placebo (N=131)
n (%) of events[a]	69 (26.5)	52 (39.7)
Treatment effect		
HR[b]	0.50	
95% CI[b]	0.35, 0.72	
2-sided p-value[c]	0.0002	
Median PFS2, months[d]	NR	41.9
Second progression free at 6 months (%)[d]	98.8	98.4
Second progression free at 12 months (%)[d]	96.3	95.1
Second progression free at 24 months (%)[d]	86.0	77.3
Second progression free at 36 months (%)[d]	75.1	60.2
Second progression free at 48 months (%)[d]	62.4	28.2
Median follow-up for second progression-free survival (months)[e]	40.9	38.2

[a] PFS2 was defined as time from randomisation until date of second RECIST progression or death.
[b] Estimated from Cox proportional hazards model including the stratification variable as a covariate.
[c] Determined using log-rank test stratified by response to previous platinum chemotherapy.
[d] Calculated using Kaplan-Meier techniques.
[e] Time from randomisation to date of censoring.

bd twice daily; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; NR not reached; PFS2 time from randomisation to second progression; RECIST Response Evaluation Criteria in Solid Tumours.
Data derived from Table 11.2.2.2

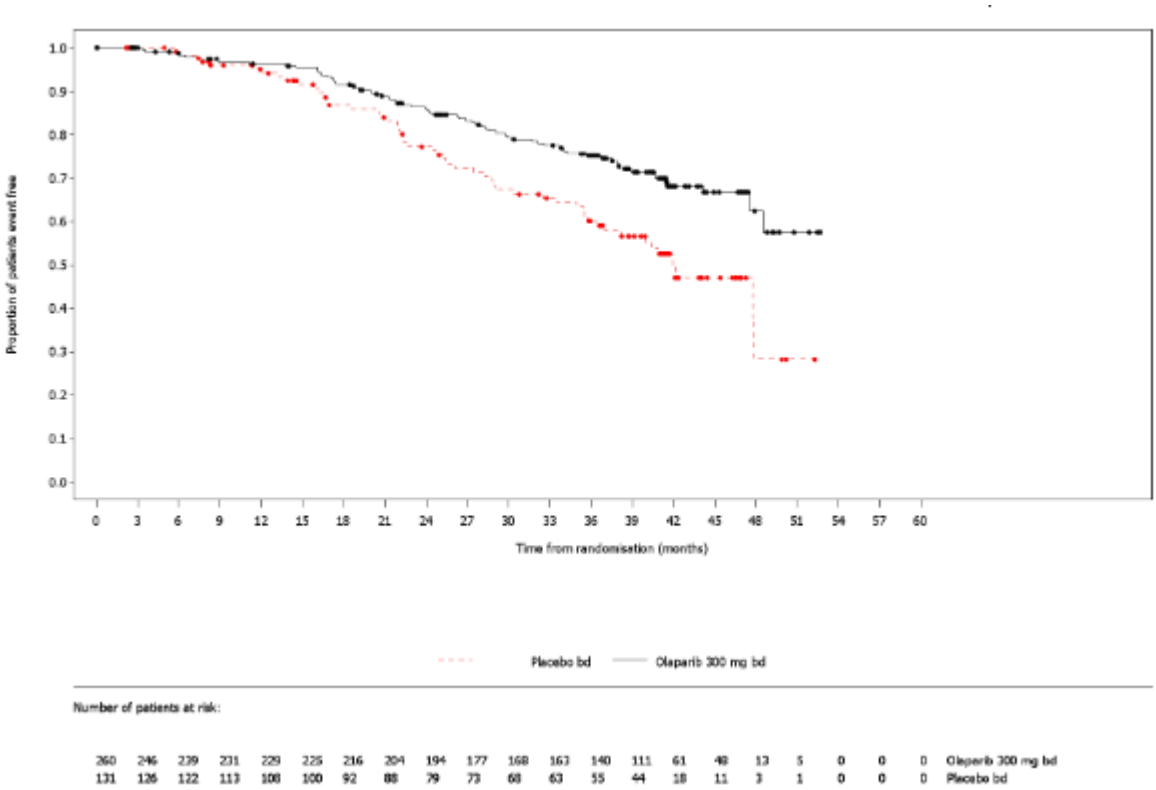


Figure 5: Second progression-free survival, Kaplan-Meier plot (FAS)

Overall survival

At the time of the DCO, 70.4% of patients in the olaparib arm and 69.5% 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 immature (82/391 events, 21.0% maturity) and the median OS was not reached in either treatment arm. Final OS analysis will be conducted at approximately 60% maturity.

Table 20: Summary of overall survival (FAS)

	Olaparib 300 mg bd (N=260)	Placebo (N=131)
n (%) of events[a]	55 (21.2)	27 (20.6)
Treatment effect		
HR[b]	0.95	
95% CI[b]	0.60, 1.53	
2-sided p-value[c]	0.8903	
Median OS, months[d]	NR	NR
Alive at 6 months (%)[d]	99.6	100.0
Alive at 12 months (%)[d]	98.0	99.2
Alive at 24 months (%)[d]	91.5	87.9
Alive at 36 months (%)[d]	84.0	80.5
Alive at 48 months (%)[d]	75.2	74.8

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

[b] Estimated from Cox proportional hazards model including the stratification variable as a covariate.

[c] Determined using log-rank test stratified by response to previous platinum chemotherapy.

[d] Calculated using Kaplan-Meier techniques.

bd twice daily; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; NR not reached; OS overall survival.

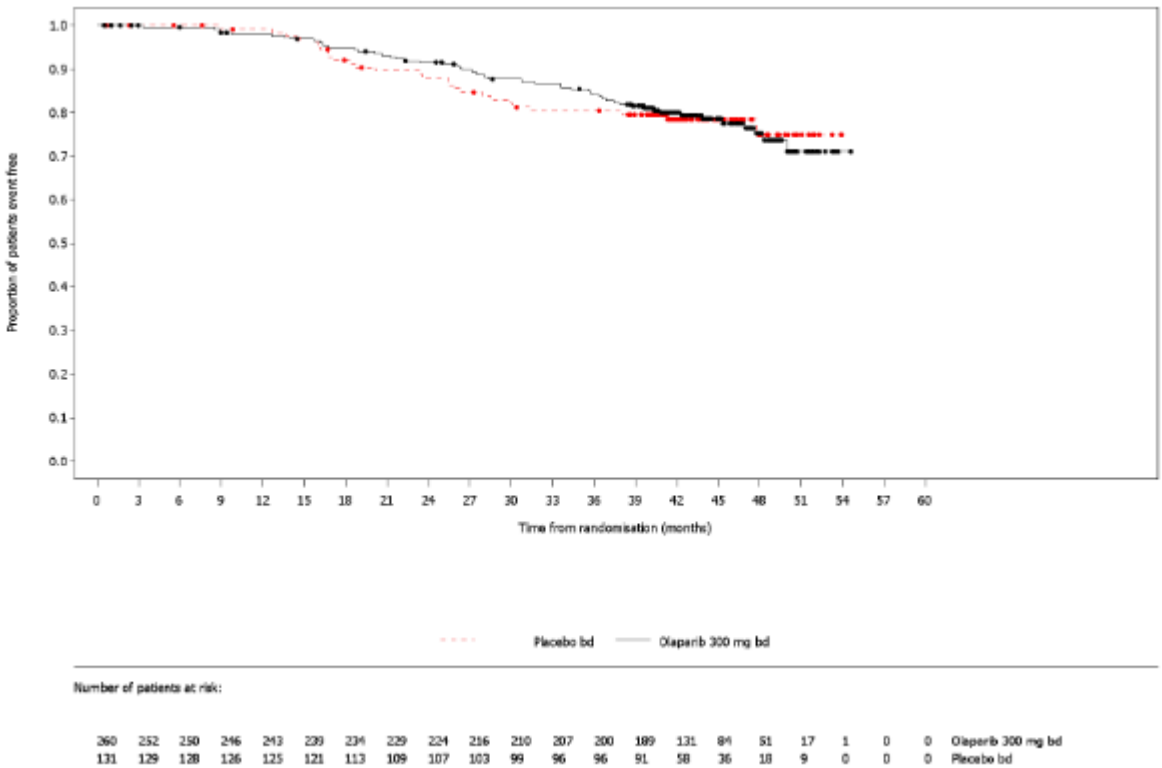


Figure 6: Overall survival, Kaplan-Meier plot (FAS)

Time from randomisation to study treatment discontinuation or death

Table 21: Summary of time from randomisation to study treatment discontinuation or death (FAS)

	Olaparib 300 mg bd (N=260)	Placebo (N=131)
n (%) of events[a]	247 (95.0)	130 (99.2)
Treatment effect		
HR[b]	0.63	
95% CI[b]	0.51, 0.79	
2-sided p-value[c]	<0.0001	
Median TDT, months[d]	24.6	13.8
Median follow-up for TDT, months[e]	47.2	45.4

[a] TDT was defined as time from randomisation until time of discontinuation of treatment.
[b] Estimated from Cox proportional hazards model including the stratification variable as a covariate.
[c] Determined using log-rank test stratified by response to previous platinum chemotherapy. Not adjusted for multiplicity.
[d] Calculated using Kaplan-Meier techniques.
[e] Time from randomisation to date of censoring.

bd twice daily; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; TDT time from randomisation to study treatment discontinuation or death.
Data derived from Table 11.2.6.1.

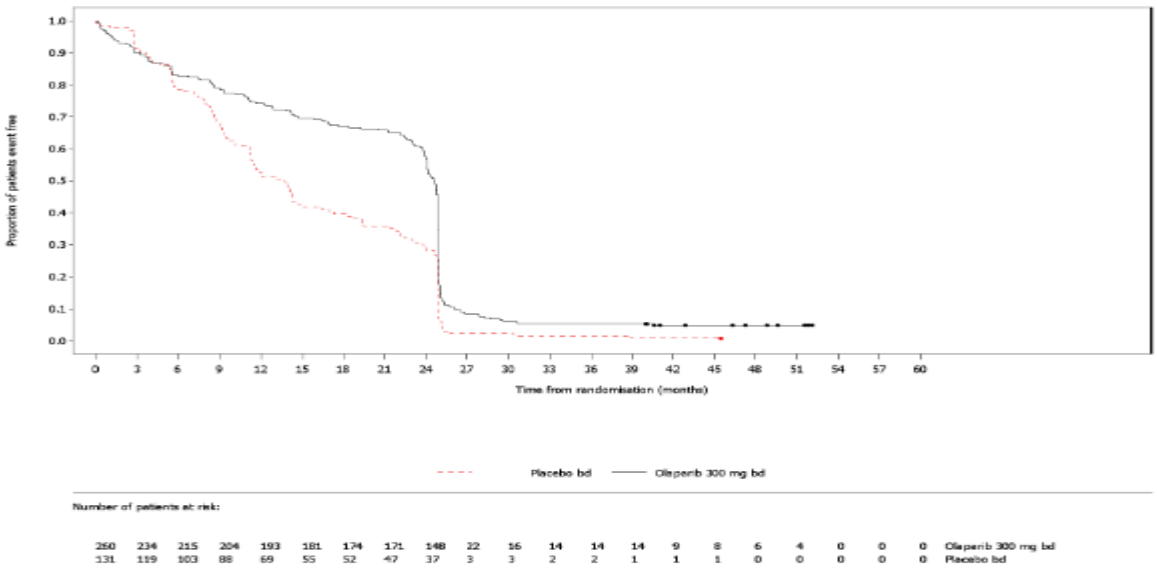


Figure 7: Time from randomisation to study treatment discontinuation or death, Kaplan-Meier plot (FAS)

Time from randomisation to start of first subsequent therapy or death

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

	Olaparib 300 mg bd (N=260)	Placebo (N=131)
n (%) of events[a]	99 (38.1)	94 (71.8)
Treatment effect		
HR[b]	0.30	
95% CI[b]	0.22, 0.40	
2-sided p-value[c]	<0.0001	
Median TFST, months[d]	51.8	15.1
Median follow-up for TFST, months[e]	41.4	41.4

[a] TFST was defined as time from randomisation until first subsequent cancer therapy or death.
[b] Estimated from Cox proportional hazards model including the stratification variable as a covariate.
[c] Determined using log-rank test stratified by response to previous platinum chemotherapy. Not adjusted for multiplicity.
[d] Calculated using Kaplan-Meier techniques.
[e] Time from randomisation to date of censoring.

bd twice daily; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; TFST time to first subsequent therapy or death.

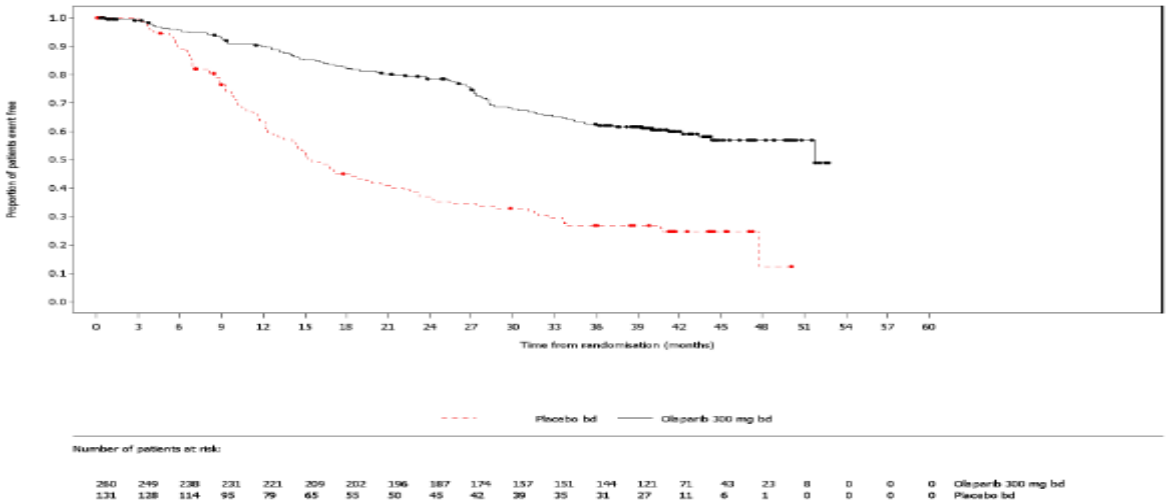


Figure 8: Time from randomisation to start of first subsequent cancer therapy or death, Kaplan-Meier plot (FAS)

Time from randomisation to start of second subsequent therapy or death

Table 23: Summary of time from randomisation to start of second subsequent cancer therapy or death (FAS)

	Olaparib 300 mg bd (N=260)	Placebo (N=131)
n (%) of events[a]	77 (29.6)	65 (49.6)
Treatment effect		
HR[b]	0.45	
95% CI[b]	0.32, 0.63	
2-sided p-value[c]	<0.0001	
Median TSST, months[d]	NR	40.7
Median follow-up for TSST, months[e]	41.5	41.4

[a] TSST was defined as time from randomisation until second subsequent cancer therapy or death.
[b] Estimated from Cox proportional hazards model including the stratification variable as a covariate.
[c] Determined using log-rank test stratified by response to previous platinum chemotherapy. Not adjusted for multiplicity.
[d] Calculated using Kaplan-Meier techniques.
[e] Time from randomisation to date of censoring.

bd twice daily; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; NR not reached; TSST time to second subsequent therapy or death.

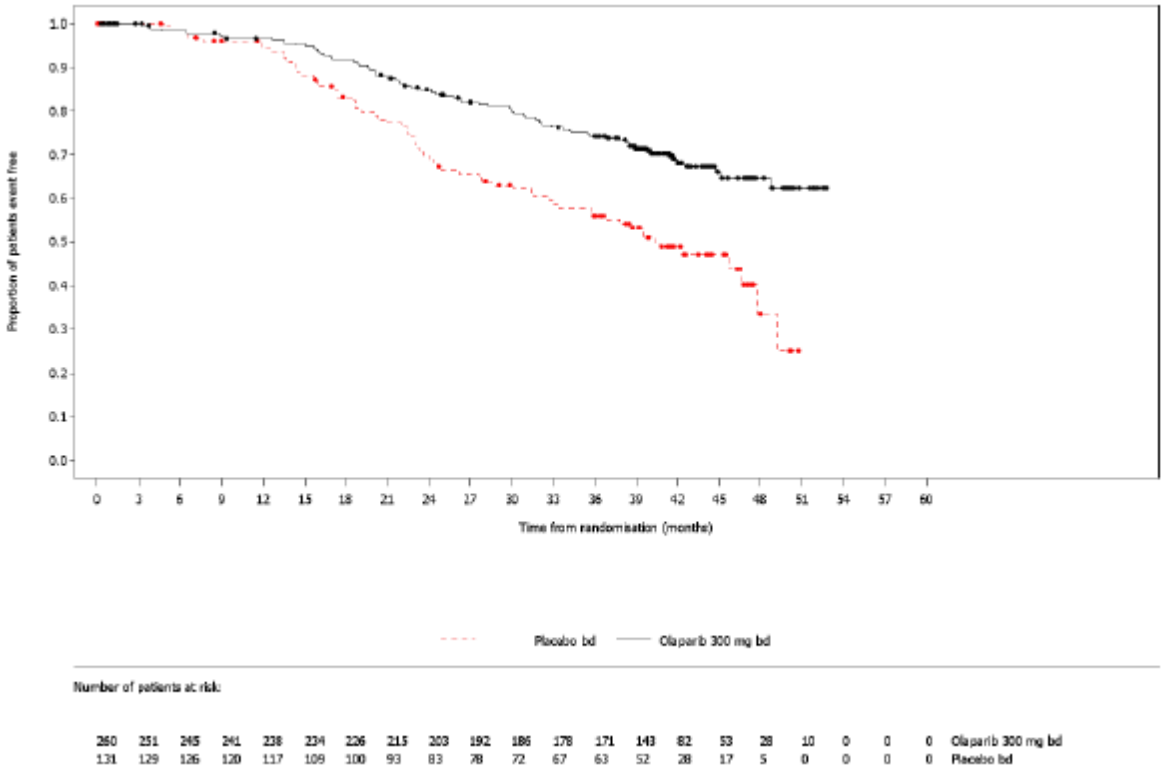


Figure 9: Time from randomisation to start of second subsequent cancer therapy or death, Kaplan-Meier plot (FAS)

Subsequent therapies

Of the patients who progressed, 90.1% (82/91) of patients received subsequent chemotherapy in the olaparib arm compared with 92.5% (86/93) of patients in the placebo arm. Furthermore, out of the patients who received a first subsequent therapy, best response as assessed by the investigator (complete or partial) was similar between the olaparib and placebo arms (40.7% [37/91] vs 48.4% [45/93], respectively). A similar proportion of patients in the olaparib and placebo arms (6.9% vs 5.3%, respectively) received no further therapy after they progressed.

Out of the patients who received subsequent anticancer treatment, the most common regimen was platinum-based chemotherapy (58/91 [63.7%] olaparib-treated patients vs 50/94 [53.2%] placebo-treated patients. Other chemotherapies (excluding platinum) were received by 13.5% (35/260) and 19.8% (26/131) of patients in the olaparib and placebo arms, respectively. Crossover to olaparib was not permitted within study design. However, patients could have received a PARP inhibitor outside of the study through other clinical trials or commercially available products. Platinum followed by a PARP inhibitor (maintenance treatment) was classified as a PARP inhibitor regimen and not a platinum-based regimen.

Table 24: Subsequent anti-cancer therapies (FAS)

	Number (%) of patients		
	Olaparib 300 mg bd (N=260)	Placebo (N=131)	Total (N=391)
Total	91 (35.0)	94 (71.8)	185 (47.3)
Platinum chemotherapy	58 (22.3)	50 (38.2)	108 (27.6)
Platinum in combination with bevacizumab	22 (8.5)	15 (11.5)	37 (9.5)
PARP inhibitor	20 (7.7)	49 (37.4)	69 (17.6)
Any other chemotherapy regimen (excluding platinum or bevacizumab containing)	35 (13.5)	26 (19.8)	61 (15.6)
Other bevacizumab containing regimen	9 (3.5)	12 (9.2)	21 (5.4)
Other investigational agents	4 (1.5)	3 (2.3)	7 (1.8)
Hormonal agent	0	4 (3.1)	4 (1.0)

Patients may appear under more than one subsequent treatment type.

To note, Table 11.2.4.3 indicates that 93 patients in the placebo arm received a subsequent cancer therapy rather than the 94 presented in this table. This is because Table 12.2.4.3 excludes the patients with missing medication start dates and the patient who did not receive any study medication in the placebo arm.

bd twice daily; FAS Full Analysis Set; PARP polyadenosine 5'diphosphoribose polymerase.

Table 25: Subsequent PARP inhibitors by line of subsequent therapy (FAS)

	Number (%) of patients		
	Olaparib 300 mg bd (N=260)	Placebo (N=131)	Total (N=391)
Received PARP inhibitor	20 (7.7)	49 (37.4)	69 (17.6)
First subsequent therapy	10 (3.8)	33 (25.2)	43 (11.0)
Second subsequent therapy	5 (1.9)	11 (8.4)	16 (4.1)
Third subsequent therapy	4 (1.5)	4 (3.1)	8 (2.0)
Fourth subsequent therapy	0	2 (1.5)	2 (0.5)
Fifth subsequent therapy	2 (0.8)	0	2 (0.5)
Patients who subsequently received olaparib	13 (5.0)	44 (33.6)	57 (14.6)

bd twice daily; FAS Full Analysis Set; PARP polyadenosine 5'diphosphoribose polymerase.

In SOLO1, only 10 patients had olaparib as part of their first subsequent treatment after receiving olaparib first line. Nine of the 10 patients received platinum-based chemotherapy followed by olaparib maintenance as their first subsequent treatment. All 10 patients had CR at study entry and their median time to progression on olaparib 1st line maintenance was 32 months, ranging from 23 to 41 months. At the time of DCO, only 3 patients had PFS2 event (progressed for a second time), whilst the remaining 7 patients were censored for PFS2, with the majority still receiving olaparib.

Time to earliest progression by RECIST 1.1, CA-125 or death

Table 26: Summary of time to earliest progression by RECIST 1.1, CA-125 or death (FAS)

	Olaparib 300 mg bd (N=260)	Placebo (N=131)
n (%) of events[a]	102 (39.2)	97 (74.0)
Treatment effect		
HR[b]	0.30	
95% CI[b]	0.23, 0.40	
2-sided p-value[c]	<0.0001	
Median PFS, months[d]	NR	12.0
Median follow-up for PFS, months[e]	38.9	41.1

[a] Time to event is defined as time from randomisation until time of earliest progression by RECIST 1.1, CA-125 or death.
[b] Estimated from Cox proportional hazards model including the stratification variable as a covariate.
[c] Determined using log-rank test stratified by response to previous platinum chemotherapy. Not adjusted for multiplicity.
[d] Calculated using Kaplan-Meier techniques.
[e] Time from randomisation to date of censoring.
bd twice daily; CA-125 cancer antigen; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; NR not reached; PFS progression-free survival; RECIST Response Evaluation Criteria in Solid Tumours.

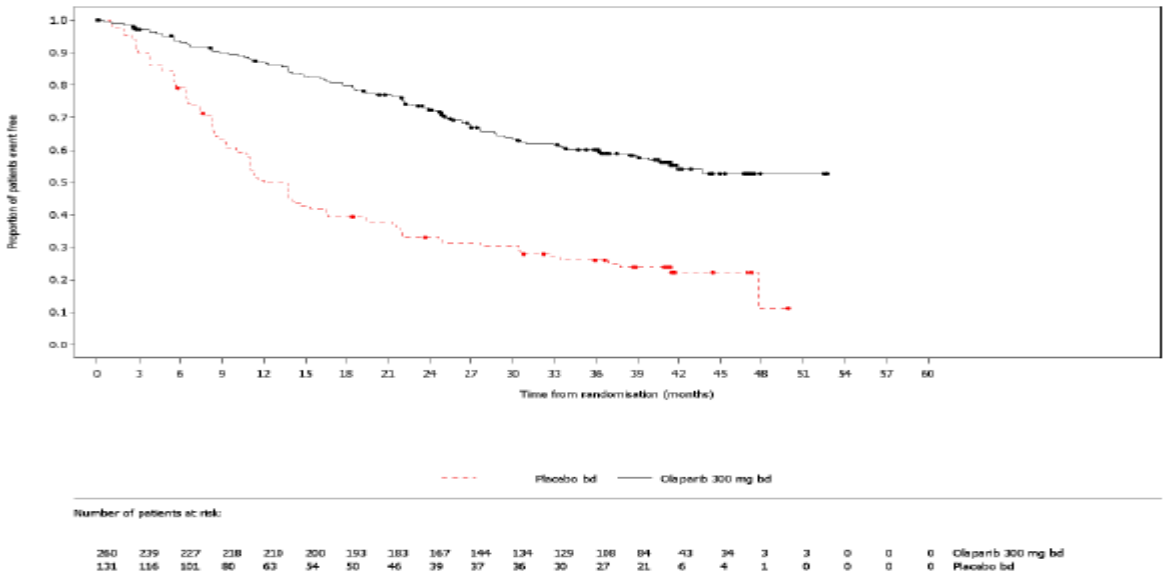


Figure 10: Time to earliest progression by RECIST, CA-125 or death, Kaplan-Meier plot (FAS)

Best overall response

Table 27: Best objective response (FAS – patients with evidence of disease at baseline).

Response status	Best objective response	Number (%) of patients	
		Olaparib 300 mg bd (N=54)	Placebo (N=26)
Response	Total	23 (42.6)	6 (23.1)
	CR[a]	15 (27.8)	3 (11.5)
	PR[a]	8 (14.8)	3 (11.5)
Non-response	Total	31 (57.4)	20 (76.9)
	SD ≥12 weeks	26 (48.1)	13 (50.0)
	Progression	4 (7.4)	7 (26.9)
	RECIST progression	4 (7.4)	7 (26.9)
	Not evaluable	1 (1.9)	0
	No evaluable follow-up assessments	1 (1.9)	0

[a] Response does not require confirmation.
Patients with evidence of disease at baseline are considered evaluable for response.
This analysis is based on investigator RECIST assessment. Modified RECIST Version 1.1.
bd twice daily; CR complete response; FAS Full Analysis Set; PR partial response; RECIST Response Evaluation Criteria in Solid Tumours; SD stable disease.

In those patients with objective response, median time from randomisation to onset of response and median duration of response were 10.8 months and 28.2 months, respectively for patients in the olaparib arm and 5.4 months and 8.6 months, respectively for patients in the placebo arm.

Table 28: Duration and onset of objective response in patients with objective response (FAS, patients with objective response)

	Olaparib 300 mg bd (N=23)	Placebo bd (N=6)
Number of responders who subsequently progressed or died	10 (43.5)	4 (66.7)
Duration of response from onset of response (days) [a][b]		
25th percentile	427.0	169.0
Median (95% CI)	858.0 (506.0, NE)	261.0 (87.0, NE)
75th percentile	NE	NE
Time to onset of response from randomisation (days)		
25th percentile	162.0	85.0
Median	329.0	166.5
75th percentile	592.0	333.0

Table 29: Summary of complete and partial responders at 12, 24 and 36 months (full analysis set)

	Number (%) patients	
	Olaparib 300 mg bd (N=260)	Placebo (N=131)
Patients with CR at randomisation and remaining CR at : n	206 (79.2)	105 (80.2)
12 months	170 (82.5)	57 (54.3)
24 months	140 (68.0)	26 (34.3)
36 months	92 (44.7)	23 (21.9)
Patients with PR at randomisation (measurable or non-measurable disease) who remain stable or have partially responded at: n	54 (20.8)	26 (19.8)
12 months	36 (66.7)	6 (23.1)
24 months	23 (42.6)	4 (15.4)
36 months	9 (16.7)	4 (15.4)
Patients with PR at randomisation (measurable or non-measurable disease) who became CR at : n	54 (20.8)	26 (19.8)
12 months	6 (11.1)	1 (3.8)
24 months	8 (14.8)	1 (3.8)
36 months	8 (14.8)	1 (3.8)

bd twice daily; CR Complete response; NED no evidence of disease
Data derived from Table 1497

Health-Related Quality of Life: FACT-O and TOI

The TOI and FACT-O scores ranged between 0 to 100 and 0 to 152, respectively, with a higher score indicating a better HRQoL. Mean baseline TOI scores were 73.6 (SD 12.8) and 75 (SD 13.1) for the olaparib and placebo arms, respectively, and mean FACT-O scores were 113.5 (SD 18.3) and 115.8 (SD 18.6) for the olaparib and placebo arm, respectively. The compliance rates for the planned on-treatment visits by FACT-O were above 80% from the baseline to Week 97 (about 24 months) in both arms.

Over the 24 months (main analysis), the average adjusted mean change from baseline was 0.3 (95%CI -0.72, 1.32) with olaparib (n=237) and 3.3 (95%CI 1.84, 4.76) with placebo (n=125). The estimated difference (-3.00; 95%CI -4.8, -1.2) between the arms in the mean change from baseline in TOI score over 24 months was statistically significant. Over the first 12 months, the average adjusted mean change from

baseline was -0.69 (95%CI -1.67, 0.29) with olaparib (n=237) and 3.47 (95%CI 2.18, 4.83) with placebo (n=125), with an estimated difference of -4.17 (95%CI -5.8, -2.5) between the arms being statistically significant. The mean TOI score change from baseline was -2.86 and -1.16 at the early timepoints (5 weeks and 13 weeks, respectively) in the olaparib arm, while it was 2.15 and 2.91 at the same timepoints in the placebo arm, respectively. An AUC (area under the curve) analysis over all visits was also performed for TOI as sensitivity analysis and supported the main analysis.

Ancillary analyses

Sensitivity analysis of progression-free survival

Sensitivity analysis of PFS by BICR

Table 30: Sensitivity analysis of progression-free using BICR (FAS)

	Olaparib 300 mg bd (N=260)	Placebo (N=131)
n (%) of events[a]	75 (28.8)	75 (57.3)
Treatment effect		
HR[b]	0.28	
95% CI[b]	0.20, 0.39	
2-sided p-value[c]	<0.0001	
Median PFS, months[d]	NR	14.1

[a] PFS was defined as time from randomisation until date of RECIST progression or death.
[b] Estimated from Cox proportional hazards model including the stratification variable as a covariate.
[c] Determined using log-rank test stratified by response to previous platinum chemotherapy.
[d] Calculated using Kaplan-Meier techniques.
bd twice daily; BICR blinded independent central review; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; NR not reached; PFS progression-free survival; RECIST Response Evaluation Criteria in Solid Tumours.

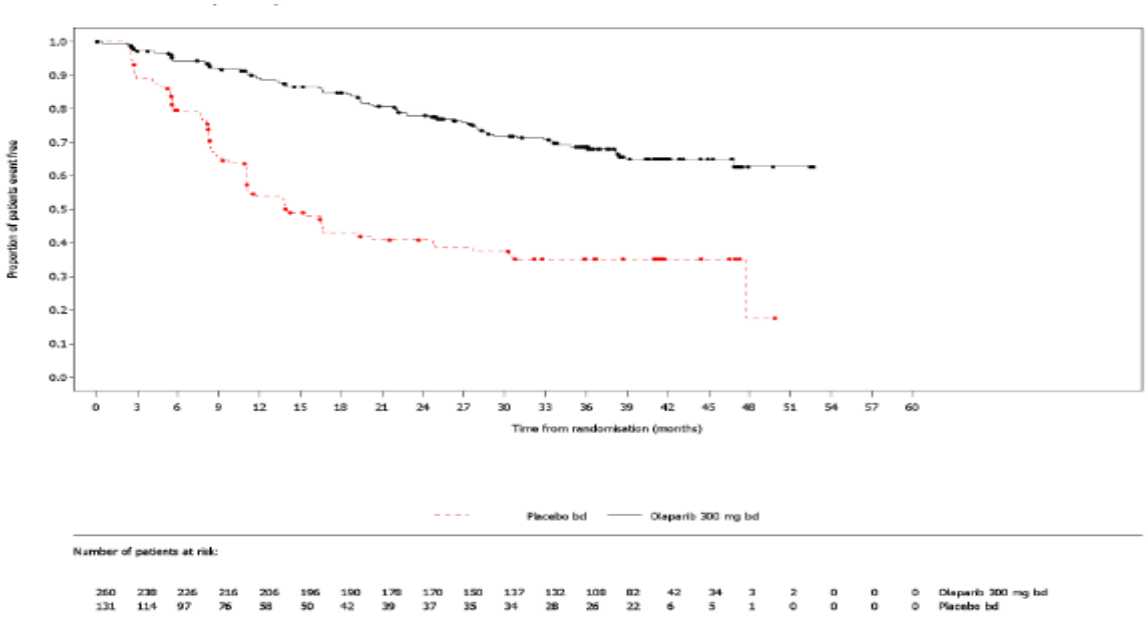


Figure 11: Progression-free survival by BICR assessment, Kaplan-Meier plot (FAS)

Table 31: Disagreement between investigator and central reviews of RECIST 1.1 progression (FAS)

	Number (%) of patients		Difference
	Olaparib 300 mg bd (N=260)	Placebo (N=131)	Olaparib 300 mg bd - Placebo
RECIST progression[a] declared by:			
Investigator and central review[b]	70 (26.9)	75 (57.3)	NA
Progression date agreement (within 2 weeks)[c]	40 (57.1)	42 (56.0)	NA
Progression date ≥2 weeks earlier by central review than by investigator[c]	26 (37.1)	31 (41.3)	NA
Progression date ≥2 weeks earlier by investigator than by central review[c]	4 (5.7)	2 (2.7)	NA
Investigator but not central review	32 (12.3)	21 (16.0)	NA
Central review but not investigator	5 (1.9)	0	NA
No progression by both	153 (58.8)	35 (26.7)	NA
Early discrepancy rate[d]	0.35	0.24	0.11
Late discrepancy rate[e]	0.46	0.57	-0.11

[a] Progression events that occurred 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] Sub-categories of this section do not include all possible eventualities.

[c] Percentages were calculated based on the number of progressions declared by both investigator and central review.

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

[e] Late discrepancy rate is the frequency of investigator declared progressions after central review as a proportion of all discrepancies. Modified RECIST Version 1.1.

bd twice daily; FAS Full Analysis Set; NA not applicable; RECIST Response Evaluation Criteria in Solid Tumours.

Other sensitivity and additional analyses of PFS

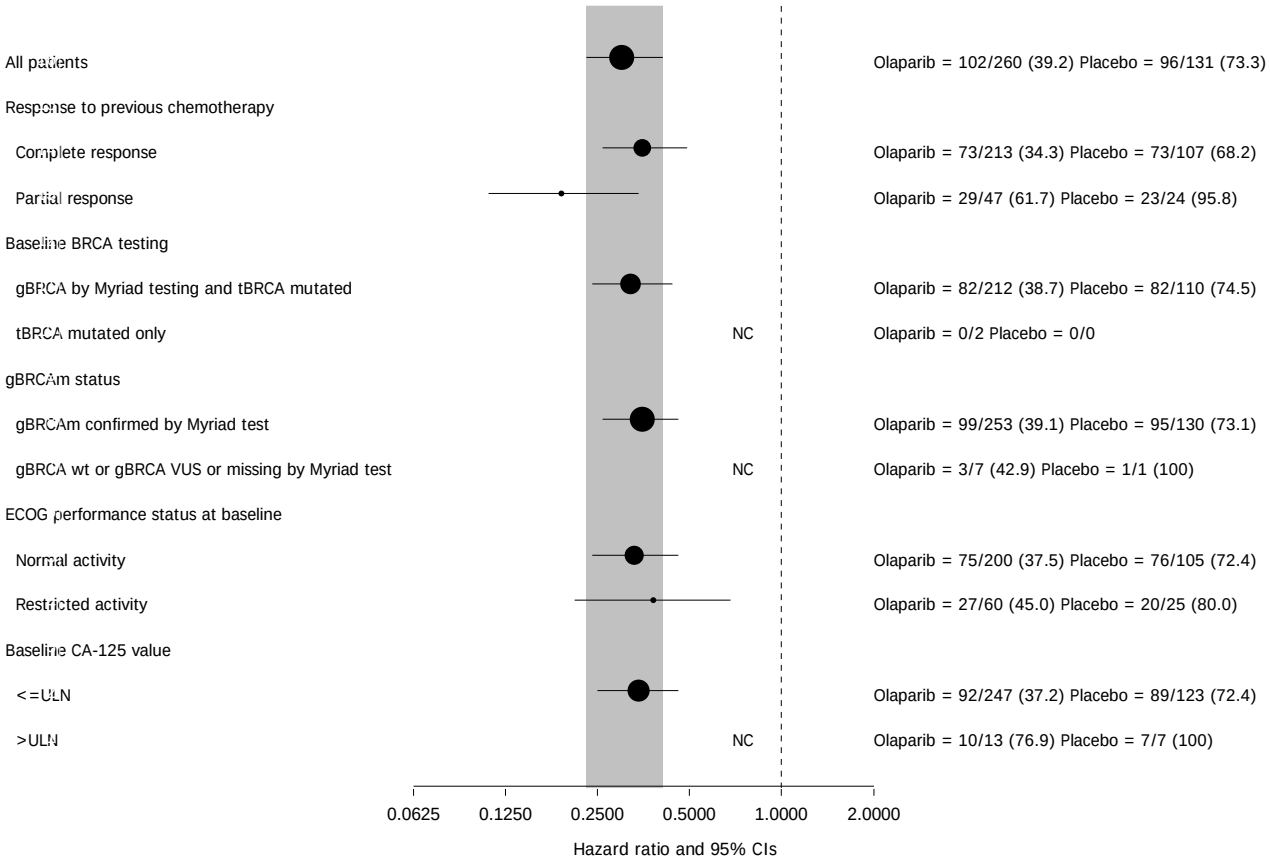
Table 32: Sensitivity and additional analyses of progression free survival (FAS).

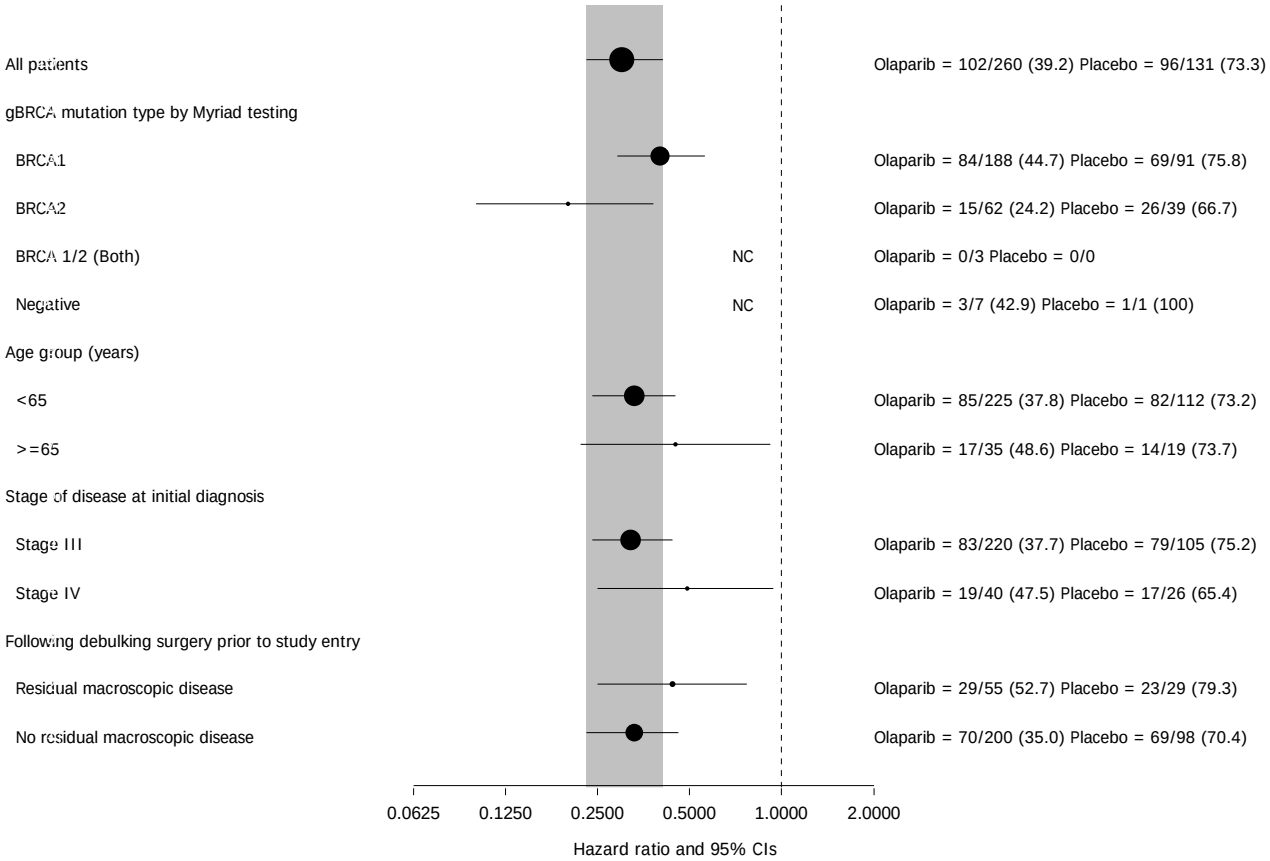
	Number (%) of patients with events Events:Patients	Median PFS (months)	HR	95% CI	p-value
Sensitivity analysis: evaluation time bias	Olaparib: 102 (39.2)	NR	0.31	0.23, 0.41	<0.0001
	Placebo: 96 (73.3)	12.4			
Sensitivity analysis: attrition bias	Olaparib: 102 (39.2)	49.9	0.31	0.23, 0.41	<0.0001
	Placebo: 93 (71.0)	13.8			
Sensitivity analysis: using the eCRF stratification variable	Olaparib: 102 (39.2)	NR	0.33	0.25, 0.44	<0.0001
	Placebo: 96 (73.3)	13.8			
Sensitivity analysis: to assess possible informative censoring (using BICR)	Olaparib: 107 (41.2)	46.9	0.31	0.24, 0.42	<0.0001
	Placebo: 96 (73.3)	11.1			
Sensitivity analysis: estimating HR using the stratified log rank test	Olaparib: 102 (39.2)	NR	0.25	0.18, 0.34	<0.0001
	Placebo: 96 (73.3)	13.8			
Additional analysis: based on earliest progression of investigator/BICR assessment of progression	Olaparib: 107 (41.2)	NR	0.31	0.24, 0.42	<0.0001
	Placebo: 96 (73.3)	11.1			

bd twice daily; BICR blinded independent central review; CI confidence interval; eCRF electronic case report form; FAS Full Analysis Set; HR hazard ratio; NR not reached; PFS progression free survival; RECIST Response Evaluation Criteria in Solid Tumours.

Data derived from Table 11.2.1.3, Table 11.2.1.4, Table 11.2.1.15, Table 11.2.1.16, Table 11.2.1.17 and Table 11.2.1.18.

Subgroup analyses of progression-free survival




All patients
Olaparib = 102/260 (39.2) Placebo = 96/131 (73.3)
gBRCA mutation type by Myriad testing
BRCA1
Olaparib = 84/188 (44.7) Placebo = 69/91 (75.8)
BRCA2
Olaparib = 15/62 (24.2) Placebo = 26/39 (66.7)
BRCA 1/2 (Both)
NC
Olaparib = 0/3 Placebo = 0/0
Negative
NC
Olaparib = 3/7 (42.9) Placebo = 1/1 (100)
Age group (years)
<65
Olaparib = 85/225 (37.8) Placebo = 82/112 (73.2)
>=65
Olaparib = 17/35 (48.6) Placebo = 14/19 (73.7)
Stage of disease at initial diagnosis
Stage III
Olaparib = 83/220 (37.7) Placebo = 79/105 (75.2)
Stage IV
Olaparib = 19/40 (47.5) Placebo = 17/26 (65.4)
Following debulking surgery prior to study entry
Residual macroscopic disease
Olaparib = 29/55 (52.7) Placebo = 23/29 (79.3)
No residual macroscopic disease
Olaparib = 70/200 (35.0) Placebo = 69/98 (70.4)
0.0625
0.1250
0.2500
0.5000
1.0000
2.0000
Hazard ratio and 95% CIs

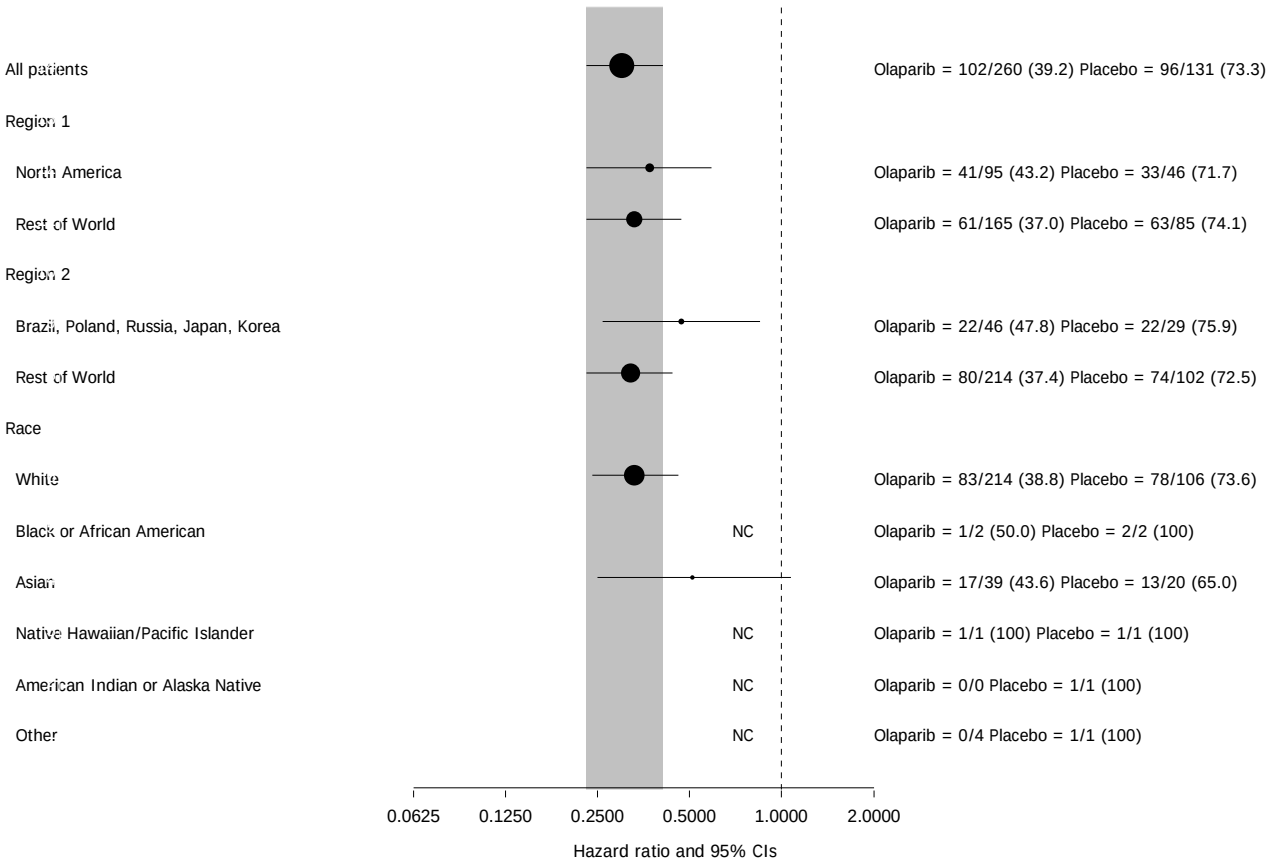

All patients
Olaparib = 102/260 (39.2) Placebo = 96/131 (73.3)
Region 1
North America
Olaparib = 41/95 (43.2) Placebo = 33/46 (71.7)
Rest of World
Olaparib = 61/165 (37.0) Placebo = 63/85 (74.1)
Region 2
Brazil, Poland, Russia, Japan, Korea
Olaparib = 22/46 (47.8) Placebo = 22/29 (75.9)
Rest of World
Olaparib = 80/214 (37.4) Placebo = 74/102 (72.5)
Race
White
Olaparib = 83/214 (38.8) Placebo = 78/106 (73.6)
Black or African American
NC
Olaparib = 1/2 (50.0) Placebo = 2/2 (100)
Asian
Olaparib = 17/39 (43.6) Placebo = 13/20 (65.0)
Native Hawaiian/Pacific Islander
NC
Olaparib = 1/1 (100) Placebo = 1/1 (100)
American Indian or Alaska Native
NC
Olaparib = 0/0 Placebo = 1/1 (100)
Other
NC
Olaparib = 0/4 Placebo = 1/1 (100)
0.0625
0.1250
0.2500
0.5000
1.0000
2.0000
Hazard ratio and 95% CIs

Figure 12: Forest plot of progression-free survival by subgroup (FAS)

Table 33: SOLO1: Investigator assessed PFS for patients with evidence of disease at baseline (DCO 17 May 2018)

	Olaparib (N=260)	Placebo (N=131)
Clinical CR (eCRF) at baseline		
PFS events, n/N (%)	66/189 (34.9)	71/101 (70.3)
Median PFS, months	NR	15.3
	HR 0.34 (95% CI 0.24–0.47)	
Clinical PR (eCRF) at baseline		
PFS events, n/N (%)	36/71 (50.7)	25/30 (83.3)
Median PFS, months	30.9	8.4
	HR 0.31 (95% CI 0.18–0.52)	

CI confidence interval; DCO Data cut-off date; eCRF electronic case report form; FAS Full Analysis Set; HR hazard ratio; NR Not reached; PFS progression free survival; RECIST Response Evaluation Criteria in Solid Tumours

Efficacy variables in Myriad confirmed g*BRCA*m patients

Table 34: Summary of key efficacy outcome variables for Myriad g*BRCA*m patients (FAS)

	Olaparib 300 mg bd (N=253)	Placebo (N=130)
PFS by investigator assessment[a]		
Total number of events (%)	99 (39.1)	95 (73.1)
HR (95% CI)[b]	0.30	
p-value (2-sided)[c]	<0.0001	
Median PFS (months)[d]	NR	13.8
PFS Sensitivity analysis: BICR assessment[a]		
Total number of events (%)	72 (28.5)	74 (56.9)
HR (95% CI)[b]	0.27	
p-value (2-sided)[c]	<0.0001	
Median PFS (months)[d]	NR	14.1
PFS2[a]		
Total number of events (%)	67 (26.5)	51 (39.2)
HR (95% CI)[b]	0.50	
p-value (2-sided)[c]	0.0003	
Median PFS2 (months)[d]	NR	42.1
OS[f]		
Total number of events (%)	52 (20.6)	26 (20.0)
HR (95% CI)[b]	0.95	
p-value (2-sided)[c]	0.8935	
Median OS (months)[d]	NR	NR
TDT[g]		
Total number of events (%)	241 (95.3)	129 (99.2)
HR (95% CI)[b]	0.64	
p-value (2-sided)[c]	0.0001	
Median TDT (months)[d]	24.6	13.9

	Olaparib 300 mg bd (N=253)	Placebo (N=130)
TFST[h]		
Total number of events (%)	96 (37.9)	93 (71.5)
HR (95% CI)[b]	0.29	
p-value (2-sided)[c]	<0.0001	
Median TFST (months)[d]	51.8	15.5
TSST[i]		
Total number of events (%)	74 (29.2)	64 (49.2)
HR (95% CI)[b]	0.44	
p-value (2-sided)[c]	<0.0001	
Median TSST (months)[d]	NR	40.7

[a] PFS is defined as the time from randomisation until data of RECIST progression or death.
[b] Estimated from Cox proportional hazards model including the stratification variable as a covariant.
[c] Determined using log-rank test stratified by response to previous platinum chemotherapy.
[d] Calculated using Kaplan-Meier techniques.
[e] PFS2 is defined as the time from randomisation until second progression or death as recorded in the CRF.
[f] OS is defined as the time from randomisation until death.
[g] TDT is defined as the time from randomisation until time of discontinuation of treatment or death.
[h] TFST is defined as time from randomisation until first subsequent cancer therapy or death.
[i] TSST is defined as time from randomisation until second subsequent cancer therapy or death.

Efficacy variables in t*BRCA*m patients confirmed retrospectively

Table 35: Summary of key efficacy outcome variables for FMI t*BRCA*m patients (FAS)

	Olaparib 300 mg bd (N=214)	Placebo (N=110)
PFS by investigator assessment[a]		
Total number of events (%)	82 (38.8)	82 (74.5)
HR (95% CI)[b]	0.28	
p-value (2-sided)[c]	<0.0001	
Median PFS (months)[d]	NR	13.7
PFS Sensitivity analysis: BICR assessment[a]		
Total number of events (%)	59 (27.6)	63 (57.3)
HR (95% CI)	0.25	
p-value (2-sided)	<0.0001	
Median PFS (months)	NR	13.8
PFS2[e]		
Total number of events (%)	55 (25.7)	44 (40.0)
HR (95% CI)[b]	0.46	
p-value (2-sided)[c]	0.0002	
Median PFS2 (months)[d]	NR	41.9
OS[f]		
Total number of events (%)	46 (21.5)	21 (19.1)
HR (95% CI)[b]	1.05	
p-value (2-sided)[c]	0.8185	
Median OS (months)[d]	NR	NR
TDT[g]		
Total number of events (%)	203 (94.9)	109 (99.1)
HR (95% CI)[b]	0.60	
p-value (2-sided)[c]	<0.0001	
Median TDT (months)[d]	24.7	12.6

	Olaparib 300 mg bd (N=214)	Placebo (N=110)
TFST[h]		
Total number of events (%)	81 (37.9)	82 (74.5)
HR (95% CI)[b]	0.28	
p-value (2-sided)[c]	<0.0001	
Median TFST (months)[d]	51.8	14.8
TSST[i]		
Total number of events (%)	63 (29.4)	56 (50.9)
HR (95% CI)[b]	0.43	
p-value (2-sided)[c]	<0.0001	
Median TSST (months)[d]	NR	40.4

[a] PFS is defined as the time from randomisation until data of RECIST progression or death.
[b] Estimated from Cox proportional hazards model including the stratification variable as a covariant.
[c] Determined using log-rank test stratified by response to previous platinum chemotherapy.
[d] Calculated using Kaplan-Meier techniques.
[e] PFS2 is defined as the time from randomisation until second progression or death as recorded in the CRF.
[f] OS is defined as the time from randomisation until death.
[g] TDT is defined as the time from randomisation until time of discontinuation of treatment or death.
[h] TFST is defined as time from randomisation until first subsequent cancer therapy or death.
[i] TSST is defined as time from randomisation until second subsequent cancer therapy or death.
Note: p-values were not adjusted for multiplicity.

Exploratory analysis in non-serous vs serous histology group

For the serous histology, PFS events occurred in 40.4% (99/245) of patients in the olaparib arm compared with 40.0% (6/15) of patients with a non-serous histology in the olaparib arm. Only 1 patient in the placebo arm had non-serous histology and this patient did not have a PFS event at the time of the data cut-off. Thus, the PFS event rate for serous histology patients in the placebo arm is 96/130 [73.8%].

In the FAS, PFS2 events occurred in 26.9% (66/245) of patients in the olaparib arm compared with 20% (3/15) of patients with a non-serous histology. In the placebo arm, the 1 patient with non-serous histology did not have a PFS2 event; the PFS2 event rate in serous patients in the placebo arm was 52/130 (40.0%).

Summary of main study

The following table 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 36: Summary of Efficacy for trial SOLO1

Title: A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with *BRCA* Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy.		
Study identifier	SOLO 1	
Design	Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study	
	Duration of main phase:	Treatment for two years or until disease progression as per modified RECIST 1.1 as assessed by the investigator. Following objective disease progression, further treatment options were at the discretion of the investigator.
	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=260
	Placebo		300 mg (2 x 150 mg tablets) orally bd N=131
Endpoints and definitions	Primary endpoint	PFS (Progression Free Survival)	the time from randomisation until the date of objective radiological disease progression according to RECIST or death (by any cause in the absence of progression) regardless of whether the patient discontinued randomised therapy or received another anticancer therapy prior to progression.
	Secondary endpoint	Interim OS (Overall Survival)	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	TDT	time from randomisation to study treatment discontinuation or death
	Secondary endpoint	TFST	time from randomisation to start of first subsequent therapy or death.
	Secondary endpoint	TSST	Time from randomisation to start of second subsequent therapy or death.
Database lock	17 May 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	FAS (Full analysis set): FAS or ITT includes all randomised patients and treatment arms are compared on the basis of randomised treatment, regardless of the treatment actually received.		
Descriptive statistics and estimate variability	Treatment group	olaparib	placebo
	Number of subject	260	131
	Median PFS (months)	Not reached	13.8
	95% CI		11.1-18.2
	Median PFS2 (months)	Not reached	41.9
	95% CI		36.5-47.9
	Median OS (months)	Not reached	Not reached
	95% CI		
	Median TDT (months)	24.6	13.8
	95% CI		
	Median TFST (months)	51.8	15.1
	95% CI	44.3-	12.7-20.5
	Median TSST (months)	Not reached	40.7
	95% CI		32.9-47.7

Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Olaparib versus placebo
		Hazard ratio	0.30
		95% CI	0.23-0.41
		2 sided P-value	<0.0001
	Secondary	Comparison groups	Olaparib versus placebo

	endpoint PFS2 (30.9% maturity)	Hazard ratio	0.50
		95% CI	0.35-0.72
		2 sided P-value	0.0002
	Secondary endpoint Interim OS (21%maturity)	Comparison groups	Olaparib versus placebo
		Hazard ratio	0.95
		95% CI	0.6-1.53
		2 sided P-value	0.893
	TDT (96.4% maturity)	Comparison groups	Olaparib versus placebo
		Hazard ratio	0.63
		95% CI	0.51-0.79
		2 sided P-value	<0.0001
	TFST (49.4% maturity)	Comparison groups	Olaparib versus placebo
		Hazard ratio	0.3
		95% CI	0.22-0.40
		2 sided P-value	<0.0001
	TSST (36.3% maturity)	Comparison groups	Olaparib versus placebo
		Hazard ratio	0.45
		95% CI	0.32-0.63
		2 sided P-value	<0.0001
Analysis description	**Key efficacy outcome variables for confirmed Myriad g*BRCA*m patients.**		
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	0.3
		95% CI	0.22-0.40
		2 sided P-value	<0.0001
	Secondary endpoint PFS2 (30.9% maturity)	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	0.50
		95% CI	0.34-0.72
		2 sided P-value	0.0003
	Secondary endpoint Interim OS (21%maturity)	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	0.95
		95% CI	0.6-1.54
		2 sided P-value	0.8935
	TDT (96.4% maturity)	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	0.64
		95% CI	0.51-0.80
		2 sided P-value	<0.0001
	TFST (49.4% maturity)	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	0.29
		95% CI	0.22-0.39
		2 sided P-value	<0.0001
	TSST (36.3% maturity)	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	0.44
		95% CI	0.32-0.63
		2 sided P-value	<0.0001
Analysis description	**Key efficacy outcome variables for confirmed FMI t*BRCA*m patients.**		
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	0.28
		95% CI	0.21-0.39
		2 sided P-value	<0.0001

	Secondary endpoint PFS2 (30.9% maturity)	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	0.46
		95% CI	0.31-0.69
		2 sided P-value	0.0002
	Secondary endpoint Interim OS (21%maturity)	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	1.05
		95% CI	0.63-1.79
		2 sided P-value	0.8185
	TDT (96.4% maturity)	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	0.6
		95% CI	0.47-0.76
		2 sided P-value	<0.0001
	TFST (49.4% maturity)	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	0.28
		95% CI	0.20-0.38
		2 sided P-value	<0.0001
	TSST (36.3% maturity)	Comparison groups	Olaparib (N=253) versus placebo (N=130)
		Hazard ratio	0.43
		95% CI	0.30-0.63
		2 sided P-value	<0.0001

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The present application is to extend the indication of olaparib tablet formulation as monotherapy for the maintenance treatment of adult patients advanced *BRCA*-mutated high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to first line platinum-based chemotherapy.

The application is based on the results of study SOLO1, a pivotal Phase III, randomised, double-blind, placebo-controlled, multicentre study, investigating olaparib maintenance treatment in *BRCA*m patients with newly diagnosed high-grade advanced (FIGO III-IV) ovarian, primary peritoneal or fallopian tube cancer who were in complete response (CR) or partial response (PR) to their first line platinum-based chemotherapy.

The dose of olaparib in SOLO1 (300 mg bd tablets) was selected based on data from the Phase I study, D0810C00024 (Study 24) in an advanced g*BRCA* mutated ovarian cancer population and is the current recommended dose for the current indication. 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 (see EPAR Lynparza).

Subjects were randomised 2:1 to receive either olaparib (300 mg bd, tablet formulation) or placebo stratified by response to fist line platinum chemotherapy (complete or partial). Cross-over was not allowed in this study.

In SOLO1, patients could continue treatment for 2 years or until disease progression, or unacceptable toxicity. Patients with a complete response (no radiological evidence of disease) at 2 years were to stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can

derive further benefit from continuous treatment, could be treated beyond 2 years. The 2 year duration was determined based on the assumption that 8 month improvement in median PFS is clinically meaningful for the maintenance treatment for advanced ovarian cancer patients if median PFS of 13 months could reach to 21 months after the olaparib administration. Considering that most olaparib-related adverse events (AEs)/serious adverse events (SAEs) occurred in the first 3 months of exposure, clustering late-onset AEs are not expected during the prolonged treatment duration (see discussion on clinical safety). To consider the potential risk of myelodysplastic syndrome (MDS)/ acute myeloid leukaemia (AML) versus the clinical benefits in patients who receive the long term treatment, patients with a complete response (no radiological evidence of disease) at 2 years had to stop treatment.

The trial was designed to recruit *BRCA*m patients i.e., germline *BRCA*m (g*BRCA*m) based on local and central testing or somatic *BRCA*m (s*BRCA*m) based on local testing. Prospective germline testing was performed using the Myriad Integrated BRACAnalysis test or the BGI g*BRCA* test. Patients with a local *BRCA* result were retested post-randomisation with the Myriad Integrated BRACAnalysis test or with the BRACAnalysis CDx test. No prospective testing of tumour samples was performed (see PD part).

Patients must have had upfront or interval debulking surgery and be in clinical complete or partial response to first line platinum-based chemotherapy and no clinical evidence of disease progression. Regarding the platinum-based chemotherapy, the course must have consisted of a minimum of 6 treatment cycles and a maximum of 9; however if platinum-based therapy was discontinued early as a result of toxicities specifically related to the platinum regimen, patients must have received a minimum of 4 cycles of the platinum regimen.

Four cycles of chemotherapy is considered as under treatment and could have confounded the results. However, only 2 patients had 4 cycles of prior chemotherapy and 3 patients had 5 cycles of prior chemotherapy in SOLO1. All other patients had 6-9 cycles of chemotherapy prior to randomisation, with the majority having 6 cycles of chemotherapy. Therefore, it is considered that the impact on PFS calculated from time of randomization to progression or death is limited.

Randomization was expected to be performed within 8 weeks after their last dose of chemotherapy (last dose was the day of the last infusion).

Study patients must not have received bevacizumab during their first-line course of treatment, either in combination or as maintenance therapy following combination therapy. This is adequately reflected in the SmPC.

At the time the study started, bevacizumab (Avastin) was approved in combination with carboplatin and paclitaxel followed by bevacizumab maintenance in the first line maintenance ovarian cancer. According to NCCN guidelines (2019), bevacizumab may be continued, regardless of *BRCA* status, as a single-agent maintenance therapy if used previously as part of a combination therapy, if partial or complete remission following: primary therapy for stage II-IV disease or recurrence therapy for platinum-sensitive disease [Evidence 3; moderately effective]. In addition, according to ESMO guidelines regardless of *BRCA* status (2013), bevacizumab is generally recommended [I, B] for patients with poor prognostic features such as stage IV or suboptimal debulking as defined in the ICON-7 trial. Bevacizumab should be given with paclitaxel or carboplatin with a treatment duration of one year. Bevacizumab is not universally used in this setting in EU and it could have been considered as a treatment option under discretion of investigator and according to local clinical practice. Treatment with bevacizumab did not show a clear benefit for *BRCA*m patients according to the results from substudy GOG-218: 1) PFS in the subgroup of patients with HRR mutations (n=228): HR 0.95, 95% CI 0.71 to 1.26 for bevacizumab + carboplatin/paclitaxel vs carboplatin/paclitaxel, and PFS in the subgroup of patients with no HRR mutation (n=581): HR 0.71, 95% CI 0.60 to 0.85 (Norquist et al 2018), 2) results were not conclusive for OS. Therefore, the use of placebo as comparator is considered to be appropriate in order to determine the efficacy of olaparib maintenance monotherapy in advanced ovarian cancer patients who had responded following first-line platinum-based chemotherapy.

To note, there is biological rationale for using PARPi in hypoxic conditions induced by VEGFi and this strategy is currently investigated in clinical trials, as PAOLA-01.

PFS was the primary endpoint in SOLO1 supported by PFS2 and OS as key secondary endpoints. Additional secondary endpoints were TDT, TFST, and TSST. Other secondary efficacy endpoints included time to earliest progression by RECIST 1.1, CA-125 or death, BoR and HRQoL measured by TOI. Primary and secondary efficacy endpoints are in line with recommendations from EMA 'Guideline on the evaluation of anticancer medicinal products in man' (EMA/CHMP/205/95/Rev 5.). Prolonged PFS is considered to be of benefit to the patient. If PFS is the selected primary endpoint, OS should be reported as a secondary. Moreover, in the context of maintenance therapy, PFS2 should be determined to evaluate the impact on tumour's drug resistance profile affected by therapy and the activity of next-line therapies.

PFS assessment was initially by BICR. Per protocol amendment 3 issued on 19 February 2016, the assessment of PFS in the primary objective was changed to investigator assessment and PFS BICR assessment was retained as a sensitivity analysis. Others protocol amendments related to the assessment of efficacy during the course of the conduct of the study were about inclusion of an additional secondary objective of assessing efficacy by TFST, TSST and TDT (amendment 1) and update the HRQoL endpoint to change from baseline in TOI score of the FACT-O using MMRM analysis (amendment 2). Initially the objective of the HRQoL analysis was to compare the rate of deterioration in of HRQoL as assessed by TOI. Patient centric endpoints have been included and subsequently deleted from the SAP. Further, the initially planned time-to-worsening analyses of HRQoL and symptoms were deleted as not considered able to reflect the introduced continuous collection of QoL data beyond objective disease progression in view of the data demonstrated in study 19 where median time-to-worsening in TOI on both arms was shorter than median PFS. Changes have been done to allow continuous collection of PRO data beyond disease progression under protocol amendment 2 and this data is expected to be provided at the time of the updated PFS2 and OS analysis.

All primary and secondary efficacy and HRQoL data were summarised and analysed using the FAS on an intention-to-treat (ITT) basis. A hierarchical testing strategy was employed to manage statistical tests for primary and key secondary endpoints of PFS2 and OS. In order to control the type I error at 2.5% (1-sided), a multiple testing procedure (MTP) was employed across primary (PFS) and key secondary endpoints (PFS2 and OS). PFS2 was tested only after statistical significance was shown for PFS. OS was tested only after the null hypotheses were rejected for PFS and PFS2.

The number of patients defined as having at least 1 important deviation in the study (defined as a deviation that could potentially have influenced the assessment of efficacy) was low (12.0%). A higher proportion (7.3%) of olaparib-treated patients had RECIST scans outside of a scheduled visit window on more than 2 occasions compared with placebo-treated patients (1.5%). This is likely a reflection of the longer time to progression on the olaparib arm compared to placebo. The important deviations reported in SOLO1 were considered unlikely to have influenced the overall study conclusions, which are considered robust and representative of the overall study data.

Efficacy data and additional analyses

In the study SOLO1, a total of 391 out of 1084 patients enrolled were randomly assigned to either the olaparib arm (260 patients) or to the placebo arm (131). All except one placebo patient (130) and all olaparib patients (260) received study treatment.

In addition to this global enrolment, a cohort of 64 patients was randomised in China. Five of these patients were included both in the global cohort and in the China cohort; the remaining 59 Chinese patients were randomised after the global recruitment was complete and closed and included only in China cohort. At the time of the DCO, a total of 14 patients (13 and 1 patients in the olaparib and placebo group, respectively)

were still in treatment and a total of 260 patients (170 and 90 in the olaparib and placebo group, respectively) remained in follow-up off treatment.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 53 years in both arms. Most patients were ECOG performance status 0 (78%). There were no patients with performance status 2 to 4 enrolled in the study (see SmPC section 5.1).

Overall, ovarian cancer was the primary tumour in > 80% of the patients. Most patients were diagnosed as FIGO stage IIIC (>65%). According to Prat 2014, most serous ovarian cancer are stage III; the vast majority (84%) of patients presenting with Stage IIIC disease. Furthermore, 12-21% of patients presented with Stage IV disease. The MAH has provided FIGO stages data from different clinical studies in the first-line maintenance that are in line with the FIGO stage distribution of the patients in SOLO1. Overall, the distribution of patients in the SOLO1 study across the different FIGO stages can be considered to be in line with historical data.

The most common histological type was serous (> 90%), endometrioid histology was reported in 3.5% of the patients.

Sixty-three percent (63%) of the patients had upfront debulking surgery and of these the majority (75%) had no macroscopic residual disease. Interval debulking surgery was performed in 35% of the patients and of these 82% had no macroscopic residual disease reported. Seven patients (1.8%), all stage IV, had no cytoreductive surgery. All patients had received first-line platinum-based therapy.

There was no evidence of disease at study entry (CR), defined by the investigator as no radiological evidence of disease and cancer antigen 125 (CA-125) within normal range, in 73% and 77% of patients in the olaparib and placebo arms, respectively. PR, defined as the presence of any measurable or non-measurable lesions at baseline or elevated CA-125, was reported in 27% and 23% of patients in the olaparib and placebo arms, respectively.

Response to prior platinum chemotherapy was complete in 82% and partial in 18% of the patients.

Results of the *BRCA* mutation status determined by local *BRCA* were highly concordant with Myriad germline testing results (only 3 patients with discordant results between local and Myriad confirmed subset). Two patients entered in the study with a local t*BRCA*m result that were later classified as g*BRCA*wt by Myriad testing. These 2 patients were confirmed by FMI as having s*BRCA* mutations. One patient entered the study with a local g*BRCA*m result and was later classified by Myriad as *BRCA* VUS. The g*BRCA*m prevalence in the prospectively tested SOLO1 patients (27.3%) was greater than the expected prevalence in all comer populations in first line (15.5% to 19%) as investigators were asked to send blood samples for central Myriad g*BRCA* testing only after Cycle 3 of first-line chemotherapy, and only for patients who had evidence of an initial response based on CA-125 or CT scan; this was done in order to reduce the number of screen failures. As at the time of study initiation a central tumour diagnostic test suitable for registration was not available, the patients recruited onto SOLO1 were predominantly g*BRCA*m. The prevalence of s*BRCA* mutations in ovarian cancer patients at diagnosis or following partial or complete response to first line chemotherapy is between 6.4% and 8.4%. Therefore, of the 611 patients who were ineligible for SOLO1 as they were non-g*BRCA*m by central testing, between 39 and 51 patients could be expected to harbour an s*BRCA* mutation.

The study met its primary objective demonstrating a statistically significant improvement in investigator assessed PFS for olaparib compared with placebo with a hazard ratio (HR) of 0.30 (95% CI 0.23, 0.41; p<0.0001; median not reached for olaparib vs 13.8 months for placebo). The investigator assessment of PFS was supported with a blinded independent central radiological (BICR) review of PFS (HR 0.28; 95% CI 0.20, 0.39; p<0.0001; median not reached for olaparib and 14.1 months for placebo). However, beyond the data cut-off the scans have not been sent for BICR. At the time of the analysis, 51.5% olaparib treated patients remained progression free compared with 24.4% placebo treated patients. In both assessments

Kaplan-Meier plots showed a more favourable effect for olaparib arm than for placebo arm with a separation of curves since the first three months.

Similar PFS results were observed in both the China cohort and the global cohort in SOLO1. However, the China cohort was not powered for assessment of statistical significance due to the limited number of participants (64 patients). Nevertheless, a significant efficacy result was achieved (hazard ratio=0.46 95% CI 0.23 0.97 p=0.0320).

The median PFS was planned to be 21 months on olaparib vs 13 months on placebo with an estimated HR about 0.62. The benefit of olaparib seems to have been underestimated in SOLO1 study. Estimation was made in relation to results from Study 19 and the target population in study 19 was heavily pre-treated patients in an advanced line setting whereas SOLO-1 targeted newly diagnosed patients.

The changes in the primary endpoint from BICR-based to INV-based PFS and in the number of events needed for the primary analysis were justified by the initial underestimation of the median PFS in patients with g*BRCA*m and by discrepancy rates observed between INV confirmed progression and BICR results. No specific report for concordance analysis between investigator and BICR assessment of PFS in SOLO1 was provided, however the disagreement between investigator and BICR of declaring progression as per RECIST 1.1 was acceptable (15%) and consistent with those in other previous studies. There was no suggestion of bias in the investigator assessment favouring the olaparib arm.

It was also noted that proportion of patients with residual disease in previously conducted studies should have been taken into account for assumptions of the primary analysis considering its prognostic value in the setting of upfront and interval debulking. The median PFS from diagnosis varies from 20 to 26 months in patients with *BRCA*m newly diagnosed advanced ovarian cancer according to epidemiology data and 19.6-30.2 months in patients with *BRCA*m (without maintenance treatment) in the previous studies. Taking the different definitions of PFS into account, the median PFS of 13.8 months observed in the control arm in SOLO1 is still consistent with the literature taking into account the clinical stage of the participants or residual disease after chemotherapy.

Overall, sensitivity and additional analyses of PFS (evaluation time bias, attrition bias, using the eCRF stratification variable, assess possible informative censoring (using BICR), estimating HR using the stratified log rank test, based on earliest progression of investigator/BICR assessment of progression) were all consistent with the primary analysis showing favourable treatment benefit for olaparib in maintenance therapy for the study population. Some differences have been reported in stratification variables and discrepancies between the randomisation and investigator reported data in the eCRF are known to occur.

Subgroup analysis of PFS across various particular subgroups did not reveal an obvious differential benefit across pre-defined subgroups compared with the overall population. The benefit of olaparib over placebo was maintained across all pre-defined subgroups, with different magnitude.

The median PFS as the primary endpoint was not reached and will not be tested at a later time point to provide a precise estimate as per planned statistical analyses. The results of the primary analysis and sensitivity analyses support that maintenance treatment during 2 years result in PFS benefit in the both subgroups of patients regardless of the primary disease status (clinical CR or clinical PR).

In patients with evidence of disease (PR) at baseline, median PFS on olaparib was 30.9 months as compared with 8.4 months on placebo arm. The currently observed results in patients with residual disease at baseline (mainly those with persisting PR or stable disease after 2 years of treatment) support the continuous olaparib maintenance treatment until disease progression as currently proposed.

Overall, in regard to the duration of treatment, the SmPC reflects that patients can continue treatment until radiological disease progression, unacceptable toxicity or for to 2 years if there is no radiological evidence of disease after 2 years of treatment. Patients with evidence of disease at 2 years, who in the opinion of the

treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years in line with the protocol of the pivotal study (see SmPC section 4.2).

At the time of analysis, a lower number of patients from olaparib arm had a second progression compared to placebo arm (26.5% vs 39.7%). The benefit on PFS was partly maintained at second progression with a HR of 0.50 (95% CI 0.35, 0.72, p<0.0001, median not reached for olaparib and 41.9 months for placebo).

The provided analysis of PFS2 is far from mature and probably over-represents patients with a short-lasting response with poor platinum sensitivity. The MAH should provide the updated and final PFS2 data from SOLO1 study (see Annex II). PFS2 might also have been influenced by inclusion of cancer antigen 125 as a biomarker for disease progression according to the PFS2 definition in this trial.

At the time of the analysis OS survival data were not yet sufficiently mature to allow comparison between two groups, with event rate of 21.2% and 20.6% in olaparib and placebo arms respectively. At 21.0% of maturity, the HR was not indicating a detriment in OS of olaparib arm compared to placebo, with a large CI (HR 0.95, 95% CI 0.60, 1.53, p= 0.8903, median was not reached in either arms). In order to further investigate the efficacy of olaparib in the claimed indication, the final OS analysis which will be done at approximately 60% maturity will be submitted by the MAH (see Annex II). Updated OS analyses are also expected to be submitted (see Annex II and RMP).

Analysis of exploratory efficacy endpoints showed a reduction in the risk of discontinuation of study treatment or death and a delay of time until the first subsequent anti-cancer therapy and the second subsequent therapy or death in the olaparib group compared with the placebo group in overall population (FAS). TDT results showed a median difference of 10.8 months favouring olaparib vs placebo arm (median of 24.6 months for olaparib vs 13.8 months for placebo, HR 0.63, 95% IC 0.51, 0.79, p<0.0001). A statistically significant delay in TFST was observed for olaparib arm compared with placebo in the overall population (HR 0.30, 95% IC 0.22, 0.40, p<0.0001, median of 51.8 months olaparib vs 15.1 months placebo). At the time of the DCO, median TSST was not reached in the olaparib arm vs 40.7 months for the placebo arm. Results showed a delay in the time to a second therapy in the olaparib arm compared with the placebo arm (HR 0.45, 95% IC 0.32, 0.63, p< 0.0001). Data from subsequent therapies showed that patients are still capable to respond to the following treatments after the administration of maintenance treatment with olaparib.

Thirty three patients (35.1%) of the 94 placebo-treated patients who had a subsequent therapy received a PARP inhibitor and only 10 patients of the 91 olaparib-treated patients (11.0%) who had a subsequent therapy received a PARP inhibitor. According to data provided from SOLO-1 study, results seemed to show a positive trend in delaying second progression (7/10 patients) in patients retreated with olaparib in maintenance following a platinum-based chemotherapy after first relapsed. However, data are too immature to conclude whether patients can benefit from PARP inhibitor re-challenge after previous exposure to olaparib. The SmPC reflects that there are no efficacy and safety data on maintenance retreatment with Lynparza following first or subsequent relapses in ovarian cancer patients or on retreatment of breast cancer patients (see sections 4.2 and 5.1).

Number of events for 'Time to earliest progression by RECIST 1.1, CA-125 or death endpoint' at the time of the analysis was lower in olaparib arm compared to placebo arm (39.2% vs 74%, respectively). Hazard ratio results benefited better the study arm than the control arm (HR 0.30, 95% IC 0.23, 0.40; p<0.0001; median was not reached for olaparib vs 12 months for placebo arm). K-M plot showed a separation of the curves. A pronounced decrease during month 3 to month 18 is observed in placebo arm while olaparib arm remained slightly decreasing.

Among the patient with evidence of disease at the time of randomization (target or non-target lesions at baseline), ORR of 42.6% was achieved in patients in the olaparib arm vs 23.1% in patients in the placebo

arm. In the olaparib arm (54 patients), 27.8% of the patients reached complete response, 14.8% reached partial response and 48.1% remained with stable disease as BoR.

Patient-reported outcome (PRO) data were assessed by the change from baseline in the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT O) as a secondary endpoint. These analyses are considered as exploratory. There was no pre-specified hypothesis and alpha allocation. Significant changes in the types of analyses have been introduced during the study. The relatively high scores at baseline likely reflect generally few cancer-related symptoms post-chemotherapy. The results at the chosen timepoints do not appear to fully capture treatment-related toxicities and the decreased tolerability. The rationale has not been comprehensively provided for the appropriateness of the timing of data collection and numerous changes in the analysis methods, in light of the patient population, disease setting and treatment regimen. The impact of missing data and of introduced collection of data beyond progression have not been discussed. Overall, limitations mentioned above precluded PRO inclusion in the SmPC.

Regarding patients with s*BRCA*m, only 2 confirmed patients were included in the SOLO-1 trial. Available data is not sufficient to allow comparison of the efficacy profile of Lynparza within the two populations (g*BRCA*m and s*BRCA*m). However, an activity similar to that in patients with germline *BRCA* mutations is expected based on strong biological rationale. In addition, available clinical data indicating efficacy of olaparib in patients with somatic *BRCA* mutations in the maintenance treatment of ovarian cancer support extrapolation in this setting. Nevertheless, the MAH is recommended to collect efficacy and safety data in patients with s*BRCA*1/2 mutations in clinical trials and/or in real-life setting in patients treated with olaparib after the first-line platinum-containing chemotherapy.

Patients with high grade endometrioid and other histology types were poorly/not represented in the patient population effectively enrolled in the SOLO1. Altogether there were 15 patients (5.8%) on the olaparib arm and 1 (0.8%) on the placebo arm with high grade endometrioid or other histology type. Exploratory analysis of the number of PFS events in the non-serous histology groups showed broadly similar results for olaparib treated patients, with the caveat of the small number of patients with non-serous histology. In addition, exploratory analysis of the number of PFS2 events in the non-serous histology groups also showed broadly similar results for olaparib treated patients. In view of consistent results in the SOLO-2 and SOLO-1 study for patients with high grade endometrioid cancer and the olaparib mechanism of action and biological rationale suggesting benefit in high grade tumours the indication is not restricted to “serous” histological type.

Although most of women with HGSOC have a good response to standard platinum-containing chemotherapy treatment, about 20 to 30% of patients relapse within 6 months (platinum-resistant disease) (Testa et al, 2018). About 15% of patients with g*BRCA*1/2 mutations are estimated to have platinum-free interval of less than 6 months after the first line chemotherapy (Chartron et al, 2019). The proportion of patients in olaparib arm (3.5%) and in placebo arm (8.4%) for which the effective progression date (by RECIST1.1, BICR) was reported to occur during first 6 months after the last dose of the platinum-based chemotherapy is considered informative and has been reflected in the SmPC.

2.4.3. Conclusions on the clinical efficacy

The study SOLO-1 provided significant evidence of PFS benefit for Lynparza in monotherapy as maintenance after a first line of platinum-based chemotherapy for patients with high-grade serous epithelial ovarian, fallopian tube and primary peritoneal cancers with *BRCA* mutations. Considering OS and PFS2 results were immature, the CHMP considers the following measures necessary to address issues related to efficacy:

PAES: In order to further investigate the efficacy of olaparib maintenance treatment in patients with advanced *BRCA*1/2-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first line platinum-based chemotherapy, the

MAH should submit the final analysis of OS and updated analyses of PFS2 from the phase 3, randomised, double-blind study SOLO1. Due date: 31 December 2023.

2.5. Clinical safety

Introduction

Across the entire clinical programme, as of 15 June 2018, approximately 9293 patients are estimated to have received treatment with olaparib. The focus of this analysis is the SOLO1 study (SOLO1) where olaparib 300 mg (or placebo) bd was given as a maintenance monotherapy in patients with newly diagnosed *BRCA* mutated advanced (FIGO Stage III-IV) ovarian cancer following platinum based chemotherapy. Supportive safety data, for olaparib 300 mg bd as a monotherapy, are provided by a pool of 1060 patients who were intended to receive this dose and received olaparib in the MAH-sponsored studies, as indicated in Table 37.

Table 37: Number of patients in the 300 mg bd pool (as of DCO: 17 May 2018)

Study/pooled dataset	Number of patients intended for the 300 mg bd cohort and received olaparib (all tumour types)
Total exposed	**1060**
D0818C00001 (SOLO1): Phase III FIGO Stage III-IV ovarian cancer SOLO1 China cohort	260 40
D0816C00002 (SOLO2): Phase III platinum-sensitive serous ovarian cancer SOLO2: China cohort	195 22
D0819C00003 (OlympiAD): Phase III HER2-negative breast cancer patients with *gBRCA1/2* mutation	205
Study 24: Phase I Relative Bioavailability (300 mg tablet bd patients only, Groups 4 and 6)	24
Study 04: Phase I Food interaction & QT	57
Study 06: Phase I Renal impairment study	43
Study 07: Phase I CYP3A4 inhibition and QT	56
Study 08: Phase I CYP induction	19
Study D081CC00001: Phase I anti-hormonal PK study	69
Study D081BC00001: Phase I Japan Monotherapy study	19
D0816C00005: Phase I hepatic impairment study	31
D081BC00002: China PK study	20

bd Twice daily; CYP Cytochrome P450; *gBRCA* Germline breast cancer susceptibility gene; FIGO International Federation of Gynecology and Obstetrics; HER2 Human epidermal growth factor receptor-2; PK Pharmacokinetic(s).

Patient exposure

Overall extent of exposure

SOLO1

At the Data Cut-Off (DCO) for the analysis of PFS, the majority of patients in the safety analysis set (SAS) had discontinued study treatment (247 [95.0%] of 260 olaparib-treated patients and 129 [99.2%] of 130 placebo-treated patients). The most common reason for discontinuation in the olaparib arm was completion of 2 years of therapy (123 [47.3%] of 260 olaparib-treated patients, compared with 35 [26.9%] of placebo-treated patients who completed 2 years of therapy); the most common reason for discontinuation in the placebo arm was disease progression (78 [60.0%] of 130 patients).

A higher proportion of patients in the olaparib arm had discontinued for an AE, compared with the placebo arm (30 [11.5%] of 260 patients vs 3 [2.3%] of 130 patients, respectively). However, a lower proportion of olaparib-treated patients discontinued due to a progression event (51 [19.6%] of 260 patients vs 78 [60.0%] of 130 patients, respectively).

Fifteen olaparib-treated patients (5.8%) had stable disease and remained on treatment as per protocol, compared with 2 (1.5%) placebo-treated patients. Eleven olaparib-treated patients (4.2%) and 1 (0.8%) placebo-treated patient had no evaluable disease or stable disease and continued on treatment in error.

The majority of olaparib-treated patients received treatment for a period of ≥18 months (compared with the majority of patients receiving treatment for ≥12 months on the placebo arm). The number of patients still on treatment began to diverge between arms at approximately 6 months (in favour of olaparib). Duration of exposure to study treatment in SOLO1 is summarised in Table 39.

Table 38: SOLO1: Overall extent of exposure (SAS)

Month (approximate)	Number (%) of patients	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Day 1	260 (100)	130 (100)
≥1 month (30.4 days)	246 (94.6)	128 (98.5)
≥3 months (91.3 days)	231 (88.8)	119 (91.5)
≥6 months (182.6 days)	213 (81.9)	102 (78.5)
≥9 months (273.9 days)	203 (78.1)	87 (66.9)
≥12 months (365.3 days)	190 (73.1)	68 (52.3)
≥18 months (547.9 days)	174 (66.9)	52 (40.0)
≥24 months (730.5 days)	115 (44.2)	36 (27.7)
≥36 months (1095.8 days)	14 (5.4)	2 (1.5)

Rows are cumulative and patients are included if they have taken treatment beyond the treatment day stated in the parenthesis. A month is defined as 365.25/12 = 30.4375 days.
bd Twice daily; CSR Clinical study report; DCO Data cut-off; SAS Safety analysis set.

Table 39: SOLO1: Duration of olaparib/placebo exposure (SAS)

Treatment duration (weeks)	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Olaparib/placebo total treatment duration[a]		
Mean (SD)	87.0 (47.13)	65.3 (38.91)
Median	106.9	60.3
Minimum; Maximum	0; 226	1; 198
Total treatment weeks	22623	8494
Olaparib/placebo actual treatment duration[b]		
Mean (SD)	84.7 (46.93)	64.6 (38.79)
Median	102.0	58.6
Minimum; Maximum	0; 226	1; 196
Total treatment weeks	22011	8396

[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.
bd Twice daily; SD standard deviation.

Table 40 summarizes study treatment interruptions and dose reductions. Per protocol, dose reductions were only allowed for toxicity management and the maximum number of dose reductions was 2. The 8 patients (7 olaparib-treated patients and 1 placebo-treated patient) who are shown in Table 40 as having more than 2 reductions were patients who had a treatment interruption (eg, a missed dose) incorrectly reported as a dose reduction.

Table 40: SOLO1: Study treatment interruptions and dose reductions (SAS)

		Number (%) of patients	
		Olaparib 300 mg bd (N=260)	Placebo (N=130)
Received planned starting dose	Yes	246 (94.6)	128 (98.5)
	No	14 (5.4)	2 (1.5)
No interruption		101 (38.8)	90 (69.2)
Number of patients with an interruption	Any	159 (61.2)	40 (30.8)
	1 interruption	54 (20.8)	23 (17.7)
	2 interruptions	35 (13.5)	10 (7.7)
	3 interruptions	26 (10.0)	4 (3.1)
	4 interruptions	15 (5.8)	1 (0.8)
	>4 interruptions	29 (11.2)	2 (1.5)
Reason for interruption[a]	Adverse event	128 (49.2)	21 (16.2)
	Surgery	42 (16.2)	13 (10.0)
	Other	51 (19.6)	18 (13.8)
No dose reduction		166 (63.8)	119 (91.5)
Number of patients with a dose reduction	Any	94 (36.2)	11 (8.5)
	1 reduction	44 (16.9)	7 (5.4)
	2 reductions	43 (16.5)	3 (2.3)
	≥3 reductions	7 (2.7)	1 (0.8)
Reason for dose reduction[b]	Adverse event	75 (28.8)	5 (3.8)
	Other	12 (4.6)	1 (0.8)
No dose modification		89 (34.2)	88 (67.7)
Number of patients with a dose modification[c]	Any	171 (65.8)	42 (32.3)
	1 modification	51 (19.6)	20 (15.4)
	2 modifications	30 (11.5)	14 (10.8)
	≥3 modifications	90 (34.6)	8 (6.2)
Reason for dose modification[d]	Adverse event	134 (51.5)	21 (16.2)
	Other	97 (37.3)	31 (23.8)
Number of patients with both an interruption and dose reduction	Any	82 (31.5)	9 (6.9)

[a] Reasons for interruptions were not mutually exclusive for patients with multiple interruptions although were counted only once per category.

Olaparib 300 mg bd pool

Long-term exposure to olaparib therapy was assessed in the 300 mg bd pool; 438 (41.3%) and 250 (23.6%) of all patients remained on treatment for ≥1 year and ≥2 years, respectively. The median total treatment duration in the 300 mg bd pool was 272 days (approximately 9 months). Compared with the olaparib arm of SOLO1, treatment duration in the 300 mg bd pool was generally shorter (probably due to the fact that 31.9% of patients in this pool were recruited to Phase I studies).

Table 41: Overall extent of exposure in the 300 mg bd pool

Month (days)	Number (%) of patients
	Olaparib 300 mg bd N=1060
0	1060 (100.0)
≥1 month (30.4 days)	984 (92.8)
≥3 months (91.3 days)	796 (75.1)
≥6 months (182.6 days)	629 (59.3)
≥12 months (365.3 days)	438 (41.3)
≥18 months (547.9 days)	342 (32.3)
≥24 months (730.5 days)	250 (23.6)
≥36 months (1095.8 days)	16 (1.5)

Duration of treatment was collected in days. A month is defined as 365.25/12 = 30.4375 days.
Rows are cumulative and patients are included if they have taken treatment beyond the treatment day stated in the parenthesis
bd Twice daily; DCO Data cut-off.

Demographics

SOLO1

The demographic and disease characteristics of patients in SOLO1 are summarised previously in Table 11.

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. Summaries of the key demographic and baseline patient characteristics for the 12 studies contributing to the pooled dataset are provided in Table 42.

Table 42: Key demographic and baseline characteristics by study: studies in olaparib 300 mg bd pool

Study Number of Subjects randomised/ treated	Age/sex/race	Performance status	Tumour type	Prior anticancer treatment	*BRCA* mutation status
SOLO1 N=391/390 (260 n the pooled dataset)	29 to 84 years (mean age 53.5 years) All Female 320 (81.8%) White, 59 (15.1%) Asian 12 (3.1%) Black, African American and Other	ECOG PS ≤1 305 (78.0%) PS0 85 (21.7%) PS1	Advanced (FIGO Stage III-IV) Ovarian Cancer	All pre-treated Median number of prior chemotherapies was 1.0	389 *gBRCAm* 2 *sBRCAm*
SOLO1 China cohort N=64/64 (44[3] in the pooled dataset)	33 to 67 years (mean age 51.0 years) All Female 64 (100%) Asian	ECOG PS ≤1 33 (51.6%) PS0 31 (48.4%) PS1	Advanced (FIGO Stage III-IV) Ovarian Cancer	All pre-treated Median number of prior chemotherapies was 1.0	All *gBRCAm*
OlympiAD N=302/296 (205 in the pooled dataset)	22 to 76 years (mean age 45.3 years) 295 (97.7%) Female, 7 (2.3%) Male 197 (65.2%) White, 94 (31.1%) Asian 11 (3.6%) Black, African American and Other	ECOG PS ≤1 210 (69.5%) PS0 92 (30.5%) PS1	Metastatic breast cancer	All pre-treated Median number of prior chemotherapies was 1.0	All *gBRCAm*

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

Study **Number of Subjects randomised/ treated**	**Age/sex/race**	**Performance status**	**Tumour type**	**Prior anticancer treatment**	***BRCA* mutation status**
Study 04 Food effect (Part C) N=60/55 (57 in pooled dataset, including 2 patients from Part B)	36 to 79 years (mean age 60.0 years) 42 (76.3%) Female, 13 (23.6%) Male 54 (98.2%) White, 1 (1.8%) other	ECOG PS ≤2 (54 [98.2%] patients were ECOG PS ≤1 and data for 1 patient was missing)	Patients with advanced solid tumours. The most common primary tumour locations were: ovary (19 [34.5%] patients), breast (9 [16.3%] patients), lung (4 [7.3%] patients), colorectal (3 [5.5%] patients), peritoneum (2 [3.6%] patients), and prostate (2 [3.6%] patients).	All pre-treated	5 *BRCAm*; 8 *BRCAwt/VUS*, 47 patients not tested
Study 06: renal impairment study (Part B only) N=44/43 (43 in pooled dataset)	32 to 76 years (mean age 61.9 years) 19 (44.2%) male, 24 (55.8%) female 42 (97.7%) White/ 1 (2.3%) Asian	41 (95.3%) patients were ECOG PS ≤1; data for 2 patients were missing	Patients with advanced solid tumours and normal renal function or mild or moderate renal impairment. Most common locations were ovary (12 [27.9%] patients), renal (5 [11.6%] patients) and breast (4 [9.3%] patients).	All pre-treated	3 *BRCAm*; 4 *BRCAwt*, 35 patients not tested
Study 07 itraconazole interaction study (Part C) N=59/54 (56 in pooled dataset including 2 patients from Part B)	34 to 82 years (mean age 61.0 years) 38 (70.4%) Female, 16 (29.6%) Male 51 (94.4%) White, 1 (1.9%) each of Asian, Black or African American, and other race	ECOG PS ≤2 (53 [98.1%] patients were ECOG PS ≤1; 1 patient was PS 2)	Patients with advanced solid tumours. The most common primary tumour locations were: ovary (20 [37.0%] patients), pancreas (6 [11.1%] patients), rectal (4 [7.4%] patients), breast, cervix, and head/neck, cervix (3 patients [5.6%] each), biliary tract, colon, colorectal, lung, peritoneum, and uterus (2 [3.7%] patients each).	All pre-treated	6 *BRCAm*; 8 *BRCAwt/VUS*, 45 patients not tested

Study **Number of Subjects randomised/ treated**	**Age/sex/race**	**Performance status**	**Tumour type**	**Prior anticancer treatment**	***BRCA* mutation status**
Study 08 rifampicin interaction study (Part B only) N=22/19 (19 in pooled dataset)	31 to 79 years (mean age 58.0 years) 16 (84.2%) Female, 3 (15.8%) Male 19 (100.0%) White	ECOG PS ≤2 (16 [84.2%] patients were ECOG PS ≤1; 3 patients were PS 2)	Patients with advanced solid tumours. The most common primary tumour locations were: breast and ovary (each with 6 patients [26.3%]); colon (2 patients [10.5%]).	All pre-treated	Unknown
D081BC00001 Japan Phase I study (Part B only) N=23/23 (19 in pooled dataset)	34 to 77 years (mean age 54.1 years) 15 (65.2%) Female, 8 (34.8%) Male 23 (100.0%) Asian	ECOG PS ≤2 (18 [78.3%] patients were ECOG PS 0)	Patients with advanced solid malignancies. The primary tumour locations in most of the patients were breast (5 [21.7%] patients), ovary (4 [17.4%] patients), cervix and uterus (2 [8.7%] patients each).	The median number of previous chemotherapy regimens at baseline was 3.	
D081CC00001: Anti-hormonal PK interaction study (Part B only) N=79/79 (69 in pooled dataset)	29 to 79 years (mean age 58.3 years) 64 (81.0%) Female, 15 (19.0%) Male 73 (92.4%) White, 2 (2.5%) Asian, 2 (2.5%) Black or African American, 2 (2.5%) other	ECOG PS ≤2 (78[98.7%] patients were ECOG PS ≤1; 1 patient was PS 2)	Patients with advanced solid cancer. The most common primary tumour locations were: ovary (36 patients [45.6%]), and breast (16 patients [20.3%]).	All pre-treated	21 *BRCAm*; 9 *BRCAwt*, 46 patients not tested, 3 missing

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

bd: Twice daily; CSR: Clinical study report; *BRCA*: Breast cancer susceptibility gene; *BRCAm*: *BRCA*-mutated; *BRCA*VUS: *BRCA* variant of uncertain significance; *BRCAwt*: *BRCA* wild type; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; PK: Pharmacokinetics; PS: Performance status; PSR platinum sensitive relapsed.
Data derived from CSRs for SOLO1, OlympiAD, Study 24, Study 04, Study 07, Study D081BC00001, Study D081BC00002, Study D081CC00001, Study D0816C00005, Study D0816C00006 and SOLO2 (including SOLO2 China Cohort).

Adverse events

The number and proportion of patients who had at least one AE in any category in SOLO1 are summarised in Table 43.

Table 43: SOLO1: Number (%) of patients who had at least 1 AE in any category (SAS)

AE category[a]	Number (%) of patients	
	Olaparib 300 mg bd N=260	Placebo bd N=130
Any AE	256 (98.5)	120 (92.3)
Any AE of CTCAE Grade 3 or higher	102 (39.2)	24 (18.5)
Any AE with outcome = Death	0	0
Any SAE (including events with outcome = death)	54 (20.8)	16 (12.3)
Any AE leading to discontinuation of study treatment	30 (11.5)	3 (2.3)
Any AE leading to dose reduction of study treatment	74 (28.5)	4 (3.1)
Any AE leading to interruption of study treatment	135 (51.9)	22 (16.9)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo.
AE adverse event; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events (v4.0); SAE serious adverse event; SAS Safety analysis set.

The most commonly reported AEs occurring in >10% of patients in either treatment group in SOLO1 are presented in Table 44. Given that the median duration of exposure of patients in the olaparib arm was approximately two times that of patients who received placebo in SOLO1, the overall frequencies of the most commonly reported AEs adjusted for patient years' exposure were also presented.

Table 44: Most common AEs (occurring in ≥10% of patients in either treatment group) (SAS)

MedDRA preferred term	Olaparib 300 mg bd (N=260)		Placebo (N=130)	
	Number (%) of patients[a]	Event rate (per 1000 pt years)	Number (%) of patients[a]	Event rate (per 1000 pt years)
Patients with any AE	256 (98.5)	17789.95	120 (92.3)	7928.73
Nausea	201 (77.3)	1747.27	49 (37.7)	420.42
Fatigue	106 (40.8)	375.75	39 (30.0)	306.10
Vomiting	104 (40.0)	346.03	19 (14.6)	124.91
Anaemia	99 (38.1)	321.48	12 (9.2)	72.78
Diarrhoea	89 (34.2)	284.83	32 (24.6)	234.12
Constipation	72 (27.7)	205.79	25 (19.2)	167.16
Dysgeusia	68 (26.2)	199.23	5 (3.8)	30.55
Arthralgia	66 (25.4)	186.57	35 (26.9)	269.14
Abdominal pain	64 (24.6)	174.99	25 (19.2)	164.25
Asthenia	63 (24.2)	176.10	16 (12.3)	101.63
Headache	59 (22.7)	157.19	31 (23.8)	208.04
Dizziness	51 (19.6)	134.95	20 (15.4)	134.78
Decreased appetite	51 (19.6)	135.14	13 (10.0)	82.91
Abdominal pain upper	46 (17.7)	121.29	17 (13.1)	108.90
Dyspepsia	43 (16.5)	110.05	16 (12.3)	103.64
Cough	42 (16.2)	106.38	28 (21.5)	190.46
Neutropenia	41 (15.8)	104.13	9 (6.9)	54.89
Back pain	40 (15.4)	99.91	16 (12.3)	103.17
Dyspnoea	39 (15.0)	95.57	7 (5.4)	41.63
Pyrexia	31 (11.9)	74.97	12 (9.2)	72.04
Urinary tract infection	31 (11.9)	75.38	8 (6.2)	48.54
Myalgia	28 (10.8)	66.88	13 (10.0)	82.56
Upper respiratory tract infection	28 (10.8)	66.71	12 (9.2)	78.13
Pain in extremity	28 (10.8)	68.42	11 (8.5)	68.05
Nasopharyngitis	27 (10.4)	65.07	17 (13.1)	106.19
Insomnia	27 (10.4)	64.78	16 (12.3)	102.29
Depression	13 (5.0)	29.72	13 (10.0)	82.82

[a] Number (%) of patients with AEs, sorted in decreasing frequency of preferred term in the olaparib 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 study drug.

MedDRA Version 21.0.

AE adverse event; bd twice daily; MedDRA Medical Dictionary for Regulatory Activities; pt patient; SAS Safety Analysis Set.

Adverse events by treatment period

The majority of AEs first occurred within the first 3 months of treatment. An assessment of AEs by treatment period of AE onset with the onset data for 0-3 months and 3-6 months presented in Table 45. For AEs of constipation and dyspnoea, the reporting frequency was higher for olaparib-treated patients over patients in the placebo arm during the first 0 to 3 months and/or 3 to 6 months of treatment.

Table 45: SOLO1: 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; (SAS)

Preferred term	Number (%) of patients			
	Onset in 0-3 months		Onset in 3-6 months	
	Olaparib 300 mg bd N=260	Placebo bd N=130	Olaparib 300 mg bd N=242	Placebo bd N=128
Nausea	184 (70.8)	36 (27.7)	26 (10.7)	6 (4.7)
Fatigue	80 (30.8)	25 (19.2)	17 (7.0)	3 (2.3)
Vomiting	57 (21.9)	11 (8.5)	32 (13.2)	1 (0.8)
Anaemia	63 (24.2)	6 (4.6)	37 (15.3)	3 (2.3)
Diarrhoea	55 (21.2)	18 (13.8)	19 (7.9)	7 (5.5)
Constipation	37 (14.2)	11 (8.5)	15 (6.2)	4 (3.1)
Dysgeusia	56 (21.5)	4 (3.1)	6 (2.5)	1 (0.8)
Arthralgia	29 (11.2)	19 (14.6)	11 (4.5)	10 (7.8)
Abdominal pain	27 (10.4)	8 (6.2)	12 (5.0)	3 (2.3)
Asthenia	43 (16.5)	8 (6.2)	22 (9.1)	2 (1.6)
Headache	30 (11.5)	13 (10.0)	9 (3.7)	9 (7.0)
Dizzinesss	26 (10.0)	13 (10.0)	11 (4.5)	3 (2.3)
Decreased appetite	36 (13.8)	6 (4.6)	7 (2.9)	3 (2.3)
Abdominal pain upper	22 (8.5)	10 (7.7)	12 (5.0)	4 (3.1)
Dyspepsia	24 (9.2)	6 (4.6)	8 (3.3)	5 (3.9)
Cough	16 (6.2)	7 (5.4)	11 (4.5)	7 (5.5)
Neutropenia	24 (9.2)	6 (4.6)	16 (6.6)	0

Preferred term	Number (%) of patients			
	Onset in 0-3 months		Onset in 3-6 months	
	Olaparib 300 mg bd N=260	Placebo bd N=130	Olaparib 300 mg bd N=242	Placebo bd N=128
Back pain	10 (3.8)	2 (1.5)	4 (1.7)	7 (5.5)
Dyspnoea	16 (6.2)	3 (2.3)	7 (2.9)	1 (0.8)
Pyrexia	5 (1.9)	2 (1.5)	10 (4.1)	3 (2.3)
Urinary tract infection	8 (3.1)	3 (2.3)	7 (2.9)	3 (2.3)
Myalgia	7 (2.7)	7 (5.4)	3 (1.2)	3 (2.3)
Pain in extremity	7 (2.7)	5 (3.8)	7 (2.9)	4 (3.1)
Upper respiratory tract infection	5 (1.9)	4 (3.1)	5 (2.1)	4 (3.1)
Nasopharyngitis	6 (2.3)	5 (3.8)	5 (2.1)	3 (2.3)
Insomnia	12 (4.6)	7 (5.4)	5 (2.1)	6 (4.7)
Depression	6 (2.3)	5 (3.8)	3 (1.2)	4 (3.1)

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.

CTCAE Grade ≥3 AEs

Table 46: SOLO1: CTCAE Grade ≥3 AEs occurring in ≥2 patients in either treatment arm (SAS)

MedDRA SOC preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Patients with any CTCAE Grade ≥3 AE	**102 (39.2)**	**24 (18.5)**
Blood and lymphatic system disorders	**63 (24.2)**	**8 (6.2)**
Anaemia	55 (21.2)	2 (1.5)
Neutropenia	13 (5.0)	4 (3.1)
Leukopenia	4 (1.5)	0
Lymphopenia	2 (0.8)	1 (0.8)
Febrile neutropenia	2 (0.8)	0
Gastrointestinal disorders	**17 (6.5)**	**3 (2.3)**
Diarrhoea	8 (3.1)	0
Abdominal pain	4 (1.5)	1 (0.8)
Small intestinal obstruction	2 (0.8)	1 (0.8)
Nausea	2 (0.8)	0
Investigations	**12 (4.6)**	**4 (3.1)**
Neutrophil count decreased	7 (2.7)	2 (1.5)
White blood cell count decreased	4 (1.5)	0
Lymphocyte decreased	2 0.8)	0
Platelet count decreased	1 (0.4)	2 (1.5)
General disorders and administration site conditions	**11 (4.2)**	**2 (1.5)**
Fatigue	5 (1.9)	2 (1.5)
Asthenia	5 (1.9)	0
Infections and infestations	**8 (3.1)**	**4 (3.1)**
Urinary Tract Infection	2 (0.8)	0
Musculoskeletal And Connective Tissue Disorders	**2 (0.8)**	**0**
Rotator cuff syndrome	2 (0.8)	0
Renal and urinary disorder	**2 (0.8)**	**0**
Urinary incontinence	2 (0.8)	0
Respiratory and mediastinal disorders	**5 (1.9)**	**0**
Pulmonary embolism	2 (0.8)	0
Nervous system disorders	**4 (1.5)**	**6 (4.6)**
Headache	1 (0.4)	3 (2.3)
Syncope	1 (0.4)	2 (1.5)
Vascular disorders	**2 (0.8)**	**2 (1.5)**
Hypertension	1 (0.4)	2 (1.5)

[a] Multiple occurrences of a system organ class/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; SOC System Organ Class.

Comparative analysis of adverse events for the olaparib treatment group in SOLO1 and the 300 mg bd pool

The proportions of patients with AEs, SAEs, AEs leading to treatment (olaparib) discontinuation, CTCAE Grade ≥3 AEs and AEs leading to death were comparable for SOLO1 and the 300 mg tablet pool.

Table 47: Number (%) of patients who had at least 1 AE in any category (olaparib treatment groups) in SOLO1 and the 300 mg bd pool

AE category[a]	Number (%) of patients	
	SOLO1 olaparib 300 mg bd (N=260)	Olaparib 300 mg bd pool (N=1060)
Any AE	256 (98.5)	1037 (97.8)
Any AE of CTCAE Grade 3 or higher	102 (39.2)	404 (38.1)
Any AE with outcome = Death	0	4 (0.4)
Any SAE (including events with outcome = death)	54 (20.8)	210 (19.8)
Any AE leading to discontinuation of study treatment	30 (11.5)	84 (7.9)
Any AE leading to dose reduction of study treatment	74 (28.5)	219 (20.7)
Any AE leading to interruption of study treatment	135 (51.9)	398 (37.5)

[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.
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.

Table 48 shows the most commonly-reported AEs for the olaparib treatment arm in SOLO1 and the 300 mg bd pool.

Table 48: Most common AEs (reported in ≥10% in the olaparib treatment arm of SOLO1 or the 300 mg bd pool

Preferred term	Number (%) of patients[a]	
	SOLO1 SAS olaparib 300 mg bd (N=260)	Olaparib 300 mg bd pool N=1060
Patients with any AE	**256 (98.5)**	**1037 (97.8)**
Nausea	201 (77.3)	682 (64.3)
Fatigue	106 (40.8)	416 (39.2)
Vomiting	104 (40.0)	381 (35.9)
Anaemia	99 (38.1)	400 (37.7)
Diarrhoea	89 (34.2)	282 (26.6)
Constipation	72 (27.7)	200 (18.9)
Dysgeusia	68 (26.2)	187 (17.6)
Arthralgia	66 (25.4)	151 (14.2)
Abdominal pain	64 (24.6)	172 (16.2)
Asthenia	63 (24.2)	171 (16.1)
Headache	59 (22.7)	194 (18.3)
Decreased appetite	51 (19.6)	246 (23.2)
Dizzinesss	51 (19.6)	135 (12.7)
Abdominal pain upper	46 (17.7)	118 (11.1)
Dyspepsia	43 (16.5)	114 (10.8)
Cough	42 (16.2)	156 (14.7)
Neutropenia	41 (15.8)	151 (14.2)
Back pain	40 (15.4)	128 (12.1)
Dyspnoea	39 (15.0)	139 (13.1)
Pyrexia	31 (11.9)	127 (12.0)
Urinary tract infection	31 (11.9)	92 (8.7)
Myalgia	28 (10.8)	66 (6.2)
Pain in extremity	28 (10.8)	72 (6.8)
Upper respiratory tract infection	28 (10.8)	104 (9.8)
Nasopharyngitis	27 (10.4)	88 (8.3)
Insomnia	27 (10.4)	75 (7.1)

[a] Table ordered by incidence of events in SOLO1
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; ALT Alanine aminotransferase; bd Twice daily; CSR Clinical study report; DCO Data cut-off.; N Total number of patients; SAS Safety analysis set.

Comparison of CTCAE Grade ≥3 adverse events

Table 49: Most common AEs of CTCAE Grade 3 or higher (reported in ≥2% patients in olaparib treatment arm of SOLO1 and the 300 mg bd pool

System organ class Preferred term	Number (%) of patients[a]	
	SOLO1 SAS olaparib 300 mg bd (N=260)	Olaparib 300 mg bd pool (N=1060)
Patients with any CTCAE Grade ≥3 AE	**102 (39.2)**	**404 (38.1)**
Blood and lymphatic system disorders	**63 (24.2)**	**215 (20.3)**
Anaemia	55 (21.2)	181 (17.1)
Neutropenia	13 (5.0)	49 (4.6)
Gastrointestinal disorders	**17 (6.5)**	**66 (6.2)**
Diarrhoea	8 (3.1)	15 (1.4)
Investigations	**12 (4.6)**	**64 (6.0)**
Neutrophil count decreased	7 (2.7)	30 (2.8)
General disorders and administration site conditions	**11 (4.2)**	**57 (5.4)**
Fatigue	5 (1.9)	29 (2.7)

[a] Table ordered by incidence of events in SOLO1

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; SAS Safety analysis set.

Adverse drug reactions

Lynparza monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE grade 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving Lynparza monotherapy (≥ 10%) were upper abdominal pain, cough, dyspneoa, anaemia, neutropenia, thrombocytopenia and leukopenia.

The Grade ≥ 3 adverse reactions occurring in > 2% of patients were anaemia (16%), neutropenia (6%), fatigue/asthenia (6%), leukopenia (3%), thrombocytopenia (2%) and vomiting (2%).

Adverse reactions that most commonly led to dose interruptions and/ or reductions were anaemia (13.9%), vomiting (7.1%), nausea (6.6%), fatigue/asthenia (6.1%) and neutropenia (5.8%). Adverse reactions that most commonly led to permanent discontinuation were anaemia (1.3%), nausea (0.8%) and thrombocytopenia (0.5%).

The list of ADRs based on pooled data from 1,826 patients with solid tumours treated with Lynparza monotherapy in clinical trials at the recommended dose is presented below.

Table 50: Tabulated list of adverse reactions

	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Blood and lymphatic system disorders	**Very common** Anaemia[a], Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Common** Lymphopenia[a]	**Very common** Anaemia[a] **Common** Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Uncommon** Lymphopenia[a]

	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Immune system disorders	**Common** Rash[a] **Uncommon** Hypersensitivity[a], Dermatitis[a]	-
Metabolism and nutrition disorders	**Very common** Decreased appetite	**Uncommon** Decreased appetite
Nervous system disorders	**Very common** Dizziness, Headache, Dysgeusia	**Uncommon** Dizziness, Headache
Respiratory, thoracic and mediastinal disorders	**Very common** Cough[a], Dyspnoea[a]	**Common** Dyspnoea[a] **Uncommon** Cough[a]
Gastrointestinal disorders	**Very common** Vomiting, Diarrhoea, Nausea, Dyspepsia, Upper abdominal pain **Common** Stomatitis[a]	**Common** Vomiting, Diarrhoea, Nausea **Uncommon** Stomatitis[a], Upper abdominal pain
General disorders and administration site conditions	**Very common** Fatigue (including asthenia)	**Common** Fatigue (including asthenia)
Investigations	**Common** Increase in blood creatinine **Uncommon** Mean corpuscular volume elevation	**Uncommon** Increase in blood creatinine

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

Dyspnoea

Following the database lock for the primary analysis of the SOLO1 study, dyspnoea was identified as an ADR for olaparib. Table 51 shows that AEs of dyspnoea were reported for a higher percentage of patients in the olaparib arm than the placebo arm.

Table 51: SOLO1: Patients who had at least one AE of dyspnoea (grouped term analysis) reported in any category (SAS)

AE category[a]	Number (%) of patients	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Any AE	40 (15.4)	8 (6.2)
Any AE of CTCAE Grade 3 or higher	0	0
Any AE with outcome = death	0	0
Any SAE	0	0
AEs leading to dose reduction	0	0
AEs leading to treatment interruption	1 (0.4)	1 (0.8)
Any AE leading to discontinuation	1 (0.4)	0

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.

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

A similar imbalance in rates of dyspnoea was seen in the SOLO2 study. In SOLO2, there were 23 (11.8%) patients in the olaparib arm with AEs of dyspnoea (single preferred term) compared with 1 (1.0%) patient in the placebo arm.

Analysis of concurrent event data suggested that dyspnoea is multifactorial. At a population level, the imbalance was not driven by imbalances in the event rates of pneumonitis, upper respiratory tract infections or nasopharyngitis. The proportion of the patients with a dyspnoea AE who also experienced another relevant AE (with an incidence of >30%) is presented in Table 52.

Table 52: SOLO1: Most common other AEs (>30%) in olaparib-treated patients with an AE of dyspnoea or exertional dyspnoea versus olaparib arm of the SAS

Preferred term	Olaparib-treated patients with dyspnoea 300 mg bd (N=40)	Olaparib arm of SOLO1 SAS 300 mg bd (N=260)
Nausea	32 (80.0)	201 (77.3)
Fatigue	27 (67.5)	106 (40.8)
Anaemia	21 (52.5)	99 (38.1)
Diarrhoea	21 (52.5)	89 (34.2)
Vomiting	20 (50.0)	104 (40.0)
Abdominal pain	17 (42.5)	64 (24.6)
Arthralgia	16 (40.0)	66 (25.4)
Constipation	16 (40.0)	72 (27.7)
Dizziness	14 (35.0)	20 (15.4)
Cough	13 (32.5)	42 (16.2)
Decreased appetite	13 (32.5)	51 (19.6)
Dysgeusia	13 (32.5)	68 (26.2)

AE Adverse event; N Total number of patients; SAS Safety analysis set.

AEs of dyspnoea were reported throughout the study period (median time to first onset was 5.72 months [range 0.2 to 23.0 months]). In the majority of patients (33/40; 82.5%), the events of dyspnoea resolved.

Importantly, all of the 39 olaparib treated patients with AEs of dyspnoea in the SOLO1 study had AEs that were mild or moderate in severity; none were SAEs. One patient had a dyspnoea AE leading to dose interruption and 1 AE led to permanent discontinuation; no dyspnoea AEs led to dose reduction. The patient with the dyspnoea event leading to permanent discontinuation also reported AEs of upper respiratory tract infection and pyrexia leading to treatment discontinuation. This patient received treatment and recovered from the AE of dyspnoea but was subsequently diagnosed with AML.

Gastrointestinal toxicities

In first-line ovarian cancer maintenance treatment, patients experienced nausea events (77% on olaparib, 38% on placebo), vomiting (40% on olaparib, 15% on placebo), diarrhoea (34% on olaparib, 25% on placebo) and dyspepsia (17% on olaparib, 12% on placebo). Nausea events led to discontinuation in 2.3% of olaparib-treated patients (CTCAE Grade 2) and 0.8% of placebo-treated patients (CTCAE Grade 1); 0.8% and 0.4% of olaparib-treated patients discontinued treatment due to low grade (CTCAE Grade 2) vomiting and dyspepsia, respectively. No olaparib or placebo-treated patients discontinued due to diarrhoea. No placebo-treated patients discontinued due to vomiting or dyspepsia. Nausea events led to dose interruption and dose reductions in 14% and 4%, respectively, of olaparib-treated patients. Vomiting events led to interruption in 10% of olaparib-treated patients; no olaparib-treated patients experienced a vomiting event leading to dose reduction.

Anaemia

Table 53 shows AEs of anaemia. AEs of anaemia were reported for a higher percentage of patients in the olaparib arm compared with the placebo arm.

Table 53: SOLO1: Patients who had at least one AE of anaemia (grouped term) reported in any category (SAS)

AE category[a]	Number (%) of patients	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Any AE	101 (38.8)	13 (10.0)
Any AE of CTCAE Grade 3 or higher	56 (21.5)	2 (1.5)
Any AE with outcome = death	0	0
Any SAE	18 (6.9)	0
AEs leading to dose reduction	44 (16.9)	1 (0.8)
AEs leading to treatment interruption	58 (22.3)	1 (0.8)
Any AE leading to discontinuation	6 (2.3)	0

[a] 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.

In clinical studies with the tablet formulation, the incidence of anaemia adverse reactions was 38.8% (CTCAE grade ≥3 17.4%) and the incidences of dose interruptions, reductions and discontinuations for anaemia were 15.7%, 10.8% and 1.9%, respectively; 20.9% of patients treated with olaparib needed one or more blood transfusions. An exposure response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (decreases) from baseline in haemoglobin was 20%, absolute neutrophils 20%, platelets 5%, lymphocytes 30% and leucocytes 20% (all % approximate).

No patients in SOLO1 had CTCAE Grade 4 haemoglobin values during the study; 19.5% of olaparib-treated patients had increases to CTCAE Grade 3 haemoglobin values (Table 30).

Table 54: SOLO1: Number (%) of patients with maximum overall CTCAE Grade shifts during treatment for haemoglobin (SAS)

Baseline CTCAE grade	Patients at baseline	Maximum overall CTCAE grade during treatment (%)				
		0	1	2	3	4
Olaparib 300 mg bd (N=260)						
0	105 (40.9)	28 (10.9)	41 (16.0)	16 (6.2)	20 (7.8)	0
1	151 (58.8)	6 (2.3)	67 (26.1)	49 (19.1)	29 (11.3)	0
2	1 (0.4)	0	0	0	1 (0.4)	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Total evaluable	257 (100)	34 (13.2)	108 (42.0)	65 (25.3)	50 (19.5)	0
Placebo bd (N=130)						
0	45 (34.6)	36 (27.7)	9 (6.9)	0	0	0
1	82 (63.1)	12 (9.2)	57 (43.8)	11 (8.5)	2 (1.5)	0
2	3 (2.3)	0	1 (0.8)	2 (1.5)	0	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Total evaluable	130 (100)	48 (36.9)	67 (51.5)	13 (10.0)	2 (1.5)	0

Haemoglobin: Grade 1 <LLN to 100 g/L, Grade 2 <100 to 80 g/L, Grade 3 <80 to 65 g/L, Grade 4 <65 g/L
bd twice daily; CTCAE Common Terminology Criteria for Adverse Events; SAS Safety Analysis Set.

Neutropenia

Table 55 shows AEs of neutropenia. AEs of neutropenia were reported for a higher percentage of patients in the olaparib arm compared with the placebo arm.

Table 55: SOLO1: Patients who had at least one AE of neutropenia (grouped term) reported in any category (SAS)

AE category[a]	Number (%) of patients	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Any AE	60 (23.1)	15 (11.5)
Any AE of CTCAE Grade 3 or higher	22 (8.5)	6 (4.6)
Any AE with outcome = death	0	0
Any SAE	4 (1.5)	0
AEs leading to dose reduction	10 (3.8)	1 (0.8)
AEs leading to treatment interruption	30 (11.5)	5 (3.8)
Any AE leading to discontinuation	1 (0.4)	0

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.

The majority (234 of 256 [91.4%] patients) of olaparib-treated patients in SOLO1 had a maximum CTCAE Grade ≤2 reported for absolute neutrophil count (ANC) values; 93.8% (121 of 129 patients) of patients in the placebo arm also had CTCAE Grade ≤2 ANC during the SOLO1 study.

Table 56: SOLO1: Number (%) of patients with maximum overall CTCAE Grade shifts during treatment for neutrophils (SAS)

Baseline CTCAE grade	Patients at baseline	Maximum overall CTCAE grade during treatment (%)				
		0	1	2	3	4
Olaparib 300 mg bd (N=260						
0	218 (85.2)	122 (47.7)	32 (12.5)	51 (19.9)	11 (4.3)	2 (0.8)
1	37 (14.5)	4 (1.6)	8 (3.1)	17 (6.6)	8 (3.1)	0
2	1 (0.4)	0	0	0	1 (0.4)	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Total evaluable	256 (100)	126 (49.2)	40 (15.6)	68 (26.6)	20 (7.8)	2 (0.8)
Placebo bd (N=130)						
0	112 (86.8)	76 (58.9)	20 (15.5)	10 (7.8)	6 (4.7)	0
1	16 (12.4)	4 (3.1)	8 (6.2)	3 (2.3)	1 (0.8)	0
2	1 (0.8)	0	0	0	1 (0.8)	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Total evaluable	129 (100)	80 (62.0)	28 (21.7)	13 (10.1)	8 (6.2)	0

Neutrophils: Grade 1 <LLN to 1.5 × 10^9/L, Grade 2 <1.5 × 10^9/L to 1.0 × 10^9/L, Grade 3 <1.0 × 10^9/L to 0.5 × 10^9/L, Grade 4 <0.5 × 10^9/L.
bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; LLN Lower limit of normal; SAS Safety Analysis Set..

Increase in creatinine

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

Table 57: SOLO1: Patients who had at least one AE of increased creatinine reported in any category (SAS)

AE category[a]	Number (%) of patients	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Any AE	21 (8.1)	2 (1.5)
Any AE of CTCAE Grade 3 or higher	0	0
Any AE with outcome = death	0	0
Any SAE	0	0
AEs leading to dose reduction	0	0
AEs leading to treatment interruption	0	0
Any AE leading to discontinuation	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.

Two patients in the olaparib arm of the SOLO1 study had a 2 grade increase in laboratory values for creatinine during the study, compared with no patients in the placebo arm; no patients in either treatment arm had a ≥3 grade increase in laboratory values for creatinine.

Table 58: Number (%) of patients with maximum overall CTCAE Grade shift increases during treatment for blood creatinine in SOLO1 (SAS)

Baseline CTCAE grade	Patients at baseline	Maximum overall CTCAE grade during treatment (%)				
		0	1	2	3	4
Olaparib 300 mg bd (N=260)						
0	249 (96.9)	170 (66.1)	77 (30.0)	2 (0.8)	0	0
1	8 (3.1)	1 (0.4)	5 (1.9)	2 (0.8)	0	0
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Total evaluable	257 (100)	171 (66.5)	82 (31.9)	4 (1.6)	0	0
Placebo bd (N=130)						
0	123 (94.6)	105 (80.8)	18 (13.8)	0	0	0
1	7 (5.4)	1 (0.8)	6 (4.6)	0	0	0
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Total evaluable	130 (100)	106 (81.5)	24 (18.5)	0	0	0

Creatinine: grade 1: >ULN - 1.5 x ULN; grade 2: >1.5 - 3.0 x ULN; grade 3: >3.0 - 6.0 x ULN; grade 4 >6.0 x ULN.
bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; SAS Safety analysis set.

In clinical studies with Lynparza (pool), the incidence of CTCAE grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 10%.

Hypersensitivity, rash and dermatitis

The analyses showed that the most commonly-reported AE associated with hypersensitivity was rash and that these types of events were reported for a similar percentage of patients in the olaparib arm compared with the placebo arm. Rash and other hypersensitivity events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment. There was no association between the reporting of AEs of rash and the length of time on olaparib treatment. AEs of rash in the olaparib-treated arm were reported throughout the study period, (median time to onset was 6.41 months [range 0.07 to 24.94 months]); the majority (24 of 27 patients) of events of rash on olaparib treatment resolved (median time to resolution of first event of 1.05 months). A higher proportion of patients in the olaparib arm with AEs of rash (12 [44.4%] of 27 olaparib-treated patients) were treated for the AE, compared with the placebo arm (4 [28.6%] of 14 placebo patients); 3 (60.0%) of 5 patients in the olaparib arm received treatment for an AE of hypersensitivity, and the single patient in the placebo-treated arm with the AE of hypersensitivity also received treatment. There were no events suggestive of a severe hypersensitivity reaction (eg, angioedema or anaphylaxis) in either arm. There were no AEs of CTCAE Grade ≥3 and no SAEs within the SMQ narrow term search.

Thrombocytopenia

Table 59 shows AEs of thrombocytopenia (grouped term consisting of thrombocytopenia, platelet production decreased, platelet count decreased and plateletcrit decreased). AEs of thrombocytopenia were reported for a higher percentage of patients in the olaparib arm compared with the placebo arm.

In the olaparib arm, 1 of the 2 patients with CTCAE Grade ≥3 AEs reported the event as an SAE (1 patient had a non serious CTCAE Grade 4 AE of platelet count decreased concurrently with an AE of anaemia which had a worst CTCAE grade of 3). There was 1 SAE of thrombocytopenia in the placebo arm and 2 patients with CTCAE Grade 4 AEs of platelet count decreased.

Table 59: SOLO1: Patients who had at least one AE of thrombocytopenia (grouped term) reported in any category (SAS)

AE category[a]	Number (%) of patients	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Any AE	29 (11.2)	5 (3.8)
Any AE of CTCAE Grade 3 or higher	2 (0.8)	2 (1.5)
Any AE with outcome = death	0	0
Any SAE	1 (0.4)	1 (0.8)
AEs leading to dose reduction	4 (1.5)	0
AEs leading to treatment interruption	6 (2.3)	0
Any AE leading to discontinuation	1 (0.4)	0

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.

The majority of patients had a worst CTCAE Grade of ≤2 reported for platelet values throughout treatment. A low proportion of olaparib-treated patients (2 patients [0.8%]) had CTCAE Grade ≥3 reductions in platelet count during the study; 2 (1.5%) patients in the placebo arm had a CTCAE Grade ≥3 reduction in platelet count.

Table 60: SOLO1: Number (%) of patients with maximum overall CTCAE Grade shifts during treatment for platelets (SAS).

Baseline CTCAE grade	Patients at baseline	Maximum overall CTCAE grade during treatment (%)				
		0	1	2	3	4
Olaparib 300 mg bd (N=260)						
0	238 (92.6)	164 (63.8)	68 (26.5)	4 (1.6)	1 (0.4)	1 (0.4)
1	19 (7.4)	4 (1.6)	12 (4.7)	2 (0.8)	1 (0.4)	0
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Total evaluable	257 (100)	168 (65.4)	80 (31.1)	6 (2.3)	2 (0.8)	1 (0.4)
Placebo bd (N=130)						
0	117 (90.0)	100 (76.9)	15 (11.5)	0	1 (0.8)	1 (0.8)
1	13 (10.0)	4 (3.1)	9 (6.9)	0	0	0
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Total evaluable	130 (100)	104 (80.0)	24 (18.5)	0	1 (0.8)	1 (0.8)

Platelets: Grade 1 <LLN to 75.0 × 10^9/L, Grade 2 <75.0 × 10^9/L to 50.0 × 10^9/L, Grade 3 <50.0 × 10^9/L to 25.0 × 10^9/L, Grade 4 <25.0 × 10^9/L.

bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; LLN Lower limit of normal; SAS Safety analysis set.

Lymphopenia

Table 61 shows AEs of lymphopenia (grouped term consisting of: B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia and T-lymphocyte count decreased). These events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment. Events of lymphopenia were generally reported early in the treatment period (median time to first onset was 3.27 months); the majority (13 of 16 patients) of events with olaparib resolved (median time to resolution of first event of 3.38 months.

Table 61: SOLO1: Patients who had at least one AE of lymphopenia (grouped term) reported in any category (SAS)

AE category[a]	Number (%) of patients	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Any AE	16 (6.2)	2 (1.5)
Any AE of CTCAE Grade 3 or higher	4 (1.5)	1 (0.8)
Any AE with outcome = death	0	0
Any SAE	0	1 (0.8)
AEs leading to dose reduction	0	0
AEs leading to treatment interruption	3 (1.2)	0
Any AE leading to discontinuation	1 (0.4)	0

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.

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 2.7.4.1.5.2.14b, Module 5.3.5.3 (DCO: 17 May 2018).

The proportion of patients with CTCAE Grade ≥3 reductions in lymphocyte count during the study was higher for the olaparib arm (15 of 231 patients [6.5%]) than for the placebo arm (3 of 110 patients [2.7%]).

Table 62: Lymphocytes, CTCAE grade change from baseline to maximum on treatment (SAS).

Baseline CTCAE grade	Patients at baseline	Maximum overall CTCAE grade during treatment (%)				
		0	1	2	3	4
Olaparib 300 mg bd (N=260)						
0	188 (81.4)	76 (32.9)	60 (26.0)	37 (16.0)	15 (6.5)	0
1	32 (13.9)	1 (0.4)	8 (3.5)	14 (6.1)	9 (3.9)	0
2	9 (3.9)	0	0	3 (1.3)	6 (2.6)	0
3	2 (0.9)	0	0	0	2 (0.9)	0
4	0	0	0	0	0	0
Total evaluable	231 (100)	77 (33.3)	68 (29.4)	54 (23.4)	32 (13.9)	0
Placebo bd (N=130)						
0	93 (84.5)	76 (69.1)	9 (8.2)	5 (4.5)	3 (2.7)	0
1	15 (13.6)	2 (1.8)	7 (6.4)	5 (4.5)	1 (0.9)	0
2	2 (1.8)	0	0	1 (0.9)	1 (0.9)	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Total evaluable	110 (100)	78 (70.9)	16 (14.5)	11 (10.0)	5 (4.5)	0

Lymphocytes: Grade 1 <LLN to 0.8 × 10^9/L, Grade 2 <0.8 × 10^9/L to 0.5 × 10^9/L, Grade 3 <0.5 × 10^9/L to 0.2 × 10^9/L, Grade 4 <0.2 × 10^9/L.

bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; LLN Lower limit of normal; SAS Safety Analysis Set..

Important potential risks

Myelodysplastic syndrome/acute myeloid leukaemia

In SOLO1, in the post-follow-up period 2 patients had AEs of AML and 1 patient had an AE of myeloproliferative neoplasm; all of these AEs occurred in patients in the olaparib arm of SOLO1.

Table 63: Events of MDS/AML occurring in SOLO1

Event	Treatment arm in SOLO1	Day of last dose of study treatment in SOLO1	Reason for treatment discontinuation	Day of MDS/AML AE onset (from start of study treatment)	Number of cycles of prior platinum therapy	AE outcome
AML	Olaparib	757	Completion of the protocol specified 2 years of treatment	807	6	Fatal; patient died on Day 1084, 328 days after her last dose of olaparib
AML	Olaparib	518	CTCAE Grade 1 AE of pyrexia and CTCAE Grade 2 AEs of dyspnoea, and upper respiratory tract infection	571	6	Fatal; patient died on Day 825, 308 days after her last dose of olaparib
Myeloproliferative neoplasm	Olaparib	437	CTCAE Grade 2 AE of anaemia and CTCAE Grade 3 AE of neutropenia	609	6	Patient died on Day 798, 363 days after her last dose of olaparib. The cause of death was given as septic shock (in the context of graft versus host disease, following a stem cell transplantation procedure); the AE of myeloproliferative neoplasm was ongoing at the time of death.

AE Adverse event; AML Acute myeloid leukaemia; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events (v4.0).

Table 64 shows the AEs and incidence rates of MDS/AML in other pivotal studies, in the olaparib all doses monotherapy pool and across the entire olaparib clinical programme.

Table 64: Summary of AEs of MDS/AML occurring across the olaparib programme

Data source	TEAEs[a] + AEs after 30 day follow-up			
	Olaparib		Comparator[b]	
	Number of AEs	Incidence	Number of AEs	Incidence
SOLO1 N=260 olaparib N=130 placebo	3	1.2%	0	0
SOLO2 N=195 olaparib N=99 placebo	4[c]	2.1%	4[d]	4.0%
Study 19 N=136 olaparib N=128 placebo	2	1.5%	1	0.8%
OlympiAD N=205 olaparib N=91 physician's choice	0	0	0	0
Olaparib monotherapy, all doses pool N=2258 olaparib	26	1.2%	NA	NA
Entire clinical programme pool N=9293 olaparib	55	0.6%	NA	NA

[a] TEAEs are events occurring on-study or during 30-day follow-up.
[b] The comparator was placebo in SOLO1, SOLO2 and Study 19. The comparator was physician's choice of chemotherapy in OlympiAD (consisting of either capecitabine, eribulin or vinorelbine).
[c] The AE of AML occurred prior to the DCO date of 19 September 2016 for SOLO2, but details of the report were not available until after the DCO date; this AE is therefore not included in the SOLO2 dataset.
[d] One of the 4 placebo patients had received olaparib treatment 3 months prior to developing AML

Most of the 26 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 g*BRCA* wildtype and in 2 patients, the *BRCA* mutation status was unknown. In 20 of the 26 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 <6 months to >2 years. The time to death after olaparib was discontinued ranged from 17 to 667 days (median 209 days).

In 4 of the 20 cases, patients died due to other causes (progressive disease [2 patients], bone marrow transplant complications [1 patient], and disseminated intravascular coagulation [1 patient]). In 5 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.

In order to assess the potential contributions of the duration of exposure to olaparib and the number of prior lines of platinum-containing chemotherapy on the risk of MDS/AML, a further analysis of data from SOLO1 and SOLO2 was conducted. In SOLO1, patients had received 1 prior line of platinum-containing chemotherapy, but the duration of exposure to olaparib and subsequent follow-up time was longer than in SOLO2. To take into account these differences, an exploratory analysis was conducted to directly compare the event rates of MDS/AML per patient-year of follow-up time in these studies (Table 65).

Table 65: Event rates of MDS/AML in SOLO1 and SOLO2

Study	Study arm	Total duration of follow-up time (patient-years)	Number of patients with AESIs of MDS or AML/Number of patients in group with follow-up data	Event rate (events per 1000 patient-years of follow-up time)[c]
SOLO1	Olaparib 300 mg bd	833.6	3/260	3.6
	Placebo	412.2	0/130	0
SOLO2	Olaparib 300 mg bd	381.4	4/195	10.5
	Placebo	185.3	3/99	16.2

AESI Adverse event of special interest; AML Acute myeloid leukaemia; MDS Myelodysplastic syndrome; PARP Polyadenosine 5'diphosphoribose polymerase.

In this analysis, the event rate for MDS/AML in SOLO1 was lower than the event rate in both olaparib and placebo-treated patients in SOLO2, despite the longer duration of exposure to olaparib and longer follow-up time in SOLO1. As a significant number of patients in the placebo arms of both SOLO1 and SOLO2 received a PARP inhibitor (either olaparib or another PARP inhibitor, such as niraparib or rucaparib) as a subsequent therapy after discontinuing study treatment, a sensitivity analysis was also conducted. Results of this analysis are presented in Table 66.

Table 66: Sensitivity analysis of event rates of MDS/AML in SOLO1 and SOLO2

Study	Group description	Total duration of follow-up time (patient-years)	Number of patients with AESIs of MDS or AML/Number of patients in group with follow-up data	Event rate (events per 1000 patient-years of follow-up time)
SOLO1	Patients who had ever received a PARP inhibitor	892.8	3/302[a]	3.4
	Patients who had never received a PARP inhibitor	353.0	0/130	0
SOLO2	Patients who had ever received a PARP inhibitor	409.4	5/222[b]	12.2
	Patients who had never received a PARP inhibitor	157.3	3/99	19.1

[a] Forty-two patients in the placebo arm of SOLO1 were subsequently treated with a PARP inhibitor and so contribute follow-up time to both groups. No AEs of MDS/AML occurred in these 42 patients.

[b] Twenty-seven patients in the placebo arm of SOLO2 were subsequently treated with a PARP inhibitor and so contribute follow-up time to both groups. One AE of MDS/AML occurred in these 27 patients (3 months after they started receiving a PARP inhibitor [olaparib] as a subsequent therapy).

New primary malignancy

In SOLO1, there were 5 (1.9%) patients in the Olaparib arm and 3 (2.3%) patients in the placebo arm with new primary malignancies. These AEs are discussed in more detail in Table 67.

Table 67: Events of potential new primary malignancies in SOLO1 (SAS)

Event	Day of onset	CTCAE Grade/ SAE/ related	Outcome
Olaparib 300 mg bd			
Invasive ductal breast carcinoma	329	3/yes/no	Patient discontinued study treatment; AE resolved after 513 days
Breast cancer female	55	3/yes/no	Patient discontinued study treatment; AE unresolved at DCO
Intraductal proliferative breast lesion	257	3/yes/no	Study treatment interrupted; AE resolved after 2 days
Lip and/or oral cavity cancer	576	3/yes/yes	Patient discontinued study treatment; AE resolved after 219 days
Thyroid cancer	506	3/yes/no	Patient continued on treatment. AE resolved after 275 days. Patient discontinued after 2 years on treatment (Day 758) per protocol.
Placebo arm			
Breast cancer female	94	2/yes/no	Patient discontinued study treatment on Day 176 to receive treatment for breast cancer; AE unresolved at DCO
Breast cancer female	666	3/yes/no	Patient discontinued study treatment; AE resolved after 73 days
Breast cancer female	240	2/yes/no	Patient discontinued study treatment on Day 247 due to progressive disease and secondary malignancy. AE unresolved at DCO.

Table 68 shows the AEs of new primary malignancies in SOLO1 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 1.0%.

Table 68: Summary of AEs of new primary malignancies occurring across the olaparib programme

Data source	TEAEs[a] + AEs after 30 day follow-up			
	Olaparib		Comparator[b]	
	Number of AEs	Incidence	Number of AEs	Incidence
SOLO1 N=260 olaparib N=130 placebo	5	1.9%	3	2.3%
SOLO2 N=195 olaparib N=99 placebo	1	1.5%	1	1.0%
Study 19 N=136 olaparib N=128 placebo	4	2.9%	1	0.8%
OlympiAD N=205 olaparib N=91 physician's choice	1	0.5%	0	0
Olaparib monotherapy, all doses pool N=2258 olaparib	29	1.3%	NA	NA
Entire clinical programme pool N=9293 olaparib	61	0.7%	NA	NA

[a] TEAEs are events occurring on-study or during 30-day follow-up.
[b] The comparator was placebo in SOLO1, SOLO2 and Study 19. The comparator was physician's choice of chemotherapy in OlympiAD (consisting of either capecitabine, eribulin or vinorelbine).

Pneumonitis

Table 69 shows the rates of pneumonitis in the clinical programme, and provides incidence rates. In the larger pool (therapeutic dose pool), the incidence of pneumonitis events was 0.7%.

Table 69: Summary of AEs of pneumonitis occurring across the olaparib programme

Data source	TEAEs[a]			
	Olaparib		Comparator[b]	
	Number of AEs	Incidence	Number of AEs	Incidence
SOLO1 N=260 olaparib N=130 placebo	5	1.9%	0	0
SOLO2 N=195 olaparib N=99 placebo	3	1.5%	0	0
Study 19 N=136 olaparib N=128 placebo	1	0.7%	1	0.8%
OlympiAD N=205 olaparib N=91 physician's choice	0	0%	0	0
Olaparib monotherapy combined therapeutic dose pool N=1826 olaparib	13	0.7%	NA	NA

[a] TEAEs are events occurring on-study or during 30-day follow-up.
[b] The comparator was placebo in SOLO1, SOLO2 and Study 19. The comparator was physician's choice of chemotherapy in OlympiAD (consisting of either capecitabine, eribulin or vinorelbine).

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 13 pneumonitis AEs in the pool had a fatal outcome.

Serious adverse event / deaths / other significant events

Deaths in SOLO1

A summary of patients who died in the SOLO1 study is presented in Table 70. The number of patients in each of the categories of deaths were similar for the SAS, the Myriad g*BRCA*m and the FMI t*BRCA*m subsets.

Table 70: SOLO1: Deaths (FAS)

Category	Number (%) of patients	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=131)
Total number of deaths	55 (21.2)	27 (20.6)
Death related to disease under investigation only[a]	1 (0.4)	0
Death related to disease under investigation only (death > 30 days after last treatment dose)	50 (19.2)	27 (20.6)
Death related to disease under investigation and with AE outcome = death	0	0
AE with outcome of death only	0	0
AE with outcome of death only (AE start date falling >30 days after last treatment dose)	2 (0.8)[c]	0
Deaths > 30 days after last treatment dose, unrelated to AE or disease under investigation	2 (0.8)[d]	0
Deaths > 30 days after last treatment dose, AE related to disease under investigation and with AE outcome of death	0	0
Patients with unknown reason for death[b]	0	0

[a] Deaths on or after the date of first dose and up to 30 days following the last dose of study medication.
[b] Patients who died and are not captured in the earlier categories.
[c] Patients E0305006 and E1003004 both died of acute myeloid leukaemia (AML)
[d] Patient E5001006 died of septic shock and also had an ongoing AE of myeloproliferative neoplasm; Patient E7846017 died due to an intentional carbon monoxide overdose.

Patients in SOLO1 whose deaths were not considered due to disease progression only are listed in Table 71, 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 71: SOLO1: Key information for deaths not due to disease progression in the olaparib arm (FAS)

Time from first dose (days)	Time from last dose to death (days)	Treatment period	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[a]
1084	328	Post Follow-up	Acute myeloid leukaemia	None specified	No	Patient discontinued olaparib on Day 757 as she had no evidence of disease after completing the protocol specified 2 years of treatment. AML was diagnosed on Day 807; the AE was considered related to treatment
825	308	Post Follow-up	Acute myeloid leukaemia	None specified	No	Patient discontinued olaparib on Day 518 due to AEs of dyspnoea, pyrexia and upper respiratory tract infection. Radiological disease progression was noted on Day 570. AML was diagnosed on Day 571; the AE was considered related to treatment.
798	363	Post Follow-up	Septic shock[b]	Immunosupression	No	At the time of death, the patient had an ongoing SAE of myeloproliferative neoplasm (CTCAE Grade 3), which started on Day 609 and was considered related to olaparib treatment. The patient was treated for this SAE by autologous stem cell transplantation and developed sepsis as a result of complications with the stem cell transplantation.
611	115	Post Follow-up	Intentional overdose	None specified	No	Patient had a medical history of depression and insomnia at baseline and discontinued olaparib treatment on Day 497 for AEs of depression and insomnia. Both AEs were CTCAE Grade 2, non-serious and neither were considered related to treatment.

[a] As assessed by the investigator

[b] The event of septic shock was not recorded as an AE as it occurred after the 30-day follow up period (after the 30-day 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); FAS Full analysis set; MedDRA Medical Dictionary for Regulatory Activities (v21.0); NA Not applicable; NAV Not available; SAE Serious adverse event.

Data derived from Tables 11.3.3.2.1, Table 11.3.3.1.2, Appendix 12.2.5.1 and Appendix 12.2.7.1.1, SOLO1 CSR, Module 5.3.5.1 (DCO: 17 May 2018).

Comparison of deaths in SOLO1 and the 300 mg bd pool

Table 72 summarises the number of deaths in the olaparib treatment arm in SOLO1 and the 300 mg bd pool.

Table 72: Patients who died in the olaparib treatment arm of SOLO1 and the 300 mg bd pool

Category	Number (%) of patients	
	SOLO1 FAS olaparib 300 mg bd (N=260)	Olaparib 300 mg bd pool (N=1060)
Total number of deaths	55 (21.2)	269 (25.4)
Death related to disease under investigation only	51 (19.6)	249 (23.5)
AE with outcome = death only	0	1 (0.1)
Death related to disease and an AE with outcome = death	0	3 (0.3)
AE with outcome of death ≥30 days after last treatment dose	2 (0.8)	2 (0.2)
Other deaths[a]	2 (0.8)[b]	14 (1.3)[c]

[a] Patients who died and are not captured in the earlier categories

[b] Patient E5001006 (septic shock with ongoing AE of myeloproliferative neoplasm) and Patient E7846017 (intentional carbon monoxide overdose) from SOLO1, reported as 'deaths >30 days after last treatment dose, unrelated to AE or disease under investigation' in the SOLO1 clinical database (see Table 13).

[c] See Table 2.7.4.1.2.4, Module 5.3.5.3 for a listing of all deaths captured in the "other" category for the tablet pool.

A listing for all patients who had AEs leading to death in the 300 mg bd pool (excluding deaths in SOLO1) is presented in Table 73.

Table 73: Listing of key information for AEs leading to death in the 300 mg bd pool (excluding SOLO1)

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/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 in SOLO1

During SOLO1, a higher proportion of patients reported SAEs in the olaparib arm compared with the placebo arm. The majority of SAEs had resolved with either no action taken or following a temporary dose interruption or dose reduction, or were resolving. Eight patients (6 in the olaparib arm and 2 in the placebo arm) had SAEs that were 'not recovered/not resolved' at the DCO date for this analysis.

Table 74: SOLO1: SAEs occurring in ≥2 patients in either treatment group (SAS)

Category	Number (%) of patients	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Patients with any SAE	**54 (20.8)**	**16 (12.3)**
Blood and lymphatic system disorders	**21 (8.1)**	**1 (0.8)**
Anaemia	17 (6.5)	0
Febrile neutropenia	2 (0.8)	0
Neutropenia	2 (0.8)	0
Infections and infestations	**10 (3.8)**	**5 (3.8)**
Urinary tract infection	3 (1.2)	0
Viral infection	2 (0.8)	0
Gastrointestinal disorders	**7 (2.7)**	**4 (3.1)**
Abdominal pain	2 (0.8)	1 (0.8)
Small intestinal obstruction	2 (0.8)	1 (0.8)
Nervous system disorders	**7 (2.7)**	**2 (1.5)**
Syncope	2 (0.8)	0
Transient ischaemic attack	2 (0.8)	0
Headache	1 (0.4)	2 (1.5)
Respiratory, thoracic and mediastinal disorders	**4 (1.5)**	**0**
Pneumonitis	2 (0.8)	0
Pulmonary embolism	2 (0.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5 (1.9)**	**4 (3.1)**
Breast cancer female	1 (0.4)	3 (2.3)
Musculoskeletal and connective tissue disorders	**2 (0.8)**	**0**
Rotator cuff syndrome	2 (0.8)	0

bd Twice daily; SAE Serious adverse event; SAS Safety analysis set

Comparison of serious adverse events in SOLO1 and the 300 mg bd pool

Most SAEs were reported by single patients in SOLO1, but the SOC where SAEs were most commonly reported was Blood and lymphatic system disorders and this was consistent for 300 mg bd pool data (see Table 75).

Table 75: Most common SAEs (reported by ≥2 patients in the olaparib treatment arm of SOLO1 and/or reported by ≥5 patients in the 300 mg bd pool)

System organ class Preferred term	Number (%) of patients	
	SOLO1 SAS olaparib 300 mg bd (N=260)	Olaparib 300 mg bd pool (N=1060)
Patients with any SAE	**54 (20.8)**	**210 (19.8)**
Blood and lymphatic system disorders	**21 (8.1)**	**69 (6.5)**
Anaemia	17 (6.5)	56 (5.3)
Febrile neutropenia	2 (0.8)	3 (0.3)
Neutropenia	2 (0.8)	7 (0.7)
Thrombocytopenia	0	5 (0.5)
Infections and infestations	**10 (3.8)**	**44 (4.2)**
Urinary tract infection	3 (1.2)	9 (0.8)
Viral infection	2 (0.8)	2 (0.2)
Pneumonia	0	7 (0.7)
Gastrointestinal disorders	**7 (2.7)**	**31 (2.9)**
Abdominal pain	2 (0.8)	7 (0.7)
Small intestinal obstruction	2 (0.8)	3 (0.3)
Constipation	0	2 (0.2)
Nervous system disorders	**7 (2.7)**	**13 (1.2)**
Syncope	2 (0.8)	2 (0.2)
Transient ischaemic attack	2 (0.8)	2 (0.2)
Headache	1 (0.4)	2 (0.2)
Respiratory, thoracic and mediastinal disorders	**4 (1.5)**	**14 (1.3)**
Pneumonitis	2 (0.8)	4 (0.4)
Pulmonary embolism	2 (0.8)	3 (0.3)

System organ class Preferred term	Number (%) of patients	
	SOLO1 SAS olaparib 300 mg bd (N=260)	Olaparib 300 mg bd pool (N=1060)
General disorders and administration site conditions	**3 (1.2)**	**17 (1.6)**
Pyrexia	1 (0.4)	6 (0.6)
Muscoskeletal and connective tissue disorders	**2 (0.8)**	**10 (0.9)**
Rotator cuff syndrome	2 (0.8)	2 (0.2)

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 11.3.4.1.1.1, SOLO1 CSR, Module 5.3.5.1 (DCO: 17 May 2018); Table 2.7.4.1.3.1, 300 mg bd pool, Module 5.3.5.3 (DCO: 17 May 2018).

Laboratory findings

Haematology

Table 76: SOLO1: 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	34/257 (13.2)	108/257 (42.0)	65/257 (25.3)	50/257 (19.5)	0
Placebo bd	48/130 (36.9)	67/130 (51.5)	13/130 (10.0)	2/130 (1.5)	0
Platelets					
Olaparib 300 mg bd	168/257 (65.4)	80/257 (31.1)	6/257 (2.3)	2/257 (0.8)	1/257 (0.4)
Placebo bd	104/130 (80.0)	24/130 (18.5)	0	1/130 (0.8)	1/130 (0.8)
Leukocytes					
Olaparib 300 mg bd	78/257 (30.4)	90/257 (35.0)	72/257 (28.0)	15/257 (5.8)	2/257 (0.8)
Placebo bd	62/130 (47.7)	49/130 (37.7)	18/130 (13.8)	1/130 (0.8)	0
Neutrophils					
Olaparib 300 mg bd	126/256 (49.2)	40/256 (15.6)	68/256 (26.6)	20/256 (7.8)	2/256 (0.8)
Placebo bd	80/129 (62.0)	28/129 (21.7)	13/129 (10.1)	8/129 (6.2)	0
Lymphocytes					
Olaparib 300 mg bd	77/231 (33.3)	68/231 (29.4)	54/231 (23.4)	32/231 (13.9)	0
Placebo bd	78/110 (70.9)	16/110 (14.5)	11/110 (10.0)	5/110 (4.5)	0

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; SAS Safety analysis set.

Clinical chemistry

Table 77: SOLO1: 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	181/257 (70.4)	67/257 (26.1)	8/257 (3.1)	1/257 (0.4)	0
Placebo bd	90/130 (69.2)	37/130 (28.5)	1/130 (0.8)	2/130 (1.5)	0
AST					
Olaparib 300 mg bd	193/256 (75.4)	61/256 (23.8)	0	2/256 (0.8)	0
Placebo bd	94/130 (72.3)	34/130 (26.2)	1/130 (0.8)	1/130 (0.8)	0
ALP					
Olaparib 300 mg bd	195/257 (75.9)	62/257 (24.1)	0	0	0
Placebo bd	85/128 (66.4)	42/128 (32.8)	1/128 (0.8)	0	0
Albumin					
Olaparib 300 mg bd	224/253 (88.5)	25/253 (9.9)	4/253 (1.6)	0	0
Placebo bd	115/129 (89.1)	14/129 (10.9)	0	0	0
Bilirubin					
Olaparib 300 mg bd	233/256 (91.0)	20/256 (7.8)	3/256 (1.2)	0	0
Placebo bd	119/129 (92.2)	8/129 (6.2)	2/129 (1.6)	0	0
Creatinine					
Olaparib 300 mg bd	171/257 (66.5)	82/257 (31.9)	4/257 (1.6)	0	0
Placebo bd	106/130 (81.5)	24/130 (18.5)	0	0	0
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
GGT					
Olaparib 300 mg bd	165/249 (66.3)	64/249 (25.7)	13/249 (5.2)	7/249 (2.8)	0
Placebo bd	77/118 (65.3)	30/118 (25.4)	8/118 6.8)	3/118 (2.5)	0

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.

Comparative analysis of clinical laboratory evaluations

The laboratory evaluations for SOLO1 and the 300 mg bd pool were comparable. Changes in haemoglobin; neutrophils; lymphocytes, platelets and MCV were the only significant haematological parameters with clinically relevant changes; these parameters are recognised ADRs for olaparib. The only significant change in clinical chemistry parameters occurred for creatinine: creatinine increases are a recognised ADR for olaparib.

Assessment of the potential for drug-induced liver injury

There were no confirmed or suspected Hy's Law cases. One (0.4%) olaparib-treated patient in SOLO1 had concurrent elevations of bilirubin and ALT; this patient had Gilbert's syndrome at study entry, which provides an explanation for her elevated liver enzymes.

Laboratory abnormalities for ALT and AST (SOLO1)

In SOLO1, there were no patients who had CTCAE Grade 4 laboratory values for ALT and AST; the proportion of patients with CTCAE Grade 3 elevations was low in both treatment arms:

- There were 2 (0.8%) of 256 patients in the olaparib arm who had a laboratory value of AST elevation of CTCAE Grade 3 (worst grade), and 1 (0.4%) patient with CTCAE Grade 3 elevated ALT during treatment. No liver diagnostic investigations data were reported for these 2 patients.

- There were 2 patients in the placebo arm who had CTCAE Grade 3 elevations of either ALT, AST or both during treatment or during follow-up.

Concomitant elevations of ALT/AST and bilirubin (SOLO1)

An assessment of ALT, AST maximal elevations during treatment by maximal total bilirubin elevations showed that 1 (0.4%) patient in the olaparib arm and no patients in the placebo arm had concurrent

elevation of bilirubin and either ALT or AST. One patient was reported to have Gilbert's syndrome and had transient concurrent elevated ALT (CTCAE Grade 2) and bilirubin (>2 x ULN) at Visit 13 (Day 227). The patient had bilirubin values above normal levels (CTCAE Grade 1 or 2) pre-treatment and from Visit 6 onwards. No AEs for liver abnormalities were reported throughout the course of the study. The patient remained on study treatment for 756 days.

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

In the 300 mg bd pool, 17 (1.6%) patients had an ALT increased laboratory value (worst grade) of CTCAE Grade 3 and 1 patient (0.1%) had an ALT increased laboratory value of CTCAE Grade 4; 25 (2.4%) 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 was higher than that in the olaparib arm of the SOLO1 study (0.4% and 0.8%, respectively).

The proportion of olaparib-treated patients with CTCAE Grade 3 AEs in the SOLO1 study and in the 300 mg bd pool was low and similar to the proportion of patients with CTCAE Grade 3 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 1060 patients, 16 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

The median change in creatinine from baseline to Visit 3 for olaparib-treated patients was an increase of 8.8 µmol/L compared with no change for placebo-treated patients. Median creatinine levels for olaparib-treated patients then remained consistent over time (maximum median change 15.0 µmol/L, median change at the majority of time points between 8.0 and 12.0 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 higher proportion of patients in the tablet pool had CTCAE grade shifts in creatinine, compared with SOLO1. In the 300 mg bd pool, 91.7% of olaparib-treated patients had normal creatinine at baseline, 7.7% had CTCAE Grade 1 at baseline and 0.5% had CTCAE Grade 2 at baseline. A total of 810/1056 (76.7%) patients had a single change in CTCAE Grade (changes were normal to Grade 1 in 780 of the 810 patients) and 163/1054 (15.4%) had 2 CTCAE grade shifts (all were normal to Grade 2); 1 patient (0.1%) had a 3 grade shift in creatinine (from Grade 0 to Grade 3).

Safety in special populations

The 300 mg bd pool has been used as the data source for this section rather than SOLO1. The pooled dataset includes patients with a range of solid tumours, including breast cancer.

Effect of age

Table 78: 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=865	Age 65 to 74 years N=161	Age 75 to 84 years N=34	Age ≥85 years N=0
Total AEs	847 (97.9)	157 (97.5)	33 (97.1)	0
Total SAEs[a]	164 (19.0)	38 (23.6)	8 (23.5)	0
Fatal	2 (0.2)	1 (0.6)	1 (2.9)	0
Hospitalisation/prolong existing hospitalisation	150 (17.3)	32 (19.9)	8 (23.5)	0
Life-threatening	16 (1.8)	7 (4.3)	0	0
Other (disability incapacity)	4 (0.5)	1 (0.6)	0	0
Other (medically significant)	47 (5.4)	8 (5.0)	1 (2.9)	0
Total DAEs	63 (7.3)	16 (9.9)	5 (14.7)	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.

AE Adverse event; bd Twice daily; CSR Clinical study report; DAEs Adverse events leading to discontinuation; 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 79.

Table 79: 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=865	Age 65 to 74 years N=161	Age 75 to 84 years N=34	Age ≥85 years N=0
Total number of patients with AEs	847 (97.9)	157 (97.5)	33 (97.1)	0
Psychiatric disorders (SOC)	155 (17.9)	25 (15.5)	6 (17.6)	0
Accidents and injuries (SMQ)	64 (7.4)	10 (6.2)	2 (5.9)	0
Cardiac disorders (SOC)	55 (6.4)	12 (7.5)	1 (2.9)	0
Vascular disorders (SOC)	91 (10.5)	20 (12.4)	2 (5.9)	0
Central nervous system vascular disorders (SMQ)	5 (0.6)	0	0	0
Infections and infestations (SOC)	408 (47.2)	78 (48.4)	14 (41.2)	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	133 (15.4)	28 (17.4)	2 (5.9)	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.

Data derived from Table 2.7.4.1.6.2.2 and Table 2.7.4.1.13.5 Module 5.3.5.3 (DCO: 17 May 2018).

Effect of race

Table 80: Number (%) of patients who had at least 1 AE in any category by race (all patients and non-White patients) in the 300 mg bd pool

AE category[a]	Number (%) of patients		
	All patients (advanced solid tumours) (N=1060)	White patients (N=806)	Non-White patients[b] (N=254)
Any AE	1037 (97.8)	789 (97.9)	248 (97.6)
Any AE of CTCAE Grade 3 or higher	404 (38.1)	289 (35.9)	115 (45.3)
Any AE with outcome = death	4 (0.4)	3 (0.4)	1 (0.4)
Any SAE (including events with outcome = death)	210 (19.8)	158 (19.6)	52 (20.5)
AE leading to dose reduction of study treatment	219 (20.7)	158 (19.6)	51 (20.1)
Any AE leading to interruption of study treatment	398 (37.5)	298 (37.0)	100 (39.4)
AE leading to discontinuation of study treatment	84 (7.9)	66 (8.2)	18 (7.1)

[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 254 Non-White patients, 234 patients were Asian; 7 patients were Black, and 13 patients were 'other'.

The most common (≥10% of either White or non-White patients) AEs by race are shown in Table 81.

Table 81: Most common AEs (≥10% of either White or non-White patients) by race in the olaparib 300 mg bd pool

Preferred term[a]	Number (%) of patients	
	White patients (N= 806)	Non-White patients (N=254)
Any AE	**789 (97.9)**	**248 (97.6)**
Nausea	527 (65.4)	155 (61.0)
Anaemia	278 (34.5)	122 (**48.0**)
Vomiting	298 (37.0)	83 (32.7)
Fatigue	338 (**41.9**)	78 (30.7)
Decreased appetite	177 (22.0)	69 (27.2)
WBC count decreased	21 (2.6)	59 (**23.2**)
Neutrophil count decreased	21 (2.6)	51 (**20.1**)
Upper respiratory tract infection	55 (6.8)	49 (**19.3**)
Diarrhoea	234 (**29.0**)	48 (18.9)
Neutropenia	106 (13.2)	45 (17.7)
ALT increased	27 (3.3)	39 (**15.4**)
Constipation	166 (**20.6**)	34 (13.4)
Headache	161 (**20.0**)	33 (13.0)
Dizziness	102 (12.7)	33 (13.0)
Leukopenia	60 (7.4)	33 **(13.0)**
AST increased	23 (2.9)	32 (**12.6**)
Dysgeusia	156 (**19.4**)	31 (12.2)
Platelet count decreased	17 (2.1)	31 (**12.2**)
Cough	127 (15.8)	29 (11.4)
Thrombocytopenia	61 (7.6)	28 (11.0)
Pyrexia	101 (12.5)	26 (10.2)
Nasopharyngitis	62 (7.7)	26 (10.2)
Malaise	13 (1.6)	26 (**10.2**)
Abdominal pain	147 (**18.2**)	25 (9.8)
Dyspepsia	93 (11.5)	21 (8.3)
Abdominal pain upper	98 (12.2)	20 (7.9)
Arthralgia	132 (**16.4**)	19 (7.5)
Dyspnoea	120 (**14.9**)	19 (7.5)
Back pain	109 **(13.5**)	19 (7.5)
Urinary tract infection	81 **(10.0**)	11 (4.3)

Preferred term[a]	Number (%) of patients	
	White patients (N= 806)	Non-White patients (N=254)
Asthenia	161 (**20.0**)	10 (3.9)

a Table ordered by incidence of preferred terms in the population of non-White 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.

Safety related to drug-drug interactions and other interactions

No new data were provided regarding safety related to drug-drug interactions.

Discontinuation due to adverse events

AE leading to discontinuation

In SOLO1, a higher proportion of patients had AEs that led to discontinuation of treatment (DAEs) in the olaparib arm, compared with the placebo arm (Table 82). Further examination of data for the 6 olaparib-treated patients in SOLO1 with DAEs for nausea showed that 5 of the 6 patients had onset of nausea ≤7 days after first dose of olaparib.

Table 82: SOLO1: AEs leading to dose discontinuation occurring in ≥2 patients in either treatment group (SAS)

MedDRA SOC preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Patients with any AE leading to discontinuation	**30 (11.5)**	**3 (2.3)**
General disorders and administration site conditions	**10 (3.8)**	**1 (0.8)**
Fatigue	4 (1.5)	1 (0.8)
Asthenia	2 (0.8)	0
Malaise	2 (0.8)	0
Blood and lymphatic system disorders	**7 (2.7)**	**0**
Anaemia	6 (2.3)	0
Gastrointestinal disorders	**6 (2.3)**	**1 (0.8)**
Nausea	6 (2.3)	1 (0.8)
Vomiting	2 (0.8)	0

[a] Multiple occurrences of a system organ class/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; SOC System organ class.

Data derived from Table 11.3.5.1.1, SOLO1 CSR, Module 5.3.5.1 (DCO: 17 May 2018).

Comparison of adverse events leading to discontinuation

Anaemia and nausea were the most common AE leading to discontinuation in both populations. A higher proportion of patients in SOLO1 discontinued for AEs of nausea compared with the 300 mg bd tablet pool.

Table 83: Most common AEs leading to discontinuation (reported by ≥2 patients in the olaparib treatment arm of SOLO1 and/or reported by ≥2 patients the 300 mg bd pool)

System organ class Preferred term	Number (%) of patients	
	SOLO1 SAS olaparib 300 mg bd (N=260)	Olaparib 300 mg bd pool (N=1060)
Any DAE	**30 (11.5)**	**84 (7.9)**
Blood and lymphatic system disorders	**7 (2.7)**	**28 (2.6)**
Anaemia	6 (2.3)	20 (1.9)
Neutropenia	1 (0.4)	4 (0.4)
Thrombocytopenia	0	4 (0.4)
Leukopenia	0	2 (0.2)
Gastrointestinal disorders	**6 (2.3)**	**13 (1.2)**
Nausea	6 (2.3)	9 (0.8)
Vomiting	2 (0.8)	5 (0.5)
General disorders and administration site conditions	**10 (3.8)**	**13 (1.2)**
Fatigue	4 (1.5)	6 (0.6)
Asthenia	2 (0.8)	2 (0.2)
Malaise	2 (0.8)	2 (0.2)
Respiratory, thoracic and mediastinal disorders	**3 (1.2)**	**6 (0.6)**
Pneumonitis	1 (0.4)	3 (0.3)
Dyspnoea	1 (0.4)	2 (0.2)
Investigations	**2 (0.8)**	**9 (0.8)**
Platelet count decreased	1 (0.4)	3 (0.3)
White blood cell count decreased	1 (0.4)	2 (0.2)
Neutrophil count decreased	0	2 (0.2)
Infections and infestations	**1 (0.4)**	**4 (0.4)**
Pneumonia	0	2 (0.2)
Psychiatric disorders	**1 (0.4)**	**3 (0.3)**
Depression	1 (0.4)	2 (0.2)
Metabolism and nutrition disorders	**1 (0.4)**	**2 (0.2)**
Decreased appetite	1 (0.4)	2 (0.2)

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

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 84.

Table 84: SOLO1: AEs leading to treatment interruption occurring in >2 patient in either treatment group (SAS)

Preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=260)	Placebo bd (N=130)
Patients with any AE leading to dose interruption	135 (51.9)	22 (16.9)
Anaemia	57 (21.9)	1 (0.8)
Nausea	35 (13.5)	0
Vomiting	25 (9.6)	3 (2.3)
Neutropenia	21 (8.1)	4 (3.1)
Diarrhoea	15 (5.8)	0
Fatigue	13 (5.0)	1 (0.8)
Leukopenia	10 (3.8)	2 (1.5)
Pyrexia	9 (3.5)	1 (0.8)
Neutrophil count decreased	8 (3.1)	1 (0.8)
Asthenia	7 (2.7)	0
Thrombocytopenia	5 (1.9)	0
Abdominal pain	4 (1.5)	1 (0.8)
Influenza like illness	4 (1.5)	0
Gastroenteritis	4 (1.5)	0
White blood cell count decreased	4 (1.5)	0
Bronchitis	3 (1.2)	0
Dyspepsia	3 (1.2)	0
Gastroenteritis viral	3 (1.2)	0
Headache	3 (1.2)	0

[a] Multiple occurrences of a system organ class/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.

Comparison of adverse events leading to dose interruption

The proportion of patients who had AEs leading to dose interruption was higher for SOLO1. 135 (51.9%) compared with the 300 mg bd pool 398 (37.5%); however, this is likely due to the longer median total treatment duration in SOLO1. The most common AEs leading to dose modification (anaemia, vomiting, neutropenia, nausea and fatigue) were comparable with those observed in SOLO1.

AEs leading to dose reduction

Table 85: SOLO1: AEs leading to dose reduction occurring in >2 patient in either treatment group (SAS)

Table 18 SOLO1: AEs leading to dose reduction occurring in >2 patients in either treatment group (SAS)		
Preferred term[b]	**Number (%) of patients[a]**	
	Olaparib 300 mg bd (N=260)	**Placebo bd (N=130)**
Patients with any AE leading to dose reduction	74 (28.5)	4 (3.1)
Anaemia	44 (16.9)	1 (0.8)
Fatigue	10 (3.8)	1 (0.8)
Nausea	10 (3.8)	0
Neutropenia	9 (3.5)	1 (0.8)
Asthenia	5 (1.9)	0
Leukopenia	4 (1.5)	0
Thrombocytopenia	3 (1.2)	0

[a] Multiple occurrences of a system organ class/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.

Comparison of adverse events leading to dose reduction

The proportion of patients who had AEs leading to dose reduction was slightly higher for SOLO1: 74 (28.5%) and the 300 mg bd pool 219 (20.7%); however, this is likely due to the longer median total treatment duration in SOLO1.

2.5.1. Discussion on clinical safety

This application is mainly supported by safety data from the phase III SOLO-1 Study where patients were dosed olaparib (or placebo) 300 mg bd as a monotherapy. Supportive safety data from a pool of 1060 patients who were intended to receive olaparib 300 mg bd as a monotherapy in the MAH-sponsored studies (12 studies, including SOLO-1 results) were also provided. Overall, the The safety profile is based on pooled data from 1,826 patients with solid tumours treated with Lynparza monotherapy in clinical trials at the recommended dose.

In SOLO-1, 98.5% of the patients from olaparib arm experienced any AE. The majority of AEs occurred within the first 3 months of treatment. The most common AEs (reported by > 30% patients) in the olaparib arm were nausea (77.3%), fatigue (40.8%), vomiting (40.0%), anaemia (38.1%) and diarrhoea (34.2%). These results were numerically similar for the 300 mg bd pool population; except for nausea (64.3%), vomiting (35.9%) and diarrhoea (26.6%).

For many of the most common events reported at a higher (≥10%) frequency on olaparib compared with placebo, the rate remained higher for olaparib-treated patients when adjusted for exposure: nausea; anemia; vomiting; fatigue; diarrhoea ; constipation; dysgeusia; upper abdominal pain; asthenia; decreased appetite; dyspepsia; dyspnoea; pyrexia and urinary tract infection. Of these, dyspnoea has been identified as a new ADRs for olaparib by the MAH and reflected in section 4.8 of the SmPC.

Dyspnoea was experienced by 15.4% (40/260 patients) of the olaparib-treated patients compared to a 6.2% of patients in the placebo arm. In addition, the exposure-adjusted event rate was higher for olaparib compared to placebo (95.57 vs 41.63). The median time of onset for dyspnoea was 5.72 months (0.2-23.0 months). Events were mostly mild or moderate in severity; none were SAEs. All the events were resolved. One event lead to dose interruption and other to permanent discontinuation.

The event dyspnoea seems to be multifactorial. Most of the patients that experienced dyspnoea, experienced as well another relevant AE; the most common ones were nausea (80.0%), fatigue (67.5%) or anemia (52.5%). However, anemia may have contributed to fatigue and dyspnea.

Frequency of previously identified ADRs for olaparib, such as neutropenia, thrombocytopenia, leukopenia and upper abdominal pain has been increased from common to very common. Section 4.8 of the SmPC has been amended accordingly.

The percentage of patients experiencing any AEs of CTCAE grade 3 higher or any SAEs in SOLO1 were higher in the olaparib-treated patients compared to placebo ones (39.2% vs 18.5% and 20.8% vs 12.3%, respectively). The most common AEs of CTCAE Grade 3 or higher occurring in two or more patients in the olaparib arm were anaemia (21.4%), neutropenia (5%), diarrhoea (3.1%), neutrophil count decreased (2.7%) and leukopenia (1.5%).

Proportions of patients with AE of CTCAE Grade 3 or higher were similar in SOLO-1 (39.2%) compared to the 300 mg bd pool (38.1%). The most commonly reported event of CTCAE Grade ≥3 was anaemia. The proportion of patients with Grade ≥3 anaemia in SOLO-1 (21.2%) was consistent with results from the 300 mg bd pool (17.1%).

Discontinuations, dose reductions and interruptions due to AEs were more common in olaparib arm than in placebo arm in SOLO1. Results showed a percentage of olaparib discontinuations due to AEs in SOLO-1 of

11.5%; a higher proportion compared to 300 mg bd pool (7.1%). In SOLO-1, the most common DAE that occurred at ≥2% difference between any of the treatment group was anemia leading to 2.3% of the olaparib discontinuations.

In SOLO-1, 20.8% (54/260 patients) of the olaparib-treated patients experienced any SAE. The most common reported SAE was anaemia (6.5%). No patients in SOLO1 had CTCAE Grade 4 decrease of haemoglobin values during the study. Results were similar for 300mg bd pool.

The incidence and severity of anaemia events following olaparib treatment in SOLO1 were consistent with the known safety profile of olaparib. Anaemia remained manageable by interrupting or reducing the olaparib dose or giving blood transfusions, when indicated and treatment discontinuation was rarely required (see SmPC sections 4.2 and 4.4).

In clinical studies with olaparib, the incidence of CTCAE grade ≥2 shifts (decreases) from baseline in haemoglobin was 20%, absolute neutrophils 20%, platelets 5%, lymphocytes 30% and leucocytes 20% (all % approximate).

Considering the difference in time exposure between the SOLO1 safety set and the olaparib monotherapy 300mg bd safety set, data adjusted by patient years' exposure were provided for common AEs, grade ≥ 3 AEs, SAEs and AEs leading to discontinuation (data not shown). The adverse event rates (per 1000 patient year) was slightly higher for the pooled olaparib 300mg (average: 1.14 times), which was consistent with the first line use of olaparib in the SOLO1 trial. The consistency between the two sets was generally observed, with 'athralgia' events rate being slightly increased among the SOLO1 patients (1.24 times) and 'decreased appetite' being almost twice less (0.52 times). CTCAE grade ≥ 3 AE diarrhoea was more present (1.4 times more AEs per 1000 patients years) during the SOLO1 trial than among patients of the pool while fatigue was twice (2.2 times) more present among the patients of the pool. Overall, these data were consistent with the incidences already provided.

Regarding serious AEs, there was overall a slightly lower presence of time adjusted AEs observed during trial SOLO1. The individual numbers are small and do not allow to draw conclusions on individual AEs.

In SOLO1, in the post-follow-up period, 2 patients had AEs of AML and 1 patient had an AE of myeloproliferative neoplasm; the outcome was fatal for the cases with AML and in the myeloproliferative neoplasm case, the patient died due to a septic shock after a stem cell transplantation.

The incidence rate of MDS/AML is 0.6% (55/9293 patients) in the entire olaparib clinical programme and 1.2% (26/2258 patients) for the pool of all doses of olaparib in monotherapy. The majority of the cases reported a fatal outcome, 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 <6 months to >2 years. The time to death after olaparib was discontinued ranged from 17 to 667 days (median 209 days).

In order to assess the potential contributions of the duration of exposure to olaparib and the number of prior lines of platinum-containing chemotherapy on the risk of MDS/AML, a further analysis of data from SOLO1 and SOLO2 was conducted. Data showed that the event rate for MDS/AML in SOLO1 (one platinum-based regimen) was lower than the event rate in both olaparib and placebo-treated patients in SOLO2 (two Platinum-based regimen): 1) event rate in SOLO1 was higher in the olaparib arm compared to placebo arms (3.4 vs 0); 2) in SOLO2 a higher event rate was observed in placebo arm compared to olaparib arm (16.2 vs 10.5). Duration of exposure and follow-up time was longer in SOLO1.

A second sensitivity study was conducted to SOLO1 and SOLO2 regarding the influence of the exposure to PARP inhibitors, even as a subsequent therapy. Results showed that the event rate of MDS/AML events was higher in SOLO2 population than in SOLO1, even if the patients had never been treated with any PARP-inhibitor. The event rate difference were of 15.7 points higher in the never PARP inhibitor treated

population in SOLO1 study (19.1) and 8.8 points higher in the ever PARP inhibitor treated population in SOLO2 study (12.2) compared to ever PARP inhibitor treated population in SOLO1 (3.4).

Therefore, results suggested that that the risk of MDS/AML is closely related to duration of exposure to platinum-containing chemotherapy, rather than the duration of exposure to olaparib. Nevertheless, a causal relationship between olaparib treatment and the incidence of MDS/AML cannot be dismissed. MDS/AML will be closely monitored as reflected in the RMP.

In SOLO1, there were 5 (1.9% incidence) patients in the Olaparib arm and 3 (2.3% incidence) patients in the placebo arm with new primary malignancies. Comparison of AEs of new primary malignancies in SOLO1 against other studies in the clinical programme suggested that when larger populations of olaparib-treated patients are considered the incidence decrease. The incidence for the pooled data of the entire clinical programme in the olaparib-treated population is 0.7% (29 events out of 9293 olaparib-treated patients).

As the risk of AML/MDS and NPM might be higher in patients with germline *BRCA*m (in whom also the blood cells carry the mutation and will thus be affected by the PARP inhibition), incidence data specifically in patients with g*BRCA*1 and g*BRCA*2 from clinical trials and post-marketing experience (up to June 2018) were provided. Furthermore, in order to understand the background incidence of MDS/AML due to chemotherapy in g*BRCA* mutated patients (who might potentially be more susceptible), available data from historical populations who received platinum but not PARPi were provided (data not shown).

The analysis of the pooled data from the clinical trials did not allow concluding on differences of either MDS/AML or NPM among the gBRACm patients treated with olaparib as relative to those treated with the comparator. This concerned both the monotherapy studies (overall 1400 olaparib patients and 402 controls patients) and the combination studies (67 patients treated with olaparib and 14 controls).

Currently MDS/AML cases have been reported in 1.4% of gBRAC1m patients and 1.6% of *BRCA*2 (gBRAC2m) treated with olaparib. Post marketing records document MDS/AML in 5 *BRCA*1m and 11 *BRCA*2m patients for an overall number of 61 MDS/AML cases. NPMs showed similar figures among the monotherapy olaparib treated patients (1.3% for g*BRCA*1m and 1.6% for g*BRCA*2m patients) but had a lower overall incidence in the post marketing data (8 cases compared to 61 for MDS/AML). It is not clear whether the lower number of NPMs cases was related to lower risk of other types of malignancies compared to MDS/AML or to differences in data collection and potentially under-reporting for NPMs.

The annual report on AML/MDS (data cut-off Dec 2018) was provided within this procedure (data not shown) and will be further discussed in the PSUR procedure. Section 4.4 of the SmPC has been updated to include the incidence of MDS/AML cases specifically among g*BRCA*1m and g*BRCA*2m patients (1.7% and 1.4%, respectively).

MDS/AML and new primary malignancies are classified in the RMP as important potential risks and will continue to be monitored closely. Long-term safety data will also continue to be collected (see RMP).

Five events of pneumonitis were reported (1.9% incidence) in SOLO-1. The incidence for the pooled data of olaparib in monotherapy combined therapeutic dose (N=1826 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.

The reports of pneumonitis from post-marketing surveillance were 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.

Pneumonitis is classified in the RMP as important potential risks and will continue to be monitored closely.

From a mechanistic point of view, patients without germline *BRCAm* (*gBRCAwt*) might have a better safety profile than patients with gBCRAm since the drug will act mainly on the tumour cells rather than on all cells

of the body. A comparison of the safety data for patients confirmed as being g*BRCA*wt vs g*BRCA*m, while taking into account other possible baseline differences was provided (data not shown). Data in only 67 patients g*BRCA*wt were presented (vs 1419 for g*BRCA*m). The relatively low number of g*BRCA*wt patients might be explained by inclusion criteria in clinical trials mostly performed in g*BRCA*m patients. Overall there was no clear difference but the low numbers of events by the 'preferred term level' made it difficult to draw meaningful conclusions.

With regards to special population, the proportion of AEs and SAEs was similar among the difference age population. Proportion of SAEs were slightly increasing from younger to older groups; 7.3% for age ≤ 65 years group, 9.9% for age from 65 to 74 years group and 14.7% for age from 75 to 84 years group. No patients above or same to 85 years old were included in the study.

In the SOLO1 trial 92.1% of the non-Whites were from Asian origin: 50.4% from China, 22.7% from Japan 15.8% from Korea and the remaining patients from 8 other countries. Although differences in incidences are observed, there were no consequences for dose adjustments as the proportions of patients requiring dose reductions, treatment interruptions and dose discontinuations were similar for White and non-White patients. Although some AEs occurred at rather similar frequencies among Non-White and White patients, other including WBC count decreased, Neutrophil count decreased, Platelet count decreased, Malaise and Asthenia have differences of incidences between the two sub populations of patients. An overview of the literature on other PARPi did not brought evidence that races led to different PK or AEs profiles but in two publications on veliparib Western patients were found more subject to nausea and vomiting. Pop PKs reached similar conclusion.

Olaparib is not recommended for use in patients with severe hepatic impairment; however, no olaparib dose adjustment is considered warranted for patients with mild or moderate hepatic impairment (See SmPC section 4.2).

Olaparib is not recommended for use in patients with severe renal impairment; the dosage should be reduced to 200 mg bd in patients with moderate renal impairment, however, no olaparib dose adjustment is considered warranted for patients with mild renal impairment. (See SmPC section 4.2)

No change to the current recommendations for patients with renal and hepatic impairment is needed based on the data provided in this application.

2.5.2. Conclusions on clinical safety

The results of study SOLO-1 did not show significant differences in safety when compared to pooled safety data from other studies. Overall, the safety profile of olaparib tablet formulation is considered manageable for the intended population taking into account current pharmacovigilance activities and risk minimisation measures in place for the product. However the safety data available are considered limited in terms of number of patients and long-term follow-up and therefore do not allow to comprehensively determine long-term toxicities. Long-term exposure to/potential toxicity to olaparib is already included in the list of safety concerns in the risk management plan, under missing information.

More data are also needed to assess the causal relationship between the exposure to olaparib and the development of events that constitute important potential risks. Routine pharmacovigilance activities including follow-up targeted safety questionnaires are in place to enable more complete data collection and assessment (see RMP). No additional pharmacovigilance activities were considered needed as a result of the present procedure.

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 CHMP endorsed the Risk Management Plan version 17.4 with the following content:

Safety concerns

Table Summary of 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

Routine pharmacovigilance activities

Specific adverse reaction follow-up questionnaires

Follow-up targeted safety questionnaires are in place to enable more complete data collection and assessment of the following important potential risks:

- MDS/AML: to obtain detailed information about the patient, the underlying disease, all potential risk factors and the sequence of events, such as previous chemotherapy details, exposure to radiotherapy, diagnostic details and classification of MDS, clinical progression and final outcome.
- New primary malignancies: to obtain detailed information about the patient, the underlying disease, all potential risk factors and the sequence of events, such as previous chemotherapy details, exposure to radiotherapy, diagnostic details, classification, staging of NPM, clinical progression, complications and final outcome.
- Pneumonitis: to obtain detailed information about the patient, the underlying disease, all potential risk factors and the sequence of events, such as previous chemotherapy details, exposure to radiotherapy, diagnostic details, clinical progression, complications and final outcome.

Other forms of routine pharmacovigilance activities

Cumulative reviews of MDS/AML

- MDS/AML: Collection and assessment of data from the ongoing clinical programme and post-marketing sources to further characterise the important potential risk of MDS/AML. A cumulative report of MDS/AML cases is provided concurrent with the annual periodic benefit risk evaluation report (PBRER) (previously categorised as a required additional pharmacovigilance activity).

Additional pharmacovigilance activities

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

Risk minimisation measures

Table 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 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.	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
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

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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, 4.4, 4.8 and 5.1 the SmPC of the tablet formulation have been updated. Sections 4.2, 4.4, 4.8 and 5.1 of the SmPC of the capsule formulation have also been modified to reflect information that is also relevant to the capsule formulation. The Package Leaflet has been updated accordingly.

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 for the following reasons: The wording of the package leaflet is similar to that already tested previously during the MA applications.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lynparza (olaparib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applied indication is for the maintenance treatment of newly diagnosed advanced *BRCA*-mutated high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to first line platinum-based chemotherapy.

3.1.2. Available therapies and unmet medical need

The current standard of care for newly diagnosed advanced ovarian cancer, including those patients with *BRCA*m high-grade ovarian cancer, consists of radical debulking surgery followed by post-operative platinum-based first line chemotherapy (NCCN Ovarian 2019). For patients for whom upfront surgery is unlikely to achieve a complete resection, treatment consists of neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy (NCCN Ovarian 2019).

First line chemotherapy is generally given for a maximum of 6 cycles. It cannot be continued until progression as it is associated with cumulative neurological, renal, and haematological toxicities. Moreover, clinical outcomes do not improve if chemotherapy is extended beyond 6 cycles (Ledermann et al 2013). Since chemotherapy is not a viable treatment option in the maintenance setting, there is a need for a well-tolerated maintenance treatment option in the first line setting. The vascular endothelial growth factor inhibitor bevacizumab (Avastin) in combination with carboplatin and paclitaxel followed by bevacizumab maintenance is the only treatment approved in the first line maintenance ovarian cancer setting.

There are currently no first line maintenance treatments approved specifically for *BRCA*m patients with advanced ovarian cancer and these patients receive the same treatment options as all other ovarian cancer patients.

3.1.3. Main clinical studies

This application is based on results from the pivotal Phase III, randomised, placebo-controlled, double-blind multicentre study (SOLO1) in which newly diagnosed, advanced (FIGO stage III-IV) *BRCA*-mutated high grade serous or high grade endometrioid ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer who are in CR or PR following completion to first line platinum-based chemotherapy, were randomised 2:1 to receive either olaparib (300 mg bd, tablet formulation) or Placebo.

The primary endpoint was PFS defined as time from randomisation to progression determined by investigator assessment using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or death. BIRC assessment was presented as sensitivity analysis. Secondary endpoints included OS, PFS2, TFST, TSST, and TDT.

3.2. Favourable effects

At the time of the DCO of 17 May 2018, 102 (39.2%) olaparib-treated patients and 96 (73.3%) had a PFS event; HR was equal to 0.30 (95% CI 0.23, 0.41; p<0.0001) indicating a 70% reduction in the risk of disease progression or death for olaparib-treated patients compared to placebo-treated ones. The median PFS from randomization was not reached for olaparib arm and was 13.8 months for placebo.

Sensitivity and additional analyses of PFS (evaluation time bias, attrition bias, using the eCRF stratification variable, assess possible informative censoring (using BICR), estimating HR using the stratified log rank test, based on earliest progression of investigator/BICR assessment of progression) were all consistent with the primary analysis showing favourable treatment benefit for olaparib in maintenance therapy for the study population.

Secondary endpoints were also supportive. PFS2 data, with 26.5% and 39.7% of events in olaparib and placebo arms, showed an initial trend towards greater reduction of risk of disease progression with next line therapy or death for patients initially allocated to olaparib arm compared to placebo (HR of 0.50 (95% CI 0.35-0.72; p=0.0002; median not reached for olaparib vs. 41.9 months for placebo).

At the time of the analysis OS survival data were not yet sufficiently mature to allow comparison between two groups, with event rate of 21.2% and 20.6% in olaparib and placebo arms respectively. At 21.0% of

maturity, the HR was not indicating a detriment in OS of olaparib arm compared to placebo, with a large CI (HR 0.95, 95% CI 0.60, 1.53, p= 0.8903, median was not reached in either arms).

A statistically significant delay in TFST was observed for olaparib arm compared with placebo in the overall population (HR 0.30, 95% IC 0.22, 0.40, p<0.0001, median of 51.8 months olaparib vs 15.1 months placebo).

3.3. Uncertainties and limitations about favourable effects

The OS survival data were not yet sufficiently mature to allow comparison between two groups. An updated OS analysis and the final OS analysis which will be done at approximately 60% maturity will be submitted by the MAH (see Annex II).

The provided analysis of PFS2 is far from mature and probably over-represents patients with a short-lasting response with poor platinum sensitivity. Updated and final PFS2 data from SOLO1 study will be provided (see Annex II).

Available data in patients with somatic *BRCA* mutations are considered limited. Uncertainty remains in regard to the magnitude of benefit in patients with somatic *BRCA* mutations, especially in this earlier setting in which patients are not pre-selected by platinum sensitivity. However, there is a biological rationale suggesting similar activity in patients with somatic *BRCA* mutations as in patients with germline origin of *BRCA* mutations in their tumours. The MAH is recommended to collect further data in these patients, including in first-line setting.As bevacizumab treated-patients were excluded from the study, no data was obtained in this population. This is adequately addressed in section 5.1 of the SmPC.

3.4. Unfavourable effects

Lynparza monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE grade 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving Lynparza monotherapy (≥10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, upper abdominal pain, cough, dyspnoea, anaemia, neutropenia, thrombocytopenia and leukopenia.

Dyspnoea experienced by 15.4% (40/260 patients) of the olaparib-treated patients has been identified as a new ADR for olaparib. The median time of onset for dyspnoea was 5.72 months (0.2-23.0 months).

Frequency of previously identified ADRs for olaparib, such as, neutropenia, thrombocytopenia, leukopenia and upper abdominal pain has been increased from common to very common (see SmPC section 4.8).

Important potential safety concerns include the risk of MDS/AML, new primary malignancies, pneumonitis, overdosing or underdosing due to medication errors associated with dual availability of capsules and tablets, effects on embryofoetal survival and abnormal development.

Overall, olaparib has been associated with adverse drug reactions generally of mild or moderate severity (CTCAE 1 or 2) and generally not requiring treatment discontinuation.

Overall, the safety profile of olaparib is well characterised. The most common (≥20% of patients) AEs in the olaparib arm were nausea (77.3%), fatigue (40.8%), vomiting (40%), anaemia (38.1%), diarrhoea (34.2%), constipation (27.7%), dysgeusia (26.2%), arthralgia (25.4%), abdominal pain (24.6%), asthenia (24.2%) and headache (22.7%). The AEs that led to discontinuations in more than 2 patients of the olaparib arm are anaemia (2.3%), nausea (2.3%), fatigue (1.5%), vomiting (0.8%), asthenia (0.8%) and malaise (0.8%). Otherwise these AEs were mostly mild or moderate in severity.

Grade ≥3 AEs were reported in a higher proportion of patients in the olaparib arm than in the placebo arm (102 [39.2%] patients and 24 [18.5%], respectively). The most common AEs of CTCAE Grade ≥3 (reported

in ≥3% of patients in either the olaparib arm and/or the placebo arm) were anaemia (grouped term: 21.5% of olaparib-treated patients vs 1.5% patients in the placebo arm), neutropenia (grouped term: 8.5% vs 4.6%, respectively) and diarrhoea (3.1% vs 0%).

Serious adverse events (SAEs) were reported in a higher proportion of the olaparib treated patients (20.8%, n=54) than in patients in the placebo arm (12.3%, n=16). The most common SAE in the olaparib arm was anaemia (17 [6.5%] olaparib treated patients vs 0% placebo arm) and urinary tract infection (3 [1.2%] vs 0). The other SAEs for olaparib occurred in <3 patients each.

The median total duration of exposure to olaparib was approximately two times longer than duration of exposure to placebo (106.9 weeks [24.6 months, reflective of the 2 year treatment cap], versus 60.3 weeks [13.9 months, reflective of the time to disease progression in the placebo arm], respectively).

Dose modifications (interruptions or reduction) were reported in 65.8% patients on olaparib and 32.3% placebo patients; the majority of these were short-term interruptions in treatment. Eleven percent of the olaparib patients had AEs that led to discontinuation.

The safety of olaparib in this study was in line with the known safety profile of olaparib.

3.5. Uncertainties and limitations about unfavourable effects

The safety data available are considered limited in terms of number of patients and long-term follow-up and therefore do not allow to comprehensively determine long-term toxicities. Long-term exposure to/potential toxicity to olaparib is included in the list of safety concerns under missing information in the risk management plan.

The most important uncertainties about unfavourable effects are related to the risk of AML/MDS, new primary malignancies and pneumonitis. The causality of olaparib in occurrence of rare cases of MDS/AML could not be firmly established in the context of previous courses of chemotherapy. MDS/AML will be closely monitored as reflected in the RMP. Causal relationship between the exposure to olaparib and the occurrence of pneumonitis events could not be established. The SmPC has been modified to reflect updated safety information in this regard.

3.6. Effects Table

Table 86: Effects Table for Olaparib in the maintenance treatment of patients with newly diagnosed advanced *BRCA*-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response following completion of first-line platinum-based chemotherapy

Effect	Short description	Unit	Olaparib	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	From randomization to progression or death.	HR Median (month)	0.30 NR	1 13.8	(95% CI 0.23, 0.41; p<0.0001)	SOLO1
PFS2	From randomisation to the earliest of the progression event subsequent to that used for the primary	HR Median (month)	0.50 NR	1 41.9	(95% CI 0.35, 0.72, p<0.0001)	SOLO1

Effect	Short description	Unit	Olaparib	Placebo	Uncertainties / Strength of evidence	References
	variable PFS or death.					
OS	From randomization until death.	HR Median (month)	0.95 NR	1 NR	OS data are immature (21%) No indication of detrimental effect.	SOLO1
TFST	From randomisation to first subsequent therapy or death	HR Median (month)	0.30 51.8	1 15.1		
Unfavourable Effects						
TEAEs	TEAEs regardless causality	%	98.5	92.3		Safety sections of ARs
Grade 3-4 TEAEs	TEAEs grade 3-4 regardless causality	%	39.2	18.5		
Serious TEAEs	Serious TEAEs regardless causality	%	20.8	12.3		
AEs leading to discontinuation of study treatment		n (%)	30 (11.5)	3 (2.3)		
AEs leading to reduction of study treatment		%	28.5	3.1		
AEs leading to interruption of study treatment		%	51.9	16.9		

Adverse Effect	Short Description	Unit	Placebo N = 130	Olaparib 300 mg bd tablets bd N = 260	Olaparib 300 mg bd monotherapy tablets N = 1060	Uncertain-ties/ Strength of evidence (tablets)	References
Blood and lymphatic disorders	anaemia, all grades	% Pts	9.2% 12/130	38.1% 99/260	37.7% 400/1060		
	anaemia, grade ≥3	% Pts	1.5% 2/130	21.2% 55/260	17.1% 181/1060		
	Neutropenia grade ≥3	% Pts	3.1% 4/130	5% 13/260	4.6% 49/1060		
Gastrointestinal disorders	Nausea all grades	% Pts	37.7% 49/130	77.3% 201/260	64.3% 682/1060		
	Vomiting all grades	% Pts	14.6% 19/130	40% 104/260	35.9% 381/1060		
	SOC Grade ≥3	% Pts	2.3% 3/130	6.5% 17/260	6.2% 66/1060		
General disorders	Fatigue All grades	% Pts	30%	40.8%	39.2%		

Note: NR= not reached; SOC= system organ class

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Lynparza was shown to delay disease progression in patients who are in response to platinum-based chemotherapy in a first line setting based on PFS results from a randomised study in patients *BRCA* mutated. The use of PFS as primary endpoint is supported by sensitivity analyses and secondary endpoints.

Although the OS data from the SOLO1 study are still immature (21.0% of maturity), the HR was not indicating a detriment in OS of olaparib arm compared to placebo. The magnitude of PFS benefit does not appear to translate into OS benefit at this timepoint. The final OS analysis which will be done at approximately 60% maturity will be submitted by the MAH (see Annex II and RMP).

PFS2 results, even immature, are showing a positive trend. Overall, from an efficacy point of view, maintenance treatment represents a valuable option to delay progression and next line of platinum-containing chemotherapy, even though more mature data are needed.

The updated OS analysis and final OS analysis will be provided (see Annex II) along with updated PFS2 data.

Fatigue, nausea and vomiting of any grade are common with olaparib and might significantly affect QoL. Haematological AEs may prompt dose reductions and transfusions if not adequately managed. Olaparib monotherapy is associated with an acceptable tolerability and relatively few toxicities that do not appear to affect the measured patient reported outcomes.

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.

3.7.2. Balance of benefits and risks

Efficacy results showed a delay in PFS, which is supported by second endpoints results. This delay is partially maintained until the second progression. In addition patients with evidence of disease seem to respond to the treatment and to maintain the response for a long period.

Safety results of SOLO1 appear 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.

Overall, the benefit risk balance of Lynparza in the maintenance treatment of patients with newly diagnosed advanced *BRCA*-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response following completion of first-line platinum-based chemotherapy is positive.

3.8. Conclusions

The overall B/R of Lynparza in the maintenance treatment of patients with newly diagnosed advanced *BRCA*-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response following completion of first-line platinum-based chemotherapy is positive.

Considering OS and PFS2 results were immature, the CHMP considers the following measures necessary to address issues related to efficacy:

PAES: In order to further investigate the efficacy of olaparib maintenance treatment in patients with advanced *BRCA*1/2-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who

are in response (complete or partial) following completion of first line platinum-based chemotherapy, the MAH should submit the updated and final analysis of PFS2 and OS from the phase 3, randomised, double-blind study SOLO1. Due date: 31 December 2023.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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 include the use of Lynparza (tablet formulation) as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA*1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 the SmPC of the tablet formulation have been updated. Sections 4.2, 4.4, 4.8 and 5.1 of the SmPC of the capsule formulation have also been modified to reflect information that is also relevant to the capsule formulation. The Package Leaflet has been updated accordingly. The RMP version 17.4 has been updated accordingly.

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

This CHMP recommendation is subject to the following new condition:

Conditions and requirements of the marketing authorisation

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
PAES: In order to further investigate the efficacy of olaparib maintenance treatment in patients with advanced *BRCA*1/2-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first line platinum-based chemotherapy, the MAH should submit the updated and final analysis of PFS2 and OS from the phase 3, randomised, double-blind study SOLO1.	31 December 2023

Similarity with authorised orphan medicinal products

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers by consensus that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include the use of Lynparza (tablet formulation) as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA*1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 the SmPC of the tablet formulation have been updated. Sections 4.2, 4.4, 4.8 and 5.1 of the SmPC of the capsule formulation have also been modified to reflect information that is also relevant to the capsule formulation. The Package Leaflet has been updated accordingly. The RMP version 17.4 has also been accepted.

Summary

Please refer to the Scientific Discussion Lynparza-H-C-3726-II-23.

Attachments

1. Product Inforamtion (changes highlighted) of Lynparza as adopted by the CHMP on 26 April 2019

Appendices

1. CHMP AR on similarity dated 26 April 2019
2. CHMP assessment report on the significant clinical benefit in comparison with existing therapies in accordance with Article 14(11) of Regulation (EC) No 726/2004

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 10 May 2019. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/documents/regulatory-procedural-guideline/principles-be-applied-deletion-commercially-confidential-information-disclosure-emea-documents_en.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.

4. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first. For additional guidance see chapter 4.1 of the *Harmonised Technical Guidance for eCTD Submissions in the EU*.